OXAZOLES: SYNTHESIS, REACTIONS, AND SPECTROSCOPY

Part B

Edited by

David C. Palmer

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Raritan, New Jersey

AN INTERSCIENCE PUBLICATION

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This is the sixtieth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR AND PETER WIPF, *Editors*

ARNOLD WEISSBERGER, *Founding Editor*

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To my wife, Vicki, with love

The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

The Chemistry of Heterocyclic Compounds has been published since 1950 under the initial editorship of Arnold Weissberger, and later, until his death in 1984, under the joint editorship of Arnold Weissberger and Edward C. Taylor. In 1997, Peter Wipf joined Prof. Taylor as editor. This series attempts to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated several years ago a parallel series entitled General Heterocyclic Chemistry, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

The chemistry and synthetic applications of oxazoles were first covered in 1986 in an comprehensive volume edited by I. J. Turchi (Volume 45 of *The Chemistry of Heterocyclic Compounds* series). In the meantime, the number of synthetic strategies directed toward oxazole assembly as well as the use of these versatile heterocycles as intermediates, catalytic ligands, and pharmaceutical building blocks has vastly increased. We felt that a supplement and update of oxazole chemistry would be welcomed by the international chemistry community, and we are delighted that Dr. Palmer and his colleagues have accomplished this onerous mission. This volume represents another outstanding service to the organic and

heterocyclic chemistry literature that we are pleased to publish within *The Chemistry of Heterocyclic Compounds* series.

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PETER WIPF

Foreword

The subject of heterocyclic chemistry, prior to 1950, had been viewed as the domain of a small group of organic chemists. The perception prevailed that these individuals simply added ingredients together to make a witch's brew, heated it to 150–250 °C, and ultimately isolated a heterocyclic compound. This may be a somewhat exaggerated description of the subject but nevertheless makes the point that up to that time, it was assumed that one needed special training and knowledge to engage in this subject. However, in spite of this, a large number of molecularly distinct heterocyclic compounds were prepared and subsequently found to have highly important uses in medicine, polymers, dyes, and a number of other areas. As biology and biochemistry matured into a true science during the past 50 years, more and more biological phenomena were found to involve heterocyclic systems. This led to an increased appreciation of heterocycles, their chemical properties, and the reactions they undergo. As a result, these ring systems were subsequently regarded as more than a narrow field of chemistry. There is now little need to convince the informed scientific community of the incredible value of heterocyclic compounds.

As organic chemistry entered a new level of sophistication in the 1950s and understanding of chemical reactions was actively pursued, heterocyclic compounds were also included in this exploration and found to play a major role in many important chemical reactions, both as intermediates and as final products.

As this writer predicted in 1974 in a monograph entitled ''Heterocycles in Synthesis,'' these ring systems will not only be crucial to the scientific areas already mentioned above but will also find great importance in the synthesis of all types of organic compounds. In fact, in the current climate, heterocycles and their properties are so well accepted that they pervade all areas of medicine and biology, as well as chemistry.

The present updated volumes relating to oxazoles, oxazolines, and oxazolones are very timely works since these simple five-membered ring heterocycles have contributed much to the knowledge we have acquired in various fields of biological and chemical sciences. For example, we may envision oxazolones as tautomeric derivatives of the old and well-known azlactones, first reported in 1883. They may also be viewed as ''cyclized'' amino acid derivatives or their dehydro analogs and therefore would be expected as constituents of many biologically active natural products. In addition, these ring systems have shown their versatility in the synthesis of a variety of ligands for metal catalysts, as well as precursors or vehicles to reach many types of functionalized compounds. Furthermore, their chiral counterparts—oxazoles, oxazolines, and oxazolones containing a stereogenic center—have been major players in a very large number of asymmetric syntheses. Hardly a day passes that some journal does not describe the involvement of these chiral, non-racemic heterocycles for preparing an organic compound in very high

enantiomeric excess. Thus, oxazoles and their derivatives, whose synthesis, properties, and reactivity are described in the following two volumes, represent an immensely versatile family of heterocyclic compounds for future exploitation by both synthetic and medicinal chemists.

Fort Collins, Colorado
November, 2002

A. I. MEYERS

Preface

By far the most comprehensive review of the synthesis and reactions of mononuclear oxazoles and derivatives is *The Chemistry of Heterocyclic Compounds, Volume 45*, edited by I. J. Turchi and published in 1986. This work is the definitive reference for oxazole chemistry through 1983. Subsequently, literally tens of thousands of references appeared in the period 1983–2001 pertaining to this remarkable small ring heterocycle. Oxazoles and derivatives continue to be of great interest and importance in all aspects of synthetic chemistry with applications in medicinal and agricultural chemistry, material sciences, photographic dyes, peptide chemistry, asymmetric catalysis, and polymer chemistry. Indeed, more than 250 reviews focusing on specific aspects of the chemistry and biology of oxazoles, oxazolones, oxazolines, and chiral bis(oxazolines) have been published from 1983 to 2001. The continuing interest in oxazoles together with the wealth of new information warrants a second review of this exciting area.

It would require a Herculean effort to prepare a complete discussion and review of every report related to the synthesis, reaction, or application of an oxazole while tabulating every oxazole, oxazolone, oxazoline, and chiral bis(oxazoline) prepared and evaluated during the period of 1983–2001. Such an undertaking is beyond the scope of this review. Furthermore, the ease with which electronic databases, including the patent literature, can be searched, the data retrieved, and the information tabulated would render such a project somewhat redundant.

Rather, the intent of the current project is to provide the reader with a discussion and leading examples of significant advances made in the synthesis, reactions, and applications of mononuclear oxazoles, oxazolones, oxazolines, and chiral bis(oxazolines) during this time frame. The material focuses on the more recent literature, although an update of the older synthetic literature is included wherever possible. In an effort to be selective, references to relevant reviews of material, not discussed in a chapter, are provided. Completely reduced oxazoles, that is, oxazolidines as well as benzo-fused derivatives, are outside the scope of this review.

The coverage is similar to that of Volume 45, although the presentation has been changed and the scope has been expanded to include a chapter devoted to the exciting area of chiral bis(oxazolines). The material is presented in nine chapters and two volumes. In some cases, the organization of the individual chapter contents is different from that in Volume 45 to reflect the changing emphasis on newer methodologies and synthetic targets. For example, in Part A, Chapter One contains an expanded section that deals specifically with the synthesis of selected naturally occurring mono-, bis-, and tris(oxazoles) to reflect the significant synthetic challenges therein. In addition, the discussion of cycloaddition and Diels–Alder reactions of oxazoles is introduced in Chapter One but is covered in detail in Chapter Three. In Part B, oxazolones are defined by the structure of the individual

regioisomer and discussed in Chapters Five, Six, and Seven, respectively. Chapter Eight describes the syntheses and reactions of oxazolines including asymmetric methodogy employing monooxazoline ligands. A new chapter, Chapter Nine, was added to include the recent developments in asymmetric synthesis utilizing chiral bis(oxazolines). Discussion of material from the patent literature has been included as an integral part of the volumes. Primary emphasis has been given to general syntheses and reactions. However, reactions that are more limited in scope and yet are singularly unique may also be described.

Tables are included in every chapter. Wherever possible, these contain a variety of selected examples to provide the reader with the scope and limitations of synthetic methods and reactions. However, in some cases a table will contain only the examples reported. No attempt has been made to provide an exhaustive compilation of every oxazole, oxazolone, or oxazoline prepared since 1983.

Part A is devoted specifically to the synthesis, reactions, and spectroscopic properties of oxazoles and encompasses four chapters: Chapter 1—Synthesis and Reactions of Oxazoles; Chapter 2—Spectroscopic Properties of Oxazoles; Chapter 3—Oxazole Diels–Alder Reactions; and Chapter 4—Mesoionic Oxazoles.

Part B is comprised of the following five chapters: Chapter 5—2(3*H*)-Oxazolones and 2(5*H*)-Oxazolones; Chapter 6—4(5*H*)-Oxazolones; Chapter 7—5(2*H*)-Oxazolones and 5(4*H*)-Oxazolones; Chapter 8—2-Oxazolines; and Chapter 9—Chiral Bis(oxazolines).

Acknowledgments: I thank the authors for their individual contributions and patience through several iterations of the chapters. I am indebted to the library staff at Johnson & Johnson Pharmaceutical Research & Development who secured even the most obscure references in a timely manner. A very special acknowledgment and thanks are due to Dr. Fuqiang Liu for his critical insights, suggestions, comments, and review of individual chapters during preparation of these volumes. I thank Dr. Mayra Reyes and Dr. Brigitte Segmuller for their help with the indices for Part B. The series editors, particularly Professor Ted Taylor, offered many helpful suggestions and guidance. I thank Dr. Darla Henderson and Ms. Amy Romano at John Wiley & Sons for their constant encouragement and support. Special thanks are due to Ms. Shirley Thomas and her staff at John Wiley & Sons for their patience and understanding during preparation of these volumes. Finally, I am deeply thankful to my wife, Vicki, for her continual support, patience, and understanding during this entire project.

The reader may well encounter errors in a work of this magnitude, particularly in one with several thousand structures. I hope such errors will not detract from the overall intent of the volumes. Nonetheless, any errors are the responsibility of the editor.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. DAVID C. PALMER
Raritan, New Jersey

Contents - Part B

Contents - Part A

Abbreviations

2-MI	2-methylimidazole
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
acac	acetylacetonate
Acm	acetamidomethyl
ADH	asymmetric dihydroxylation
ADHD	attention-deficit hyperactivity disorder
AHMHA	4-amino-3-hydroxy-6-methylheptanoic acid
AHPBA	3-amino-2-hydroxy-4-phenylbutyric acid
Aib	2-aminoisobutyric
AIBN	2,2′-azobisisobutyronitrile
Alloc or AOC	allyloxycarbonyl
AMNT	aminomalononitrile *p*-toluenesulfonate
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BDMS	biphenyldimethylsilyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	[1,1′]binaphthalenyl-2,2′-diol
BINOL-box	3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc-Ox	2-oxo-3(2*H*)-oxazolecarboxylic acid *tert*-butyl ester
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	*N,N*-bis-(2-oxo-3-oxazolidinyl)phosphonic chloride
BPA	L-4-boronophenylalanine
BPO	dibenzoyl peroxide
Bt	benzotriazol-1-yl or 1-benzotriazolyl
Bz	benzoyl
C_3diPhe	*trans*-1-amino-2,3-diphenyl-1-cyclopropanecarboxylic acid
Cbz	benzyloxycarbonyl
Cbz-Ox	2-oxo-3(2*H*)-oxazolecarboxylic acid benzyl ester
CDI	1,1′-carbonyldiimidazole
CIP	2-chloro-1,3-dimethylimidazolium hexafluorophosphate
CNS	central nervous system
cod	cyclooctadiene
Cp	cyclopentadiene
CPTS	collidine *p*-toluenesulfonate
CSA	camphorsulfonic acid
CSI	chlorosulfonylisocyanate

Cy	cyclohexyl
CZE	capillary zone electrophoresis
DAST	diaminosulfur trifluoride
dba	dibenzylideneacetone
dbg	dibenzylglycine
DBF-box	2,2′-(4,6-dibenzofurandiyl)bis[4,5-dihydro-4-phenyloxazole]
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-4,5-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DECP or DEPC	diethylcyanophosphonate, diethylphosphoryl cyanide
Deoxo-fluor	bis(2-methoxyethyl)aminosulfur trifluoride
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAC	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMT	dimethoxytrityl
DOPA	3,4-dihydroxyphenylalanine
Dpg	dipropylglycine
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
DPPC	diphenylphosphoryl chloride, diphenyl phosphochloridate
dppe	1,4-bis(diphenylphosphino)ethane
dppf	1,4-bis(diphenylphosphino)ferrocene
DPPOx	diphenyl-(2-oxo-3(2*H*)-oxazolyl)phosphonate
dppp	1,4-bis(diphenylphosphino)propane
ECF	ethyl chloroformate
EDCI or EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EEDQ	2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline
EGB	electrogenerated base
ETHP	2-ethyl-1,4,5,6-tetrahydropyrimidine
ETMG	2-ethyl-1,1,3,3-tetramethylguanidine
EVL	ethoxyvinyllithium
EWG	electron-withdrawing group
FMO	frontier molecular orbital

Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HBTU	*O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
^{1}H NMR	proton NMR
Het	heterocycle
HMPA	hexamethylphosphoric triamide
HMTA	hexamethylenetetraamine
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HydrOx	hydroxy-oxazoline
IBCF	isobutyl chloroformate
ICI	Imperial Chemical Industries
IIDQ	2-isobutoxy-*N*-isobutoxycarbonyl-1,2-dihydroquinoline
Im	imidazole
KDN	3-deoxy-D-glycero-D-galacto-2-monulosonic acid
KHMDS	potassium hexamethyldisilazane, potassium bis(trimethylsilyl)amide
L-(+)-DET	L-(+)-diethyl L-tartrate
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LDEA	lithium diethylamide
LG	learning group
LiHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)amide (LHMDS)
LTMP	lithium 2,2,6,6-tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
m-CPBA	*m*-chloroperoxybenzoic acid (MCPBA)
MeBmt	(2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid
MEK	methyl ethyl ketone
MEM	2-methoxyethoxymethyl
2-MI	2-methylimidazole
MIBK	methyl isobutyl ketone
MOM	methoxymethyl
morphoCDI	*N*-cyclohexyl-*N′*-2-(*N*-methylmorpholinio)ethylcarbodiimide *p*-toluenesulfonate
Ms	methanesulfonyl (mesyl)
MTM	methylthiomethyl
NaHMDS	sodium hexamethyldisilazane, sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NIS	*N*-iodosuccinimide
NLO	nonlinear optical
NMM	4-methylmorpholine (*N*-methylmorpholine)
NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NOE	nuclear Overhauser effect
Nos	*p*-nitrobenzenesulfonyl (nosyl)
NPM	*N*-phenylmaleimide
PB	probase
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	poly(ethylene)glycol
PET	positron emission tomography
PhosOx	phosphine-oxazoline
Phth	phthaloyl
piv	pivaloyl
PMB	*p*-methoxybenzyl
PPA	poly(phosphoric acid)
PPE	polyphosphate ester
PPL	porcine pancreatic lipase
PPTS	pyridinium *p*-toluenesulfonate
PyBOP	benzotriazol-1-yl-*N*-oxytris(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	bromotris(pyrrolidino)phosphonium hexafluorophosphate
PyrOx	pyridine-oxazoline
RaNi	Raney nickel
SelOx	selenide-oxazoline
SEM	2-(trimethylsilyl)ethoxymethyl
SES	2-(trimethylsilyl)ethanesulfonyl
SulfOx	sulfide-oxazoline
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAB	tetrabutyl ammonium bromide
TBAF	tetra *n*-butylammonium fluoride
TBDMS or TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBTU	*O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
TCNE	tetracyanoethylene
TEAHC	tetraethylammonium hydrogen carbonate
TEAP	tetraethylammonium perchlorate
TECM	tandem Erlenmeyer condensation macrolactamization
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TEOF	triethyl orthoformate
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIA	*N,N,N′*-triisopropylacetamidine
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TIG	1,2,3-triisopropylguanidine
TIPP	H- Tyr- Tic- Phe- Phe-NH_2
TIPS	triisopropylsilyl
TMANO	trimethylamine *N*-oxide
TMEDA	*N,N,N′,N′*-tetramethyl-1,2-ethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Toac	2,2,6,6,tetramethyl-4-amino-1-oxypiperidine-4-carboxylic acid
Tol-BINAP	2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TosMIC	tosylmethyl isocyanide, [(*p*-toluenesulfonyl)methyl] isocyanide
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Troc	2,2,2-trichloroethoxycarbonyl
Ts or Tos	*p*-toluenesulfonyl (tosyl)
VDMO	4,4-dimethyl-2-vinyl-5(4*H*)-oxazolone

CHAPTER 5

2(3*H*)-Oxazolones and 2(5*H*)-Oxazolones

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The Chemistry of Heterocyclic Compounds, *Volume 60: Oxazoles: Synthesis, Reactions, and Spectroscopy, Part B,* edited by David C. Palmer
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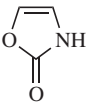
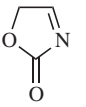
This chapter deals with recent advances in the chemistry of 2-oxazolones, namely, 2(3*H*)-oxazolone (4-oxazolin-2-one, **1**) and 2(5*H*)-oxazolone (3-oxazolin-2-one, **2**). Of the five isomeric oxazolones, the former is prominently cited in nearly all the literature reported since the 1980s.



1

2(3*H*)-Oxazolone



2

2(5*H*)-Oxazolone

Figure 5.1

5.1. 2(3*H*)-OXAZOLONES (4-OXAZOLIN-2-ONES)

5.1.1. Introduction

The first example of 2(3*H*)-oxazolone heterocycles appeared in 1905, as part of a description of the intramolecular cyclodehydration of *N*-phenacylurethane.[1] This methodology has been widely modified for a versatile synthesis of this class of compounds. The 2(3*H*)-oxazolones (4-oxazolin-2-ones) exsist predominantly in the keto rather than the enol forms and contains both enol and enamine moieties as masked amino and hydroxy molecules. Thus, a wide variety of possible addition modes at the 4,5-olefinic moiety strongly suggest the potential versatility of the heterocycles as a building block for 2-amino alcohols of biological and of general synthetic interest. Enantiocontrolled ionic, radical, and pericyclic additions at the 4,5-olefinic moiety of the 2-oxazolone ring followed by ring opening provide a useful strategy for the chiral construction of 2-amino alcohols. The 2-amino alcohol skeleton is a structural unit that is found in a substantial number of bioactive compounds such as peptide enzyme inhibitors, amino sugar antibiotics, and sympathomimetic amines as well as alkaloids. Such functional structures also serve as chelating bidentate ligands for metal catalysts in organic synthesis. Another aspect is based on the chemical stability of 2-oxazolone heterocycles that permits their synthetic use as protecting groups and leaving groups.

The important advances in the chemistry of 2(3*H*)-oxazolones since 1984 have been surveyed in this chapter, which is divided into two sections, synthesis and reactions.

5.1.2. Synthesis

5.1.2.1. From Acyclic Carbamates

A strategy involving the intramolecular cyclization of acyclic urethanes as a key step has been widely employed since the first synthesis of this class of compounds.[2]

The reaction of ethyl *N*-arylcarbamates **3** with 1-bromo-3,3-dimethyl-2-butanone or 1-bromo-3-ethyl-3-methyl-2-pentanone **4** in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) results in the one-step synthesis of 3-aryl-5-*tert*-butyl-2(3*H*)-oxazolones **7** in fair to good yields (Fig. 5.2; Table 5.1, Fig. 5.3).[3] This method is efficient for the preparation of bulky 5-substituted-2(3*H*)-oxazolones.

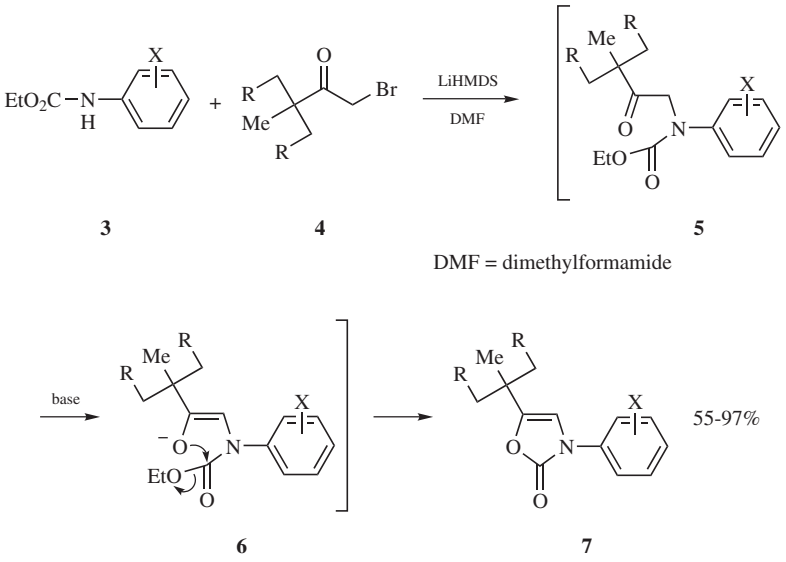
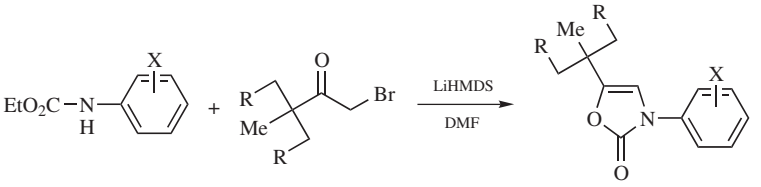


Figure 5.2

The *N*-(α-hydroxyphenacyl)urethanes **8** react smoothly with aromatics in concentrated sulfuric acid to give Friedel–Crafts type products **9**, which are readily converted into 4-aryl-5-phenyl-2(3*H*)-oxazolones **10** on heating or by treatment with phosphorus pentachloride (Fig. 5.4).[4]

Treatment of 1,3-dihalo-2-propyl and 2,3-dichloropropyl *N*-arylcarbamates **11** and **14** with ammonium fluoride results in the regioselective transformation to the 2(3*H*)-oxazolones **12** and **15** or to the exocyclic methylene derivatives **13** and **16** depending on the temperature (Fig. 5.5).[5]

TABLE 5.1. SYNTHESIS OF 3-ARYL-5-*tert*-BUTYL-2(3*H*)-OXAZOLONES FROM ETHYL *N*-ARYLCARBAMATES AND α-BROMO KETONES[a]

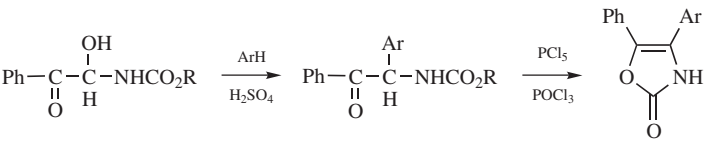


3 **4** **7**

Figure 5.3

R	X	% Yield
H	4-Cl	60
H	4-F	86
H	2,4-di-Cl	97
H	3,4-di-Cl	55
H	3,5-di-Cl	56
H	2-F, 4-Cl	80
H	3-CF_3	78
H	4-MeO	90
Me	2-F, 4-Cl	63

[a] Data from Ref. 3.



8
(R=Me, Et)

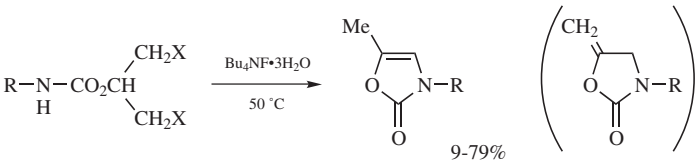
9

10
Ar=Ph: 73%
Ar=Tol: 75%

Figure 5.4

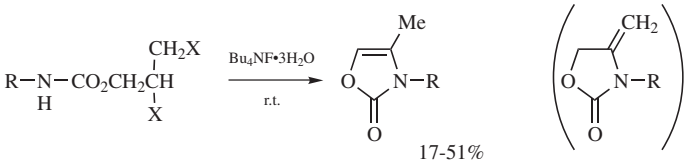
Anodic oxidation of the carbamates **17** and **23** in methanol, followed by reaction with chlorodiphenylphosphine affords the α-diphenylphosphinylcarbamates **20** and **25**, from which the readily generated carbanions react with aldehydes to give the 4-phosphinyl-2-oxazolidinones **21** and **26**. The removal of the diphenylphosphinyl group by a mild thermal treatment provides a route to the 2(3*H*)-oxazolones **22** and **27** (Fig. 5.6).[6]

Lead tetraacetate oxidative cyclization of the *N*-(1-naphthylvinyl)urethane **30**, derived from 1′-acetonaphthone **28**, yields 4-naphthyl-2(3*H*)-oxazolone **32** as the



11 **12** **13**

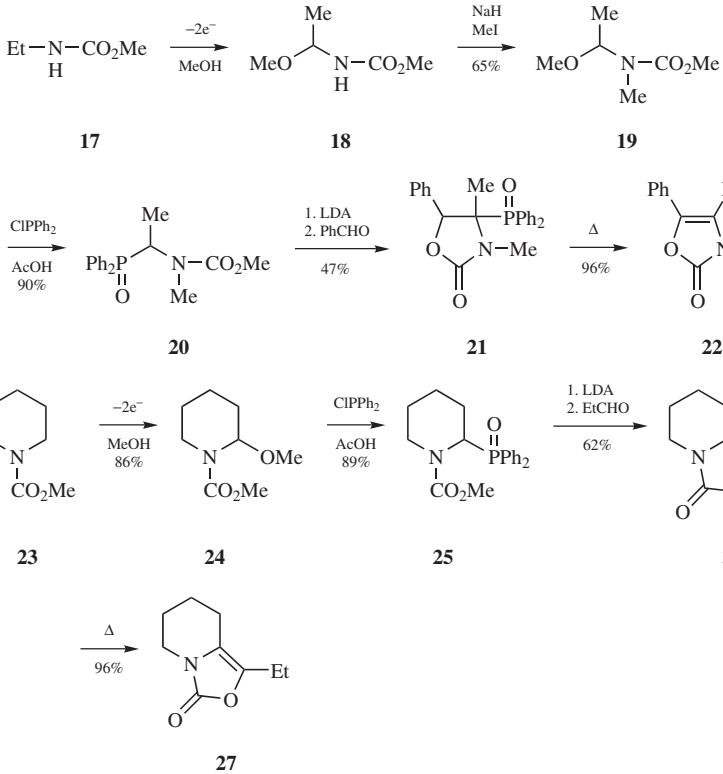
R=Ph, 4-ClC$_6$H$_4$, 1-naphthyl, *c*-C$_6$H$_{11}$
X=F, Cl, Br



14 **15** **16**

R=Ph, *c*-C$_6$H$_{11}$
X=Cl

Figure 5.5



17 **18** **19**

20 **21** **22**

23 **24** **25** **26**

27

Figure 5.6

major product, in addition to a rearranged product, the 1-naphthaleneacetamide **33** (Fig. 5.7).[7]

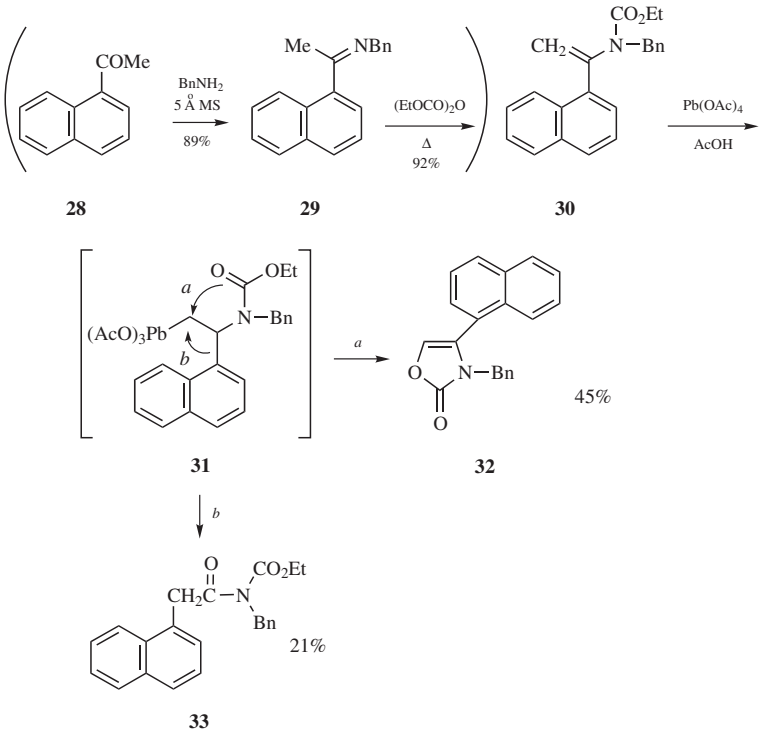


Figure 5.7

Treatment of the α-methoxycarbonylbenzyl carbamate **34** with diisobutylaluminum hydride (DIBAL-H), followed by dehydration of the resulting 4-hydroxy-2-oxazolidinone **35** with NH_4Cl gives the 5-phenyl-2(3*H*)-oxazolone **36** (Fig. 5.8).[8]

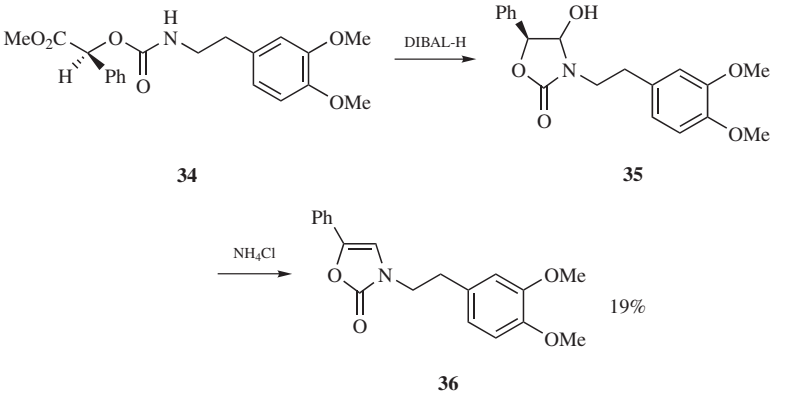


Figure 5.8

Protonation of the *N*-aryl-*N*-(3-triisopropylsilylpropargyl) carbamate **37** with trifluoromethanesulfonic acid generates a β-silylvinyl cationic intermediate **38** that is attacked by the carbamate carbonyl group (but not the aromatic ring) to give good yields of the 2(3*H*)-oxazolone **40** (Fig. 5.9).[9]

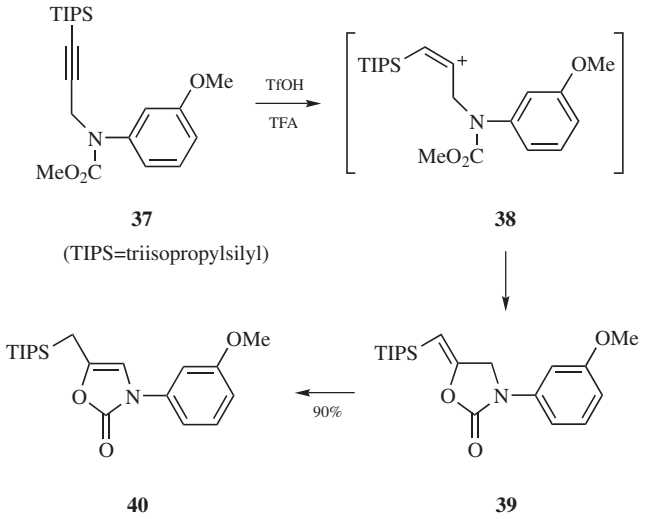


Figure 5.9

5.1.2.2. From 2-Allyloxyoxazoles

The scope of the thermal [3,3]-sigmatropic rearrangement of a series of 2-allyloxy-substituted 4,5-diphenyloxazoles **41** has been examined.[10,11] These systems, on heating, undergo a facile aza-Claisen rearrangement to give 3-allyl-4,5-diphenyl-2(3*H*)-oxazolones **42** (Fig. 5.10). In marked contrast to the thermal results, photolysis of the 2-allyloxy- or 2-benzyloxy-substituted oxazole gives rise to an isomeric mixture of 2(5*H*)- and 2(3*H*)-oxazolones, indicative of the recombination of a radical pair generated by allyl-*O* bond scission.

5.1.2.3. From α-Amino Acid Esters

α-Amino acids serve as good precursors to 5-alkoxy-2(3*H*)-oxazolones **47**. The compounds are synthesized by the *N*-chlorocarbonylation of an α-amino acid ester **45** with phosgene or the equivalent, followed by treatment with a variety of bases (Fig. 5.11; Table 5.2, Figs. 5.12, 5.13).[12]

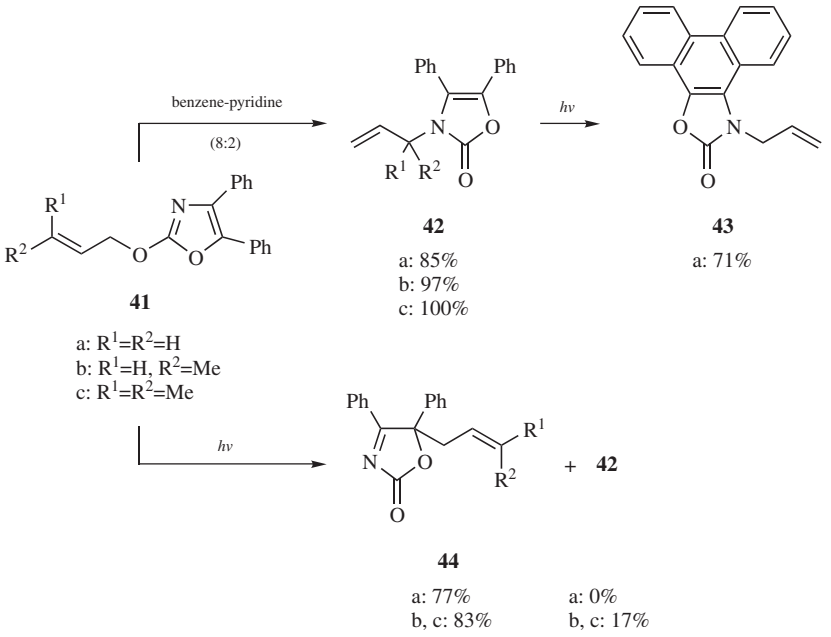


Figure 5.10

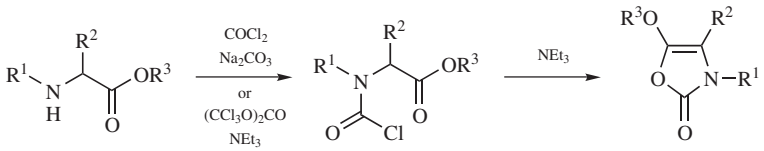


Figure 5.11

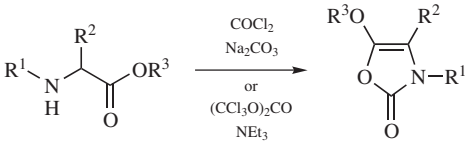
5.1.2.4. From Benzoin and Isocyanates

Aromatic α-ketols **48** react with (diethylamino)tributyltin to afford a mixture of (*Z*)- and (*E*)-1,2-enediol-types of bis-organostannylated compounds **49** that cyclize upon heating with phenyl isocyanate to give a 3,4,5-triaryl-2(3*H*)-oxazolone **50** (Fig. 5.14).[13]

5.1.2.5. From 1,2-Diketones

Reduction of α-imino ketones **52**, prepared from 1,2-diketones **51** and 1 equiv of an amine, with sodium in ether, followed by treatment with ethyl chloroformate or

TABLE 5.2. SYNTHESIS OF 5-ALKOXY-2(3*H*)-OXAZOLONES FROM α-AMINO ACID ESTERS



45 **47** **Figure 12**

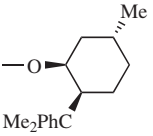
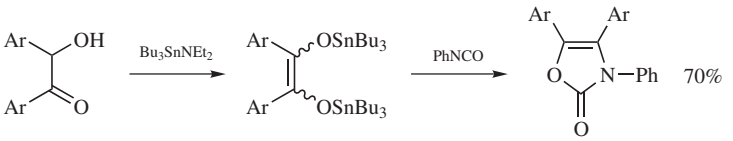
R^1	R^2	R^3	Reagents[a, b]	% Yield
i-Pr	H	Me	A	82
CH_2Ph	H	Me	B	26
CH_2Ph	H	(ℓ)-Menthyl	B	76
CH_2Tol	H	Me	B	86
(*dl*)-CHMePh	H	Me	B	76
(*R*)-CHMePh	H	Me	B	67
(*S*)-CHMePh	H	*i*-Pr	A	98
(*S*)-1-Phenylethyl	H	Ph	A	98
(*R*)-1-Phenylethyl	H	(ℓ)-Menthyl	B	69
(*S*)-1-Phenylethyl	H	(ℓ)-Menthyl	B	68
3,4-di-MeO-$C_6H_3CH_2$	H	Me	B	33
(1-Naphthyl)methyl	H	Me	B	43
(*R*)-1-(1-Naphthyl)ethyl	H	Me	B	60
$CHPh_2$	H	Me	B	66
$CHPh_2$	H	(ℓ)-Menthyl	B	62
$CHPh_2$	H		B	95
i-Pr	Me	Me	B	76
i-Pr	Me	Et	B	75
i-Pr	Me	*c*-C_6H_{11}	B	67
Ph	Me	Me	B	68
(*R*)-1-Phenylethyl	Me	Me	A	62
(*R*)-1-(1-Naphthyl)ethyl	Me	*i*-Pr	B	65
$CHPh_2$	Me	Me	A	95
Furfuryl	Et	Me	B	49
Furfuryl	Et	4-Pentenyl	B	8

Figure 13

[a] A = triphosgene, NEt_3; B = $COCl_2$, Na_2CO_3.
[b] Data from Ref. 12.



48 **49** **50**

Figure 5.14

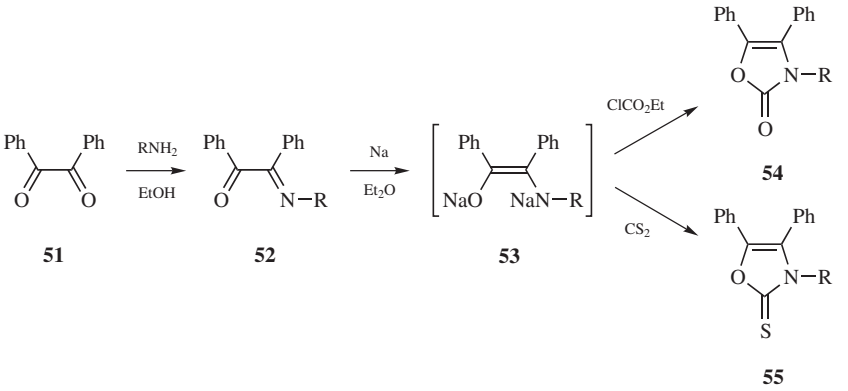


Figure 5.15

carbon disulfide, leads to the 4,5-disubstituted-2(3*H*)-oxazolones **54** and the corresponding 2-thiones **55**, respectively (Fig. 5.15; Table 5.3, Fig. 5.16).[14,15]

A one-pot, highly convergent synthetic strategy from 1,2-diketones **56** and isocyanates, has been used for the preparation of 4,5-dimethylene-2-oxazolidinones **57**. Thermal Diels–Alder reactions of the *N*-substituted-4,5-dialkylidene-2-oxazolidinones **57** with the dienophiles **58–61** proceed stereo- and regioselectively to afford a variety of bicyclic 2(3*H*)-oxazolones **62–67**. The regioselectivity is greatly improved by the use of Lewis acids such as $TiCl_4$ and $AlCl_3$, and the nitrogen atom

TABLE 5.3. CYCLIZATION OF α-IMINO KETONES TO 4,5-DIPHENYL-2(3*H*)-OXAZOLONES AND 2-THIONES[a]

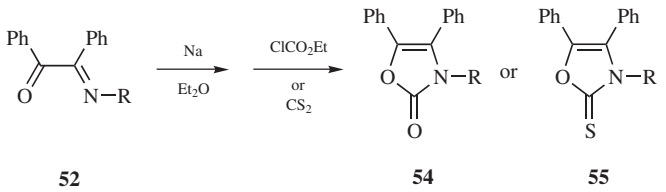


Figure 5.16

R	% Yield of **54**	% Yield of **55**
Pr	33	35
i-Pr	35	32
Bu	35	36
Ph	45	48
Tolyl	55	50
CHMePh	35	49

[a] Data from Refs. 14, 15.

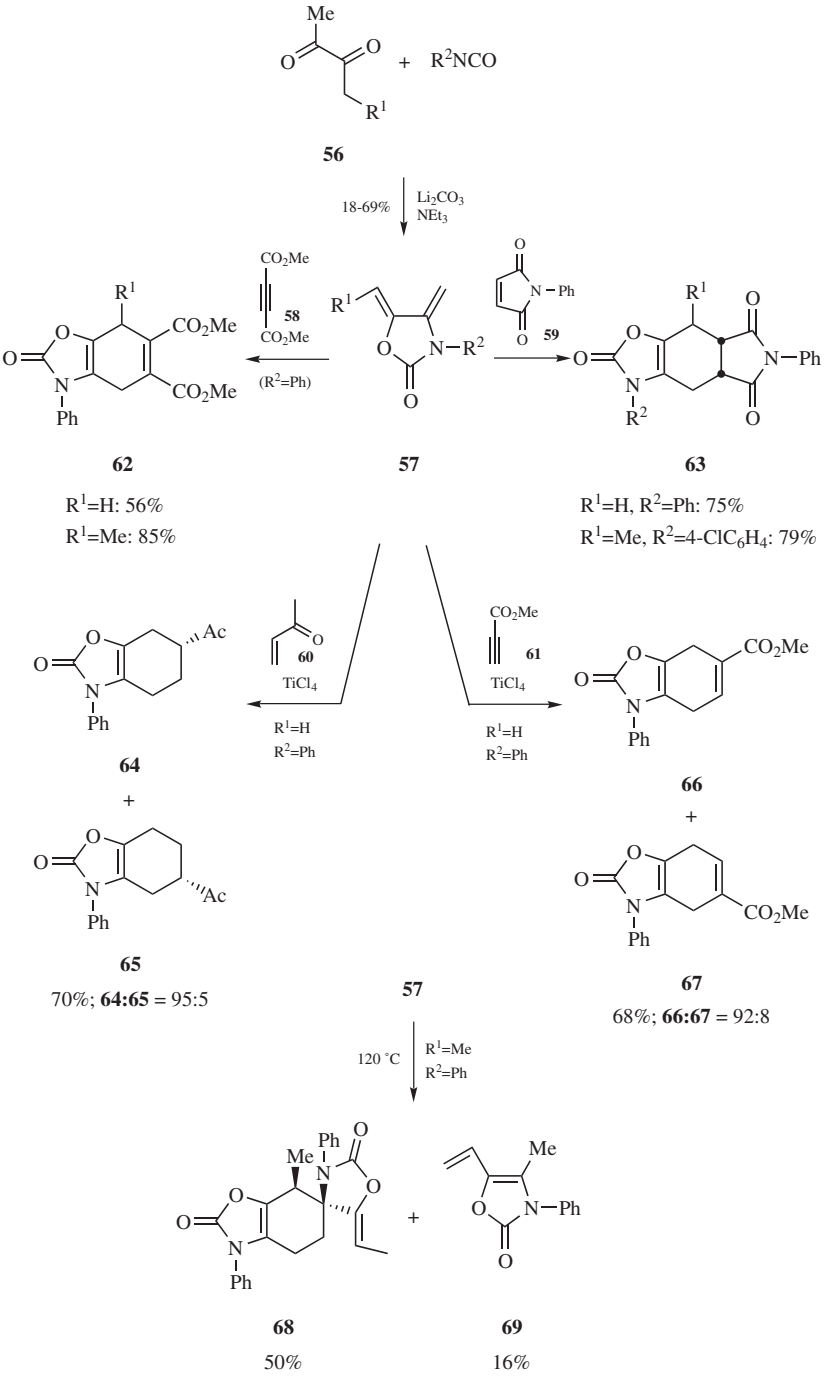
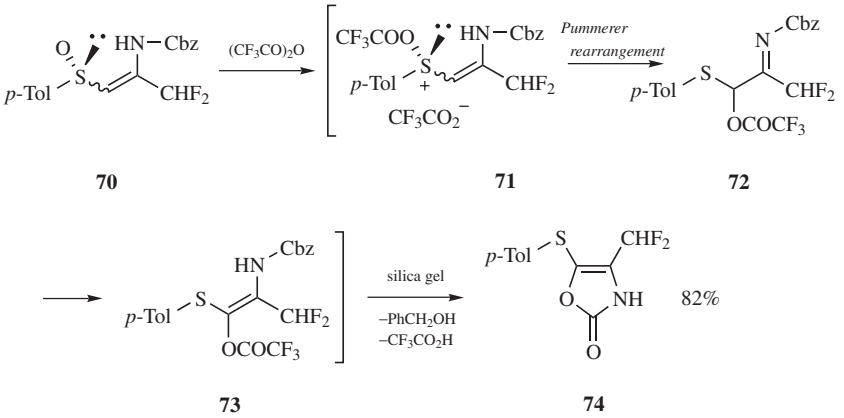

Me
O
O
+ R2NCO
R1
56
18-69%
Li2CO3
NEt3
CO2Me
58
CO2Me
(R2=Ph)
O
N – Ph
O
59
R1
O
N–R2
O
57
R1
O
O
N–Ph
O
N
R2
63
R1=H, R2=Ph: 75%
R1=Me, R2=4-ClC6H4: 79%
R1
CO2Me
CO2Me
O
O
N
Ph
62
R1=H: 56%
R1=Me: 85%
Ac
O
60
TiCl4
R1=H
R2=Ph
CO2Me
61
TiCl4
R1=H
R2=Ph
CO2Me
64
+
Ac
65
70%; 64:65 = 95:5
66
+
CO2Me
67
68%; 66:67 = 92:8
57
120 °C
R1=Me
R2=Ph
Ph
Me
N
O
68
50%
Me
69
16%

Figure 5.17

of the 2-oxazolidinone ring appears to control the orientation of the dienophile approach. Dimerization of the dienes **57** proceeds in a highly selective manner to give only one dimeric isomer **68**, in addition to the [1,5] rearranged product, 4-methyl-3-phenyl-5-vinyl-2(3*H*)-oxazolone **69** (Fig. 5.17).[16]

5.1.2.6. *From* β-*Enaminosulfoxide*

The one-pot reaction of the α-(difluoromethyl)-β-sulfinylenamine **70** with trifluoroacetic anhydride in $CHCl_3$, followed by treatment with silica gel affords 4-(difluoromethyl)-5-*p*-tolylthio-2(3*H*)-oxazolone **74** (Fig. 5.18). This reaction proceeds via a Pummerer-type rearrangement, followed by [1,3]-proton shift and the simultaneous elimination of trifluoroacetic acid and benzyl alcohol.[17,18]



70 **71** **72** **73** **74**

Figure 5.18

5.1.2.7. *From Hydroxamic Acids*

The reaction of *N*-aryl-*N*-(hydroxy)acylacetamides **75** with 4-nitrobenzenesulfonyl chloride (nosyl chloride) in the presence of NEt_3 gives 3-aryl-5-substituted-2(3*H*)-oxazolones **78** via the three-membered ring α-lactams **77**, which have also been proposed as intermediates in the isoxazoline–oxazoline transformation.[19] A good leaving group on the nitrogen atom greatly accelerates the reaction. In the same manner, 5-alkyl-3-aryl-4-halo-2(3*H*)-oxazolones **80** are synthesized from the corresponding *N*-aryl-*N*-(hydroxy)-α-halo acylacetamides **79** that are prepared via halogenation of **75** (Fig. 5.19; Table 5.4, Fig. 5.20; Table 5.5, Fig. 5.21).[20]

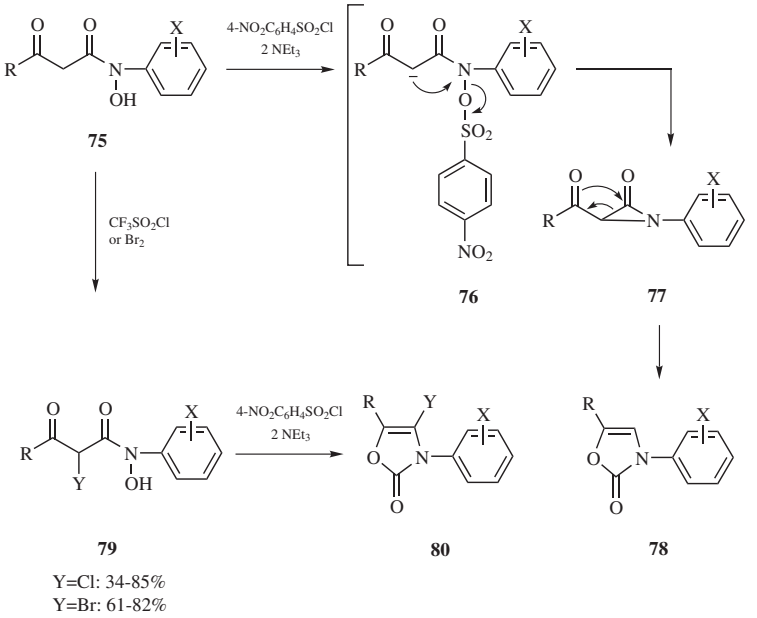


Figure 5.19

TABLE 5.4. SYNTHESIS OF 5-ALKYL-3-ARYL-2(3*H*)-OXAZOLONES FROM *N*-ARYL-*N*-(HYDROXY)ACYLACETAMIDES[a]

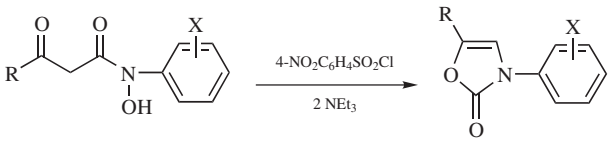
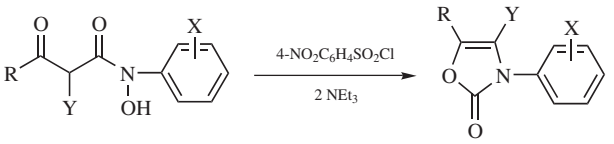


Figure 5.20

X	R	% Yield
H	Et	58
H	Pr	39
4-F	Me	69
3-Cl	Me	65
4-Cl	Me	80
4-Cl	Et	63
4-Cl	Pr	39
4-Br	Me	75
3-Me	Me	75
4-Me	Me	66
4-Me	Et	42

[a] Data from Ref. 20.

TABLE 5.5. SYNTHESIS OF 5-ALKYL-3-ARYL-4-HALO-2(3*H*)-OXAZOLONES FROM *N*-ARYL-*N*-(HYDROXY)-α-HALO ACYLACETAMIDES



79 **80**

Figure 5.21

X	Y	R	% Yield
H	Cl	Me	37
H	Br	Me	40
3-Cl	Cl	Me	73
4-F	Cl	Me	53
4-F	Br	Me	(unstable)
4-Cl	Cl	Me	56
4-Cl	Cl	Et	51
4-Cl	Cl	Pr	60
4-Cl	Cl	*i*-Pr	57
4-Cl	Br	Me	28
4-Cl	Br	Et	40
4-Br	Cl	Me	60
4-Br	Br	Me	(unstable)

[a] Data from Ref. 20.

5.1.2.8. From 2-Oxazolidinones

Both 4-hydroxy- and 4-methoxy-2-oxazolidinones are routinely employed as good synthetic precursors for 2(3*H*)-oxazolones.

Anodic oxidation of 2-oxazolidinones **81** in methanol using $Et_4N^+OTs^-$ as a supporting electrolyte yields the 4-methoxylated derivatives **82** that undergo a facile elimination of methanol to give 2(3*H*)-oxazolones such as **83** and **84**.[21]

An improved procedure for the preparation of 2(3*H*)-oxazolone **1** involves refluxing **82** with an equimolar amount of acetic anhydride in acetic acid (Fig. 5.22).[22]

Treatment of 4-methoxy-2-oxazolidinone **86** with indolylmagnesium bromide **87**, followed by *N*-protection with a *tert*-butoxycarbonyl (Boc) group affords *N*,*N*′-di-Boc-4-(3-indolyl)-2-oxazolidinone **88**. Subsequent treatment with *N*-bromosuccinimide (NBS) in the presence of azobisisobutyronitrile (AIBN) followed by electrochemical reduction yields the protected 4-(3-indolyl)-2(3*H*)-oxazolone **90** (Fig. 5.23). The Boc groups are easily removed by pyrolysis.[23,24]

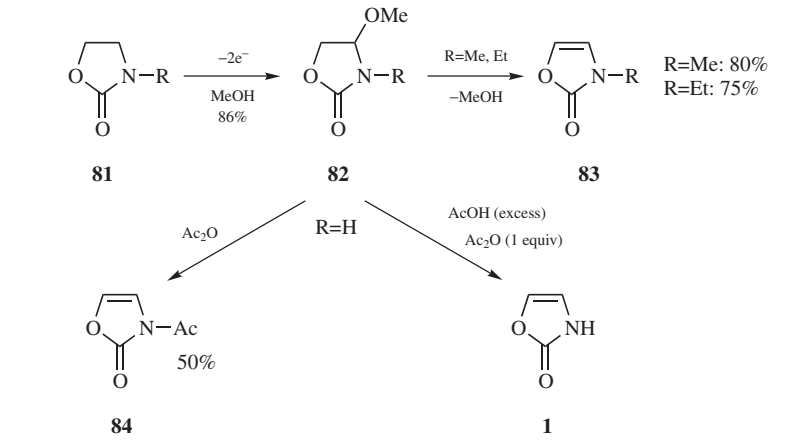


Figure 5.22

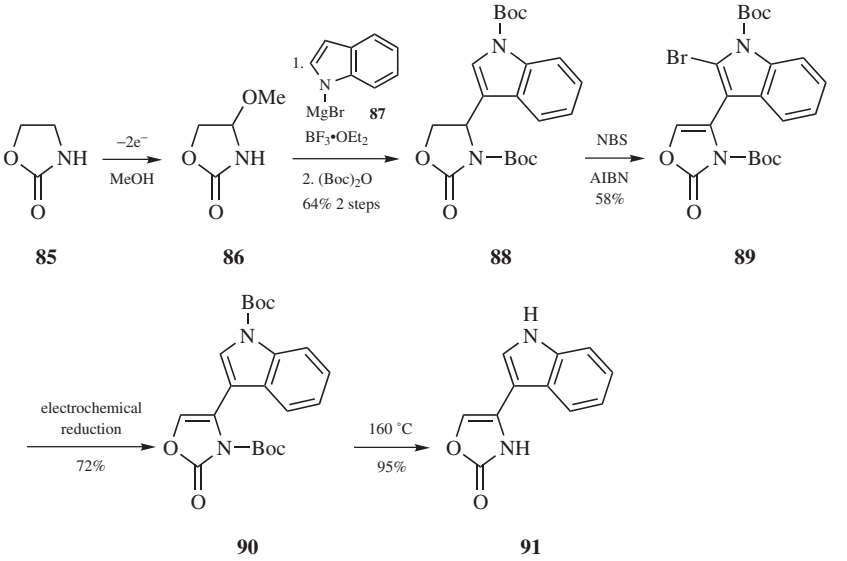


Figure 5.23

The addition of hydrazine to diphenylvinylene carbonate **92** quantitatively affords a 1:1 mixture of perhydro-1,3,4-oxadiazin-2-one **93** and 2-oxazolidinone **94** derivatives, both of which are smoothly dehydrated with P_2O_5 to afford 1,3,4-oxadiazin-2-one **95** and 3-amino-2(3*H*)-oxazolone **96** (Fig. 5.24), respectively.[25] Addition of primary amines to diphenylvinylene carbonate results in exclusive formation of 3-alkyl-2(3*H*)-oxazolones, previously investigated as amino protecting groups in peptide synthesis.[26,27]

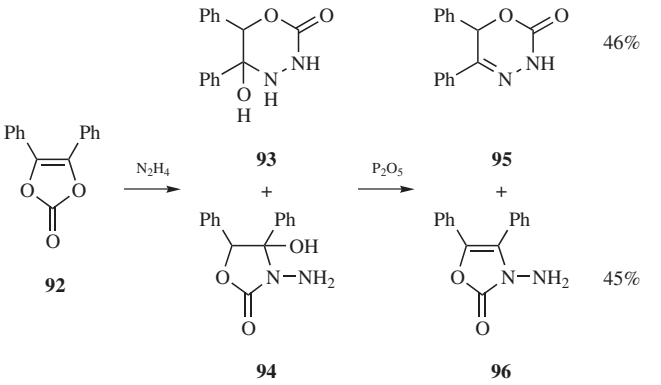


Figure 5.24

5.1.2.9. From Oximes

The reaction of aliphatic and aromatic ketone oximes **97** with a dialkyl carbonate **98** in the presence of K_2CO_3 at 180–190 °C yields 3-alkyl-4,5-disubstituted-2(3*H*)-oxazolones **104** in 22–48% yields. Mechanistically, it is proposed that N-alkylation of the initially formed oxime *O*-carbonate **99** yields **100**, which affords the enamine **101** in the presence of base. A [3,3] sigmatropic rearrangement ensues to produce **102**, which then cyclizes to **104**. In cases where **97** contains two methylene groups in proximity to the C=N bond, one of which is benzylic, the above reaction sequence is regioselective for the benzylic methylene group (Fig. 5.25; Table 5.6, Fig. 5.26).[28]

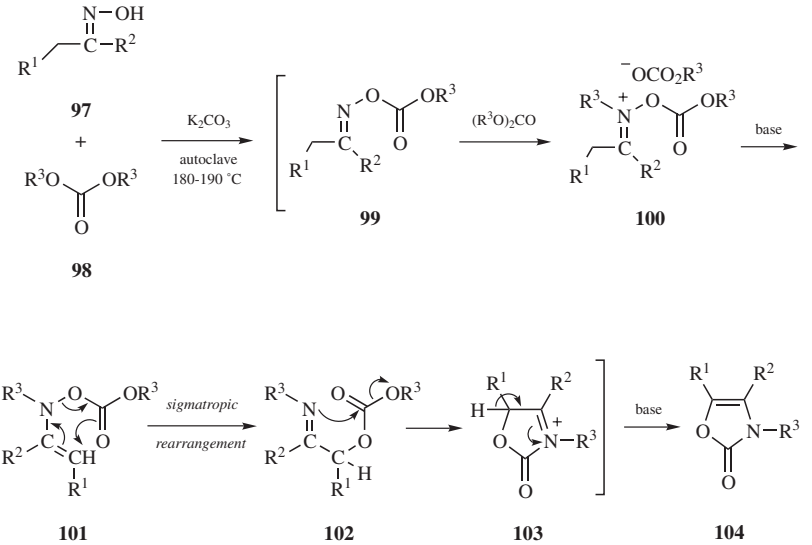
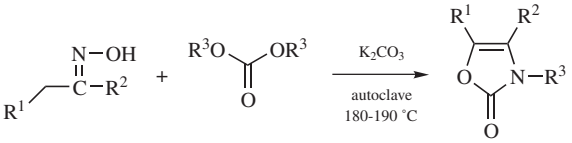


Figure 5.25

TABLE 5.6. 3-ALKYL-4,5-DISUBSTITUTED-2(3*H*)-OXAZOLONES FROM OXIMES AND DIALKYLCARBONATES[a]



97 **98** **104**

Figure 5.26

R^1	R^2	R^3	%Yield
$-(CH_2)_4-$		Me	48
$-(CH_2)_5-$		Me	22
Me	Ph	Me	28
Et	Pr	Me	22
Ph	Me	Me	31
Ph	Et	Me	37
Ph	Ph	Me	37
$-(CH_2)_4-$		Et	31
Ph	Me	Et	35

[a] Data from Ref. 28.

5.1.2.10. From 2,4-Thiazolidinediones

The intramolecular base-induced ring transformation of 3-phenacyl-2,4-thiazolidinediones **105** with sodium hydroxide or triethylamine smoothly proceeds to give 5-aryl-2(3*H*)-oxazolones **108** (Fig. 5.27).[29]

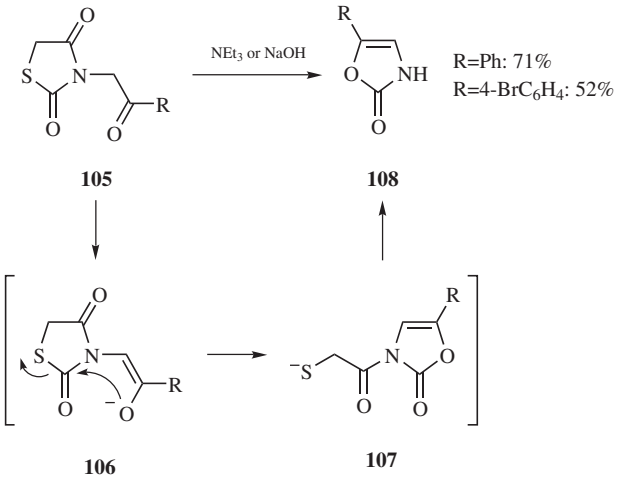


Figure 5.27

Similarly, 6-methyl-3-phenacyl-1,3-oxazine-2,4(3*H*)-diones **110** are transformed into 5-aryl-2(3*H*)-oxazolones **108** under phase-transfer catalysis (Fig. 5.28).[30]

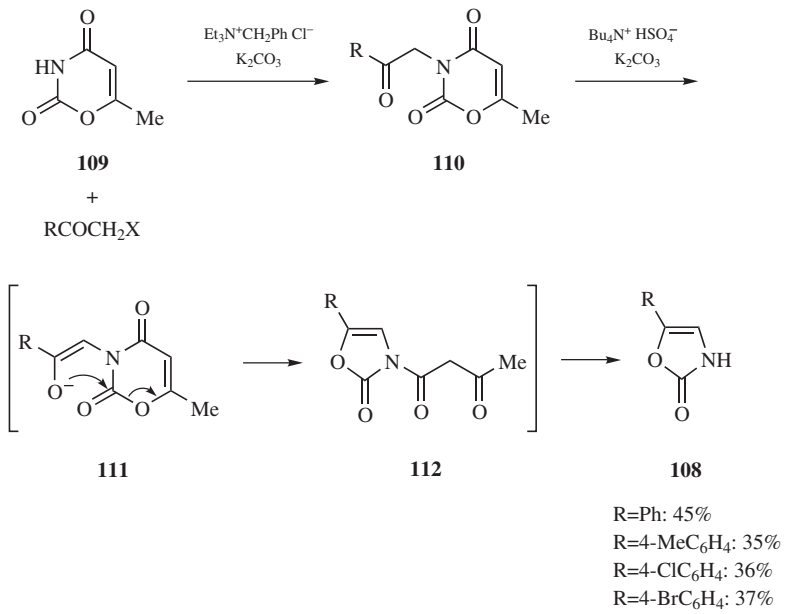


Figure 5.28

5.1.2.11. From 1,2,4-Triazolium Salts

Treatment of the phenacyliminium salt **114**, derived from 5,7-dimethyl[1,2,4]-triazolo[1,5-*a*]pyrimidine **113** and phenacyl bromide, with 2 equiv of triethylamine gives rise to the 2-iminooxazoline **118** by way of the *in situ* generated intermediary *N*-ylides **115**. Acidic hydrolysis affords the 3-(2-pyrimidinyl)-2(3*H*)-oxazolone **119**.[31,32]

Similarly, the [1,2,4]triazolo[1,5-*a*]pyridinium salt **121** affords 5-phenyl-3-(2-pyridinyl)-2(3*H*)-oxazolone **122** (Fig. 5.29).[33]

5.1.2.12. Via Three Component Condensation

The 2(3*H*)-oxazolones may be synthesized by the direct condensation of three components. Thus, a mixture of α-halo ketones **123**, carbon dioxide, and primary amines can be heated at 80–100 °C under gas pressure of 50 kg/cm^2 to result in the direct formation of 3-substituted 2-oxazolones **124** in 4–25% yield (Fig. 5.30).[34]

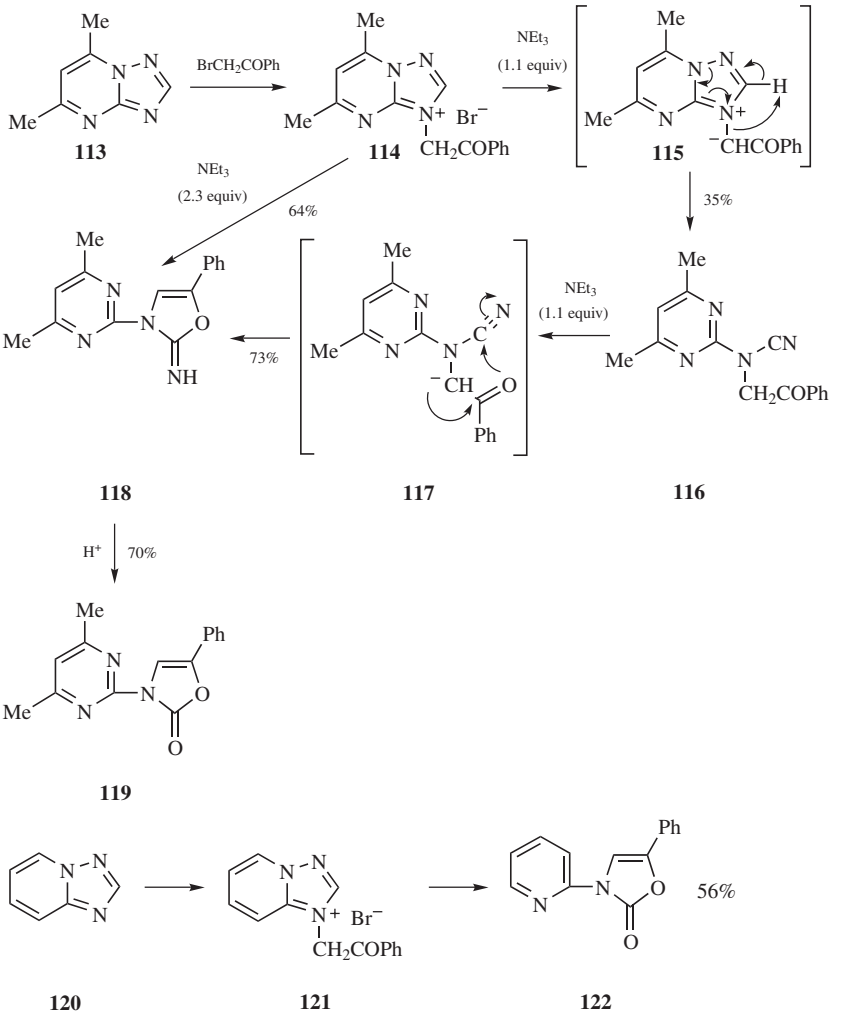
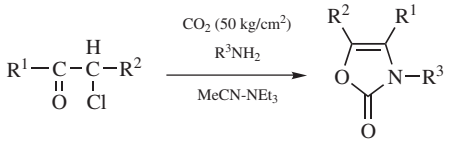


Figure 5.29



R^1=Me, R^2=H, R^3=Pr: 5%
R^1=Me, R^2=H, R^3=Ph: 4%
R^1=R^2=Me, R^3=Pr: 25%
R^1=Ph, R^2=H, R^3=Pr: 6%

Figure 5.30

Direct condensation of propargyl alcohols **125** (Fig. 5.31), carbon dioxide, and propylamine can be realized by $Ru_3(CO)_{12}$ catalysis at 80 °C under CO_2 pressure of 50 kg/cm^2. The reaction mechanism is rationalized as shown below. When diethylamine is used in place of a primary amine, 2-oxoalkyl *N*,*N*-diethylcarbamates are isolated in moderate yields.[35]

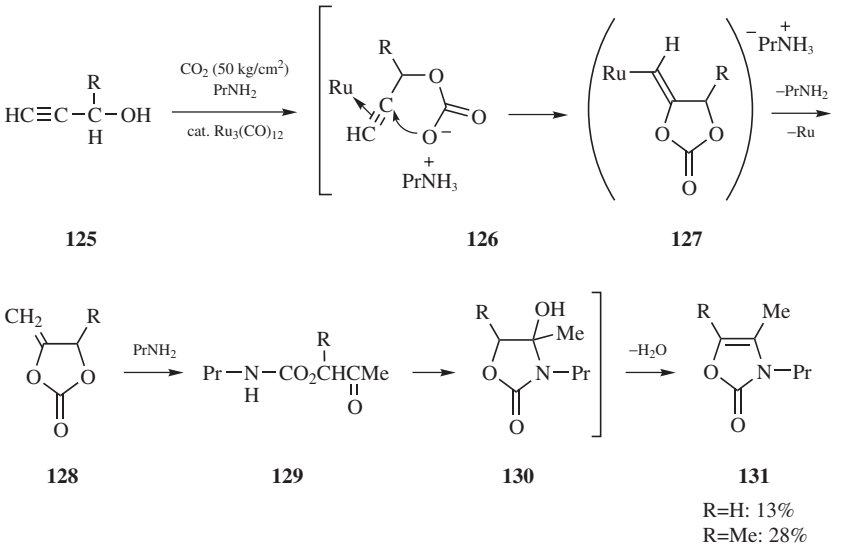


Figure 5.31

5.1.2.13. Miscellaneous

The 1,3-dipolar cycloaddition of α-keto carbenoids to the polar double bond of heterocumulenes provides a direct access to five-membered heterocycles. The reaction of α-diazo ketones **132** with phenyl isocyanate in the presence of a $Rh_2(OAc)_4$ catalyst affords the 1,3-cycloadduct, 3-phenyl-2(3*H*)-oxazolones **133** (Fig. 5.32).[36]

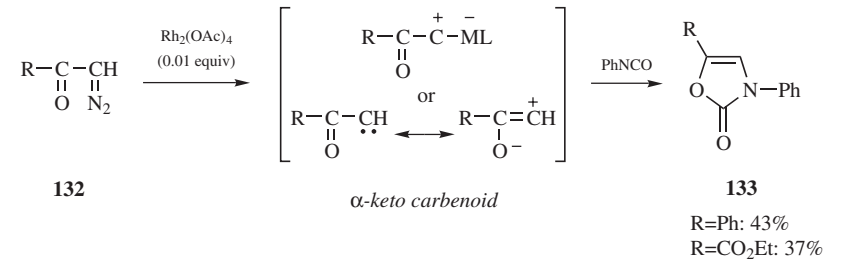


Figure 5.32

Heating α-hydroxy amides **135** in xylene with the cumulated phosphorus ylide **134** gives the 2(3*H*)-oxazolones **140**. The reaction proceeds via an addition–cyclization–intermolecular-Wittig olefination sequence, which implies three different types of phosphorus ylides, **134**, **136**, and **137**, respectively, of increasing ''ylide activity'' (Fig. 5.33; Table 5.7, Figs. 5.34, 5.35). [37]

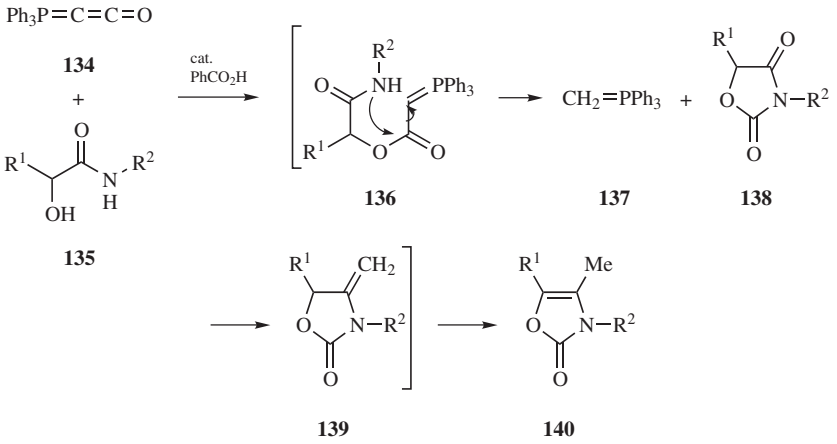


Figure 5.33

TABLE 5.7. 2(3*H*)-OXAZOLONES FROM α-HYDROXY AMIDES AND PHOSPHORUS YLIDE **134**[a]

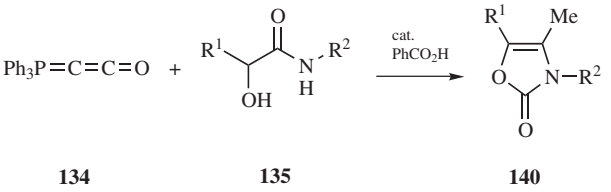


Figure 5.34

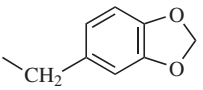
R^1	R^2	% Yield
H	CH_2Ph	51
Me	CH_2Ph	81
Me	CHMePh	40
Me		

Figure 5.35

Ph	*c*-C_6H_{11}	48
Ph	CH_2Ph	71
Ph	CHMePh	40
Ph	4-$MeOC_6H_4$	50

[a] Data from Ref. 37.

The condensation of a 2-aminobenzoxazole **141** with α-bromo ketones **142** gives 2(3*H*)-oxazolones **148** on heating in ethanol. Isotope labeling studies with ^{18}O have shown that the additional oxygen that is incorporated into the ring is derived from the solvent, ethanol (Fig. 5.36).[38]

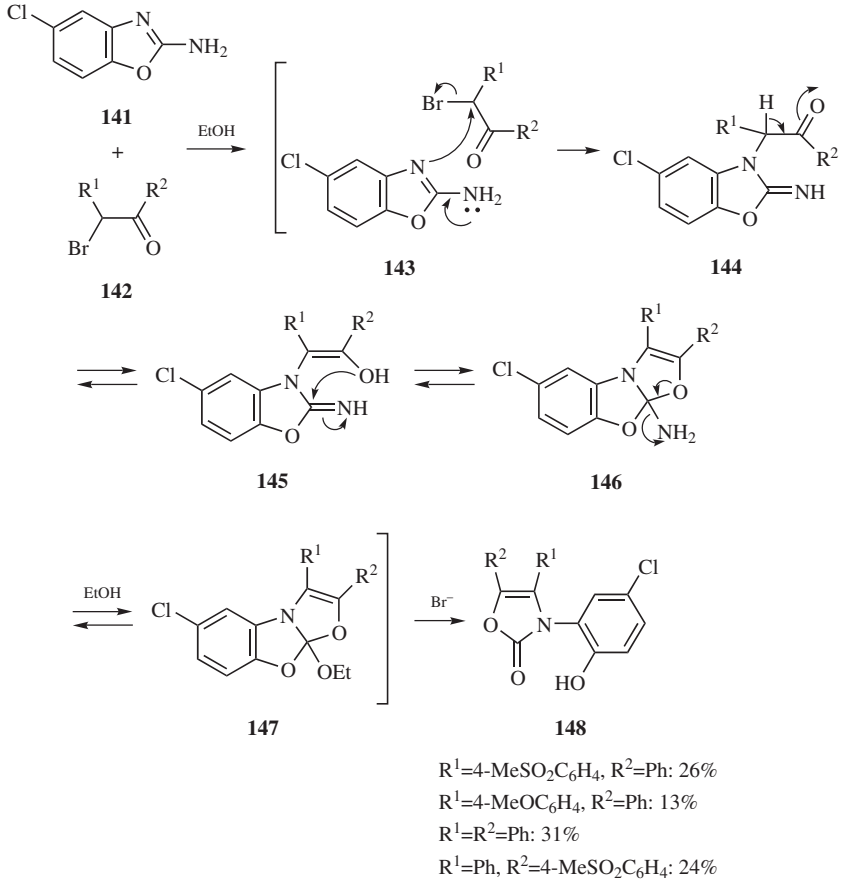


Figure 5.36

5.1.3. Reactions

5.1.3.1. Hydrogenation

Certain *erythro*-2-amino alcohols such as (±)-ephedrine **150**, (±)-*N*-methylephedrine **151** and (±)-conhydrine **153** are synthesized with complete stereochemical control by the catalytic hydrogenation of the corresponding 4,5-disubstituted 2(3*H*)-oxazolone derivatives **22** and **27**, followed by ring opening (Fig. 5.37).[6]

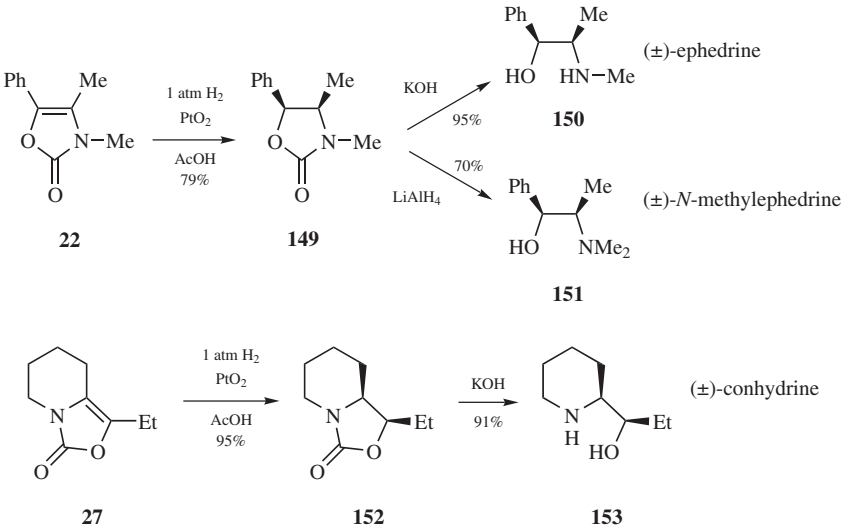
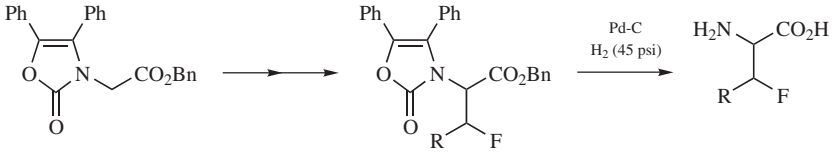


Figure 5.37

Condensation of benzyl glycinate *p*-toluenesulfonate salt with 4,5-diphenyl-1,3-dioxol-2-one affords **154**, which can be converted to the 4,5-diphenyl-3-substituted-2(3*H*)-oxazolones **155** by sequential treatment with an aldehyde/LiHMDS followed by diaminosulfur trifluoride (DAST). Hydrogenolysis then affords the β-fluoro-α-amino acids **156** in excellent yields without any concomitant cleavage of the carbon–fluorine bond (Fig. 5.38).[39]



154

155

R=Me: 41%
R=Et: 40%
R=Pr: 52%
R=*i*-Bu: 45%

156

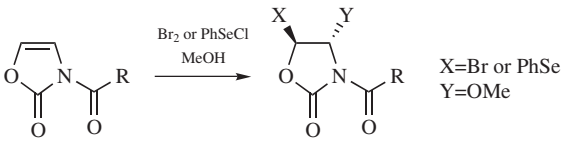
R=Me: 99%
R=Et: 88%
R=Pr: 89%
R=*i*-Bu: 91%

Figure 5.38

5.1.3.2. Electrophilic Additions

A 3-acyl-4,5-unsubstituted-2(3*H*)-oxazolone **157** smoothly undergoes electrophilic addition with Br_2 (or NBS) and PhSeCl in methanol to give *trans*-5-bromo-4-methoxy- and *trans*-4-methoxy-5-phenylselenenyl-2-oxazolidinones **158**, respectively, with full regio- and trans-selectivity (Fig. 5.39). Both substituents thus

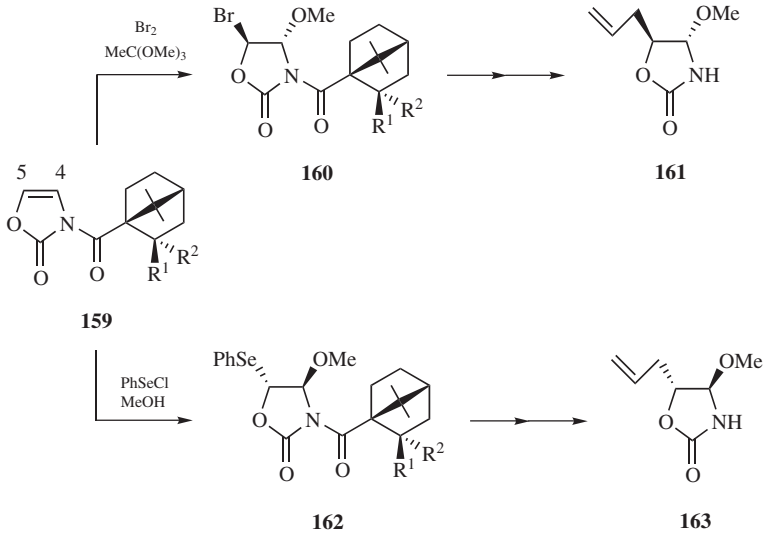
introduced are sufficiently reactive to be replaced in a stepwise manner under ionic and radical conditions, indicative of the versatility of the 2(3*H*)-oxazolone heterocycle as a building block for the stereodefined construction of 2-amino alcohols.[40–46]



157 **158**

Figure 5.39

Optically active 3-(2-*exo*-alkoxy-1-apocamphanecarbonyl)-2(3*H*)-oxazolones **159** can be used successfully for the preparation of the versatile chiral synthons **161** and **163** (Fig. 5.40). The reactions proceed with excellent diastereoselectivity [>96% diastereomeric excess (de)] and interestingly with a thoroughly reversed enantiomeric selectivity.[40] This finding is rationalized by assuming that selenenium ions approach the less hindered diastereotopic face in the most predominant conformer to give thermodynamically favored intermediates, whereas coordination of bromine with the oxygen atoms of the 2-alkoxy substituents (see Fig. 5.41; Table 5.8, Fig. 5.42 and Table 5.9, Figs. 5.43 and 5.44) accelerates the attack from the alkoxy substituent site. The versatility of the synthons **161** and **163** is demonstrated by the chiral synthesis of typical hydroxy-amino acids such as 3-hydroxyglutamic acid **168**,[41,42] statine **165**,[41] AHPBA **164**,[43] AHMHA **166**,[43] and others[44] as well as the bicyclic lactone **172**.[45]



159 **160** **161** **162** **163**

Figure 5.40

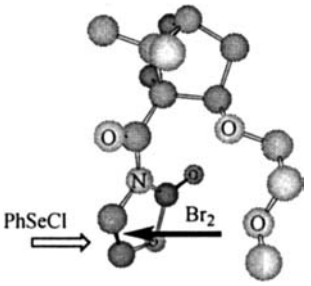
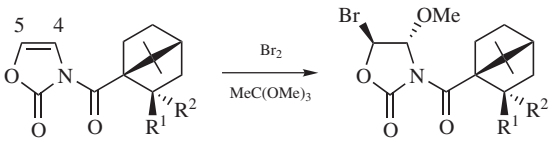


Figure 5.41. Proposed electrophilic attack on the 2-oxazolone moiety.

TABLE 5.8. DIASTEREOSELECTIVE METHOXYBROMINATION OF 3-ACYL-2(3*H*)-OXAZOLONES **159**[a]



159 **160**

Figure 5.42

R^1 (exo)	R^2 (endo)	Temp (°C)	% Yield (% de)
=O		−78	58 (80)
OMe	H	−78	89 (85)
OBu	H	−78	85 (85)
OCH_2CH_2OMe	H	−78	79 (89)
OCH_2OEt	H	−78	79 (96)
H	OMe	−78	36 (0)
Me	H	−78	80 (0)

[a] Data from Ref. 40.

The (+)- and (−)-4,5-dialkoxy-2-oxazolidinones **173** and **174** prepared through the 5-bromo-4-methoxy- derivatives serve as reliable chiral synthons for the preparation of a wide variety of optically active α-amino acids **176** and α-amino aldehydes **177** (Fig. 5.45).[46]

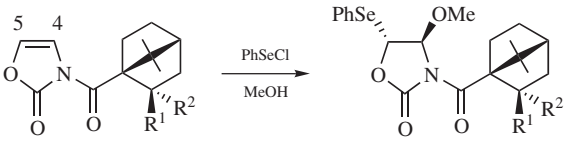
5.1.3.3. Radical Additions

5.1.3.3.1. Attack of Alkyl Radicals

The 4,5-olefinic moiety of 2(3*H*)-oxazolones functions well as a radical acceptor in a variety of radical reactions.

The $RuCl_2(PPh_3)_3$ catalyzed addition of polyhalomethanes, CCl_4 and $CBrCl_3$, to 3-acetyl-2(3*H*)-oxazolone **84** leads to the exclusive formation of the *trans*-4-halo-5-(trichloromethyl)-3-acetyl-2-oxazolidinones **178**.[47] In the presence of a radical

TABLE 5.9. DIASTEREOSELECTIVE METHOXYSELENYLATION OF 3-ACYL-2(3*H*)-OXAZOLONES **159**[a]



159 **162**

Figure 5.43

R^1 (exo)	R^2 (endo)	Temp (°C)	% Yield (% de)
=O		0	52 (71)
OMe	H	0	83 (60)
OBu	H	0	76 (85)
OCH_2CH_2OMe	H	0	94 (90)
OCH_2CH_2OMe	H	−20	82 (96)
H	OMe	0	94 (0)
Me	H	0	80 (0)

[a] Data from Ref. 40.

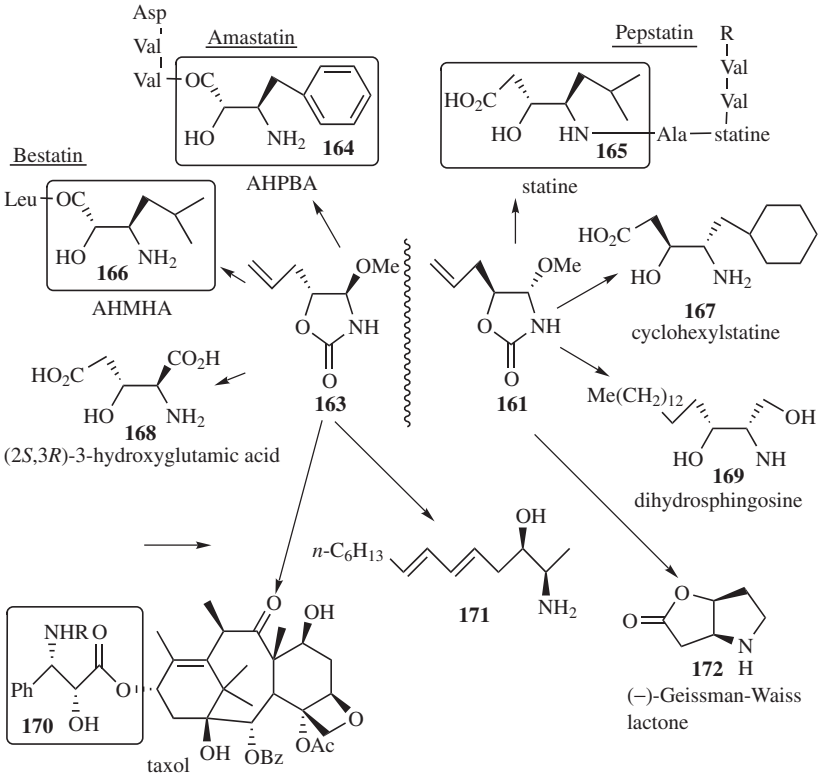


Figure 5.44

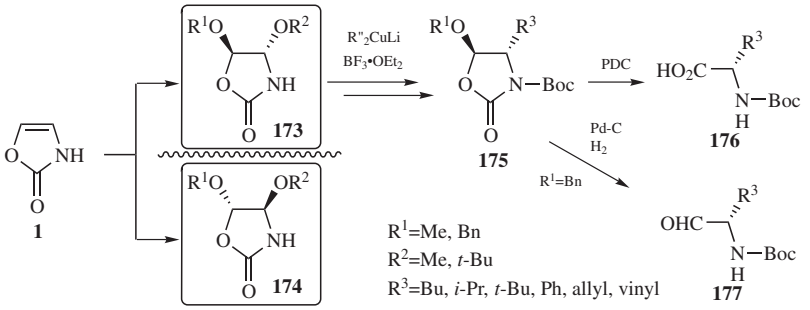


Figure 5.45

initiator, benzoyl peroxide (BPO), free-radical telomerization of **84** with a chain-transfer agent, CCl_4, proceeds smoothly at 80°C to give the polyfunctional telomers **179** with high trans- and head-to-tail selectivity.[48,49] The Ru(II)-catalyzed addition of polyhalomethyls to 3-(2-*exo*-alkoxy-1-apocamphanecarbonyl)-2(3*H*)-oxazolone **180** gives a 1:1 mixture of trans-stereoisomers **181** and **182** with no diastereoselectivity.[47] This result is in sharp contrast to the intramolecular radical cyclization of the derivative with a pendant trichloroacetyl group **185**, which proceeds in excellent diastereoselectivity (>99% de) and high yield.[50] The straightforward manipulation of the resulting 12-membered macrolides **186** yield

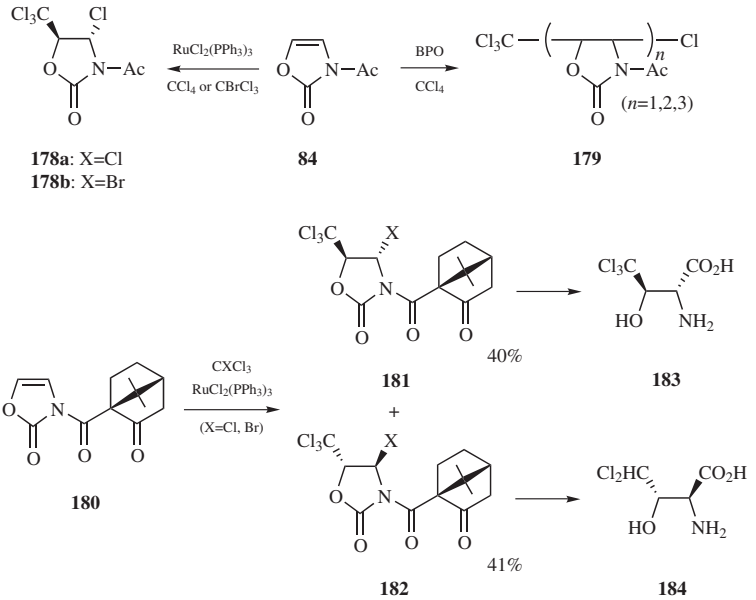


Figure 5.46

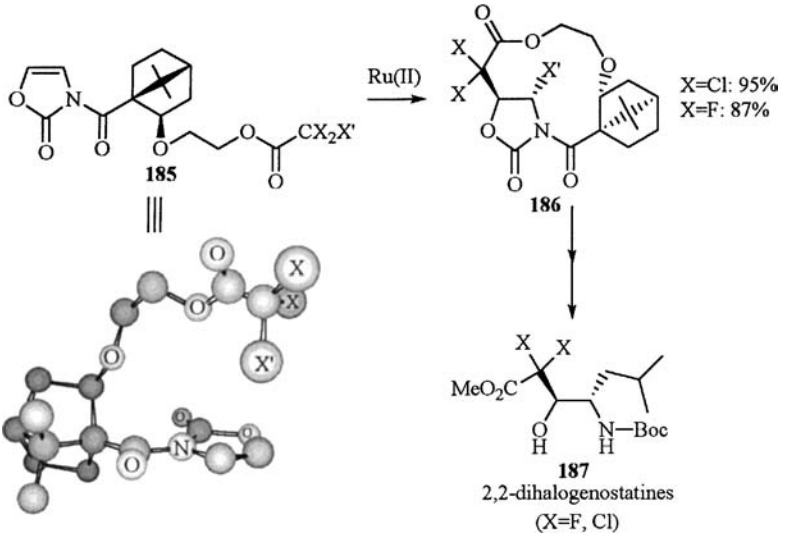


Figure 5.47

optically active β-hydroxy-α-amino acids including *N-tert*-Boc-2,2-difluorostatine methyl ester **187** (Figs. 5.46, 5.47).

This methodology can be successfully applied to a chiral synthesis of the key amino acid components with three contiguous chiral centers found in cyclosporins (MeBmt, **190**) [51] and bleomycins **191** (Fig. 5.48).[52]

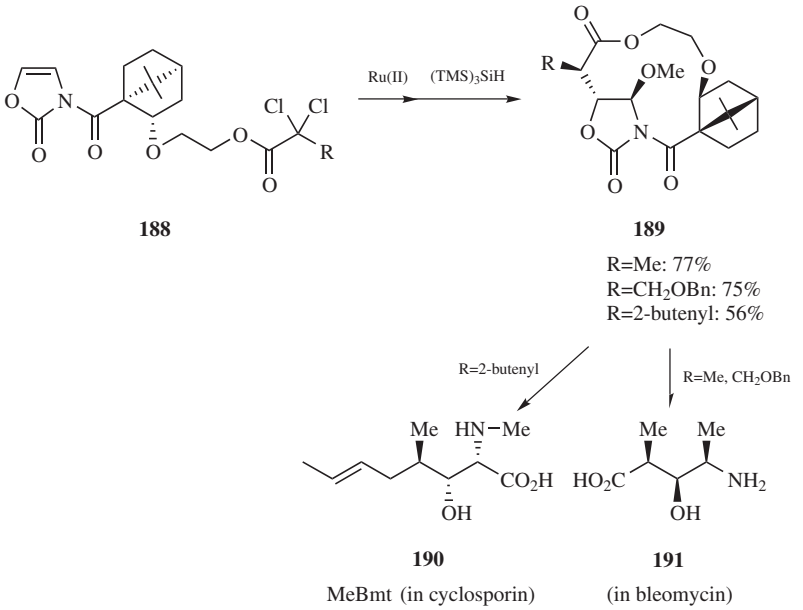


Figure 5.48

Other examples include the intramolecular radical cyclization of 3-bromoalkyl-2(3*H*)-oxazolones **192** and **196** with tributyltin hydride/azobisisobutyronitrile to give the pyrrolooxazolidinones **194**, **198**, and **199**. The 2,5-disubstituted pyrrolidine derivatives **195** are produced enantioselectively (Fig. 5.49).[53,54]

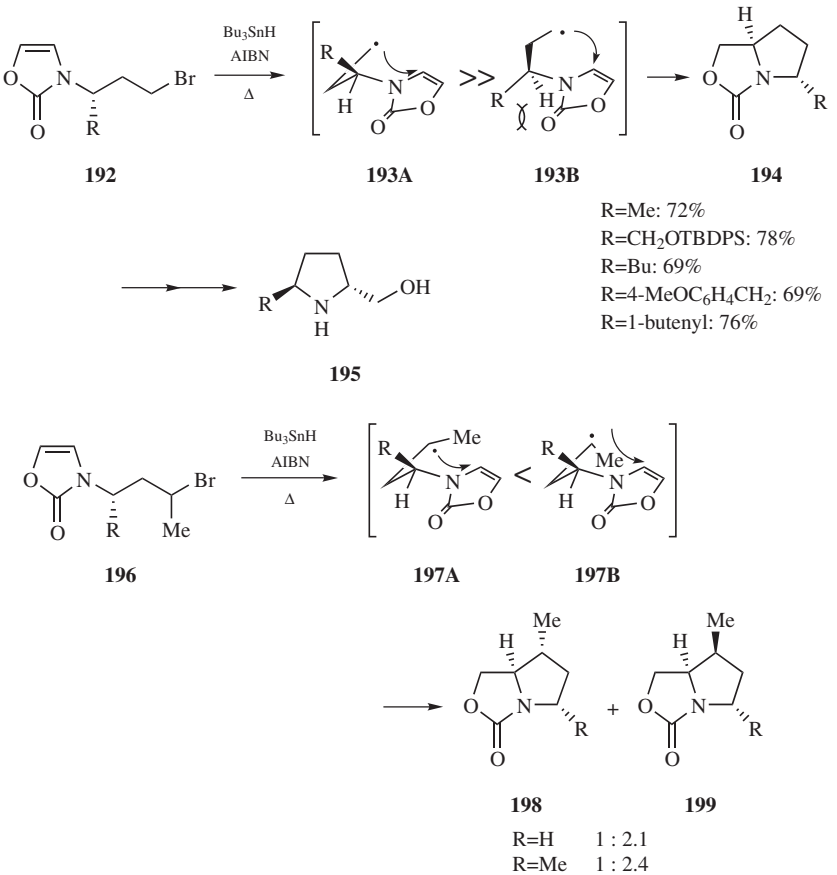


Figure 5.49

In a similar manner, intramolecular cyclization of the *O*-stannyl ketyl derivatives **201** and **206**, generated from the oxazolyl aldehydes **200** and **205**, provides a facile method for the chiral synthesis of 3-hydroxy-2-(hydroxymethyl)-5-substituted-pyrrolidines **202** and **203** and the piperidine analogues **207** and **208** that can be successfully transformed into naturally occurring amino alcohols, (+)-bulgecinine **204** and (−)-desoxoprosopinine **209**, respectively (Fig. 5.50).[55,56]

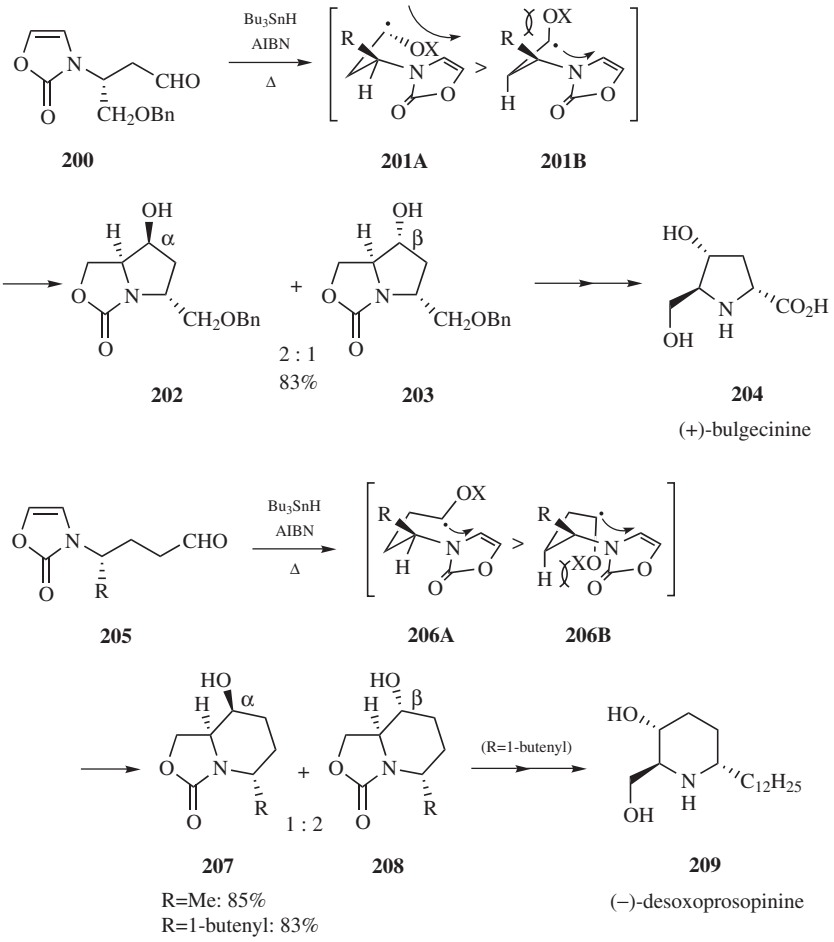


Figure 5.50

5.1.3.3.2. Attack of Alkenyl Radicals

Treatment of the alkenyl bromides **210** with tributyltin hydride in the presence of AIBN involves an intramolecular radical addition to the 2(3*H*)-oxazolone moiety, resulting in the diastereoselective formation of the oxazolidinopiperidines **211**. These are readily converted to the protected 2,6-disubstituted 3-hydroxypiperidine derivatives **212** (Fig. 5.51).[57]

Hudlicky and co-workers[58,59] reported a stepwise radical cyclization approach for the preparation of the complete morphinan ring skeleton **216** (Fig. 5.52). One of the key steps involves the intramolecular radical cyclization of cyclohexenyl

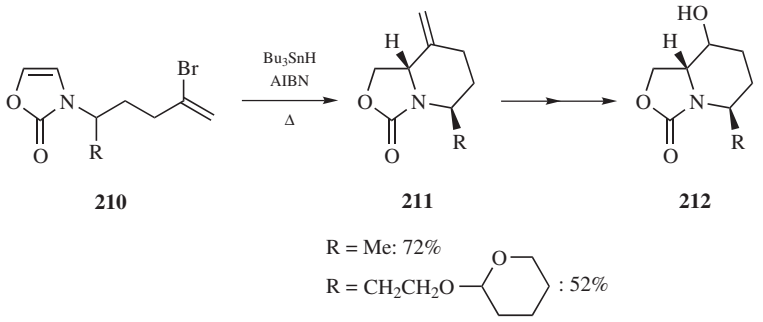


Figure 5.51

radicals, generated from the vinylic bromide **213**, to the 2(3*H*)-oxazolone ring, giving rise to a 1 : 2 mixture of the isomeric isoquinoline derivatives **214** and **215** in excellent combined yield. The lack of selectivity in the ring closure was attributed to the lack of a significant steric effect by the distant acetonide group (Fig. 5.52).

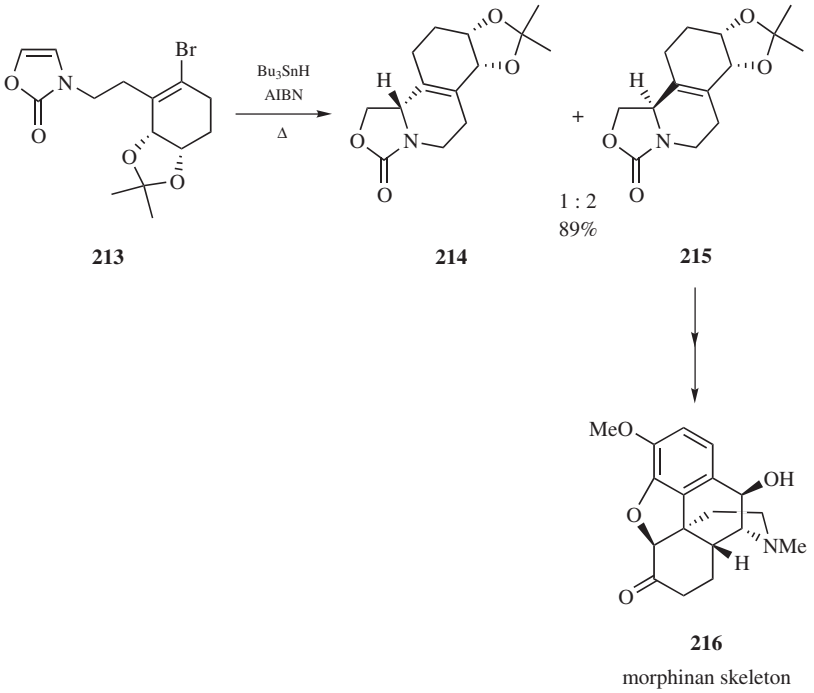


Figure 5.52

5.1.3.3.3. Polymers

The 2(3*H*)-oxazolone homopolymer **217** and the 2(3*H*)-oxazolone copolymer **219** with a carbon–carbon bond backbone structure are readily obtained by heating a 3-acyl-2(3*H*)-oxazolone alone or with styrene, respectively, at 70 °C in the presence of BPO with the exclusion of air.[48,49,60] The *N*-acetyl polymers serve as regioselective and chemoselective acylating reagents for amines and alcohols (Fig. 5.53).[60–63]

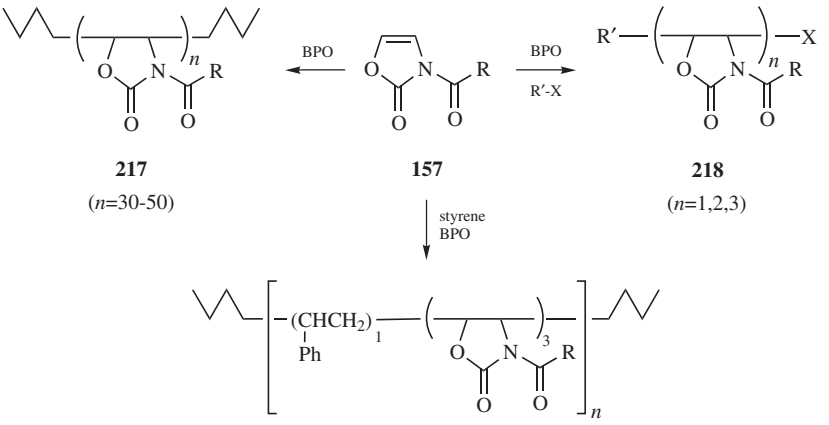


Figure 5.53

5.1.3.4. Pericyclic Additions

5.1.3.4.1. [4+2] Cycloadditions

The 3-acyl-2(3*H*)-oxazolones function as good dienophiles in cycloaddition reactions with cyclic 2,4-dienes such as cyclopentadienes and anthracenes.[64,65] Thus, the thermal reaction of 3-acetyl-2(3*H*)-oxazolone with cyclopentadiene and the hexachloro and hexamethyl derivatives gives endo-cycloadducts exclusively. In particular, the chiral cycloadducts **221** and **223** derived from the diastereoselective Diels–Alder reactions of 3-(2-*exo*-alkoxy-1-apocamphanecarbonyl)-2(3*H*)-oxazolones with hexamethylcyclopentadiene and 9,10-dimethylanthracene, respectively, are highly useful as chiral 2-oxazolidinone auxiliaries.[66–71] The conformationally rigid ''roofed'' structures play a crucial role in affording excellent chiral induction (Fig. 5.54).

The thermal [4 + 2] cycloaddition of 3-acetyl-2(3*H*)-oxazolone **84** to the reactive dienes, *o*-quinodimethane **224** and isobenzofuran **226**, generated from benzocyclobutane and 1-ethoxydihydroisobenzofuran, respectively, proceeds

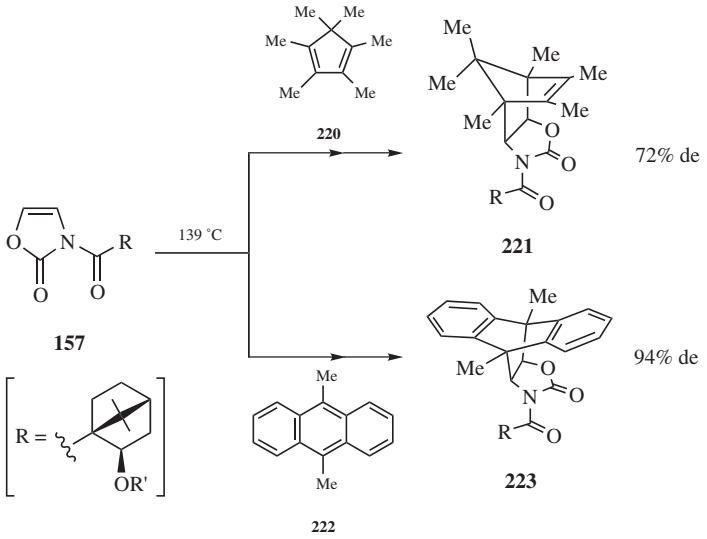


Figure 5.54

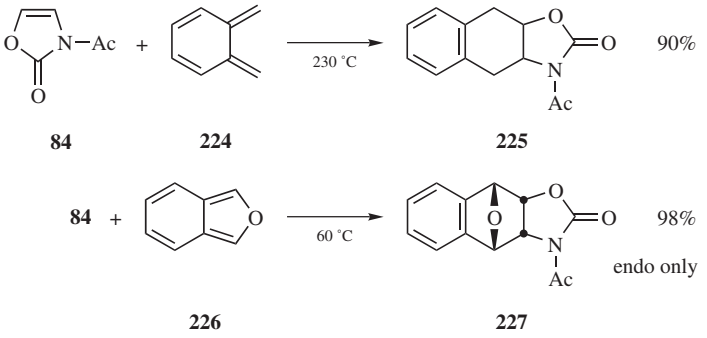


Figure 5.55

smoothly to afford the polycyclic 2,3-diheterotetrahydronaphthalene derivatives **225** and **227** (Fig. 5.55).[72]

The thermal cycloaddition of 3-acyl-2(3*H*)-oxazolones **157** to dialkyl azodicarboxylates **228** proceeds smoothly under mild conditions (at 80 °C) to give the regiocontrolled cycloadducts **229** exclusively, although two other possible addition modes exist: neither diazetidines **230** (1,2-addition) nor isoxazolidines **231** (1,3-addition) are detected. In the case of chiral N-substituents diastereoselectivities of up to 72% de have been obtained. Treatment of the chiral cycloadducts **229** with acidic methanol gives *trans*-5-hydrazino-4-methoxy-2-oxazolidinone derivatives **232** that are precursors for a variety of optically active α-amino acids **233** and 2-oxazolidinone auxiliaries **234** (Fig. 5.56; Table 5.10, Fig. 5.57).[73,74]

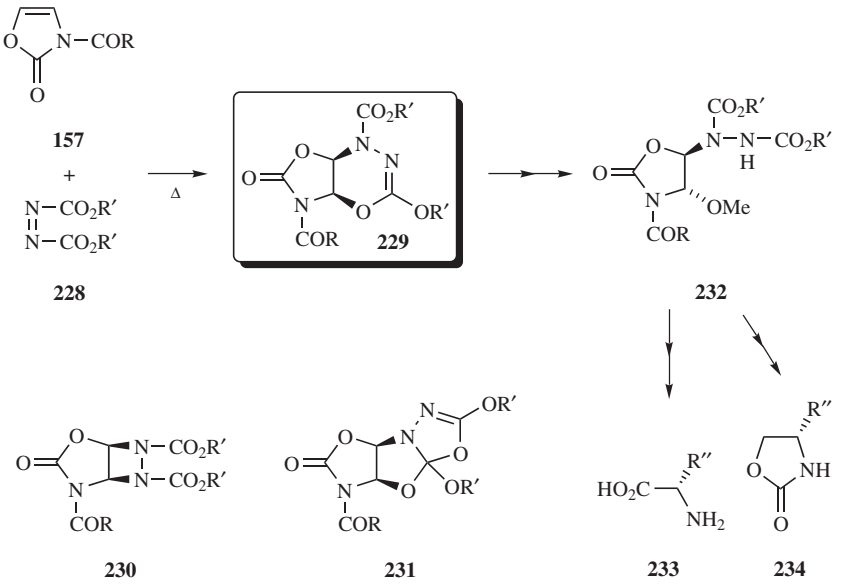


Figure 5.56

TABLE 5.10. DIASTEREOSELECTIVE [4+2] CYCLOADDITION OF AZODICARBOXYLATES TO 2(3*H*)-OXAZOLONES[a]

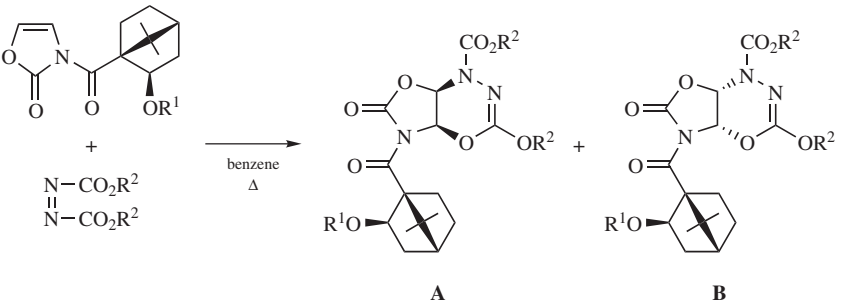


Figure 5.57

R^1	R^2	Time (h)	% Yield	**A:B**	% de
Me	Me	6	83	34:66	32
Me	*i*-Pr	12	93	24:76	52
Pr	*i*-Pr	12	76	22:78	56
Pr	Bn	6	86	18:82	64
CH_2CMe_3	*i*-Pr	19	85	15:85	70
CH_2CMe_3	Bn	18	93	14:86	72

[a] Data from Refs. 73, 74.

The ene-reaction, which is mechanistically related to the Diels–Alder reaction, has also been reported. The thermal addition of 3-*tert*-butoxycarbonyl-2(3*H*)-oxazolone **236** to 2,2′-biindole **235** affords 4-(2,2′-biindol-3-yl)-2-oxazolidinone **237**, probably via the indoline derivative. The product is further converted to the fused aromatic compound **238** by bromination with NBS and AIBN, followed by dehydrobromination (Fig. 5.58).[23,24]

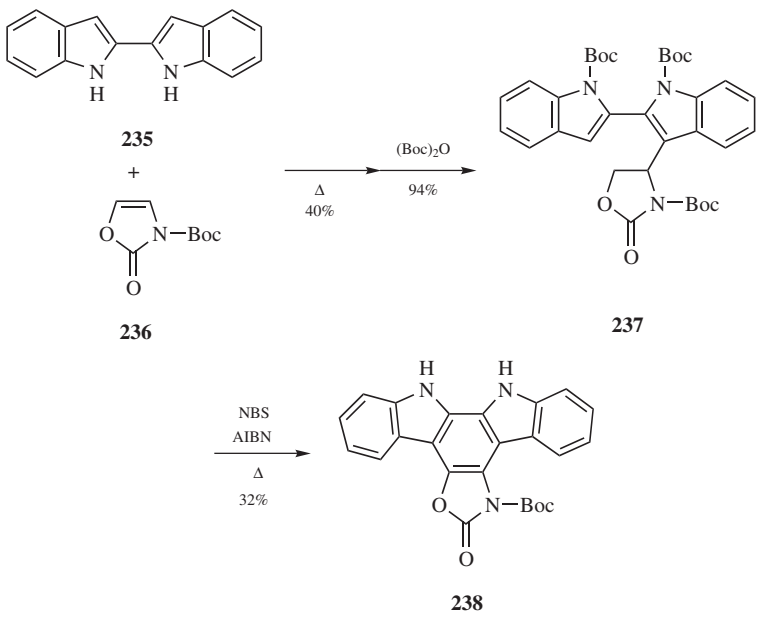


Figure 5.58

5.1.3.4.2. [3+2] Cycloaddition

3-Acetyl-2(3*H*)-oxazolone **84** serves as a good 1,3-dipolarophile in the [3+2] cycloaddition to *N*-alkyl-α-phenylnitrones **239**, giving a mixture of the four possible isomers **240**–**243**, but with the predominant formation of the *exo-syn* adduct **240** (Fig. 5.59). Diastereoselective cycloadditions proceed when mixtures of optically active 3-(2-*exo*-alkoxy-1-apocamphanecarbonyl)-2(3*H*)-oxazolones and *N*-benzyl- and *N*-*tert*-butyl-α-phenylnitrones are heated at 110 °C.[75]

5.1.3.4.3. [2+2] Cycloaddition

The photocycloaddition of 3-acetyl-2(3*H*)-oxazolone **84** with 9,10-phenanthrenequinone **244** gives the spirooxetane **245** regioselectively as a major cycloadduct. Irradiation of 3,4,5-trisubstituted-2(3*H*)-oxazolones **247** in the presence of **244** results in the predominant formation of dioxane derivatives **248**. When duroquinone **249** is irradiated in the presence of the 3,4,5-trisubstituted-2(3*H*)-oxazolone **247a**,

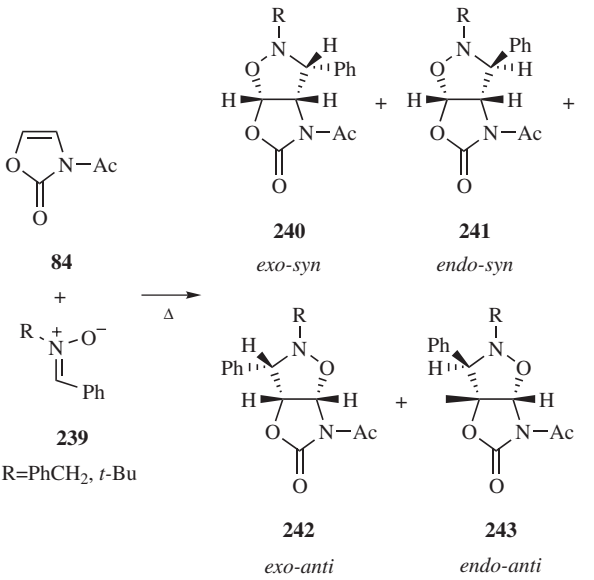


Figure 5.59

the initially formed, photochemically labile 2,5-cyclohexadienones **250** rearrange to the spirooxetanes **251** (Fig. 5.60).[76]

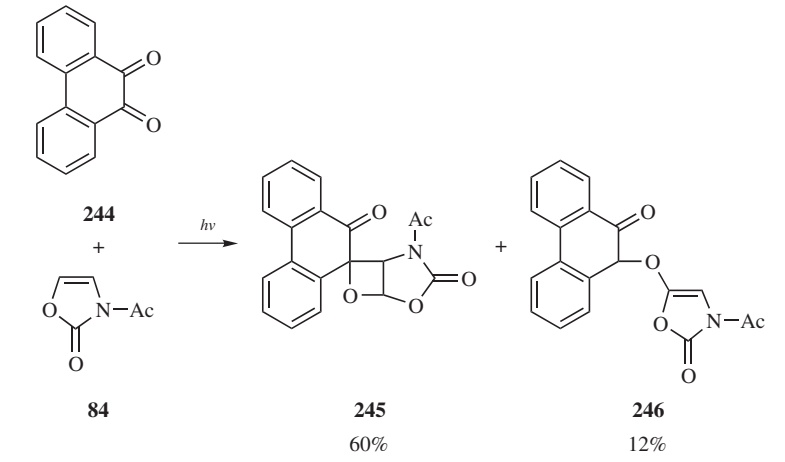
Acetone-sensitized [2+2]-photocycloaddition of 2(3*H*)-oxazolones **247a** to maleic anhydride and dimethylmaleic anhydride gives the corresponding *anti*-cyclobutane cycloadducts **253** as the major products. Similar photoreaction of 2(3*H*)-oxazolones with 1,6-anhydro-4-*O*-benzyl-2,3-dideoxy-β-D-*erythro*-2-hexenopyranose **254** results in the exclusive formation of the *anti*-cyclobutane-type adduct **255** (Fig. 5.61).[77]

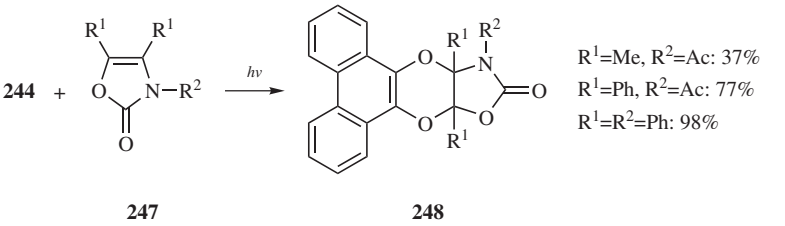
5.1.3.5. C-Substitution

The Friedel–Crafts type acylation of 4-methyl-2(3*H*)-oxazolone **256** with acyl chlorides in the presence of $AlCl_3$ proceeds smoothly to give the 5-acyl-4-methyl-2(3*H*)-oxazolones **257** (Fig. 5.62).[78]

Treatment of 3-trimethylsilylethoxymethyl(SEM)-2(3*H*)-oxazolone **258** with *tert*-BuLi at −78 °C, followed by the addition of tributyltin chloride gives the stannyloxazolones **259**. Cross-coupling of **259** with 2-formyl-3-iodoindole in the presence of $Pd(PPh_3)_4$ catalyst affords a 1 : 1 mixture of isomeric 4- and 5-(3-indolyl)-2(3*H*)-oxazolones **260**. These compounds can be further transformed into the tetracyclic carbazoles **262** (Fig. 5.63).[79]

The 5-methyl-2(3*H*)-oxazolone sulfonamide derivatives **265** are obtained from the sulfonamides **263** via bromination and subsequent Stille coupling reaction with tetramethyltin in the presence of palladium catalyst (Fig. 5.64).[80]


O
O
244
+
hv
Ac
N
O
O
O
O
O
O
O
N–Ac
O
O
84
245
60%
246
12%


244
+
R1
R1
O
N–R2
O
hv
R1
R2
N
O
O
O
O
R1
R1=Me, R2=Ac: 37%
R1=Ph, R2=Ac: 77%
R1=R2=Ph: 98%
247
248

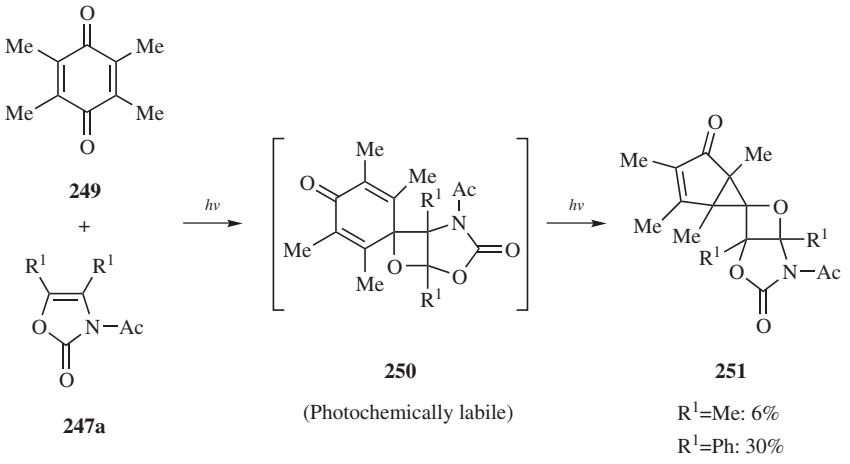
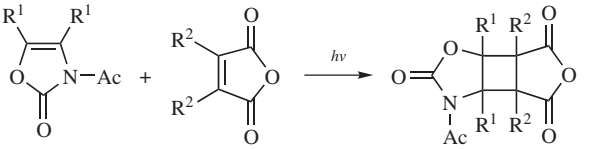

Me
Me
Me
Me
O
O
249
+
R1
R1
O
N–Ac
O
247a
hv
Me
Me
O
R1
Ac
N
Me
O
O
O
Me
R1
hv
O
Me
Me
Me
Me
O
R1
R1
O
N–Ac
O
250
(Photochemically labile)
251
R1=Me: 6%
R1=Ph: 30%

Figure 5.60

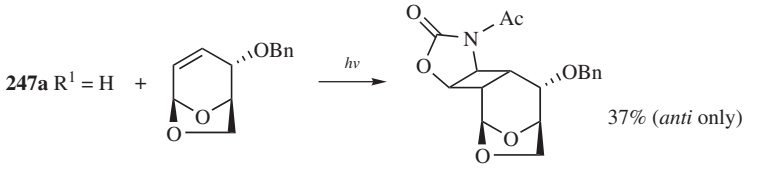


247a **252** **253**

R^1=R^2=H: 43%

R^1=H, R^2=Me: 56% (*syn*: 16%; *anti*: 40%)

R^1=R^2=Me: 43%



254 **255**

Figure 5.61

256 **257**

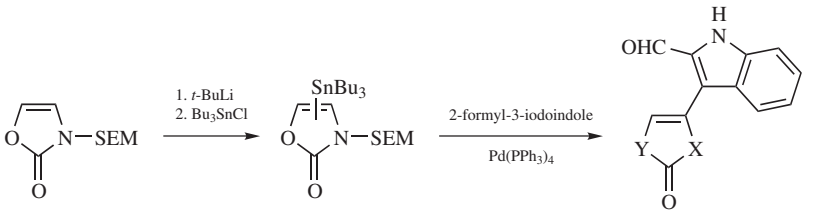
RCO = 4-(1*H*-imidazol-1-yl)carbonyl, benzoyl, pentanoyl, (4-pyridinyl)carbonyl

Figure 5.62

5.1.3.6. N-Substitution

5.1.3.6.1. N-Acylation and N-Alkoxycarbonylation

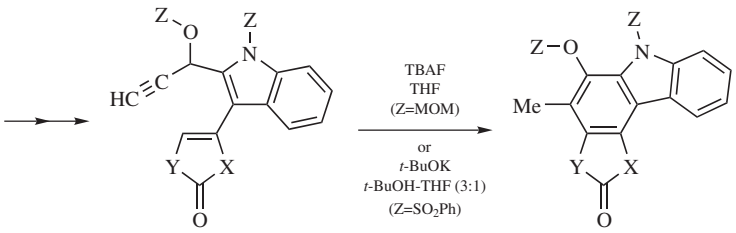
The parent 2(3*H*)-oxazolone moiety functions as a bifunctional leaving group when carboxyl groups are activated for acylations and condensations, similar to other five- and six-membered heterocycles such as imidazole, triazole, and 2-pyridinethiol. The excellent leaving ability of a 2(3*H*)-oxazolone moiety has led to the development of versatile reagents.[81] Thus, 3-acyl- and 3-alkoxycarbonyl-2(3*H*)-oxazolones serve as ''ready-to-use''-type agents for the regioselective and chemoselective N-protection of amino alcohols, amino phenols and polyamines.[60,61] The 2-benzoxazolinone moiety is also effective for carboxy-activation as a comparable leaving group. In contrast, the saturated 2-oxazolidinone skeleton fails to show such a high leaving ability.[62] Regioselective acylation of the primary



258 **259** **260**

SEM = 2-(trimethylsilyl)ethoxymethyl

X=N-SEM, Y=O: 33%
X=O, Y=N-SEM: 29%



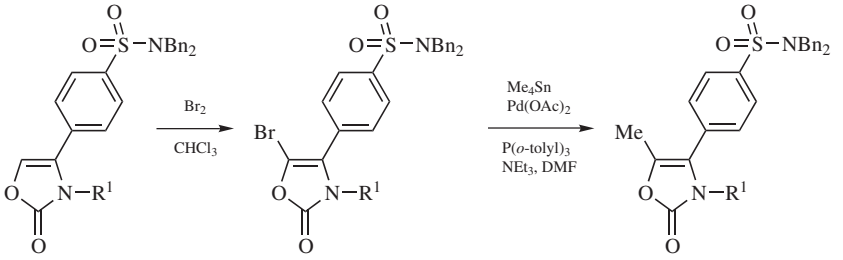
261 **262**

MOM = methoxymethyl

Z=MOM:
X=N-SEM, Y=O: 80%
X=O, Y=N-SEM: 82%

Z=SO_2Ph:
X=N-SEM, Y=O: 24%
X=O, Y=N-SEM: 11%

Figure 5.63



263 **264** **265**

R^1=C_6H_5: 71%
R^1=4-FC_6H_4: 40%
R^1=3-MeC_6H_4: 79%
R^1=4-MeC_6H_4: 37%
R^1=3,4-di-Cl-C_6H_3: 53%

Figure 5.64

hydroxyl group of polyalcohols is readily achieved with **157** in the presence of zirconium complexes.[63]

N-Acylation and 3-alkoxycarbonylation reactions may be achieved by conventional acylation procedures. A variety of 3-acyl derivatives **157** can be prepared most conveniently by the treatment of DPPOx **266** with carboxylic acids in the presence of a tertiary amine.[82] *tert*-Butoxycarbonyl (Boc-Ox, **236**) and benzyloxy carbonyl (Cbz-Ox, **267**) (Cbz = benzyloxycarbonyl) compounds are of practical use for introduction of nitrogen protecting groups.[61]

Homo and copolymers **268** derived from 3-acetyl-2(3*H*)-oxazolone are sufficiently reactive to support the smooth acetylation of the amino groups under heterogeneous conditions (Fig. 5.65).[61]

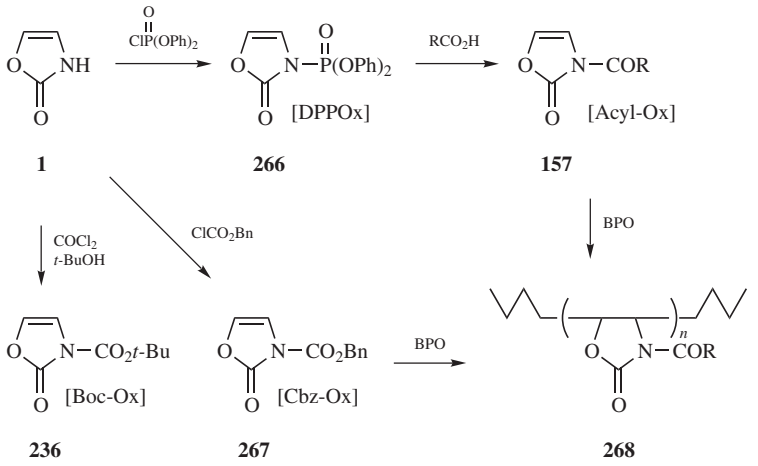
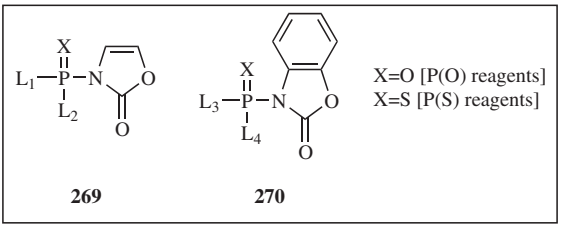


Figure 5.65

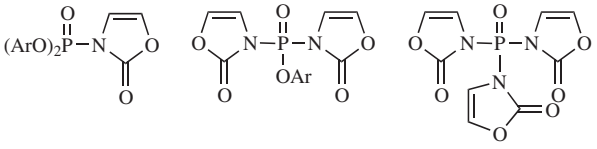
5.1.3.6.2. N-Phosphorylation

The activated phosphorus reagents **269** and **270** are conventionally prepared by the reaction of 2(3*H*)-oxazolone with the corresponding phosphorus chlorides in the presence of triethylamine. The phosphorus chlorides employed include phosphoryl chloride, thiophosphoryl chloride, mono- and dichlorophosphates, and phosphinic chloride (Fig. 5.66).

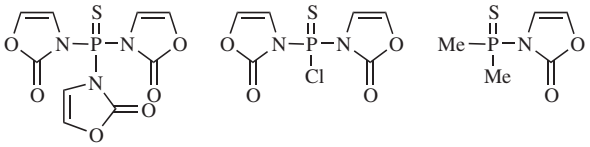
The above reagents serve as condensing reagents and have different reactivities for peptides **279**,[82,83] β-lactams **281**,[84,85] esters,[85] thioesters,[85,86] and mixed phosphates,[87] as well as for the direct preparation of 3-acyl-2(3*H*)-oxazolones.[82] The bis(2-oxo-3-oxazolinyl)phosphinate **282** is useful for Zr(IV)-catalyzed phosphorylation of alcohols, leading to the general synthesis of acid- and base-labile mixed phosphate esters **284** (Fig. 5.67).[87]



269 **270**

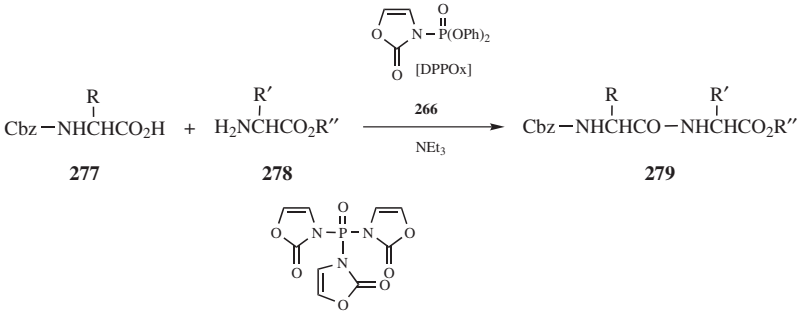


271 **272** **273**



274 **275** **276**

Figure 5.66



277 **278** **279**

280 **281**

282 **283** **284**

acac = acetylacetonate

(R^1, R^2 = 1°, 2°)

Figure 5.67

5.1.3.7. Miscellaneous

The PCC oxidation of 3-amino-4,5-diphenyl-2(3*H*)-oxazolone **96** affords monodiazobenzyl **286** as the primary decomposition product obtained via loss of carbon monoxide from the postulated *N*-nitrenolactam **285**.[25] Oxidation of **96** with *tert*-BuOCl / NEt_3 at −108 °C results in a deep green solution of **285**, which reacts with dimethyl sulfoxide (DMSO) to give the sulfoximide **288** (Fig. 5.68).[88]

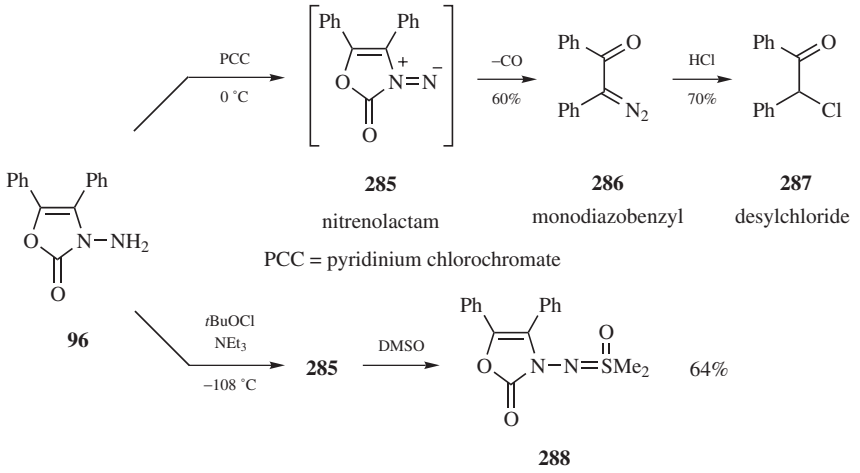


Figure 5.68

The alkylation of the 2(3*H*)-oxazolones **289** with Meerwein's salt (Et_3O^+ BF_4^-) occurs readily and in excellent yield, thus providing an efficient route to the 2-ethoxyoxazoles **290**. Although the yield of **290** (R = Me) is low, the process can be carried out on large scale starting from commercially inexpensive acetoin (Fig. 5.69).[89]

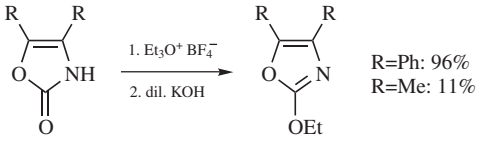


Figure 5.69

5-Alkoxy-2(3*H*)-oxazolones **47** react with aliphatic and aromatic aldehydes in the presence of Lewis acid catalysts to produce alkyl 2-oxazolidinone-4-carboxylates **291**[90] by successive ring opening and reclosure.

Similarly, reaction with imines affords alkyl 2-imidazolidinone-4-carboxylates **293** via [2+2] cycloadducts **292**. Treatment of the isolated cycloadducts **292** with trifluoroacetic acid (TFA) yields 2,3-diaminocarboxylates **294**.[91]

5,5-Dialkoxy-2-oxazolidinones **295**, which are prepared by reaction of 5-alkoxy-2(3*H*)-oxazolones **47** with acetals in the presence of Lewis acid catalysts, are hydrolyzed in the presence of a protonic acid to produce α-amino acid esters **296** (Fig. 5.70; Table 5.11, Fig. 5.71; Table 5.12, Fig. 5.72; Table 5.13, Fig. 5.73; Table 5.14, Fig. 5.74).[92]

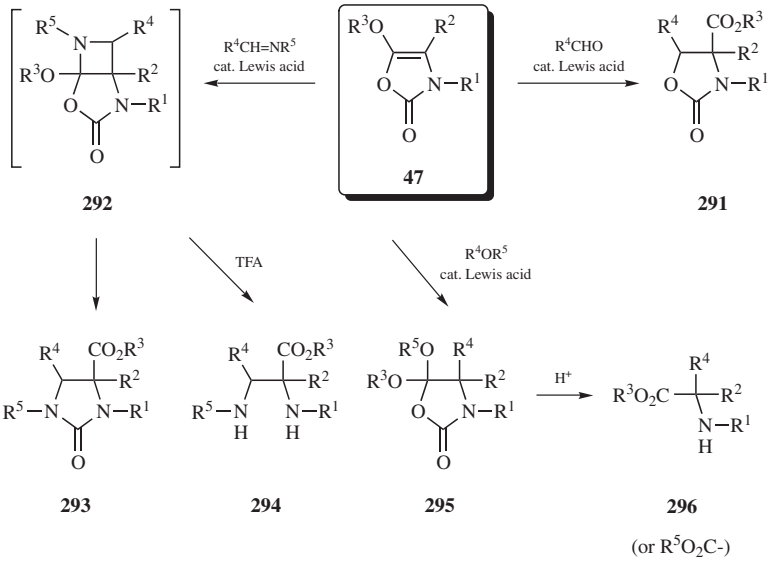


Figure 5.70

TABLE 5.11. SYNTHESIS OF ALKYL 2-OXAZOLIDINONE-4-CARBOXYLATES FROM 5-ALKOXY-2(3*H*)-OXAZOLONES[a]

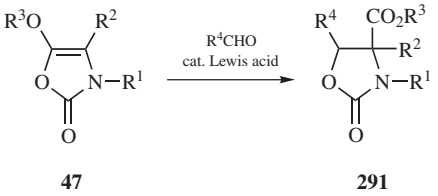
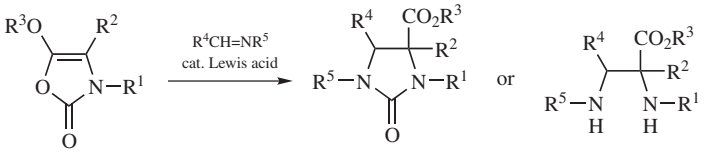


Figure 5.71

R^1	R^2	R^3	R^4	Lewis Acid	% Yield
Ph_2CH	H	Me	Ph	$BF_3{\bullet}OEt_2$	100
Ph_2CH	H	Me	*i*-Pr	$BF_3{\bullet}OEt_2$	100
Ph_2CH	H	Me	CO_2Me	TMSOTf	28
(*R*)-1-Phenylethyl	H	Me	Ph	TMSOTf	95
(*S*)-1-Phenylethyl	H	*i*-Pr	Ph	TMSOTf	97
Ph_2CH	Me	Me	Ph	TMSOTf	95
$PhCH_2$	Me	Me	Ph	TMSOTf	97

[a] Data from Ref. 90.

TABLE 5.12. SYNTHESIS OF ALKYL 2-IMIDAZOLIDINONE-4-CARBOXYLATES AND ALKYL 2,3-DIAMINOPROPANE-1-CARBOXYLATES FROM 5-ALKOXY-2(3*H*)-OXAZOLONES[a]



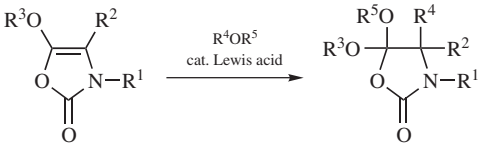
47 **293** **294**

Figure 5.72

Compd. No.	R^1	R^2	R^3	R^4	R^5	Lewis Acid	% Yield
293	Ph_2CH	H	Me	Ph	Ts	TMSOTf	99
293	Ph_2CH	H	Me	CO_2Me	Ph_2CH	TMSOTf	99
293	Ph_2CH	H	Me	CO_2Me	(*R*)-1-Phenylethyl	TMSOTf	94
293	(*R*)-1-Phenylethyl	H	Menthyl	CO_2Me	Ph_2CH	BF_3•OEt_2	97
293	(*R*)-1-(1-Naphthyl)ethyl	H	Me	Ph	Ts	BF_3•OEt_2	100
293	Ph_2CH	Me	Me	CO_2Me	Ph_2CH	TMSOTf	99
294	Ph_2CH	H	Me	CO_2Me	Ph_2CH	BF_3•OEt_2	45

[a] Data from Ref. 91.

TABLE 5.13. SYNTHESIS OF 5,5-DIALKOXY-2-OXAZOLIDINONES FROM 5-ALKOXY-2(3*H*)-OXAZOLONES[a]



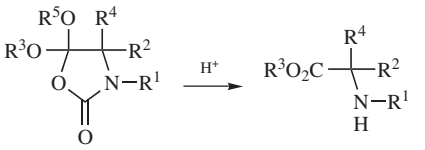
47 **295**

Figure 5.73

R^1	R^2	R^3	R^4	R^5	Lewis Acid	% Yield
Ph_2CH	H	Me	H	Me	TMSOTf	81
Ph_2CH	H	Me	CH(OMe)Ph	Me	TMSOTf	96
(*R*)-1-Phenylethyl	H	Me	CH(OMe)Ph	Me	TMSOTf	89
(*R*)-1-(1-Naphthyl)ethyl	H	Me	CH(OMe)Ph	Me	TMSOTf	83
(*R*)-1-(1-Naphthyl)ethyl	Me	Me	H	Me	BF_3•OEt_2	90

[a] Data from Ref. 92.

TABLE 5.14. SYNTHESIS OF α-AMINO ACID ESTERS FROM 5,5-DIALKOXY-2-OXAZOLIDINONES[a]



295 **296** (or R^5O_2C-)

Figure 5.74

R^1	R^2	R^3	R^4	R^5	% Yield
Ph_2CH	H	Me	H	Me	100
Ph_2CH	H	Me	CH(OMe)Ph	Me	100
(*R*)-1-(1-Naphthyl)ethyl	Me	Me	H	Me	95

[a] Data from Ref. 92.

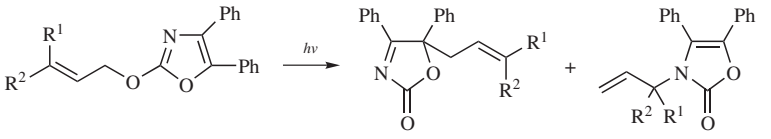
5.2. 2(5*H*)-OXAZOLONES (3-OXAZOLIN-2-ONES)

5.2.1. Introduction

Only a few compounds of this class have been reported since 1984 and three papers are surveyed in this section.

5.2.2. Synthesis

The UV irradiation of the 2-allyloxy-4,5-diphenyloxazole **41** results in the predominant formation of 5-substituted-2(5*H*)-oxazolones **44**, in contrast to the thermal aza-Claisen rearrangement which readily affords the 2(3*H*)-oxazolones **42**. The photolysis proceeds via allyl-O bond scission with the generation of a radical pair that subsequently recombines to produce 5-substituted-2(5*H*)-oxazolones. Similar results were obtained with 2-(benzyloxy)-4,5-diphenyloxazole (Fig. 5.75).[10]



41

a: R^1=R^2=H
b: R^1=H, R^2=Me
c: R^1=R^2=Me

44

a: 77%
b, c: 83%

42

a: 0%
b, c: 17%

Figure 5.75

On treatment with phosphorus pentachloride, 4,5-diaryl-2(3*H*)-oxazolones **297** are reported to afford 5-chloro-4,5-diaryl-2(5*H*)-oxazolones **298**, rather than the expected 2-chloro-4,5-diaryloxazoles. The 5-chloro-products react with methanol to give 4,5-diaryl-4,5-dimethoxy-2-oxazolidinones **299**, which are further converted on heating to 4,5-diaryl-5-methoxy-2(5*H*)-oxazolones **300** (Fig. 5.76).[93]

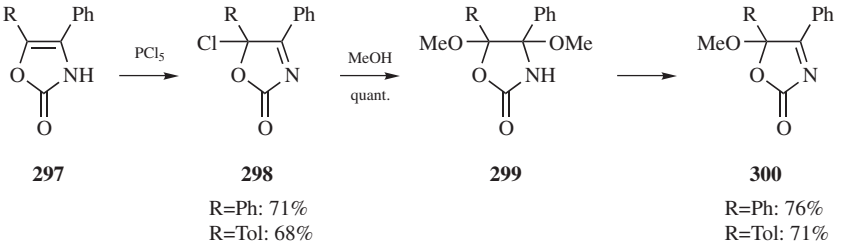


Figure 5.76

Dehydration of 4-hydroxy-4,5,5-trimethyl-2-oxazolidinone **301** with a catalytic amount of *p*-toluenesulfonic acid affords the isomeric dimers **303** and **304** in a ratio of 1 : 2. The former type of dimer, that is, **303** likely results from coupling of the isomeric 2(5*H*)-oxazolone **302A** with 4-methylene-2-oxazolidinone **302B**, which are the initially formed dehydration products. On prolonged heating in CH_2Cl_2, the 2(5*H*)-oxazolone dimer **303**, completely isomerizes to the 4-methylene-2-oxazolidinone dimer **304** (Fig. 5.77).[94]

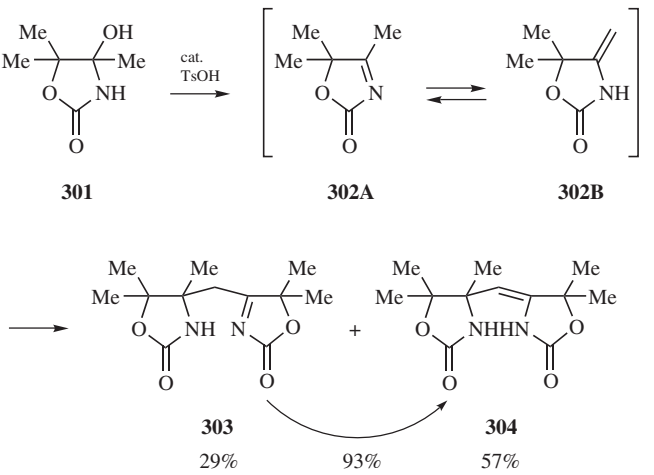


Figure 5.77

5.2.3. Reactions

There is nothing new to report on reactions of 2(5*H*)-oxazolones.

5.3. SUMMARY

Most of the reports, since the 1980s, on the chemistry of 2-oxazolones concern 2(3*H*)-oxazolones (4-oxazolin-2-ones) **1** and only few reports have appeared on the isomeric 2(5*H*)-oxazolones (5-oxazolin-2-ones) **2**. Thus, the emphasis of this chapter has been to survey information on the synthesis and reactions of the 2(3*H*)-oxazolones **1** that has appeared over the past two decades.

The synthetic methods used to prepare 2(3*H*)-oxazolones since 1984 are largely based on minor modification of previous methodologies. However, some entirely new strategies for the construction of this class of heterocycles have also appeared, which include the application of intramolecular rearrangements such as Claisen-type and Pummerer rearrangements, ring formation catalyzed by transition metal reagents such as $Ru_3(CO)_{12}$, $Rh_2(OAc)_4$, and $Pd(OAc)_4$, and the ingenious use of *in situ* generated *N*- and *P*-ylides.

Recent developments have largely focused on the synthetic potential of the 2(3*H*)-oxazolone **1** as a building block that contains both masked amino and hydroxy moieties. Enantiocontrolled addition reactions at the 4,5-olefinic moiety of the 2(3*H*)-oxazolone ring in a variety of ionic, radical, and concerted addition modes provide a versatile strategy for achieving a chiral synthesis leading to the preparation of 2-amino alcohols of biological interest. The reactions also open up routes to chiral 2-oxazolidinone auxiliaries and chiral amino alcohol ligands that are of general use in asymmetric synthesis. Another feature based on the chemical stability of the 2(3*H*)-oxazolone ring skeleton permits its use as a protecting group, as well as for ''ready-to-use''-type of reagents.

5.4. ADDENDUM

Condensation of 3-nosyloxy-2-keto esters **305** with methyl carbamate in refluxing toluene in the presence of *p*-toluenesulfonic acid provides 2(3*H*)-oxazolone-4-carboxylates **306** in good yields (41–80%). Alternatively, condensation of 3-bromo-2-keto esters **307**, derived from the bromination of α-keto esters with $CuBr_2$, with methyl carbamate in the presence of AgOTf and *p*-toluenesulfonic acid under similar conditions provides the 2(3*H*)-oxazolone-4-carboxylates **306** in comparable yields (30–79%) (Fig. 5.78; Table 5.15, Fig. 5.79).[95,96]

The tandem condensation of isocyanates with an α-ketol in DMF leads to the 2-oxazolidinone derivatives **308** that are dehydrated to the 2(3*H*)-oxazolones **309** by refluxing in DMSO (Fig. 5.80).[97]

Treatment of the *N*-mesyloxyamide **310** with sodium hydride yields 5-ethoxy-3-methyl-2(3*H*)-oxazolone **311**. This intramolecular cyclization is considerably enhanced under sonication (Fig. 5.81).[98]

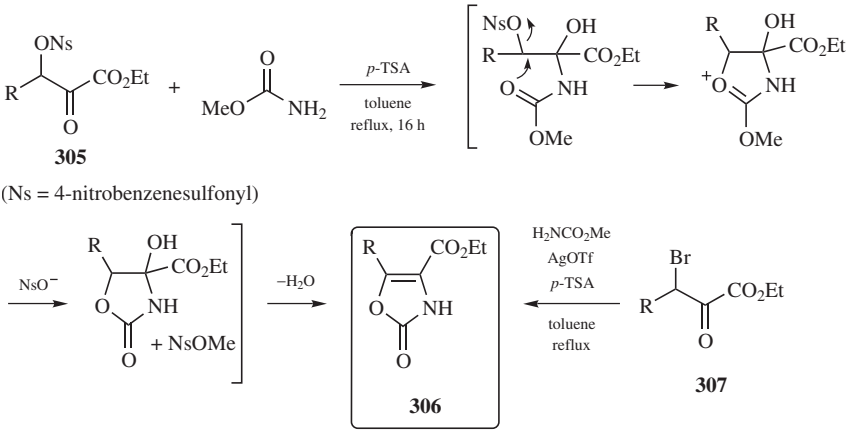


Figure 5.78

TABLE 5.15. SYNTHESIS OF ETHYL 2(3*H*)-OXAZOLONE-4-CARBOXYLATES FROM 3-NOSYLOXY-2-KETO ESTERS OR 3-BROMO-2-KETO ESTERS[a]

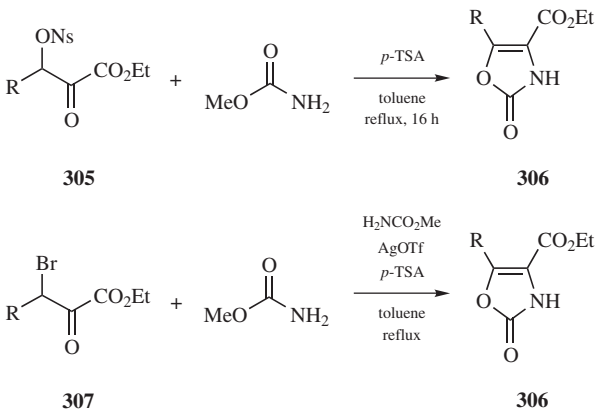
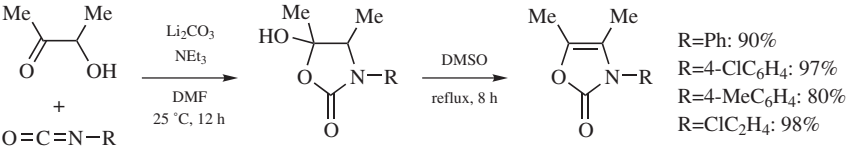


Figure 5.79

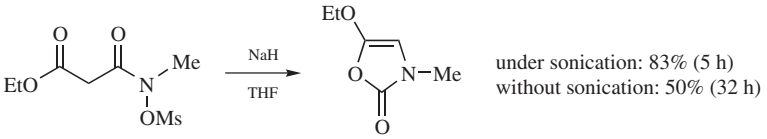
R	% Yield from **305**	% Yield from **307**	% Yield from **307** (with *p*-TSA)
Bn	80	64	75
H (Me ester)	51	43	54
Pentyl	84	63	79
i-Bu	70	68	75
i-Pr	41	30	
Me	56	60	60
Ph	46	64	
MeO_2CCH_2 (Me ester)			49

[a] Data from Refs. 95, 96.



308 **309**

Figure 5.80



310 **311**

Figure 5.81

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CHAPTER 6

4(5*H*)-Oxazolones

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6.1. INTRODUCTION

The first derivatives of the 4(5*H*)-oxazolone ring system **1** were prepared almost 90 years ago when Traube and Ascher[1] described the synthesis of 2-amino-4(5*H*)-oxazolones (pseudohydantoins) **2** via condensation of guanidine with α-hydroxy esters (Scheme 6.1). This is quite remarkable in that it was 36 years later before Sheehan and Izzo[2] prepared the first example of a simple 2-aryl analogue via

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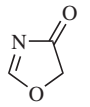
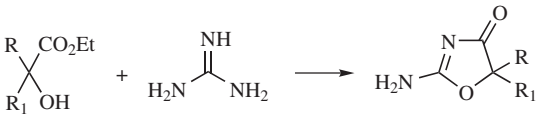


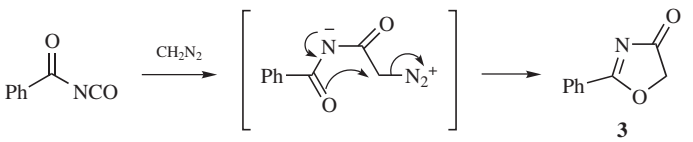
1



2

Scheme 6.1

reaction of benzoyl isocyanate with diazomethane to afford 2-phenyl-4(5*H*)-oxazolone, **3** (Scheme 6.2). Since these two reports, the 4(5*H*)-oxazolone ring system has been a rich source of derivatives and analogues prepared and evaluated as antibiotics, tranquilizers, antiinflammatory agents, antidepressants, antimalarials, fungicides, herbicides, antiviral agents, antidiabetic agents, dual 5-lipoxygenase (5-LO) and cyclooxygenase (CO) inhibitors, antiulcer agents, agents for the treatment of metabolic bone disorders, as selective cyclooxygenase (CO) inhibitors, photographic dyes, and nonlinear optical materials.



3

Scheme 6.2

A comprehensive review of the synthesis and reactions of 4(5*H*)-oxazolones and analogues was published over 15 years ago.[3] In addition, there are several reviews more limited in scope that have appeared recently.[4–7] This chapter will survey the synthesis and reactions of 4(5*H*)-oxazolones and derivatives covering the period from 1983 to 2001. It will follow the basic format presented by Rao and Filler[3] although several areas will be covered in more detail.

In those cases where tautomeric structures are possible, the exclusive or predominant tautomer will be shown (Fig. 6.1). Thus, **1** is predicted to be the most stable tautomer in the gas phase and in solution. It is the only tautomer observed experimentally in solution and will be used to represent 4(5*H*)-oxazolones.[8,9] The tautomeric mesoionic anhydro-4-hydroxyoxazolium hydroxide **1b** has not been observed spectroscopically but has been trapped in cycloaddition reactions.[5,10,11] The amino tautomer **2** has been shown to be the exclusive and/or predominant tautomer for simple 2-amino-4(5*H*)-oxazolones.[7,12,13] Rapi and

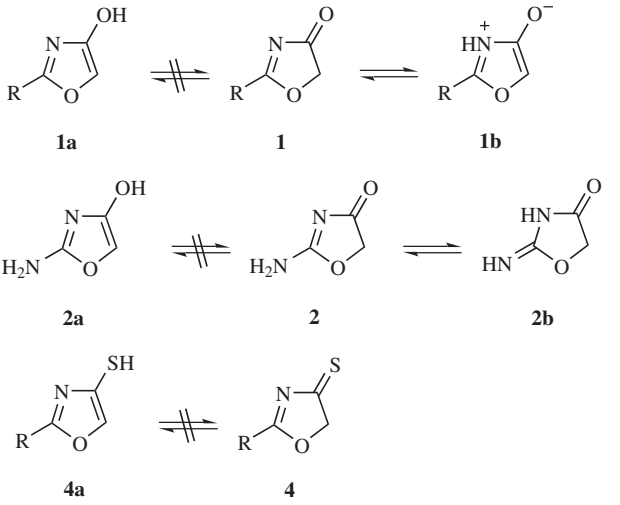


Figure 6.1. 4(5*H*)-Oxazolone tautomers.

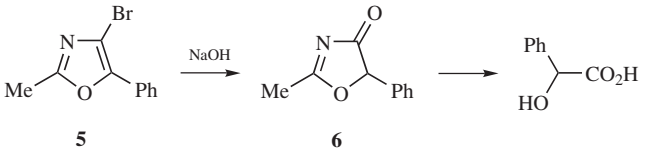
co-workers[13] presented an excellent discussion of tautomerism in 2-amino-4(5*H*)-oxazolones. Similarly, the thione **4** is the predominant tautomer.[5]

6.2. 2-ALKYL(ARYL)-4-(5*H*)-OXAZOLONES AND THIOOXAZOLONES

6.2.1. Synthesis

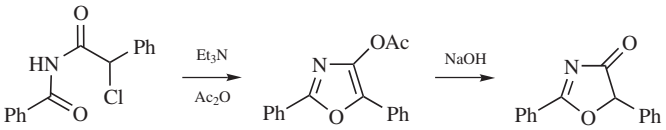
There are relatively few syntheses of simple 2-alkyl- or 2-aryl-4(5*H*)-oxazolones and these have been summarized previously.[3] An excellent and comprehensive review of the synthesis and reactions of 4(5*H*)-oxazolones covering the early literature up to ~1983 has been published.[6] Subsequent to this work extensions of earlier methods and a few additional examples have appeared in the literature and these will be described in detail.

Hydrolysis of a suitably 4-substituted oxazole has been reported to produce the corresponding oxazolone but the yields are not very high and the isolations can be difficult. For example, alkaline hydrolysis of **5** affords a low yield of mandelic acid presumably via the intermediacy of **6** (Scheme 6.3).[14] As part of a study



Scheme 6.3

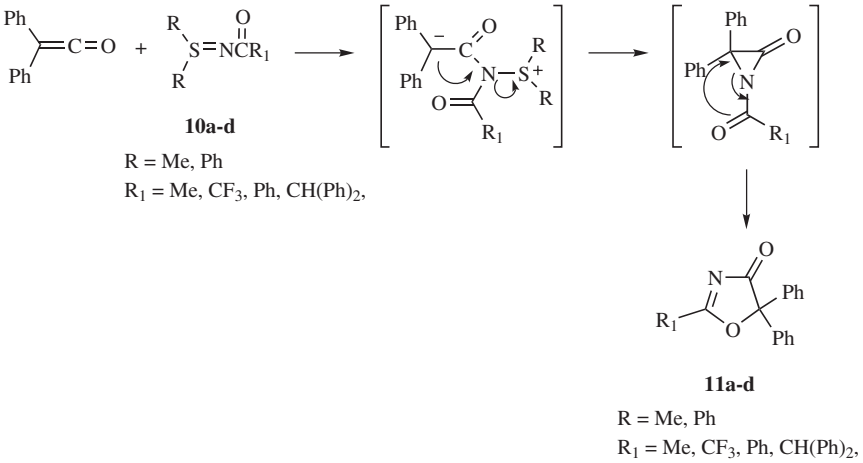
to prepare all eight metabolites of 2,5-diphenyloxazole, the 4-acetoxy derivative, **8** was prepared via cyclization of **7** (Scheme 6.4). Brief alkaline hydrolysis of **8** produced **9** as part of a complex mixture. Only after treatment of this mixture with 1-iodopropane/$(n\text{-Bu})_4^+OH^-$ was it possible to isolate a propylated derivative.[15]



7 **8** **9**

Scheme 6.4

Abou-Gharbia and co-workers[16] described a general synthesis of 5,5-diphenyl-2-substituted-4(5*H*)-oxazolones as an extension of their earlier work.[17] Reaction of diphenylketene with a series of *N*-acylsulfilimines **10a–d** produced an intermediate *N*-acyl α-lactam that then rearranged to afford **11a–d** in 56–80% yield (Scheme 6.5). Examples are shown in Table 6.1 (Fig. 6.2).



10a-d

R = Me, Ph

R_1 = Me, CF_3, Ph, $CH(Ph)_2$,

11a-d

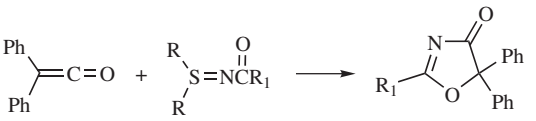
R = Me, Ph

R_1 = Me, CF_3, Ph, $CH(Ph)_2$,

Scheme 6.5

The reaction was sensitive to substitutents present in the aromatic ring of **10**. For example, *S*,*S*-dimethyl-*N*-benzoylsulfilimine, **10b**, reacted completely with diphenylketene after 4 h in refluxing toluene. In contrast, the corresponding

TABLE 6.1. 5,5-DIPHENYL-2-SUBSTITUTED-4(5*H*)-OXAZOLONES FROM SULFILIMINES AND DIPHENYLKETENE[a]



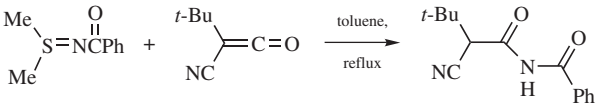
10a-d **11a-d**

Figure 6.2

Product	R	R_1	Conditions	% Yield
11a	Ph	$CH(Ph)_2$	CH_2Cl_2/reflux	73
11b	Me	Ph	toluene/reflux	80
11c	Ph	Me	CH_2Cl_2/reflux	56
11d	Ph	CF_3	xylene/reflux	68

[a]Data from Ref. 16.

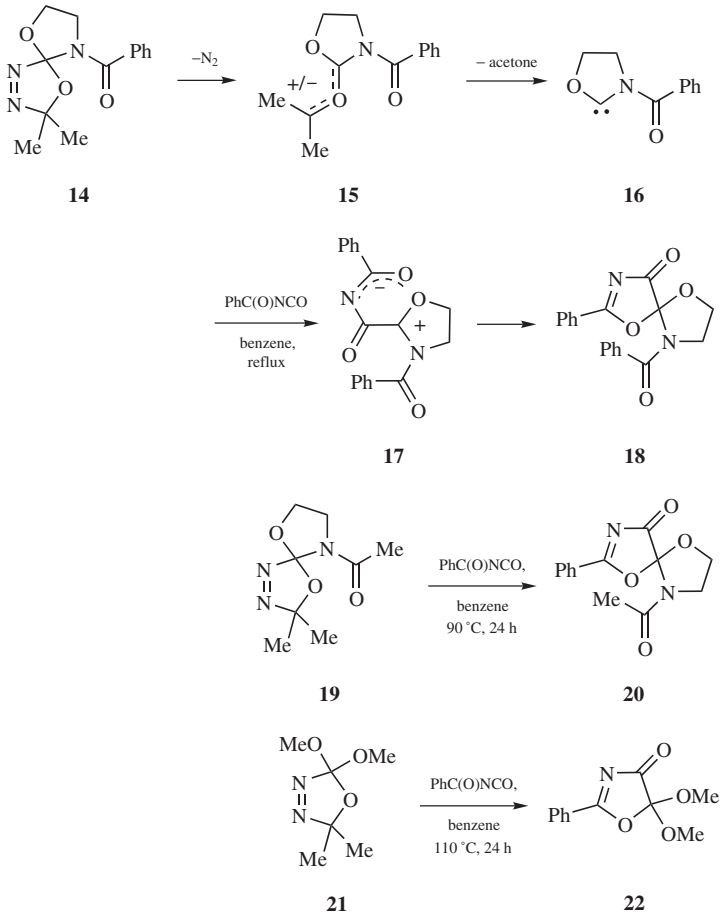
N-p-nitrobenzoyl analogue was unreactive after 24 h under the same reaction conditions. Reaction of **10b** with *tert*-butylcyanoketene **12** produced none of the expected 4(5*H*)-oxazolone. Instead, the imide **13**, the product of an apparent Pummerer reaction,[18] was isolated in low yield (Scheme 6.6).



10b **12** **13**

Scheme 6.6

As part of a mechanistic and synthetic study of nucleophilic carbenes the spirocyclic 4(5*H*)-oxazolone **18** has been obtained from benzoyl isocyanate (Scheme 6.7).[19] Thermal extrusion of nitrogen from the 1,3,4-oxadiazoline **14** produced the carbonyl ylide **15** that fragmented via loss of acetone to the aminooxycarbene **16**. Spectroscopic data [gas chromatography–mass spectrometry (GC–MS), infrared (IR), proton and C-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR)] of the crude thermolysate was consistent with **18**. The formation of **18** was rationalized to result from nucleophilic addition of **16** to benzoyl isocyanate followed by cyclization of the dipolar intermediate **17**. Thermolysis of **19** and **21** under similar reaction conditions afforded **20** and **22** respectively, also identified spectroscopically as the major products in the thermolysate.



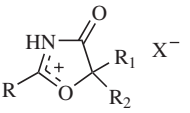
14 **15** **16** **17** **18** **19** **20** **21** **22**

Scheme 6.7

The syntheses and reactions of salts of variously substituted 4(5*H*)-oxazolones were described in Ref. 3. This area is the subject of extensive investigations in the Russian chemical literature and has been reviewed recently.[6] Several very well established and preparatively useful methods to prepare analogues of **23** (Fig. 6.3) are presented in these references and will not be described further.

They include

- Reaction of α-haloacetyl bromides with amides in the presence of strong acids ($pK < 1$).
- Reaction of α-chloroacetamides with acid chlorides.
- Cyclization of α-hydroxy carboxylic acid amides with anhydrides in the presence of strong acids ($pK < 1$).
- Cyclization of cyanohydrins with aliphatic acid anhydrides in the presence of strong acids ($pK < 1$) or aromatic acids halides in the presence of $SnCl_4$.

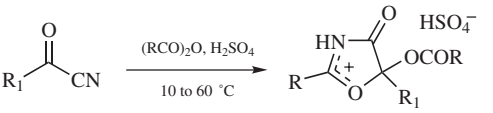


23

R = alkyl, aryl
R_1 = H, alkyl, aryl, cycloalkyl
R_2 = H, alkyl, aryl, cycloalkyl
X^- = ClO_4, Br, $SbCl_6$, 1/2 $SnCl_6^{-2}$, HSO_4, CF_3CO_2, polyphosphate

Figure 6.3. 4(5*H*)-Oxazolonium salts.

German workers[20] reported that 5-acyloxy-4(5*H*)-oxazolonium salts **24** are readily prepared by reaction of acyl cyanides and acid anhydrides in the presence of a strong acid (Scheme 6.8). Analogues like **24** are not available using the traditional methods (see above).

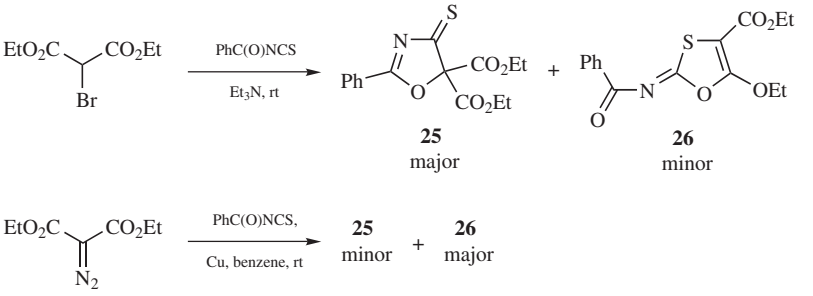


24

R = alkyl, chloroalkyl, Ph
R_1 = alkyl, cycloalkyl, aryl, heteroaryl

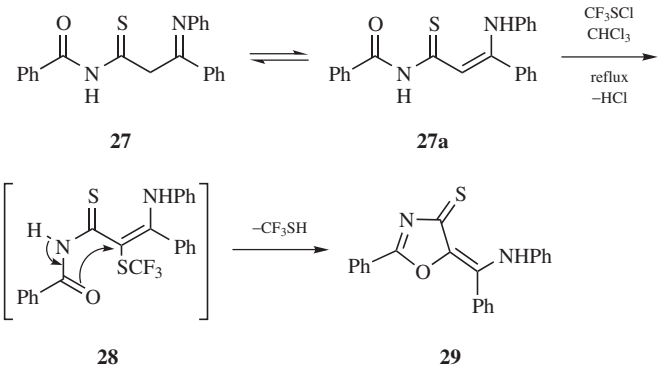
Scheme 6.8

The manner in which a carbene was generated was found to be critical to the product distribution in a synthesis of 4(5*H*)-thiooxazolones (Scheme 6.9). Treatment of diethyl bromomalonate with excess triethylamine in the presence of benzoyl isothiocyanate afforded a mixture of the 4(5*H*)-thiooxazolone **25** (44%) and the 1,3-oxathiole **26** (minor). However, if the carbene was generated via copper-catalyzed decomposition of diethyl diazomalonate, then **26** was isolated as the major product, albeit in low yield (22%).[21]



Scheme 6.9

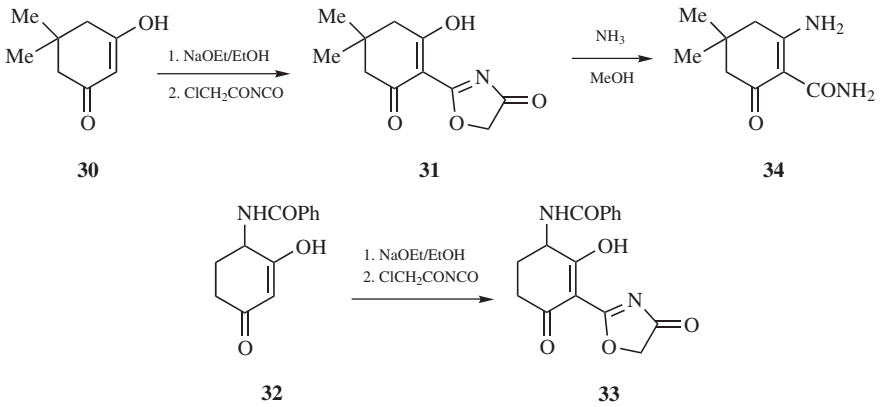
A recent report on trifluoromethylsulfenylation of β-keto acids and derivatives describes isolation of **29** in good yield from reaction of **27** with trifluoromethylsulfenyl chloride (Scheme 6.10).[22] Mechanistically, this was rationalized via electrophilic attack of trifluoromethylsulfenyl chloride on the enamine tautomer **27a** to generate **28** followed by intramolecular cyclization through the imide oxygen with concomitant loss of CF_3SH to produce **29**. The product was characterized spectroscopically.



27 **27a** **28** **29**

Scheme 6.10

During investigations of the synthesis of tetracycline ring A analogues, Moskalyk and co-workers[23] unexpectedly isolated 4(5*H*)-oxazolones **31** and **33** following reaction of **30** and **32** with sodium ethoxide then chloroacetyl isocyanate. Further reaction of **31** effected ring opening of the 4(5*H*)-oxazolone to yield **34** (Scheme 6.11).

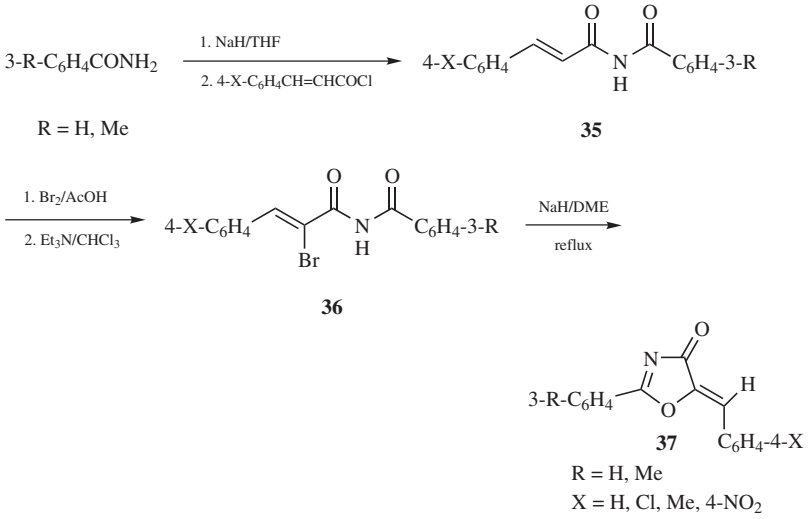


30 **31** **34**

32 **33**

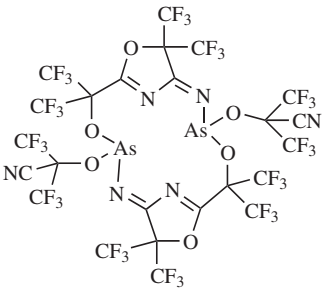
Scheme 6.11

Base-catalyzed cyclization of *N*-benzoyl-α-chloroacetamide is a classical method used to prepare 2-phenyl-4(5*H*)-oxazolone.[3] Extension of this methodology to the *N*-aroylcinnamides **35** afforded a series of 5-arylidene analogues **37** albeit in unstated yield (Scheme 6.12).[24] Thus, acylation of the sodium salt of a benzamide with a cinnamoyl chloride gave the imides **35** that were converted to **36** via a bromination–dehydrobromination sequence. Cyclization to **37** was affected with sodium hydride in 1,2-dimethoxyethane (DME). The authors noted that catalytic reduction of **37** afforded the 5-(arylidene)oxazolidine from which **37** could be regenerated in the presence of air.



Scheme 6.12

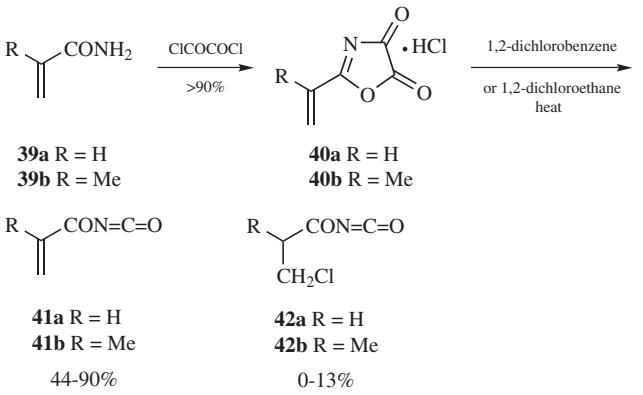
Roesky and co-workers[25] unexpectedly isolated the unique 14 membered macrocycle **38** containing arsenic, carbon, oxygen, and nitrogen atoms in the skeletal framework from reaction of arsenic(III) cyanide and hexafluoroacetone (Fig. 6.4). The structure of **38** was confirmed by single-crystal X-ray.



38

Figure 6.4. Arsenic containing macrocyclic 4(5*H*)-oxazolone.

Japanese workers[26–28] prepared examples of 2-alkenyl-4,5-oxazolediones **40a** and **40b**, which are key intermediates in the synthesis of alkenoyl isocyanates **41a** and **41b** (Scheme 6.13). These reactive monomers are precursors to a variety of functionalized polymers including instantaneously curable compositions. Thus, reaction of oxalyl chloride with acrylamide **39a** or methacrylamide **39b** affords **40a** and **40b** isolated as hydrochloride salts in high yields. Subsequent decomposition of the 2-alkenyl-4,5-oxazolediones in the presence of a metal halide or synthetic zeolite affords **41a** and **41b** contaminated with varying amounts of **42a** and **42b**. The synthesis and reactions of other 2-substituted 4,5-oxazolediones have been described independently by Speziale and co-workers[29,30] and Sasaki and co-workers.[31,32]



Scheme 6.13

Almazole D, **43a** is a relatively rare naturally occurring 2,5-disubstituted oxazole that was isolated recently (Fig. 6.5).[33] The proposed structure is based on NMR evidence and conversion of **43a** to **43b** by reaction with diazomethane but it has not yet been confirmed by total synthesis.

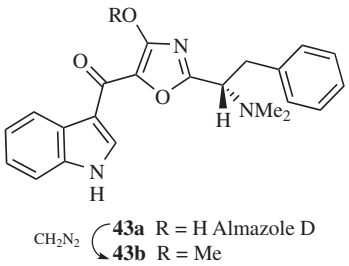
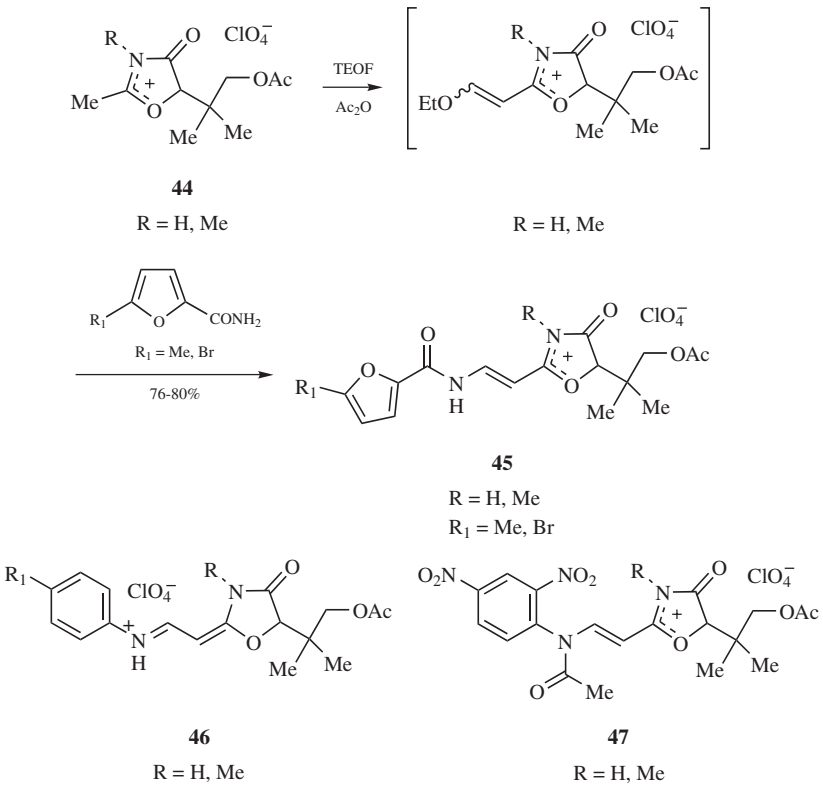


Figure 6.5. Almazole D.

6.2.2. Reactions

For a brief survey of typical reactions of 4(5*H*)-oxazolones the reader is directed to Rao and Filler's previous review.[3] Kul'nevich and co-workers[6] presented a more comprehensive discussion of this topic. Extensions of previous methodology or new reactions will be presented in this section.

Condensation products of 4(5*H*)-oxazolonium salts with aldehydes and ortho-esters are the subject of a series of papers by Kosulina and co-workers.[34–36] Reaction of 2-methyl-4(5*H*)-oxazolonium perchlorates **44** with an ortho ester gives rise to an enol ether, which reacts with furanamides to afford the *trans*-eneamides **45** (Scheme 6.14).[34] Using electron deficient anilines in a three component condensation affords either **46** or **47** in 64–80% and 78–84% yields, respectively, depending on whether the reaction is performed in acetic acid or acetic anhydride. Electron-rich anilines are unreactive since they are merely protonated by the perchloric acid present in the reaction medium.[36]



44
R = H, Me

R = H, Me

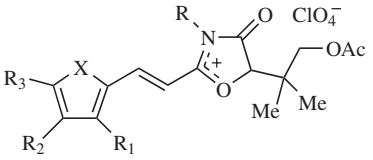
45
R = H, Me
R_1 = Me, Br

46
R = H, Me

47
R = H, Me

Scheme 6.14

TABLE 6.2. 2-[2-(α-HETEROARYL)ETHENYL]-4(5*H*)-OXAZOLONIUM PERCHLORATES FROM OXAZOLONIUM SALTS AND ALDEHYDES[a]



R = H, Me
X = O, S, CH=CH

48

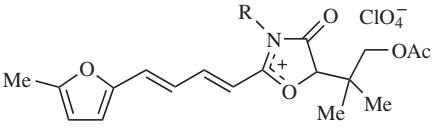
Figure 6.6

X	R	R_1	R_2	R_3	% Yield	Product
O	H	H	H	Ph	73	**38a**
O	H	H	H	4-Me–C_6H_4	83	**38b**
O	H	H	H	4-Br–C_6H_4	74	**38c**
O	H	H	H	4-NO_2–C_6H_4	64	**38d**
O	H	H	H	3-NO_2–C_6H_4	56	**38e**
S	H	H	H	H	60	**38f**
S	H	H	H	Br	70	**38g**

[a]Data from Ref. 35.

A recent extension of this methodology includes condensation of **44** with a variety of substituted benzaldehydes, furfurals, and thiophene carboxaldehydes afforded analogues of **48** in good to excellent yield as shown in Table 6.2 (Fig. 6.6). These products were completely characterized spectroscopically with an excellent discussion of the effects of substituents on the corresponding UV, IR, MS, and NMR spectra. Neutralization of **48** with sodium bicarbonate in aqueous ethanol produced the corresponding free bases uneventfully. These compounds were evaluated both as cyanine dyes and for biological activity.[35] Condensation of **44** with (*E*)-3-(5-methylfuran-2-yl)-2-propenal affords the expected (*E, E*)-dienes **49a** and **49b** in 50 and 90% yield, respectively (Fig. 6.7).

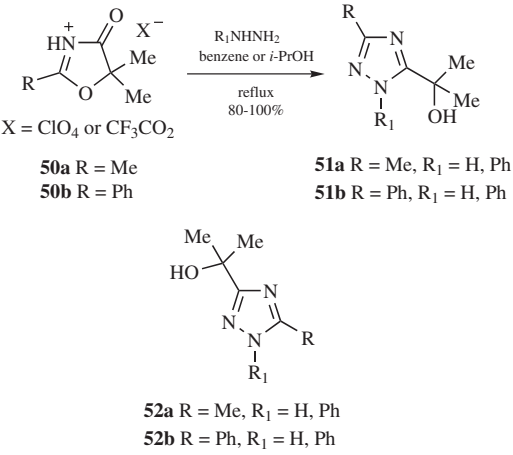
Russian workers[37] reported a high-yield synthesis of the 1,2,4-triazoles **51a** and **51b** from reaction of **50a** or **50b** with hydrazines in a continuation of their earlier



49a R = H
49b R = Me

Figure 6.7. (*E,E*)-Dienes from a 2-methyl-4(5*H*)-oxazolonium perchlorate.

studies (Scheme 6.15). For $R_1 \neq H$ there was no evidence for formation of regioisomers **52a** or **52b** consistent with attack at C-2 by the primary amino group of the hydrazine. The synthesis of triazolium salts and 1,3,5-triazines from reactions of **50a** and **50b** with other hydrazines and guanidines has been described previously.[6]



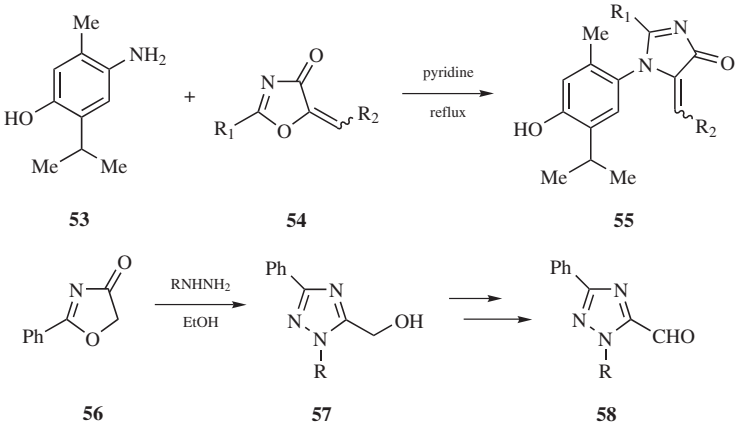
50a R = Me
50b R = Ph

51a R = Me, R_1 = H, Ph
51b R = Ph, R_1 = H, Ph

52a R = Me, R_1 = H, Ph
52b R = Ph, R_1 = H, Ph

Scheme 6.15

Additional examples of the utility of ring cleavage and recyclization of 4(5*H*)-oxazolones to prepare interesting heterocycles have been described (Scheme 6.16). Ttreatment of 4-aminothymol **53** with **54** in refluxing pyridine yields the 4-imidazolidinones **55** evaluated as antimicrobial and antitubercular agents.[38] The authors listed an extensive series of analogues (25 compounds) but reported a yield for only one example, **55** (63% for $R_1 = Ph$, $R_2 = 4\text{-MeO}{-}C_6H_4$). Condensation of 2-phenyl-4(5*H*)-oxazolone **56** with substituted hydrazines affords excellent yields of the 1,2,4-triazoles **57**, important precursors to the previously unknown 1(*H*)-1,2,4-triazole-5-carboxaldehydes **58**.[39] Representative examples are shown in Table 6.3 (Fig. 6.8).

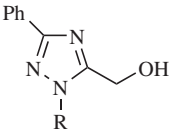


53 **54** **55**

56 **57** **58**

Scheme 6.16

TABLE 6.3. 5-(HYDROXYMETHYL)-3-PHENYL-1*H*-1,2,4-TRIAZOLES FROM 2-PHENYL-4(5*H*)-OXAZOLONE AND HYDRAZINES[a]



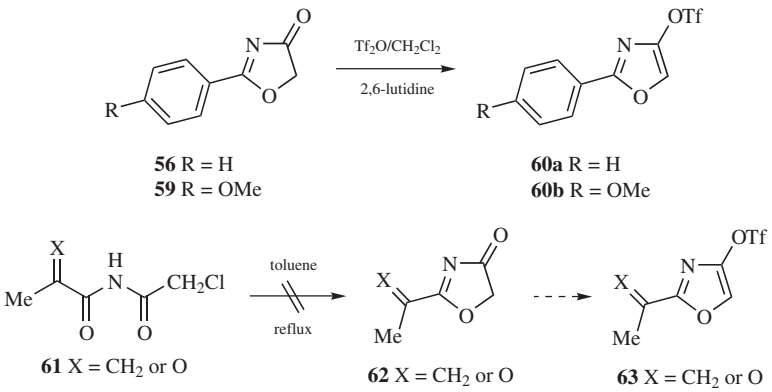
57

Figure 6.8

Entry	R	% Yield
57a	Me	91
57b	Bn	94
57c	Ph	94
57d	4-Me–C_6H_4	87
57e	4-Br–C_6H_4	87
57f	4-NO_2–C_6H_4	95

[a]Data from Ref. 39.

Barrett and Kohrt[40] and Kelly and Lang[41] independently reported the first examples of oxazole triflates (Scheme 6.17). In both cases, the requisite 2-aryl-4(5*H*)-oxazolone, **56** or **59**, was treated with trifluoromethanesulfonic anhydride (Tf_2O) to afford **60a** or **60b**, respectively, which were then coupled successfully with a variety of organostannanes. Kelly and Lang[41] attempted to extend this methodology to prepare the key oxazole triflates **63** in their approach to sulfomycin I. However, they were unexpectedly thwarted when **61** could not be cyclized to the requisite 4(5*H*)-oxazolone precursors **62**.[41] Schaus and Panek[42] described an improved procedure to prepare **56** in 90% yield very recently.



56 R = H
59 R = OMe

60a R = H
60b R = OMe

61 X = CH_2 or O

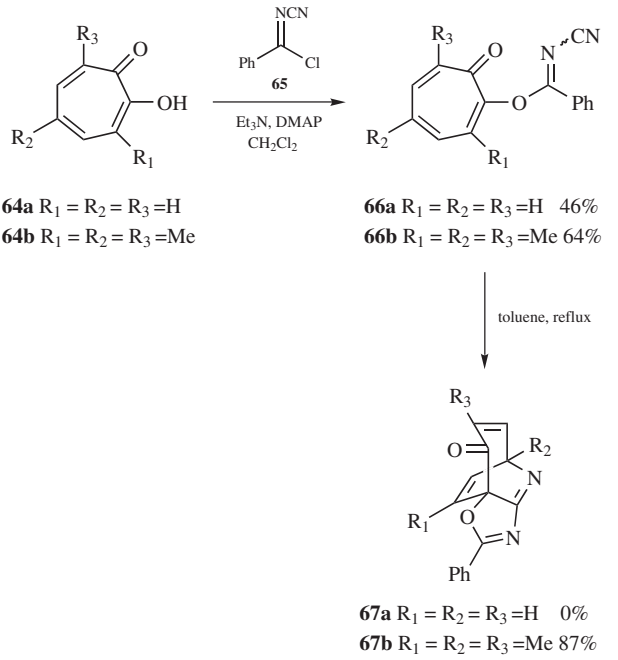
62 X = CH_2 or O

63 X = CH_2 or O

Scheme 6.17

Theoretically, the regioselectivity observed in photochemical [2 + 2] cycloaddition of **56** with 1,1-dimethoxyethene is in good agreement with experimental results and has been explained on the basis of pertubational molecular orbital theory.[43]

Hartke and co-workers[44,45] described an interesting contrast in the reactivity of tropolones in an intramolecular Diels–Alder reaction (Scheme 6.18). Thus, alkylation of **64a** and **64b** with **65** gave **66a** and **66b**, respectively, that were subjected to cyclization in refluxing toluene. Whereas **66a** decomposed under the reaction conditions, **66b** afforded **67b** in high yield.



64a $R_1 = R_2 = R_3 = H$
64b $R_1 = R_2 = R_3 = Me$

66a $R_1 = R_2 = R_3 = H$ 46%
66b $R_1 = R_2 = R_3 = Me$ 64%

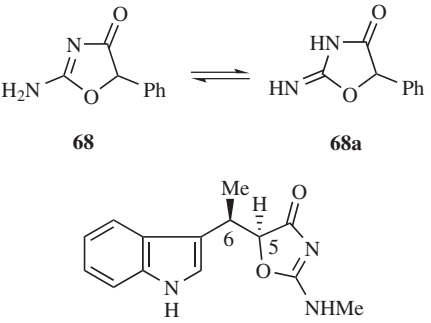
67a $R_1 = R_2 = R_3 = H$ 0%
67b $R_1 = R_2 = R_3 = Me$ 87%

Scheme 6.18

6.3. 2-AMINO-4(5*H*)-OXAZOLONES

6.3.1. Introduction

The synthesis of 2-amino-4(5*H*)-oxazolones has been a very productive area of research since Traube and Ascher[1] first prepared **2** nearly 90 years ago. Subsequently, literally hundreds of analogues have been prepared and evaluated, primarily as medicinal agents. For example, pemoline (Cylert®) **68** (Fig. 6.9), a central nervous system (CNS) stimulant relatively devoid of side affects has been



69

Figure 6.9. Pemoline and indolmycin.

used clinically to treat attention-deficit hyperactivity disorder (ADHD).[46] On the other hand, the naturally occurring analogue, indolmycin **69** (Fig. 6.9), is a potent, selective inhibitor of bacterial tryptophanyl enzyme and, as such, has stimulated interest in the design of new antibacterial agents.[47]

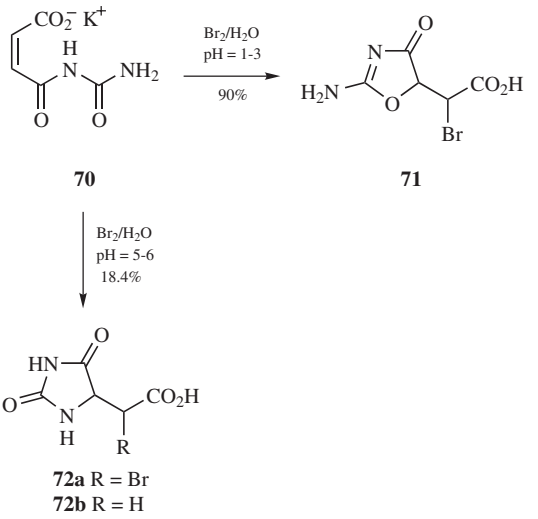
The classical approaches to analogues of **2** were described briefly[3] and reviewed more extensively by Nekrasov[7] and include

- Cyclization of α-hydroxy esters with guanidine.
- Cyclization of α-halo carboxylic acid ureides.
- Cyclization of α-hydroxy or α-halo amides.
- Aminolysis or hydrazinolysis of 2-thiones.
- Displacement of the 2-amino group with primary and secondary amines.
- Alkylation of **2** or other analogues.

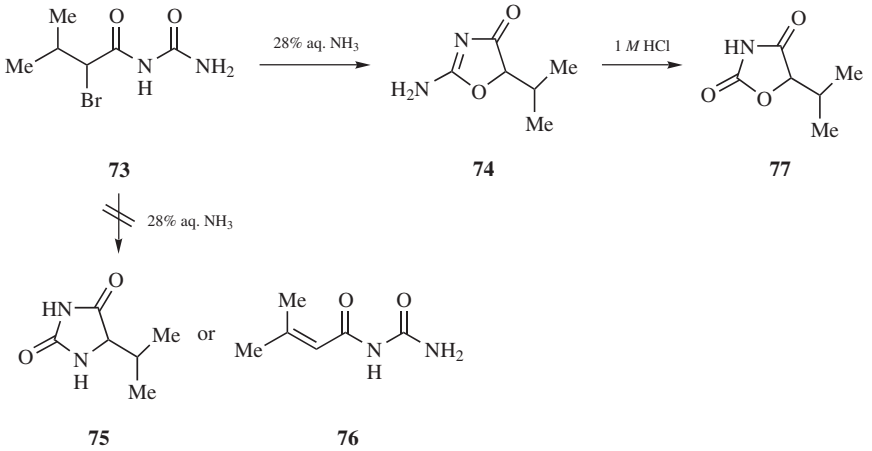
In addition, Rapi and co-workers[13] summarized their investigations of tautomerism in 2-amino-4(5*H*)-oxazolones (Section 6.1 and Fig. 6.1). Interesting extensions of the earlier approaches to **2** as well as discussions of synthetic work related to **68** and **69** will be described in more detail in this section.

6.3.2. Synthesis

The cyclization of α-halo carboxylic acid ureides can be complicated with products from different modes of cyclization. For example, bromination of **70** at low pH affords the 2-amino-4(5*H*)-oxazolone **71** in excellent yield, whereas bromination at pH 5–6 generates a mixture of hydantoins **72** and **73** in poor yield (Scheme 6.19).[48] Japanese workers[49] reported that cyclization of α-bromoisovaleryl-urea with 28% aqueous ammonia yields 2-amino-5-isopropyl-4(5*H*)-oxazolone **74**, not **75** or **76**. The structure of **74** was established spectroscopically and confirmed by hydrolysis to **77** (Scheme 6.20).

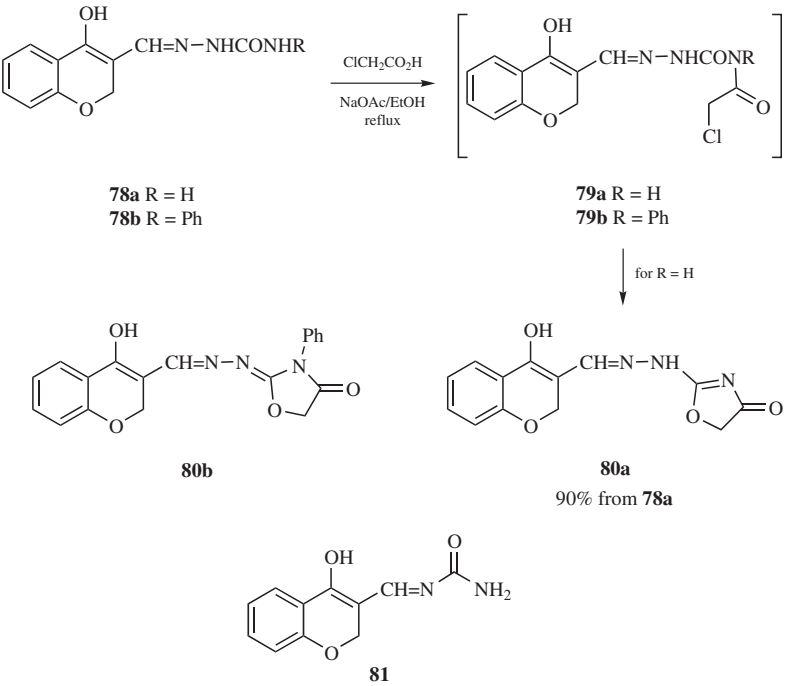


Scheme 6.19



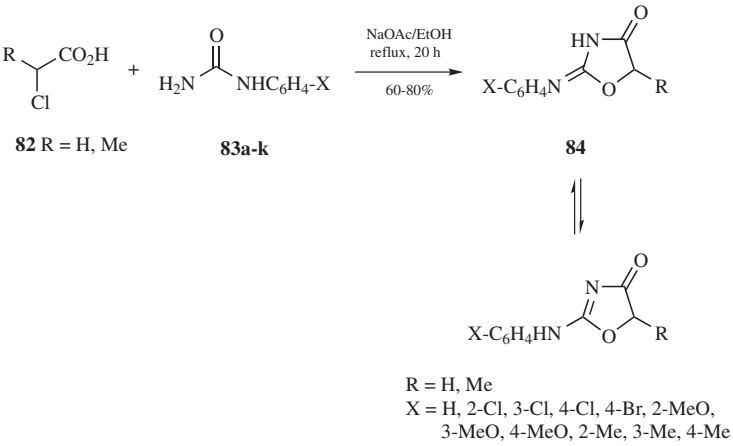
Scheme 6.20

An example of anomalous behavior in closely related systems was reported some time ago during an investigation of the cyclization products derived from coumarin semicarbazones (Scheme 6.21).[50] Thus, **78a** reacted cleanly with chloroacetic acid to yield **79a**, which cyclized to the expected product **80a** upon treatment with sodium acetate. On the other hand, **79b** did not cyclize under the same reaction conditions. This was attributed to the absence of the ''enolizable'' hydrogen (Ph vs. H). The authors did not comment on the possibility of cyclization of **79b** to **80b**. The closely related urea analogue **81** did not react with chloroacetic acid thereby



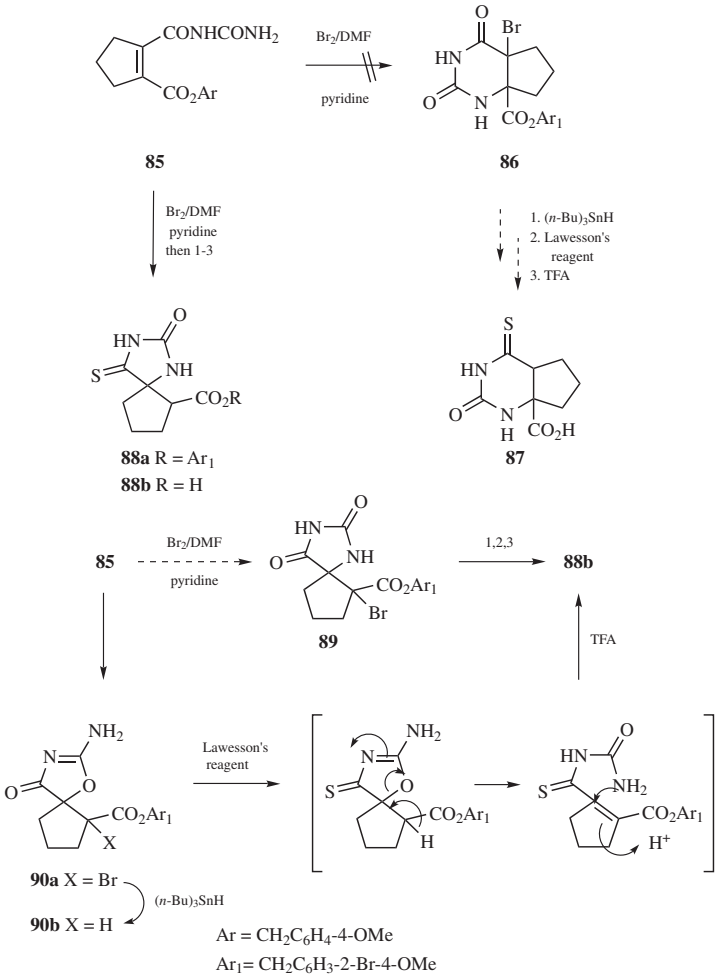
Scheme 6.21

precluding cyclization to the corresponding 2-amino-4(5*H*)-oxazolone. On the other hand, condensation–cyclization of the chloroacetic acids **82** with a series of *N*-aryl ureas **83** afforded good-to-excellent yields of the corresponding 2-(arylimino)-4(5*H*)-oxazolones **84**, which showed some promise as antifungal agents (Scheme 6.22).[51]



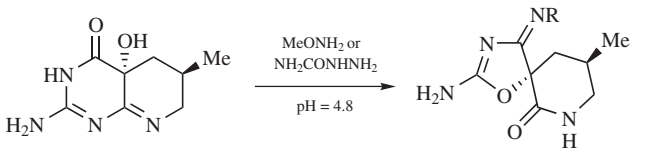
Scheme 6.22

Recently, Manthey, Christopherson, and co-workers[52] unexpectedly isolated a spirocyclic 2-amino-4(5*H*)-oxazolone during their investigations of dihydroorotase inhibitors as potential antimalarial agents (Scheme 6.23). The authors anticipated that bromination of the ureide **85** with concomitant cyclization would yield **86** that would then be converted to the potential dihydroorotase inhibitor **87** as shown. However, the product isolated from this four-step reaction sequence was the thiohydantoin **88b**. It was assumed that bromination of **85** produced the hydantoin **89** that was then converted to **88b** (see above). Surprisingly, the product isolated in 89% yield from the bromination reaction was not **89** but the spirocyclic 2-amino-4(5*H*)-oxazolone **90a** that was treated with tributyltin hydride to afford **90b**. It was postulated that **90b** rearranged to **88a** during the thiation reaction. Subsequent cleavage of the 2-bromo-4-methoxybenzyl group (Ar_1) with trifluoroacetic acid then produced **88b**.



Scheme 6.23

Benkovic and co-workers[53] also isolated spirocyclic 2-amino-4(5*H*)-oxazolones during their studies on pterin-dependent amino acid hydroxylases (Scheme 6.24). Reaction of **91** with *O*-methyl hydroxylamine or semicarbazide at pH 4.8 yielded **92a** and **92b**, respectively. The authors showed that **92** does not simply result from reaction of the corresponding oxazolidinedione with either reagent. Further, by using $H_2{}^{18}O$ as the solvent they demonstrated that there was no ^{18}O incorporation into the product. Two different but precedented mechanisms were proposed to account for this rearrangement. The stereochemistry of **92b** was confirmed by single-crystal X-ray.



91

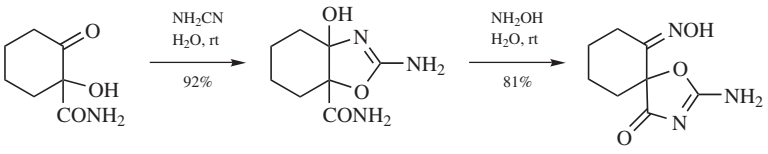
92a R = OMe, 39%
92b R = $NHCONH_2$, 57%

Scheme 6.24

Other examples of spirocyclic 2-amino-4(5*H*)-oxazolones have been prepared and evaluated for their CNS activity and as potential antiviral agents.[54,55] In these reports, cyclization of the appropriate α-hydroxy ester with guanidine afforded the novel analogues **93**, albeit in low-to-modest yields. Representative examples are shown in Table 6.4 (Fig. 6.10).

German workers[56] have also isolated a novel spirocyclic 4(5*H*)-oxazolone **96** in high yield by reaction of **95** with hydroxylamine sulfate (Scheme 6.25). This was part of an investigation of the synthesis and reactions of **95**.

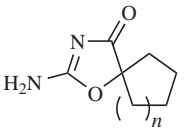
The classical cyclization routes to pemoline **68** and similar 2-amino-4(5*H*)-oxazolone analogues continue to be refined and improved. For example, Japanese workers[57] have prepared an extensive series of heterocyclic analogues, **100**, via several classical routes including cyclization of α-hydroxy esters or activated acids



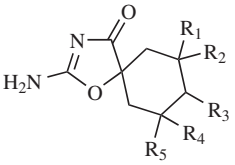
94 **95** **96**

Scheme 6.25

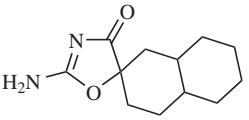
TABLE 6.4. SPIROCYCLIC 2-AMINO-4(5*H*)-OXAZOLONES FROM α-HYDROXY ESTERS AND GUANIDINE



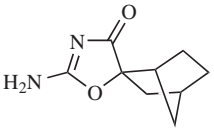
93a-e



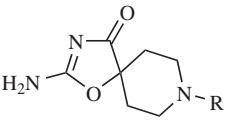
93f-j



93k



93l



93m-q

Figure 6.10

Compound	*n*	%Yield	Reference
93a	0	15	54
93b	1	16	54
93c	2	16	54
93d	3	21	54
93e	4	31	54

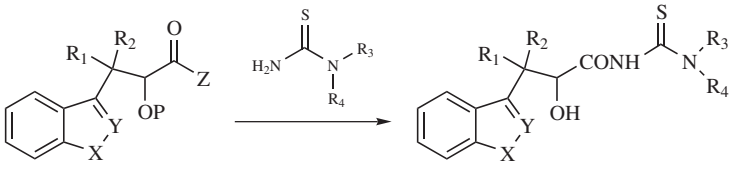
Compound	R_1	R_2	R_3	R_4	R_5	% Yield	Reference
93f	H	H	H	Me	H	11	54
93g	Me	H	H	H	H	31	54
93h	Me	Me	Me	H	H	15	54
93i	Me	Me	H	Me	Me	28	54
93j	Me	H	Me	H	Me	36	54

Compound	% Yield	Reference
93k	13	54
93l	31	54

Compound	R	% Yield	References
93m	H	32[a]	54, 55
93n	$PhCH_2CH_2$	48	54
93o	Bn	50	54
93p	Et	37	54
93q	*i*-Pr	36[a]	54, 55

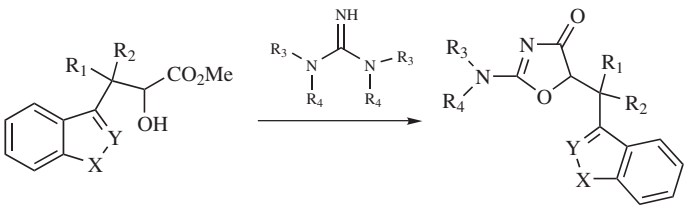
[a]% yield from Ref. 54.

with thioureas or guanidines (Scheme 6.26). Some of these have shown excellent promise as anti-*Heliobacter pylori* agents.



97 **98**

Z = Cl, N_3, OCOR, OSu, OBt, etc.
P = MOM, MEM, MTM, THP, Bn, etc
MOM = methoxymethyl
MEM = 2-methoxyethoxymethyl
MTM = methylthiomethyl
THP = tetrahydropyran-2-yl

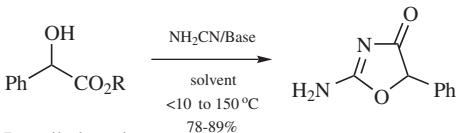


99 **100**

X = NH, O, S; Y = CH or N
R_1 = H or Me; R_2 = H or Me; R_3 = H or Me
R_4 = CONHR, CONHAr, CONHHet, CO_2R, COAr, COHet, COCH=CHHet, SO_2R, SO_2Ar

Scheme 6.26

Subtle yet significant refinements in the stoichiometry and reaction conditions for the base catalyzed reaction of cyanamide with a mandelate ester have been described recently in the patent literature (Scheme 6.27).[58,59] The advantages include fewer impurities and avoidance of the notoriously unstable guanidine free base. In both cases, excellent yields of very pure **68** (up to 99.87A%) have



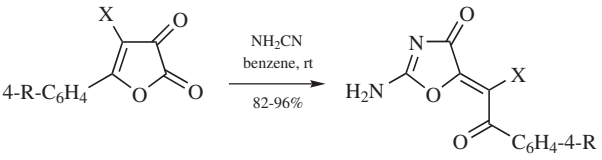
R = alkyl, aryl **68**

Scheme 6.27

been obtained from a wide variety of conditions. Interestingly, it does not appear to be critical to prepare a single enantiomer of **68** since rapid epimerization of the benzylic hydrogen "obscures any potential enantioselective pharmacology."[46] However, very recently, Bonk and co-workers[60] described a spontaneous resolution of the enantiomers of pemoline with >96% enantiomeric excesses possible.

Chinese workers[61] reported the first separation of the enantiomers of **68** using cyclodextrin-mediated capillary zone electrophoresis (CZE). Enantioselective high-performance liquid chromatography (HPLC) separations employing chiral stationary phases have been an area of intense investigation. Armstrong's group[62] recently demonstrated this technique as applied to **68** using a covalently bonded macrocylic antibiotic, ristocetin A as the chiral stationary phase.

Nekrasov and co-workers[63,64] prepared 2-amino-5-substituted-4(5*H*)-oxazolones **102** as part of a program to investigate the chemistry of 2,3-dihydrofuran-2,3-diones (Scheme 6.28). The target oxazolones were evaluated as antispasmodics, analgesics, antiinflammatory agents, antihypoxic agents, and antimicrobial agents. Thus, ring opening of a 5-substituted 2,3-dihydrofuran-2,3-dione **101** with cyanamide followed by recyclization affords the desired 2-amino-5-substituted-4(5*H*)-oxazolones **102** in excellent yields.

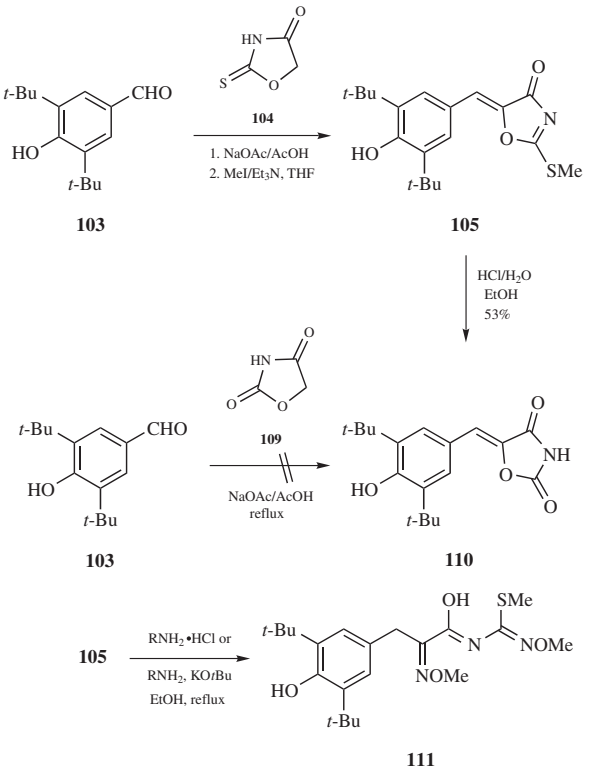


101 **102**

X = H, Br, Me
R = H, MeO, Cl, Me

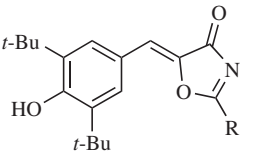
Scheme 6.28

Displacement of a suitable leaving group is a usually reliable method to introduce a nitrogen substituent at C-2 although there can be considerable variation in the yields.[3,7] Recently, reports have employed this methodology to prepare substituted di-*tert*-butylphenols for evaluation as dual 5-lipoxygenase and cyclooxygenase inhibitors or as selective cyclooxygenase-2 inhibitors (Scheme 6.29).[65–67] Knoevenagel condensation of **103** with **104** followed by methylation gave **105**. Examples of products obtained from **105** by displacement with hydroxylamines **106**, cyanamide **107**, and guanidine **108**, respectively, are shown in Table 6.5 (Fig. 6.11). Interestingly, attempts to prepare **110** by Knoevenagel condensation of **103** with **109** failed. However, hydrolysis of **105** afforded **110** in acceptable yield. The unusual ring-opened product **111** was isolated from reaction of **105** with *O*-methyl hydroxylamine in refluxing ethanol. The structure of **111** was confirmed by X-ray crystallography.



Scheme 6.29

TABLE 6.5. 5-(BENZYLIDENE)-2-SUBSTITUTED-4(5*H*)-OXAZOLONES FROM 5-(BENZYLIDENE)-2-(METHYLTHIO)-4(5*H*)-OXAZOLONE

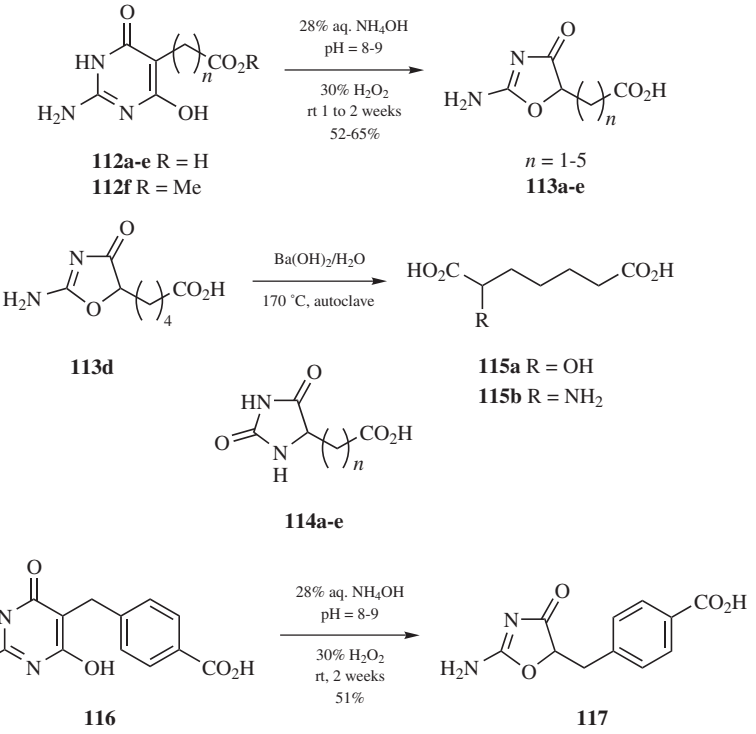


106 - 108

Figure 6.11

Compound	R	Conditions	% Yield	References
106a	NHOH	NHOH · HCl, KO*t*Bu/EtOH, rt	13	67
106b	NHOMe	NHOMe · HCl, KO*t*Bu/EtOH, 0 °C to rt	29	67
106c	NHOEt	NHOEt · HCl, KO*t*Bu/EtOH, −30 °C	7	67
106d	NHOallyl	NHOallyl · HCl, KO*t*Bu/EtOH, −40 °C	18	67
107	NHCN	NH_2CN, KO*t*Bu/EtOH, reflux	38	66
108	NHC(=NH)NH_2	$NH_2C(=NH)NH_2$ · HCl, KO*t*Bu/EtOH, reflux	55	65, 66

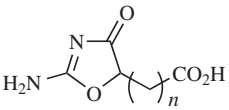
Czech workers[68] described an interesting oxidative ring contraction that affords 2-amino-5-(carboxyalkyl)-4(5*H*)-oxazolones **113a–e** (Scheme 6.30; Table 6.6, Fig. 6.12). Prolonged reaction of an ω-(2-amino-6-hydroxy-4-oxo-3,4-dihydropyrimidine-5-yl)alkane acid or ester **112a–f** with 30% hydrogen peroxide in concentrated aqueous ammonia gave **113a–e** in 52–65% yield. The structures of **113a–e** were confirmed spectroscopically. The authors ruled out the isomeric hydantoins **114a–e** as possible products based on the following evidence. Hydrolysis of **113d** ($n = 4$) gave **115a**, whereas hydrolysis of the isomeric hydantoin **114d** ($n = 4$) would have yielded **115b**. Finally, the hydantoins were independently synthesized and were clearly different from the isolated products. Conversion of **116** to **117** was effected in comparable yield.



Scheme 6.30

Mechanistically, the authors proposed initial hydroxylation at C-5 followed by anion formation of the 5-hydroxyl group, attack at C-2 and rearrangement to the 2-amino-4(5*H*)-oxazolone upon work-up (Scheme 6.31). To support this premise they oxidized **112d** to **118**, which rearranged to **113d** upon exposure to 5% aqueous ammonia at room temperature, consistent with previous work.[69]

TABLE 6.6. 2-AMINO-5-(CARBOXYALKYL)-4(5*H*)-OXAZOLONES FROM OXIDATIVE RING CONTRACTION OF 2-AMINOPYRIMIDINONES[a]

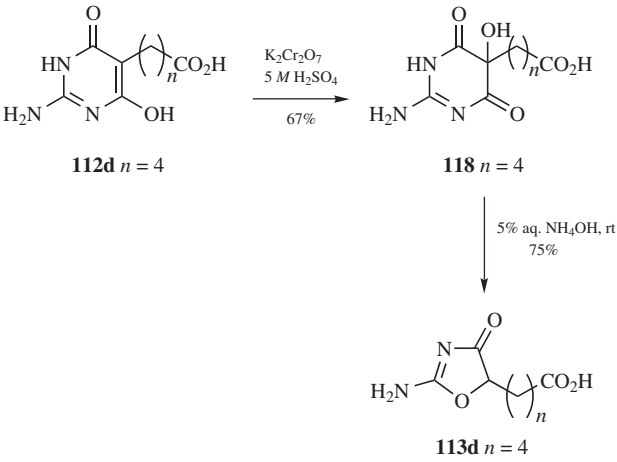


113a-e

Figure 6.12

Compound	*n*	% Yield
113a	1	58
113b	2	52
113c	3	60
113d	4	60–65
113e	5	62

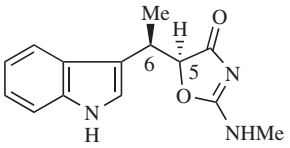
[a]Data from Ref. 68.



112d $n = 4$ **118** $n = 4$ **113d** $n = 4$

Scheme 6.31

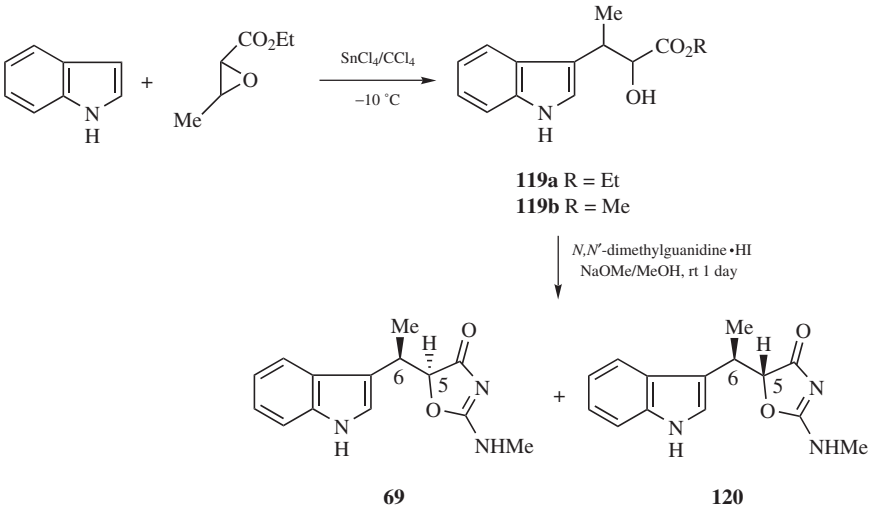
The naturally occurring 4(5*H*)-oxazolone antibiotic indolmycin **69** (Fig. 6.13) has been a focus of several synthetic programs since the structure was first elucidated by Schach von Wittenau and Els nearly 40 years ago.[70] These syntheses can be broadly classified as either involving classical cyclization to construct the 4(5*H*)-oxazolone ring or as elaboration of an existing 4(5*H*)-oxazolone. The classical cyclization routes will be discussed at this time, whereas routes involving elaboration of an existing 4(5*H*)-oxazolone will be described in Section 6.3.3.



69

Figure 6.13. Indolmycin.

The first, and one of the most straightforward, syntheses of racemic **69** was that of Schach von Wittenau and Els[70] after they had determined the structure. Friedel–Crafts alkylation of indole with ethyl 2,3-epoxybutyrate gave the α-indolmycenic acid ester **119a**. Cyclization of **119a** with *N*,*N*′-dimethylguanidine yielded both **69** and isoindolmycin **120** (Scheme 6.32). In this case, facile epimerization of H-5 had occurred under the basic cyclization conditions.

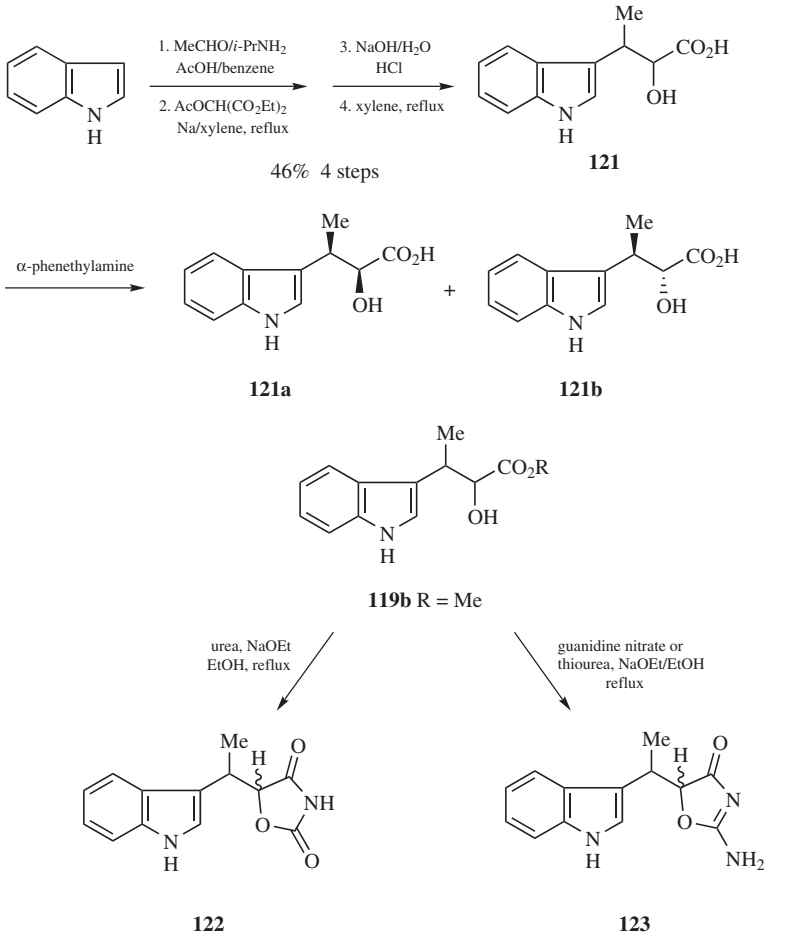


119a R = Et
119b R = Me

69 **120**

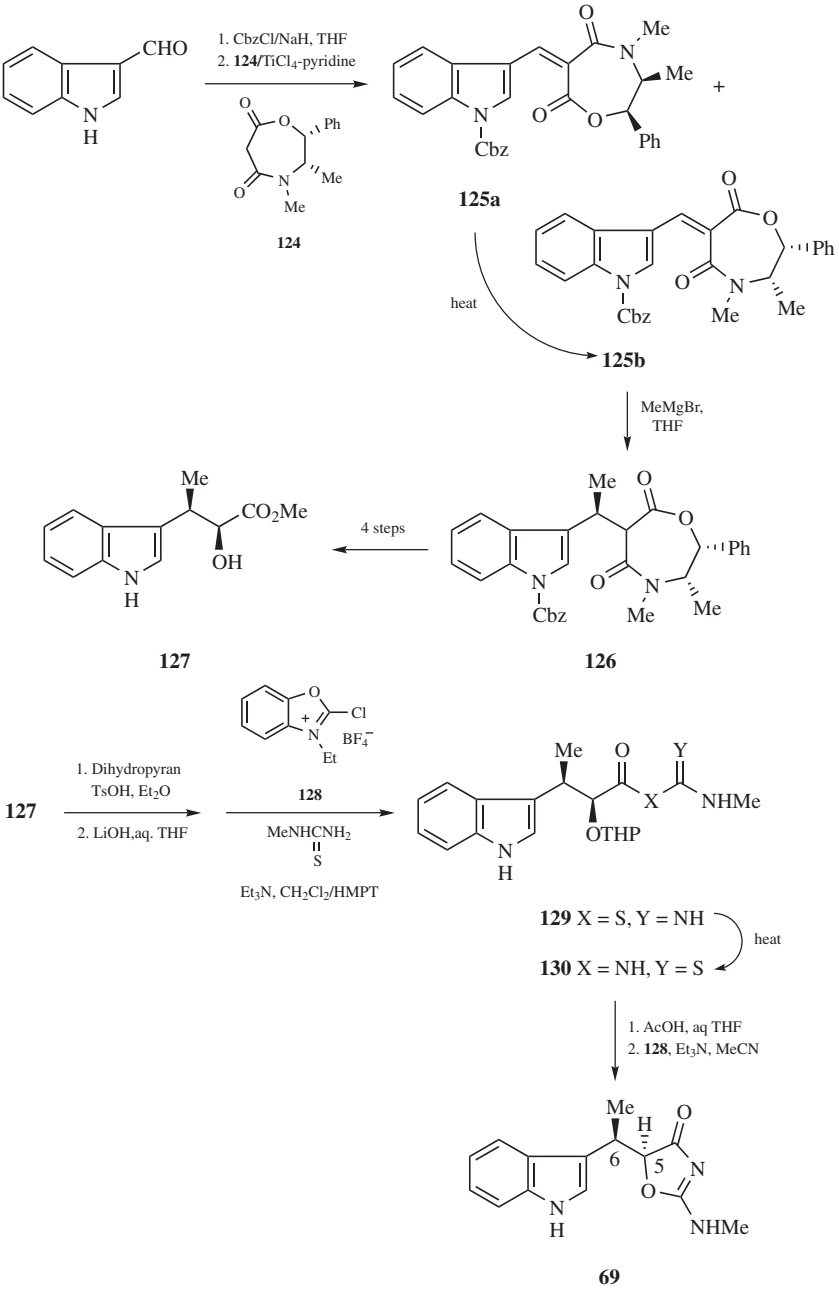
Scheme 6.32

Preobrazhenskaya and co-workers[71] employed a similar cyclization strategy in their synthesis of optically active indolmycin (Scheme 6.33). Conversion of indole to the requisite indolmycenic acids **121** was uneventful. Resolution of **121** with α-phenethylamine yielded α-indolmycenic acid **121a** and β-indolemycenic acid **121b**. These were separated, independently esterified with diazomethane and then cyclized with *N*,*N*′-dimethylguanidine to afford **69** and **120**, which were separated by fractional crystallization. In addition, these authors also prepared **122** and **123** from cyclization of **119b** with urea or thiourea and guanidine, respectively. Shortly after this work, Chan and Hill[72] reported the absolute configuration of **69** to be (5*S*, 6*R*).



Scheme 6.33

Mukaiyama and Takeda[73] described the first asymmetric synthesis of **69** in which **127** was obtained utilizing their methodology to prepare enantiomerically enriched 3-substituted alkanoic acids (Scheme 6.34).[74,75] In their approach, 3-formylindole was first protected as the carbobenzyloxy (Cbz) derivative and then treated with **124** to yield **125a** and **125b** as a 1.5 : 1 ratio of (*Z*/*E*) isomers. Thermal isomerization of **125a** to **125b** followed by addition of methylmagnesium bromide gave **126**, which was transformed into **127** in four steps. With the synthesis of **127** secured, they turned their attention to prepare the 4(5*H*)-oxazolone using conditions that would preclude epimerization at C-5. Thus, protection of the alcohol and saponification followed by a benzoxazolium **128** mediated coupling with *N*-methylthiourea gave a mixture of **129** and **130**. Thermal rearrangement of the isothiourea **129**, hydrolysis of the tetrahydropyran-2-yl (THP) protecting group and now, a benzoxazolium **128** mediated ring closure completed the synthesis of **69**.

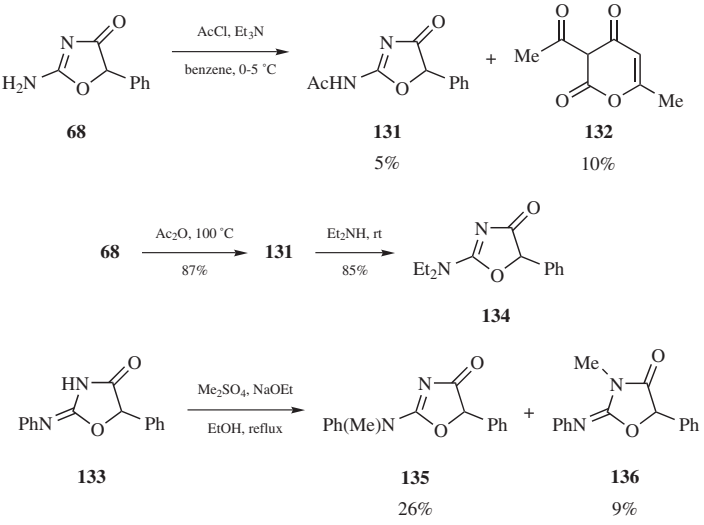

1. CbzCl/NaH, THF
2. 124/TiCl4-pyridine
124
125a
heat
125b
MeMgBr, THF
4 steps
126
127
1. Dihydropyran TsOH, Et2O
2. LiOH,aq. THF
128
MeNHCNH2
S
Et3N, CH2Cl2/HMPT
129 X = S, Y = NH
130 X = NH, Y = S
heat
1. AcOH, aq THF
2. 128, Et3N, MeCN
69

Scheme 6.34

6.3.3. Reactions

2-Amino-4(5*H*)-oxazolones can react with or without ring opening depending upon the reaction conditions.[3,7] Examples of synthetically useful reactions without ring cleavage include hydrolysis to 2,4-oxazolidinediones, transamination of the 2-amino group with primary and secondary amines, and aldol condensations with aromatic aldehydes. However, in some cases, simple alkylation or acylation reactions are complicated by regioselectivity issues and frustratingly poor yields. Similarly, Mannich reactions can yield multiple and sometimes unexpected products. Hydrolysis can affect ring cleavage to produce both α-hydroxy acids and α-hydroxy amides although this is not usually a synthetically useful process. On the other hand, hydrolytic ring cleavage with concomitant recyclization can be a useful method to prepare hydantoins. Hydrazinolysis also affects ring cleavage to afford intermediate acylamino guanidines that undergo cyclodehydration to generate 5-(α-hydroxyalkyl)-1,2,4-triazolines. Recent representative examples of some of these reactions together with noncyclization approaches to indolmycin **69** will be described in this section.

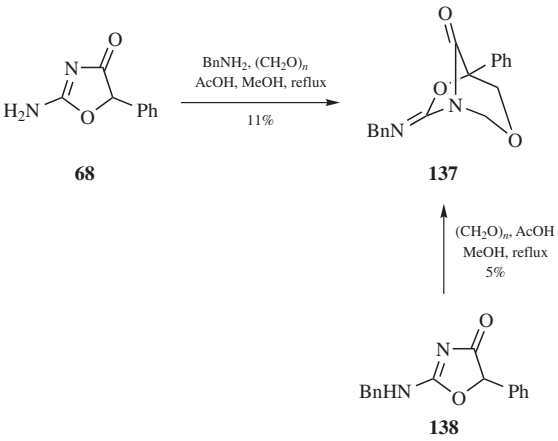
The frustrating and sometimes capricious nature of simple reactions of 2-amino-4(5*H*)-oxazolones is exemplified in the following reports. Ramsh and co-workers[76] acetylated **68** with acetyl chloride in benzene but isolated both a poor yield and a poor mass balance of **131** together with dehydroacetic acid **132**. Attempts to transaminate **131** with diethylamine in the absence of a solvent or with aniline in benzene failed. The authors recovered **68**, which is in stark contrast to an earlier report from Hansen and Masch[77] that acetylation of **68** with acetic anhydride gave **131** in 87% yield. In addition, these same authors reported that reaction of **131** with diethylamine at room temperature gave **134** in excellent yield (Scheme 6.35).



Scheme 6.35

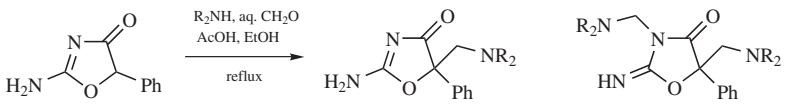
Finally, Ramsh and co-workers[78] methylated **133** and isolated a 3:1 mixture of **135** and **136** albeit, in only 35% combined yield. The Russian authors offered a much different mechanistic rationale to account for these results than earlier work.[79]

Mannich reactions of **68** lead to markedly different results depending on the amine component (Schemes 6.36; 6.37). For example, **137** was isolated in poor yield after refluxing a mixture of **68**, benzylamine, paraformaldehyde, and acetic acid in methanol.[80] The same material was also prepared from **138** under similar conditions. In a continuation of this work, Ramsh and co-workers[81] investigated reactions using other primary and secondary amines. When **68** was treated with an excess of formalin and a secondary amine either **139** or **140** was isolated, albeit in fair to modest yield. However, some primary amines gave rise to the oxazolo[3,2-*a*]1,3,5-triazines **141a–d**, whereas other primary amines led to the



68 **137** **138**

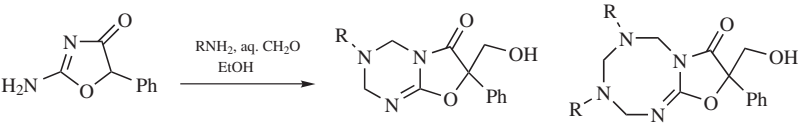
Scheme 6.36



68

139a R = Et, 30%
139b R = $(CH_2)_5$, 11%

140a R = Pr, 14%



68

141a R = *n*-Bu, 5%
141b R = *t*-Bu, 12%
141c R = $Me_2NCH_2CH_2$, 3%
141d R = Ph, 100%

142a R = Me, 9%
142b R = cyclohexyl, 6%

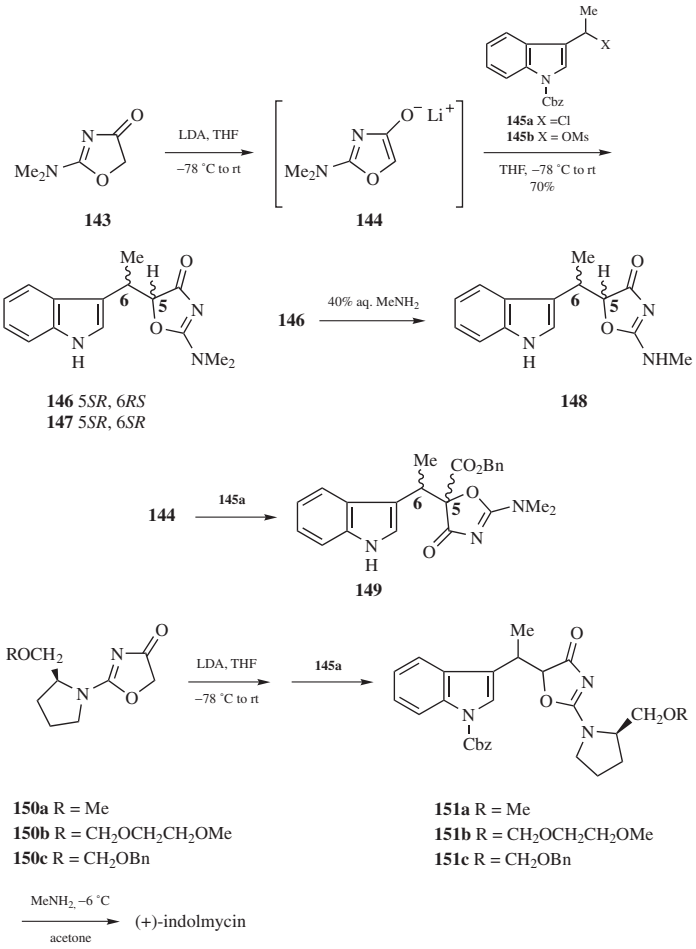
Scheme 6.37

oxazolo[3,2-*a*]1,3,5,7-tetrazocines **142a** and **142b**. Among these bicyclic analogues only **141d**, derived from aniline, was isolated in a synthetically useful yield.

Lee and co-workers[82] reported an interesting example of a conjugated polymer obtained by polymerizing 5-phenyl-2-(propynylamino)-4(5*H*)-oxazolone in the presence of palladium or platinum chlorides. The authors predict this unique material may have applications for polymer electrolytes, semiconductors, and nonlinear optical (NLO) materials.

Indolmycin continues to attract the interest of synthetic chemists as a lead compound for preparation of new antibacterial agents. As such, considerable effort has been expended to develop shorter, more efficient syntheses that can be readily adapted for preparation of analogues.

A Pfizer group[83] described the first preparation of **148** that did not involve a late stage construction of the 4(5*H*)-oxazolone (Scheme 6.38). Instead, their strategy



Scheme 6.38

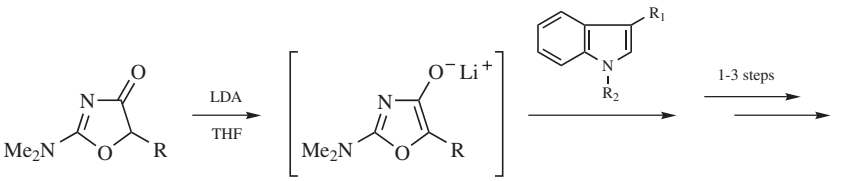
employed **143** as a key intermediate to install this ring system very early in the synthetic scheme. Thus, treatment of **143** with lithium diisopropylamide (LDA) gave the enolate **144**, which was alkylated with **145a** to afford a 2.2:1 mixture of the diastereomers **146** and **147** in 70% yield. These were separated chromatographically and **146** was converted quantitatively into racemic indolmycin **148**.

However, efforts to adapt this strategy for an asymmetric synthesis of **69** were uniformly disappointing. All attempts to prepare an optically active alkylating agent **145a** (X = Cl) gave completely racemic material. A model study for alkylation of **144** with racemic **145b** (X = OMs) yielded the unexpected 5-carbobenzyloxy derivative **149** thereby precluding this approach. Preparation of **150a–c** incorporating a proline chiral auxillary was straightforward. Alkylation of these analogues with **145a** gave **151a–c** from which amine exchange with methylamine under nonepimerizing conditions afforded (+)-indolmycin. However, the enantiomeric excess (ee) was a disappointing 9–17%. Nonetheless, the authors demonstrated an overall strategy that was efficient and convergent requiring only five steps to prepare racemic indolmycin in 34% yield.

More recent syntheses of indolmycin derivatives and analogues have also capitalized on the strategy of the Pfizer group (see above). For example, Witty and co-workers[84] utilized **143** and **152** to prepare a series of analogues that were evaluated as inhibitors of *Staphylococcus aureus* (Scheme 6.39). In their work, the lithium enolates **144** and **153** were reacted with **145a** and **154a–g** followed by a straightforward reaction sequence to yield the target compounds **148** and **155–163**. The respective diastereomers of **148**, **155**, **156**, and **159–163** were separated chromatographically and evaluated individually. In all cases, the diastereomers with the same relative stereochemistry as indolmycin were the most active.

This same group[47] also utilized **144** in their attempts to prepare the conformationally restricted indolmycin analogue **164**. Initially, the authors envisioned construction of the [5,6,6] tricylic ring on a fully elaborated intermediate containing a 4(5*H*)-oxazolone side chain (Scheme 6.40). Conversion of 2-methyl-3-nitrobenzoic acid to the requisite indole precursor **165** was readily accomplished in five steps. Reaction of **165** with **144** gave **166** quantitatively, isolated as a mixture of diastereomers. However, at this point the strategy to prepare the [5,6,6] tricyclic ring system was completely frustrated by their inability to functionalize or eliminate the tertiary hydroxyl group. Ultimately, **166** was converted to the open-chain indolymycin homologue **167** without incident.

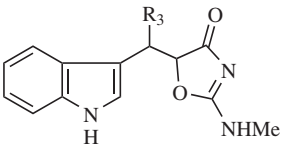
An alternative strategy involving addition of **144** to an appropriately functionalized tricyclic system proved to be successful (Scheme 6.41). In this approach, protection of the indole nitrogen fortuitously proved unnecessary. Conversion of **168** to the unstable iodide **169a** or to the phenylselenide **169b** was straightforward. The key intermediate unsaturated oxindole **170** was isolated in 50% overall yield from **169b**. Only one racemic diastereomer **171** of four possible pairs was isolated from low-temperature addition of **144** to **170**. Conversion of **171** to the target **172** occurred without detectable epimerization at C-8 or C-11. The C-8 (*S*), C-11 (*S*) relative stereochemistry was confirmed crystallographically. Complete



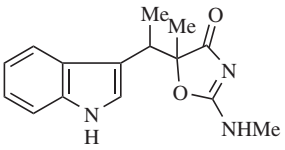
143 R = H
152 R = Me

144 R = H
153 R = Me

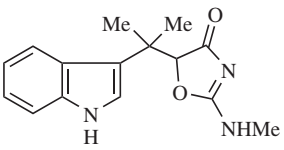
145a R_1 = CHClMe, R_2 = Cbz
154a R_1 = CHClEt, R_2 = Cbz
154b R_1 = $CF(Me)_2$, R_2 = Cbz
154c R_1 = $CH_2NMe_3^+$, R_2 = H
154d R_1= CH=$CHCO_2t$Bu, R_2 = TBDMS
154e R_1 = CH=$CHNO_2$, R_2 = SEM
154f R_1 = CHO, R_2 = TBDMS
154g R_1 = COMe, R_2 = TBDMS



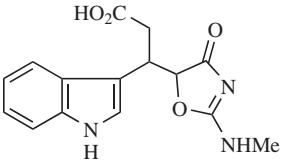
148 R_3 = Me
155 R_3 = Et
158 R_3 = H
162 R_3 = OH



156



157



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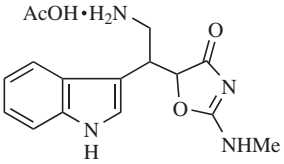
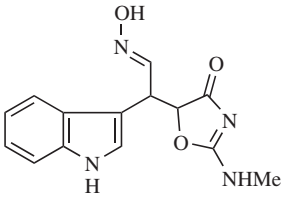
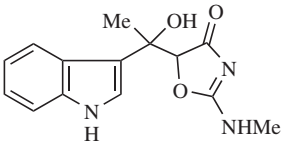


160

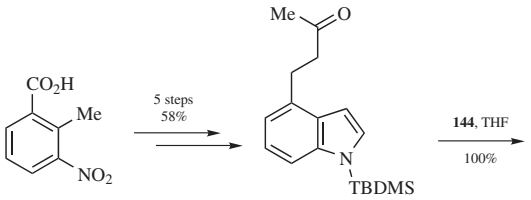


161



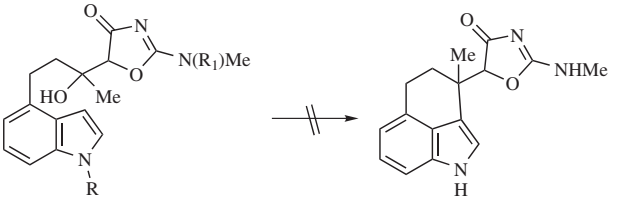
163

Scheme 6.39



165

TBDMS = *tert*-butyldimethylsilyl



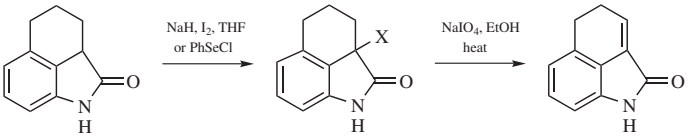
2 steps
85%

166 R = TBDMS, R_1 = Me

167 R = R_1 = H

164

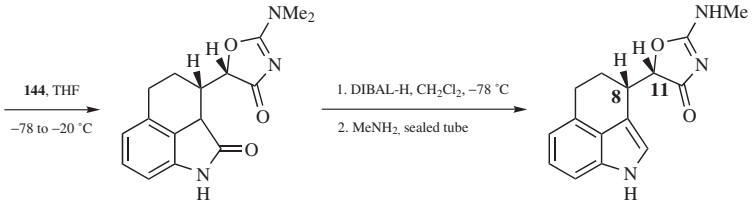
Scheme 6.40



168

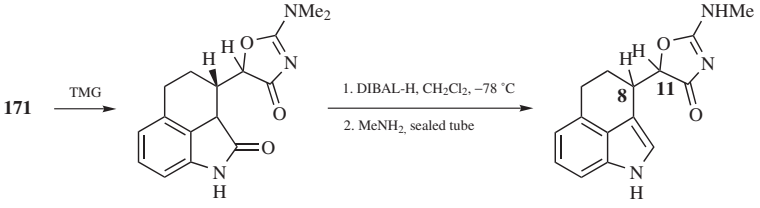
169a X = I
169b X = SePh

170



171

172



173

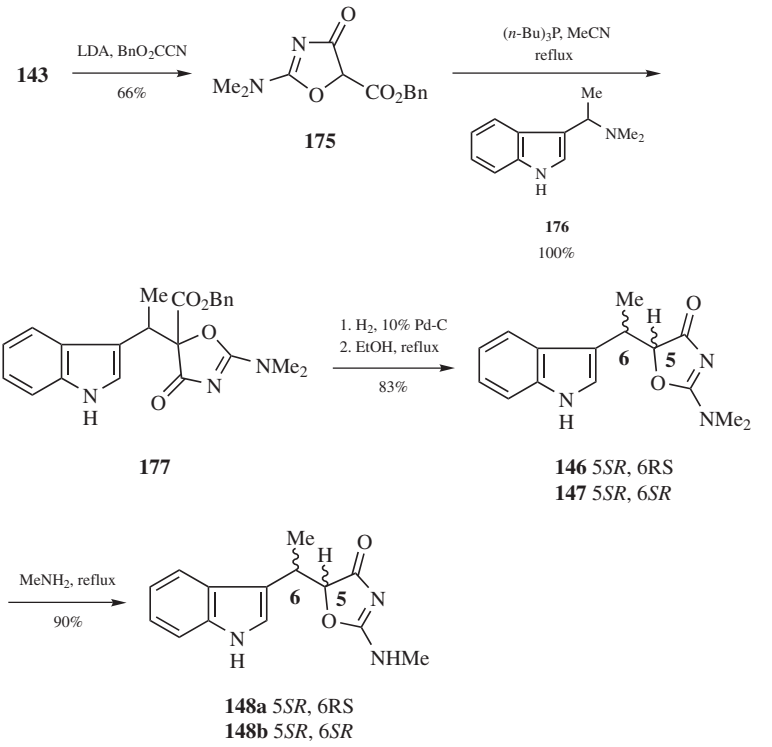
174

TMG = 1,1,3,3-tetramethylguanidine

Scheme 6.41

epimerization occurred at C-11 to produce **173** when **171** was treated with tetramethylguanidine.

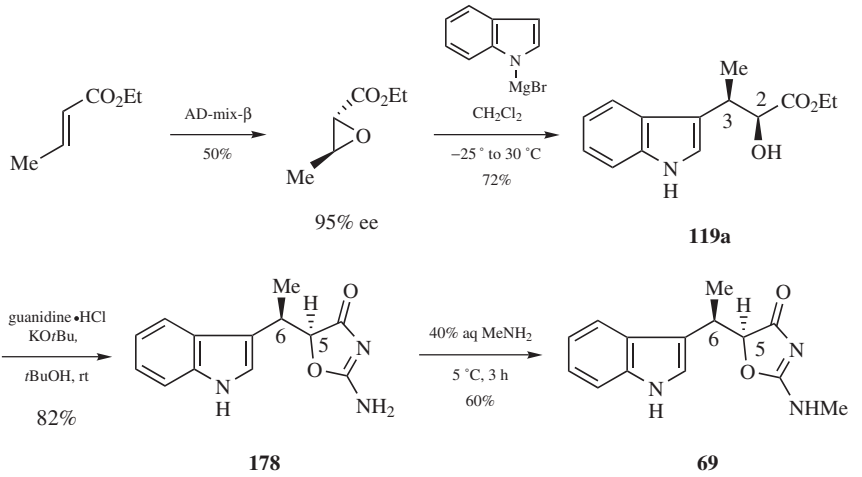
Recently, Shue[85] described further refinements and improvements to the Pfizer strategy (Scheme 6.42). Acylation of **143** with benzyl cyanoformate gave the requisite starting 4(5*H*)-oxazolone **175**. Alkylation of **175** with the gramine analogue **176** yielded **177** quantitatively from which **146** and **147** were obtained as a 1:1.5 mixture of diastereomer pairs. After chromatographic separation each pair was converted independently to (±)-indolmycin **148a** and (±)-isoindolmycin **148b**. This synthesis requires four steps to produce **148a** in 47% overall yield from readily available starting materials.



Scheme 6.42

Very recently, Kamiyama and co-workers[86] described a stereocontrolled synthesis of **69** based on Schach von Wittenau and Els original route.[70] In this newer approach (Scheme 6.43), ethyl crotonate was converted to ethyl (2*S*, 3*R*)-2,3-epoxybutanoate using the commercially available asymmetric dihydroxylation mixture, AD-mix-β (Aldrich Chemical Company). The epoxide was then ring opened with indolemagnesium bromide to give ethyl (2*S*, 3*R*)-2-hydroxy-3-(indol-3-yl)butanoate **119a** in very good yield. Cyclization of **119a** with guanidine at room temperature afforded **178** in which the 4(5*H*)-oxazolone ring was created

without epimerization at C-5. Finally, amine exchange then completed the synthesis of **69**.



Scheme 6.43

6.4. 2-ALKOXY-4(5*H*)-OXAZOLONES AND 2-HYDROXY-4(5*H*)-OXAZOLONES (2,4-OXAZOLIDINEDIONES)

6.4.1. Introduction

There are only a few reports of 2-alkoxy-4(5*H*)-oxazolones and these are limited to highly substituted 4-(arylimino)-2-ethoxy- or 4-(alkylimino)-2-ethoxy-analogues.[87–89] There are no reports of a 2-hydroxy-3-unsubstituted-4(5*H*)-oxazolone that exists as a hydroxy tautomer **179a**–**179d**. Rather, the predominant tautomer for a 2-hydroxy-3-unsubstituted-4(5*H*)-oxazolone is the 2,4-oxazolidinedione, **179** (Fig. 6.14).[5] For example, Codding[90] determined the structure of 5,5-diphenyl-2,4-oxazolidinedione to be **180** by X-ray crystallography. More recently, Japanese workers[91] crystallographically determined the structure of 5-(4-methoxybenzylidene)-2,4-oxazolidinedione to be **181** during their studies of hydrogen-bonding effects in potential nonlinear optical materials.

In principle then, these saturated imides and derivatives are beyond the scope of this chapter. However, the synthesis and reactions of some 3-unsubstituted derivatives of **179** are included in the interest of completeness. No attempt has been made to provide an exhaustive review of all examples of 2,4-oxazolidinediones.[92] Rather, selected examples from the recent literature that illustrate general synthetic approaches or novel reactions are described.

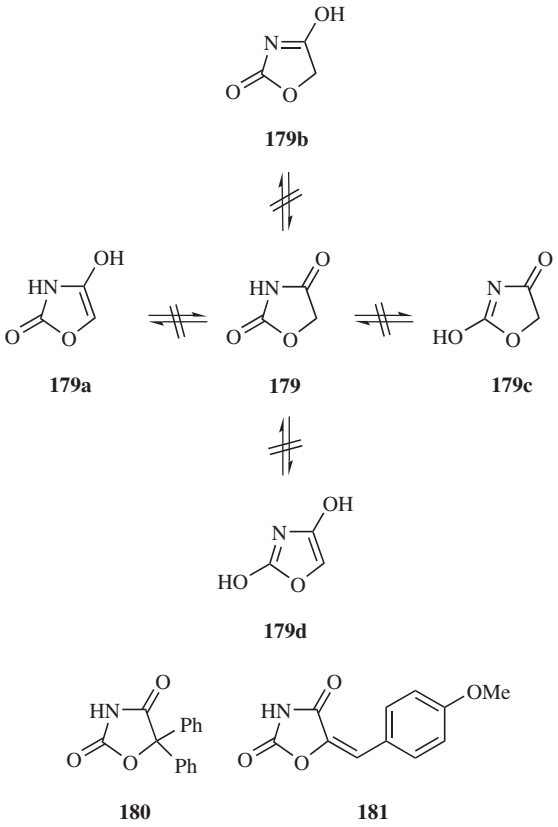
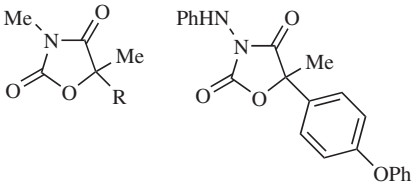


Figure 6.14. 2,4-Oxazolidinedione tautomers.

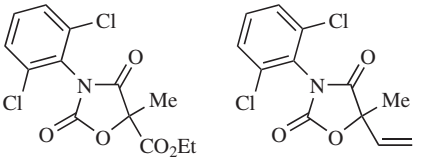
Derivatives that are 3-substituted such as the antiepileptic agents, trimethadione (Tridione®), **182a**, or dimethadione (Paradione®), **182b**, the fungicides, famoxadone (Famoxate®), **183**, chlozolinate, **184** and the herbicide vinchlozolin, **185** are beyond the scope of this chapter (Fig. 6.15). Nonetheless, Refs. 93–100 and references cited therein contain an interesting description of the syntheses and reactions of such analogues. In addition, the reader should also consult the following selected references for further examples.

- 3-Alkyl- or 3-aryl-2,4-oxazolidinediones via photochemical cyclization,[101] organonickel-mediated carbonylation,[102] cyclization of *N*-alkenyl-α-acetamides,[103] carboxylation and cyclization of 2-propynamides,[104] cyclization of *O*-carbamates of α-hydroxy acetic acids and esters,[105,106] cyclization of α-hydroxy acetamides,[107] and catalytic asymmetric dihydroxylation (ADH) of *N*-alkenoyl-2-oxazolidinones.[108]
- 3-(Arylideneamino)-2,4-oxazolidinediones via cyclization of arylidine benzilic acid hydrazides[109] and 3-amino-2,4-oxazolidinediones from perhydro-1,5,2-dioxazine-3,6-diones.[110]



182a R = Me
182b R = Et

183



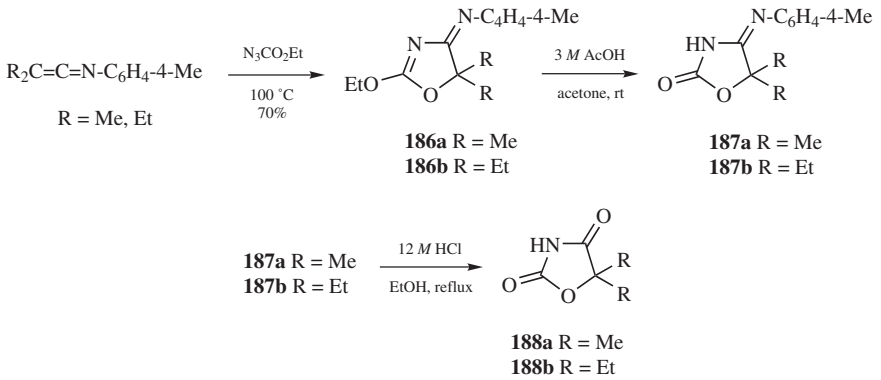
184 **185**

Figure 6.15. 3-Substituted 2,4-oxazolidinediones.

- 3-Alkoxy-2,4-oxazolidinediones via cyclization of *N*-alkoxy-2-hydroxycarboxamides,[111,113–116] and cyclization of 2-hydroxycarbohydroxamic acids.[112]

6.4.2. 2-Alkoxy-4(5*H*)-Oxazolones

Kauffman[87] prepared the 2-ethoxy-4-(*p*-tolylimino) derivatives **186a** and **186b** by thermolysis of ethyl azidoformate in the presence of keteneimines. Mild acid hydrolysis afforded **187a** and **187b** that were independently converted to 5,5-dimethyl- and 5,5-diethyl-2,4-oxazolidinedione, **188a** and **188b**, respectively, upon more vigorous hydrolysis. Interestingly, **187a** and **187b** were recovered unchanged after refluxing 8 h in 6 *M* hydrochloric acid (Scheme 6.44).



186a R = Me
186b R = Et

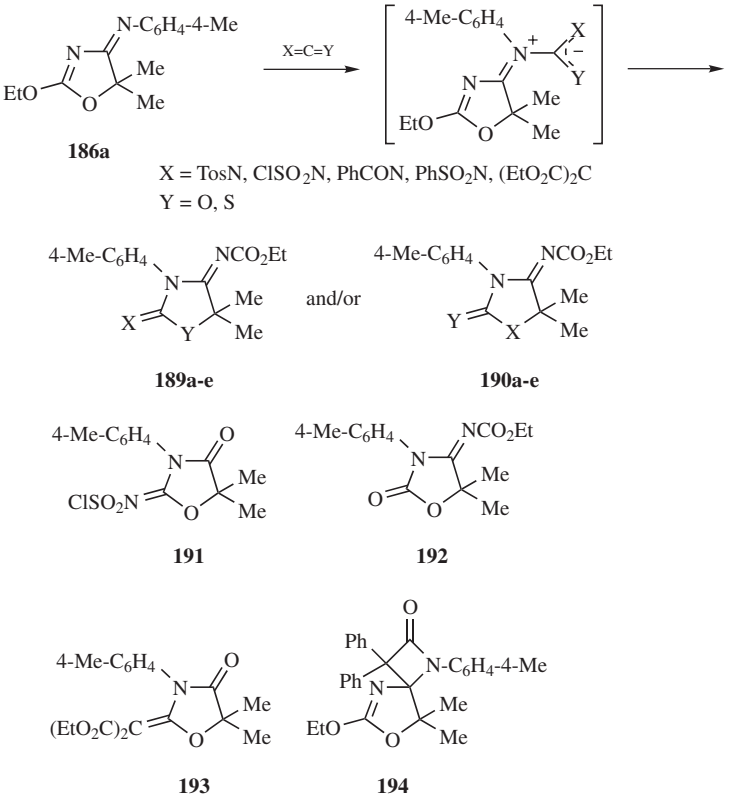
187a R = Me
187b R = Et

187a R = Me
187b R = Et

188a R = Me
188b R = Et

Scheme 6.44

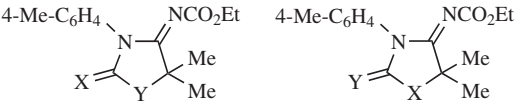
L'abbé and co-workers[88] described reactions of **186a** with a variety of heterocumulenes (X=C=Y) to generate **189a–e** and/or **190a–e** (Table 6.7, Fig. 6.16). The authors proposed a ring-opening cycloaddition that is mechanistically related to the Boulton-Katritzky rearrangement.[117] Reaction of **186a** with chlorosulfonyl isocyanate also produced the hydrolysis product **191** that was the only isolable product after chromatographic purification. Chromatographic purification of **189c** affected hydrolysis of the benzamide yielding only **192**. Similarly, **193** was isolated as the sole product from reaction of **186a** with bis(ethoxycarbonyl)ketene, whereas diphenylketene reacted with **186a** to give the spirocyclic adduct, **194** (Scheme 6.45). No cycloadducts were isolated from phenyl isocyanate, phenyl isothiocyanate, benzoyl isothiocyanate, methyl acrylate, methyl vinyl ketone, or acrylonitrile.



Scheme 6.45

This same group[89] also investigated the thermolysis of α-bromo amidines as a means to prepare 2-alkoxy-4(5*H*)-oxazolones. Here, an α-bromo imide **195a** or **195b** was converted to the corresponding amidine **196a** or **196b**, which upon

TABLE 6.7. BOULTON-KATRITZKY REARRANGEMENT PRODUCTS FROM 5,5-DIMETHYL-2-ETHOXY-4-(*p*-TOLYLIMINO)-4(5*H*)-OXAZOLONE AND HETEROCUMULENES[a]



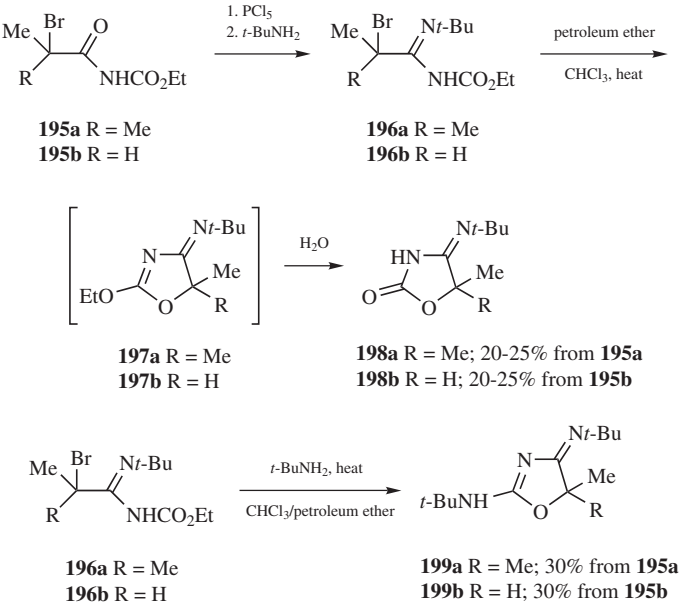
189 **190**

Figure 6.16

X	Y	Compound	% Yield	Compound	% Yield	Conditions
TosN	O	**189a**	11%	**190a**	47	benzene, reflux, 7 days
$ClSO_2N$	O	**189b**	25%	**191**	20	benzene, 70 °C
PhCON	O	**189c**	34%			MeCN, reflux
$PhSO_2N$	S			**190d**	76	benzene, 75 °C
TosN	S			**190e**	71	benzene, 75 °C
$(EtO_2C)_2C$	O			**193**	17	benzene, 80 °C

[a]Data from Ref. 88.

heating, eliminated hydrogen bromide with concomitant cyclization and produced the intermediate 2-ethoxy-4(5*H*)-oxazolone **197a** or **197b**. Hydrolytic work-up of **197a** or **197b** then afforded **198a** or **198b**. Thermolysis of **196a** or **196b** in the presence of *tert*-butylamine produced **199a** or **199b** (Scheme 6.46).



195a R = Me
195b R = H

196a R = Me
196b R = H

197a R = Me
197b R = H

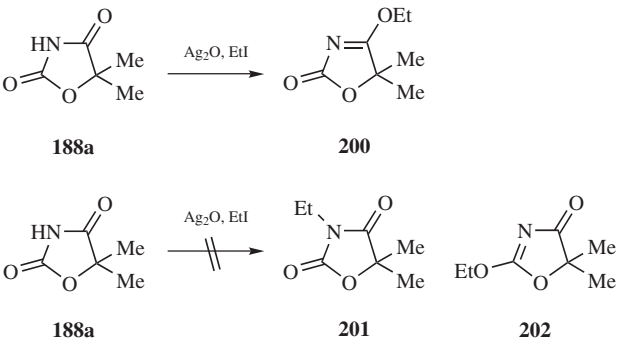
198a R = Me; 20-25% from **195a**
198b R = H; 20-25% from **195b**

196a R = Me
196b R = H

199a R = Me; 30% from **195a**
199b R = H; 30% from **195b**

Scheme 6.46

There are no reports that alkylation of a 2,4-oxazolidinedione generates a 2-alkoxy-4(5*H*)-oxazolone. Alkylation of the sodium or potassium salt of a 2,4-oxazolidinedione was described >50 years ago and is an excellent means to prepare the corresponding *N*-alkyl derivatives.[118–121] Reaction of the silver salt of 5,5-dimethyl-2,4-oxazolidinedione **188a** with ethyl iodide was shown to yield 5,5-dimethyl-4-ethoxy-2(5*H*)-oxazolone **200**[118,119] and not **201** as originally reported.[122] There was no evidence for the formation of 5,5-dimethyl-2-ethoxy-4(5*H*)-oxazolone **202** (Scheme 6.47). Further examples of 4-alkoxy-5-substituted-4(5*H*)-oxazolones will be described in Section 6.4.3.1.



Scheme 6.47

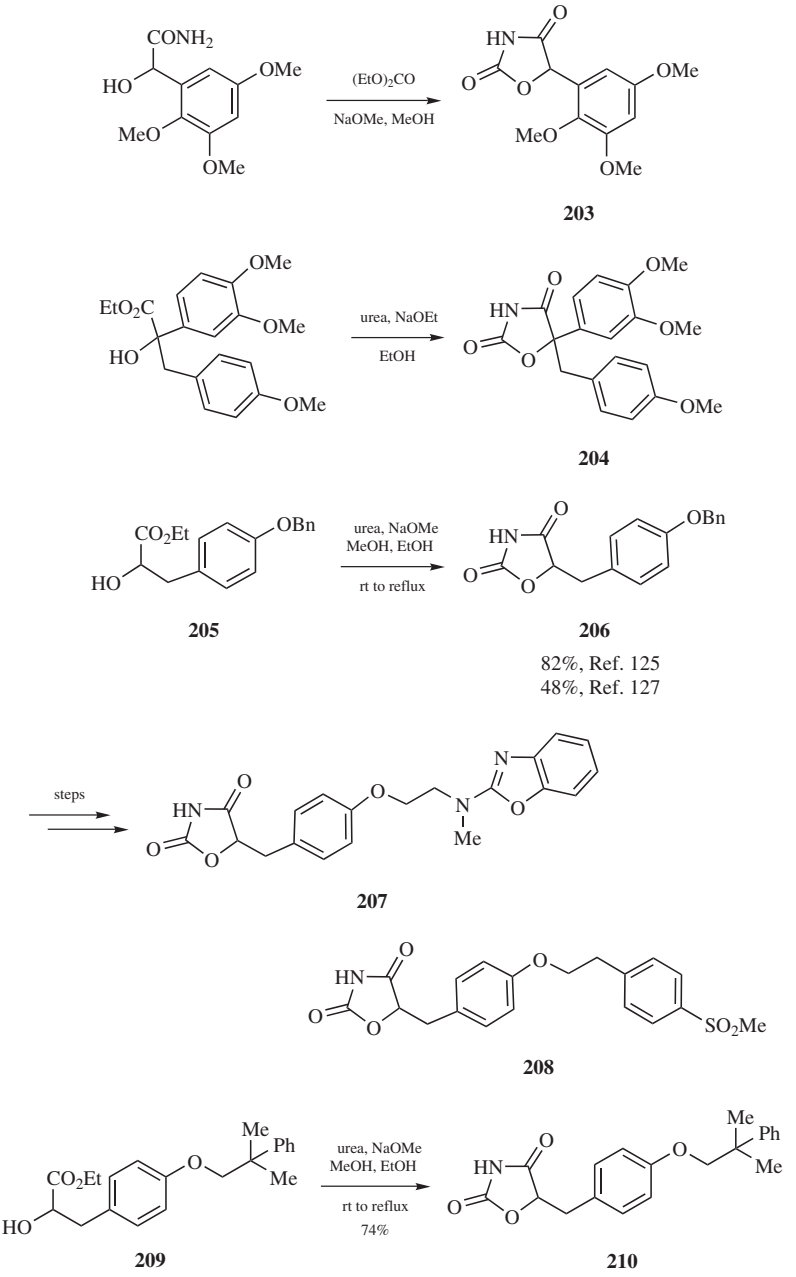
6.4.3. 2-Hydroxy-4(5*H*)-Oxazolones (2,4-Oxazolidinediones)

6.4.3.1. Synthesis

The most versatile syntheses of 3-unsubstituted-2,4-oxazolidinediones involve either cyclization of α-hydroxy esters with urea or cyclization of α-hydroxy amides with a carbonate or phosgene.[5] A third very useful approach is cyclodehydration of *O*-carbamoyloxy acetic acids. Normally, this method affords 3-substituted analogues in which the 3-substitutent is derived from an isocyanate.[5,99] However, examples in which an α-*O*-carbamoyloxy ester has been prepared via chlorosulfonyl isocyanate or an equivalent will also be described in this section. Extensions of these methodologies together with new approaches to 2,4-oxazolidinediones follow. Many of the analogues prepared, particularly as potential antidiabetic agents, employ α-hydroxy esters or α-hydroxy amides as precursors, which provides clear evidence of the versatility and generality of these classical approaches. A selection of recent examples will illustrate this point.[123–129]

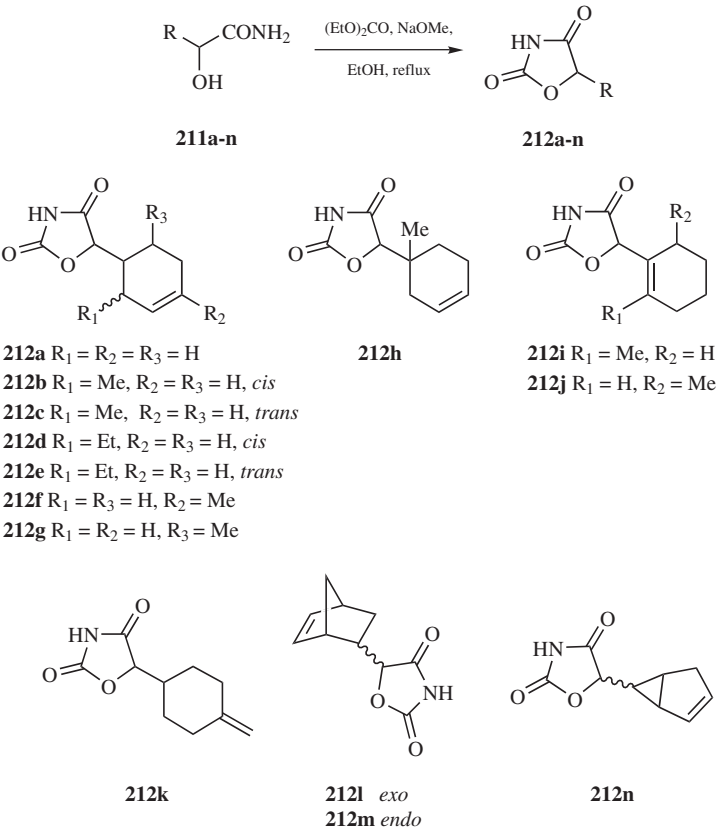
Sánchez-Viesca and co-workers[123,124] employed both synthetic routes to prepare **203** and **204** (Scheme 6.48). Cyclization of **205** was used to prepare **206**, a key intermediate in the synthesis of potential antihyperglycemic agents like **207** and

208.[125–127] Alternatively, Japanese workers[128] cyclized **209**, a fully elaborated analogue of **205** and prepared **210**, which was also evaluated as an antidiabetic agent.



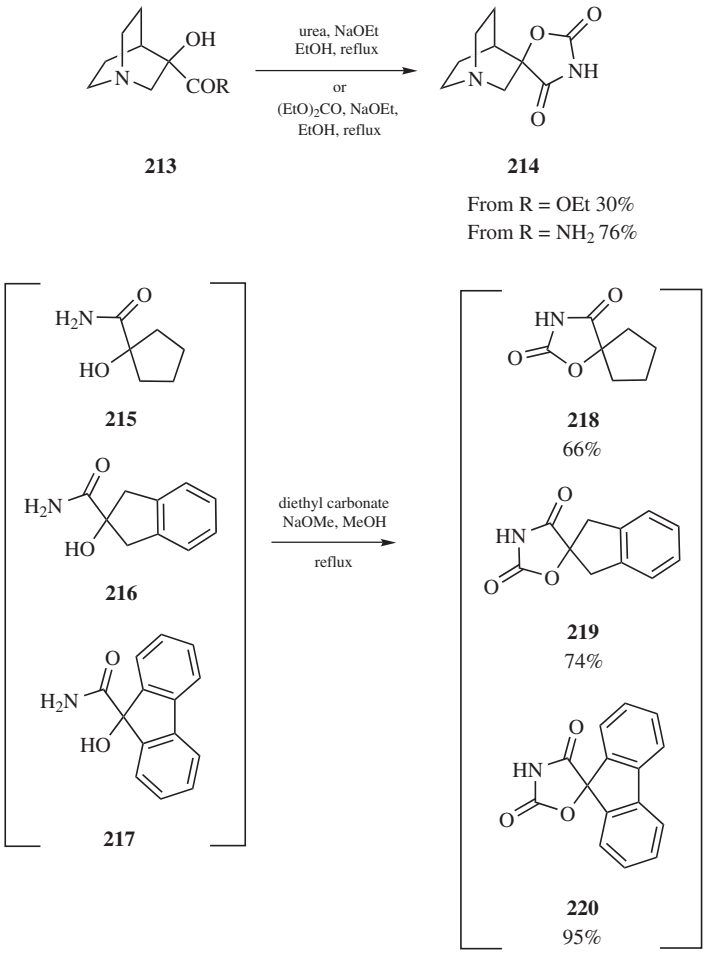
Scheme 6.48

Pfizer chemists[129] prepared a novel series of 5-substituted-2,4-oxazolidinediones **212a–n** via cyclization of the corresponding α-hydroxy amides, **211a–n** (Scheme 6.49). Among the derivatives prepared, **212a–d**, **212g**, **212h**, **212l**, and **212m** showed statistically significant hypoglycemic activity.



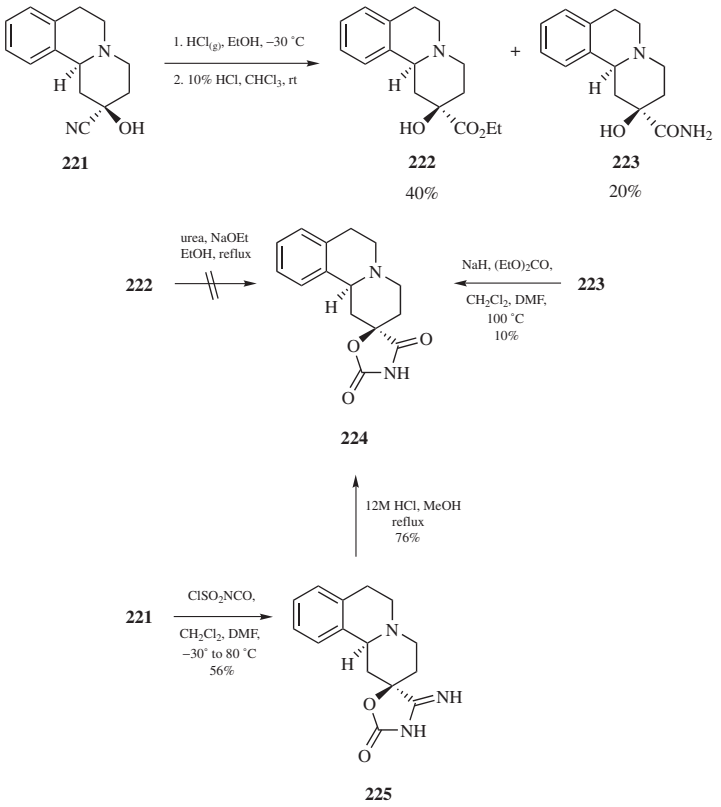
Scheme 6.49

Spriocyclic analogues of 2,4-oxazolidinediones are readily prepared via either methodology although not always in comparable yield or efficiency (Scheme 6.50). For example, Trigo and co-workers[130] cyclized ethyl 3-hydroxyquinuclidine-3-carboxylate, **213** (R = OEt) with urea to furnish **214** in fair yield. In contrast, cyclization of the corresponding α-hydroxy amide, **213** ($R = NH_2$) afforded **214** in 76% yield. This same group[131] found that cyclization of the α-hydroxy amides, **215–217** afforded **218–220** in 66–95% yields. This improvement was significant relative to their earlier work using the corresponding α-hydroxy esters.[132]



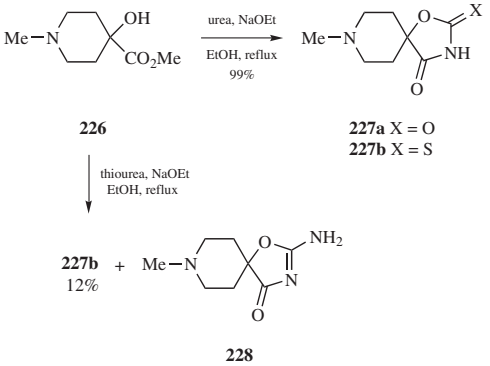
Scheme 6.50

Söllhuber and co-workers[133] also described similar results during their work on ester and sulfonamide bioisosteres (Scheme 6.51). Here, multiple attempts to prepare the spirocyclic 2,4-oxazolidinedione **224** via cyclization of **222** failed completely, starting material was recovered. Alternatively, cyclization of **223** afforded **224** in poor yield. The solution to this problem was treatment of the cyanohydrin **221** with chlorosulfonyl isocyanate to generate **225** from which **224** was isolated after hydrolysis. The trans quinolizidine ring junction was supported by ^{13}C NMR data together with the presence of Bohlmann bands[134] in the IR spectrum. The stereochemistry of **225** (2*R*, 11b*S*) was based on the ^{1}H NMR spectrum that shows a deshielding affect on the chemical shift of the 11b proton. This finding was attributed to the presence of the C-4′ imino group.



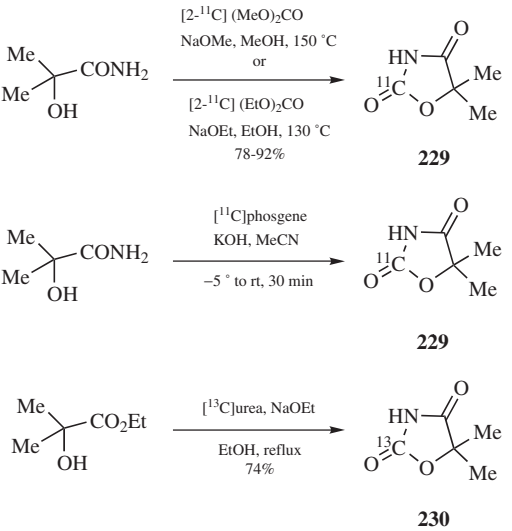
Scheme 6.51

Spirocyclic 2,4-oxazolidinedione analogues have been prepared and evaluated as cholinergic agents by Japanese workers (Scheme 6.52).[135] For example, condensation of the α-hydroxy ester **226** with urea produced **227a** quantitatively, whereas reaction with thiourea afforded **227b** in poor yield together with **228**.



Scheme 6.52

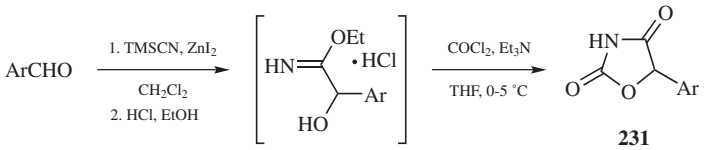
Radiolabeled analogues of dimethadione (Paradione®) **182b** have been synthesized employing both cyclization methods (Scheme 6.53). Ginos and co-workers[136] condensed [2-^{11}C]dimethyl carbonate with 2-hydroxyisobutyramide to prepare [2-^{11}C]5,5-dimethyl-2,4-oxazolidinedione **229** for positron emission tomography (PET) studies. Independently, French chemists[137] employed the same strategy to prepare **229** using [2-^{11}C]diethyl carbonate. In both cases, these groups reported comparable chemical and radiochemical yields. Shortly thereafter, Ginos[138] reported the results of synthetic approaches to **229** with or without dimethyl carbonate as a carrier. With excess dimethyl carbonate as a carrier, **229** was obtained in higher yields and purity but with a lower specific activity. Diksic[139] showed that [^{11}C]phosgene condensed rapidly with 2-hydroxyisobutyramide using powdered potassium hydroxide in acetonitrile to afford **229** in 40–60% radiochemical yield with extremely high chemical (98%) and radiochemical (99%) purity. This ''no-carrier-added'' approach was superior to previous methods in that no high temperatures (130–150 °C) or extensive HPLC purification was required. A Japanese group[140] has prepared [2-^{13}C]5,5-dimethyl-2,4-oxazolidinedione **230**, the penultimate precursor to [2-^{13}C]trimethadione via condensation of [^{13}C]urea with ethyl α-hydroxyisobutyrate.



Scheme 6.53

Schnur and colleagues at Pfizer[141–145] prepared a wide variety of 2,4-oxazolidinediones that have been evaluated as hypoglycemic agents and as aldose reductase inhibitors (Tables 6.8, Fig. 6.17; 6.9, Fig. 6.18; Fig. 6.19). Several approaches were evaluated including a trimethylsilylcyanide-mediated synthesis of cyanohydrins that were then converted to the corresponding imidates *in situ* followed by cyclization and work-up. This methodology has been successfully

TABLE 6.8. 5-ARYL-2,4-OXAZOLIDINEDIONES FROM CYCLIZATION OF α-HYDROXY IMIDATES[a]



231

Figure 6.17

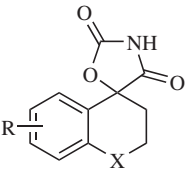
Ar	% Yield
2-MeO–C_6H_4–	42
2-F–C_6H_4–	60
2-EtO–C_6H_4–	70
5-Cl-2-MeO–C_6H_3–	69
5-F-2-MeO–C_6H_3–	60
2-Cl–C_6H_4–	68
3-Cl–C_6H_4–	56
2-MeO-5-NO_2–C_6H_3–	60
3-F–C_6H_4–	56
2-Me–C_6H_4–	77
2-CF_3–C_6H_4–	54
3-PhO–C_6H_4–	66
2-BnO–C_6H_4–	55
3-CF_3–C_6H_4–	53
2-Cl-6-MeO–C_6H_3–	74
2-Cl-6-F–C_6H_3–	83
2-MeO-5-Me–C_6H_3–	63
Ph–	62
2-MeO–6-NO_2–C_6H_3–	86
2,6-di-F–C_6H_3–	57

[a]Data from Ref. 143.

applied to the synthesis of 5-aryl derivatives **231** as well as spirocyclic analogues **232a** and **232b**.[143,144] Other spirocyclic derivatives **232c–f** were prepared from an imidate using 1,1′-carbonyldiimidazole (CDI).[145] Furanyl- and thienyl-C-5 substituted analogues **233** were also prepared via an α-hydroxy imidate. In contrast, analogues such as **234** were derived from base-catalyzed ring contraction of alloxans.[141] Other 5-heteroaryl-2,4-oxazoloidinediones prepared by Schnur and co-workers include **235–240**.[142]

Doya[146] disclosed an improved process for preparation of 2,4-oxazolidinediones from α-hydroxy esters and urea in a recent patent. The process effects condensation of the starting materials using a metal oxide, for example, lead oxide at 100–250 °C followed by fractional distillation to recover any unreacted α-hydroxy ester. The product is then isolated by distillation. The recovered starting material can be recycled. 5-Methyl-2,4-oxazolidinedione, **212** (R = Me) was isolated in 80.4% yield of 99.4% purity in this manner.

TABLE 6.9. SPIROCYCLIC 2,4-OXAZOLIDINEDIONES FROM CYCLIZATION OF α-HYDROXY IMIDATES[a]

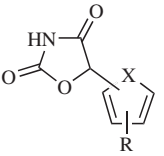


232

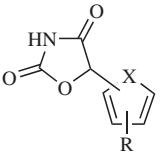
Figure 6.18

Structure	R	X	% Yield
232a	H	O	57
232b	6-Cl	O	79
232c	6-Br	O	38
232d	H	S	45
232e	6-F	S	41
232f	H	CH_2	28

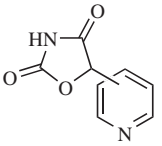
[a]Data from Ref. 144.



233a X = O; furan-2-yl; R = H, Cl, Br,
233b X = O; furan-3-yl; R = H
233c X = S; thien-2-yl; R = H, Me, Ph, F, Cl, Br, EtO
233d X = S; thien-3-yl; R = H, F, Br, MeO, MeS



234a X = O; furan-2-yl; R = MeO, Me, Ph,
234b X = O; furan-3-yl; R = H, I
234c X = S; thien-2-yl; R = H, MeO
234d X = S; thien-3-yl; R = H



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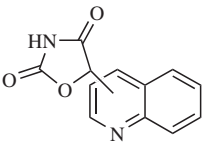

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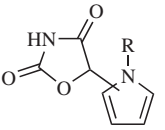

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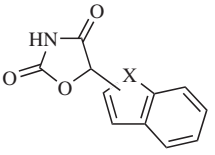
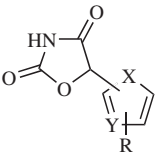
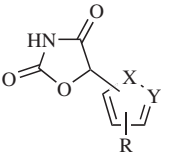


238a X = NR
238b X = O
238c X = S

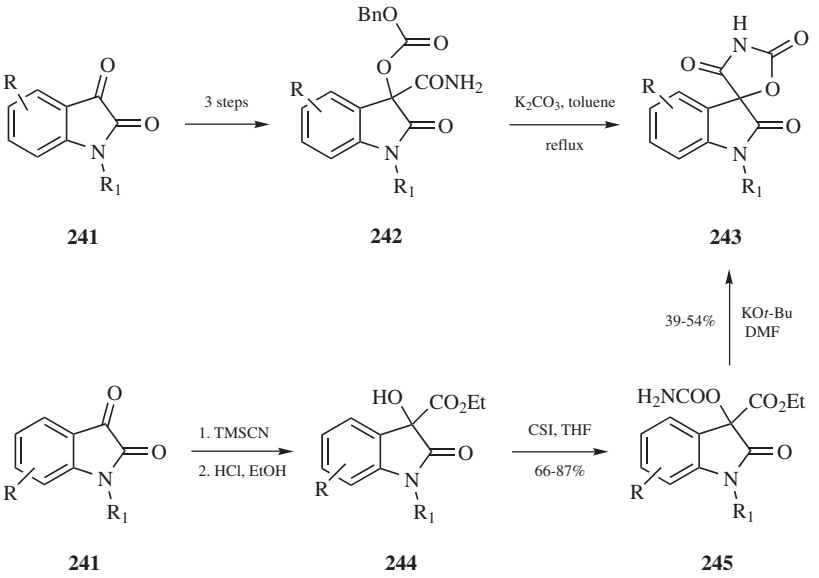


239a X = S, Y = N
239b X = O, Y = N



240a X = S, Y = N
240b X = O, Y = N

Figure 6.19. 5-Heteroaryl-2,4-oxazolidinediones.



241 **242** **243**

241 **244** **245**

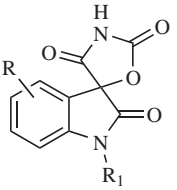
Scheme 6.54

Imperial Chemical Industries (ICI) chemists[147] prepared a novel series of spirocyclic 2,4-oxazolidinediones **243** derived from 7-substituted isatins (Scheme 6.54). The key intermediate α-acyloxy amides **242** were readily prepared from **241** in three steps. Base-catalyzed cyclization of **242** then afforded the target compounds that were reported to be potent inhibitors of aldose reductase. Pfizer chemists[148] approached 5-substituted isatin spirocyclic analogues **243** via α-hydroxy esters **244** that were converted to the corresponding α-carbamyloxy esters **245** in good yield using chlorosulfonyl isocyanate. Cyclization of **245** with potassium *tert*-butoxide then produced **243** in acceptable yield (Scheme 6.54; Table 6.10, Fig. 6.20).

Söllhuber's group[149] extended the scope of their earlier work[133] using chlorosulfonyl isocyanate to synthesize spirocyclic 2,4-oxazolidinediones. They prepared **188a**, **214**, **218**, and **232** together with several additional examples using this methodology.

On the other hand, Wyeth-Ayerst chemists[150] encountered limitations with this methodology during their syntheses of spirocyclic 2,4-oxazolidinediones derived from isoindole (Scheme 6.55). For example, reaction of **246** with chlorosulfonyl isocyanate followed by cyclization with potassium *tert*-butoxide afforded poor to modest yields of **247** when R was a substituted benzyl group. Cyclization of **246** using ethyl chloroformate (ECF), triethylamine and 4-(dimethylamino)pyridine (DMAP) in refluxing tetrahydrofuran (THF) gave **247** in only 29% yield when R was methyl and failed completely if R was an isopropyl group. However,

TABLE 6.10. SPIROCYCLIC 2,4-OXAZOLIDINEDIONES FROM 5- OR 7-SUBSTITUTED ISATINS



243

Figure 6.20

Compound	R	R_1	% Yield[a]	Reference
243a	7-F	3,4-di-Cl–Bn	NR	147
243b	7-CF_3	4-Br–Bn	NR	147
243c	7-Cl	3-CF_3–Bn	NR	147
243d	7-CH_3	2-F-4-Br–Bn	NR	147
243e	H	Ph	NR	148
243f	5-F	4-F–C_6H_4	54	148
243g	5-Cl	Me	49	148
243h	5-Cl	*i*-Pr	48	148
243i	5-Cl	4-Cl–Bn	39	148

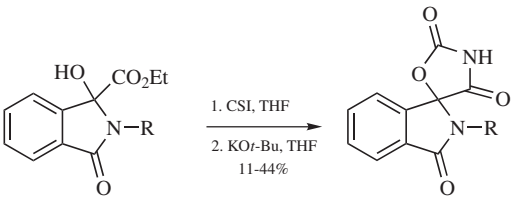
[a]Not reported = NR.

conversion of **246** to the α-hydroxy amide **248** followed by anion formation with LiHMDS and cyclization with carbonyldiimidazole produced **247** in good yield if R was a cyclohexyl group. The same reaction sequence was also very successful when it was applied to prepare analogues of **250**.

Cyclization of an α-hydroxy ester with a metal cyanate is also a useful approach to prepare 2,4-oxazolidinediones.[151–153] Japanese workers have employed this method to prepare a variety of analogues that have been evaluated as antiulcer agents **251**,[151] antidiabetic agents **252a–c**,[152] and as antitumor agents **253a–c** (Scheme 6.56).[153]

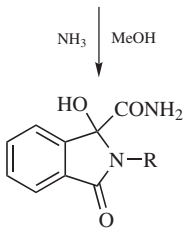
2,4-Oxazolidinediones can be obtained from electrochemical reduction of α-halo amides in the presence of carbon dioxide.[154–156] Originally, the 2,4-oxazolidinediones were observed as a component in a product mixture isolated during efforts to develop a synthetically useful synthesis of malonamides.[154] Mechanistically, the authors proposed that carbon dioxide was reduced to the radical anion at low working potentials. This radical anion then generated the conjugate base of the α-halo amide followed by carboxylation and cyclization. The yields were modest but the authors noted this was the first example where the carbon dioxide radical anion functioned as an electrogenerated base.

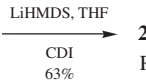
Further refinements in the reaction conditions resulted in a general synthesis of 3,5-dialkyl- and 3,5,5-trialkyl-2,4-oxazolidinediones including trimethadione



246 **247**

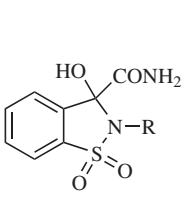
R = 4-Br-Bn
R = 2-F-4-Br-Bn

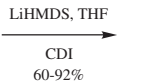


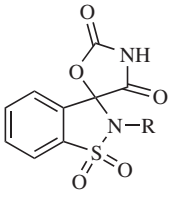


247
R = cyclohexyl

248



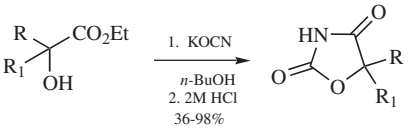




249 **250**

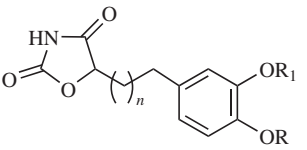
R = Me, *t*-Bu, 2-F-4-Br-Bn

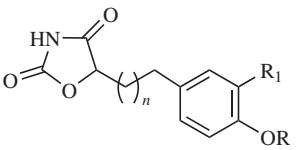
Scheme 6.55



251

R = H, Me
R_1 = H, Me, Et, Bn, Ph



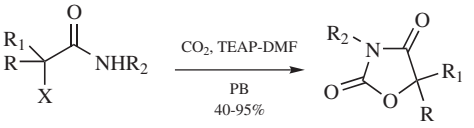


252a *n* = 1, R = Bn, R_1 = Et
252b *n* = 1, R = Me, R_1 = Bn
252c *n* = 3, R = Bn, R_1 = Me

253a *n* = 1, R = H, R_1 = OMe
253b *n* = 3, R = Bn, R_1 = H
253c *n* = 5, R = Bn, R_1 = H

Scheme 6.56

(Tridione®), **182a**.[155] Now, the reaction of **255** and carbon dioxide was carried out in the presence of a probase (PB), for example, tetraethyl ethylenetetracarboxylate, **256** (Scheme 6.57). In this way, the electrogenerated base (EGB) derived from **256** affected quantitative conversion of **255** to the conjugate base. Following carboxylation and cyclization, **182a**, and analogues of **257** were isolated in modest to excellent yield.



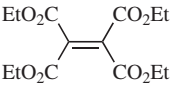
255

R, R_1 = H, Me,
R_2 = H, Me, Bn, allyl
X = Cl, Br, OTs

257

R, R_1 = H, Me,
R_2 = H, Me, Bn, allyl

TEAP = tetraethylammonium perchlorate
PB = probase

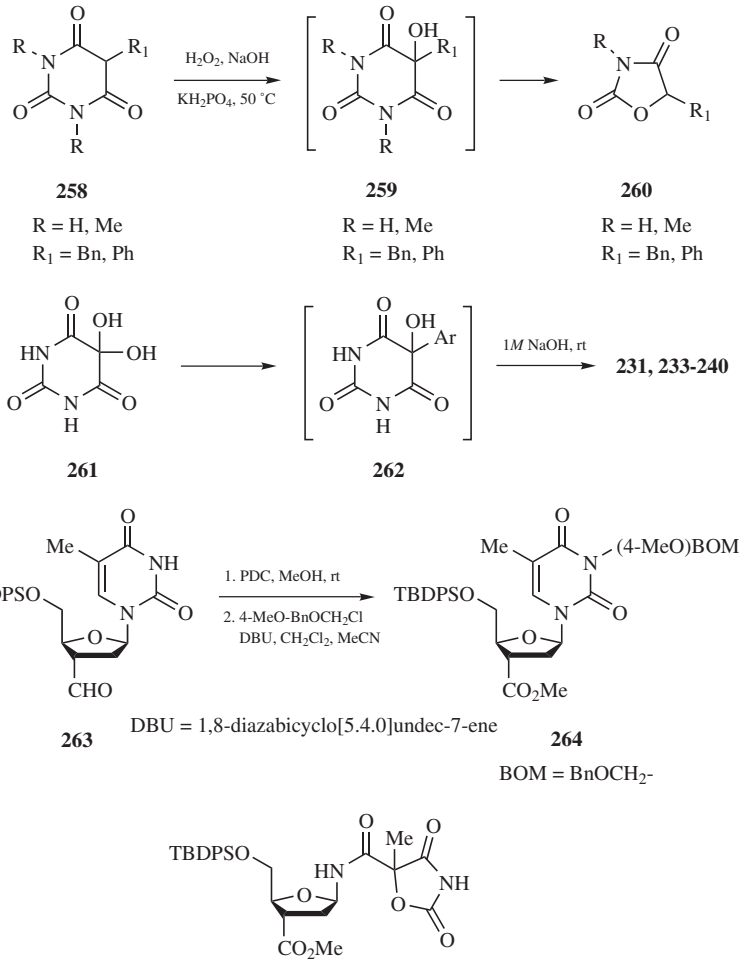


256

Scheme 6.57

These same authors[156] reported that electrochemically generated superoxide ion can also function effectively to activate carbon dioxide to yield a carboxylating agent. In this case, mechanistically, they proposed a peroxycarbonate radical anion. Interestingly, a nonelectrochemical system using carbon dioxide, dicyclohexyl-18-crown-6, and a molar equivalent of potassium superoxide was ineffective. Yields of **257** comparable to the electrochemical process were obtained only using a molar excess of potassium superoxide. Very recently, this group[157] has succeeded in developing a synthetically useful, nonelectrochemical process. Condensation of an α-halo amide with an excess of tetraethylammonium hydrogen carbonate (TEAHC) in acetonitrile gave **182a** and **257** analogues in excellent yields. Similar reaction of α-halo or α-tosyl acetanilides afforded modest yields of **257** (R_2 = Ph) owing to the attenuated nucleophilicity of the amide anion.

Oxidation of 5-substituted barbituric acids **258** with concomitant ring contraction has been shown to afford 2,4-oxazolidinediones **260** (Scheme 6.58).[158] Similarly, examples of 5-aryl- and 5-heteroaryl-2,4-oxazolidinediones, for example, **231** and **233**–**240** (Table 6.8 and Fig. 6.19) have been prepared from alloxan hydrate **261**. Thus, conversion of **261** to the dilauric acid intermediates **262** and reaction with sodium hydroxide gave the target compounds.[141–143,159] Swiss chemists[160] isolated **265** as a side product (12% yield) from the oxidation of the thymidine base in **263** during their preparation of **264** (Scheme 6.58).



258 R = H, Me; R_1 = Bn, Ph

259 R = H, Me; R_1 = Bn, Ph

260 R = H, Me; R_1 = Bn, Ph

261

262

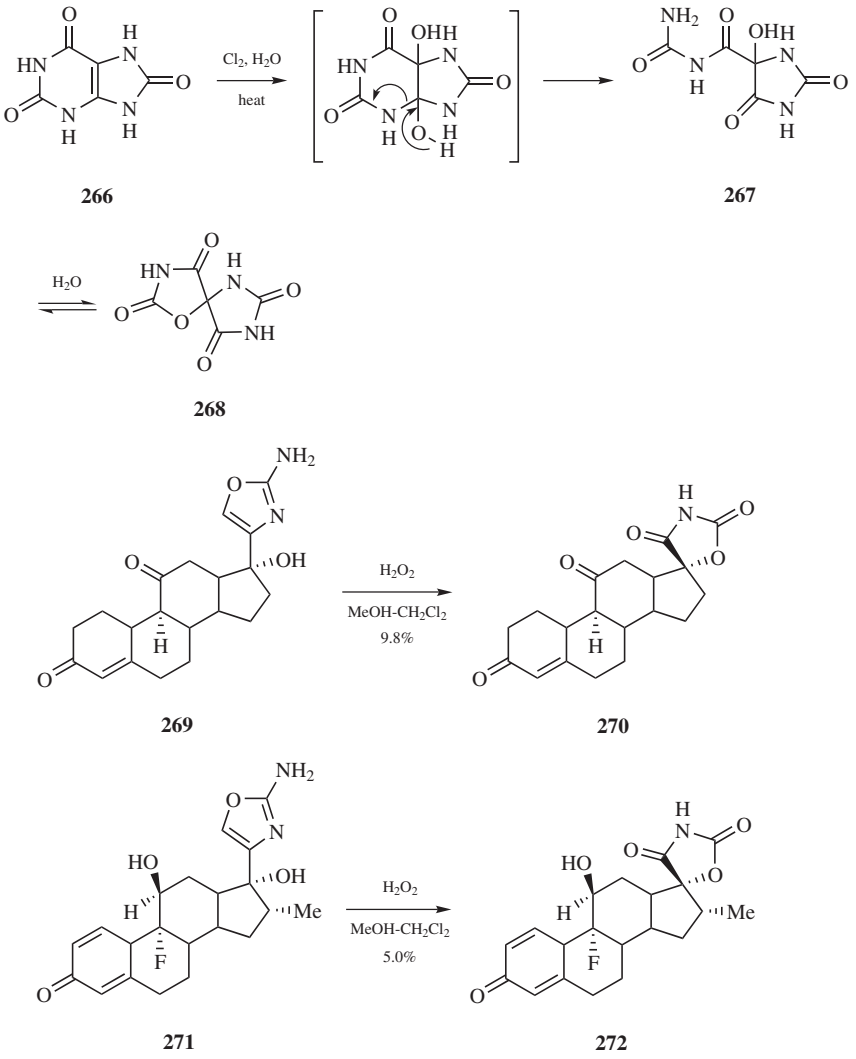
263

264

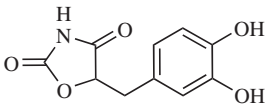
265

Scheme 6.58

Poje and co-workers[161] obtained the caffolide **268** from uric acid **266** via the alloxanic acid ureide **267** during their studies on biomimetic intermediates in oxidative transformations of purines (Scheme 6.59). Rapi and co-workers[162] proposed that oxidation of the 2-aminooxazole moiety in some 17β-(2-amino-oxazol-4-yl) steroids allowed these compounds to act as peroxide scavengers (Scheme 6.59). Oxidation of **269** and **271** with hydrogen peroxide generated **270** and **272** among the isolated products. A Japanese group[163] isolated the antioxidant **273** from roasted perilla seed (Fig. 6.21), which is the first example of a naturally occurring 2,4-oxazolidinedione. The absolute configuration of **273** has not been determined.



Scheme 6.59

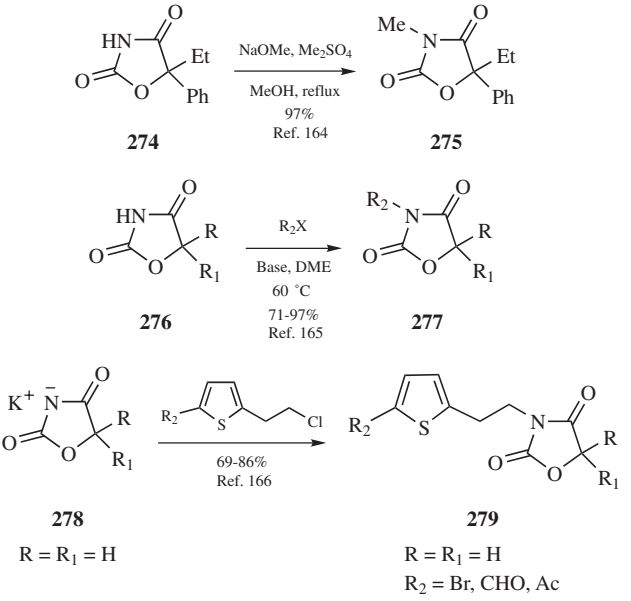


273

Figure 6.21. A naturally occurring 2,4-oxazolidinedione from roasted perilla seed.

6.4.3.2. Reactions

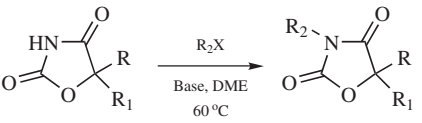
The 2,4-oxazolidinedione ring system readily undergoes reactions at N-3 and C-5 without ring opening or with ring opening and recyclization to generate new heterocyclic systems. Many 3-substituted-2,4-oxazolidinediones, particularly 3-aryl analogues, are conveniently prepared by reaction of an α-hydroxy ester or α-hydroxy acid with an isocyanate.[92,99,135] On the other hand, direct alkylation of N-3 has been used to incorporate a variety of functional groups in modest to acceptable yields.[92,118–122,135,152,153] Direct alkylation can be complicated in that both N- and O-alkylation can and often do occur[92,118,119,121] although very efficient and clean N-alkylations have been reported (Scheme 6.60).[164–166] Additional examples of N-alkylated 2,4-oxazolidindiones are shown in Table 6.11 (Fig. 6.22).



Scheme 6.60

A variety of 2,4-oxazolidinedione moieties have been prepared as precursors to *N*-acyliminium ions. These, in turn, have been used in synthetic approaches to 13-aza-16-oxasteroids,[167] interesting and novel heterocycles,[168–174] and natural products such as (±)-β-conhydrine, **294b**,[175] (±)-*O*-methylpallidinine, **297**,[176] 4-oxa-2-aza-podophyllotoxin, **299**,[177] and morphine, **302**.[178] Introduction of the 2,4-oxazolidinedione can be achieved by conventional alkylation.[178] However, it is normally introduced through Mitsunobu chemistry[179] using diisopropyl azodicarboxylate[167–173] or diethyl azodicarboxylate.[174–177] The former reagent is favored by

TABLE 6.11. 3-ALKYL-2,4-OXAZOLIDINEDIONES FROM ALKYLATION OF 2,4-OXAZOLIDINEDIONES[a]



276 **277**

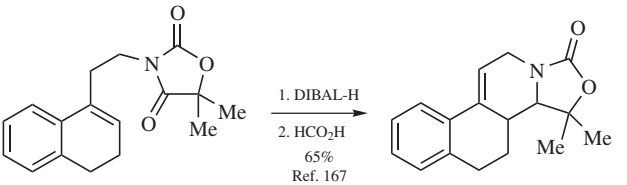
Figure 6.22

Structure	R_2X	Base	R	R_1	R_2	% Yield
277a	allyl bromide	TMG[b]	H	Me	allyl	89
277b	$ClCH_2CN$	DBN[c]	H	Me	CH_2CN	71
277c	EtI	2-MI[d]	Me	Me	Et	82
277d	MeI		Me	Et	Me	87
277e	thien-2-ylCH_2Cl	TIG[e]	Me	4-Cl–C_6H_4	thien-2-ylCH_2	92
277f	4-NO_2–BnCl	ETMG[f]	Ph	Ph	4-NO_2-Bn	97
277g	$BrCH_2CH_2CO_2Et$	TIA[g]	1-Naphthyl	H	$CH_2CH_2CO_2Et$	81
277h	$BrCH_2CH_2CH_2OH$	ETHP[h]	Me	Me	$CH_2CH_2CH_2OH$	86
277i	Me_2SO_4	ETHP	H	Me	Me	87

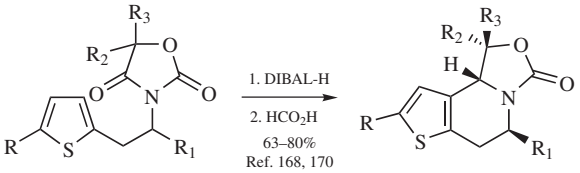
[a]Data from Ref. 165.
[b]TMG = 1,1,3,3-tetramethylguanidine.
[c]DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.
[d]2-MI = 2-methylimidazole.
[e]TIG = 1,2,3-triisopropylguanidine.
[f]ETMG = 2-ethyl-1,1,3,3-tetramethylguanidine.
[g]TIA = *N,N,N′*-triisopropylacetamidine.
[h]ETHP = 2-ethyl-1,4,5,6-tetrahydropyrimidine.

Kano and co-workers.[167–173] Once the 2,4-oxazolidinedione moiety has been incorporated, amide reduction then affords an α-hydroxy lactam, the key *N*-acyliminium ion precursor. Representative examples of 2,4-oxazolidinediones and the products derived from *N*-acyliminium ion cyclization are shown in Schemes 6.61–6.63, pp. 110–112.

Acylation at N-3 normally occurs uneventfully with 5-alkyl-2,4-oxazolidinediones, for example, **251** (R = H, R_1 = Me) or 5,5-disubstituted 2,4-oxazolidinediones, for example, **180** and **188a** to afford the corresponding N-acylated analogues (Scheme 6.64, p. 113).[180,181] These *N*-acyl derivatives have been evaluated as herbicides and as potential antiinflammatory agents. Schulte and co-workers[181] converted **251** (R = H, R_1 = Me), **180** and **188a** to the *N*-aroyl or *N*-arylsulfonyl analogues in good yield with no byproducts. Thus, reaction of a 2,4-oxazolidinedione with benzoyl chloride or an arenesulfonyl chloride in the presence of $AlCl_3$/pyridine cleanly afforded **303** or **304** in 56–82% yield. However, 5-phenyl-2,4-oxazolidinedione, **251** (R = H, R_1 = Ph) did not yield the expected *N*-3 aroyl or *N*-3 arenesulfonyl analogue. Instead, the pyridylated derivatives **305–307** were isolated in low to modest yield.

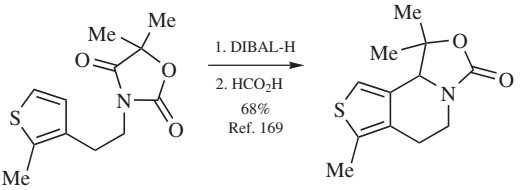


280 **281**

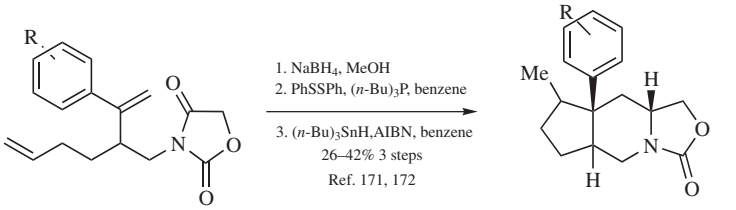


282a R = R_1 = H; R_2 = R_3 = Me
282b R = H; R_1 = R_2 = R_3 = Me
282c R = Me; R_1 = R_2 = H; R_3 = Ph

283a R = R_1 = H; R_2 = R_3 = Me
283b R = H; R_1 = R_2 = R_3 = Me
283c R = Me; R_1 = R_2 = H; R_3 = Ph



284 **285**



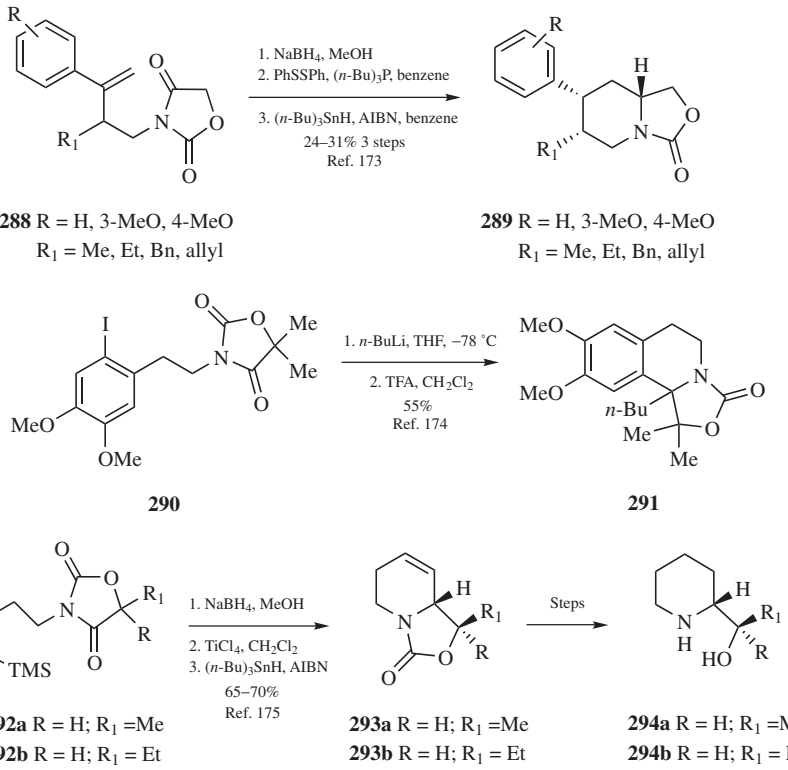
286 R = H, 3-MeO, 4-MeO

287 R = H, 3-MeO, 4-MeO

Scheme 6.61

Mannich reactions of 2,4-oxazolidinediones, particularly spirocyclic analogues, for example, **214**, and **218–220**, usually proceed readily at N-3 in good to excellent yields (Scheme 6.65, p. 114).[130,131] Similarly, 5-(arylidene)-2-thio-4-oxazolidinones **312** react readily with formaldehyde to yield the 3-hydroxymethyl derivatives, **313**.[182]

Functionalizing C-5 of 2,4-oxazolidinediones is generally accomplished by alkylation or Knovenagel reaction (Schemes 6.66–6.69). For example, treating **251** (R = H, R_1 = Me) with 3 equiv of LDA followed by two equivalents of a protected bromo alcohol and deprotection with dilute hydrochloric acid gave the



288 R = H, 3-MeO, 4-MeO
R_1 = Me, Et, Bn, allyl

289 R = H, 3-MeO, 4-MeO
R_1 = Me, Et, Bn, allyl

290

291

292a R = H; R_1 =Me
292b R = H; R_1 = Et

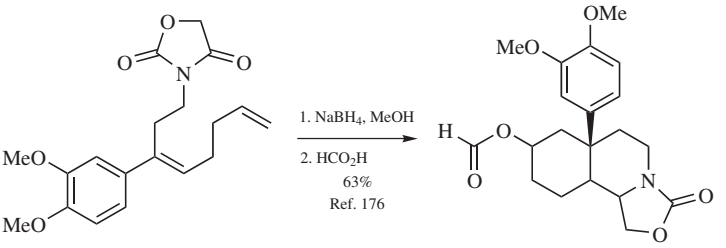
293a R = H; R_1 =Me
293b R = H; R_1 = Et

294a R = H; R_1 =Me
294b R = H; R_1 = Et

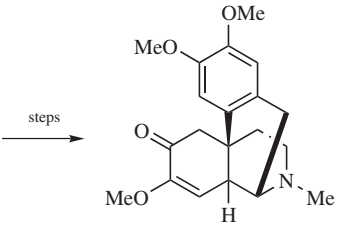
Scheme 6.62

5,5-disubstituted derivatives, **314a** and **314b**, in fair yields (Scheme 6.66). However, only **314b** could be converted to an [^{18}F] labeled analogue, which was evaluated as a potential indicator of tissue pH.[183] A series of 5-benzyl-2,4-oxazoldinediones were prepared by Pfizer chemists[184] and found to be potent hypoglycemic agents (Scheme 6.66, p. 115). Their initial approach to these compounds involved protection of **179** with a trityl group to produce **316**. Treatment of **316** with methyl magnesium carbonate[185] generated the anion, which was added to a benzyl halide to yield **317**. Deprotection with TFA then yielded the target **318**. Overall, this route was unsatisfactory owing to the low yields (<20%) encountered during the alkylation. However, they were able to develop an alternate and very successful approach involving Knovenagel chemistry (see Scheme 6.68, p. 117).

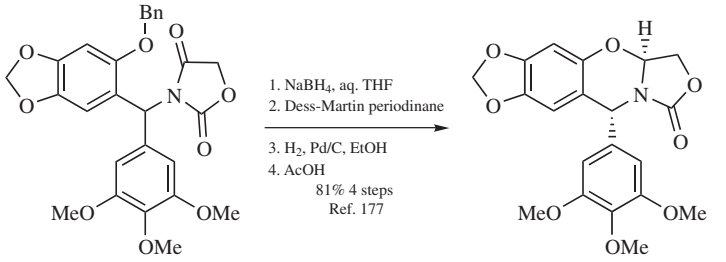
Zask[186] described a very clever and general approach to prepare 3-hydroxy-2(5*H*)-furanones in which he described the first report of a dianion of **179** that was utilized to prepare the key intermediate (Scheme 6.67, p. 116). After some experimentation he found that treatment of **179** with 2 equiv of *tert*-butyllithium and 6 equiv of lithium chloride gave **319** that reacted cleanly with an α-halo ketone to produce **320**. Hydrolysis of **320** with refluxing 6 *M* hydrochloric acid then



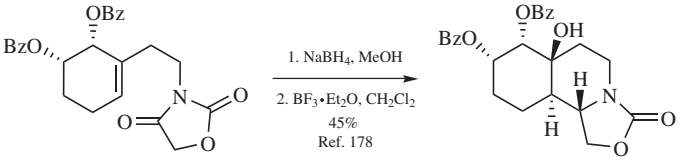
295 **296**



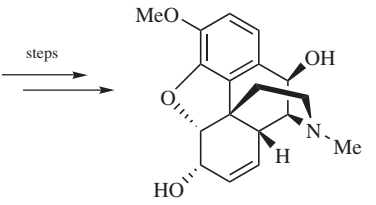
297



298 **299**

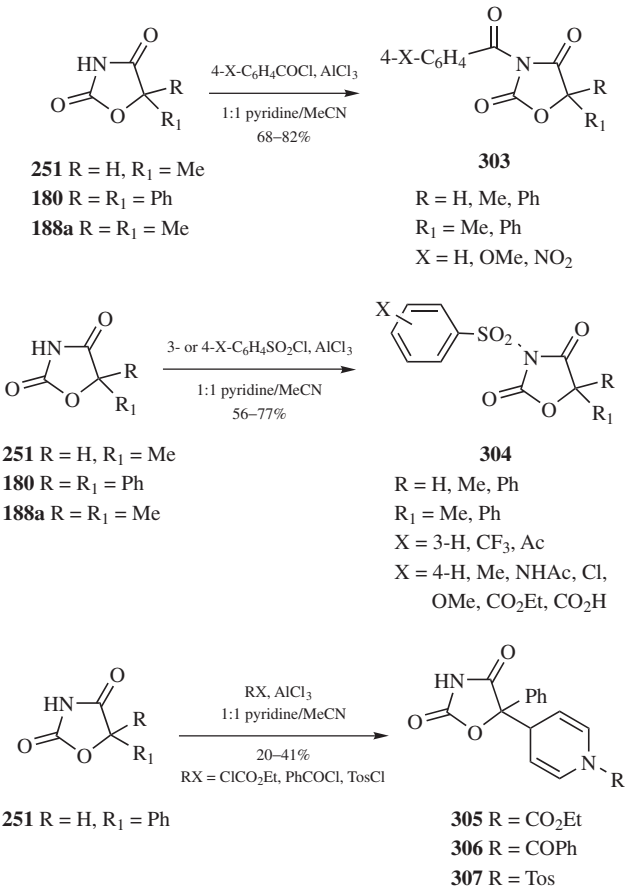


300 **301**



302

Scheme 6.63

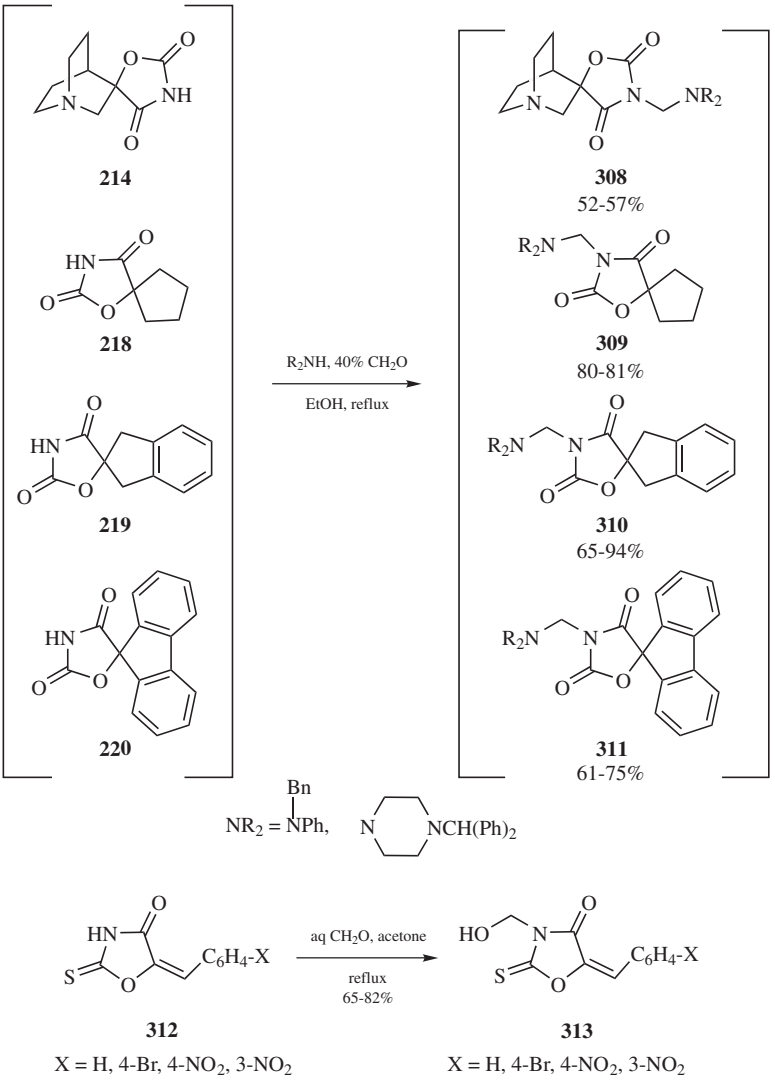


Scheme 6.64

afforded **321** in good to excellent yield. Mechanistically, it was proposed that **319** added to the α-halo ketone to generate a chlorohydrin that cyclized to an intermediate epoxide, which was transformed to the allylic alcohol via proton abstraction at C-5 with concomitant epoxide ring opening. This methodology was used to convert **322** to the naturally occurring fungal metabolite W-3681, **323**, which has shown aldose reductase inhibitory activity (Scheme 6.67, p. 116).

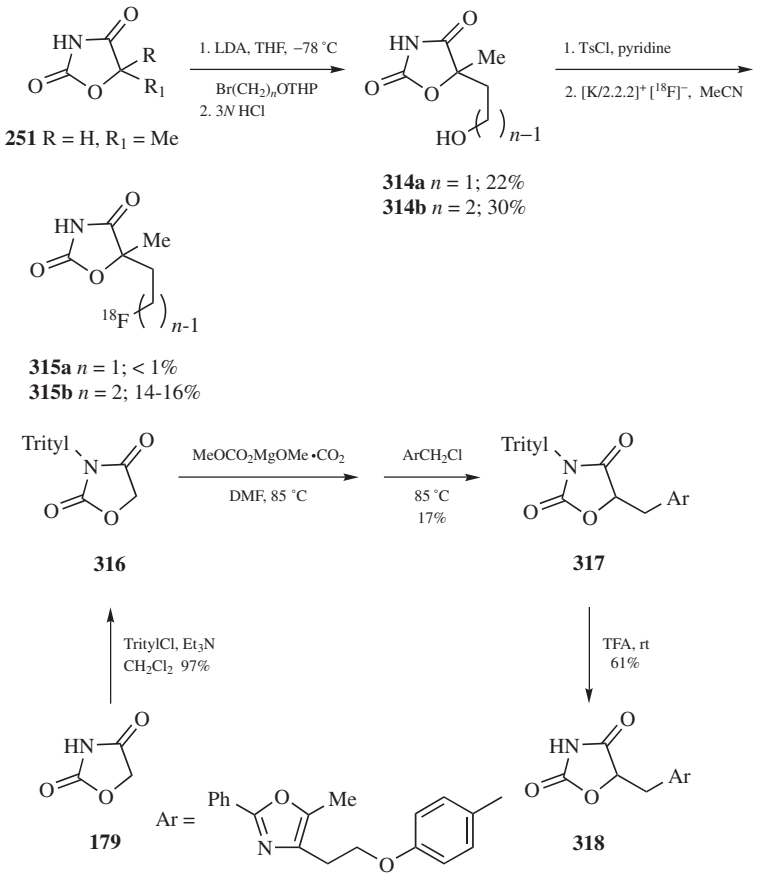
The Knoevengal reaction has been an extremely versatile method to functionalize C-5. Literally hundreds of 5-alkenyl- and 5-alkyl-2,4-oxazolidinedione analogues have been prepared in this manner. Generally, 2-thio-2,4-oxazolidinedione, **104**, is used in these reactions although **179** has been used successfully as well. Some representative examples follow.

Unangst and co-workers[65,66] condensed **104** with several 3,5-dialkyl-4-hydroxybenzaldehydes followed by alkylation and hydrolysis to afford **110** and other



Scheme 6.65

3,5-dialkyl analogues, which were evaluated as dual 5-lipoxygenase and cyclooxygenase inhibitors (Scheme 6.29). Chemists from Fuji Film Company[187] adopted a similar synthetic approach to prepare a series of 5-(benzylidene)-2,4-oxazolidinediones **326** that were evaluated as photosensitive materials and organic nonlinear optical materials (Scheme 6.68, p. 117). Here, the 5-(arylidene)-2-thio-2,4-oxazolidinediones, **324**, were methylated to the give **325** from which **326** were obtained by acid hydrolysis. This same strategy has proven to be very useful to prepare



251 R = H, R_1 = Me

314a *n* = 1; 22%
314b *n* = 2; 30%

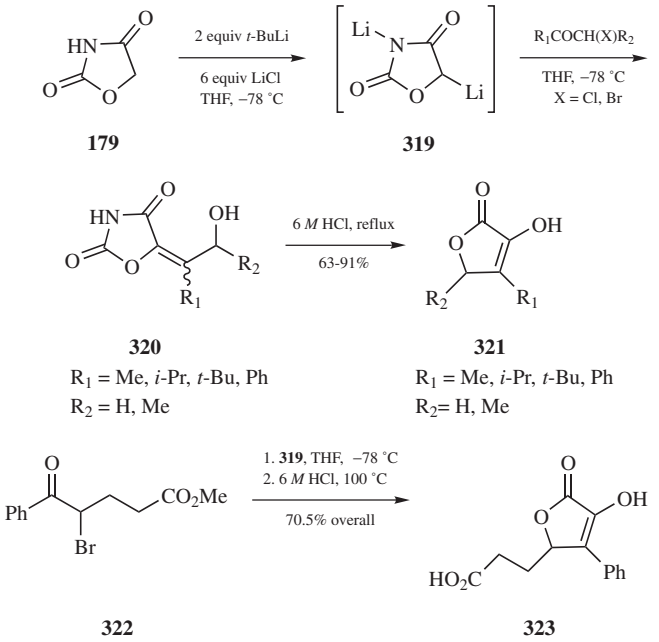
315a *n* = 1; < 1%
315b *n* = 2; 14-16%

316 **317** **179** **318**

Scheme 6.66

analogues evaluated as potential antidiabetic agents[188] and analogues for the treatment of metabolic bone disorders.[189] In the latter example, Roche chemists adopted an alternative process to prepare their targets (Scheme 6.68). Knoevenagel reaction of **104** with aromatic and heterocyclic aldehydes gave **324** as expected. However, they opted to convert the 2-thiones directly to **326** using *meta*-chloroperbenzoic acid. Reduction of **326** then provided the desired target compounds **327** uneventfully.

Variability in the reaction yield is commonly encountered with Knoevenegal condensations of **104**. Pfizer chemists[184] developed a solution to this problem (Scheme 6.68) to address the poor yields of **318** they obtained by direct alkylation of **316** (see Scheme 6.66). Initially, they found a dramatic disparity in yields of **324** (25–60%) following the literature conditions that used sodium acetate, acetic acid and benzene at reflux.[190] This variability in the yields was traced to incomplete reaction since significant amounts of both **104** and the aldehyde were recovered.

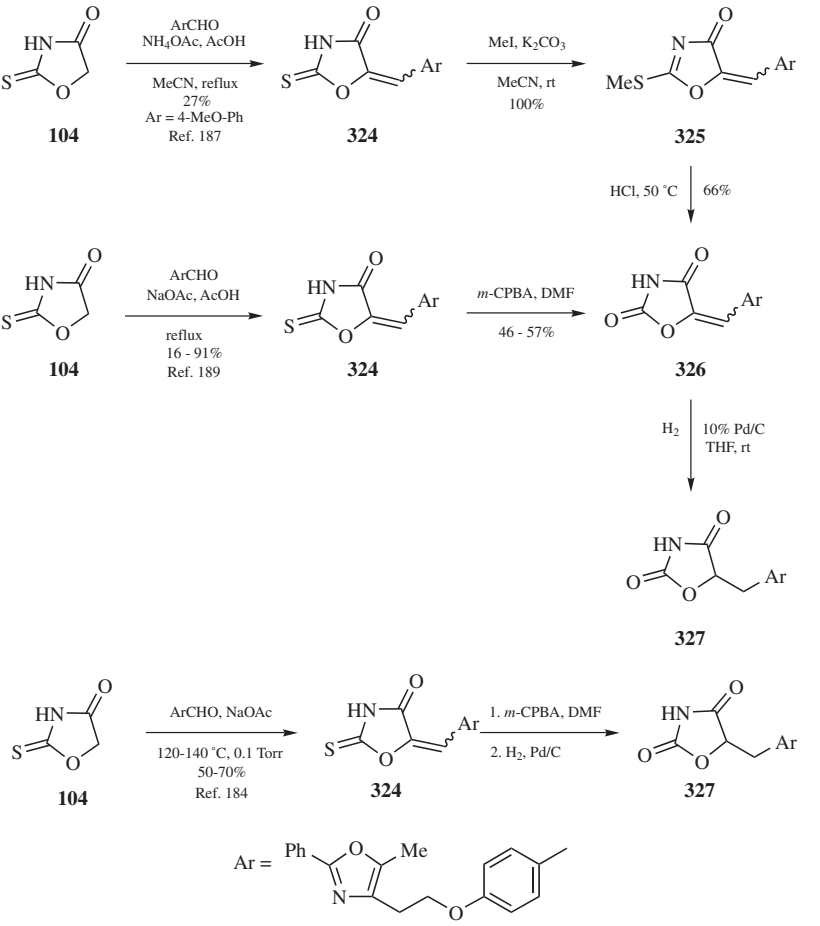


Scheme 6.67

Modifying the reaction conditions to continuously remove water by heating an intimate mixture of **104**, sodium acetate, and the aldehyde under vacuum then produced **324** consistently in 50–70% yields. The synthesis of **318** was then completed uneventfully by oxidation of **324** with *meta*-chloroperbenzoic acid and hydrogenation.

It is well known that **179** does not react with aromatic aldehydes under basic conditions.[92] However, Knoevenagel reactions of **179** have been reported (Scheme 6.69). Thus, in an alternative route to potential antidiabetic agents, Japanese chemists[152] condensed **179** with aromatic and heterocyclic aldehydes using piperidine in refluxing acetic acid to generate **328** in a single step. This product could be isolated or immediately converted to **329** via catalytic hydrogenation. The use of **104** to prepare the representative examples shown would have been problematic given the reaction sequence required to convert a 2-thio-2,4-oxazolidinedione to **329** (see above).

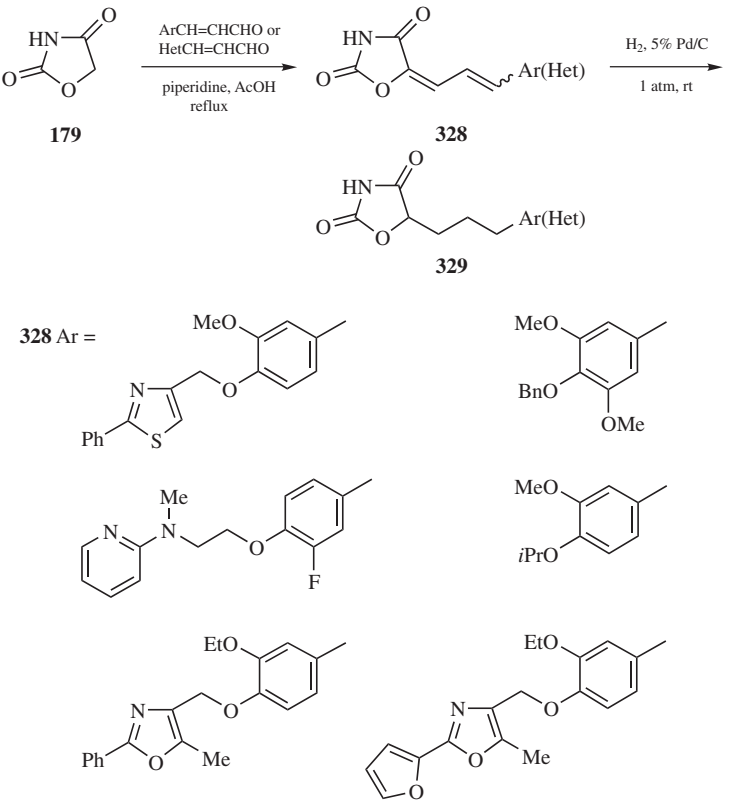
Schnur and co-workers[145] summarized typical reactions that can be performed on functional groups of substituted 2,4-oxazolidinediones without ring opening. These reactions include reduction with iron-acetic acid, chlorosulfonation, nucleophilic displacements of aromatic fluorides, and acid hydrolysis with HCl/formic acid. Nonetheless, there are examples of useful ring cleavage reactions involving 2,4-oxazolidinediones.



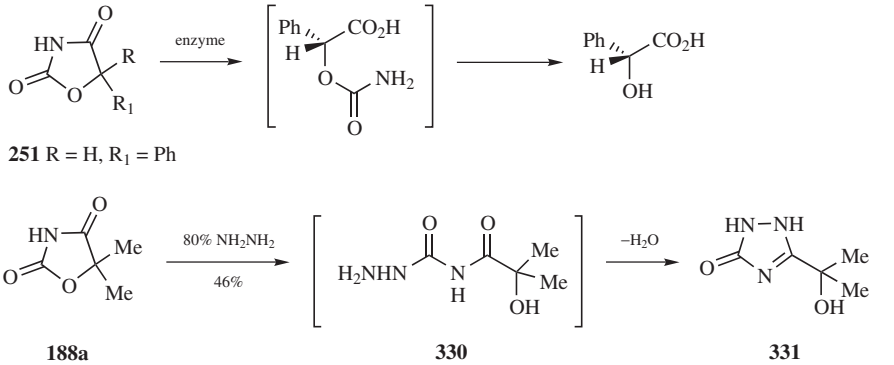
Scheme 6.68

Enzymatic hydrolysis of racemic 5-phenyl-2,4-oxazolidinedione, **251** (R=H, R_1 = Ph) afforded D-mandelic acid after refluxing the intermediate carbamoyl-D-mandelic acid in water (Scheme 6.70).[191] This process is a particularly attractive synthesis of optically active α-hydroxy acids in that the L-enantiomer is epimerized under the reaction conditions. A German group found that reaction of **188a** with 80% hydrazine produced the 1,2,4-triazolone **331** (Scheme 6.70).[192] It was proposed that hydrazine affected ring opening to give the α-hydroxy acylsemicarbazide **330** that was cyclodehydrated to yield the triazolone.

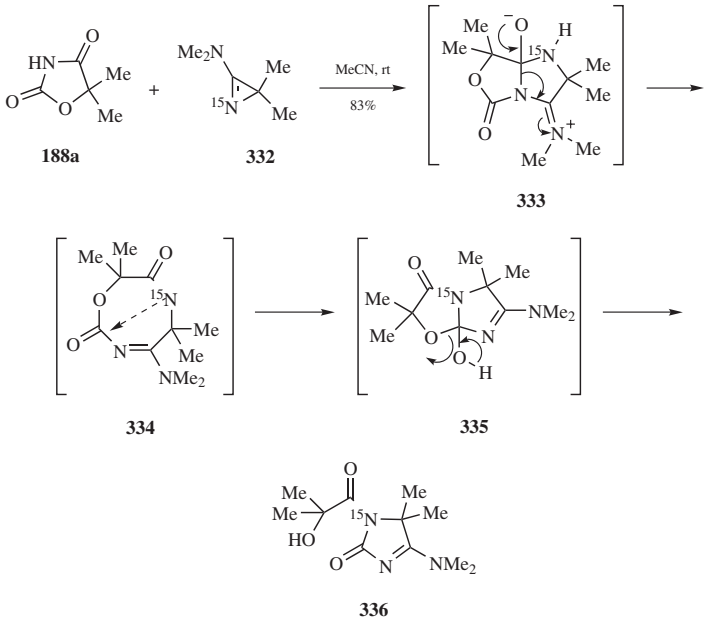
Heimgartner and co-workers[193] conducted a detailed mechanistic investigation of the reaction of [^{15}N]labeled 2,2-dimethyl-3-(dimethylamino)-2*H*-azirine **332** with NH-acidic heterocycles (Scheme 6.71). Based on these studies the authors proved that ring opening of **188a** with **332** afforded the imidazolone **336** in which



Scheme 6.69



Scheme 6.70

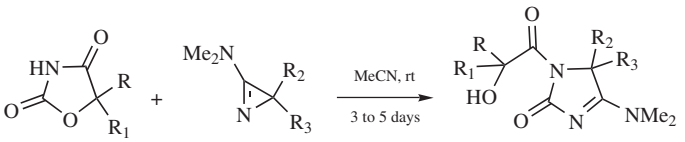


188a **332** **333** **334** **335** **336**

Scheme 6.71

only N-3 was labeled. This interesting and unexpected result was mechanistically consistent with the formation of a ring-expanded lactam **334** from the initial bicyclo[3.3.0] adduct **333**. Transannular cyclization of the [^{15}N]labeled nitrogen

TABLE 6.12. IMIDAZOLONES FROM 5,5-DIMETHYL-2,4-OXAZOLIDINEDIONE AND 2*H*-AZIRINES[a]



337 **338**

Figure 6.23

2,4-Oxazolidindione	R	R_1	R_2		R_3	% Yield
188a	Me	Me	Me		Me	83
188a	Me	Me		$-(CH_2)_4-$		88
179	H	H	Me		Me	79
179	H	H		$-(CH_2)_4-$		95
180	Ph	Ph	Me		Me	85
180	Ph	Ph		$-(CH_2)_4-$		73
251	H	Ph	Me		Me	77
251	H	Ph		$-(CH_2)_4-$		64

[a]Data from Ref. 194.

atom in **333** with the urethane carbonyl group then produced a second bicyclo[3.3.0] adduct **335** that ring opened to afford **336**. The authors have extended this work and developed a high yield, general synthesis of imidazolones including spirocyclic analogues.[194] Examples are shown in Table 6.12 (Fig. 6.23).

6.5. SUMMARY

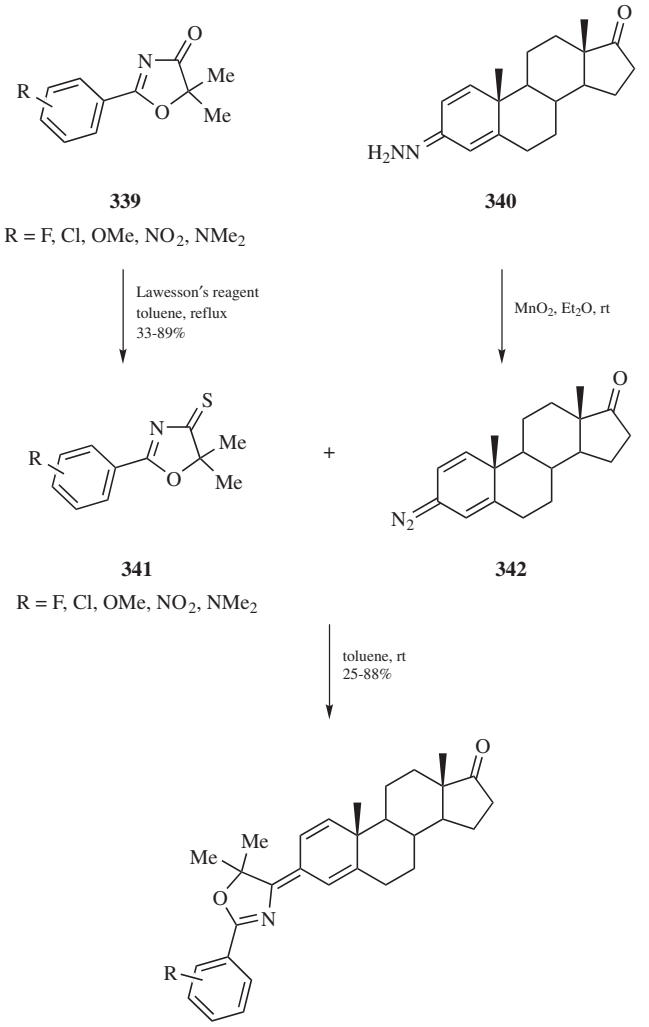
The 4(5*H*)-oxazolone ring system has been and continues to be a rich source of interesting chemistry that has produced a number of useful compounds including trimethadione, dimethadione, famoxadone, chlozolinate, and vinchlozolin. In addition, such diverse areas of research as nonlinear optical materials, photographic and luminescence dyes, antidiabetic, antiulcer, antibacterial, and antitumor agents continues to provide a strong stimulus for further developments in this area.

6.6. ADDENDUM

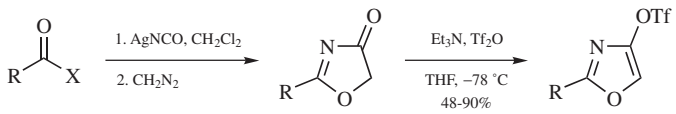
Weiss and co-workers[195] prepared a series of oxazolinylidene steroids **343** as luminescence dyes for application as potential intracellular diagnostic agents (Scheme 6.72). The key intermediate 2-aryl-5,5-dimethyl-4(5*H*)-thiooxazolones **341** were readily available from the corresponding 4(5*H*)-oxazolones **339**. Reaction of **341** with **342**, generated *in situ* from the hydrazone **340**, gave **343** as expected. It was not possible to prepare **343** from 3-thio-androsta-1,4-dien-17-one since the requisite corresponding heterocyclic diazo compounds could not be prepared.

Smith and co-workers[196] adapted Sheehan and Izzo's[2] original synthesis of 2-aryl-4(5*H*)-oxazolones and developed a general synthesis of 2-alkyl-4(5*H*)-oxazolones. Teatment of an acid halide with AgNCO followed by diazomethane produced **344** that were immediately converted to the 2-alkyl-4-oxazole triflates **345**. The authors noted that ethanol-free diazomethane was required to prepare **344**. The oxazole triflates **345** were, in turn, key intermediates leading to a variety of 2,4-disubstituted oxazoles required for natural products (Scheme 6.73).

Kamiyama and colleagues[197] at Takeda Chemical Industries described improvements to their earlier stereoselective synthesis of indolmycin **69**.[86] Most significantly, the authors noted that **69** was recently shown to be a potent anti-*H. pylori* agent.[198] This finding further emphasized the need and interest in a scaleable, stereoselective syntheses. They abandoned their one-step approach to **178** from **119a** (Scheme 6.43). Instead, **119a** was saponified to the α-hydroxy acid **121a** that was rigorously purified. This material was then converted to **178** in two-steps using guanidine rather than *N*,*N*-dimethylguanidine. The authors reported that the use of guanidine in *tert*-BuOH in the presence of 4-Å molecular sieves was critical to install the 4(5*H*)-oxazolone ring system with minimal epimerization at C-5. Overall, **69** was prepared in 22% yield and 99.4% ee from ethyl (2*S*, 3*R*)-epoxybutanoate. This methodology was also applied to prepare metabolites of **69** as well (Scheme 6.74).



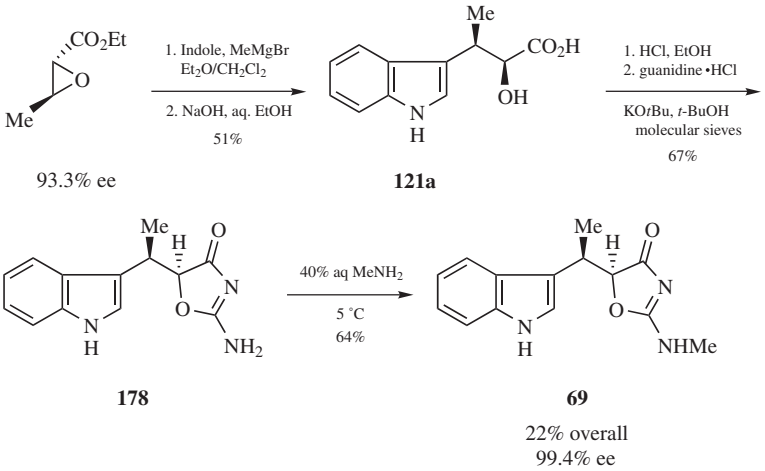
Scheme 6.72



X = Cl, Br **344** **345**

R = Me, Et, *t*Bu, Ph, CH_2Br, $(CH_2)_2Ph$, CH(Br)Me

Scheme 6.73



Scheme 6.74

Acknowledgments

I thank Dr. F. Liu for review of this chapter.

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CHAPTER 7

5(2*H*)-Oxazolones and 5(4*H*)-Oxazolones

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7.1. INTRODUCTION

The 5-oxazolones or oxazolin-5-ones are very interesting heterocyclic compounds that have been used as intermediates in the synthesis of a variety of organic molecules. Two structural classes are possible, the 5(2*H*)-oxazolones (or 3-oxazolin-5-ones) and 5(4*H*)-oxazolones (or 2-oxazolin-5-ones). These structures differ only in the position of the double bond. Apart from the presence of the heteroatoms (N and O), the carbonyl group and the double bond, the 2- or 4-position, respectively, can be saturated or unsaturated. The isomeric 5-oxazolones are

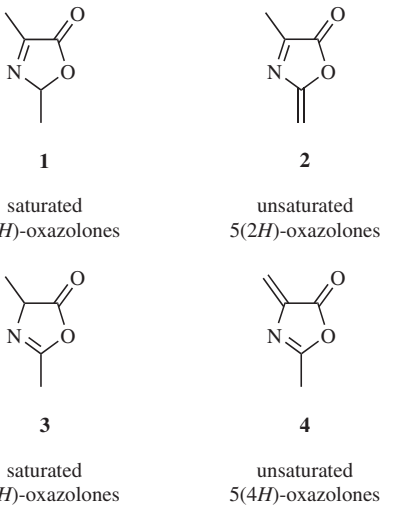


Figure 7.1. General structures of 5-(2*H*)-oxazolones and 5-(4*H*)-oxazolones.

shown in Figure 7.1. The saturated analogues **1** and **3** do not have an exocyclic double bond, whereas the unsaturated analogues **2** and **4** do contain an exocyclic double bond.

These compounds are very important and, apart from two brief reviews of oxazoles that include oxazolones,[1,2] numerous reviews have been published, although the most recent of these was almost 20 years ago.[3] Thus, this chapter will survey the significant results published during the last two decades and will discuss new syntheses of 5-oxazolones and focus attention on the use of these intermediates as versatile reagents in organic chemistry. Particular emphasis will be given to their use as building blocks to prepare other important heterocyclic compounds and as suitable reagents for the synthesis of α-amino acids and peptides.

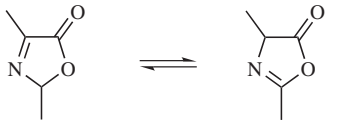
7.2. 5(2*H*)-OXAZOLONES (3-OXAZOLIN-5-ONES)

7.2.1. Synthesis

The following section covers only those procedures for the synthesis of 5(2*H*)-oxazolones described during the last 20 years and it should be borne in mind that a number of classical procedures have been described before.[3]

7.2.1.1. From Amino Acids: Tautomerism and Racemization

A saturated 5(2*H*)-oxazolone, also known as a 3-oxazolin-5-one or a pseudoxazolone, can be considered as the tautomer of a saturated 5(4*H*)-oxazolone (or 2-oxazolin-5-one) by a 1,3-prototropic shift (Scheme 7.1).



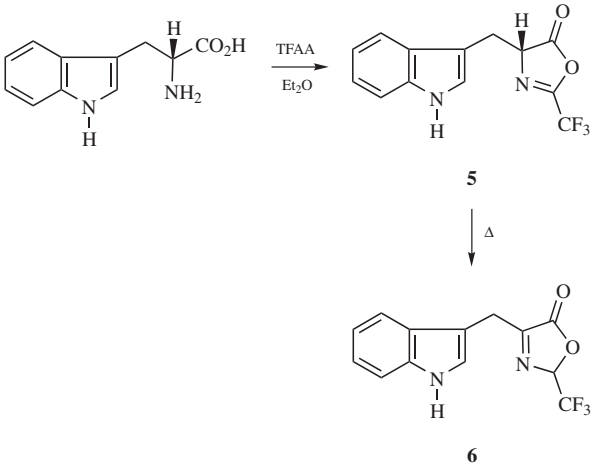
1 **3**

5(2*H*)-oxazolone 5(4*H*)-oxazolone

Scheme 7.1

In fact, the first saturated pseudoxazolone reported, 4-methyl-2-(trifluoromethyl)-5(2*H*)-oxazolone, was incorrectly assigned as the tautomeric 5(4*H*)-oxazolone and only later did nuclear magnetic resonance (NMR) studies establish the correct structure. This compound was synthesized from alanine and trifluoroacetic anhydride (TFFA). This methodology constitutes, under standard conditions, the most general procedure for the synthesis of 5(2*H*)-oxazolones.

Saturated 5(4*H*)-oxazolones are easily obtained from *N*-acylamino acids in the presence of a cyclization agent and have been used extensively in coupling reactions as synthetic equivalents of α-amino acids in the synthesis of peptides. In this context, tautomeric equilibrium can be a significant problem due to the racemization associated with the isomerization. For example, trifluoroacetylation of tryptophan in ether affords the 5(4*H*)-oxazolone **5** without racemization. However, upon dissolution in acetonitrile, **5** completely racemizes.[4,5] Further, upon heating, an aqueous dioxane solution of **5** cleanly isomerizes to the isomeric 5(2*H*)-oxazolone **6** (Scheme 7.2).



5

6

Scheme 7.2

Interestingly, treating bromotyrosine with TFAA in an autoclave at 80–120 °C, affords the corresponding 5(2*H*)-oxazolone that was used as an intermediate in the synthesis of psammaplin.[6]

TABLE 7.1. SYNTHESIS OF 5(2*H*)-OXAZOLONES VIA CYCLIZATION OF AMINO ACIDS OR AMINO NITRILES

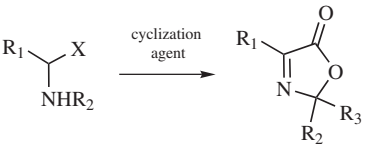
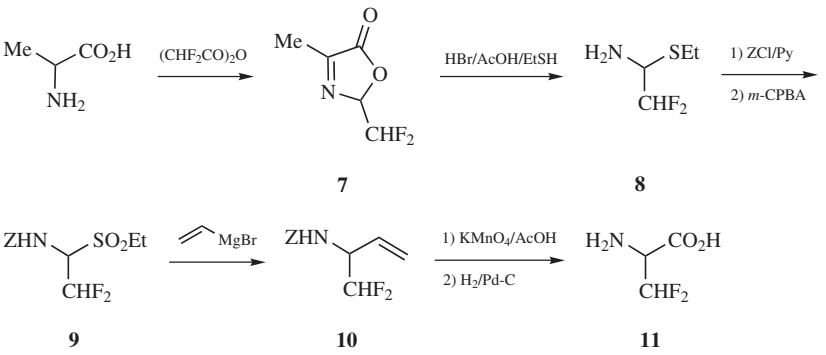


Figure 7.2

X	Cyclization Agent	R_1	R_2	R_3	% Yield	References
CO_2H	TFAA	indol-3-ylmethyl	H	CF_3	90	4,5
CO_2H	TFAA/PCl_3	4-ClC_6H_4	H	CF_3	≈ 100	7
CN	TsOH	4-ClC_6H_4	$COCF_3$	H	56	9
CO_2H	DFAA	Ph	H	CHF_2	48	10
CO_2H	TFAA	*i*-Pr	H	CF_3	80–90	11
CO_2H	TFAA	*s*-Bu	H	CF_3	80–90	11
CO_2H	TFAA	Ph	H	CF_3	80–90	11

Cyclizations with perfluoroacylating agents seem to be quite general for the synthesis of 5(2*H*)-oxazolones with aromatic substituents directly bonded to the heterocyclic ring. For example, perfluoroacylation of a solution of an arylglycine containing a phosphorus trihalide affords 4-aryl-2-(perfluoroalkyl)-5(2*H*)-oxazolones (Table 7.1, Fig. 7.2).[7] Similar results were obtained when amino nitriles were used as starting materials.[8,9]

Difluoroacetic anhydride reacts similarly with alanine and this process affords 2-(difluoromethyl)-4-methyl-5(2*H*)-oxazolone **7**. Treatment of **7** with hydrogen bromide in acetic acid in the presence of ethanethiol yields **8** that was converted to 3,3-difluoroalanine **11** in several steps as shown in Scheme 7.3.[10] This reaction opened the way to prepare β,β-difluoro amino acids.



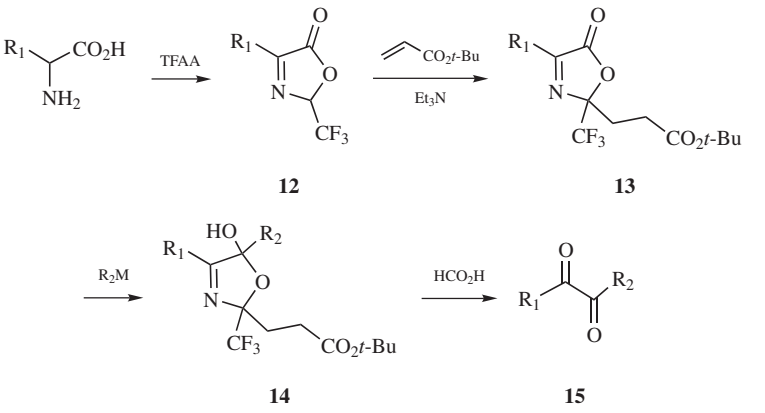
m-CPBA = *meta*-chloroperoxybenzoic acid

Scheme 7.3

Racemization observed during coupling reactions in the synthesis of peptides can be attributed, at least in part, to the influence of the base used on the equilibrium of the tautomeric oxazolones. Numerous studies have been undertaken to avoid this problem or, alternatively, to direct the equilibrium to the desired compound. For example, the triethylamine-promoted tautomerization of 4-alkyl-5(4*H*)-oxazolones to 4-alkyl-5(2*H*)-oxazolones has been studied by proton NMR (^{1}H NMR) long-range coupling.[12] In addition, the kinetics of racemization of 2,4-disubstituted-5(4*H*)-oxazolones obtained from *N*-acetyl, *N*-benzoyl, and *N*-benzyloxycarbonylamino acids have been studied in several solvents, both alone and in the presence of tertiary amines.[13] The racemization process is governed by electronic effects of the substituent at C-2 and by steric effects of the substituent at C-4. The thermodynamic data suggest that the 4-benzyl-2-substituted-5(4*H*)-oxazolones racemize more readily than the corresponding 4-alkyl analogues (alkyl $\neq$ benzyl) and that the rate of the base-catalyzed reaction depends on the steric bulk at the nitrogen atom of the tertiary amine as well as on the basicity.

7.2.1.2. C-2 versus C-4 Alkylations

The availability of a general procedure to prepare 4-alkyl-2-(trifluoromethyl)-5(2*H*)-oxazolones **12** from α-amino acids and TFAA, and taking into account the tautomerization process, has led to many efforts to direct the alkylation reaction toward C-2 or C-4. For example, in the presence of triethylamine, Michael addition of **12** occurs at C-2 when *tert*-butylacrylate is used as electrophile.[11] The resulting dialkylated products **13** could be easily transformed into α-diketones **15** (Scheme 7.4; Table 7.2, Fig. 7.3).



Scheme 7.4

TABLE 7.2. SYNTHESIS OF 5(2*H*)-OXAZOLONES VIA ALKYLATION AT C-2

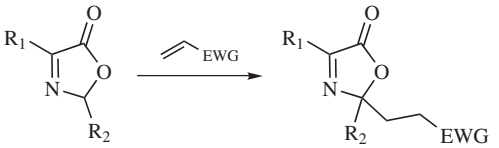
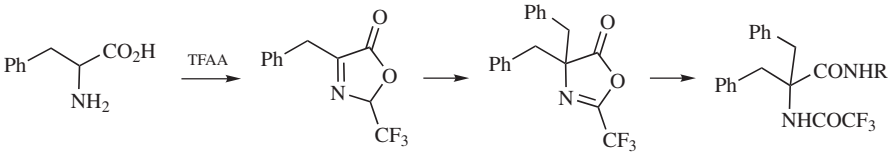


Figure 7.3

R_1	R_2	EWG[b]	% Yield
i-Pr	CF_3	CO_2tBu	≈80
Ph	CF_3	CO_2tBu	≈80
$MeSCH_2CH_2$	CF_3	CO_2tBu	≈80

[a] Data from Ref. 11.
[b] EWG = electron-withdrawing group.

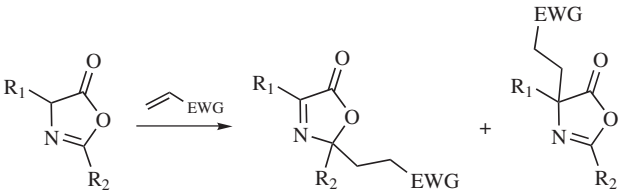
Alternatively, alkylation of 4-benzyl-2-(trifluoromethyl)-5(2*H*)-oxazolone **16** in the presence of mild base using active alkyl halides as electrophiles occurs at C-4.[14] Subsequent aminolysis of a 4,4-dialkyl-5(4*H*)-oxazolone like **17** gave an *N*-(trifluoroacetyl)-α,α-dialkylglycine amide **18** that was used to prepare important peptides incorporating an α,α-dibenzylglycine unit (Scheme 7.5).



16 **17** **18**

Scheme 7.5

In principle, 5(4*H*)-oxazolones **19** could also be used as starting materials to prepare 5(2*H*)-oxazolones **20** via an alkylation reaction, but this approach depends on many factors. Several years ago[3] it was reported that a mixture of isomeric products **20** and **21** is usually obtained (Scheme 7.6) and the site of reaction in base-catalyzed addition reaction of 5(4*H*)-oxazolones with activated multiple bonds is determined primarily by the nature of the activated multiple bond.

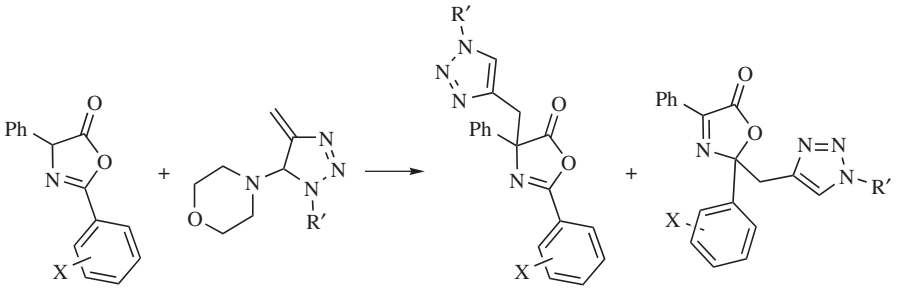


19 **20** **21**

EWG = electron-withdrawing group

Scheme 7.6

The reaction of 2-aryl-4-phenyl-5(4*H*)-oxazolones **22** with 4-methylenetriazoles **23** was also studied.[15] The direction of the alkylation was strongly dependent on the nature of the substituent on the aromatic ring at C-2 in **22**. Thus, oxazolones with electron-rich aryl substituents gave predominantly alkylation at C-4 to yield **24**. In contrast, the isomeric products **25** are preferentially obtained when using substrates with electron-withdrawing substituents (Scheme 7.7).



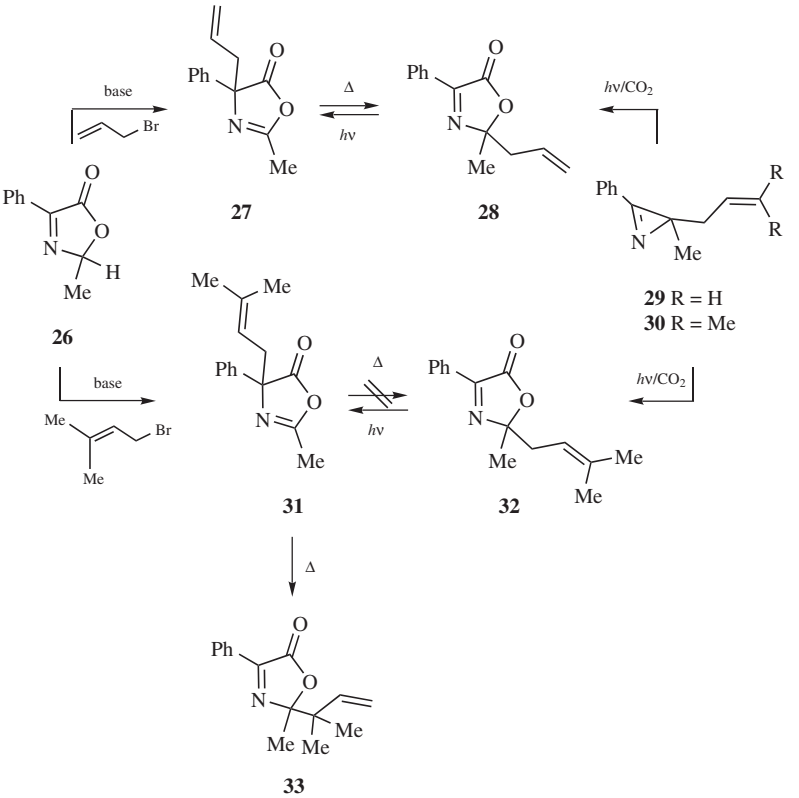
22 **23** **24** (X = EDG) **25** (X = EWG)

EDG = electron-donating group

Scheme 7.7

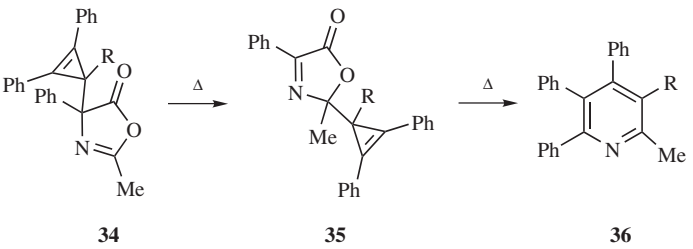
7.2.1.3. Via Sigmatropic Rearrangements

Very interesting interconversions between allyl substituted-5(4*H*)-oxazolones and allyl substituted-5(2*H*)-oxazolones have also been described.[16,17] In particular, 4-allyl-2-methyl-4-phenyl-5(4*H*)-oxazolone **27** and 4-(3,3-dimethylallyl)-2-methyl-4-phenyl-5(4*H*)-oxazolone **31** were found to undergo a [3,3] sigmatropic allyl shift on thermolysis to give the corresponding isomeric 5(2*H*)-oxazolones **28** and **33**, respectively. In contrast, on direct irradiation **28** and **32** undergo a [1,3] allyl shift to give the corresponding 5(4*H*)-isomers **27** and **31**. To elucidate the mechanism of these reactions all compounds were synthesized unambiguously; the 5(4*H*)-oxazolones **27** and **31** by alkylation of **26** and the 5(2*H*)-oxazolones **28** and **32** by irradiation of azirines **29** and **30** in the presence of carbon dioxide.[18] These reactions are shown in Scheme 7.8.



Scheme 7.8

Analogously, cyclopropenyl systems **34**, **35** were also studied (Scheme 7.9; Table 7.3, Fig. 7.4). Here, further heating of **35** afforded substituted pyridines **36**.[17,19]



Scheme 7.9

A new synthesis of 2-allyl-4-phenyl-5(2*H*)-oxazolones **39** has been published[20] starting from the corresponding allyl *N*-acylphenylglycinates **37**. The reaction proceeds via the nonisolable oxazoles **38** that undergo a sigmatropic rearrangement under the cyclization conditions. The reductive ring cleavage of the oxazolones is a

TABLE 7.3. SYNTHESIS OF 5(2*H*)-OXAZOLONES VIA SIGMATROPIC REARRANGEMENT

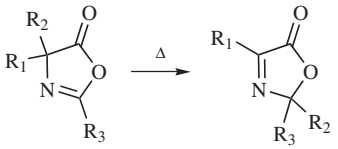
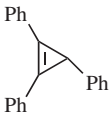
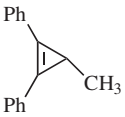


Figure 7.4

R_1	R_2	R_3	% Yield	References
Ph	$CH_2=CHCH_2$	Me	98	16
Ph		Me	≈100	17
Ph		Me	≈100	17,19

very useful procedure for the synthesis of β,γ-unsaturated ketones **40** (Scheme 7.10; Table 7.4, Fig. 7.5). The utility of the reaction was extended to include other allyl, propargyl, and cinnamyl *N*-acylphenylglycinates. Catalytic hydrogenation of the resulting 5(2*H*)-oxazolones **43** and subsequent reductive ring cleavage gave the corresponding ketones **44**. Complete transfer of the chirality was observed starting

TABLE 7.4. SYNTHESIS OF 5(2*H*)-OXAZOLONES VIA REARRANGEMENT OF 5-ALKOXYOXAZOLES[a]

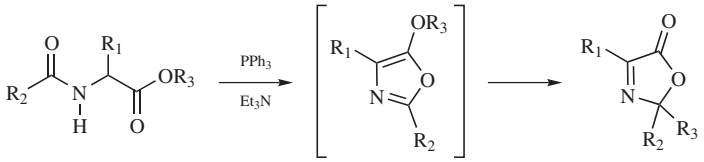
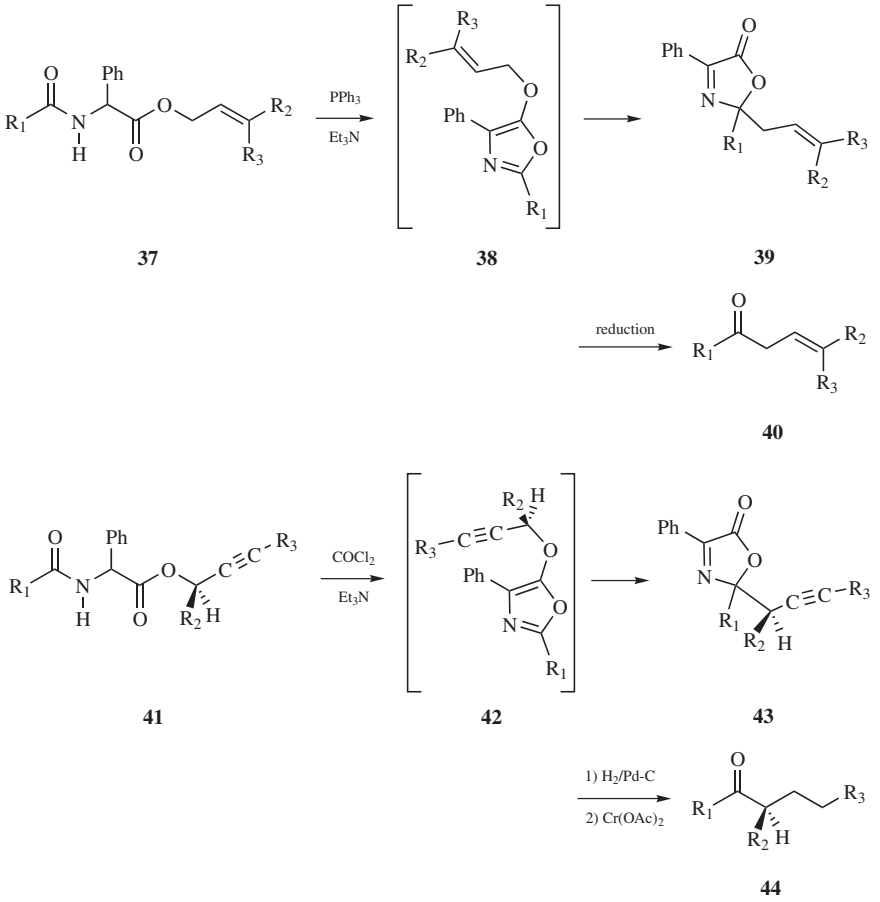


Figure 7.5

R_1	R_2	R_3	% Yield
Ph	4-ClC_6H_4	$PhC{\equiv}CCH_2$	50
Ph	4-ClC_6H_4	$PhC{\equiv}CCH(Me)$	83
Ph	Ph	$PhC{\equiv}CCH(Me)$	56
Ph	4-ClC_6H_4	$PhCH{=}CHCH_2$	40
Ph	4-ClC_6H_4	PhCH=CHCH(Ph)	45

[a]Data from Ref. 21.



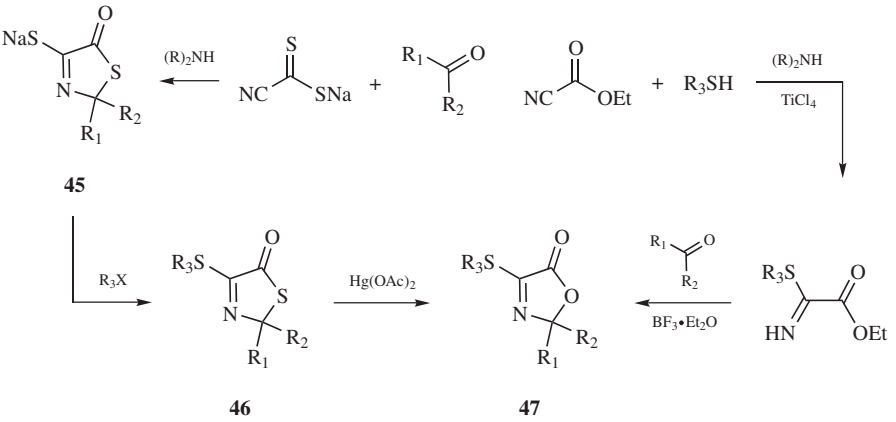
37 **38** **39** **40** **41** **42** **43** **44**

Scheme 7.10

from enantiomerically pure alcohols. Interestingly, either enantiomer of 1,4-diphenyl-2-methylbutan-1-one could be obtained from (*E*)- or (*Z*)-(*R*)-4-phenyl-3-buten-1-ol.[21]

7.2.1.4. 4-Arylthio, 4-Alkoxy, and 4-Amino Derivatives

The nature of the arylthio substituent at C-4 of a 5(2*H*)-oxazolone dictates which of two different synthetic strategies can be used.[22,23] The first involves the use of sodium cyanodithioformate and the corresponding ketone as starting materials. The reaction occurs through a thiazolone **45** that must be alkylated on the sulfur atom followed by treatment with $Hg(OAc)_2$ to afford the corresponding 4-(alkylthio)-5(2*H*)-oxazolone **47**. The second strategy involves the addition of thiophenol to



Scheme 7.11

ethyl cyanoformate to afford a thioimidate followed by the addition of the ketone and a Lewis acid (Scheme 7.11; Table 7.5, Fig. 7.6; Table 7.6, Fig. 7.7). Both synthetic pathways, which are complementary for alkyl or aryl sulfide derivatives, are limited with respect to variation of the substituent on the ketone.

Two different methods have also been described[24] for the synthesis of 4-alkoxy-5(2*H*)-oxazolones **50**. In the first case, 4-(phenylthio)-5(2*H*)-oxazolones **48** are oxidized to the 4-phenylsulfinyl derivatives that react with the alcohol present in the reaction medium to afford the corresponding 4-alkoxy derivatives. Alternatively, 4-alkoxy-5(2*H*)-oxazolones **50** have been obtained by condensation of iminooxalates and ketones in acidic medium. (Scheme 7.12; Table 7.7, Fig. 7.8; Table 7.8, Fig. 7.9).

TABLE 7.5. SYNTHESIS OF 4-(ALKYLTHIO)-5(2*H*)-OXAZOLONES FROM SODIUM CYANODITHIOFORMATE, KETONES AND ALKYLATING AGENTS[a]

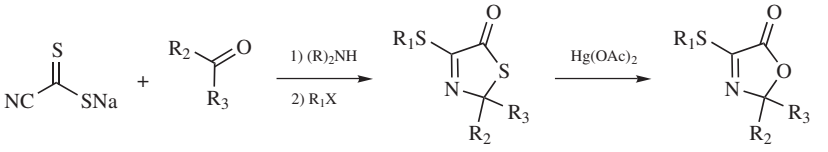


Figure 7.6

R_1	R_2	R_3	% Yield
$PhCH_2$		$(CH_2)_5$	31
2,4-$(NO_2)_2C_6H_3$		$(CH_2)_5$	8

[a]Data from Ref. 23.

TABLE 7.6. SYNTHESIS OF 4-(ARYLTHIO)-5(2*H*)-OXAZOLONES FROM ETHYLCYANOFORMATE, KETONES, AND ARYLTHIOLS[a]

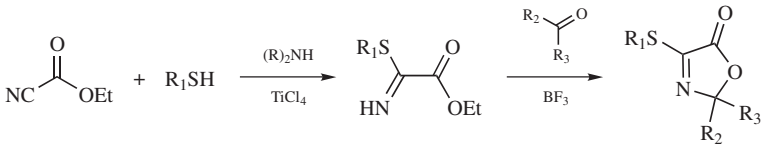
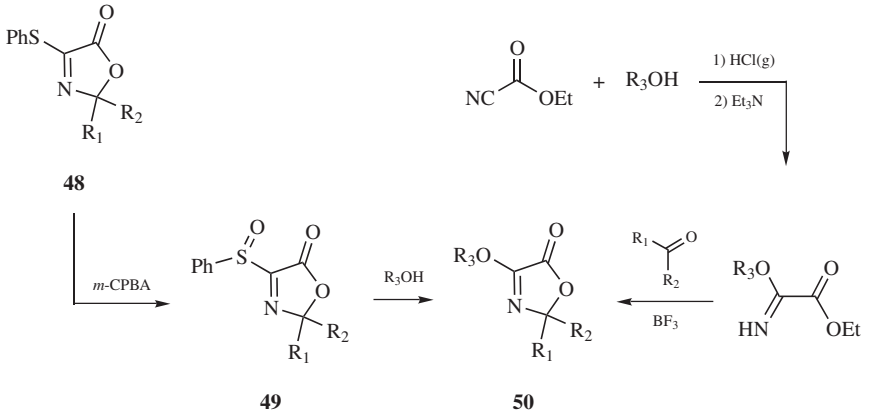


Figure 7.7

R_1	R_2	R_3	% Yield
Ph	$(CH_2)_5$		28–32
Ph	Me	Me	≈12
2-naphthyl	$(CH_2)_5$		21
2-naphthyl	Ph	CF_3	17

[a]Data from Refs. 22 and 23.



Scheme 7.12

TABLE 7.7. SYNTHESIS OF 4-ALKOXY-5(2*H*)-OXAZOLONES FROM 4-(PHENYLTHIO)-5(2*H*)-OXAZOLONES[a]

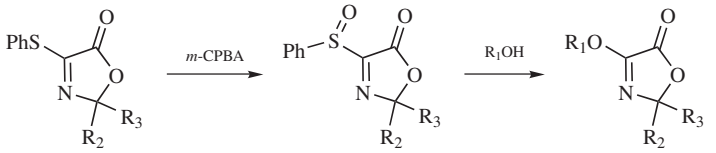


Figure 7.8

R_1	R_2	R_3	% Yield
Et	$(CH_2)_5$		40
i-Pr	$(CH_2)_5$		4

[a]Data from Ref. 24.

TABLE 7.8. SYNTHESIS OF 4-ALKOXY-5(2*H*)-OXAZOLONES FROM IMINOOXALATES AND KETONES OR ALDEHYDES[a]

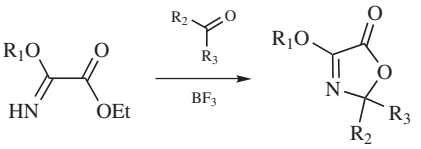
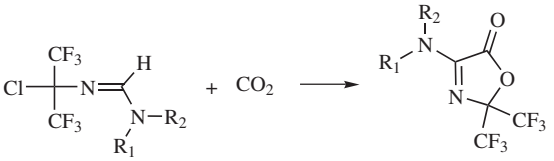


Figure 7.9

R_1	R_2	R_3	% Yield
Et	CF_3	Ph	14
i-Pr	CF_3	Ph	28
i-Pr	H	Ph	7

[a]Data from Ref. 24.

Reaction of carbon dioxide with *N*-[1-chloro-2,2,2-trifluoro-1-(trifluoromethyl)-ethyl]-*N*′,*N*′-dialkylformamidines has been described[25] as a procedure to prepare 4-(dialkylamino)-5(2*H*)-oxazolones **51** (Scheme 7.13; Table 7.9, Fig. 7.10). Mechanistically, this reaction probably does not proceed via a nitrile ylide given the observed regioselectivities and the dependence of the reaction rate on the solvent.



51

Scheme 7.13

Finally, it has also been reported[26] that the reaction of anilines with ethylimino-(ethylthio) acetate fluoroborate and treatment of the resulting product with formaldehyde is an interesting and general procedure for the synthesis of 4-(alkylamino)-5(2*H*)-oxazolones.

TABLE 7.9. SYNTHESIS OF 4-(*N*,*N*-DIALKYLAMINO)-5(2*H*)-OXAZOLONES FROM AMIDINES AND CARBON DIOXIDE[a]

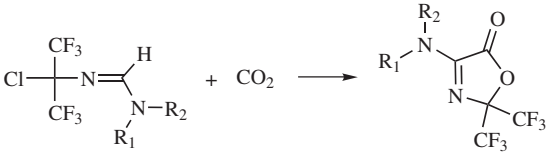


Figure 7.10

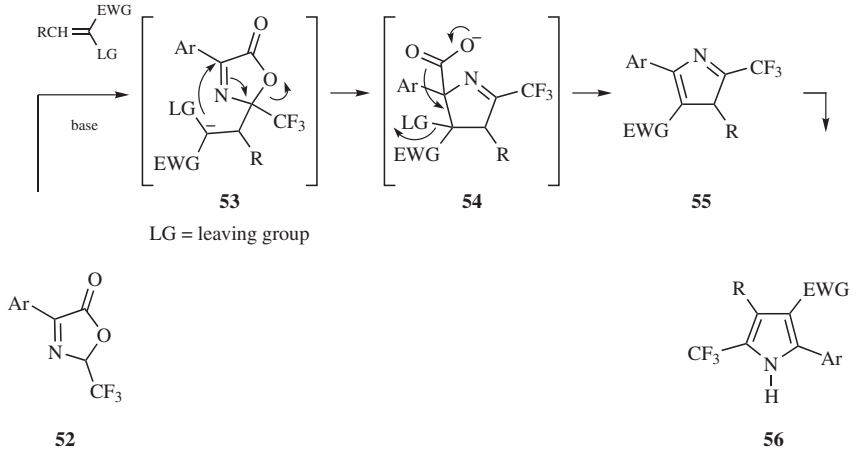
R_1	R_2	% Yield
Me	Me	98
	$(CH_2)_2O(CH_2)_2$	91

[a]Data from Ref. 25.

7.2.2. Reactions

7.2.2.1. Synthesis of Pyrroles

4-Alkyl(aryl)-2-(trifluoromethyl)-5(2*H*)-oxazolones have been used as intermediates to prepare 2-(trifluoromethyl)pyrroles interesting compounds frequently used as insecticides and acaricides. The oxazolones react with electron-deficient unsaturated compounds in the presence of a base. Reaction of 5(2*H*)-oxazolones, usually with a substituted aryl ring at C-4, with a wide variety of alkynes and alkenes has given rise to numerous 2-(trifluoromethyl)pyrroles **56**. For example, dimethyl acetylenedicarboxylate,[27,28] 2-chloroacrylonitrile,[29,30] haloacrylates or haloacrylonitriles,[31–35] perhaloalkenes,[36] *N*-[(α-(4-chlorostyryl)pyridinium] tetrafluoroborate,[37] 2-ethynylpyridine,[38] 2-(1-chlorovinyl)pyridine[39] and, more recently, [60]fullerene[40] all have been used as electron-deficient unsaturated compounds. Mechanistically, it is postulated that the anion of the 4-aryl-2-(trifluoromethyl)-5(2*H*)-oxazolone undergoes Michael addition to the activated alkene to generate an intermediate that sequentially cyclizes and decarboxylates to afford a 3*H*-pyrrole. Subsequent 1,3-proton shift leads to the 1*H*-(trifluoromethyl)pyrrole[41] (Scheme 7.14; Table 7.10, Fig. 7.11).



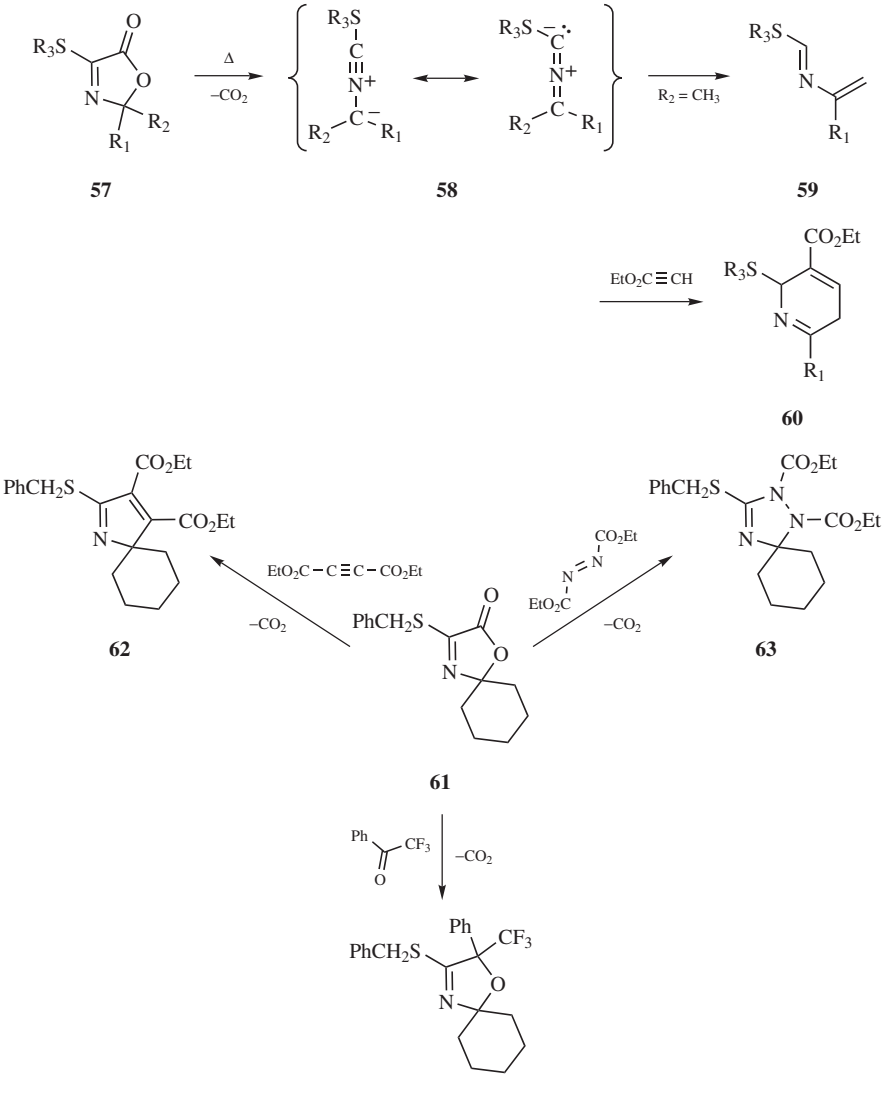
Scheme 7.14

Similarly, reaction of 4-aryl-2-(trifluoromethyl)-5(2*H*)-oxazolones **52** with substituted azo compounds, for example, PhN=NCO_2Et affords (trifluoromethyl)dihydrotriazoles.[42]

7.2.2.2. Generation of Nitrile Ylides

The thermolysis of 4-(alkylthio or arylthio)-5(2*H*)-oxazolones **57** in the presence of dipolarophiles with activated double bonds leads to five-membered cycloadducts.

These results are rationalized on the basis of the intermediate formation of thio-substituted nitrile ylides **58** that undergo regioselective 1,3-dipolar cycloadditions with the dipolarophiles. Some examples are shown in Scheme 7.15. If a dipolarophile is not present in the reaction mixture the nitrile ylides **58** ($R_2 = Me$) isomerize to give the 2-aza-1,3-butadienes **59** that can be trapped in a Diels–Alder reaction.[43,44]



Scheme 7.15

TABLE 7.10. 2-(TRIFLUOROMETHYL)PYRROLES FROM REACTION OF 5(2*H*)-OXAZOLONES WITH ELECTRON-DEFICIENT UNSATURATED COMPOUNDS

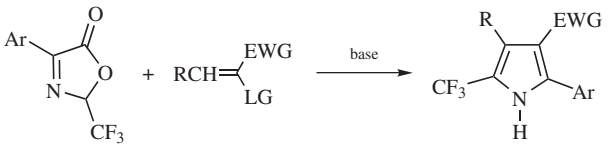
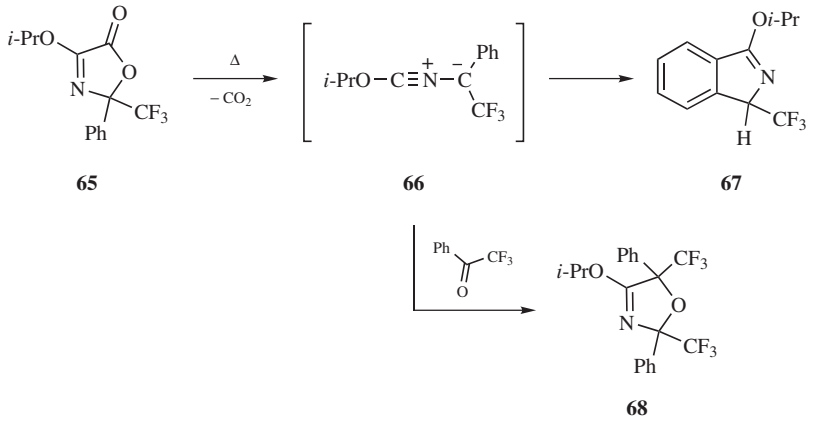


Figure 7.11

R	Ar	EWG	% Yield	References
H	Ph	CN	70–78	32,41
CF_3	4-ClC_6H_4	CF_3	70	36
H	3,5-$(Me_2)C_6H_3$	2-pyridyl	87	39
H	4-BrC_6H_4	CN	65	41
H	4-$MeOC_6H_4$	CN	74	41
H	Ph	CF_3	87	41

On heating, 4-(isopropoxy)-2-phenyl-2-(trifluoromethyl)-5(2*H*)-oxazolone **65** underwent decarboxylation to the alkoxy-substituted nitrile ylide **66** that was trapped in a 1,3-dipolar cycloaddition by trifluoroacetophenone to generate **68**.[45] Other dipolarophiles reacted similarly. In the absence of a dipolarophile, cyclization of **66** yielded the isoindole **67** (Scheme 7.16; Table 7.11, Fig. 7.12).



Scheme 7.16

7.2.2.3. Other Reactions

Aminolysis of some 4-alkyl-2-(trifluoromethyl)-5(2*H*)-oxazolones **69** has been published (Scheme 7.17; Table 7.12, Fig. 7.13).[46–48] Some degree of asymmetric

TABLE 7.11. GENERATION OF NITRILE YLIDES FROM 5(2*H*)-OXAZOLONES

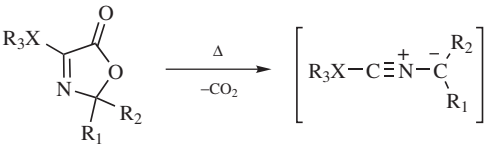
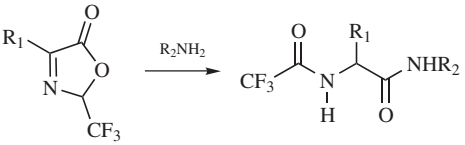


Figure 7.12

R_1	R_2	R_3X	% Yield	References
$(CH_2)_5$		$PhCH_2S$	not isolated	43,44
Me	Me	PhS	not isolated	43,44
CF_3	Ph	2-naphthylS	not isolated	43,44
CF_3	Ph	*i*-PrO	not isolated	45

induction is observed when chiral amines are used, a phenomenon that depends largely on solvents and on the nature of the amine. For example, aminolysis of **69** with (*S*)-phenylethylamine gave **70** mainly as the (*S*,*S*)-diastereomer. The same direction of induction was observed when chiral amino acid esters were used. For example, (*S*)-alanine or (*S*)-valine methyl esters afforded ring opening with high diastereoselectivity to afford (*S*,*S*)-dipeptides. In contrast, aminolysis with (*S*)-proline methyl ester gave mostly (*R*,*S*)-dipeptides.



69 **70**

Scheme 7.17

TABLE 7.12. AMINOLYSIS OF 5(2*H*)-OXAZOLONES

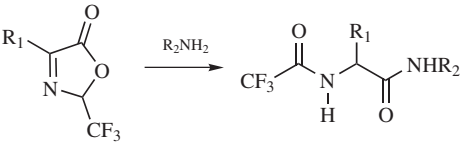
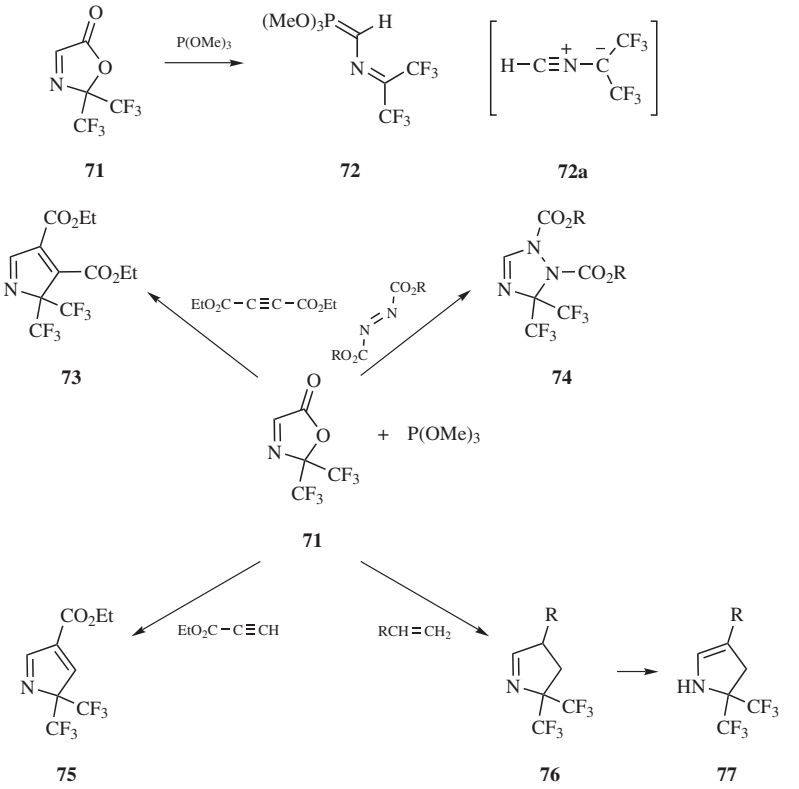


Figure 7.13

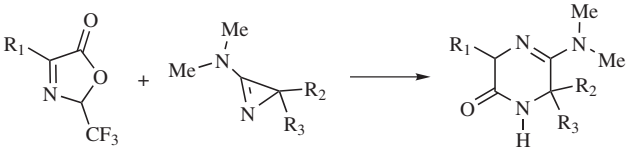
R_1	R_2	% Yield	Reference
$PhCH_2$	(*S*)-Ph(Me)CH	not described	47
i-Pr	(*S*)-Ph(Me)CH	not described	47
$PhCH_2$	(*S*)-$PhCH_2CHCO_2Me$	not described	48
i-Pr	(*S*)-$PhCH_2CHCO_2Me$	not described	48
$PhCH_2$	(*S*)-*i*-$PrCHCO_2Me$	not described	48
i-Pr	(*S*)-*i*-$PrCHCO_2Me$	not described	48



Scheme 7.18

Phosphites and 2,2-bis(trifluoromethyl)-5(2*H*)-oxazolone **71** react with elimination of carbon dioxide to give 2-aza-4-phospha-1,1-bis(trifluoromethyl)-1,3-butadiene **72** that can be used as a synthon for the previously unknown hydrogen-substituted nitrile ylide **72a** in [3 + 2]-cycloaddition reactions.[49] Examples of cycloadditions of **72a** with dipolarophiles to give heterocyclic compounds **73–77** are shown in Scheme 7.18.

4-Alkyl-2-(trifluoromethyl)-5(2*H*)-oxazolones **78** react with 3-(dimethylamino)-2*H*-azirines **79** (Scheme 7.19; Table 7.13, Fig. 7.14). This reaction, investigated mechanistically, has been described as a new procedure for the synthesis of 5-(dimethylamino)-3,6-dihydropyrazin-2(1*H*)-ones **80**.[50]



Scheme 7.19

TABLE 7.13. 5-(DIMETHYLAMINO)-3,6-DIHYDROPYRAZIN-2(1*H*)-ONES FROM REACTION OF 5(2*H*)-OXAZOLONES WITH 3-(DIMETHYLAMINO)-2*H*-AZIRINES

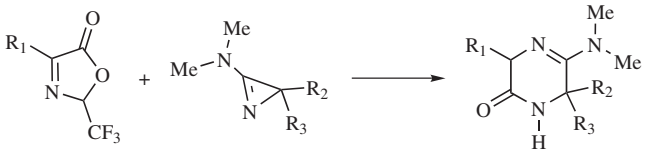
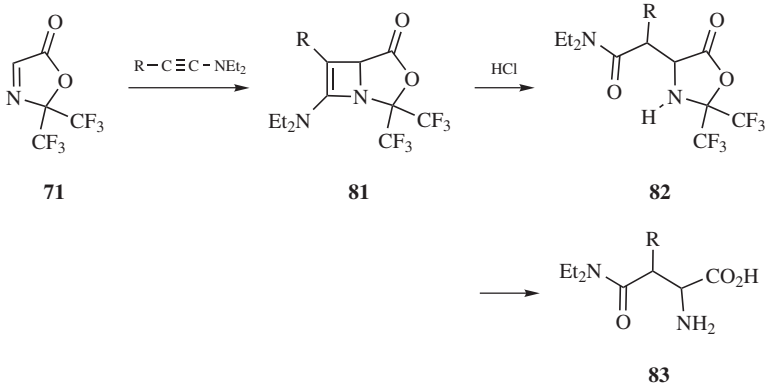


Figure 7.14

R_1	R_2	R_3	% Yield
$PhCH_2$	$(CH_2)_5$		57
i-Pr	Me	Me	60
$PhCH_2$	Me	Me	48
Ph	Me	Me	58

[a]Data from Ref. 50.

The double bond of 2,2-bis(trifluoromethyl)-5(2*H*)-oxazolone **71** reacts with ynamines[51] and the resulting cycloadduct **81** is converted into the corresponding amino acid after hydrolysis. The procedure constitutes a new route to 3-alkyl-substituted aspartic acid derivatives **83** (Scheme 7.20; Table 7.14, Fig. 7.15).



Scheme 7.20

Some unusual reactions have been described for 2-(4-chlorophenyl)-2-(3,3-dimethylallyl)-4-phenyl-5(2*H*)-oxazolone **84**. This compound undergoes a Lewis acid-catalyzed rearrangement to give a tetrahydrofuropyrrole **85**.[52] On the other hand, depending on the reaction conditions, thermolysis of **84** produces the azabicyclohexene **86** or a substituted 2,3-dihydropyridine **87** together with the caged compound **88** formed by dimerization of the 2,3-dihydropyridine and the azabicyclohexene (Scheme 7.21).[53,54]

TABLE 7.14. 3-ALKYL ASPARTIC ACID DERIVATIVES FROM REACTION OF 5(2*H*)-OXAZOLONES WITH YNAMINES[a]

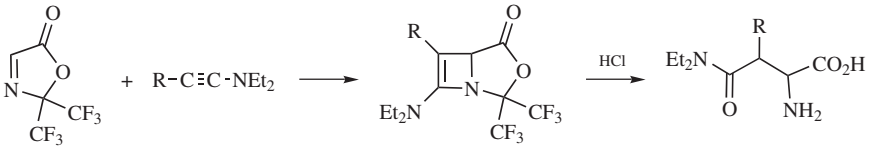
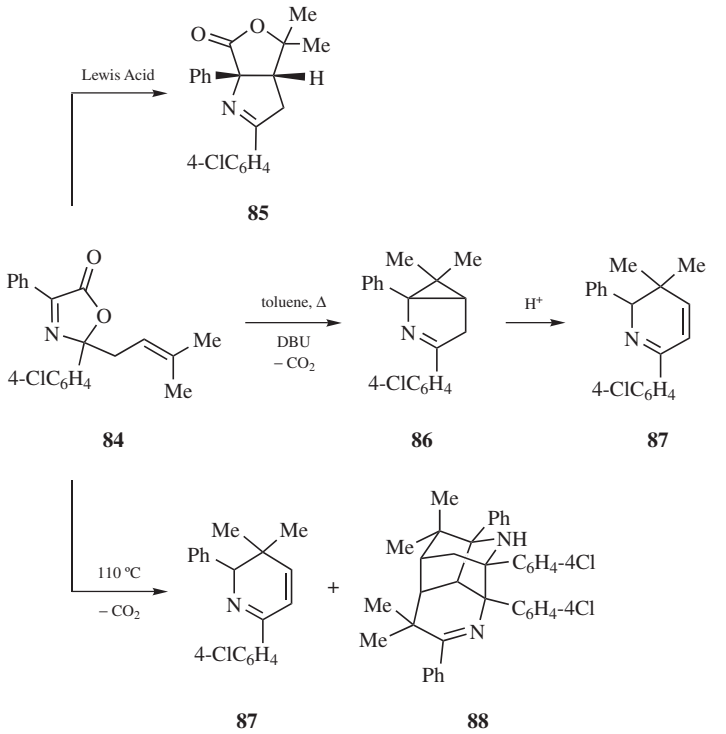


Figure 7.15

R	% Yield
Me	95
Et	95

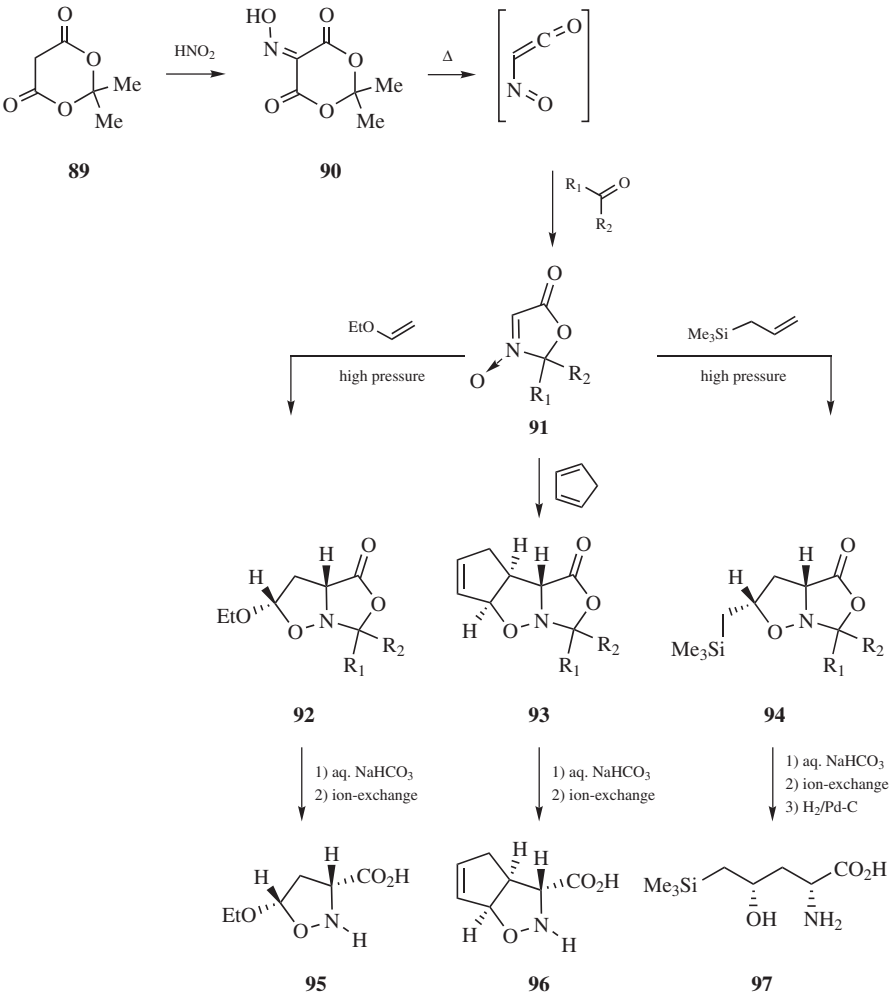
[a]Data from Ref. 51.



Scheme 7.21

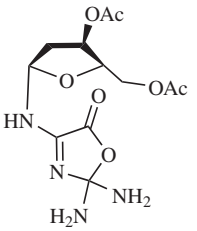
5(2*H*)-Oxazolone *N*-oxides **91** have been obtained by heating a solution of 5-isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione **90** with the corresponding ketone in toluene. It has been postulated that the reaction occurs through an intermediate nitrosoketene that is generated from **90** via loss of CO_2 and acetone, respectively.

These cyclic nitrones **91** react with electron-rich olefins in 1,3-cycloaddition reactions to afford fused isoxazolidines **92–94** from which several unusual amino acids **95–97** have been obtained (Scheme 7.22).[55]



Scheme 7.22

Several research groups have focused their attention on the photooxidation of 2′-deoxyguanosine that is used as a model compound for DNA. The major photooxidation products of this nucleoside were identified and classified according to their formation through a radical mechanism (type I) or a singlet oxygen-mediated mechanism (type II). The major type I product was identified as 2,2-diamino-[(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-amino]-5(2*H*)-oxazolone **98** (Fig. 7.16).[56–64]



98

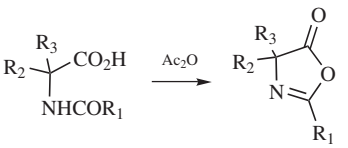
Figure 7.16. 2,2-Diamino-[(2-deoxy-β-D-*erythro*-pentofuranosyl)-4-amino]-5-(2*H*)-oxazolone **98**.

7.3. SATURATED 5(4*H*)-OXAZOLONES (2-OXAZOLIN-5-ONES)

7.3.1. Synthesis

7.3.1.1. Cyclization from Amino Acid Derivatives

It was shown previously that saturated 5(4*H*)-oxazolones or 2-oxazolin-5-ones with only one substituent at C-4 can be considered as the tautomeric form of saturated 5(2*H*)-oxazolones or 3-oxazolin-5-ones. These compounds can also be considered as amino acid derivatives and, indeed, cyclization procedures are the most commonly used to prepare these compounds. The cyclization reaction employs a variety of cyclodehydrating agents and the general method is shown in Scheme 7.23, with an *N*-acyl-α-amino acid being the most typical starting material used. In this way, 5(4*H*)-oxazolones derived from most natural amino acids **99** ($R_3 = H$) have been obtained by heating the corresponding *N*-acyl derivatives in the presence of acetic anhydride.[1,65–68]

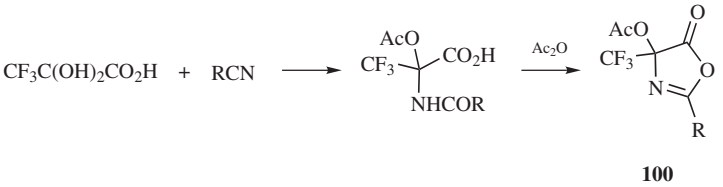


99

Scheme 7.23

The procedure is also useful for the synthesis of 4,4-disubstituted 5(4*H*)-oxazolones. For example, cyclization of a 2-aryl(hetaryl)carbonylamino-2-arylpropionic acid afforded the corresponding oxazolones **99** ($R_3 = Me$) that were evaluated as selective herbicides.[69]

A slight modification of this procedure using *N*-acyl-α-amino acids obtained from trifluoropyruvic acid and the corresponding nitrile has been described.[70] In



100

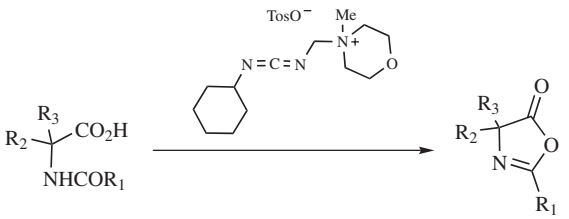
Scheme 7.24

this case, 4-acetoxy-2-substituted-4-(trifluoromethyl)-5(4*H*)-oxazolones **100** are obtained (Scheme 7.24).

The synthesis of 2-(trifluoromethyl) derivatives is more difficult and the compound preferentially obtained depends on the substituents and on the reaction conditions. Thus, the reaction of tryptophan with TFAA gives the 5(4*H*)-oxazolone without racemization.[4,5] However, when this optically active product is dissolved in acetonitrile the racemic 5(4*H*)-oxazolone is obtained. On the other hand, treatment of the optically active compound with hot aqueous dioxane gave the isomeric 5(2*H*)-oxazolone (see Scheme 7.2).

Treatment of 2-(1-adamantyl)glycine with TFAA gave 4-(1-adamantyl)-2-(trifluoromethyl)-5(4*H*)-oxazolone in high yield.[71] A 2-(trifluoromethyl)-5(4*H*)-oxazolone derived from serine has been obtained from *O*-trimethylsilyl-*N*-(trifluoroacetyl)serine diethylamide.[72]

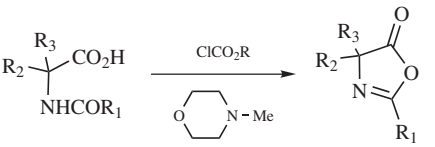
Cyclization of *N*-acyl-α-amino acids under acidic reaction conditions is sometimes problematic due to the difficulty in separation of the desired oxazolone from by-products while avoiding decomposition of the reactive oxazolone. This finding is particularly true in the case of 2-phenyl-5(4*H*)-oxazolone, an interesting compound that is a very useful intermediate to prepare a variety of novel products. The use of carbodiimides as dehydrating agents has been described as a means to improve the results. In particular, treatment of an *N*-acyl-α-amino acid with *N*-cyclohexyl-*N*′-2-(*N*-methylmorpholinio)ethylcarbodiimide *p*-toluensulfonate (Scheme 7.25) is especially useful as a general synthesis of the desired saturated 5(4*H*)-oxazolones **101** in excellent yields.[73,74] This same carbodiimide was used to study the kinetics of the formation of saturated 5(4*H*)-oxazolones from N-protected dipeptides.[75]



101

Scheme 7.25

The use of mixed anhydrides derived from *N*-acyl-α-amino acids has become an interesting strategy for synthesis of saturated 5(4*H*)-oxazolones **101** (Scheme 7.26). For example, reaction of *N*-acyl-α-amino acids with methyl chloroformate in the presence of *N*-methylmorpholine affords racemic 5(4*H*)-oxazolones.



101

Scheme 7.26

In the cases where optically active substrates were used as starting materials, chiral, saturated 5(4*H*)-oxazolones were obtained with good enantiomeric excesses (ee).[76] Oxazolones derived from *N*-formyl-α-amino acids are better prepared using isopropenyl chloroformate, rather than methyl chloroformate, in the presence of *N*-methylmorpholine.[77]

2-Phenyl-5(4*H*)-oxazolone has been obtained during alkaline hydrolysis of *p*-nitrophenyl *N*-benzoylglycinate. A detailed study of this process has shown that the leaving group expulsion is the rate-determining step for conversion of the glycinate to the 5(4*H*)-oxazolone.[78]

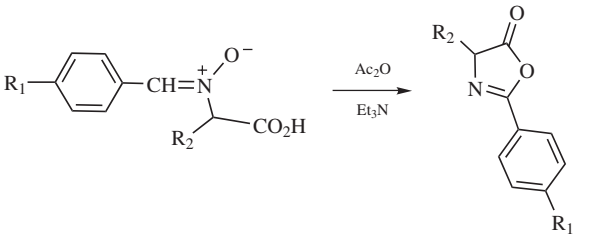
In addition to the typical cyclization procedures described above, methods involving the use of other mild, cyclodehydrating agents have been published. For example, cyanuric chloride in the presence of triethylamine,[79] 2-ethoxy-*N*-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) or 2-isobutoxy-*N*-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ),[80] *N*,*N*-dimethylchlorosulfitemethaniminium chloride[81] and several haloiminium salts[82] have proved to be very useful reagents.

The use of N-acylated-α-amino nitriles,[83] nitrones,[84] or α-amino amides[85] as starting compounds have also been reported. N-Acylated-α-amino nitriles were converted into 5(4*H*)-oxazolones **101** in the presence of ethyl chlorooxoacetate (Scheme 7.27).[83]

101

Scheme 7.27

Nitrones such as **102** gave 2-aryl-4-substituted-5(4*H*)-oxazolones **103** in the presence of acetic anhydride and triethylamine (Scheme 7.28).[84] Selected examples of saturated-5(4*H*)-oxazolones prepared via cyclization of amino acids are shown in Table 7.15 (Fig. 7.17).



102 **103**

Scheme 7.28

2-Acylamino-*N*,*N*-2-trimethylpropionamides **104**, obtained from 2,2-dimethyl-3-(dimethylamino)-2*H*-azirine and carboxylic acids, were hydrolyzed to the corresponding carboxylic acids and then cyclized to the 4,4-dimethyl-2-substituted-5(4*H*)-oxazolones **105**. This reaction sequence including ring opening of the 5(4*H*)-oxazolone with amino acids is a very interesting methodology to prepare Aib-containing peptides **106** (Scheme 7.29).[86]

TABLE 7.15. SYNTHESIS OF SATURATED 5(4*H*)-OXAZOLONES VIA CYCLIZATION OF AMINO ACID DERIVATIVES

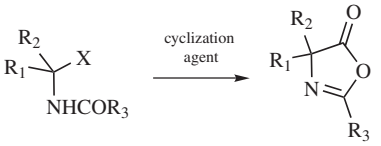
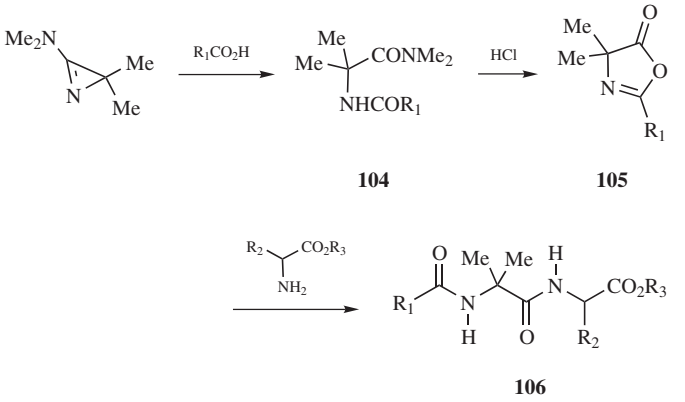


Figure 7.17

X	Cyclization Agent	R_1	R_2	R_3	% Yield	References
CO_2H	TFAA	indol-3-ylmethyl	H	CF_3	90	4,5
CO_2H	Ac_2O	4-MeC_6H_4	H	3-ClC_6H_4	80	69
CO_2H	TFAA	H	1-adamantyl	CF_3	86	71
CO_2H	morphoCDI[a]	H	H	Ph	90	74
CO_2H	morphoCDI[a]	H	H	*t*-Bu	84	74
CO_2H	morphoCDI[a]	Me	Me	Ph	82	74
CO_2H	$ClS(O)CHNMe_2Cl$	H	Me	Ph	~85	81
$CONMe_2$	HCl/toluene	Me	Me	Ph	90	85
$CONMe_2$	HCl/toluene	Me	Me	2-HOC_6H_4	85	85
$CONMe_2$	HCl/toluene	Me	Me	$Ph_2C(OH)$	90	85

[a]*N*-Cyclohexyl-*N*′-2-(*N*-methylmorpholinio)ethylcarbodiimide *p*-toluensulfonate.



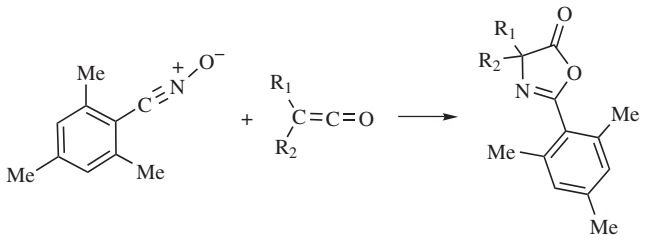
104 **105**

106

Scheme 7.29

7.3.1.2. Other Cyclization Procedures

A new and completely different methodology involving a cycloaddition reaction has been described.[87] The reaction between diphenylketene, *tert*-butylcyanoketene or dimethylketene with 2,4,6-trimethylbenzonitrile *N*-oxide gave the corresponding 5(4*H*)-oxazolones **107** in moderate yields (Scheme 7.30).

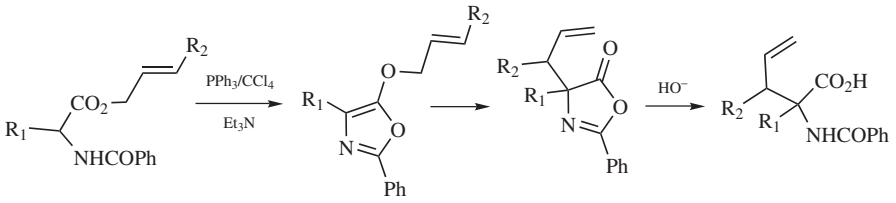


107

Scheme 7.30

7.3.1.3. Rearrangement of Oxazoles

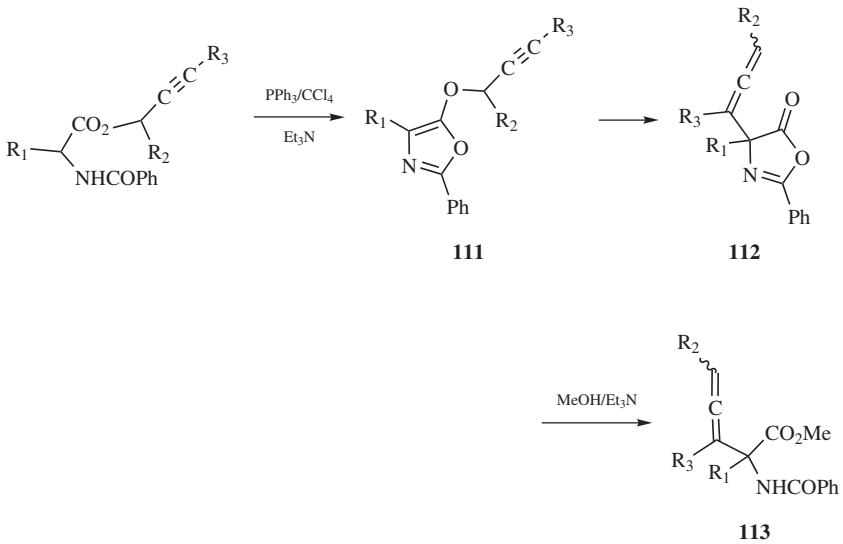
Allylic esters of *N*-acyl-α-amino acids were rearranged to the γ,δ-unsaturated α-amino acids **110** through an Ireland–Claisen rearrangement in moderate to good yields and with good diastereoselectivities.[88] Under certain conditions this process involves the formation of an intermediate oxazole **108** that was converted to the corresponding oxazolone **109** by [3,3] sigmatropic rearrangement (Scheme 7.31).



108 **109** **110**

Scheme 7.31

In a similar way, propargyl esters of *N*-benzoyl-α-amino acids have been converted into α-allenyl-α-amino acid esters **113** by cyclization to oxazoles **111** followed by Claisen rearrangement to the 4-allenyl-2-phenyl-5(4*H*)-oxazolones **112**. Oxazolone ring opening with methanol then afforded **113** (Scheme 7.32).[89]

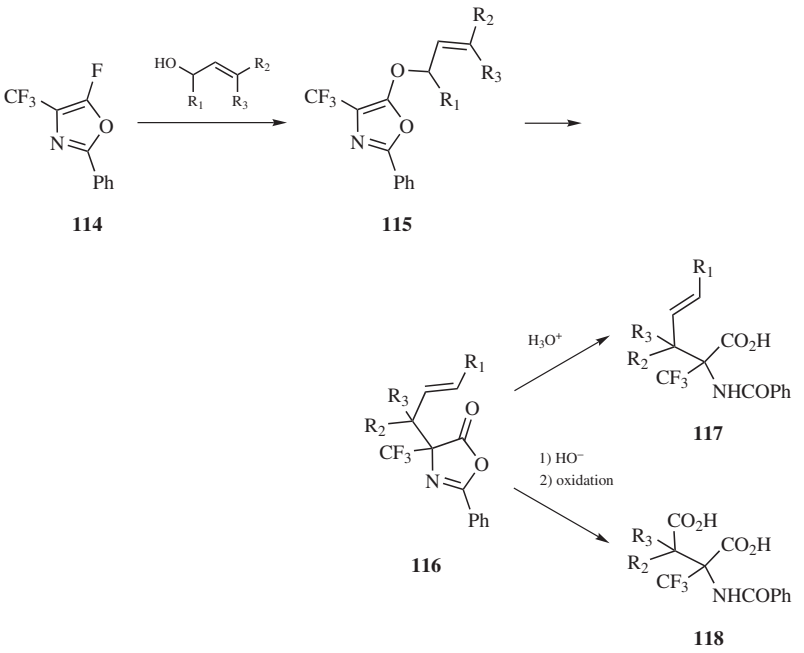


111 **112**

113

Scheme 7.32

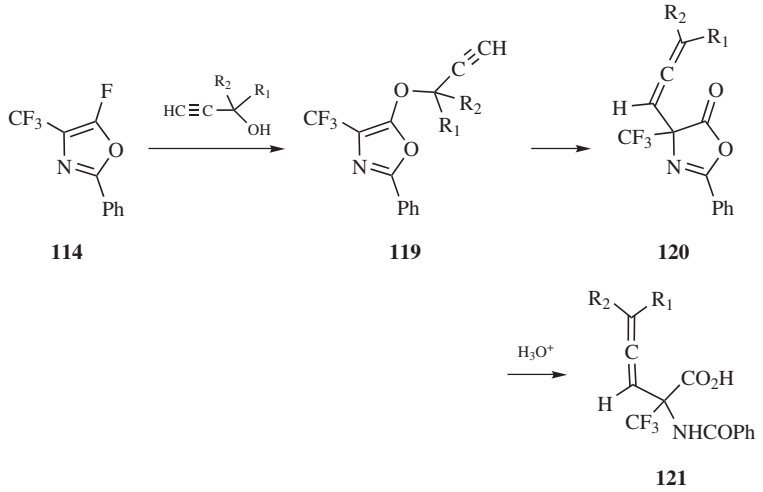
Since the rearrangement occurs via the corresponding 5-alkoxyoxazoles, a new strategy was developed starting from these heterocycles. Nucleophilic displacement of fluoride in 5-fluoro-2-phenyl-4-(trifluoromethyl)oxazole **114** with allylic alcohols gave the allylic ethers **115** that subsequently yielded the saturated oxazolones **116** through a Claisen rearrangement. 2-Substituted 3,3,3-trifluoroalanine derivatives **117**[90] or α-(trifluoromethyl)-β-substituted aspartic acid derivatives **118**[91] could be obtained readily from **116** after hydrolysis or hydrolysis followed by oxidation (Scheme 7.33).



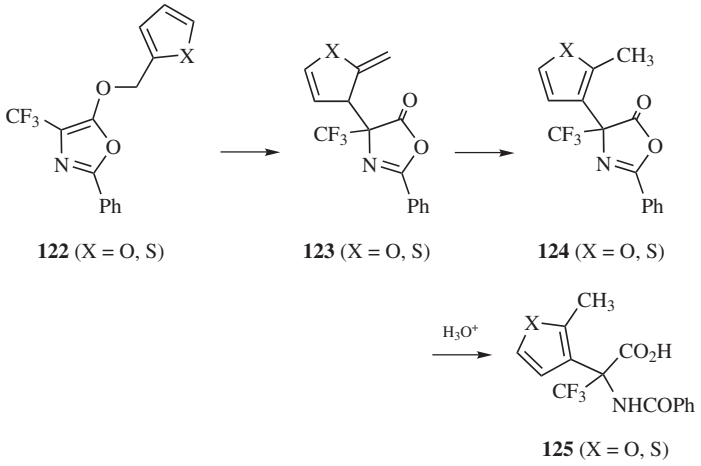
Scheme 7.33

Similarly, the allenic derivatives **120** and **121** have been obtained from propargylic alcohols as shown in Scheme 7.34.[90]

The use of 2-(hydroxymethyl)furan or 2-(hydroxymethyl)thiophene as allylic alcohols gives rise to α-(trifluoromethyl)-α-(2-heteroaryl)glycine derivatives **125** after hydrolysis of the corresponding oxazolone **124** as shown in Scheme 7.35.[91]

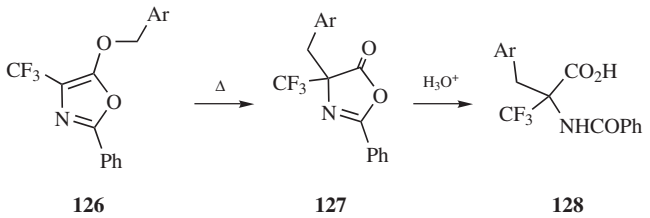


Scheme 7.34



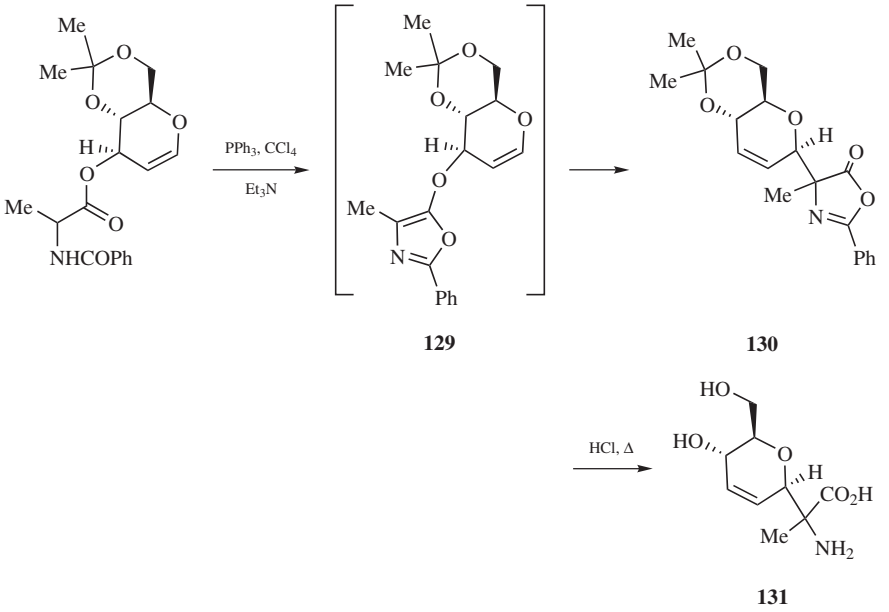
Scheme 7.35

Heating 5-(arylmethyloxy)-2-phenyl-4-(trifluoromethyl)oxazoles **126** effects thermal rearrangement to 4-(arylmethyl)-2-phenyl-4-(trifluoromethyl)-5(4*H*)-oxazolones **127**.[92–94] In some cases, the formation of 2-(arylmethyl)-2-phenyl-4-(trifluoromethyl)-5(2*H*)-oxazolones has been reported.[93] Hydrolysis of **127** constitutes a new general route to α-(arylmethyl)-α-(trifluoromethyl) α-amino acids **128** (Scheme 7.36).[92] In this case, isolation of mixed products in crossover experiments indicates that the rearrangement is not a sigmatropic process but involves a 1,3-benzyl shift. 5-(Benzyloxy)-2-phenyl-4-(trifluoromethyl)oxazole and 4-benzyl-2-phenyl-4-(trifluoromethyl)-5(4*H*)-oxazolone have been studied as enzyme inhibitors for amino acid decarboxylases and transaminases.[94]



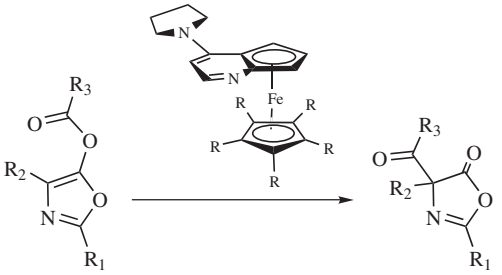
Scheme 7.36

β-D-*C*-Allosyl-(*R*)-alanine **131** was synthesized from the β-*C*-glycosyloxazolone **130** that was obtained from the corresponding protected D-glucal by a sequential coupling with *N*-benzoylalanine followed by a Claisen rearrangement (Scheme 7.37). The oxazolone was obtained as a mixture of two diastereoisomers in a 3:1 ratio. The process involves the formation and rearrangement of an intermediate oxazole **129** that could not be detected.[95]



Scheme 7.37

It is known that 5-acyloxyoxazoles **132** rearrange to 4-acyl-5(4*H*)-oxazolones **133** in the presence of 4-(dimethylamino)pyridine or 4-(pyrrolidino)pyridine. Recently, an asymmetric variant of this nucleophile-catalyzed rearrangement that employs a chiral derivative of 4-(pyrrolidino)pyridine has been described. This procedure allows the construction of quaternary stereocenters with high levels of enantioselectivity (Scheme 7.38).[96,97] Representative examples of saturated 5(4*H*)-oxazolones prepared via sigmatropic rearrangements are shown in Table 7.16 (Fig. 7.18).



132 **133**
ee = 42-95 %

Scheme 7.38

TABLE 7.16. SYNTHESIS OF SATURATED 5(4*H*)-OXAZOLONES VIA SIGMATROPIC REARRANGEMENT OF 5-ALKOXYOXAZOLES

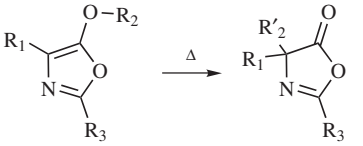


Figure 7.18

R_1	R_2	R'_2	R_3	% Yield	References
H	$MeCH{=}CHCH_2$	$MeCHCH{=}CH_2$	Ph	65	88
Me	$MeCH{=}CHCH_2$	$MeCHCH{=}CH_2$	Ph	71	88
$PhCH_2$	$HC{\equiv}CCH_2$	$CH{=}C{=}CH_2$	Ph	~100	89
$PhCH_2$	$MeC{\equiv}CCH_2$	$MeC{=}C{=}CH_2$	Ph	~100	89
$PhCH_2$	$HC{\equiv}CCHMe$	$CH{=}C{=}CHMe$	Ph	~100	89
CF_3	2-furylmethyl	5-methyl-2-furyl	Ph	47	92
Me	CO_2Bn	CO_2Bn	4-$MeOC_6H_4$	94	96,97

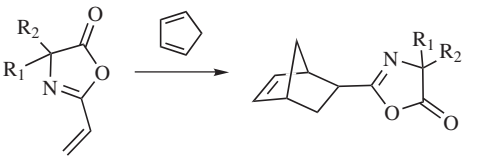
7.3.1.4. From Other Oxazolones

7.3.1.4.1. From 5(2*H*)-Oxazolones

As discussed previously, alkylation of 4-benzyl-2-(trifluoromethyl)-5(2*H*)-oxazolone **16** in the presence of mild base using active alkyl halides occurs at C-4 to afford α,α-dialkyl-5(4*H*)-oxazolones (Scheme 7.5).[14]

7.3.1.4.2. Saturated 5(4*H*)-Oxazolones via Modifications at C-2

Saturated 2-vinyl-5(4*H*)-oxazolones have been widely used as intermediates for the synthesis of polymeric compounds that will be described in Section 7.3.2.9. Apart from these polymerization reactions, the Diels–Alder reactions of 4-substituted-2-vinyl-5(4*H*)-oxazolones **134** with cyclopentadiene are reported to give norbornenyl oxazolones **135**[98,99] that are useful to prepare norbornenyl functionalized resins by azlactone ring-opening addition reactions (Scheme 7.39).

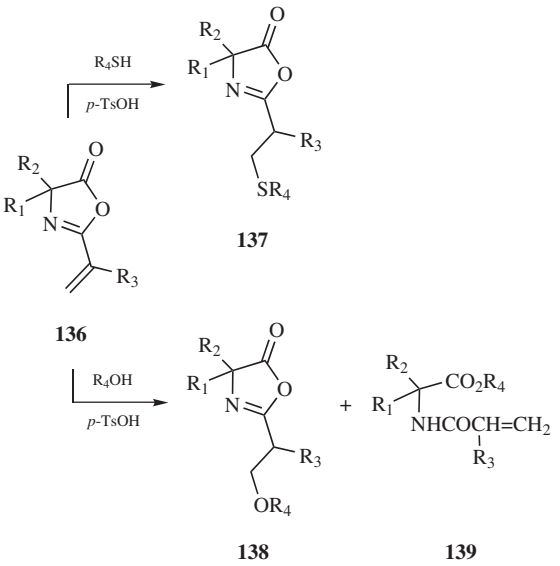


134 **135**

Scheme 7.39

The vinyl substituent at C-2 can also act as a Michael acceptor and reaction with certain nucleophiles gives rise to 1,4-addition compounds. For example, *p*-toluenesulfonic acid catalyzed addition of thiols to 2-vinyl- or 2-isopropenyl-5(4*H*)-oxazolones **136** gave, almost exclusively, the Michael adducts **137** that were used

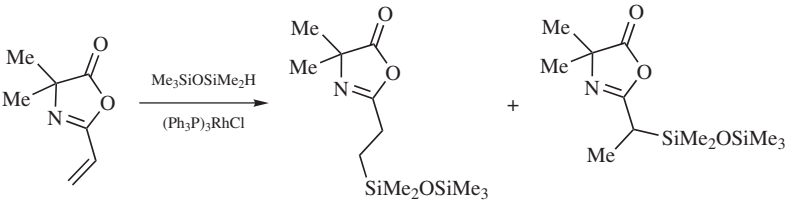
as curing agents for epoxy and isocyanate resins.[100] On the other hand, acid-catalyzed addition of primary alcohols to 4,4-dimethyl-2-vinyl-5(4*H*)-oxazolone **136** ($R_1 = R_2 = Me$, $R_3 = H$) gave **138** and **139** as an ~50:50 mixture, whereas with secondary and tertiary alcohols the Michael adducts **138** were preferentially obtained. Interestingly, the reaction of 4,4-dimethyl-2-isopropenyl-5(4*H*)-oxazolone **136** ($R_1 = R_2 = R_3 = Me$) with phenethyl alcohol effected ring opening to afford compound **139** ($R_1 = R_2 = R_3 = Me$, $R_4 = CH_2CH_2Ph$) cleanly (Scheme 7.40).[101]



136 **137** **138** **139**

Scheme 7.40

Finally, hydrosilylation of 2-alkenyl-5(4*H*)-oxazolones in the presence of an appropriate catalyst normally afforded β-addition compounds, for example, **141**, although 4,4-dimethyl-2-vinyl-5(4*H*)-oxazolone **140** also yielded the corresponding α-addition compound **142** (Scheme 7.41).[102]



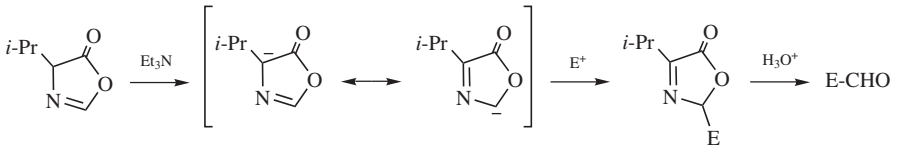
140 **141** **142**

Scheme 7.41

7.3.1.4.3. Saturated 5(4*H*)-Oxazolones via Modifications at C-4

ALKYLATION. Saturated 5(4*H*)-oxazolones are readily available compounds that can be easily obtained from a wide variety of natural amino acid derivatives. These heterocyclic compounds can be considered as nucleophilic synthons of α-amino acids and their most exploited reactivity, apart from oxazolone ring opening, is the reaction at C-4 with a variety of electrophiles.

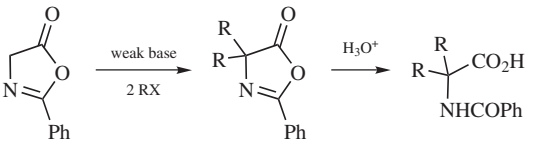
The behavior of 2-substituted- or 2-unsubstituted-5(4*H*)-oxazolones is completely different. Reaction of electrophiles with 2-substituted-5(4*H*)-oxazolones usually occurs at C-4, whereas reaction of electrophiles with 2-unsubstituted-5(4*H*)-oxazolones affords the corresponding 5(2*H*)-oxazolones. The best example of the behavior of 2-unsubstituted-5(4*H*)-oxazolones involves 4-isopropyl-5(4*H*)-oxazolone **143**, the anion of which can be considered as a formyl anion equivalent.[103,104] Thus, reaction of **143** with a catalytic amount of triethylamine gives **144** that reacts with α,β-unsaturated carbonyl compounds to afford Michael adducts or with aldehydes to produce the corresponding aldol adducts. Mild acid hydrolysis of **145** yields the corresponding aldehydes (Scheme 7.42).



143 **144** **145**

Scheme 7.42

Alkylation of saturated 5(4*H*)-oxazolones at C-4 is a well-known reaction that can be achieved under a wide variety of conditions. Numerous articles have described this reaction as a means to prepare 4,4-dialkyl-5(4*H*)-oxazolones **147** that are valuable intermediates to prepare α,α-disubstituted α-amino acids. For instance,[105] 2-phenyl-5(4*H*)-oxazolone **146** readily obtained from hippuric acid and *N*,*N*′-dicyclohexylcarbodiimide (DCC), is alkylated at C-4 with allyl, benzyl, or phenacyl halides if the reaction is conducted in dipolar aprotic solvents in the presence of weak bases. Hydrolysis of the resulting 5(4*H*)-oxazolones leads to α,α-dialkylglycines **148** (Scheme 7.43).



146 **147** **148**

Scheme 7.43

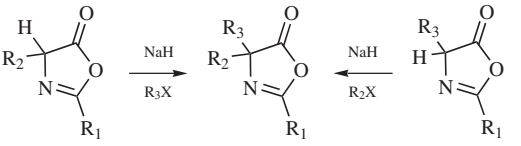
The alkylation of 2-aryl-4-phenyl-5(4*H*)-oxazolones like **22** is strongly dependent upon the nature of the substituent on the aromatic ring at C-2. For electron-rich

aryl substituents, the C-4 alkylated compounds are the main products as shown in Scheme 7.7.[15] In other cases, alkylation occurs exclusively at C-4.[106]

Alkylation of 2,4-disubstituted-5(4*H*)-oxazolones can be conveniently performed via phase-transfer catalysis. For example, the substrate and an alkyl halide are dissolved in an organic solvent and stirred with an aqueous sodium carbonate solution containing tetrabutylammonium bromide as a phase-transfer catalyst.[107]

4,4-(Diarylmethyl)-2-phenyl-5(4*H*)-oxazolones can be prepared in one-step by dialkylation of **146** using magnesium methyl carbonate and the corresponding arylmethyl halide.[108,109] 4-Methyl(or benzyl)-2-phenyl-5(4*H*)-oxazolone is benzylated or methylated in the presence of potassium carbonate, potassium hydroxide or diisopropylethylamine and a phase-transfer catalyst to yield the corresponding 4,4-dialkyl-5(4*H*)-oxazolone, which upon hydrolysis affords α-methyl- or α-benzylphenylalanine.[110]

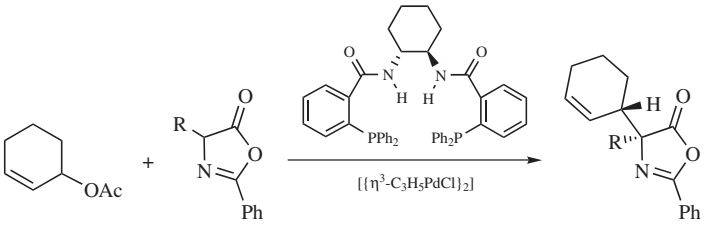
Recently, a new and generally applicable procedure for efficient α-alkylation of 2-phenyl-4-substituted-5(4*H*)-oxazolones **149** and **151** has been described.[111] A valuable feature of this approach is that, depending on the availability and ease of preparation of the starting oxazolone and the reactivity of the electrophile, two complementary approaches are available (Scheme 7.44). This synthetic methodology opens interesting possibilities for the synthesis of novel α-amino acids that combine two side chains of proteinogenic and non-proteinogenic amino acids—so-called ''chimeras''.



149 **150** **151**

Scheme 7.44

An asymmetric alkylation of 2-phenyl-4-substituted-5(4*H*)-oxazolones **152** has been described recently.[112,113] This approach is based on palladium-catalyzed allylic alkylations of **152** using 3-acetoxycyclohexene as reagent. The reaction occurs with excellent enantioselectivity for the major diastereoisomer and opens the way for the asymmetric synthesis of quaternary α-amino acids, important building blocks in peptide synthesis (Scheme 7.45).

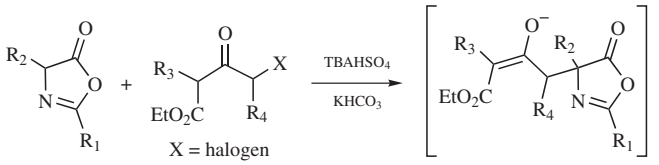


152 **153**

Scheme 7.45

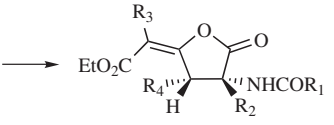
Other allylating agents have been employed in this enantioselective reaction with different results. Moderate-to-low ee's are obtained with highly symmetrical allylating agents, whereas 1-monosubstituted and 1,1-disubstituted allyl reagents gave ee's >90%.[114,115] This allylation was the key step in the stereoselective synthesis of some sphingosine analogues.[116]

Alkylation of oxazolones with α-halo ketones under phase-transfer catalysis generated an enolate **155** from initial alkylation at C-4 that immediately translactonized to produce an enol lactone **156** (Scheme 7.46).[117] Selected examples of 5(4*H*)-oxazolones prepared via alkylation are shown in Table 7.17 (Fig. 7.19).



154 **155**

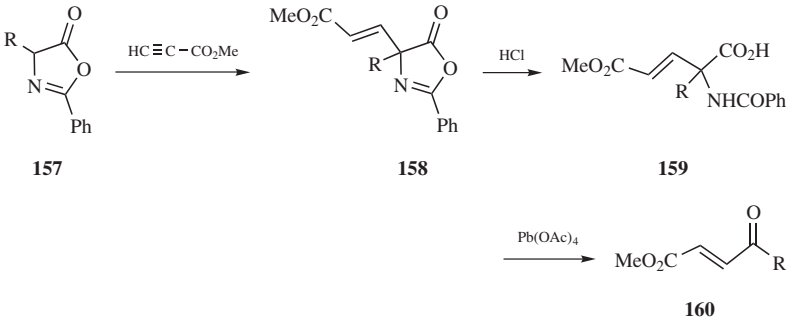
$TBAHSO_4$ = tetrabutylammonium hydrogensulfate



156

Scheme 7.46

MICHAEL REACTION. 5(4*H*)-Oxazolones undergo base-catalyzed conjugate addition to activated unsaturated compounds to afford the corresponding C-4 Michael adducts. For example, base-catalyzed addition of a 4-monosubstituted-5(4*H*)-oxazolone **157** to methyl propiolate yields a mixture of diastereomeric methyl 3-(5-oxo-2-phenyl-2-oxazolin-4-yl)acrylates **158**. Hydrolytic ring opening of **158** and subsequent oxidation with lead tetraacetate affords 3-acylacrylates **160** (Scheme 7.47).[118]

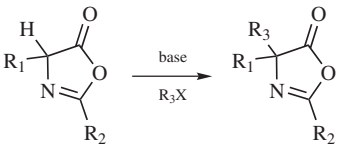


157 **158** **159**

160

Scheme 7.47

TABLE 7.17. SYNTHESIS OF SATURATED 2,4,4-TRISUBSTITUTED 5(4*H*)-OXAZOLONES VIA ALKYLATION OF SATURATED 5(4*H*)-OXAZOLONES AT C-4

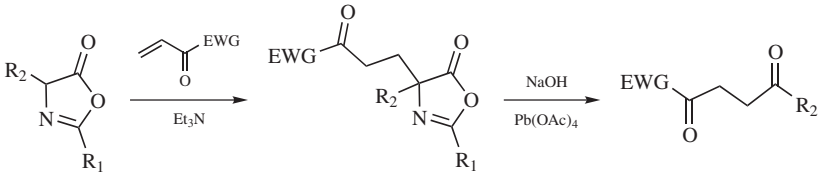


X = Br, I, OAc

Figure 7.19

R_1	R_2	R_3	% Yield	Reference
Ph	Ph	Me	61	107
Ph	Ph	CH_2=$CHCH_2$	77	107
Ph	Ph	EtO_2CCH_2	57	107
Me	Ph	Me	19	107
Me	Ph	CH_2=$CHCH_2$	49	107
Me	Ph	EtO_2CCH_2	40	107
$PhCH_2$	Ph	*t*-BuO_2CCH_2	69	111
i-Bu	Ph	*t*-BuO_2CCH_2	68	111
t-$BuO_2CCH_2CH_2$	Ph	Me	50	111
Me	Ph	2-cyclohexen-1-yl	73	112
$PhCH_2$	Ph	2-cyclohexen-1-yl	75	112
t-Bu	Ph	2-cyclohexen-1-yl	91	112
Me	Ph	Me_2C=$CHCH_2$	67	115
$PhCH_2$	Ph	Me_2C=$CHCH_2$	62–78	115
i-Pr	Ph	Me_2C=$CHCH_2$	47	115

This procedure is an excellent method to prepare 1,4-dicarbonyl compounds **163** (Scheme 7.48) and, using triethylamine, has been extended to include other activated double bonds.[119] Thus, the starting α-amino acids can be considered as nucleophilic acyl equivalents. Representative examples of 5(4*H*)-oxazolones prepared via Michael additions are shown in Table 7.18 (Fig. 7.20).



161 **162** **163**

Scheme 7.48

In those cases, where conjugated 1,3-dicarbonyl compounds have a leaving group in the β-position, reaction with a 5(4*H*)-oxazolone occurs via an addition–elimination reaction sequence to give, after cyclization, pyran-2-ones **165**

TABLE 7.18. SYNTHESIS OF SATURATED 2,4,4-TRISUBSTITUTED 5(4*H*)-OXAZOLONES BY REACTION OF SATURATED 5(4*H*)-OXAZOLONES WITH MICHAEL ACCEPTORS

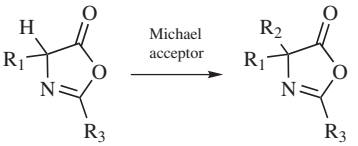
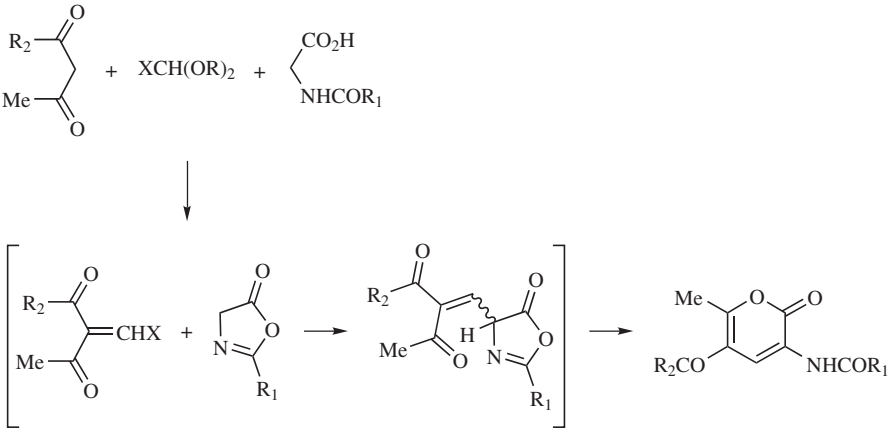


Figure 7.20

R_1	Michael Acceptor	R_2	R_3	% Yield	Reference
t-Bu	$HC{\equiv}CCO_2Me$	$MeO_2CCH{=}CH$	Ph	87	118
$PhCH_2$	$HC{\equiv}CCO_2Me$	$MeO_2CCH{=}CH$	Ph	76	118
$MeO_2C(CH_2)_2$	$HC{\equiv}CCO_2Me$	$MeO_2CCH{=}CH$	Ph	85	118
$PhCONH(CH_2)_4$	$HC{\equiv}CCO_2Me$	$MeO_2CCH{=}CH$	Ph	84	118
i-Pr	$CH_2{=}CHCOMe$	$MeCOCH_2CH_2$	$2,4,6\text{-}Me_3C_6H_2$	82	119
i-Pr	$CH_2{=}CHCN$	$NCCH_2CH_2$	$2,4,6\text{-}Me_3C_6H_2$	82	119
$PhCH_2$	$CH_2{=}CHCOMe$	$MeCOCH_2CH_2$	$2,4,6\text{-}Me_3C_6H_2$	89	119
$PhCH_2$	$CH_2{=}CHCOPr$	$PrCOCH_2CH_2$	$2,4,6\text{-}Me_3C_6H_2$	85	119
$PhCH_2$	$CH_2{=}CHCN$	$NCCH_2CH_2$	$2,4,6\text{-}Me_3C_6H_2$	87	119
$PhCH_2$	$CH_2{=}CHCO_2Me$	$MeO_2CCH_2CH_2$	$2,4,6\text{-}Me_3C_6H_2$	83	119

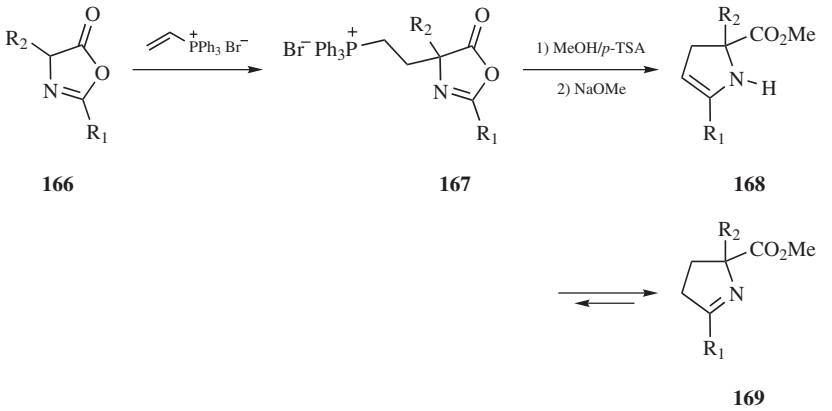
(Scheme 7.49). The requisite activated double bond is generated *in situ* from the 1,3-dicarbonyl compound and a one-carbon synthon such as a trialkyl orthoformate, diethoxymethyl acetate or *N*,*N*-dimethylformamide dimethyl acetal.[120]

It has also been reported[121] that some 4-substituted-5(4*H*)-oxazolones **166** undergo Michael addition to triphenylvinylphosphonium bromide to give the corresponding 4,4-disubstituted-5(4*H*)-oxazolones **167** from which ring opening



164 **165**

Scheme 7.49



166 **167** **168**

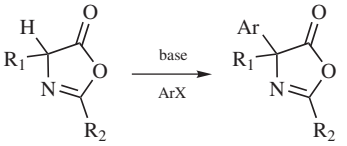
169

Scheme 7.50

and intramolecular Wittig reaction afford pyrroline-2-carboxylic acid esters **169** (Scheme 7.50).

ARYLATION. Arylation of 2,4-diaryl-5(4*H*)-oxazolones **170** with activated aryl halides has been reported to proceed under phase-transfer conditions (Scheme 7.51).[122] The yields of 2,4-diaryl-4-(2,4-dinitroaryl)-5(4*H*)-oxazolones **171** are often modest. Heteroarylation of **170** was accomplished using 2-chloro-3,5-dinitropyridine. Representative examples are shown in Table 7.19 (Fig. 7.21).

TABLE 7.19. SYNTHESIS OF SATURATED 2,4,4-TRISUBSTITUTED 5(4*H*)-OXAZOLONES VIA ARYLATION OF SATURATED 5(4*H*)-OXAZOLONES AT C-4

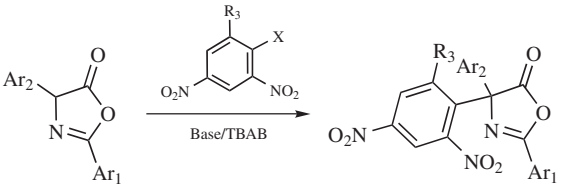


X = F, Cl

Figure 7.21

R_1	R_2	Ar	% Yield
Ph	4-$MeOC_6H_4$	2,4-$(NO_2)_2C_6H_3$	35
Ph	4-$MeOC_6H_4$	2,4,6-$(NO_2)_3C_6H_2$	34
i-Pr	Ph	2,4-$(NO_2)_2C_6H_3$	28
Ph	*i*-Pr	2,4-$(NO_2)_2C_6H_3$	49
4-ClC_6H_4	4-MeC_6H_4	2,4-$(NO_2)_2C_6H_3$	20
4-$MeOC_6H_4$	4-MeC_6H_4	2,4-$(NO_2)_2C_6H_3$	52

[a]Data from Ref. 122.

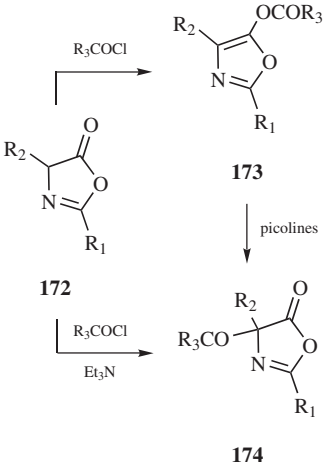


170 **171**

TBAB = tetrabutylammonium bromide

Scheme 7.51

ACYLATION. Acylation at C-4 of 4-unsubstituted or 4-monosubstituted 5(4*H*)-oxazolones **172** has been described using two different strategies. Depending on the nature of the substituents in the starting oxazolone, the nature of the acylating agent and the experimental conditions, two different products can be obtained. In general, it should be noted that, in the presence of triethylamine, acylation occurs at C-4, although in some cases the major product is the 5-acyloxyoxazole **173** that arises from O-acylation. In these cases, **173** can be rearranged to the desired 4-acyl-5(4*H*)-oxazolone **174** with 2- or 4-picoline (Scheme 7.52). For example, acylation of 2-phenyl-5(4*H*)-oxazolone **172** ($R_1 = Ph$, $R_2 = H$) with propionyl choride in the presence of 2-picoline gives 2-phenyl-4-propionyl-5(4*H*)-oxazolone.[123] However, acylation of the same oxazolone with ethyl 7-(chloroformyl)heptanoate in the presence of triethylamine gives the corresponding 5-acyloxy-2-phenyloxazole that rearranges to the desired 5(4*H*)-oxazolone in 4-picoline.[124]



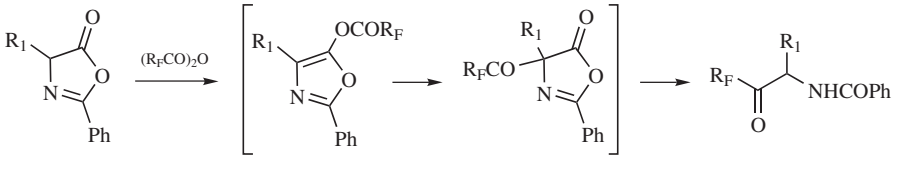
173

172

174

Scheme 7.52

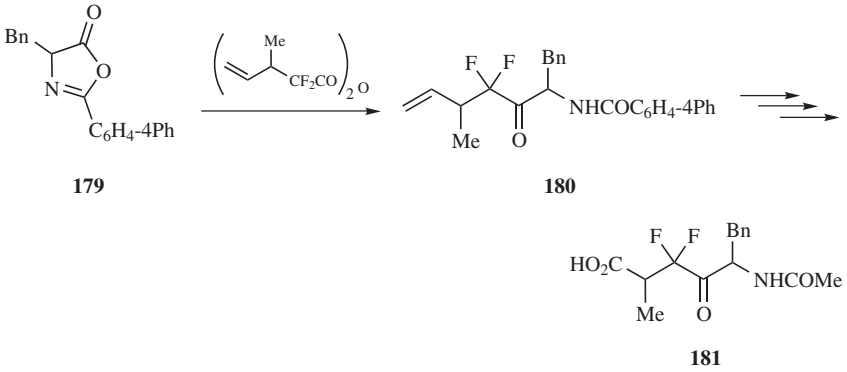
Reaction of 4-alkyl(aralkyl)-2-phenyl-5(4*H*)-oxazolones **175** with difluoro- and trifluoroacetic anhydride yields α-(benzamidoalkyl)-difluoro- and trifluoroketones **178** in good yield in a one-pot procedure (Scheme 7.53).[125]



175 **176** **177** **178**

Scheme 7.53

Acylation of **179** with 2,2-difluoro-3-methyl-4-pentenoic acid anhydride yields α-amino ketones **180** that can serve as intermediates to prepare pseudopeptides such as peptidyl α,α-difluoroalkylketones **181**[126] (Scheme 7.54) or ketomethylene pseudopeptides.[127]

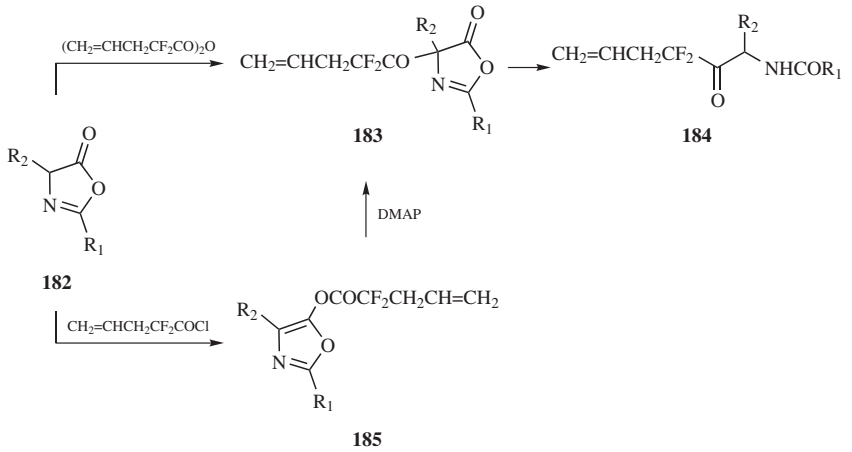


179 **180**

181

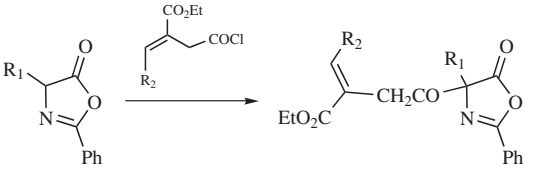
Scheme 7.54

In some cases, the product depends on the nature of the acylating agent. Acylation of **182** with 2,2-difluoro-4-pentenoic acid anhydride leads to acylation at C-4, whereas acylation with 2,2-difluoro-4-pentenoic acid choride yields the 5-acyloxyoxazole **185** as the major compound.[128] The 5-acyloxyoxazole can be rearranged to the 5(4*H*)-oxazolone **183** upon treatment with 4-(dimethylamino)pyridine. Treatement of **183** with anhydrous oxalic acid promotes decarbonylation to give fluorinated α-amino ketones **184** (Scheme 7.55). Selected examples of 4-acyl-5(4*H*)-oxazolones are shown in Table 7.20 (Fig. 7.22).



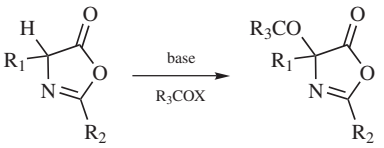
Scheme 7.55

Acylation of **186** with an α-substituted ethyl succinyl chloride generates the expected 4-acyl-5(4*H*)-oxazolones **187** that serve as precursors to ketomethylene and dehydro ketomethylene pseudodipeptides (Scheme 7.56).[129]



Scheme 7.56

TABLE 7.20. SYNTHESIS OF SATURATED 4-ACYL-2,4-DISUBSTITUTED 5(4*H*)-OXAZOLONES VIA ACYLATION OF 2,4-DISUBSTITUTED 5(4*H*)-OXAZOLONES AT C-4



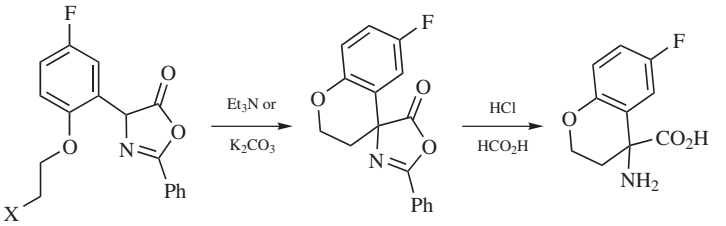
X = O_2CCF_3, O_2CHF_2, Cl

Figure 7.22

R_1	R_2	R_3CO	% Yield	Reference
$PhCH_2$	Ph	CF_3CO	63	125
i-Bu	Ph	CF_3CO	60	125
$PhCH_2$	Ph	CF_2HCO	50	125
i-Bu	Ph	CF_2HCO	22	125
$PhCH_2$	Ph	$CH_2{=}CHCF_2CO$	38	128
i-Bu	Ph	$CH_2{=}CHCF_2CO$	46	128

A general procedure for acylation of 2-aryl-5(4*H*)-oxazolones using an acylating agent in the presence of 4-(dimethylamino)pyridine and triethylamine has been described.[130] The resulting products are useful intermediates for agrochemicals and drugs.

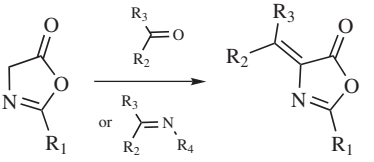
INTRAMOLECULAR ALKYLATIONS. Intramolecular spiroalkylation of the suitably functionalized 5(4*H*)-oxazolone **188** produced **189** in good to excellent yield. Acid hydrolysis of **189** then gave the cyclic amino acid **190** required in the synthesis of the aldose reductase inhibitor sorbinil (Scheme 7.57).[131]



188 **189** **190**

Scheme 7.57

IMINES AND CARBONYL COMPOUNDS. Simple 2-alkyl(aryl)-5-(4*H*)-oxazolones like **191** can react with aldehydes, ketones, imines, and oximes to afford the corresponding unsaturated analogues **192** (Scheme 7.58). In some cases, this procedure is especially advantageous over the classical one-pot synthesis.[132–148] The chemistry of unsaturated 5(4*H*)-oxazolones like **192** will be discussed in detail in Section 7.4.



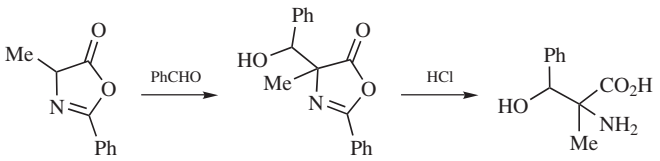
191 **192**

Scheme 7.58

Imines are particularly useful reagents when hindered electrophiles are considered. In this context, *N*-(α-methylbenzylidene)benzylamines have been described as alternatives to acetophenones.[149] Similarly *N*-methylbenzophenonimine serves as an alternative to benzophenone[150] itself in reactions with 2-phenyl-5(4*H*)-oxazolone **146** to prepare 2-phenyl-4-(α-phenylethylidene)- and 4-(diphenylmethylene)-2-phenyl-5(4*H*)-oxazolone, respectively.

When carbonyl compounds are used as electrophiles reaction with 4-monosubstituted-5(4*H*)-oxazolones affords substituted serines after subsequent hydrolytic ring opening of the initial aldol product. As an example, 4-methyl-2-phenyl-5(4*H*)-oxazolone **193**, prepared from alanine, reacts with benzaldehyde in a base-catalyzed addition to give, after hydrolysis, a 3:1 mixture of *threo*- and

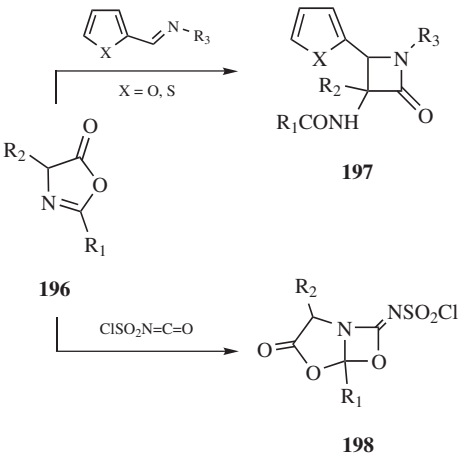
erythro-2-methyl-3-phenylserine **195** (Scheme 7.59).[151] Iron sulfate has also been used to catalyze the condensation reaction of 2-phenyl-5(4*H*)-oxazolone and aromatic aldehydes.[79]



193 **194** **195**

Scheme 7.59

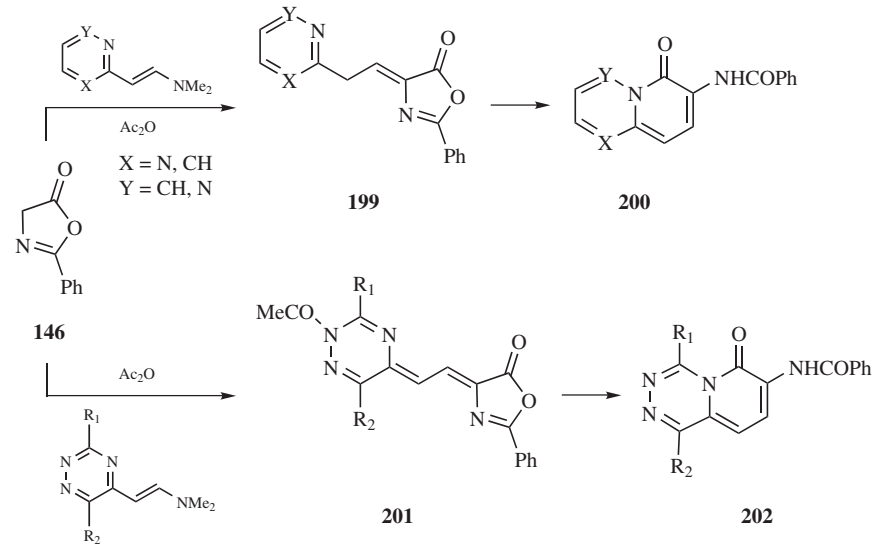
4-Monosubstituted-5(4*H*)-oxazolones behave differently upon reaction with imines. Here, 4-methyl-2-phenyl-5(4*H*)-oxazolone **196** ($R_1 = Ph$, $R_2 = Me$) reacts with imines derived from 2-furancarboxaldehyde or 2-thiophenecarboxaldehyde to give 3-amino-β-lactams **197**.[152,153] On the other hand, **196** reacts with chlorosulfonyl isocyanate in a [2 + 2] cycloaddition to give dioxazabicycloheptanones **198** as shown in Scheme 7.60.[154]



Scheme 7.60

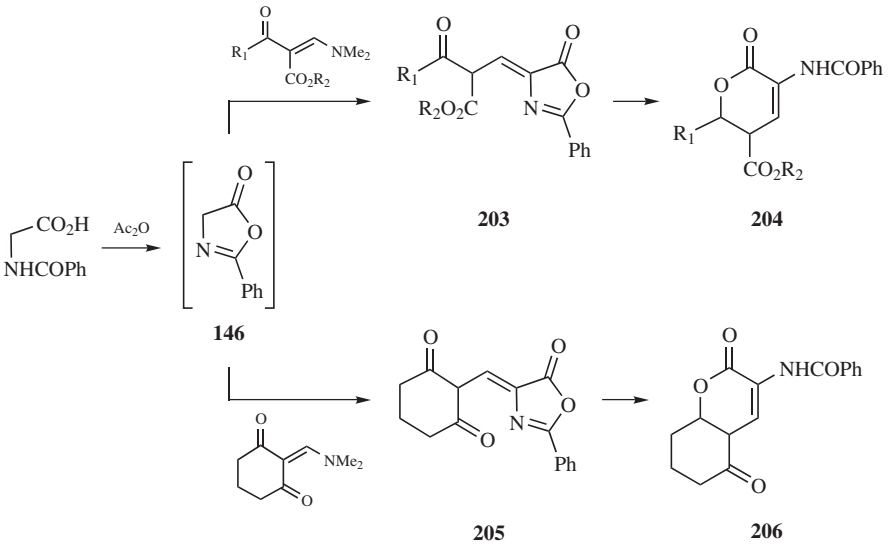
Reaction of carbon disulfide with 2-phenyl-5(4*H*)-oxazolone **146** followed by S-alkylation with a methyl halide gives 4-[bis(methylthio)methylene]-2-phenyl-5(4*H*)-oxazolone. The solvolysis and aminolysis of this compound have also been studied.[155,156]

Enamines and Formamidines. Enamines, prepared from methylpyridines, methylpyridazines, methylpyrimidines or methyltriazine, and *N*,*N*-dimethylformamide dimethylacetal or *tert*-butoxybis(dimethylamino)methane, react with 2-phenyl-5(4*H*)-oxazolone **146** to afford the unsaturated 5(4*H*)-oxazolones **199** and **201** that are intermediates in the synthesis of fused pyridones **200**[157] and pyridotriazinones **202**, respectively (Scheme 7.61).[158]



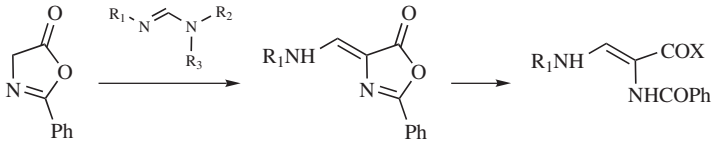
Scheme 7.61

Similarly, reaction of 2-dimethylaminomethylene-3-oxoalkanoates or 2-dimethylaminomethylene-1,3-cyclohexanediones with 2-phenyl-5(4*H*)-oxazolone **146**, generated *in situ* from hippuric acid, affords 6-substituted 3-(benzoylamino)-2-oxo-2*H*-pyran-5-carboxylates **204** and 3-(benzoylamino)-7,8-dihydro-2*H*-1-benzopyran-2,5(6*H*)-diones **206**, respectively. These compounds showed strong local anesthetic activity (Scheme 7.62).[159]



Scheme 7.62

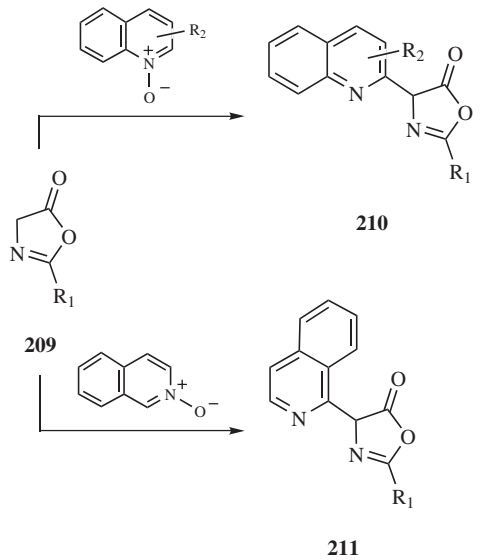
Condensation of an *N*′-heteroaryl-*N*,*N*-dimethylformamidine or *N*,*N*′-diphenylformamidine with 2-phenyl-5(4*H*)-oxazolone **146** gives 4-(aminomethylene)-2-phenyl-5(4*H*)-oxazolones **207** that are synthetic equivalents of β-amino-α,β-dehydro-α-amino acid derivatives **208** (Scheme 7.63).[160–163]



146 **207** **208**

Scheme 7.63

AZINE *N*-OXIDES. Quinoline and isoquinoline *N*-oxides react readily with 2-phenyl-5(4*H*)-oxazolone **209** ($R_1 = Ph$) and 2-methyl-5(4*H*)-oxazolone **209** ($R_1 = Me$) in the presence of acetic anhydride to afford 2-substituted 4-(quinol-2-yl)- **210** and 4-(isoquinol-1-yl)-5(4*H*)-oxazolones **211**, respectively, in good yields (Scheme 7.64).[164]



210

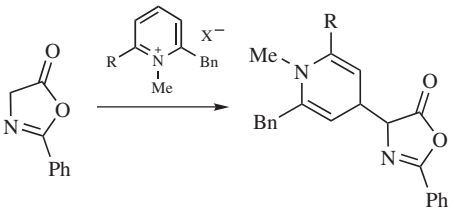
209

211

Scheme 7.64

Similar results are obtained from reaction of pyridine *N*-oxide derivatives with **146** and several transformations, including ring opening, have been described.[165]

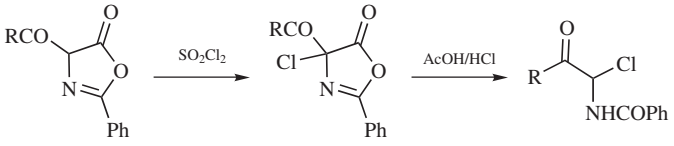
Reaction of pyridinium salts and **146**[166] gives the corresponding 4-substituted-1,4-dihydropyridine derivatives **212** (Scheme 7.65).



146 **212**

Scheme 7.65

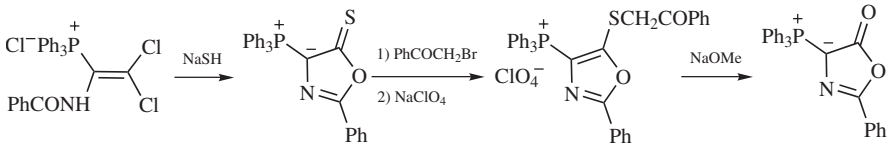
HALOGENATION REACTIONS. Chlorination of 4-acyl-2-phenyl-5(4*H*)-oxazolones **213** with sulfuryl chloride leads to the corresponding 4-chloro derivatives **214** (Scheme 7.66). These compounds are useful intermediates in organic synthesis. In particular, hydrolytic cleavage of **214** affords α-chloro-α-acylamino ketones **215**.[167] Moreover, they are the logical intermediates to prepare 4-(phosphoranylidene)-5(4*H*)-oxazolones that are very important and useful synthons.



213 **214** **215**

Scheme 7.66

The first attempt to prepare 2-phenyl-4-(phosphoranylidene)-5(4*H*)-oxazolone **219** started with 1-benzoylamino-(2,2-dichloroethenyl)triphenylphosphonium chloride **216** and involved the complex reaction sequence shown in Scheme 7.67. The structure and properties of **219** were studied and it was shown that **219** underwent Wittig olefination with benzaldehyde to give the well-known (*Z*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolone.[168]

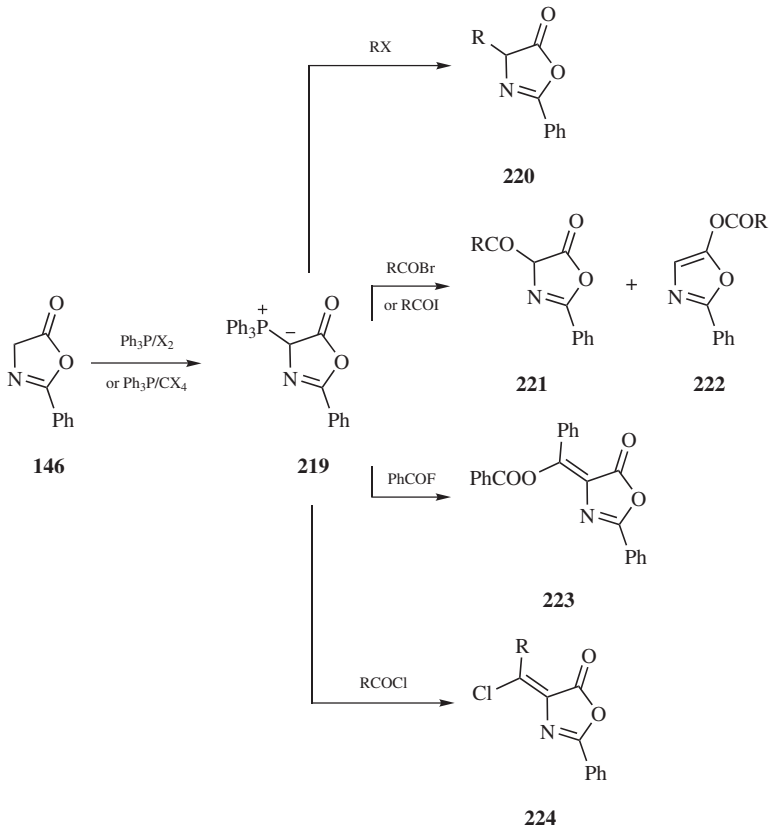


216 **217** **218** **219**

Scheme 7.67

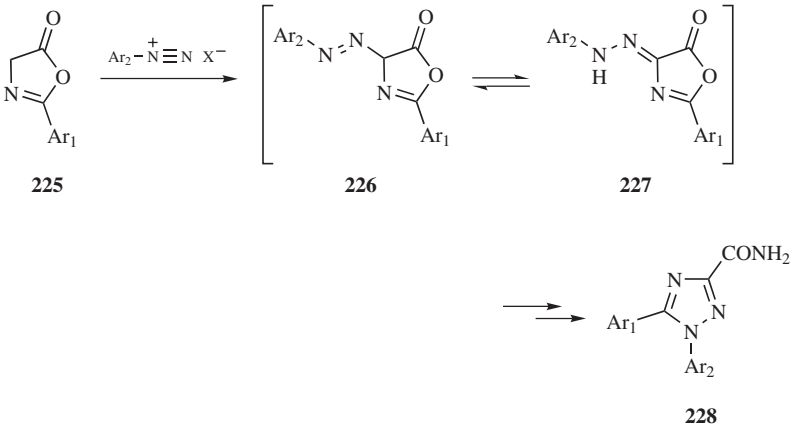
A more efficient one-pot procedure for the synthesis of 4-(phosphoranylidene)-2-substituted-5(4*H*)-oxazolones from the corresponding 4-unsubstituted-5(4*H*)-oxazolones has also been described and uses trialkyl- or triarylphosphines in the presence of a halogenation agent.[169] Wittig reaction of 4-(phosphoranylidene)-2-substituted-5(4*H*)-oxazolones has been used to prepare fluorooxazolones from fluorine-containing carbonyl compounds.[170]

Reaction of the 2-phenyl-4-(phosphoranylidene)-5(4*H*)-oxazolone **219** with alkyl halides gives 4-alkyl-2-phenyl-5(4*H*)-oxazolones **220** in good yields.[171] Reaction of **219** with acyl iodides or bromides gives C-4- or *O*-acyl products **221** or **222**. Reaction of **219** with acyl chlorides gives 4-(1-chloroalkylidene)-2-phenyl-5(4*H*)-oxazolones **224** that are Wittig-like products. The use of benzoyl fluoride gives rise to 4-(1-benzoyloxybenzylidene)-2-phenyl-5(4*H*)-oxazolone **223**.[172] These reactions are summarized in Scheme 7.68.



Scheme 7.68

Diazonium Salts as Electrophiles. 2-Aryl-5(4*H*)-oxazolones **225** couple readily with aryldiazonium salts to give the corresponding 4-arylazo derivatives **226** or 2-aryl-4,5-oxazoledione-4-arylhydrazones **227**.[173,174] Structural studies revealed that these compounds exist as the hydrazone tautomers **227**.[175] These compounds are valuable synthetic intermediates. For example, nucleophilic ring opening with active methylene compounds[176,177] and alcohols[178,179] has been described. More interestingly, ring opening with amines and subsequent recyclization affords 1,5-diaryl-1,2,4-triazole-3-carboxamides **228** (Scheme 7.69) that have been used in the preparation of agrochemicals, particularly, herbicides, and fungicides.[180–195]



225 **226** **227** **228**

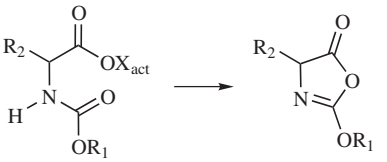
Scheme 7.69

7.3.1.4.4. From Unsaturated 5(4*H*)-Oxazolones

One strategy to prepare saturated 5(4*H*)-oxazolones from unsaturated oxazolones takes advantage of the reactivity of the exocyclic double bond. In this context, numerous reactions have been explored including reductions, Michael reactions, cycloaddition reactions, and many others. These reactions will be discussed in the context of the reactivity of the exocyclic double bond of the unsaturated oxazolones and will be described in Section 7.4.3.

7.3.1.5. 2-Alkoxy Derivatives

N-Alkoxycarbonyl-α-amino acids are chirally stable compounds under normal coupling conditions. In the presence of a tertiary amine, most activated *N*-alkoxycarbonyl-α-amino acids generate 2-alkoxy-5(4*H*)-oxazolones that are not chirally stable in the presence of the base. Consequently, enantiomerization occurs in the presence of the tertiary amine if the activated residue is not immediately consumed by aminolysis. Many studies have explored this process to minimize the enantiomerization in the coupling reaction including isolation of the intermediate 2-alkoxy-5(4*H*)-oxazolones. Several methods are now available to prepare 2-alkoxy-5(4*H*)-oxazolones. For example, the action of triethylamine on *N*-benzyloxycarbonyl-α-amino acid chlorides gives the 2-benzyloxy-5(4*H*)-oxazolones. Similarly, 2-[(9-fluorenylmethyl)oxy]-5(4*H*)-oxazolones with acid-stable protecting groups are accessible from the acid chlorides. Other analogues can be obtained from carbodiimides including DCC and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDAC). A general route to all types of 2-alkoxy-5(4*H*)-oxazolones **229** was developed using mixed anhydrides prepared from reaction of an acid with isopropenyl chloroformate in the presence of *N*-methylmorpholine. The general synthetic procedure is shown in Scheme 7.70.



229

Scheme 7.70

In cases where 2-alkoxy-5(4*H*)-oxazolones are generated from *N*-alkoxycarbonyl-α-amino acids, the enantiomerization that occurs during preparation and incorporation of these residues into peptides, the properties, and methods of preparation of the 2-alkoxy-5(4*H*)-oxazolones together with the practical uses of these compounds have recently been reviewed.[196]

For α,α-dialkylamino acids enantiomerization is not a problem. The preparation of 4,4-dimethyl-2-[(9-fluorenylmethyl)oxy]-5(4*H*)-oxazolone, an intermediate used in the synthesis of (−)-mirabazole C has been described.[197] Recently, two new 2-alkoxy-5(4*H*)-oxazolones derived from Toac (2,2,6,6-tetramethyl-4-amino-1-oxy-piperidine-4-carboxylic acid) that incorporate Z or 9-fluorenylmethoxycarbonyl (Fmoc) protection at C-2 have been described.[198] The Toac analogues were synthesized as part of a study of the crystal structure and ab initio calculations for these interesting systems.

Finally, cationic ring-opening polymerization of 2-alkoxy-5(4*H*)-oxazolones has been used to prepare poly *N*-alkoxycarbonyl amino acids.[199,200] The polymerization was found to be dependent on the nature of the amino acid side chain and the substituent on C-2.

7.3.2. Reactions

7.3.2.1. Hydrolysis and Alcoholysis

The most important reaction in the chemistry of oxazolones is nucleophilic ring opening of the heterocyclic ring. Hydrolysis of 5(4*H*)-oxazolones gives the corresponding *N*-acylamino acids that are the usual starting materials for the synthesis of these heterocyclic compounds. Therefore, in principle, this reaction is synthetically unimportant, although it is worth considering certain aspects about the process.

However, important transformations can be made, for example, at C-4 and thus the sequence of cyclization of a typical amino acid to the oxazolone, followed by modification at C-4 and subsequent hydrolysis, has become a useful strategy to prepare new, non-proteinogenic amino acids.

In addition, the use of an enantioselective or diastereoselective hydrolysis of racemic oxazolones offers another possibility to obtain new synthetic amino acids. Similarly, alcoholysis of 5(4*H*)-oxazolones gives the corresponding *N*-acylamino acid esters.

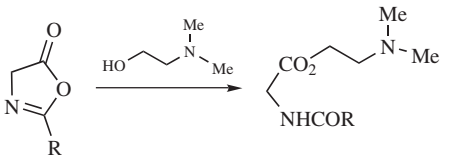
Finally, it is well known that amino acids can cyclize to oxazolones during the protection–activation reaction sequence. This important reaction must be avoided since tautomerism between saturated 5(4*H*)-oxazolones and 5(2*H*)-oxazolones results in undesired epimerization of the amino acid.

A number of points should be considered to determine the most appropriate experimental conditions for the desired reaction and, to that end, the kinetics of hydrolysis and ionization of 4-methyl-2-phenyl-, 4-benzyl-2-phenyl-, and 4-benzyl-2-methyl-5(4*H*)-oxazolones have been investigated.[201] Deprotonation of 5(4*H*)-oxazolones in aqueous media, which leads to racemization of optically active 5(4*H*)-oxazolones, is a fast process that competes with the ring opening. The difference between the rate constant for racemization and the ring opening is greater in solvents with dielectric constants less than water and thus, oxazolones racemize faster than they hydrolyze.

The rate and equilibrium constants for the reaction of oxyanions with 2-phenyl-5(4*H*)-oxazolones has been also studied.[202] This work suggests that attack of phenoxide ion at the carbonyl group is a concerted displacement.

In addition, detailed geometric and energetic characteristics of the elementary reaction pathways for the addition of water and ammonia to 2-methyl-5(4*H*)-oxazolone have been determined at the AM1 level using MOPAC programs.[203] The authors concluded that an *N*-acetylamino acid or amide are formed through a two-step procedure that involves the formation of the α-hydroxyimine and subsequent tautomerization.

Ring opening of 2-aryl-5(4*H*)-oxazolones **230**, obtained from *N*-acylglycines, with *N*,*N*-dimethyl-2-aminoethanol provides choline esters of *N*-substituted amino acids **231** (Scheme 7.71).[204]



230 **231**

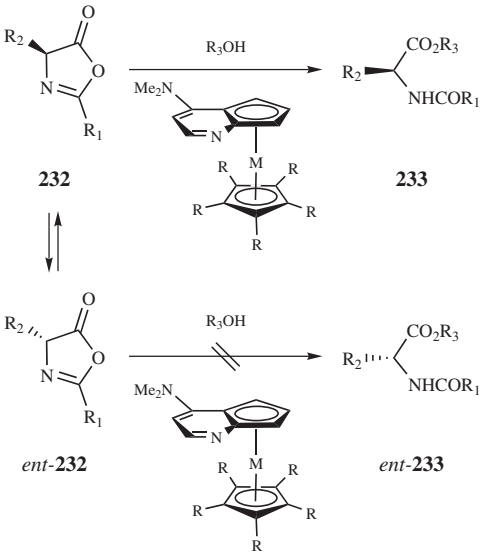
Scheme 7.71

The use of chiral organometallic compounds as catalysts in the enantioselective hydrolysis of saturated oxazolones was reported several years ago and the mechanism of the hydrolysis of 4-benzyl-2-methyl-5(4*H*)-oxazolone catalyzed by the copper(II) complex of (*S*)-[(*N*-benzylprolyl)amino]benzaldoxime has been described.[205]

Other compounds studied as chiral catalysts include α- and β-cyclodextrins that were used in the hydrolysis of oxazolones although the enantioselectivity in the ring-opening reaction was rather low.[206–208] When a phenyl group is present at C-2 in these systems the enantioselectivity of the reaction is somewhat higher.

Dynamic kinetic resolution is an excellent methodology to prepare enantiomerically pure compounds[209–212] and, in this context, chiral 4-(dimethylamino)pyridine (DMAP) iron[213] and ruthenium[214] complexes have been reported to catalyze the

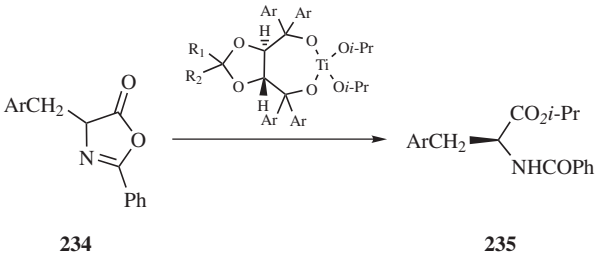
ring opening of 5(4*H*)-oxazolones by alcohols. As a result, the dynamic kinetic resolution (deracemization) of chiral saturated oxazolones **232** is possible and leads to enantioenriched protected α-amino acids **233** (Scheme 7.72). The solvent and nucleophile are critical variables that dramatically affect the levels of enantioselectivity observed in these reactions.



Scheme 7.72

Chiral titanium complexes with α, α, α′, α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligands are versatile auxiliaries in the Lewis acid catalyzed alcoholysis of racemic 4-(arylmethyl)-2-phenyl-5(4*H*)-oxazolones **234**, providing the corresponding enantiomerically enriched N-protected amino acid esters **235** (Scheme 7.73). The enantioselectivity of the reaction is dependent on the solvent, temperature, and chiral ligand.[215,216] Selected examples of the alcoholysis of saturated 5(4*H*)-oxazolones are shown in Table 7.21 (Fig. 7.23).

Recently, it was reported[217] that some dipeptide derivatives containing a histidine residue such as cyclo[(*S*)-His-(*S*)-Phe] (CHP) catalyze the alcoholysis of



234 235

Scheme 7.73

TABLE 7.21. *N*-ACYLAMINO ACID ESTERS FROM ALCOHOLYSIS OF SATURATED 5(4*H*)-OXAZOLONES

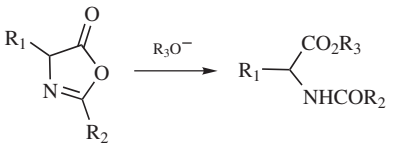


Figure 7.23

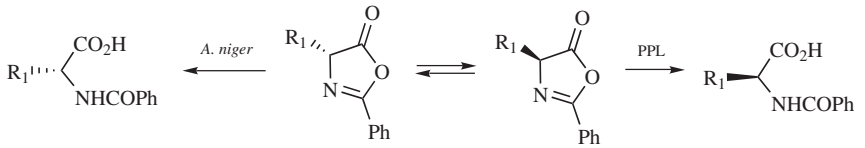
R_1	R_2	R_3	% Yield	Reference
H	4-*i*-PrOC_6H_4	$Me_2N(CH_2)_2$	70	204
Me	Ph	Me	98	213
Et	Ph	Me	94	213
CH_2=CH	Ph	Me	94	213
i-Pr	Ph	Me	95	213
Ph	Ph	Me	94	213
$PhCH_2$	Ph	*i*-Pr	75	215
4-MeC_6H_4	Ph	*i*-Pr	60	216
4-$MeOC_6H_4$	Ph	*i*-Pr	65	216
4-ClC_6H_4	Ph	*i*-Pr	48	216
4-$NO_2C_6H_4$	Ph	*i*-Pr	74	216

4-benzyl-2-phenyl-5(4*H*)-oxazolone to afford the corresponding *N*-benzoyl-L-phenylalanine esters albeit with low or moderate enantioselectivity. Cyclo[(*S*)-His-(*S*)-Phe] was a more effective and enantioselective catalyst when used together with a chiral auxiliary that possesed both a hydrogen-bond donor and a hydrogen-bond acceptor.

Enzymatic systems have been used successfully to effect asymmetric synthesis of amino acids by dynamic kinetic resolution of saturated oxazolones. Oxazolones are versatile substrates for enzyme-catalyzed hydrolysis and alcoholysis using both lipases and proteases to catalyze the nucleophilic ring opening. The first attempts to hydrolyze 2,4-disubstituted-5(4*H*)-oxazolones using proteases such as α-chymotrypsin, trypsin, and subtilisin were only moderately successful, but a significant breakthrough in this method was achieved when lipases were employed instead of proteases. Initially, it was shown that 4-methyl-2-phenyl-5(4*H*)-oxazolone undergoes *Mucor miehe*i lipase-catalyzed enantioselective ring opening with 1-butanol in diisopropyl ether. This process, in conjunction with partial racemization of the less reactive isomer of the oxazolone under the reaction conditions, yields enantioenriched (*S*)-*N*-benzoylalanine *n*-butyl ester but with modest optical purity.[218]

Lipases from porcine pancreas (PPL) and from *Aspergillus niger* are uniquely suited for oxazolone hydrolysis since they catalyze the ring-opening reaction with a high degree of enantioselectivity. Moreover, these lipases exhibited opposite stereochemical preference, thus providing access to both enantiomers of *N*-benzoyl

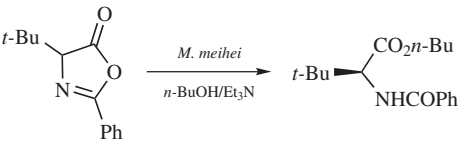
amino acids **237** and *ent*-**237** in excellent chemical and optical yields. Although both lipases retained their chiral preference with variation of the C-4 substituent, the reaction rate and the degree of enantioselectivity varied markedly depending on the nature of the substituents[219,220] and on the solvent used.[221] For substrates with limited steric hindrance, the hydrolysis proceeded with moderate to good selectivities, but the reaction rate decreased for substrates bearing bulky C-4 substituents. More importantly, dynamic resolution is achieved owing to the low pK_a values of the C-4 proton. Thus, when the hydrolysis is conducted near the pH optimum of the lipase, *in situ* racemization is sufficient to ensure complete transformation of the substrate (Scheme 7.74).



237 **236** *ent*-**236** *ent*-**237**

Scheme 7.74

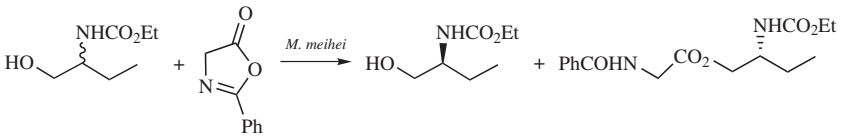
An elegant method to suppress the undesired spontaneous hydrolysis of a 5(4*H*)-oxazolone in aqueous media uses a lipase-catalyzed alcoholysis reaction. Of particular importance is the synthesis of *tert*-leucine,[222] a non-proteinogenic α-amino acid that has found widespread use both as a chiral auxiliary and as a component of potentially therapeutic pseudopeptides. Racemic 4-*tert*-butyl-2-phenyl-5(4*H*)-oxazolone **238** was submitted to *Mucor miehei* catalyzed alcoholysis using butanol as a nucleophile. Addition of a catalytic amount of triethylamine promoted *in situ* racemization. In this way, the enantiomerically pure butyl ester of (*S*)-*N*-benzoyl-*tert*-leucine **239** was obtained in excellent yield (Scheme 7.75).



238 **239**

Scheme 7.75

The preparation of protected derivatives of D-*allo*- and L-*allo*-threonine by enzymatic hydrolysis of 5(4*H*)-oxazolones using hog kidney acylase has also been described.[223] This methodology has been extended to a wide variety of amino acids and, at present, constitutes a general procedure to prepare non-quaternary amino acids in enantiomerically pure form.[224–227] For example, racemic *N*-ethoxycarbonyl-2-amino-1-butanol, *rac*-**240** was resolved via kinetic resolution using *M. miehei*. In this case, 2-phenyl-5(4*H*)-oxazolone **146** was used as a convenient derivatizing agent to afford **241**, a precursor of Ethambutol as shown in Scheme 7.76.[228]



rac-**240** **146** **240** **241**

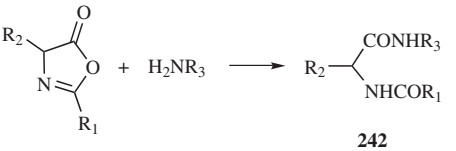
Scheme 7.76

Although 5(4*H*)-oxazolones have been considered too unstable stereochemically for use in peptide synthesis, it has been shown[229] that they function as acyl donors in protease-catalyzed segment condensations. This methodology represents an interesting approach to prepare peptides containing acidic amino acids. As an example, α-chymotrypsin reacts with the oxazolone ring of a peptide fragment to generate an acyl-enzyme intermediate. This activated intermediate then couples with an amino acid or with the N-terminus of another peptide chain to afford the corresponding oligopeptide. A limitation of this methodology occurs if hydrolysis of the acyl-enzyme intermediate is competitive with the coupling reaction.

7.3.2.2. Aminolysis with Amines

By far the most important ring-opening reaction using nitrogen nucleophiles is that using amino acids and this will be considered in Section 7.3.2.3. Apart from this very important case, other nitrogen nucleophiles have been used to prepare compounds of particular interest and some examples have been reported. The general aminolysis reaction is shown in Scheme 7.77 and has been applied to the synthesis of numerous compounds. For example, *N*,*N*-disubstituted amides of α-methyltryptophan were synthesized by nucleophilic ring opening of the corresponding oxazolone.[230] Acetamidopiperidines were prepared from 4-aminopiperidines and 2-phenyl-5(4*H*)-oxazolones and the resulting products have been shown to reduce blood pressure.[231] 2-(4-Nitrophenyl)-4-substituted-5(4*H*)-oxazolones were ring opened with thiosemicarbazides to prepare compounds with potential antitumor activity.[232] Herbicidal benzenesulfonylcarboxamides were prepared by ring-opening oxazolones with *p*-toluenesulfonamide.[233] Finally, ring opening of 2-(4-nitrophenyl)-4-substituted-5(4*H*)-oxazolones with bis(2-chloroethyl)amine afforded potential antitumor agents.[234] 2-Phenyl-5(4*H*)-oxazolone has been also used as an acylating agent for nitrogen-containing heterocycles.[235]

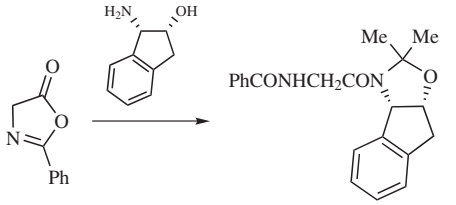
Nucleophilic ring opening of 2-phenyl-5(4*H*)-oxazolone **146** with (1*S*, 2*R*)-1-aminoindan-2-ol provides an amido alcohol that, upon treatment with



242

Scheme 7.77

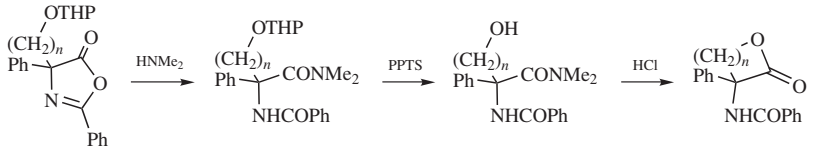
2-methoxypropene affords **243**, a versatile chiral glycine enolate equivalent. Alkylation of **243** with a variety of alkyl halides gives the corresponding amino acid derivatives with 90–99% diastereoselectivity (Scheme 7.78).[236]



146 **243**

Scheme 7.78

Ring opening of a 4-(hydroxyalkyl)-substituted oxazolone using dimethylamine gives an amide **245** that can be used as an intermediate in a subsequent intramolecular cyclization to prepare lactones **247** (Scheme 7.79).[237]

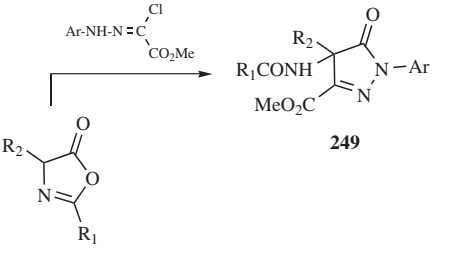


244 **245** **246** **247**

PPTS = pyridinium *p*-toluenesulfonate

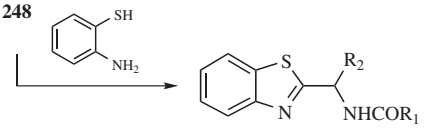
Scheme 7.79

In some cases, ring opening of oxazolones and subsequent cyclization of the intermediate leads to new heterocyclic systems. For example, reaction of saturated 5(4*H*)-oxazolones with hydrazonoyl halides under phase-transfer conditions yields the 5-pyrazolones **249**.[238] Ring opening of **248** with 2-aminothiophenol generates benzothiazoles **250** (Scheme 7.80).[239]



249

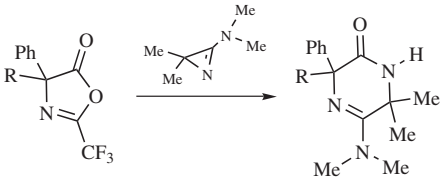
248



250

Scheme 7.80

It was also reported[240] that the reaction of 4,4-disubstituted-2-(trifluoromethyl)-5(4*H*)-oxazolones **251** with 2,2-dimethyl-3-(dimethylamino)-2*H*-azirine afforded 5-(dimethylamino)-3,6-dihydropyrazin-2(1*H*)-ones **252** (Scheme 7.81). In this case, the reaction only occurs when electron-withdrawing substituents are present at C-2 of the oxazolone.



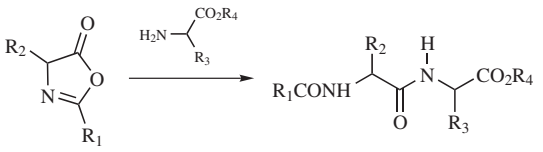
251 **252**

Scheme 7.81

Several papers have described attempted ring opening of an oxazolone with chiral amines to achieve stereoselective reactions. For example, a chiral bornylamine effected ring opening of racemic oxazolones to produce enantioenriched (*S*)-*N*-acylamino acid bornylamides.[241] Ring opening of 4-isopropyl-, 4-*sec*-butyl- and 4-benzyl-5(4*H*)-oxazolones with (*S*)-phenylethylamine also produced some degree of chiral induction.[242–244] In these cases, the reaction rate and the extent of chiral induction depended on the solvent and on the oxazolone substituent. Mechanistically, the authors attributed the results to involve neutral or ionic species.

7.3.2.3. Aminolysis with Amino Acid Derivatives

Amino acids have been used as nucleophiles to effect the ring opening of saturated 5(4*H*)-oxazolones **253** as a coupling method in an attempt to describe a general procedure for peptide synthesis (Scheme 7.82). However, the problems arising from racemization, that is, when a proton is present at C-4 of the oxazolone, render this procedure of limited synthetic utility.



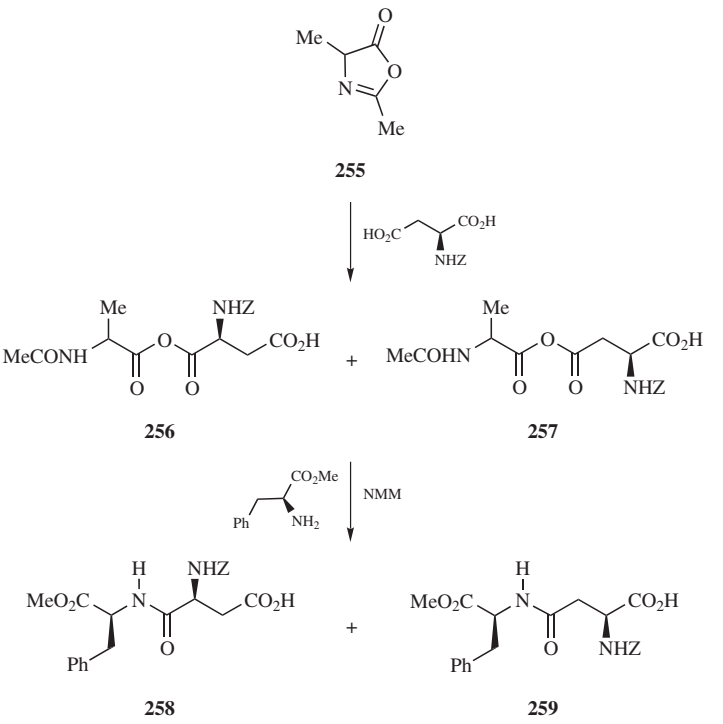
253 **254**

Scheme 7.82

On the other hand, there have been several attempts to achieve some degree of asymmetric induction during the ring opening of racemic oxazolones with protected chiral amino acids. In these cases the influence of the solvent, temperature and, in general, the experimental conditions, has been studied extensively.[245–248] Although some degree of asymmetric induction has been achieved in most cases, this methodology can not be considered as a general procedure for the stereoselective

synthesis of peptides. Nevertheless, the diastereoisomers obtained from the reaction of oxazolones with chiral amino acid derivatives are readily separated using high-performance liquid chromatography (HPLC), a fact that makes this technique suitable for the determination of enantiomeric ratios.[249]

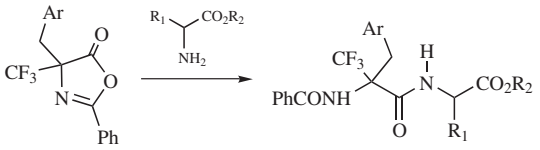
Alternatively, oxazolones have been used as reagents to activate and to couple N-protected dicarboxylic amino acids wherein the carboxylate moiety acts as the nucleophile. For example, 2,4-dimethyl-5(4*H*)-oxazolone **255** reacts with *N*-benzyloxycarbonyl-L-aspartic acid to give a mixture of the anhydrides **256** and **257**. Subsequent reaction of **256** and **257** with phenylalanine methyl ester hydrochloride and *N*-methylmorpholine produces a mixture of the α-isomer **258** and β-isomer **259** of *N*-benzyloxycarbonyl-aspartylphenylalanine methyl ester (Scheme 7.83).[250]



Scheme 7.83

Racemization is not encountered when 4-unsubstituted-5(4*H*)-oxazolones or 4,4-disubstituted-5(4*H*)-oxazolones are used as reagents. Indeed, 4-unsubstituted-5(4*H*)-oxazolones function as glycine synthons in the synthesis of *N*-acylglycyl-α-amino acids. For example, aminolysis of 2-(trifluoromethyl)-5(4*H*)-oxazolone with α-methylphenylalanine affords *N*-(trifluoroacetyl)glycyl-α-methylphenylalanine.[251]

4,4-Disubstituted-5(4*H*)-oxazolones, readily available by alkylation of the monosubstituted derivatives, are very useful intermediates in the synthesis of peptides that incorporate α,α-disubstituted amino acids. As an example, 4-(aryl-methyl)-2-phenyl-4-(trifluoromethyl)-5(4*H*)-oxazolones **260** are key intermediates



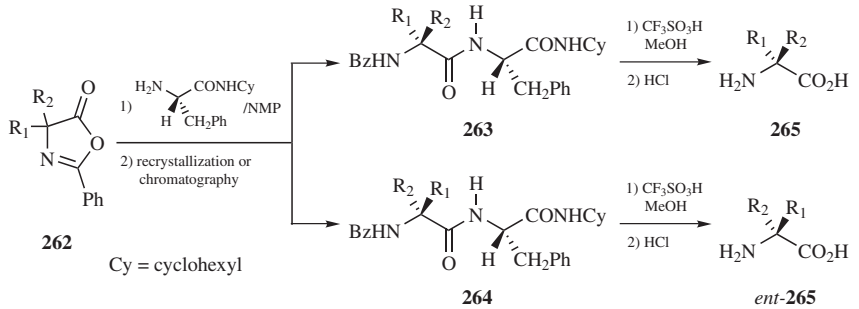
260 **261**

Scheme 7.84

in the synthesis of peptides that incorporate α-(trifluoromethyl)amino acids **261** (Scheme 7.84).[252]

Modification of the properties of bioactive peptides incorporating constrained amino acids into the backbone structures has been explored in recent years. One of the best strategies to obtain good results in this area is to use an α,α-disubstituted amino acid, which has necessitated development of various methodologies to prepare these non-proteinogenic amino acids in enantiomerically pure form.[253,254]

Resolution of diastereoisomers derived from racemic α,α-dialkylamino acids has become a useful tool to isolate enantiomerically pure compounds. Among the different possibilities, Obrecht's methodology, which is based on the facile separation of di- and tripeptides containing a phenylalanine residue and an *N*-acyl-α,α-dialkylamino acid, is particularly effective and versatile.[255,256] The starting racemic 4,4-disubstituted-2-phenyl-5(4*H*)-oxazolones **262** are obtained from the corresponding *N*-benzoylamino acids through the action of an activating agent such as *N*,*N*-dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole. Alternatively, alkylation of a 2-phenyl-4-substituted-5(4*H*)-oxazolone with an electrophile in the presence of sodium hydride is also an effective synthetic strategy.[111] Treatment of a dialkylated 5(4*H*)-oxazolone **262** with a chiral amide derived from phenylalanine provides the diastereomeric dipeptides **263** and **264** that are easily separated by crystallization or column chromatography.[257] The bests results are obtained when phenylalanine cyclohexylamide is used to resolve the α,α-dialkylamino acids. This methodology has afforded both enantiomers of α-methylphenylalanine, α-methylvaline, α-methylphenylglycine,[258] 2-(aminomethyl)alanine, 2-(aminomethyl)leucine,[259] α-methylglutamic acid, α-methylaspartic acid, α-isobutylaspartic acid,[260] and some α,α-disubstituted tyrosine analogues.[261] These reactions are shown in Scheme 7.85.

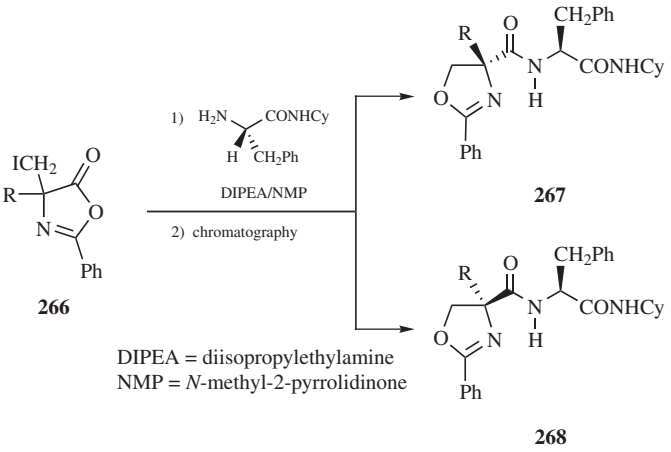


262 **263** **264** **265** *ent*-**265**

Cy = cyclohexyl

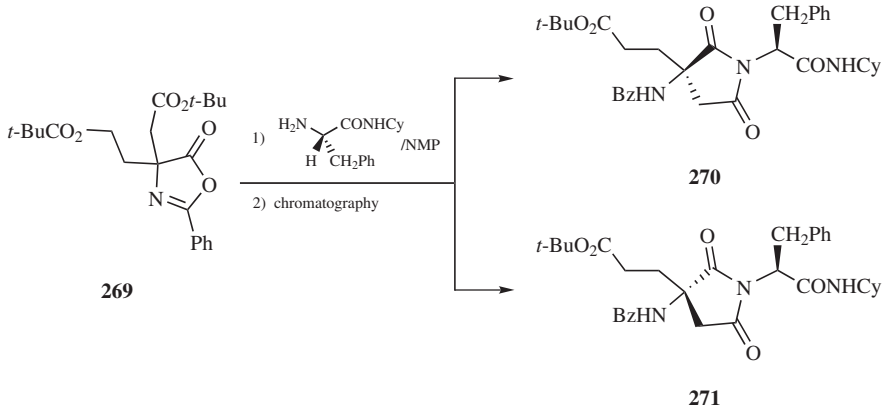
Scheme 7.85

The authors applied the same synthetic strategy to racemic 4-alkyl-4-(iodomethyl)-2-phenyl-5(4*H*)-oxazolones **266** and obtained a diastereomeric mixture of oxazolines **267** and **268** (Scheme 7.86). The diastereoisomers were separated chromatographically and then converted into dipeptides incorporating an α-alkylserine residue.[262,263]



Scheme 7.86

Finally, when oxazolones **269** bearing a carboxyalkyl chain at C-4 were used, the separation was effected on the mixture of diastereomeric succinimides **270** and **271**.[263] In this case, the resolved amino acid contains both an aspartic acid and a glutamic acid side chain (Scheme 7.87). Selected examples of amino acids that illustrate the general applicability of Obrecht's methodology are shown in Table 7.22 (Fig. 7.24).



Scheme 7.87

TABLE 7.22. SUBSTITUTED AMINO ACID AMIDES VIA OBRECHT'S METHODOLOGY FOR AMINOLYSIS OF SATURATED 5(4*H*)-OXAZOLONES

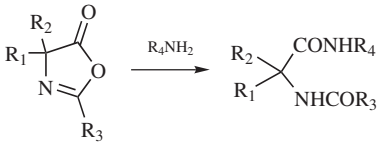
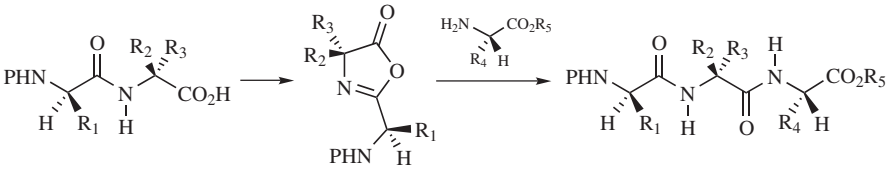


Figure 7.24

R_1	R_2	R_3	R_4	% Yield	Reference
H	*i*-Pr	Me	(*S*)-$PhCH_2(CONMe_2)CH$	80	257
H	$PhCH_2$	$PhCH_2$	(*S*)-$PhCH_2(CONMe_2)CH$	73	257
Me	4-$MeOC_6H_4CH_2$	Me	(*S*)-$PhCH_2(CONMe_2)CH$	72	257
Me	$PhCH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_4]CH$	78	257
Me	$PhCH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	77	258
Me	Ph	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	95	258
Me	*i*-Pr	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	93	258
Me	$PhCONHCH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	80	259
i-Pr	$PhCONHCH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	86	259
Me	4-$MeOC_6H_4CH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	82	261
i-Pr	4-$MeOC_6H_4CH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	81	261
Ph	4-$MeOC_6H_4CH_2$	Ph	(*S*)-$PhCH_2[CON(CH_2)_5]CH$	87	261

7.3.2.4. Incorporation of Dialkylamino Acids into Peptides

The use of oxazolones that readily racemize as starting materials in peptide synthesis is precluded by the loss of optical purity during the coupling reactions used to prepare the oxazolones. Therefore, new reactants that prevent the formation of the oxazolone or minimize the racemization process have been developed. In the early 1960s Kenner and co-workers[264–266] showed that the oxazolones **273** obtained from α,α-dialkylamino acid derivatives **272** are excellent intermediates to prepare peptides **274** incorporating such amino acids. The process proceeds via ring opening of the oxazolone with the appropriate nucleophile and is shown in Scheme 7.88. Since then, this strategy, which implies the 4,4-disubstituted-5(4*H*)-oxazolones **273** as intermediates, has been used extensively. In particular, for achiral analogues of **273** ($R_2 = R_3$) the synthesis is easier.

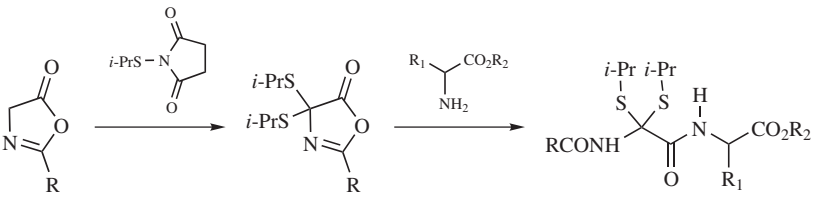


272 **273** **274**

Scheme 7.88

The simplest amino acid in the series, dimethylglycine or 2-aminoisobutyric acid (Aib), has been widely studied and 4,4-dimethyl-2-substituted-5(4*H*)-oxazolones have been used to incorporate Aib into model small peptides[267–269] and into linear oligopeptides in order to perform structural studies.[270–274] Dipropylglycine (Dpg) has been incorporated into model peptides using 4,4-dipropyl-2-(trifluoromethyl)-5(4*H*)-oxazolone[275,276] and the structures of the corresponding homooligopeptides have been studied.[277] Similar studies have been published that involve dibenzylglycine (Dbg) and use 4,4-dibenzyl-2-(trifluoromethyl)-5(4*H*)-oxazolone as the starting material.[278,279]

N-Acyl peptides **277** containing an α,α-di(isopropylthio)glycine residue have also been described. These compounds were prepared as shown in Scheme 7.89. Thus, a 4,4-di(isopropylthio)-2-substituted-5(4*H*)-oxazolone **276** was prepared from a 2-substituted-5(4*H*)-oxazolone **275** by reaction with *N*-(isopropylsulfenyl)-succinimide. The starting 2-substituted-5(4*H*)-oxazolone was prepared by cyclization of an *N*-acylglycine.[280]



Scheme 7.89

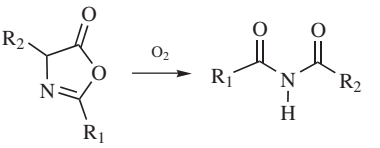
It is more difficult to prepare a chiral α,α-dialkylamino acid. Nevertheless, when such analogues are incorporated into the backbone of a peptide chain, analogues with modified properties are obtained. In this context, such residues have been evaluated as a new type of conformational constraint for the synthesis of enzyme-resistant agonists and antagonists of bioactive peptides. Here, the asymmetric synthesis or the resolution of the chiral quaternary amino acid is necessary and numerous procedures, which have recently been reviewed,[253] were developed to produce the requisite amino acids in enantiomerically pure form.

Incorporation of an α-methylamino acid into a small model peptide is achieved using oxazolone methodology. α-Methylvaline (αMe)Val[281–283] and α-methylphenylalanine (αMe)Phe[284,285] have been used frequently in such studies and conformational analyses of the corresponding peptides in solution and in the crystal state have been reported. A comparative study of the influence of the α-methylamino acid on conformation has also been published.[286]

Achiral cycloalkyl quaternary amino acids have also been incorporated into model peptides using 5(4*H*)-oxazolones as intermediates. A comparative study between cyclic and acyclic derivatives has been described.[287] The influence of the ring size of a homologous series from 1-aminocyclopropanecarboxylic acid to 1-aminocyclononanecarboxylic acid has been studied.[288–296]

7.3.2.5. *Other Ring-Opening Reactions*

The oxidation by molecular oxygen[297] or the base-catalyzed oxidative decarboxylation of saturated 5(4*H*)-oxazolones **278**[298] yields diacylamines and provides an efficient procedure to prepare imides **279** from *N*-acylamino acids (Scheme 7.90).



278 **279**

Scheme 7.90

Potassium superoxide in aprotic solvents has also been used as the oxidant but the resulting products depend on the substitution at C-4 of the oxazolone ring. Monosubstituted oxazolones give the corresponding imides. In contrast, with disubstituted analogues, such as 4,4-dimethyl-2-phenyl-5(4*H*)-oxazolone, potassium superoxide acts as a nucleophile and effects ring opening of the oxazolone to generate an *N*-benzoylamino acid.[299]

Saturated oxazolones undergo an acylaminoacylation reaction with aromatic compounds in the presence of Lewis acids to give amino ketones. Subsequent cyclodehydration of these amino ketones then affords 2,5-diaryloxazoles. Some examples of 2,5-diaryloxazoles prepared in this manner are shown in Table 7.23 (Fig. 7.25).

The reaction also has been applied to the oxazolone derived from hippuric acid[300,301] but it is particularly important for bis(oxazolones) such as **280** that are useful precursors to the bisoxazoles **281** (Scheme 7.91).[302,303]

TABLE 7.23. 2,5-DIARYLOXAZOLES FROM REACTION OF SATURATED 5(4*H*)-OXAZOLONES WITH ARENES

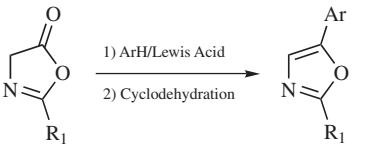
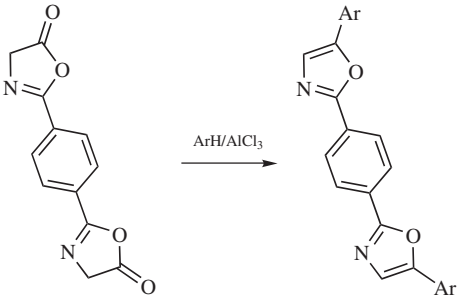


Figure 7.25

R_1	Ar	% Yield
4-FC_6H_4	Ph	~ 47
4-FC_6H_4	4-MeC_6H_4	~ 47
4-FC_6H_4	2,4-$Me_2C_6H_3$	~ 38
4-FC_6H_4	2,5-$Me_2C_6H_3$	~ 35

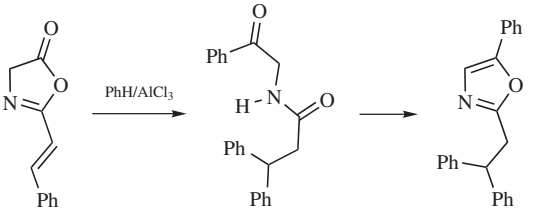
[a]Data from Ref. 300.



280 **281**

Scheme 7.91

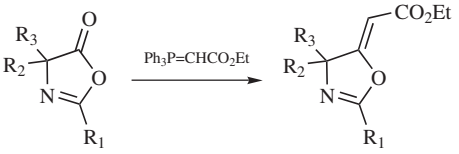
The same reaction applied to 2-styryl-5(4*H*)-oxazolone **282** gives simultaneous acylation and alkylation of the arene to produce the corresponding α-acylamino ketones **283**.[304] Cyclodehydration of **283** then readily affords a 2,5-disubstituted oxazole (e.g. **284** as shown in Scheme 7.92).



282 **283** **284**

Scheme 7.92

Wittig olefination of 5(4*H*)-oxazolones with triphenylphosphonium methylides affords product mixtures that depend on the ylide and the starting oxazolone.[305] The product mixtures can include, apart from the expected 5(4*H*)-oxazolylideneacetates, 5-oxazoleacetates, and other byproducts. Nevertheless, Wittig reaction of ethyl (triphenylphosphoranylidene)acetate with a 4,4-disubstituted-5(4*H*)-oxazolone **285** affords the corresponding ethyl 5(4*H*)-oxazolylideneacetates **286** in satisfactory yields (Scheme 7.93; Table 7.24, Fig. 7.26).



285 **286**

Scheme 7.93

TABLE 7.24. 5(4*H*)-OXAZOLYLIDENEACETATES FROM REACTION OF SATURATED 5(4*H*)-OXAZOLONES WITH TRIPHENYLPHOSPHONIUM METHYLIDES[a]

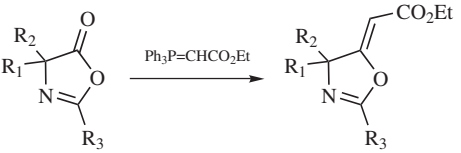
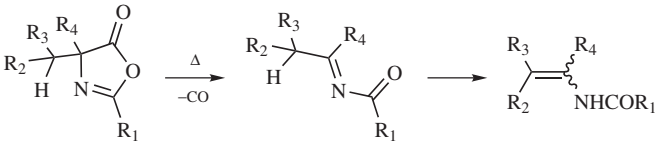


Figure 7.26

R_1	R_2	R_3	% Yield
Ph	Ph	4-$MeOC_6H_4$	67
Ph	Me	Ph	62
Me	Me	Ph	77

[a]Data from Ref. 305.

Heating 4-alkyl-2-substituted-5(4*H*)-oxazolones **287** (R_1 = Me, Ph) effects elimination of CO to generate *N*-acylimines **288** that rearrange to the more stable enamides **289** if an acidic α-hydrogen is present (Scheme 7.94). Representative examples of enamides prepared in this manner are shown in Table 7.25 (Fig. 7.27).



287 **288** **289**

Scheme 7.94

TABLE 7.25. ENAMIDES FROM THERMOLYSIS OF SATURATED 5(4*H*)-OXAZOLONES

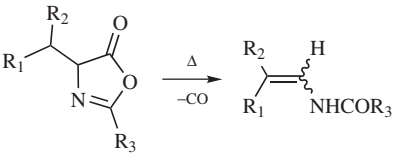


Figure 7.27

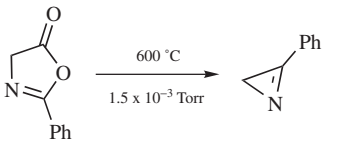
R_1	R_2	R_3	% Yield
Me	H	Me	95
Me	H	Ph	99
Me	Me	Me	100
Me	Me	Ph	95
i-Pr	H	Me	90
i-Pr	H	Ph	75

[a]Data from Ref. 306.

However, in the presence of a quaternary α-carbon this rearrangement is precluded and the *N*-acylimines **288** may be isolated. Finally, pyrolysis of 4,4-dialkyl-5(4*H*)-oxazolones affords mixtures of *N*-acylimines and enamides. The composition of the mixture depends on the pyrolysis temperature.[306]

The mechanism of the thermal conversion of 4-cyclopropenyl-4-substituted-5(4*H*)-oxazolones to pyridines has been studied. A stepwise cycloaddition of the initially generated nitrile ylide has been proposed to account for the observed products.[307]

Flash vacuum pyrolysis of 2-phenyl-5(4*H*)-oxazolone **146** effects extrusion of carbon dioxide to produce 3-phenyl-2*H*-azirine **290** in moderate yield (Scheme 7.95).[308]

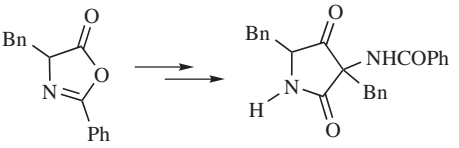


146 **290**

Scheme 7.95

7.3.2.6. Dimerization Reactions

Dimerization of 5(4*H*)-oxazolones affords two different products depending on the reaction conditions. In one case, 4-benzyl-2-phenyl-5(4*H*)-oxazolone **291** was converted to the pyrrolidinedione **292** with potassium carbonate followed by acidic hydrolysis (Scheme 7.96).[309]

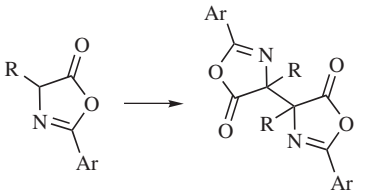


291 **292**

Scheme 7.96

A kinetic study of the base-catalyzed dimerization of 5(4*H*)-oxazolones has shown that 5(4*H*)-oxazolones with sterically demanding or electron-donating substituents at C-2 are less prone to dimerization.[310]

Dimerization can also be achieved using nickel peroxide[311,312] or through a photooxidation reaction.[313] In these cases, 4-monosubstituted-5(4*H*)-oxazolones **293** are converted to the corresponding 4,4′-bis(oxazolones) **294** (Scheme 7.97;



293 **294**

Scheme 7.97

Table 7.26, Fig. 7.28). A variety of reactions involving free radical generation from such bis(oxazolones) have been described.[314–317]

7.3.2.7. Cycloaddition Reactions

Mesoionic oxazolones (munchnones) **297** can be generated by cyclodehydration of N-substituted α-amino acids **295** or by alkylation of oxazolones **296** (Scheme 7.98). These compounds are reactive and versatile 1,3-dipoles that undergo cycloaddition reactions with dipolarophiles to generate a variety of heterocyclic systems. In particular, this is an extremely versatile methodology to prepare pyrroles that result from elimination of carbon dioxide from the initial cycloadduct. Numerous examples have appeared in the literature in recent years and several have been selected for discussion. The reader should consult Part A, Chapter 4 for an extensive discussion and additional examples.

TABLE 7.26. 4,4′-BIS(OXAZOLONES) FROM DIMERIZATION OF SATURATED 5(4*H*)-OXAZOLONES

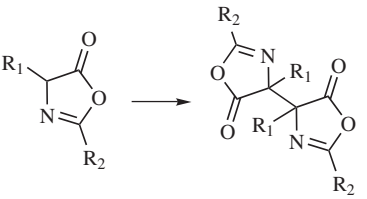
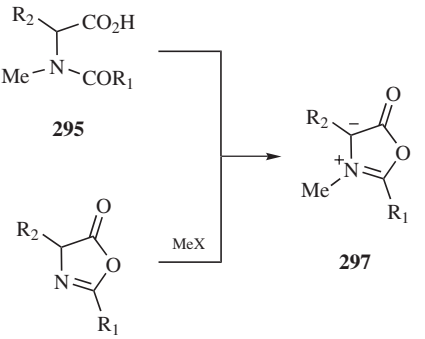


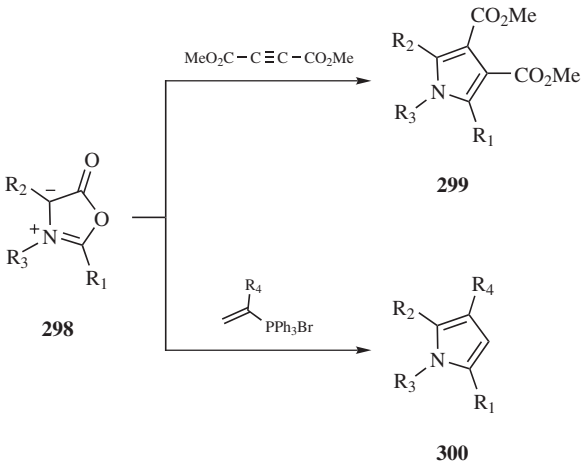
Figure 7.28

R_1	R_2	% Yield	Reference
Ph	4-$MeOC_6H_4$	> 75	311
Ph	Ph	> 75	311
4-ClC_6H_4	Ph	> 70	312
Ph	2-FC_6H_4	69	316
Ph	2-ClC_6H_4	66	316
Ph	4-ClC_6H_4	74	316



Scheme 7.98

Munchnones **298** obtained *in situ* by N-alkylation of 5(4*H*)-oxazolones undergo 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to give *N*-alkylpyrroles **299**.[318] 1,3-Dipolar cycloaddition of munchnones with triphenylvinylphosphonium bromides affords tri- and tetrasubstituted pyrroles **300**. In this case, the interaction of the phosphonium group with the carbonyl group leads to high levels of regioselectivity (Scheme 7.99; Table 7.27, Fig. 7.29).[319]



Scheme 7.99

Oxazolones[320] react with fumarates and fumaronitrile or acrylates to afford the corresponding cycloadducts **302** or **304**. These cycloadducts, in turn, rearrange to **303** and **305** depending on the substituents (Scheme 7.100).

TABLE 7.27. SUBSTITUTED PYRROLES VIA CYCLOADDITION OF DIPOLAROPHILES WITH MUNCHNONES PREPARED FROM SATURATED 5(4*H*)-OXAZOLONES

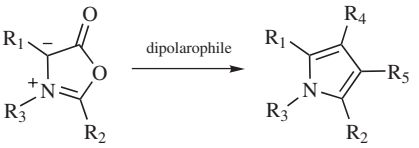
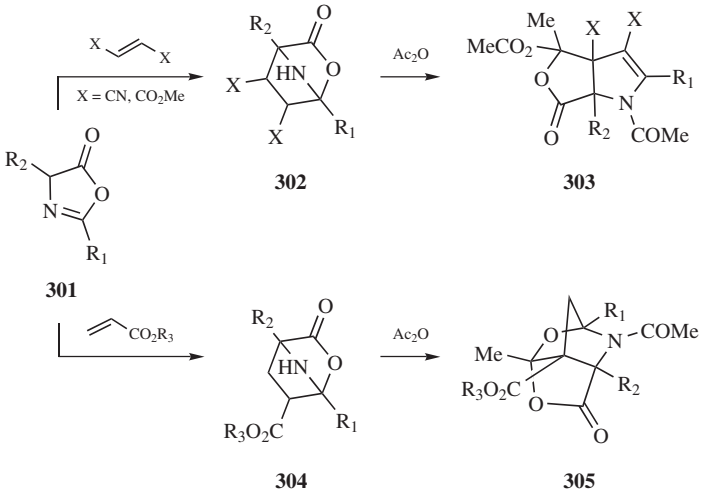


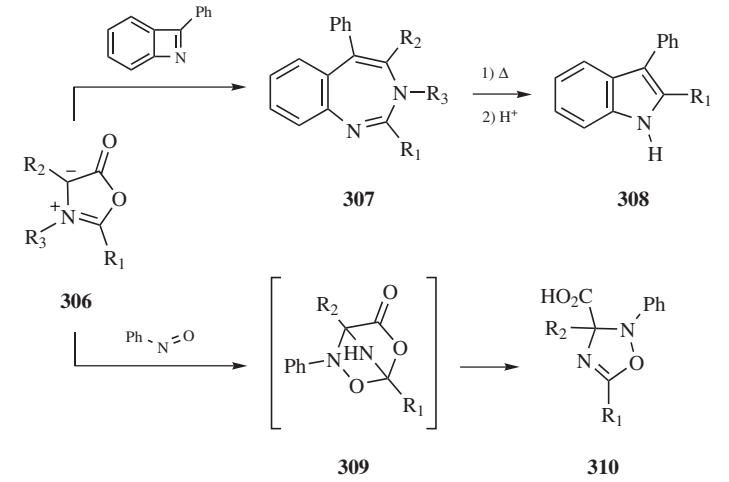
Figure 7.29

R_1	R_2	R_3	Dipolarophile	R_4	R_5	% Yield	Reference
$PhCH_2$	Me	Me	$MeO_2CC{\equiv}CCO_2Me$	CO_2Me	CO_2Me	87	318
$PhCH_2$	Me	Et	$MeO_2CC{\equiv}CCO_2Me$	CO_2Me	CO_2Me	80	318
Ph	Ph	H	$CH_2{=}CHPPh_3Br$	H	H	40	319
4-ClC_6H_4	Ph	H	$CH_2{=}CHPPh_3Br$	H	H	35	319
Ph	4-MeC_6H_4	H	$CH_2{=}CMePPh_3Br$	Me	H	30	319
Ph	*i*-Pr	H	$CH_2{=}CMePPh_3Br$	Me	H	41	319
Ph	Ph	Me	$CH_2{=}CHPPh_3Br$	H	H	53	319
4-ClC_6H_4	Ph	Me	$CH_2{=}CHPPh_3Br$	H	H	49	319
Ph	4-ClC_6H_4	Me	$CH_2{=}CMePPh_3Br$	Me	H	34	319
4-$MeOC_6H_4$	Ph	Me	$CH_2{=}CMePPh_3Br$	Me	H	35	319



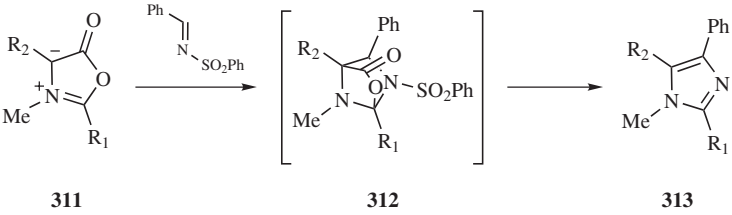
Scheme 7.100

Reaction of munchnones **306** with 2-phenylbenzazete provides a simple route to 1,3-benzodiazepines **307**[321] that thermally rearrange to the corresponding 3*H*-indoles **308**. 1,3-Dipolar cycloaddition reactions of nitrosobenzene and munchnones give the corresponding cycloadducts **309** with a high degree of regioselectivity. Subsequent ring opening of the cycloadducts leads to a variety of substituted 1,2,4-oxadiazoline-3-carboxylic acids **310** (Scheme 7.101).[322–325]



Scheme 7.101

Cycloaddition reactions of *N*-(phenylmethylene)benzenesulfonamide with mesoionic oxazolones **311** produces 2,5-disubstituted imidazoles **313** in a highly regioselective process via cycloreversion of cycloadduct **312** and subsequent loss of benzenesulfinic acid.[326]

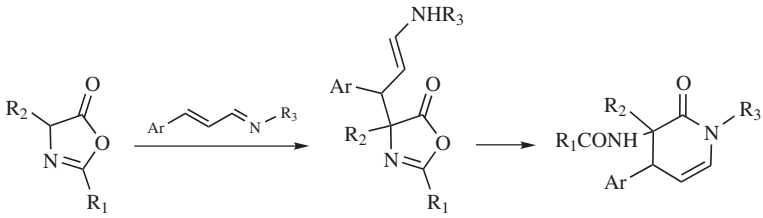


Scheme 7.102

Finally, 5(4*H*)-oxazolones react as masked 1,3-dipoles with nitrileimines,[327] 1-nitroso-2-naphthol[328] and [60]fullerene[329] to give 1,2,4-triazoles, naphth[1,2-*d*]-oxazoles and 5′-phenyl-2′*H*-pyrrolo[3′,4′:1,2][60]fullerene, respectively.

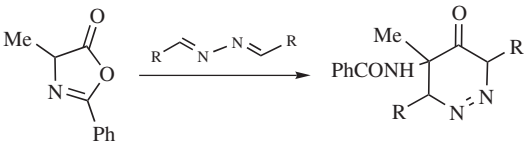
7.3.2.8. Reactions with Dienes and Azadienes

Reaction of oxazolones with 1-azadienes, for example, imines prepared from 3-(2-furyl)acrolein[330] or cinnamaldehyde,[331–334] affords 2-pyridones **316**. Several mechanisms have been proposed to explain the formation of **316**. However, products like **315** have also been isolated. The authors proposed that **315** arises from alkylation at C-4 of the oxazolone by the 1-azadiene. Subsequent nucleophilic attack by the amino group with ring opening then yields the 2-pyridone (Scheme 7.103). Representative examples of 2-pyridones prepared from 1-azadienes are shown in Table 7.28 (Fig. 7.30).



314 **315** **316**

Scheme 7.103



193 **317**

Scheme 7.104

In a similar manner, aldazines afford pyridazinones **317** (Scheme 7.104).[335]

1,3-Diazadienes such as 1-aryl-4-(dimethylamino)-2-phenyl-1,3-diaza-1,3-butadienes or 1-aryl-4-(dimethylamino)-2-methylthio-1,3-diaza-1,3-butadienes react with oxazolones and give rise to pyrimidin-6-ones **319** and **320** as single diastereo-

TABLE 7.28. 2-PYRIDONES FROM CYCLOADDITION REACTIONS OF SATURATED 5(4*H*)-OXAZOLONES WITH 1-AZADIENES

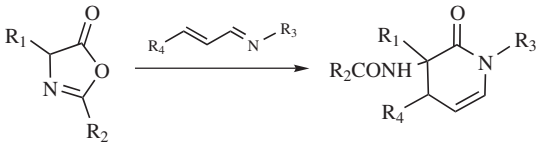
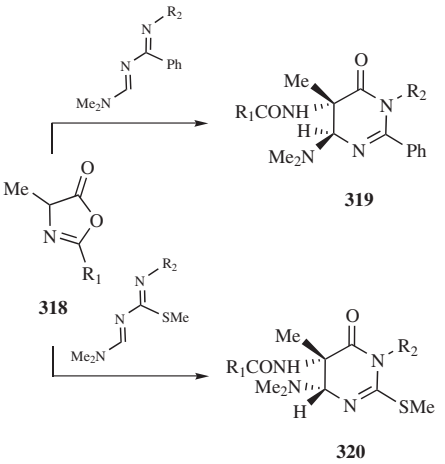


Figure 7.30

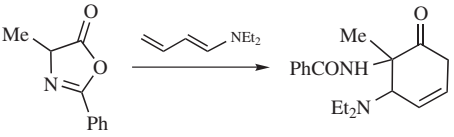
R_1	R_2	R_3	R_4	% Yield	Reference
Me	4-ClC_6H_4	Ph	Ph	74	332
Me	4-$MeOC_6H_4$	4-ClC_6H_4	Ph	82	332
Me	4-$NO_2C_6H_4$	4-MeC_6H_4	Ph	72	332
Me	$PhCH_2$	4-$MeOC_6H_4$	Ph	80	332
Ph	Ph	Me	Ph	60	333
Ph	Ph	C_6H_{11}	Ph	60	333
Ph	Ph	C_6H_{11}	Me	78	334
Me	Ph	C_6H_{11}	Me	88	334
Me	$PhCH_2$	C_6H_{11}	Me	78	334
Ph	Ph	*i*-Pr	Me	65	334
Me	Ph	*i*-Pr	Me	72	334
Ph	Ph	Ts	Ph	80	339



Scheme 7.105

isomers. Interestingly, **319** and **320** are formed with a reversal in stereochemistry (Scheme 7.105; Table 7.29, Fig. 7.31).[336,337]

Highly substituted cyclohexenones **321** are efficiently prepared from dienamines and 5(4*H*)-oxazolones (Scheme 7.106).[338]



Scheme 7.106

TABLE 7.29. PYRIMIDIN-6-ONES FROM CYCLOADDITION REACTIONS OF SATURATED 5(4*H*)-OXAZOLONES WITH 1,3-DIAZADIENES[a]

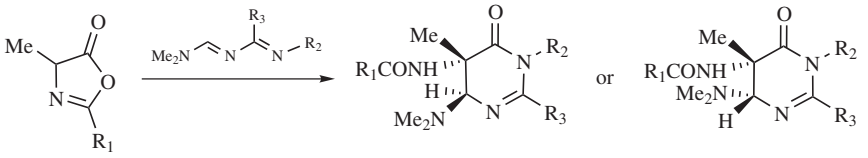
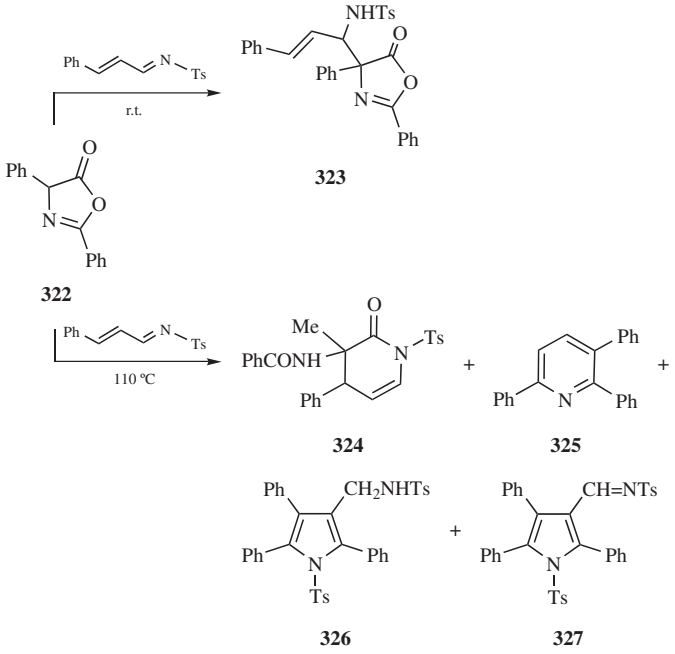


Figure 7.31

R_1	R_2	R_3	% Yield **A**	% Yield **B**
4-ClC_6H_4	Ph	Ph	90	
Ph	Ph	Ph	82	
Ph	4-MeC_6H_4	Ph	87	
4-ClC_6H_4	Ph	SMe		94
Ph	Ph	SMe		91
Ph	4-ClC_6H_4	SMe		83

[a]Data from Ref. 337.

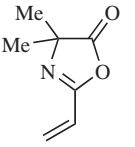
Finally, reaction of 2,4-diphenyl-5(4*H*)-oxazolone **322** with 4-phenyl-*N*-tosyl-1-azabuta-1,3-diene was found to be highly dependent on the experimental conditions. At room temperature the sole product was **323** that arises from alkylation of **322** by addition at the imine carbon. However, heating **322** and 4-phenyl-*N*-tosyl-1-azabuta-1,3-diene gave rise to several products including a 2-pyridone **324**, 2,3,6-triphenylpyridine **325**, and the pentasubstituted pyrroles **326** and **327**. The authors postulated two different reaction mechanisms. Here, both a 1,3-dipolar cycloaddition of the oxazolone and a nucleophilic addition of the oxazolone are possible and that may account for the formation of **324–327**. The marked differences in reactivity of 4-phenyl-*N*-tosyl-1-azabuta-1,3-diene relative to *N*-alkyl- or *N*-aryl-1-aza-1,3-dienes was attributed to the powerful electron-withdrawing nature of the tosyl group (Scheme 7.107).[339]



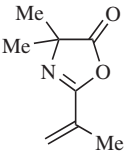
Scheme 7.107

7.3.2.9. Polymerization Reactions

Much effort has been invested to use oxazolones as intermediates for the synthesis of polymers. Probably the most important group of oxazolones used for this purpose is the 2-alkenyl-4,4-disubstituted-5(4*H*)-oxazolones. The reactivity of the exocyclic double bond at C-2 can be exploited to prepare new functionalized oxazolones as well as for copolymerization with other monomers. This possibility, together with the facile ring opening with nucleophiles, has opened very interesting routes to new polymers of industrial interest.



140



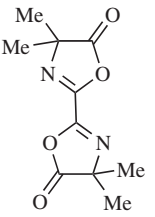
328

Figure 7.32. 2-Alkenyl-4,4-dimethyl-5(4*H*)-oxazolone monomers for polymerization reactions.

4,4-Dimethyl-2-vinyl-5(4*H*)-oxazolone (VDMO) **140** and 4,4-dimethyl-2-isopropenyl-5(4*H*)-oxazolone **328** have been extensively investigated as monomers (Fig. 7.32). Copolymerization of **140** or **328** with other monomers, for example, acrylates or acrylamides produces reactive polymers that are conveniently further modified by nucleophilic reaction with alcohols, amines, or other nucleophiles.[340–383]

The preparation of 2-(4-alkenylphenyl)-4,4-disubstituted-5(4*H*)-oxazolones[384] and their use as monomers has also been reported.[385]

The second group of saturated 5(4*H*)-oxazolones used as intermediates for polymer synthesis are the 2,2′-bis(oxazolones) with 2,2′-bis[4,4-dimethyl-5(4*H*)-oxazolone] **329** being the simplest member of the series (Fig. 7.33). These compounds, are prepared by cyclization of the corresponding bis(amino acids) and give a wide variety of polymers after ring opening with diamines, dialcohols or other nucleophiles. The physical chemical properties of these polymers depend on the nature of the substituents and the size of the chain. Some selected references describe representative examples.[386–396]



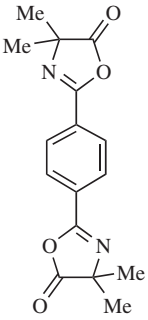
329

Figure 7.33. 2,2′-Bis[4,4-dimethyl-5(4*H*)-oxazolone] **329**.

Alternatively, a spacer can be inserted between the heterocyclic rings to further modify the properties of the polymer. Although various spacers have been used, aromatic rings are probably the most frequently employed. In this case, 2,2′-(*p*-phenylene)bis[4,4′-dimethyl-5(4*H*)-oxazolone] **330** is the most common monomer (Fig. 7.34). Again, representative examples are described in selected references.[397–405]

7.3.2.10. Organometallic Complexes

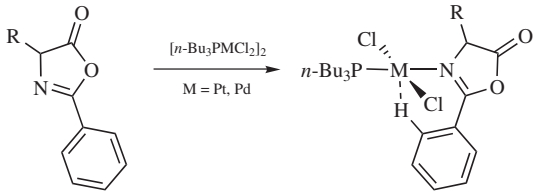
As multifunctional compounds, 5(4*H*)-oxazolones can act as ligands and, as such, they provide interesting organometallic transition metal complexes depending



330

Figure 7.34. 2,2′-(*p*-Phenylene)bis[4,4′-dimethyl-5(4*H*)-oxazolone] **330**.

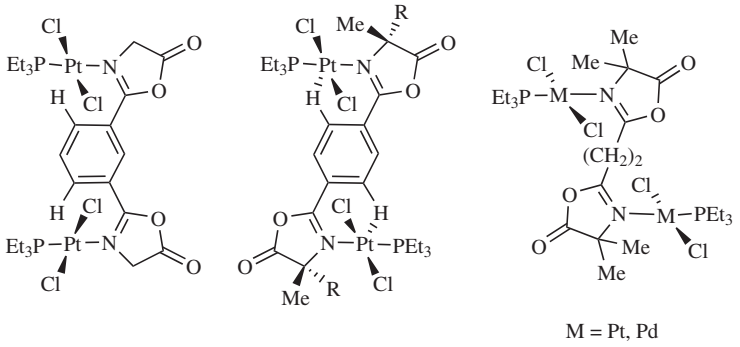
upon the coordination mode of the 5(4*H*)-oxazolone to the metal atom. Reaction of $[n\text{-Bu}_3\text{PMCl}_2]_2$ with 2-phenyl-4-substituted-5(4*H*)-oxazolones **331** generates the corresponding palladium(II) and platinum(II) complexes **332** (Scheme 7.108).[406]



331 **332**

Scheme 7.108

When phenylene- and ethylene-bridged bis(oxazolones) are used as ligands, dinuclear palladium(II) and platinum(II) **333**, **334**, and **335** complexes are obtained (Fig. 7.35).[407] In some cases, the close proximity of the ortho phenyl-H-atom to the metal rendered these complexes suitable precursors for ortho metalation.

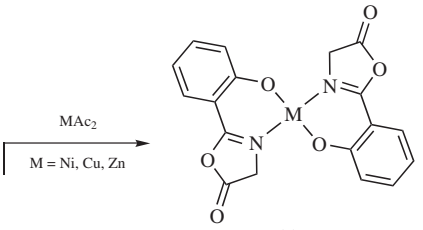


333 **334** **335**

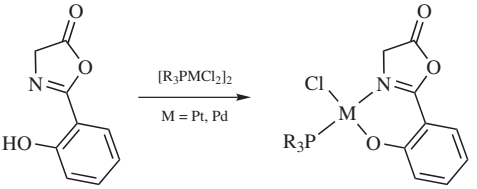
Figure 7.35. Dinuclear palladium(II) and platinum(II) complexes with phenylene- and ethylene-bridged bis(oxazolone) ligands.

If the anion of 2-(2′-hydroxyphenyl)-5(4*H*)-oxazolone **336** is used as a ligand, bis-chelate complexes **337** of copper(II), nickel(II), and zinc(II) have been prepared from the corresponding metal acetates. Alternatively, **336** and 2-(2′-aminophenyl)-5(4*H*)-oxazolone **340** can act as ligands with metals including palladium(II), platinum(II), ruthenium(II), nickel(II), and copper(II) to produce a variety of structurally diverse complexes **338**, **339**, and **341** as shown in Schemes 7.109 and 7.110.[407]

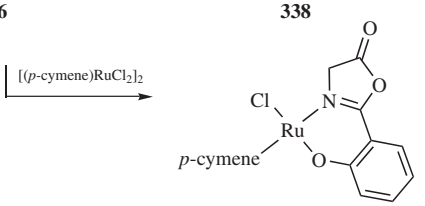
4-Alkyl-2-phenyl-5(4*H*)-oxazolones **342** react with the chloro-bridged iridium(III) complex $[(\eta^5\text{-}C_5Me_5)IrCl_2]_2$ to give cyclometalated mononuclear complexes **343**.



337

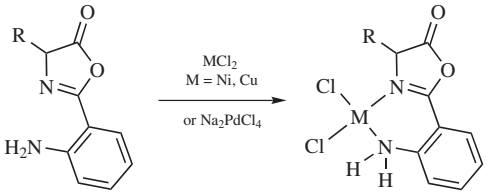


336 **338**



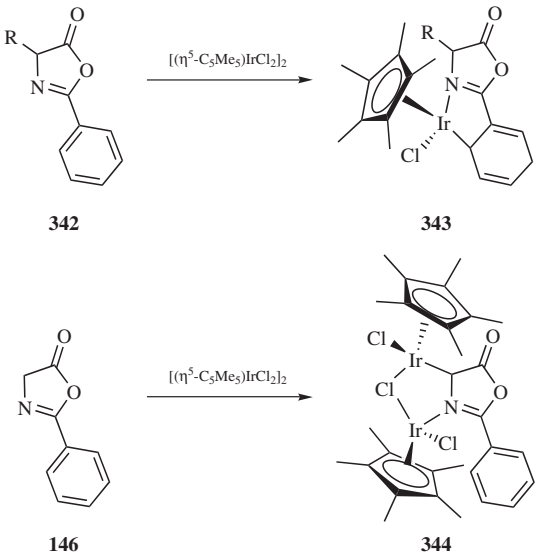
339

Scheme 7.109



340 **341**

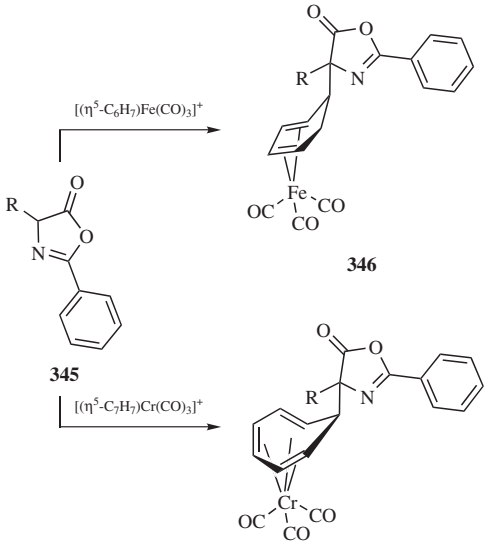
Scheme 7.110



Scheme 7.111

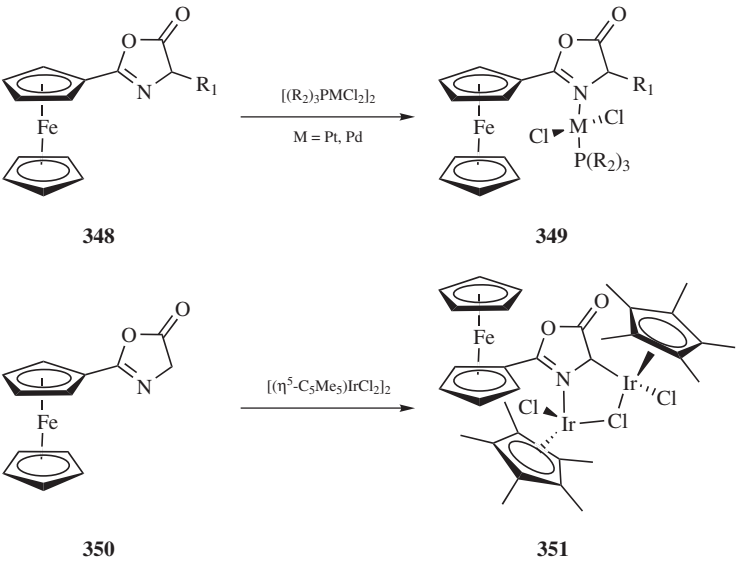
The same iridium(III) complex also reacts with 2-phenyl-5(4*H*)-oxazolone **146** to give dinuclear complexes **344** (Scheme 7.111).[408]

Anions of 2-phenyloxazolones **345** add to the π ligands of iron and chromium complexes, for example, $[(\eta^5\text{-}C_6H_7)Fe(CO)_3]^+$ and $[(\eta^7\text{-}C_7H_7)Cr(CO)_3]^+$ to give new organometallic complexes **346** and **347** (Scheme 7.112).[408]



Scheme 7.112

Ferrocenoylamino acids have been converted into 2-ferrocenyl-5(4*H*)-oxazolones **348** and **350** that act as N donors in palladium, platinum, and iridium complexes. Reaction of **348** with chloro-bridged palladium(II) and platinum(II) complexes affords a series of N-coordinated oxazolone complexes **349**. Reaction of the unsubstituted 2-ferrocenyl-5(4*H*)-oxazolone **350** with the chloro-bridged iridium(III) complex $[(\eta^5\text{-}C_5Me_5)IrCl_2]_2$ produces a dinuclear complex **351**, analogous to that obtained from 2-phenyl-5(4*H*)-oxazolone (Scheme 7.113).[409]



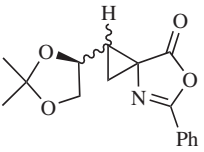
348 **349**

350 **351**

Scheme 7.113

7.3.3. Structural Analysis

A number of systematic structural analyses have been described for families of saturated oxazolones. First, as mentioned previously, detailed studies of ^{1}H NMR long-range coupling in 2,4-disubstituted-5(4*H*)-oxazolones and in 5(2*H*)-oxazolones have been reported.[11] Similarly, detailed ^{1}H NMR studies of the kinetics of racemization of 2,4-disubstituted-5(4*H*)-oxazolones have been performed.[12] A theoretical study of the spectral-luminescence properties of some 4-alkyl-2-phenyl-5(4*H*)-oxazolones has been reported[410] and an investigation of the infrared (IR) and Raman spectra of 5(4*H*)-oxazolones, particularly of the carbonyl group vibration, has been reported.[411] Electron impact mass spectra of saturated 5(4*H*)-oxazolones have been published.[412] More recently this technique has been used to distinguish between the stereoisomers of some spirocyclopropane oxazolones **352** (Fig. 7.36).[413] Finally, several studies of the HPLC behavior of 5(4*H*)-oxazolones complete a general view for this family of compounds.[414,415]

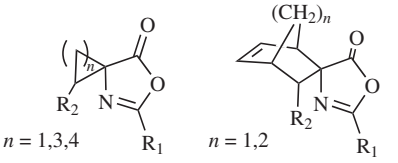


352

Figure 7.36. A spirocyclopropane 5(4*H*)-oxazolone studied by mass spectrometry.

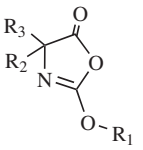
During the last 20 years, X-ray analyses of several saturated 5(4*H*)-oxazolones have been performed. Most of the compounds studied are 5(4*H*)-oxazolones derived from *N*-acylamino acids and, in particular, from quaternary amino acids since these compounds possess excellent chemical stability and high crystallinity. For example, the X-ray structure of 2-(4-bromophenyl)-4,4-dimethyl-5(4*H*)-oxazolone, derived from *N*-2-(4-bromobenzoyl)aminoisobutyric acid,[416] 2-(4-bromophenyl)-4,4-diphenyl-5(4*H*)-oxazolone, derived from *N*-2-(4-bromobenzoyl)diphenylglycine,[417] 2-(4-bromophenyl)-4-ethyl-4-methyl-5(4*H*)-oxazolone, derived from *N*-2-(4-bromobenzoyl)isovaline,[418] and 2-(4-chlorophenyl)-4-(2-cyclohexen-1-yl)-4-phenyl-5(4*H*)-oxazolone[419] have been reported. In general, the ring system of such 4,4-disubstituted-5(4*H*)-oxazolones is nearly planar and the two carbons at C-4 are displaced on the opposite sides of the average plane of the ring. It is noteworthy that the C—N bond length corresponds to a C=N bond that indicates that this bond is not conjugated with the carbonyl group of the oxazolone moiety. On the other hand, electron delocalization through the C—O—C group of the oxazolone moiety is small, although it is still significant.[420]

X-ray crystal structures for spirooxazolones including 4-spirocyclopropane **353** ($n = 1$, $R_2 = H$),[421] 4-spiro-(phenyl)cyclopropane **353** ($n = 1$, $R_2 = Ph$),[422] 4-spiro-(triphenyl)cyclopropane,[423] 4-spiro-(pivaloyloxy)cyclopropane **353** [$n = 1$, $R_2 =$ PivO (Piv = pivaloyl)],[424] 4-spirocyclopentane **353** ($n = 3$, $R_2 = H$),[425] 4-spirocyclohexane **353** [$n = 4$, $R_2 = H$],[426] 4-spiro-(2,2,4,4-tetramethyl-3-oxyl-3-aza)cyclohexane,[427] substituted 4-spirocyclohexanone,[428] substituted 4-spirocyclohexene,[429] substituted 4-spirobicyclo[2.2.1]heptene **354** [$n = 1$, $R_2 = (S)$-2,2-dimethyl-1,3-dioxolan-4-yl][430,431] and substituted 4-spirobicyclo[2.2.2]octene **354** [$n = 2$, $R_2 =$ (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl][432] have been determined (Fig. 7.37). The X-ray data for the oxazolone moiety of these compounds did not show striking differences from other 4,4-disubstituted-5(4*H*)-oxazolones.



353 **354**

Figure 7.37. General structure of spirocyclic 5(4*H*)-oxazolones analyzed by X-ray crystallography.

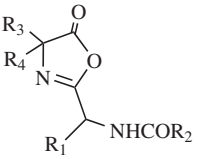


355

Figure 7.38. General structure of 2-alkoxy-5(4*H*)-oxazolones analyzed by X-ray crystallography.

Crystal structures of the 2-alkoxy-5(4*H*)-oxazolones investigated **355** (Fig. 7.38) indicate that the oxazolone ring is also nearly planar with bond distances and bond angles similar to those of 2-alkyl-5(4*H*)-oxazolones.[433,434] However, **355** do have a shorter (C-2)—O distance that indicates a slightly more effective intraring electron delocalization. In these compounds the lone pair of the exocyclic oxygen on C-2 is properly positioned for effective interaction with the C=N π-system and the length of the exocyclic C—O bond is shorter than that expected for an sp^2 single bond.

Finally, crystal structures of 5(4*H*)-oxazolones **356** obtained from peptides containing C-terminal 2-aminoisobutyric acid,[435,436] isovaline,[437,438] phenylalanine,[439] α-methylphenylalanine,[440] or α-methylleucine[441] residues have been discussed (Fig. 7.39). In these compounds the conformation of the amino acid preceding that involved in the ring system is generally not helical even if this residue is a strong helix former. This may result from the minimization of intramolecular interactions between the atoms of the oxazolone ring, which is nearly planar, and those of the preceding residue.

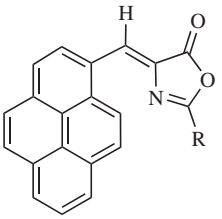


356

Figure 7.39. General structure of dipeptide 5(4*H*)-oxazolones analyzed by X-ray crystallography.

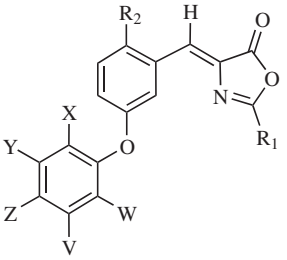
7.4. UNSATURATED 5(4*H*)-OXAZOLONES (2-OXAZOLIN-5-ONES)

Unsaturated 5(4*H*)-oxazolones have been well known for many years and new examples are constantly described every year in specialized organic journals. In general, a wide variety of substituted unsaturated oxazolones have been prepared and many applications have been described for these compounds (Fig. 7.40).



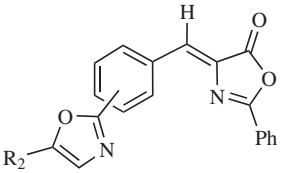
357

Disperse dyes



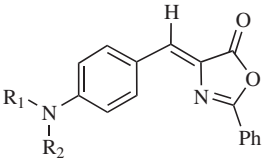
358

Herbicides and fungicides



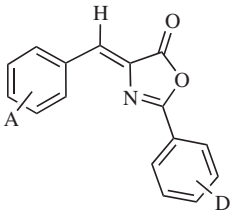
359

Luminophores



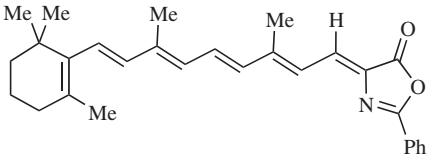
360

Electrophotographic light sensitive materials



361

NLO materials



362

Monomolecular films

Figure 7.40. Structurally diverse unsaturated 5(4*H*)-oxazolones and their applications.

Unsaturated 5(4*H*)-oxazolones have been studied as ultraviolet (UV)-absorbing layers,[442] as fungicides,[443] and as antibacterial agents.[444] For example, 4-(3-phenoxybenzylidene)-2-substituted-5(4*H*)-oxazolones **358** have been prepared and used as herbicides and fungicides.[445]

Many other applications have been described for these compounds and the list is so extensive that it is impossible to cover each example here. Nevertheless, it is noteworthy that appropriately substituted 4-arylidene-5(4*H*)-oxazolones, for example, **359** and **360** have been reported as organic luminophores[446–449] and electrophotographic light-sensitive materials,[450–455] respectively. The use of apocarotenoid derivatives such as **362** as monomolecular films has also been described.[456]

For new materials, a number of water-insoluble oxazolones have been used for dyeing or printing synthetic fibers[457] and, in this context, 4-(pyren-1-ylmethylene)-2-substituted-5(4*H*)-oxazolones **357**, prepared from pyrene-1-carboxaldehyde, have

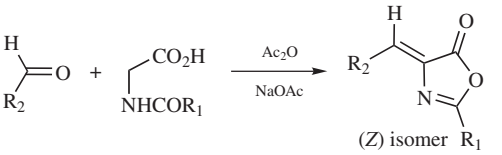
been used as dyes for polyester fibers.[458] Applications of unsaturated 5(4*H*)-oxazolones, for example, **361** as organic nonlinear optical materials have also been described.[459,460]

Unsaturated 5(4*H*)-oxazolones have also been used as intermediates to prepare analogues with diverse biological activities. For example, the oxazolone derived from 4-biphenylcarboxaldehyde is a synthetic precursor of the antiinflammatory agent 4-biphenylacetic acid.[461] In addition, 2-substituted oxazolones derived from 2-thioarylbenzaldehydes are starting materials for the preparation of dibenzothiepine derivatives that are useful to treat schizophrenia.[462] Other oxazolones have been used as intermediates to prepare insecticides and acaricides.[463a]

7.4.1. Synthesis

7.4.1.1. From N-Acylglycines and Carbonyl Compounds

The first procedure to prepare unsaturated 5(4*H*)-oxazolones was the Erlenmeyer synthesis[463b,c] that was described more than one hundred years ago and is still used extensively with some variations in the experimental conditions. In general, the reaction employs an acylamino acid, for example, *N*-acetyl- or *N*-benzoylglycine are the most common, and a carbonyl compound, usually an aldehyde, in the presence of a cyclodehydrating agent such as acetic anhydride (Scheme 7.114). Hundreds of unsaturated oxazolones **363** have been obtained via this procedure and these compounds are valuable intermediates for the synthesis of many interesting organic compounds.



363

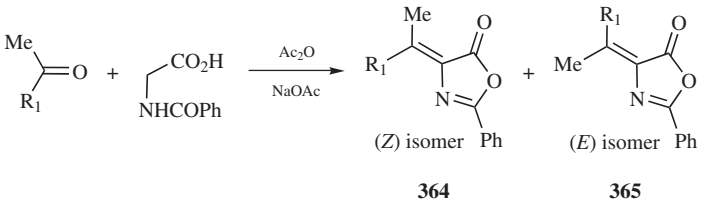
Scheme 7.114

The Erlenmeyer synthesis usually proceeds with a very high degree of stereoselectivity to favor the thermodynamically more stable (*Z*) isomer that is easily isolated by recrystallization. In some cases, the (*Z*) isomer is the only product obtained. This general methodology has been used extensively to prepare of a wide variety of unsaturated oxazolones.[1–3,464–467]

Heterocyclic aldehydes have been used as the carbonyl component and yield the corresponding 4-(heteroarylmethylene)-2-substituted-5(4*H*)-oxazolones that are also valuable synthetic intermediates. Examples of (heteroarylmethylene)-5(4*H*)-oxazolones of particular interest that have been synthesized include oxazolones derived from furfural,[468] pyrazolecarboxaldehyde,[469] and chromonecarboxaldehyde.[470,471] Indole-containing oxazolones are of special interest owing to the

diverse biological and pharmacological properties and numerous derivatives have been prepared and studied.[472–476]

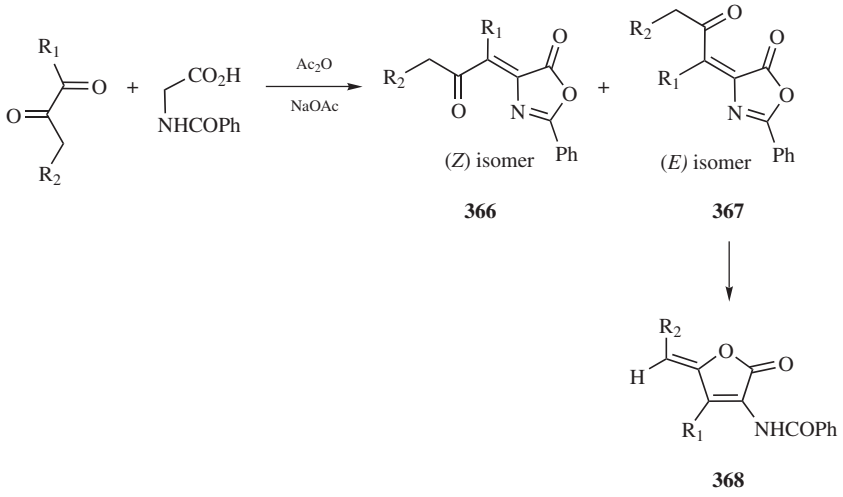
A limited number of references have appeared that use ketones as the carbonyl component. The first example reported[477] that acetophenones condense with *N*-benzoylglycine under Erlenmeyer conditions to afford a mixture of (*Z*)- and (*E*)-unsaturated-5(4*H*)-oxazolones **364** and **365** in which the (*Z*)-isomer **364** is the major compound, obtained in moderate to good stereoselectivity (Scheme 7.115). The pure (*Z*) isomer was obtained by recrystallization of the mixture.



364 **365**

Scheme 7.115

In the second study, diketones were used as electrophiles and reacted with *N*-benzoylglycine to give a (*Z*/*E*) mixture of oxazolones **366** and **367** derived from condensation at the less hindered carbonyl group of the 1,2-dicarbonyl compound (Scheme 7.116). The (*E*)-isomers **367** were used as starting materials to prepare (*Z*)-5-alkylidene-3-(benzoylamino)-2(5*H*)-furanones **368**.[478]



366 **367** **368**

Scheme 7.116

Mechanistic studies of the Erlenmeyer reaction suggest that the reaction proceeds through initial rapid and reversible formation of the saturated oxazolone followed by an aldol condensation of the latter with the carbonyl compound and subsequent dehydration.[479]

The classical experimental conditions of the Erlenmeyer synthesis use anhydrous sodium acetate and acetic anhydride to effect cyclodehydration. However, many other reagent combinations have been used to improve the yield and the stereoselectivity of the reaction. With these aims in mind, zinc acetate,[480] anhydrous zinc chloride,[481] trimethylsilylchloride and acetic anhydride,[482] or a mixture of alumina–boric acid in the presence of acetic anhydride[483] have also been used. Diethyl pyrocarbonate[484] or haloiminium salts, such as *N*,*N*-dimethylchlorosulfite methaniminium chloride[485] or 2-chloro-1,3-dimethylimidazolium chloride[82] have also been described as suitable cyclodehydrating agents. Ion-exchange resins,[486] potassium fluoride and alumina[487] and zeolites under mild conditions[488] are examples of heterogeneous catalysts to prepare unsaturated 5(4*H*)-oxazolones. Interestingly, microwave accelerated condensations using DCC and dimethylacetamide (DMA) are reported to furnish 4-arylidene-2-phenyl-5(4*H*)-oxazolones in better yields than simply heating the reagents.[489,490] A variety of 5(4*H*)-oxazolones prepared via the Erlenmeyer synthesis are shown in Table 7.30 (Fig. 7.41).

Since most procedures afford the more stable (*Z*)-isomer **369**, some attention has been focused to find specific methods to generate the (*E*)-isomer **370**. Among these

TABLE 7.30. SYNTHESIS OF UNSATURATED 5(4*H*)-OXAZOLONES FROM *N*-ACYLGLYCINES AND CARBONYL COMPOUNDS

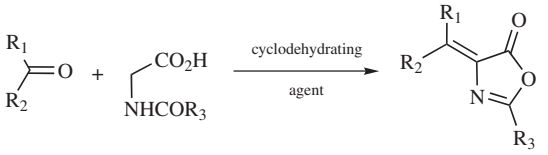


Figure 7.41

R_1	R_2	R_3	Cyclodehydrating Agent	% Yield	Reference
H	2-$NO_2C_6H_4$	Me	Ac_2O/NaOAc	63 ($Z+E$)	465
H	Ph	Me	zeolite-HY	73	488
H	4-$AcOC_6H_4$	Me	zeolite-HY	70	488
H	3,4-$(MeO)_2C_6H_3$	Me	zeolite-HY	78	488
H	Ph	Ph	zeolite-HY	80	488
H	4-$Me_2NC_6H_4$	Ph	zeolite-HY	85	488
H	3-MeO-4-HOC_6H_3	Ph	zeolite-HY	72	488
H	CF_3MeCH	Ph	$Zn(OAc)_2$	100 ($Z+E$)	480
H	5-ethoxycarbonylmethylfur-2-yl	Ph	Ac_2O/NaOAc	70	468
H	thien-2-yl	Ph	ion-exchange resin	38	486
H	5-nitrothien-2-yl	Ph	ion-exchange resin	62	486
H	fur-2-yl	Ph	ion-exchange resin	71	486
H	5-nitrofur-2-yl	Ph	ion-exchange resin	77	486
Me	Ph	Ph	$Ac_2O/Pb(OAc)_2$	46	477
Me	4-MeC_6H_4	Ph	$Ac_2O/Pb(OAc)_2$	38	477
Me	4-ClC_6H_4	Ph	$Ac_2O/Pb(OAc)_2$	40	477
Me	MeCO	Ph	$Ac_2O/Pb(OAc)_2$	36	478
Me	EtCO	Ph	$Ac_2O/Pb(OAc)_2$	25	478
Me	PhCO	Ph	$Ac_2O/Pb(OAc)_2$	86	478

TABLE 7.31. UNSATURATED (*E*)-5(4*H*)-OXAZOLONES VIA ISOMERIZATION OF UNSATURATED (*Z*)-5(4*H*)-OXAZOLONES

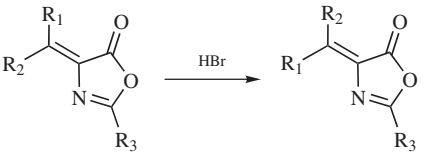
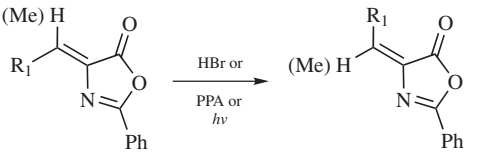


Figure 7.42

R_1	R_2	R_3	% Yield	Reference
H	Ph	Ph	90	491
H	2-$MeOC_6H_4$	Ph	90	491
H	4-$MeOC_6H_4$	Ph	96	491
Me	Ph	Ph	90	477
Me	4-$MeOC_6H_4$	Ph	90	477
Me	4-MeC_6H_4	Ph	92	477
Me	4-ClC_6H_4	Ph	89	477
Me	4-$NO_2C_6H_4$	Ph	85	477

procedures isomerization using hydrobromic acid,[477] polyphosphoric acid,[491] or irradiation through a pyrex filter with a 450 W medium pressure mercury arc lamp[492] are the most noteworthy (Scheme 7.117). Representative examples are shown in Table 7.31 (Fig. 7.42).



369 **370**

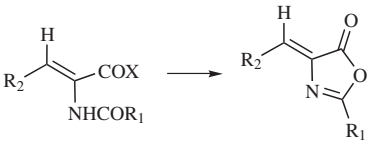
PPA = poly(phosphoric acid)

Scheme 7.117

Other electrophiles such as succinic anhydride,[493] imines,[494] or 2-(2-aminomethylene)-3-indolinones[495] have also been used to prepare 5(4*H*)-oxazolones.

7.4.1.2. From Other N-Acylamino Acid Derivatives and Glycine Equivalents

Other amino acid precursors have been used as starting materials in the Erlenmeyer reaction. A classical reaction of oxazolones is ring opening to give dehydroamino acid derivatives but there are a number of examples when the reverse reaction has been exploited including cyclizations of *N*-benzoyl-α,β-dehydrophenylalanine,[496] α-(acetylamino)cinnamic esters,[497] and 2-(acylamino)-2-alkenamides (Scheme 7.118).[498]

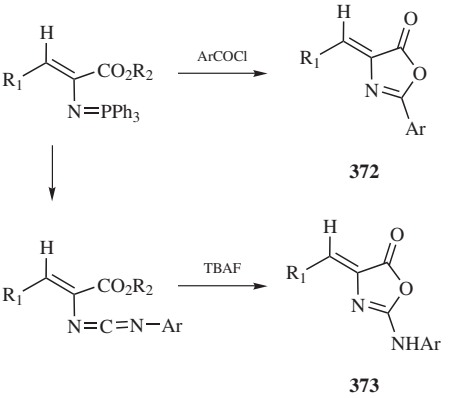


371

Scheme 7.118

When β-arylserines rather than glycine are used as the starting amino acid, cyclization occurs concomitant with dehydration to afford the corresponding unsaturated 5(4*H*)-oxazolone.[499]

Iminophosphoranes derived from readily available α-azidocinnamates react with aroyl chlorides to give the corresponding 2-aryl-4-arylidene-5(4*H*)-oxazolones **372**.[500,501] Alternatively, these iminophosphoranes are converted to the corresponding 2-arylamino-4-arylidene-5(4*H*)-oxazolones **373** via heterocyclization of an intermediate carbodiimide as shown in Scheme 7.119 (Table 7.32, Fig. 7.43).[502,503]



372

373

Scheme 7.119

TABLE 7.32. SYNTHESIS OF UNSATURATED 5(4*H*)-OXAZOLONES VIA CYCLIZATION OF α,β-DIDEHYDROAMINO ACIDS OR α,β-UNSATURATED CARBODIIMIDES

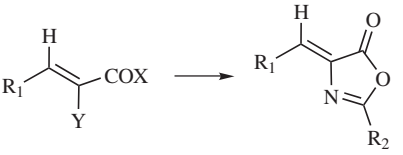
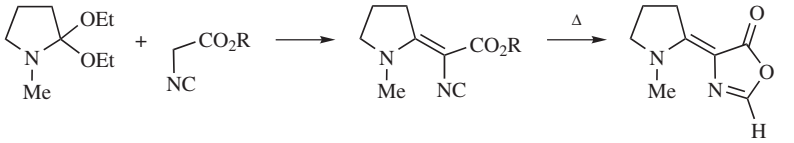


Figure 7.43

R_1	Y	R_2	% Yield	Reference
Ph	NHCOPh	Ph	84	496
Ph	N=C=N-Ph	NHPh	70	502
Ph	N=C=N-(4-MeC_6H_4)	NH-(4-MeC_6H_4)	96	502
Ph	N=C=N-(4-$MeOC_6H_4$)	NH-(4-$MeOC_6H_4$)	90	502
Ph	N=C=N-(4-ClC_6H_4)	NH-(4-ClC_6H_4)	90	502

Isocyanides have also been used to prepare unsaturated 5(4*H*)-oxazolones and they are particularly useful for the synthesis of 4-(aminomethylene)-5(4*H*)-oxazolones **374**. For instance, cyclization of an unsaturated isocyanide obtained from condensation of alkyl isocyanoacetates and lactam acetals has been reported (Scheme 7.120).[504]

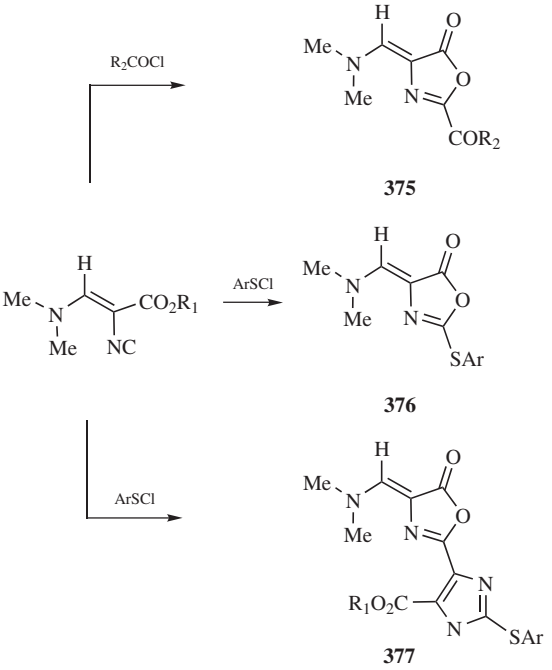


374

Scheme 7.120

Reaction of methyl 3-(dimethylamino)-2-isocyanoacrylate ($R_1 = Me$) with acyl chlorides gave 2-acyl-4-(dimethylaminomethylene)-5(4*H*)-oxazolones **375**.[505] The same reaction with arenesulfenyl chlorides gave either 2-arylthio-4-(dimethylaminomethylene)-5(4*H*)-oxazolones **376** or an unsaturated 5(4*H*)-oxazolone **377** containing an imidazole at C-2 depending on the substitution present in the arenesulfenyl chloride. Nitroarenesulfenyl chlorides favored **376**.[506,507] Selected examples of **372**, **375**, and **376** are shown in Table 7.33 (Fig. 7.44; Scheme 7.121).

4-(Dimethylaminomethylene)-5(4*H*)-oxazolones **378** can also be obtained directly from *N*-acylamino acids,[508] *N*-acylamino esters,[509] or *N*-acylamino



Scheme 7.121

TABLE 7.33. SYNTHESIS OF UNSATURATED 5(4*H*)-OXAZOLONES VIA CYCLIZATION OF α,β-UNSATURATED IMINOPHOSPHORANES OR α,β-UNSATURATED ISOCYANIDES

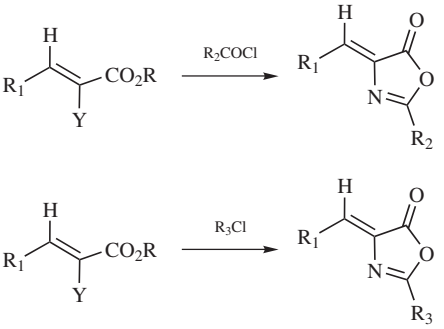
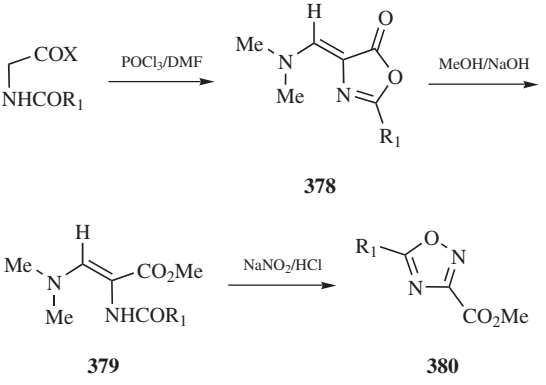


Figure 7.44

R_1	Y	R_2	R_3	% Yield	Reference
4-MeC_6H_4	N=PPh_3	4-$NO_2C_6H_4$		78–82	501
2-$MeOC_6H_4$	N=PPh_3	4-MeC_6H_4		78–82	501
3,4-$(MeO)_2C_6H_3$	N=PPh_3	Ph		78–82	501
3,4-$(MeO)_2C_6H_3$	N=PPh_3	4-ClC_6H_4		78–82	501
Me_2N	NC	Me		not described	505
Me_2N	NC	Ph		not described	505
Me_2N	NC		2-NO_2-4-ClC_6H_3S	~ 100	506
Me_2N	NC		2-$NO_2C_6H_4S$	~ 100	506
Me_2N	NC		2,4-$(NO_2)_2C_6H_3S$	~ 100	506

amides[510] using the Vilsmeier reagent. In some cases[508] ring opening followed by nitrosation of the intermediate α,β-didehydroamino acid derivative **379** affords the corresponding alkyl 5-substituted-1,2,4-oxadiazole-3-carboxylate **380** (Scheme 7.122; Table 7.34, Fig. 7.45).



378

379 **380**

Scheme 7.122

TABLE 7.34. SYNTHESIS OF UNSATURATED 5(4*H*)-OXAZOLONES FROM *N*-ACYLAMINO ACID DERIVATIVES AND VILSMEIER-HAACK REAGENT

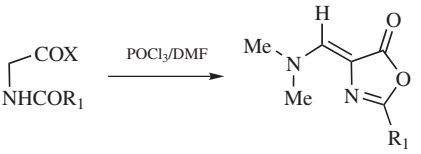


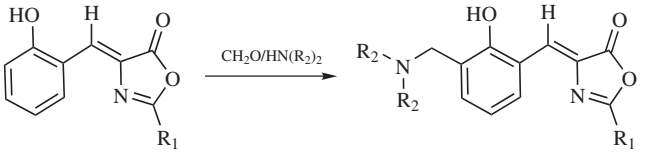
Figure 7.45

R_1	COX	% Yield	Reference
PhCH=CH	CO_2H	77	508
4-MeC_6H_4CH=CH	CO_2H	68	508
2-$MeOC_6H_4CH$=CH	CO_2H	64	508
Ph	CONHPh	90	510
4-$MeOC_6H_4$	CONH-4-MeC_6H_4	87–94	510
4-MeC_6H_4	CONH-4-MeC_6H_4	87–94	510
4-ClC_6H_4	CONH-4-$MeOC_6H_4$	87–94	510
4-$NO_2C_6H_4$	CONH-4-$MeOC_6H_4$	87–94	510
Ph	CONHNHPh	90	510

7.4.1.3. From Other Unsaturated 5(4H)-Oxazolones

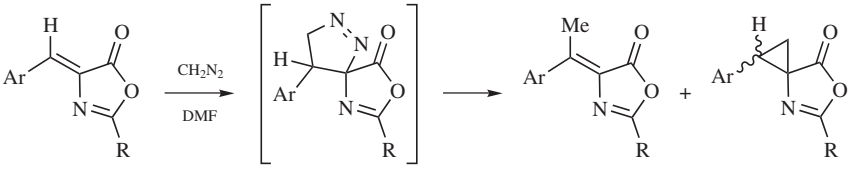
There are cases in which appropriate modification of one unsaturated oxazolone yields a new unsaturated oxazolone analogue. Most of the examples described in the literature involve modification of the substituent on the exocyclic double bond. For example, a series of 4-[2-hydroxy-3-(aminomethyl)benzylidene]-5(4*H*)-oxazolones **382** that were evaluated for bactericidal and fungicidal activities were obtained from Mannich reaction of 4-(2-hydroxybenzylidene)-5(4*H*)-oxazolones **381** (Scheme 7.123).[511]

The exocyclic double bond of 4-arylidene-5(4*H*)oxazolones **383** reacts with diazomethane in a 1,3-dipolar cycloaddition reaction to give the corresponding



381 **382**

Scheme 7.123



383 **384** **385** **386**

Scheme 7.124

spiropyrazolines **384**, which usually cannot be isolated. Further reaction of **384** gives a mixture of diastereomeric spiroxazolones **386** together with a 4-(α-arylethylidene)-5(4*H*)-oxazolone **385** in which the double-bond geometry of **383** has been retained (Scheme 7.124). The ratio of the isolated products depends on the stereochemistry of the starting oxazolone and on the experimental conditions of the cycloaddition reaction. Starting from (*Z*)-oxazolones the 4-(α-arylethylidene)-5(4*H*)-oxazolone **385** is the major product when the reaction is carried out in polar solvents.[477,512] Representative examples are shown in Table 7.35 (Fig. 7.46).

The synthesis and reactivity of 4-heteromethylene-2-substituted-5(4*H*)-oxazolones has been reviewed.[513] These readily available compounds are easily interconverted using a classical addition–elimination reaction (Scheme 7.125).

TABLE 7.35. SYNTHESIS OF 4-(α-ARYLETHYLIDENE)-5(4*H*)-OXAZOLONES FROM REACTION OF 4-ARYLIDENE-5(4*H*)-OXAZOLONES WITH DIAZOMETHANE[a]

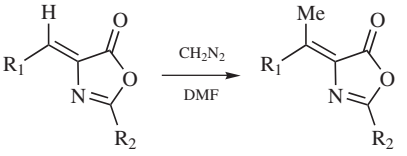
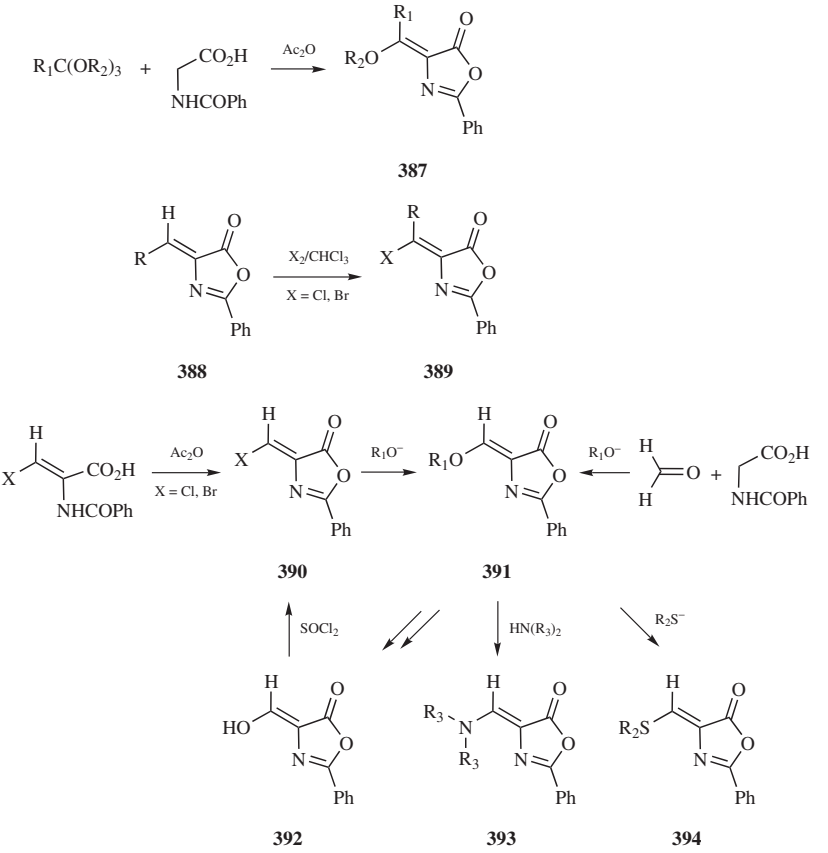


Figure 7.46

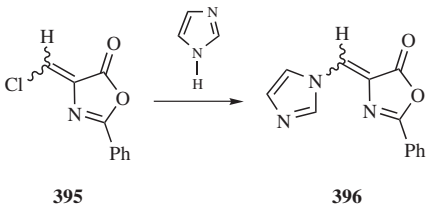
R_1	R_2	% Yield
Ph	Me	42
4-$MeOC_6H_4$	Me	33
4-MeC_6H_4	Me	28
Ph	Ph	48
4-$MeOC_6H_4$	Ph	50
4-MeC_6H_4	Ph	30

[a]Data from Ref. 477.



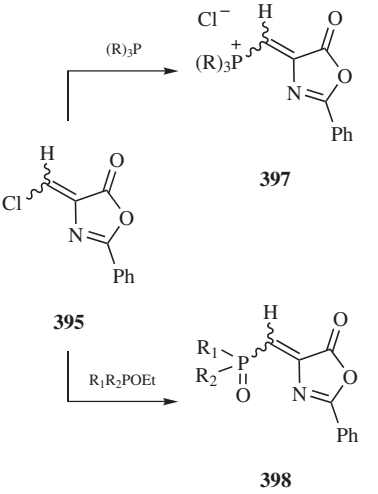
Scheme 7.125

Reaction of unsaturated 5(4*H*)-oxazolones with appropriate nucleophiles affords new unsaturated 5(4*H*)-oxazolone analogues used as intermediates to prepare a variety of interesting compounds. 4-(Chloromethylene)-5(4*H*)-oxazolones react with a variety of nucleophiles. For example, 4-(chloromethylene)-2-phenyl-5(4*H*)-oxazolone **395** reacts with imidazole to afford 4-[(imidazol-1-yl)methylene]-2-phenyl-5(4*H*)-oxazolone **396**.[514] The authors found no evidence for the product derived from carbon–carbon bond formation, that is, 4-[(imidazol-4-yl)methylene]-2-phenyl-5(4*H*)-oxazolone (Scheme 7.126).



Scheme 7.126

The displacement of the chlorine atom in **395** by triphenylphosphine or other phosphorus derivatives leads to the corresponding phosphorylated oxazolones **397** or **398** that have been used to prepare new and interesting substituted vinylphosphonium salts (Scheme 7.127).[515,516] Of particular interest is the synthesis of *N*-acyl-α-(triphenylphosphonio)glycinates as new cationic glycine equivalents.[517]



Scheme 7.127

Displacement of the chlorine atom in **395** by sodium thiomethoxide or other mercaptans was reported recently.[518] The same authors also described an efficient synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones **399** from **395** and organostannanes via palladium catalyzed Stille reaction (Scheme 7.128).[519] Selected examples are shown in Table 7.36 (Fig. 7.47).

TABLE 7.36. SYNTHESIS OF 4-ARYLIDENE-2-PHENYL-5(4*H*)-OXAZOLONES FROM STILLE REACTION OF 4-(CHLOROMETHYLENE)-2-PHENYL-5(4*H*)-OXAZOLONE[a]

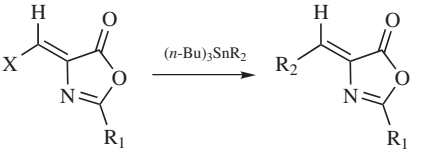
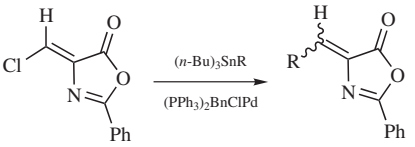


Figure 7.47

R_1	X	R_2	% Yield
Ph	Cl	Ph	98
Ph	Cl	4-$MeOC_6H_4$	80
Ph	Cl	fur-2-yl	97
Ph	Cl	thien-2-yl	82

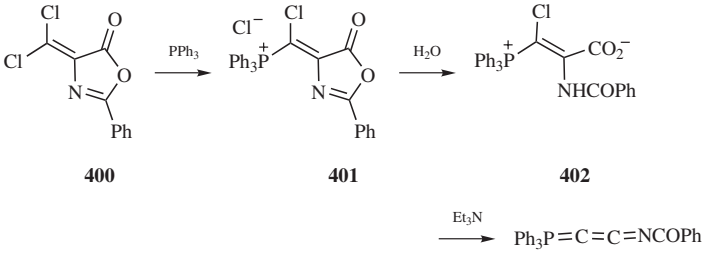
[a] Data from Ref. 519.



395 **399**

Scheme 7.128

The reaction of 4-(dichloromethylene)-2-phenyl-5(4*H*)-oxazolone **400** and triphenylphosphine affords the vinylphosphonium salt **401**, from which *N*-benzoyl (triphenylphosphoranylidene)ketenimine **403** is obtained by hydrolytic ring opening of **401** and subsequent treatment of **402** with triethylamine (Scheme 7.129).[520]



400 **401** **402** **403**

Scheme 7.129

4-(Ethoxymethylene)-2-phenyl-5(4*H*)-oxazolone **404**, readily available from hippuric acid and triethyl orthoformate, has also been used as a starting material for other unsaturated oxazolones via addition–elimination reactions. Nitrogen nucleophiles are most commonly used and amines give rise to 4-(aminomethylene)-2-phenyl-5(4*H*)-oxazolones **405** (Scheme 7.130; Table 7.37, Fig. 7.48) which, in many cases have been evaluated as antihypertensives.[521–526]

TABLE 7.37. SYNTHESIS OF 4-(AMINOMETHYLENE)-5(4*H*)-OXAZOLONES FROM 4-HETEROMETHYLENE-5(4*H*)-OXAZOLONES

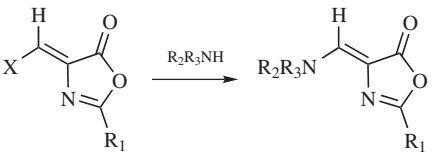
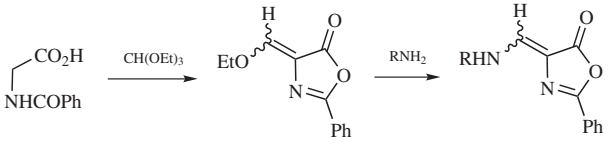


Figure 7.48

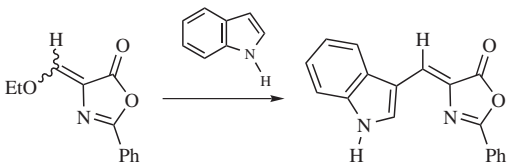
R_1	X	R_2R_3N	% Yield	Reference
Ph	Cl	imidazol-1-yl	~ 50	514
Ph	Cl	2-methylimidazol-1-yl	~ 50	514
Ph	Cl	4-methylimidazol-1-yl	~ 50	514
Ph	EtO	2-$MeOC_6H_4CH_2NH$	97	522



404 **405**

Scheme 7.130

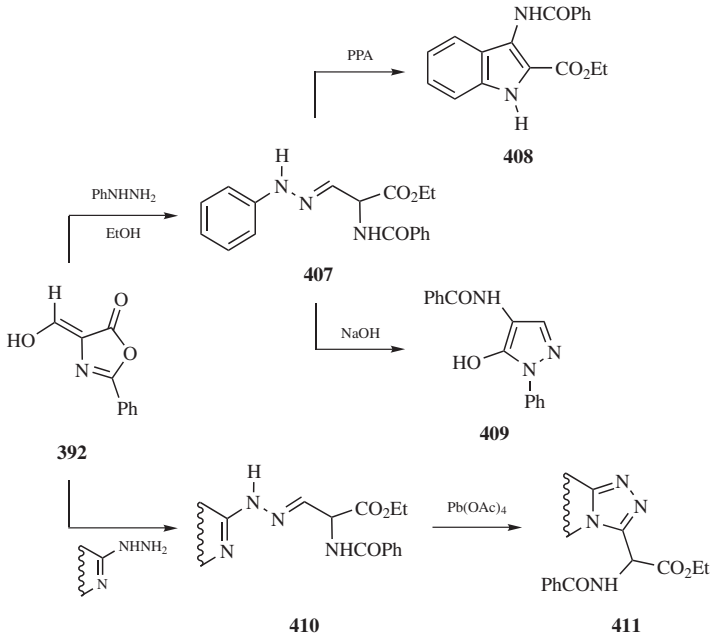
Heterocyclic amines also react as nucleophiles and, in this context, indole reacts with **404** to yield the unsaturated oxazolone **406**, an intermediate in the synthesis of tryptophan (Scheme 7.131).[527,528] It is noteworthy that **406** is the product of carbon–carbon bond formation. Imidazole also reacts with **404** but in this case the product is **396**, identical with that obtained from the 4-(chloromethylene) derivative **395**.[528]



404 **406**

Scheme 7.131

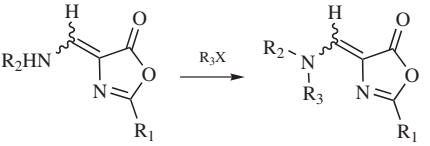
4-(Hydroxymethylene)-2-phenyl-5(4*H*)-oxazolone **392**, obtained from **404**, can be used to prepare indoles **408**, pyrazoles **409**, and fused 1,2,4-triazoles **411** by reaction with phenylhydrazines[529] or heteroarylhydrazines.[530] Selected examples are shown in Scheme 7.132.



408 **407** **392** **409** **410** **411**

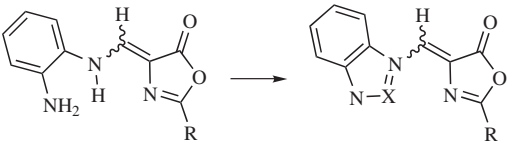
Scheme 7.132

4-(Aminomethylene)-5(4*H*)-oxazolones **412** have also been used as starting materials to prepare unsaturated oxazolones. Alkylation of the exocyclic nitrogen gives 4-(*N,N*-disubstituted-1-aminoalkylidene)-5(4*H*)-oxazolones **413** that are intermediates for peptides, pharmaceuticals and pesticides (Scheme 7.133).[531,532] Heterocyclic rings such benzimidazole or benzotriazole have been prepared as well (Scheme 7.134).[533]



412 **413**

Scheme 7.133

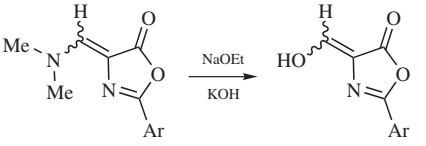


414 **415**

X = CH, N

Scheme 7.134

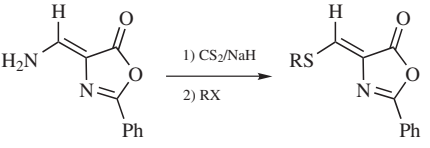
Carefully controlled base hydrolysis of a 2-aryl-4-(dimethylaminomethylene)-5(4*H*)-oxazolone **416** affords a 2-aryl-4-(hydroxymethylene)-5(4*H*)-oxazolone **417** (Scheme 7.135).[534]



416 **417**

Scheme 7.135

4-(Aminomethylene)-2-phenyl-5(4*H*)-oxazolone **418** has been converted to 4-(alkylthiomethylene)-2-phenyl-5(4*H*)-oxazolones **419** by treatment with carbon disulfide and subsequent alkylation. These 4-(alkylthiomethylene) analogues are useful intermediates for biologically active peptides, pharmaceuticals, and plant-protective agents (Scheme 7.136; Table 7.38, Fig. 7.49).[535,536]



418 **419**

Scheme 7.136

TABLE 7.38. SYNTHESIS OF 4-(ALKYLTHIOMETHYLENE)-5(4*H*)-OXAZOLONES FROM 4-(AMINOMETHYLENE)-5(4*H*)-OXAZOLONES[a]

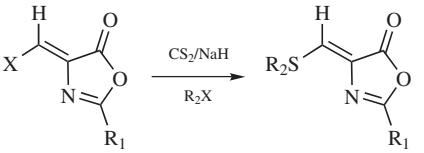
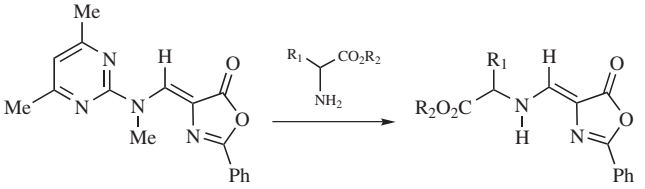


Figure 7.49

R_1	X	R_2	% Yield
Ph	H_2N	Me	84
Ph	H_2N	Pr	85
Ph	H_2N	$PhCH_2$	68

[a]Data from Ref. 536.

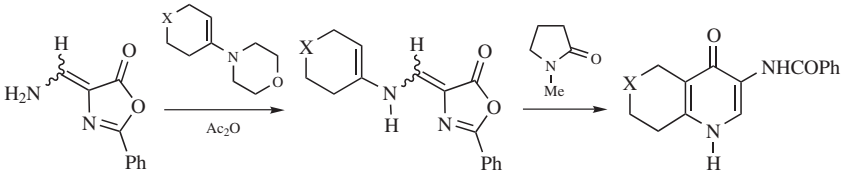
Transamination reactions have also been described for 4-(aminomethylene)-2-substituted-5(4*H*)-oxazolones. As an example, displacement of the *N*-methyl-heteroarylamino group of a 4-[(*N*-heteroaryl-*N*-methyl)aminomethylene]-2-phenyl-5(4*H*)-oxazolone **420** by an α-amino acid derivative produces β-amino-α,β-dehydro-α-amino acid precursors **421** (Scheme 7.137).[537]



420 **421**

Scheme 7.137

Enamine exchange with the weakly basic amino group of 4-(aminomethylene)-2-phenyl-5(4*H*)-oxazolone **418** leads to the 4-[(*N*-cycloalkenyl)aminomethylene]-5(4*H*)-oxazolones **422**, that thermally cyclize to afford [*b*]-fused bicyclic 4-pyridones **423** (Scheme 7.138).[538]



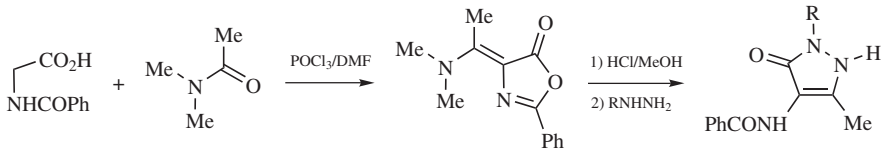
418 **422** **423**

X = CH_2, O, S, CH_2CH_2, bond

Scheme 7.138

4-(*N*,*N*-Dimethylaminomethylene)-2-phenyl-5(4*H*)-oxazolone and 4-(anilinomethylene)-2-phenyl-5(4*H*)-oxazolone react readily with primary alkylamines via transamination to provide an efficient route to 4-(alkylaminomethylene)-2-phenyl-5(4*H*)-oxazolones.[539]

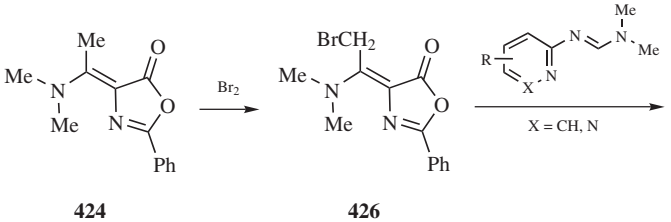
Reaction of hippuric acid and *N*,*N*-dimethylacetamide in the presence of phosphorous oxychloride affords 4-[1-(dimethylamino)ethylidene]-2-phenyl-5(4*H*)-oxazolone **424**[540] that is converted to 4-benzoylaminopyrazolones **425** via ring opening and cyclization with hydrazines (Scheme 7.139).[540] 4-(*N*,*N*-Dimethylaminomethylene)-2-substituted-5(4*H*)-oxazolones react similarly.[541]



424 **425**

Scheme 7.139

4-[2-Bromo-1-(dimethylaminoethylidene)]-2-phenyl-5(4*H*)-oxazolone **426**, obtained by bromination of **424**, reacts with *N*,*N*-dimethyl-*N*′-heteroarylformamidines to afford the interesting heterocyclic unsaturated oxazolones **428** (Scheme 7.140).[542]

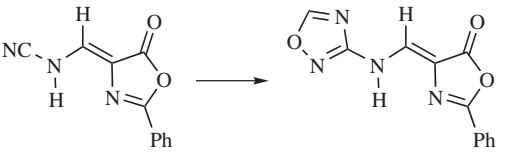


424 **426**

427 **428**

Scheme 7.140

Finally, 4-[(1,2,4-oxadiazol-3-yl)aminomethylene]-2-phenyl-5(4*H*)-oxazolone **430** has been prepared from 4-[(cyanoamino)methylene]-2-phenyl-5(4*H*)-oxazolone **429** (Scheme 7.141).[543]

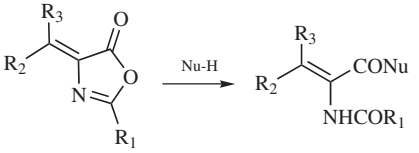


429 **430**

Scheme 7.141

7.4.2. Ring-Opening Reactions

In general, unsaturated oxazolones are very useful synthetic intermediates. In this context, one of the most important reactions is the classical nucleophilic opening of the oxazolone ring; the key-step in the synthesis of a wide array of compounds. Hydrolysis, alcoholysis, aminolysis, hydrazinolysis, as well as many other reactions of 2-alkyl(aryl)-4-arylidene-5(4*H*)-oxazolones,[544–546] 2-alkyl(aryl)-4-heteroarylidene-5(4*H*)-oxazolones,[547–552] or 2-2′-(*m*-phenylene)bis[4-arylidene-5(4*H*)-oxazolones][553] lead to heterocyclic ring opening to afford the corresponding acids, esters, amides, hydrazides, hydroxamic acids, etc. (Scheme 7.142). In some cases, sonication has been used to promote the nucleophilic ring opening.[554]



431 **432**

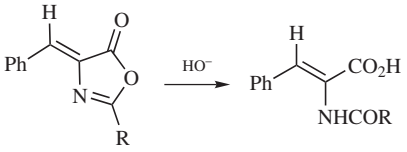
Nu-H = HO-H, RO-H, R_2N-H, RNHNH-H, H_2NO-H.....

Scheme 7.142

In this chapter, when the product arising from the ring opening is used as a synthetic intermediate, the subsequent reaction of this intermediate will be also considered.

7.4.2.1. Hydrolysis and Alcoholysis

One of the fundamental cleavage reactions of the heterocyclic ring in unsaturated oxazolones is the conversion to acids or esters. This process leads to dehydroamino acid derivatives from which a wide variety of amino acids are prepared by hydrogenation. The side chain of the final amino acid is determined by the aldehyde used to prepare the unsaturated oxazolone. For example, benzaldehyde and an *N*-acylglycine afford 2-acylaminocinnamic acids **434** after hydrolysis of the oxazolone **433**.[555–557] In turn, **434** are excellent precursors to phenylalanine.



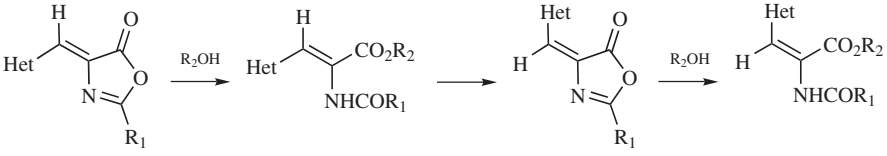
433 **434**

Scheme 7.143

The mechanism of the hydrolysis of 4-benzylidene-2-methyl(phenyl)-5(4*H*)-oxazolone has been studied.[558] There are several general procedures to prepare 2-acylamino-3-arylpropenoic acids that employ various experimental conditions[559–561] including phase-transfer catalyzed hydrolysis.[562,563] In addition, general procedures for alcoholysis of unsaturated oxazolones leading to the corresponding acrylates have been published.[564] Hydrolysis and alcoholysis have been applied to prepare compounds of special interest. For example, 2-acylamino-2-butenoic acid esters prepared from 2-methoxyacetaldehyde have been evaluated as plant growth regulators.[565] 2-Methoxy-1-naphthaldehyde has been used to generate an unsaturated oxazolone that was hydrolyzed to the corresponding acrylic acid using barium hydroxide in aqueous alcohol.[566] Other acrylic acid derivatives that have herbicidal activity[567] or are useful intermediates for the synthesis of the antiinflammatory agent lonazolac have been prepared via this methodology.[568]

Other alcohols ring-open unsaturated oxazolones including glycerol that was used to prepare monoglycerides of acylamino acids.[569] In addition, alcoholysis with 3,4,4-trifluorobut-3-enol leads to amino acid fluorobutenyl esters that are used as pesticides.[570] Finally, (dimethylamino)ethanol[571] and other amino alcohols[572] have also been used to obtain the corresponding aminoalkyl esters.

The hydrolysis and alcoholysis reactions have been extended to the heterocyclic series. A systematic study has been published of the hydrolysis of unsaturated oxazolones derived from a selection of heterocyclic aldehydes.[573] A detailed study[574] of the synthesis and stereospecific hydrolysis and methanolysis of the (*Z*) and (*E*) isomers of 2-methyl (or phenyl)-4-(thienylmethylene)-5(4*H*)-oxazolones **435** and **437** has also been described (Scheme 7.144). The synthesis of 2-acylamino-3-(indol-3-yl or carbazol-3-yl)acrylic acid derivatives as potential antifertility agents via oxazolone hydrolysis has also been published.[575]

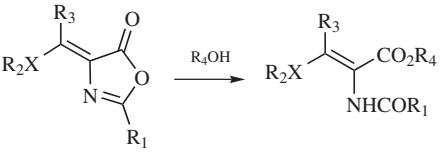


435 **436** **437** **438**

Het = heterocycle

Scheme 7.144

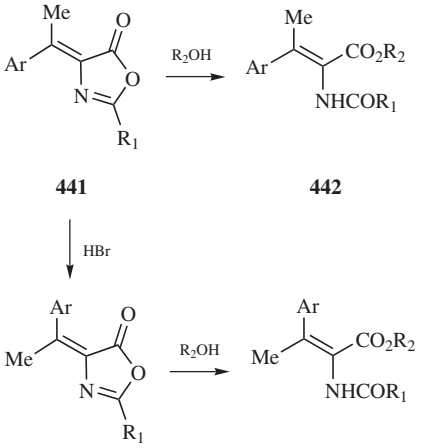
4-Heteromethylene-5(4*H*)-oxazolones **439** show similar behavior to that described above. Hydrolysis or alcoholysis of **439** provides the corresponding β-substituted acrylic acids or acrylates **440** (Scheme 7.145). In this context, ring-opening reactions of 4-bis[(methylthio)methylene]- and 4-bis[(benzylthio)-methylene]-,[576] 4-(alkylaminomethylene)-,[577] 4-(dialkylaminomethylene)-,[578] and other 4-heteromethylene-5(4*H*)-oxazolones[579] have recently been described.



439 **440**

Scheme 7.145

Both stereoisomers of a 4-(α-arylethylidene)-5(4*H*)-oxazolone **441** and **443**, undergo stereospecific hydrolysis–methanolysis to furnish the corresponding (*Z*) and (*E*) isomers of 2-acetylamino(or benzoylamino)-3-aryl-2-butenoic acid or methyl ester, **442** and **444**, respectively (Scheme 7.146).[580,581] The requisite starting oxazolones were prepared by condensation of an acetophenone with an acylglycine or by methylene insertion into the vinyl C—H bond of a 4-arylidene-5(4*H*)-oxazolone.



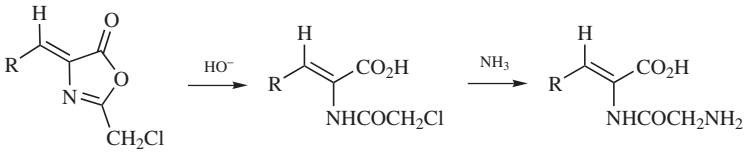
441 **442**

443 **444**

Scheme 7.146

If the starting *N*-acylamino acid contains a leaving group in the acyl group moiety then hydrolysis of the corresponding oxazolone **445** generates an acrylic acid derivative such as **446**. Treatment of **446** with ammonia then produces glycyl-(β-aryl)-dehydroalanines **447**.[582] This interesting procedure opens the way for the

synthesis of peptides directly incorporating dehydroamino acids (Scheme 7.147). Representative examples of dehydroamino acids and esters prepared via hydrolysis and alcoholysis of unsaturated 5(4*H*)-oxazolones are shown in Table 7.39 (Fig. 7.50).



445 **446** **447**

Scheme 7.147

TABLE 7.39. *N*-ACYL DEHYDROAMINO ACIDS AND ESTERS FROM HYDROLYSIS AND ALCOHOLYSIS OF UNSATURATED 5(4*H*)-OXAZOLONES

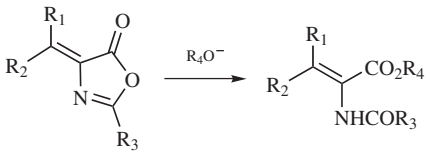
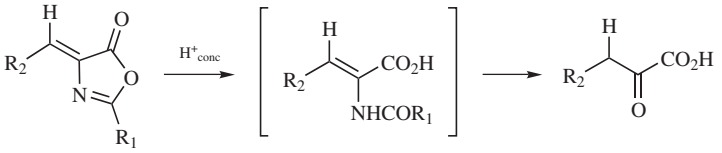


Figure 7.50

R_1	R_2	R_3	R_4	% Yield	Reference
H	Ph	Me	H	98	560
H	Ph	Ph	H	60	559
H	3-$NO_2C_6H_4$	Ph	H	58	559
H	fur-2-yl	Ph	H	55	559
H	PhCH=CH	Ph	H	84	559
H	thien-2-yl	Me	H	50	573
H	pyrid-3-yl	Me	H	70	573
H	quinol-3-yl	Me	H	65	573
H	thien-2-yl	Ph	H	70	573
H	pyrid-3-yl	Ph	H	48	573
H	quinol-3-yl	Ph	H	50	573
H	Ph	CH_2Cl	H	72	582
H	4-$MeOC_6H_4$	CH_2Cl	H	45	582
H	4-MeC_6H_4	CH_2Cl	H	75	582
H	thien-2-yl	CH_2Cl	H	93	582
H	thien-2-yl	Me	Me	81	574
H	thien-3-yl	Me	Me	73	574
H	thien-2-yl	Ph	Me	87	574
H	thien-3-yl	Ph	Me	65	574
Me	Ph	Me	Me	87	581
Me	4-$MeOC_6H_4$	Me	Me	85	581
Me	Ph	Ph	Me	95	581
Me	4-$MeOC_6H_4$	Ph	Me	93	581

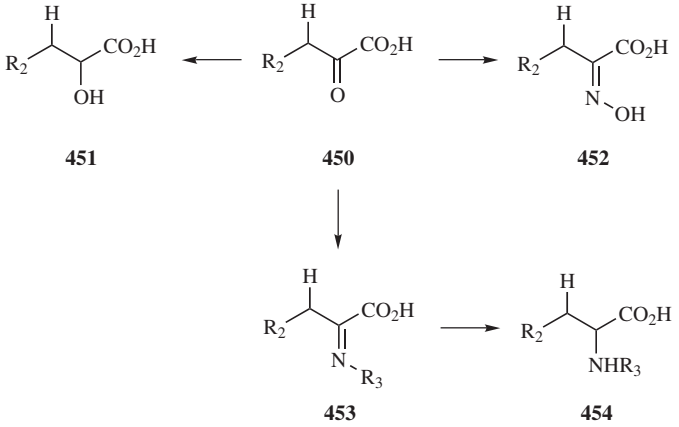
More drastic hydrolysis conditions of unsaturated oxazolones **448** leads to further hydrolysis of the intermediate 2-acylamino-2-alkenoic acid **449** and produces the corresponding α-keto acids **450**. For example, phenylpyruvic acid[583,584] and other aryl(heteroaryl)pyruvic acids[585–587] of biological interest have been obtained in this manner (Scheme 7.148).



448 **449** **450**

Scheme 7.148

The α-keto acids are extremely versatile intermediates. For example, reduction of an arylpyruvic acid **450** yields the corresponding β-aryllactic acid **451**,[588,589] condensation of **450** with amines followed by reduction affords amino acid derivatives **454**,[590] and condensation of **450** with hydroxylamine yields α-oximinoacids **452** as shown in Scheme 7.149.[591]



451 **450** **452**

453 **454**

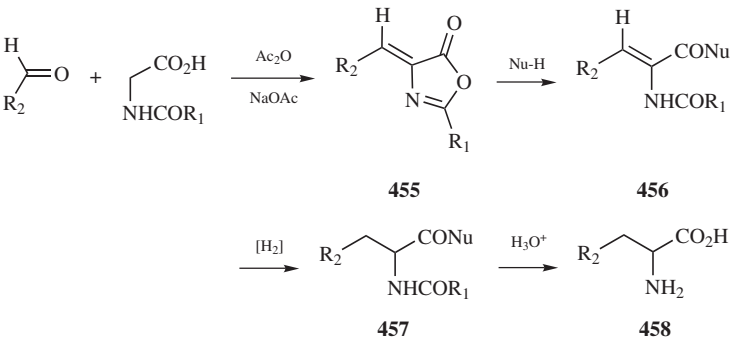
Scheme 7.149

The dehydroamino acids or esters obtained have been used as intermediates to prepare a diverse array of interesting compounds and some important, representative examples are described in the following sections.

Catalytic Hydrogenation of Dehydroamino Acid Derivatives. Probably the most important reaction of dehydroamino acid derivatives obtained from 5(4*H*)-oxazolones is hydrogenation of the double bond. Typically, this reaction is performed

using catalytic systems such as Raney Ni, Na/Hg, or a metal on a support and leads to amino acids after removal of the protecting groups. Among such metal systems, Pd/C or other supports is used most frequently and usually leads to easy and quantitative hydrogenations. This general methodology is a well-known procedure and is especially useful for the synthesis of phenylalanine,[592] aryl-substituted analogues of phenylalanine,[593–600] tyrosine analogues,[601,602] and 3,4-dihydroxyphenylalanine (DOPA).[603] In all cases, the amino acids are prepared from the corresponding benzaldehyde and proceed via the intermediate unsaturated oxazolone.

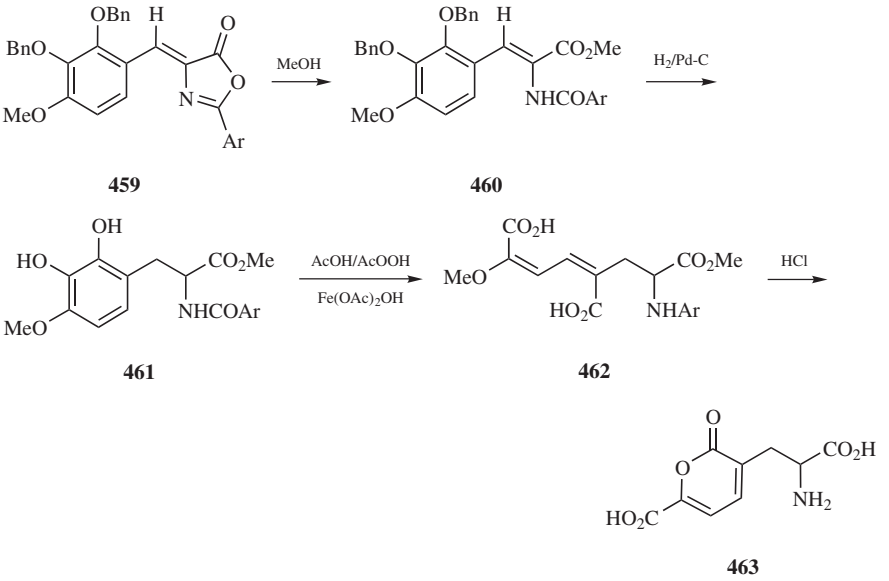
In the heterocyclic series, racemic 3-(fur-2-yl)alanine has been prepared from furfural using this approach.[604] In addition, β-(pyrid-3-yl)alanine,[605] β-(quinol-3-yl)alanine,[606] a β-(benzofuranyl)alanine derivative,[607] 2-amino-3-(2,2′-bipyridinyl)propanoic acid,[608] and some interesting derivatives of histidines—in particular 1-alkylhistidines with amphiphilic properties[609] have all been synthesized using this methodology. The complete reaction sequence starting from an aldehyde and an *N*-acylamino acid derivative is shown in Scheme 7.150.



Scheme 7.150

Racemic [3-^{11}C] phenylalanine and [3-^{11}C] DOPA have been prepared using this methodology starting with aldehydes labeled at the carbonyl carbon.[610] In addition, fluorine-containing amino acids such as N-acylated 2- and 4-fluorophenylalanines,[611,612] 4-(polyfluoromethyl)phenylalanines,[613,614] 4-(trifluoromethyl)valine,[615] 3-(2,6-difluoro-3,4-dihydroxyphenyl)alanine,[616] as well as other fluoro analogues of amino acids[617,618] have all been prepared starting from the appropriate fluorine-containing carbonyl compound. New metallocene phenylalanine analogues were obtained from the appropriate aldehyde following similar methodology. For example, the unsaturated oxazolone prepared from cyclopentadienylcarboxaldehyde manganese tricarbonyl is an intermediate in the synthesis of the corresponding phenylalanine analogue.[619]

Several cases warrant special mention. As an example, ring opening, hydrogenation, and subsequent transformations of the 5(4*H*)-oxazolone **459** derived from 2,3-dihydroxy-4-methoxybenzaldehyde affords a biomimetic synthesis of racemic stizolobinic acid **463** as shown in Scheme 7.151.[620]

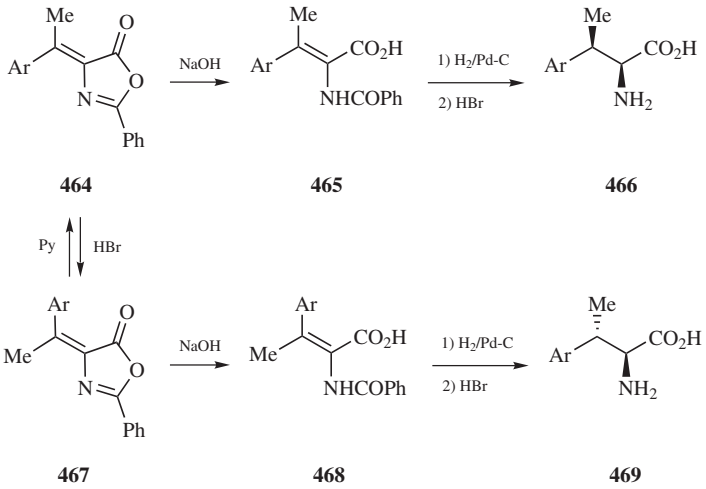


Scheme 7.151

Hydrogenation of the double bond in dehydroamino acids prepared from unsaturated 5(4*H*)-oxazolones derived from unsymmetrical ketones gives rise to two stereogenic centers. As a consequence, four stereoisomers are possible. If the hydrogenation of each geometric isomer is performed separately, then the erythro and threo pair of enantiomers can be obtained independently. In this respect, the unsaturated oxazolones from 2-butanone have been prepared as a (*Z*/*E*) mixture. The mixture was separated and each stereoisomer was independently converted to the erythro and threo pairs of enantiomers.[621]

The geometric isomers **464** and **467** of 5(4*H*)-oxazolones prepared from acetophenones can be separated. Alternatively, the mixture can be isomerized under the appropriate reaction conditions to obtain the pure of (*Z*) or (*E*) isomer. Each isomer can be converted to a pair of enantiomers **466** and **469** (only one enantiomer shown) (Scheme 7.152).[622] The β-methyl phenylalanine analogues thus obtained are constrained phenylalanines and the effect of incorporation of a β-MePhe or β-MeTyr residue on the biological properties of H-Tyr-Tic-Phe-Phe-NH_2 (TIPP, where Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) a delta opioid receptor antagonist, has been studied.[623]

The traditional approaches to obtain enantiomerically pure amino acid derivatives from racemic amino acids involve classical chemical resolution using chiral amines[624] or enzymatic procedures using hydrolytic enzymes.[593–595,603,605–608,617,618] Alternatively, the diastereoselective or enantioselective hydrogenation of the double bond has been explored as a means to prepare amino acid derivatives asymmetrically. To that end ring opening of an unsaturated oxazolone with a chiral alcohol followed by hydrogenation of the double bond has been investigated but the degree of asymmetric induction is usually not very high.



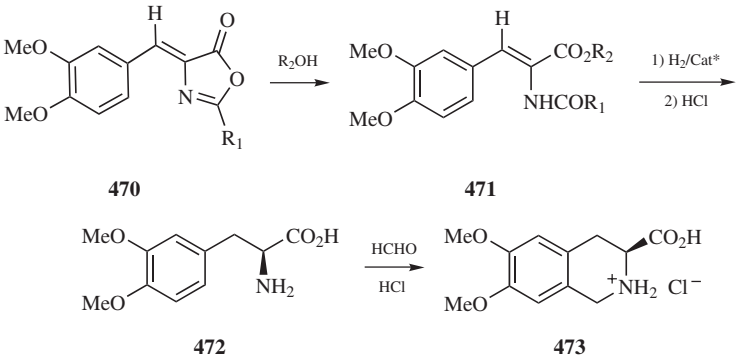
Scheme 7.152

Asymmetric hydrogenation of dehydroamino acids or their esters with homogeneous organometallic catalysts containing chiral ligands has revolutionized the synthesis of enantiomerically pure amino acids. Many modifications have been described in terms of the nature of the catalyst and/or the nature of the amino acid obtained. Rhodium catalysts that incorporate chiral ligands, particularly diphosphines or aminophosphines among others are usually the most efficient. Starting from the requisite unsaturated 5(4*H*)-oxazolone such rhodium catalysts permit access to phenylalanine,[625] most analogues of phenylalanine,[626–628] and a wide variety of fluorine-containing phenylalanines,[629] all obtained with extremely high enantiomeric purity. Of particular interest is the synthesis of L-4-boronophenylalanine (BPA) in 96% ee starting from the oxazolone derived from 4-boronobenzaldehyde.[630]

In the heterocyclic series several heteroarylalanines have been obtained by asymmetric hydrogenation using chiral homogeneous catalysts. For example, replacement of the phenyl ring by furan, thiophene, selenophene, pyridine, or indole yields furylalanines,[631,632] thienylalanines,[633] 2- and 3-selenienylalanines,[634] 3- and 4-pyridylalanines,[635,636] or tryptophan,[637] respectively. A comparative study of the reaction rates and enantioselectivities in substrates with different heterocyclic rings during homogeneous catalytic hydrogenation has been reported.[638]

A study on the combined use of a chiral substrate obtained by alcoholysis of a 4-benzylidene-5(4*H*)-oxazolone with a chiral alcohol coupled with hydrogenation using a chiral catalyst has also been described.[639] This work shows that the matching effect of double asymmetric induction in hydrogenation can be modulated by a solvent effect.

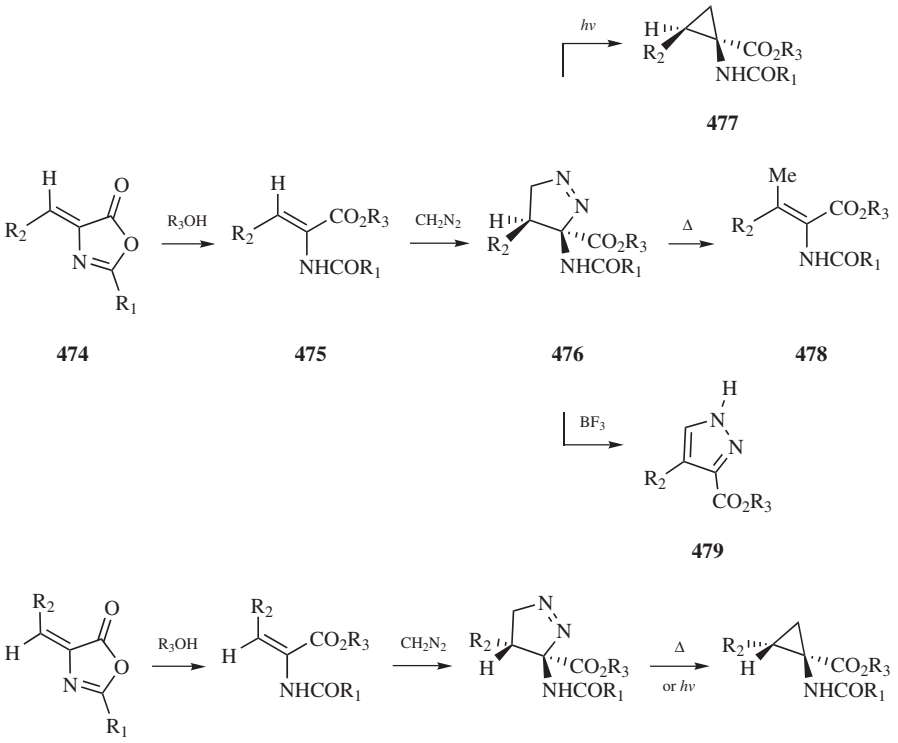
In the case of electron-rich aromatic rings, for example, **472** it is possible to take advantage of the activating substituents to effect a Pictet–Spengler reaction to prepare the tetrahydroisoquinoline derivative **473** as shown in Scheme 7.153.[640]



470 **471** **472** **473**

Scheme 7.153

1,3-Dipolar Cycloaddition Reactions. Dehydroamino acid derivatives behave as dipolarophiles in 1,3-dipolar cycloaddition reactions that leads to a variety of interesting compounds. For example, 1,3-dipolar cycloaddition of diazomethane to dehydroamino acid esters **475** and **481** gives the corresponding pyrazolines **476** and



474 **475** **476** **477** **478** **479** **480** **481** **482** **483**

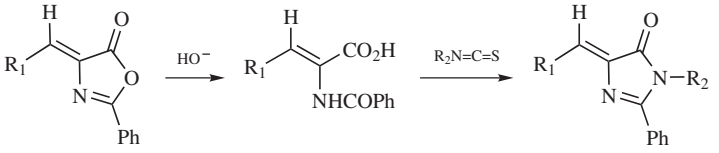
Scheme 7.154

482. Thermal or photochemical extrusion of nitrogen from *trans*-pyrazolines, for example, **482** gives *trans*-cyclopropylamino acid derivatives **483**.[641] Photochemical decomposition of *cis*-pyrazolines **476** leads to *cis*-cyclopropylamino acid derivatives **477**,[642–644] whereas thermal decomposition of **476** affords the corresponding 2-acylamino-2-butenoic acid derivatives **478** via methylene insertion into the vinyl C—H bond.[581] Moreover, in the presence of a Lewis acid, *cis*-pyrazolines eliminate the acylamino substituent to afford the corresponding 4-substituted-pyrazole-3-carboxylic acid esters **479** (Scheme 7.154).[645,646]

1,3-Dipolar cycloadditions of nitrile oxides[647] and nitrile imines[647,648] with dehydroamino acid derivatives have also been described.

DECARBOXYLATION. Under certain experimental conditions dehydroamino acid derivatives can decarboxylate to produce unsaturated benzamides. In particular, *N*-[2-(*p*-hydroxyphenyl)ethyl]-*p*-chlorobenzamide[649] and *N*-(*E*)-(4-methoxystyryl)-benzamide (alatamide)[650] have been prepared in this manner.

SYNTHESIS OF HETEROCYCLIC COMPOUNDS. In some cases, dehydroamino acids obtained from unsaturated 5(4*H*)-oxazolones have been used as intermediates to prepare other heterocyclic compounds. For example, reaction of 2-benzoylamino-3-substituted-2-alkenoic acids **485** with alkyl or arylisothiocyanates affords 4-arylmethylene-1,2-disubstituted-5-oxo-4,5-dihydroimidazoles **486** (Scheme 7.155).[651]



484 **485** **486**

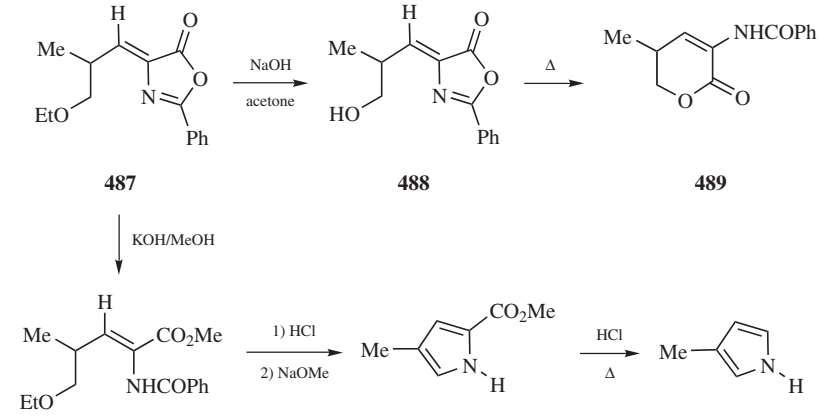
Scheme 7.155

Depending on the reaction conditions used for hydrolysis, either 3-benzoylamino-5-methylpyran-2-one **489** or 3-methylpyrrole **492** have been obtained from the 3-ethoxy-2-methylpropanal derived unsaturated oxazolone **487** (Scheme 7.156).[652]

Nitrosation of methyl 2-acylamino-3-(dimethylamino)propenoates **494** obtained from the corresponding oxazolones **493** effects the conversion of *N*-acylglycines to 5-substituted-1,2,4-oxadiazole-3-carboxylates **496** as shown in Scheme 7.157.[653]

7.4.2.2. Aminolysis with Amines and Related Compounds

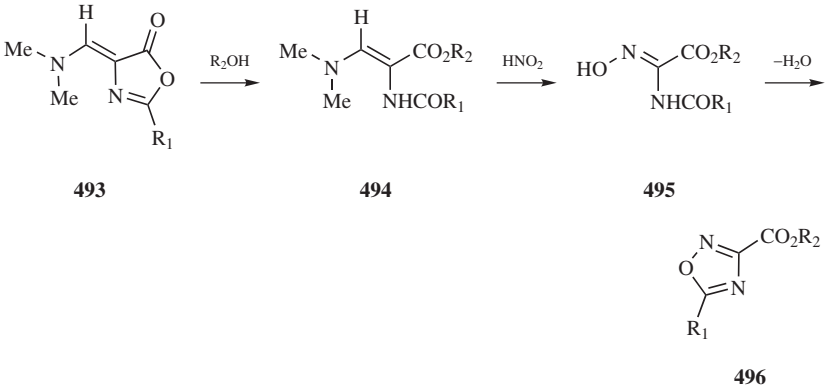
In general, the reaction of unsaturated 5(4*H*)-oxazolones **497** with nitrogen nucleophiles effects ring opening to give the corresponding unsaturated acylamino amides **498** (Scheme 7.158). Depending on the nucleophile, for example, amines, hydrazines, oximes, and so on, the products obtained can be cyclized and this process allows the synthesis of a wide variety of new heterocyclic compounds.



487 **488** **489**

490 **491** **492**

Scheme 7.156

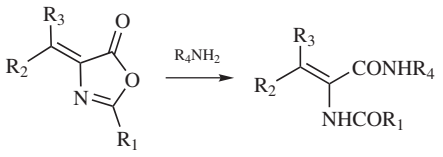


493 **494** **495**

496

Scheme 7.157

There are a number of comprehensive studies reported of the reactions of a particular unsaturated oxazolone with nitrogen nucleophiles.[654–657] On the other hand, unsaturated 5(4*H*)-oxazolones react with a variety of amines to yield acylamino amides with interesting agrochemical properties.[658–661]



497 **498**

Scheme 7.158

The mechanism of the aminolysis[662] and the electronic effects of substituents at C-2 or C-4 on the kinetics of amide bond formation have been studied.[663] In some cases, ring opening with amines occurs with partial isomerization of the exocyclic double bond. However, with more hindered compounds, such as unsaturated oxazolones derived from ketones, ring opening is stereospecific.[664,665] Ring opening using diamines has also been described.[666] Selected examples of dehydroamino acid amides prepared by aminolysis of unsaturated 5(4*H*)-oxazolones are shown in Table 7.40 (Fig. 7.51).

The direct condensation of unsaturated oxazolones with tryptamine in hydrochloric acid is an important and interesting case that deserves special attention. The reaction occurs via *in situ* hydrolysis of the oxazolone to a keto acid followed by a Pictet–Spengler-like reaction with tryptamine. This protocol affords a tetrahydro-β-carboline wherein the oxazolone is the synthetic equivalent of an arylacetaldehyde.[667] The reaction has been extended to substituted tryptamines **500** thus, allowing access to 1,3,4-trisubstituted tetrahydro-β-carbolines **501** as shown in Scheme 7.159.[668–675] Some of these compounds have shown promising central nervous system activity.

Bis-4-arylidene-5(4*H*)-oxazolones are easily obtained from aromatic dialdehydes by the Erlenmeyer synthesis. Such bis(oxazolones) react with α,ω-diamines to provide a convenient approach to macrolactams.[676] Tandem Erlenmeyer condensation-macrolactamization (TECM) has been used to prepare analogues of naturally occurring, biologically active cyclic peptides such as bastadin-5.

TABLE 7.40. *N*-ACYLDEHYDROAMINO ACID AMIDES FROM AMINOLYSIS OF UNSATURATED 5(4*H*)-OXAZOLONES

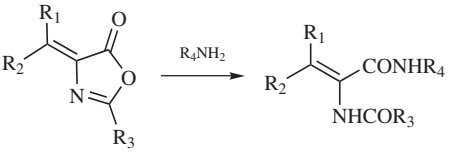
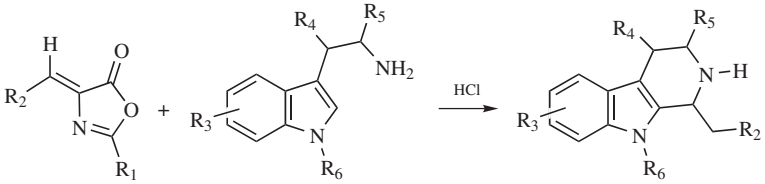


Figure 7.51

R_1	R_2	R_3	R_4	% Yield	Reference
H	4-CNC_6H_4	Ph	*i*-Pr	83	658
H	Ph	Ph	Ph	88	684
H	Ph	Ph	*n*-Bu	93	684
H	Ph	Ph	$PhCH_2$	80	684
H	Ph	Me	Ph	90	684
Me	Ph	Ph	4-MeC_6H_4	68	664
Ph	Me	Ph	4-MeC_6H_4	69	664
Me	Ph	Ph	4-$MeOC_6H_4$	71	664
Ph	Me	Ph	4-$MeOC_6H_4$	79	664
Me	Ph	Ph	$PhCH_2$	98	664
Ph	Me	Ph	$PhCH_2$	86	664

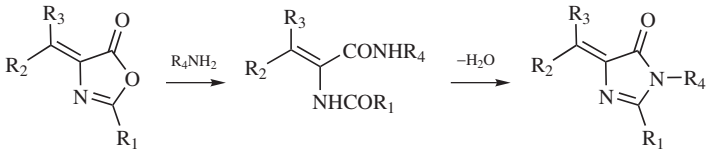


499 **500** **501**

Scheme 7.159

CYCLIZATION OF DEHYDROAMINO AMIDES TO IMIDAZOLONES. Aminolysis of unsaturated oxazolones has been studied extensively. However, the major focus has been directed to use of the resulting acylamino amides as starting materials to prepare novel heterocyclic compounds. Among these possibilities, cyclization of acylamino amides to unsaturated imidazolinones has been studied in great depth given that these compounds have a diverse range of biological and pharmacological activities. Hundreds of unsaturated oxazolones with a wide variety of substituents at C-2 and C-4 have been described. Most of these compounds were reacted with amines to give the corresponding acylamino amide that can be cyclized to the corresponding imidazolinones. The shear number of compounds described makes coverage of this area beyond the scope of this chapter.

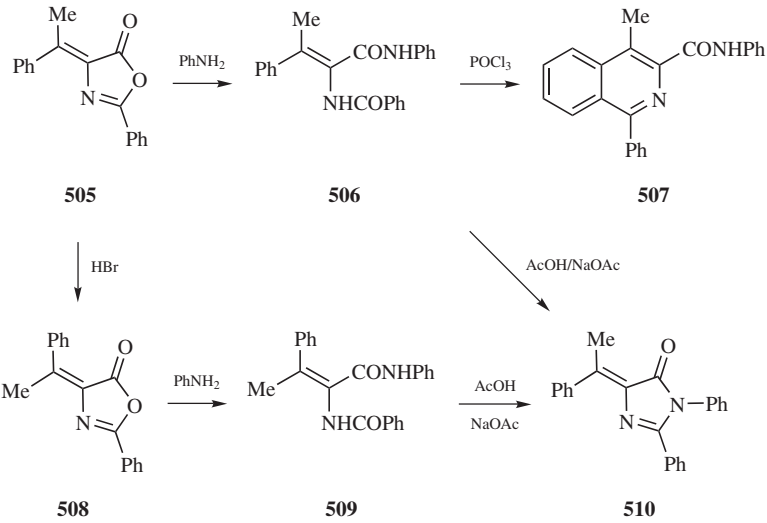
Generally speaking, cyclization occurs in the presence of a cyclodehydrating agent to give 4-alkylidene(arylidene)-1,2-disubstituted-2-imidazolin-5(4*H*)-ones **504** in which the configuration of the exocyclic double bond is retained (Scheme 7.160). The most typical case is exemplified by the reaction of 4-arylidene-5(4*H*)-oxazolones with a wide variety of substituted anilines or alkylamines and subsequent cyclization of the product. Indeed, numerous papers have been published on this subject[677–692] and many pharmacological assays have been performed on the resulting products.



502 **503** **504**

Scheme 7.160

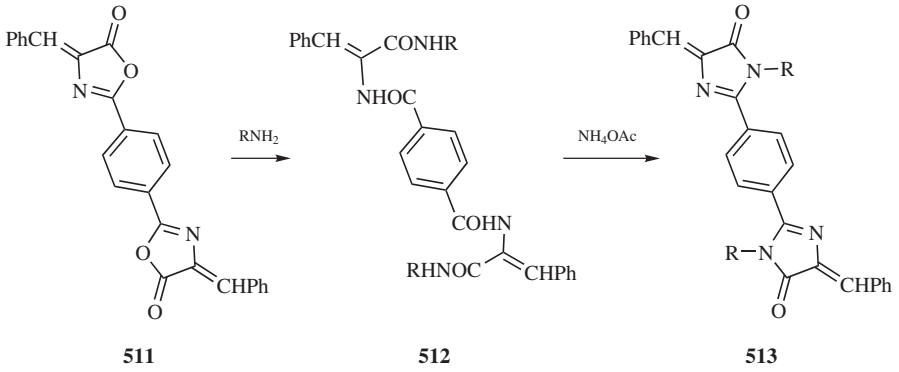
For amides obtained by stereospecific ring opening of (*Z*)- and (*E*)-2-phenyl-4-(α-phenylethylidene)-5(4*H*)-oxazolone **505** and **508**, cyclization gives the imidazolone **510** or 4-methyl-1-phenyl-3-isoquinolinecarboxylic acid anilide **507**. The products are determined by the double-bond geometry in the starting material and by the experimental conditions (Scheme 7.161).[693]



Scheme 7.161

Aminolysis of 1,4-phenylene bis(oxazolones) **511** and subsequent cyclization to the bis-2-imidazolin-5(4*H*)-ones **513** has also been described (Scheme 7.162).[694]

N^1-(Sulfonamidophenyl)imidazolones are of particular interest as antineoplastic, antibacterial, and antifungal agents and a number of examples have been prepared analogously using the appropriate sulfonamidoaniline.[695–697]



Scheme 7.162

Diamines have also been used to ring-open unsaturated 5(4*H*)-oxazolones. Here, one amino group reacts with the oxazolone while the other amino group is used to incorporate other substituents. Examples include aliphatic diamines,[698–700] *o*-phenylenediamines,[701,702] and *p*-phenylenediamines.[703–709]

Heterocyclic amines have also been used for aminolysis. Subsequent cyclization of the acylamino amides leads to imidazolones that show a diverse range of biological activities as antibacterial, antifungal, antiviral, antihelmintic, and anti-Parkinsonian agents, as well as central nervous systems (CNS) stimulants.

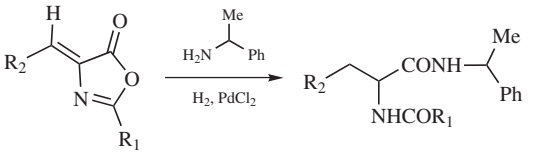
Noteworthy among these systems are aminopyrazolones,[710] 3-aminoindoles,[711] 2-aminothiazoles,[712–715] 2-amino-1,3,4-oxadiazoles,[716] 2-amino-1,3,4-thiadiazoles,[717–720] and aminoquinazolinones[721–724] together with other heterocyclic compounds.[725–732]

Unsaturated 5(4*H*)-oxazolones derived from aromatic and heterocyclic aldehydes including phthalic anhydride,[733] antipyrine,[734] chromone,[735] indoles,[736–739] pyridines,[740] quinolines,[741] diazines,[742] benzoxazoles,[743] and benzimidazoles[744] have been prepared. Reaction with nitrogen nucleophiles and subsequent cyclization leads to the expected 5(4*H*)-imidazolones.

Amino acids[745–747] and aminobenzoic acids[748,749] react as nitrogen nucleophiles to effect ring opening of unsaturated 5(4*H*)-oxazolones. Cyclization of the intermediate acylamino amide has opened the way for the synthesis of new series of imidazolones that now incorporate a carboxylic acid moiety into the N-1 substituent. These compounds are readily further elaborated into derivatives with diverse biological activity.

7.4.2.3. Reductive Aminolysis

Ring opening of unsaturated 5(4*H*)-oxazolones **514** with a chiral amine, usually (*S*)-α-phenylethylamine (although chiral amino acids can be also used), in the presence of a catalyst under a hydrogen atmosphere is an excellent procedure for the direct synthesis of chiral amino acid precursors **515**. The reaction occurs sequentially via hydrogenation of the dehydroamino acid that is generated *in situ* from ring opening of the oxazolone. This method has been applied for the synthesis of numerous amino acids with moderate optical purity (Scheme 7.163; Table 7.41, Fig. 7.52).[47,48,750–757] Prior to the development of efficient chiral catalysts for enantioselective hydrogenation of dehydroamino acid derivatives, this procedure was explored as an interesting methodology for the asymmetric synthesis of new non-proteinogenic amino acids.



514 **515**

Scheme 7.163

The influence of different variables including the solvent[758–760] and experimental conditions[761–767] has been studied and attempts to improve the results using polymer-bonded palladium catalysts[768] or chiral palladium-containing macromolecular catalysts[769] have been reported. The reductive cleavage of heteromethylene oxazolones using $NaBH_4$ in the presence of NH_3 has generated racemic β-(heteroarylamino)-α-amino acid derivatives.[770]

TABLE 7.41. *N*-ACYLAMINO ACID AMIDES FROM REDUCTIVE AMINOLYSIS OF UNSATURATED 5(4*H*)-OXAZOLONES

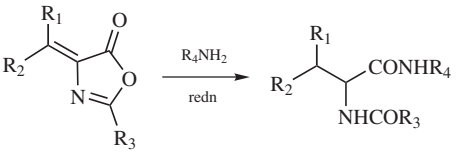


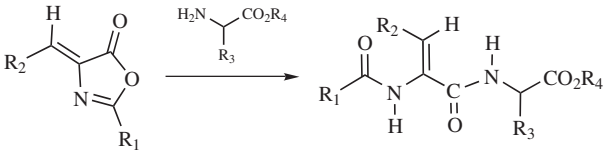
Figure 7.52

R_1	R_2	R_3	R_4	% Yield	Reference
H	Ph	Me	PhMeCH	90–95	753
H	4-$AcOC_6H_4$	Me	PhMeCH	90–95	753
H	Ph	Ph	PhMeCH	90–95	753
H	4-$AcOC_6H_4$	Ph	PhMeCH	90–95	753
Me	Me	Ph	PhMeCH	90–95	753
Me	Et	Ph	PhMeCH	90–95	753
H	3-MeO-4-$AcOC_6H_3$	Ph	PhMeCH	98	762
H	pyrimidin-2-yl	Ph	H	36	770
H	4-chloro-6-methylpyrimidin-2-yl	Ph	H	55	770
H	6-chloropyridazin-3-yl	Ph	H	60	770
H	pyrazinyl	Ph	H	39	770

7.4.2.4. Aminolysis with Amino Acids

Unsaturated 5(4*H*)-oxazolones react with amino acids to produce acylamino amides. Ring closure of the acylamino amides leads to the corresponding imidazolinones (cf. Section 7.4.2.2) or, alternatively, to 3-ylidenepiperazine-2,5-diones that are versatile organic substrates.[771] Ring opening in the presence of hydrogen and a catalyst affords the corresponding amino acid derivatives (cf. Section 7.4.2.3). However, ring opening in the absence of a reducing agent generates an α,β-dehydropeptide. α,β-Dehydropeptides are very interesting compounds that are found in natural peptides of biological interest. In addition, incorporation of an α,β-dehydropeptide residue into peptides can restrict the conformational freedom of the peptide thereby allowing the design of new compounds with improved biological and pharmacological properties.

Therefore, suitable unsaturated oxazolones can be used as intermediates to prepare dehydropeptides wherein the synthetic strategy used will depend on the position of the double bond in the final compound. If the double bond is located in the N-terminal amino acid, ring opening of the oxazolone **516** with the appropriate amino acid or peptide generates the desired dehydropeptide **517** directly.[772–775] This reaction, shown in Scheme 7.164, has been used frequently starting from 4-arylmethylene-[776–778] or 4-heteroarylmethylene-5(4*H*)-oxazolones reacting with a series of amino acid esters.[779–781]

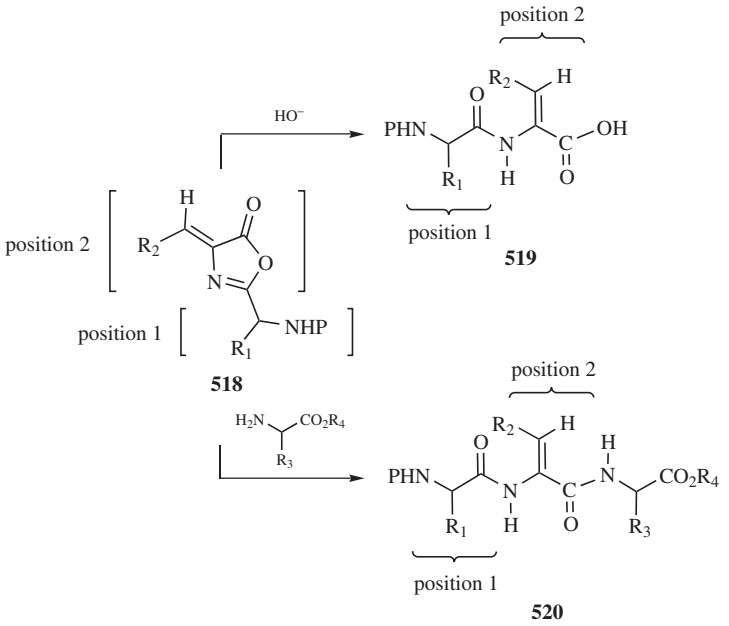


516 **517**

Scheme 7.164

This synthetic strategy has been used to prepare some interesting dehydropeptides such as chromophoric dehydro analogues of leucine enkephalin,[782] potential angiotensin-converting enzyme inhibitors,[783] and dehydropeptides substituted with a β-lactam moiety.[784]

Alternatively, if the dehydroamino acid is C-terminal or is central in the peptide chain, then the oxazolone precursor to the dehydropeptide must be in position two in order to apply this methodology (Scheme 7.165). The requisite unsaturated 5(4*H*)-oxazolone intermediate **518** is obtained from the appropriate precursors following standard cyclization procedures and avoiding experimental conditions that would epimerize the chiral center. This methodology has been applied to access analogues of important peptides including dehydroaspartame,[785] somatostatin,[786] and dermorphin.[787] In these cases, a dehydroamino acid was incorporated into the peptide backbone to study the relationship between conformational restriction and biological properties of the modified peptide.

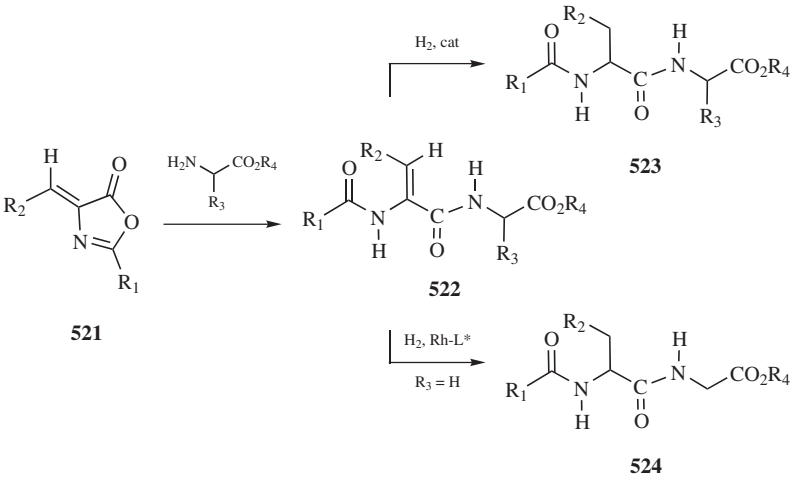


518 **519** **520**

Scheme 7.165

SYNTHESIS OF PEPTIDES BY HYDROGENATION OF DEHYDROPEPTIDES. In addition to the interest in dehydropeptides in their own right, these compounds are also used to prepare non-proteinogenic peptides by simple reduction. For example, the electrochemical reduction of dehydropeptides derived from 2,3-dimethoxybenzaldehyde has been described.[788]

Asymmetric reduction of the double bond of the dehydroamino acid residue in **522** can be effected in different ways since the peptide moiety can act as a chiral auxiliary. Heterogeneous hydrogenations using a Pd/C catalyst are the most frequently used conditions.[789] Among the different amino acids evaluated as chiral auxiliaries, proline is the auxiliary of choice and has led to the best diastereodifferentiation.[790] It is noteworthy that complexation of a dehydropeptide with Ca^{2+} or Mg^{2+} prior to hydrogenation has been reported to improve diastereoselection.[791] In cases where a glycine moiety is used, an asymmetric hydrogenation has to be performed (Scheme 7.166). For achiral dehydroamino acids the influence of ligand chirality on the enantioselectivity of hydrogenation has been studied.[792]

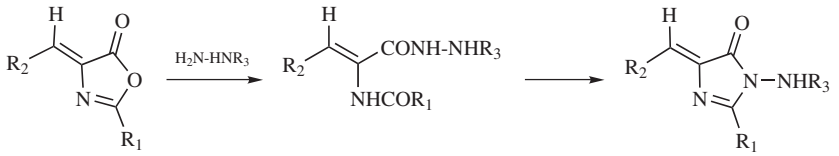


Scheme 7.166

Finally, the appropriate combination of both chiral auxiliary and chiral organometallic catalyst can lead to excellent levels of stereodifferentiation.[793–796]

7.4.2.5. Other Nitrogen Nucleophiles

Other nitrogen nucleophiles such as hydrazines, hydrazides, and Schiff bases have affected ring opening of oxazolones. Most often, hydrazine or substituted hydrazines are used. For example, hydrazinolysis of **525** affords the corresponding hydrazides **526** that, depending upon the substituents and the reaction conditions, can cyclize in the reaction medium to the aminoimidazolone **527** (Scheme 7.167;



525 **526** **527**

Scheme 7.167

Table 7.42, Fig. 7.53).[797–809] Starting from an (*E*)-oxazolone affords an (*E*)-configured hydrazide.[797–798]

Hydrazinolysis products obtained from oxazolones **528** are versatile synthetic intermediates and can be further elaborated to a variety of different heterocycles depending on the substituents and on the experimental conditions. For example, *N*-aminoimidazolones **529**, isolated from reaction of **528** and hydrazine, have been acylated[810] or condensed with carbonyl compounds[811] to produce **530** and **531**, respectively. On the other hand, ring-opening **528** with hydrazine affords a dehydroamino acid hydrazide **532**. Condensation of **532** with aldehydes yields a hydrazone **533** that can be cyclized to an *N*-iminoimidazolone **534** (Scheme 7.168).[812]

TABLE 7.42. α-ACYLAMINO HYDRAZIDES FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH HYDRAZINES

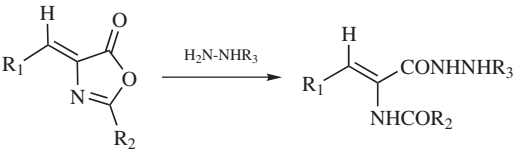
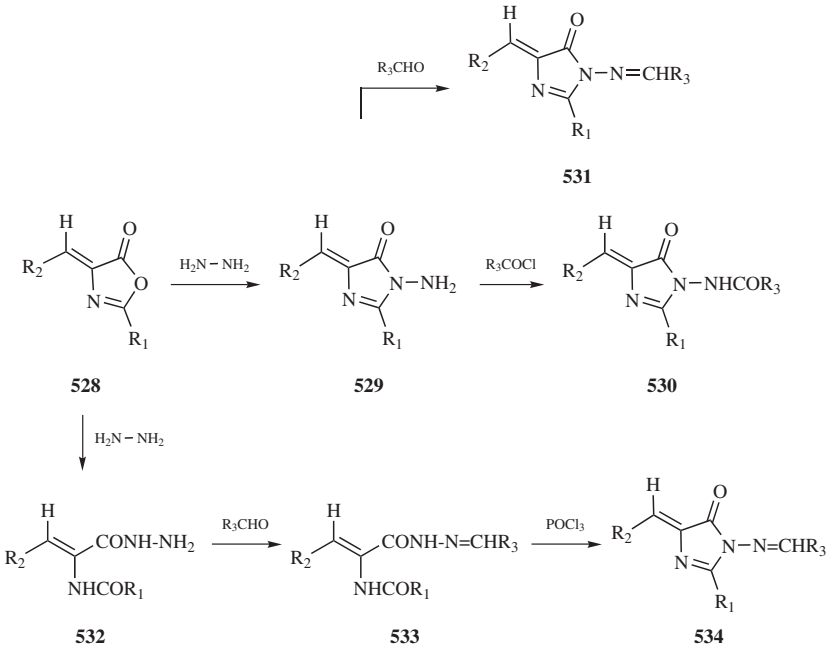


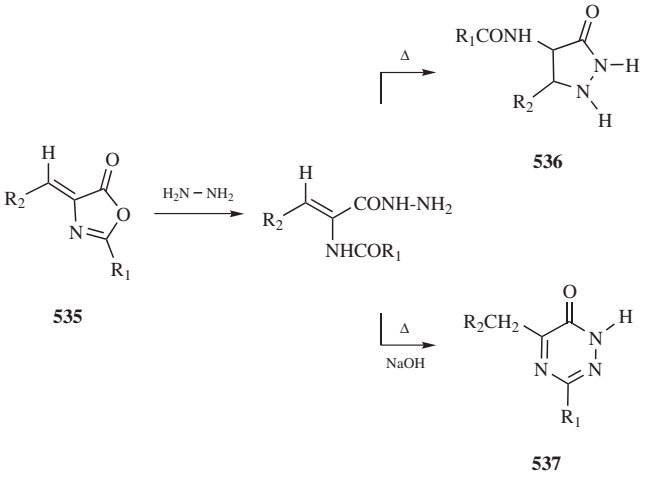
Figure 7.53

R_1	R_2	R_3	% Yield	Reference
Me	Me	H	22–52	798
4-ClC_6H_4	Ph	H	22–52	798
4-$NO_2C_6H_4$	Ph	H	22–52	798
3,4-$(MeO)_2C_6H_3$	Ph	H	22–52	798
2-HOC_6H_4	Ph	H	22–52	798
Ph	Ph	H	90	799
fur-2-yl	Ph	H	72	799
Ph	Ph	Ph	60	799
fur-2-yl	Ph	Ph	70	799
4-chloro-6-methylpyrimidin-2-yl	Ph	H	92	770
4,6-dimethylpyrimidin-4-yl	Ph	H	55	770
6-chloropyridazin-3-yl	Ph	H	65	770



Scheme 7.168

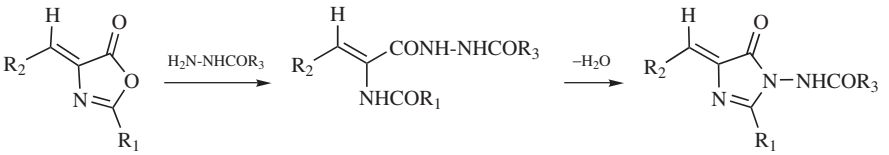
In some cases triazines have been reported from the reaction of unsaturated oxazolones with hydrazine[813] or via alkaline cyclization of the initially formed acylamino hydrazide.[799] For example, cyclization of an acylamino hydrazide by heating in the presence of sodium hydroxide affords 1,2,4-triazin-6-ones **537**.[814–817] In contrast, heating an acylamino hydrazide in the absence of base leads to pyrazolidin-5-ones **536** (Scheme 7.169).[814–817] In the particular case where the original oxazolone was derived from cyclohexanone, a spiropyrazolidin-5-one was obtained.[818]



Scheme 7.169

Pyrazolinoxazolines have been isolated, albeit in low yields, from the reaction of some oxazolones with phenylhydrazine.[819]

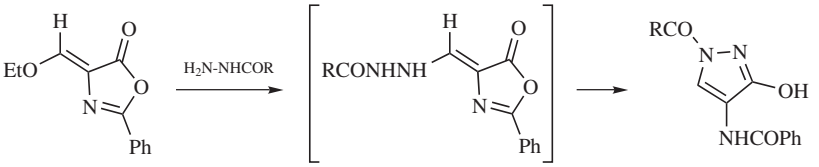
Hydrazides have also been used as nucleophiles for ring opening to give the corresponding bis(acylhydrazides) **540**.[820] Subsequent cyclodehydration of **540** leads to the 4-alkylidene(arylidene)imidazolones **541** that have been evaluated as anticonvulsant, antihelmintic, antibacterial, antifungal, antiviral, and antitubercular agents (Scheme 7.170).[821–824]



539 **540** **541**

Scheme 7.170

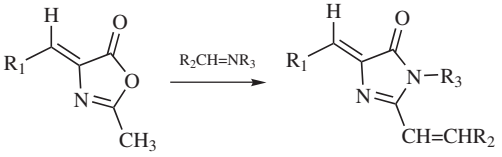
Reaction of 4-(ethoxymethylene)-2-phenyl-5(4*H*)-oxazolone **542** with a hydrazide gives 1-acyl-3-hydroxy-1*H*-pyrazoles **544** via an addition–elimination sequence to generate **543** followed by cyclization as shown in Scheme 7.171.[825]



542 **543** **544**

Scheme 7.171

Schiff bases also react with unsaturated 5(4*H*)-oxazolones and afford different products depending on the substituent at C-2. With 2-methyl-5(4*H*)-oxazolones **545** as starting materials, 2-styryl-1-substituted imidazolones **546** are obtained (Scheme 7.172).[826–830] Selected examples are shown in Table 7.43 (Fig. 7.54).



545 **546**

Scheme 7.172

TABLE 7.43. 2-STYRYL-1-SUBSTITUTED IMIDAZOLONES FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH SCHIFF BASES

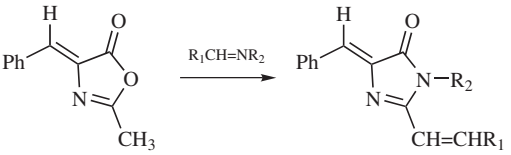
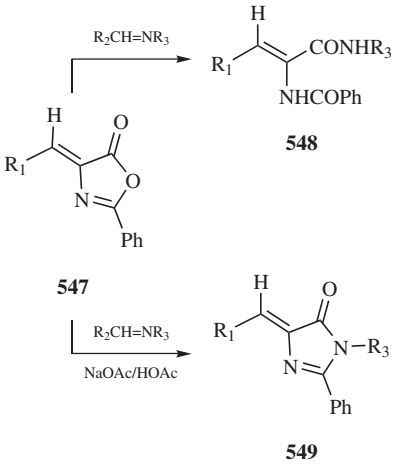


Figure 7.54

R_1	R_2	% Yield	Reference
Ph	Ph	85	826
Ph	4-ClC_6H_4	63	826
3-$NO_2C_6H_4$	Ph	66	826
Ph	4-MeC_6H_4	67	827
Ph	4-$MeOC_6H_4$	68	827

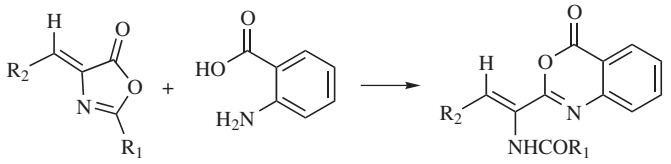
On the other hand, if a 2-phenyl-5(4*H*)-oxazolone **547** is the starting material, *N*-(benzoyl)dehydroamino acid amides **548** or unsaturated imidazolones **549** are obtained depending on the reaction conditions (Scheme 7.173).[831]



Scheme 7.173

7.4.2.6. 1,3-Bis(nucleophiles)

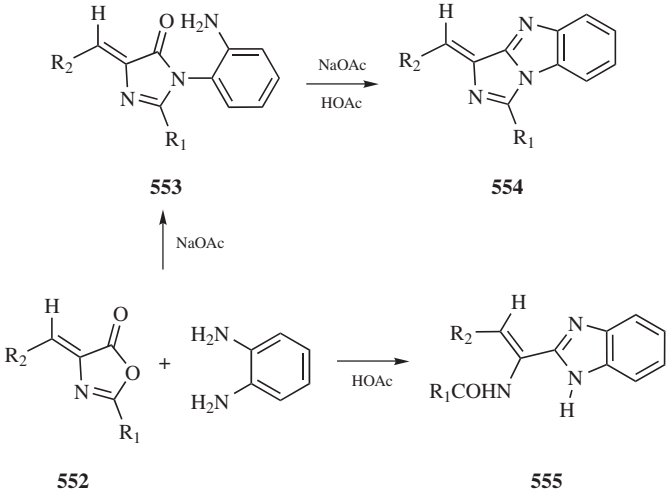
Reaction of unsaturated 5(4*H*)-oxazolones with bis(nucleophiles) opens the way for the preparation of diverse heterocyclic compounds depending on the nucleophilic atoms of the reagent. First, if we consider nitrogen-containing bis(nucleophiles), the reaction of anthranilic acid with unsaturated oxazolones **550** gives rise to substituted 3,1-benzoxazin-4-ones **551** (Scheme 7.174).[832–840]



550 **551**

Scheme 7.174

A widely used bis(nucleophile) is *o*-phenylenediamine. Several heterocyclic systems have been synthesized depending on the experimental conditions, although benzimidazoles **555** are obtained as the major reaction products (Scheme 7.175).[841–847] Alternatively, ring-opening **552** with *o*-phenylenediamine can produce an *N*′-(2-aminophenyl)imidazolone **553** that cyclizes to an imidazobenzimidazole **554**. A complete study of the reactivity of 4-arylidene-2-phenyl-5(4*H*)-oxazolones with various nitrogen-containing bis(nucleophiles) and evaluation of the products as antimicrobial agents has recently been published.[848]



553 **554**

552 **555**

Scheme 7.175

o-Aminothiophenol also reacts analogously as a bis(nucleophile) to afford benzothiazoles.[842,849] Finally, 1,8-diaminonaphthalene reacts with unsaturated 5(4*H*)-oxazolones to afford perimidines.[850] Examples of benzimidazoles and benzothiazoles derived from unsaturated 5(4*H*)-oxazolones are shown in Table 7.44 (Fig. 7.55).

Azoles or azines with an amino group at C-2 have also been used as bis(nucleophiles) to prepare a variety of fused heterocyclic systems. In these cases, the geometry of the bis(nucleophile) permits reaction with both electrophilic centers of the oxazolone. Thus, initial Michael reaction and subsequent ring

TABLE 7.44. BENZIMIDAZOLES AND BENZOTHIAZOLES FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH 2-SUBSTITUTED ANILINES

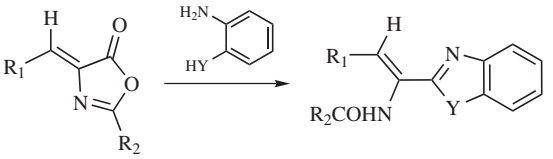
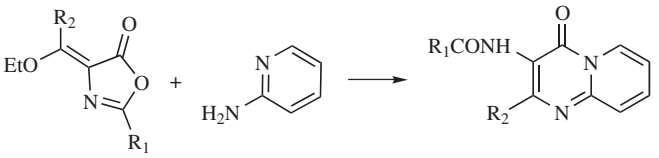


Figure 7.55

R_1	R_2	Y	% Yield	Reference
Ph	Ph	NH	70–75	841
4-$MeOC_6H_4$	Ph	NH	70–75	841
4-$NO_2C_6H_4$	Ph	NH	70–75	841
Ph	Ph	NH	72	842
4-ClC_6H_4	Ph	NH	78	842
thien-2-yl	Ph	NH	66	842
Ph	4-$NO_2C_6H_4$	NH	75	842
4-$MeOC_6H_4$	4-$NO_2C_6H_4$	NH	70	842
Ph	Ph	S	56	842
4-ClC_6H_4	Ph	S	72	842
thien-2-yl	Ph	S	55	842
Ph	4-$NO_2C_6H_4$	S	75	842
4-$MeOC_6H_4$	4-$NO_2C_6H_4$	S	75	842

opening of the oxazolone leads to new heterocyclic compounds. The nature of the bis(nucleophile) and the β-substituent at the C-4 vinyl group determine the structure of the products. Among the 2-aminoheterocycles employed in this reaction are 2-aminopyridines[851] (Scheme 7.176) and 2-aminoazoles[852] including pyrazoles,[853–855] imidazoles,[856] thiazoles,[851] oxadiazoles,[857–859] thiadiazoles,[858,860] and triazoles[853–855] (Scheme 7.177).

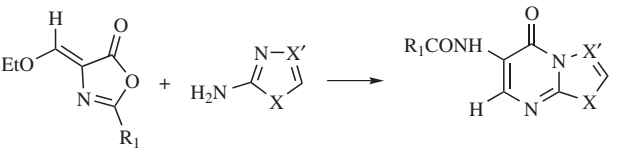


556 **557**

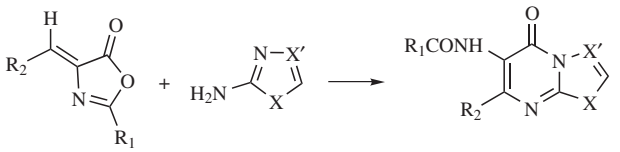
Scheme 7.176

Reaction of α-hydrazinoheterocycles with 4-(hydroxymethylene)-2-phenyl-5(4*H*)-oxazolone **406** gives rise to *N*-benzoyl-α-(heteroaryl)glycinates **563** containing a fused 1,2,4-triazole after oxidative cyclization (Scheme 7.178).[861]

Urea, thiourea, and *S*-alkylisothiouronium halides have also been used as bis(nucleophiles) in reactions with unsaturated oxazolones.[862–865] Reaction with urea and thiourea leads to the corresponding imidazolones. The use of

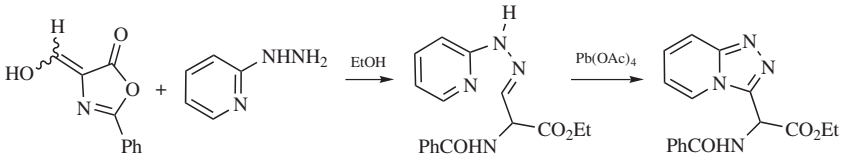


558 **559**



560 **561**

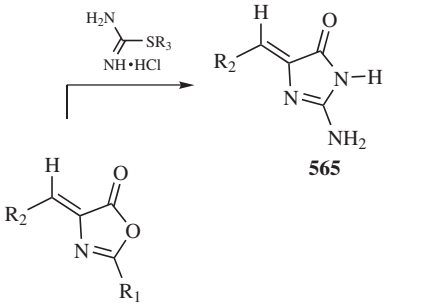
Scheme 7.177



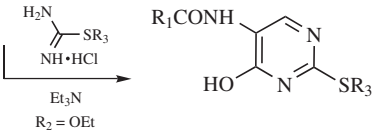
406 **562** **563**

Scheme 7.178

S-alkylisothiouronium halides usually leads to 2-amino-5-imidazolones **565** although in some cases, depending on the substituents and on the experimental conditions, other products such as pyrimidines **566** have been obtained.[862] In this case, Michael reaction and ring opening lead to the observed product (Scheme 7.179).



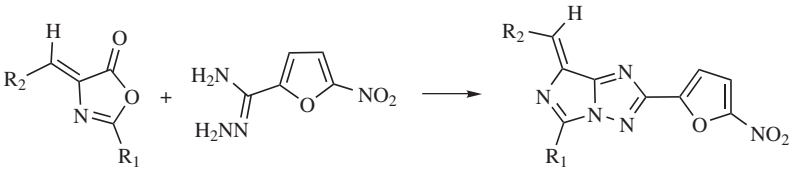
564 **565**



566

Scheme 7.179

Antimicrobial imidazotriazoles **568** are obtained when a hydrazidimide, for example, 5-nitro-2-furancarboximidic acid hydrazide, reacts as the bis(nucleophile) with **567** (Scheme 7.180).[866]

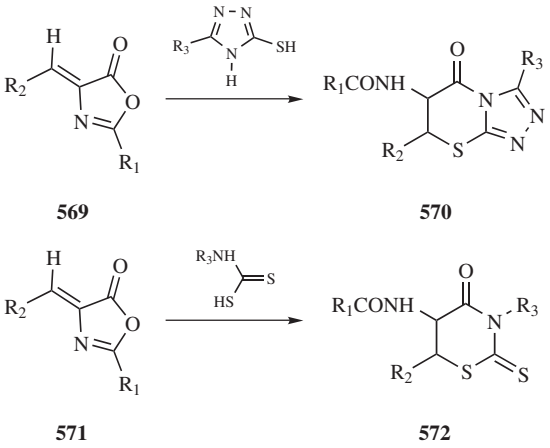


567 **568**

Scheme 7.180

A variety of N,S-bis(nucleophiles) react with unsaturated 5(4*H*)-oxazolones to produce triazolo-1,3-thiazin-4-ones **570** and 1,3-thiazin-4-ones **572**. Mechanistically, Michael addition of the bis(nucleophile) to **569** and **571** followed by ring opening with concomitant cyclization leads to the observed products.

3-Mercapto-1,2,4-triazoles,[867–869] 2-imidazolidinethione, 2-mercaptobenzimidazole,[870] and N-substituted dithiocarbamic acids[871–873] have also been used frequently as bis(nucleophiles) (Scheme 7.181).

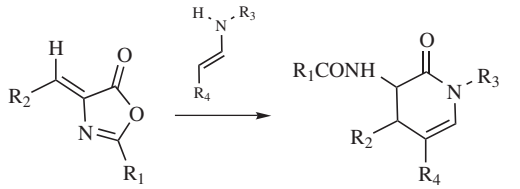


569 **570**

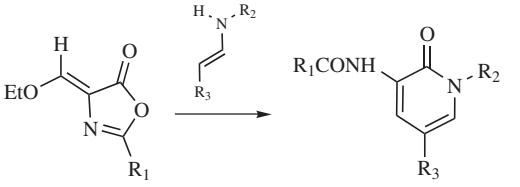
571 **572**

Scheme 7.181

Bis(nucleophiles) involving carbon atoms also react with unsaturated 5(4*H*)-oxazolones. Among these, enamines[874–877] and other related compounds such as iminophosphoranes[878] and 2-benzimidazolyl-, 2-benzoxazolyl-, and 2-benzothiazolylacetates[879,880] are commonly used. A mechanistically similar process involving initial Michael reaction to the exocyclic double bond followed by ring opening gives 2-pyridones. The degree of unsaturation in the 2-pyridone depends on the

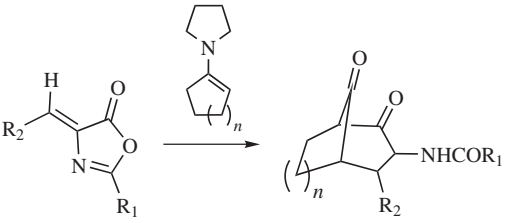


573 **574**



575 **576**

Scheme 7.182



577 **578**

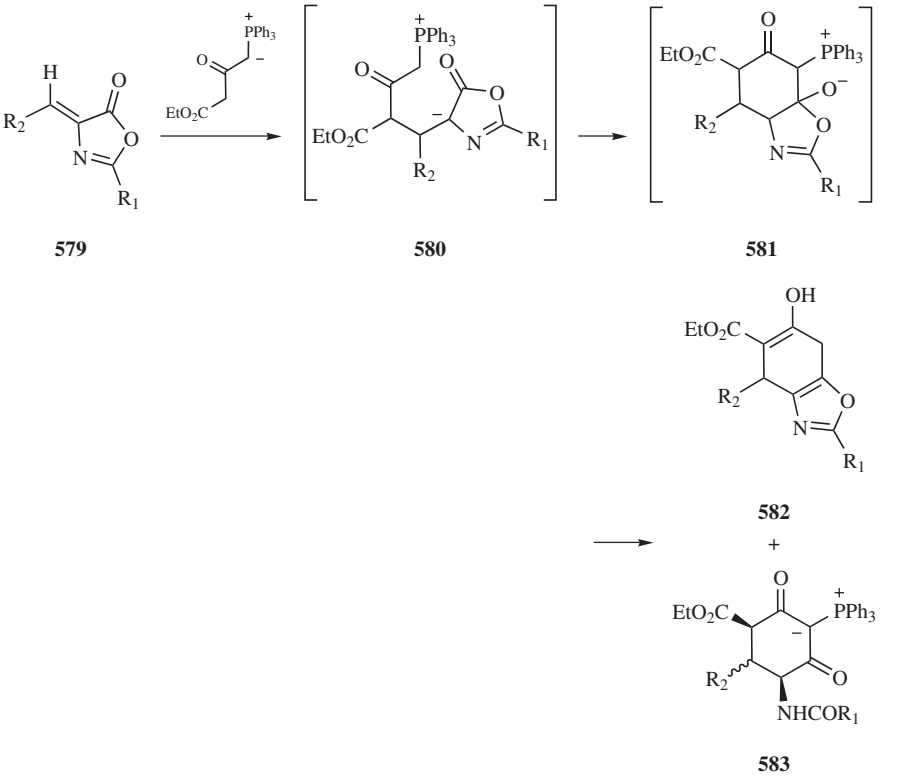
Scheme 7.183

starting unsaturated 5(4*H*)-oxazolones; 4-alkylidene(arylidene)-5(4*H*)-oxazolones **573** lead to dihydropyridone derivatives **574**, whereas 4-(ethoxymethylene)-5(4*H*)-oxazolones **575** give pyridones **576** (Scheme 7.182).

Bis C-alkylation is observed using *N*,*N*-disubstituted enamines of cycloalkanones and leads to the bicyclic β-diketones **578** (Scheme 7.183).[881]

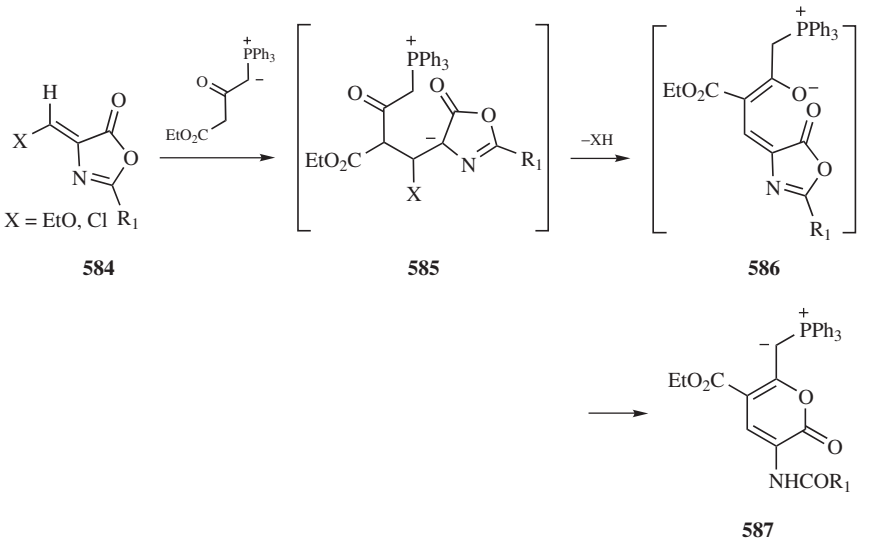
Reaction of suitably functionalized phosphonium ylides with unsaturated 5(4*H*)-oxazolones **579** has opened the way for the use of new C,C-bis(nucleophiles). Of particular interest is ethyl 3-oxo-4-(triphenylphosphoranylidene)butyrate used to prepare dihydrobenzoxazoles **582** and diastereoisomeric 1,3-cyclohexanedione ylides **583** (Scheme 7.184).[882]

In contrast, ethyl 3-oxo-4-(triphenylphosphoranylidene)butyrate behaves as a C,O-bis(nucleophile) when reacted with unsaturated 5(4*H*)-oxazolones **584** with a leaving group at the exocyclic β-carbon.[883] In this case, initial Michael reaction generates **585** that eliminates HX to produce a resonance stabilized ylide **586**. Cyclization of **586** with ring opening leads to the interesting ylide intermediate **587** used for the synthesis of 2*H*-pyran-2-ones (Scheme 7.185).



579 **580** **581** **582** **583**

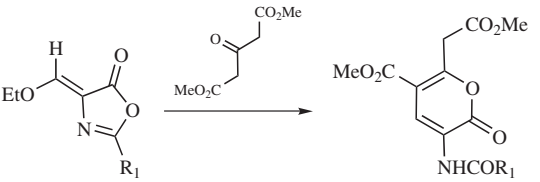
Scheme 7.184



584 **585** **586** **587**

Scheme 7.185

Similar reactivity was observed with typical activated methylene compounds such as dimethyl 1,3-acetonedicarboxylate. With this C,O-bis(nucleophile) the products are also 2*H*-pyran-2-ones **589** (Scheme 7.186).[884]

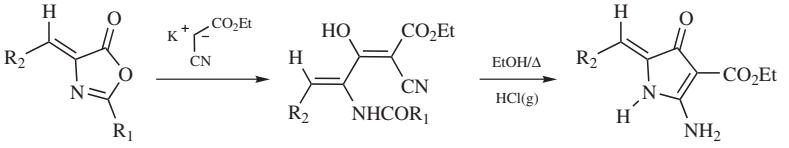


588 **589**

Scheme 7.186

7.4.2.7. Other Nucleophiles

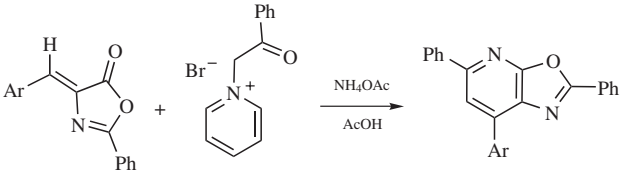
A variety of other nucleophiles effect ring opening of unsaturated 5(4*H*)-oxazolones. Reaction with active methylene compounds containing an electrophilic center is a known procedure to prepare heterocyclic compounds through ring opening and subsequent cyclization.[885–887] For example, reaction of unsaturated 5(4*H*)-oxazolones **590** with alkyl cyanoacetates gives 3-acylamino-1-cyano-2-hydroxy-4-substituted-1,3-butadiencarboxylates **591** that are cyclized to pyrrolidin-3-ones **592** (Scheme 7.187).



590 **591** **592**

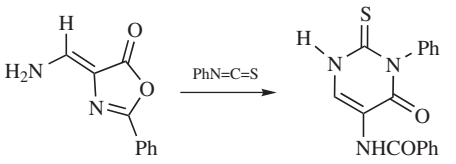
Scheme 7.187

Reaction of 4-arylidene-2-phenyl-5(4*H*)-oxazolones **593** with *N*-phenacylpyridinium bromide[888] proceeds by the same sequence to give oxazolo[5,4-*b*]pyridines **594** (Scheme 7.188) while the reaction of 4-(aminomethylene)-2-phenyl-5(4*H*)-oxazolone **418** and phenyl isothiocyanate[889] gives pyrimidin-2-thiones **595** (Scheme 7.189). In this latter case initial attack of the exocylic amino group produces an intermediate thiourea (not shown) that subsequently cyclizes to **595**.



593 **594**

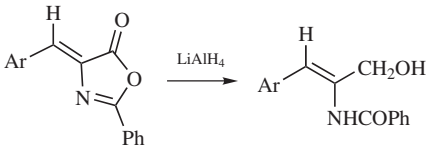
Scheme 7.188



418 **595**

Scheme 7.189

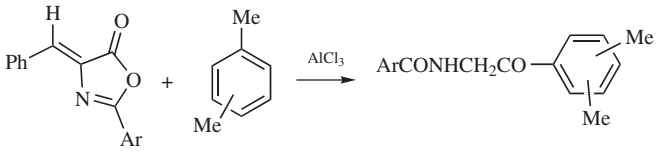
Hydride reduction of a 4-arylidene-5(4*H*)-oxazolone can also be considered as a nucleophilic ring opening. Here, this process, shown in Scheme 7.190, generates α-(benzoylamino)cinnamyl alcohols **597**.[890]



596 **597**

Scheme 7.190

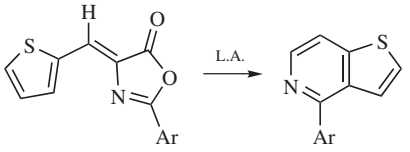
Unsaturated 5(4*H*)-oxazolones undergo a Friedel–Crafts reaction with aromatic hydrocarbons in the presence of a Lewis acid. In particular, a 2-aryl-4-benzylidene-5(4*H*)-oxazolone **598** reacts with *o*- or *p*-xylene in the presence of aluminum chloride via ring opening and subsequent dearylation to yield **599** as indicated in Scheme 7.191.[891]



598 **599**

Scheme 7.191

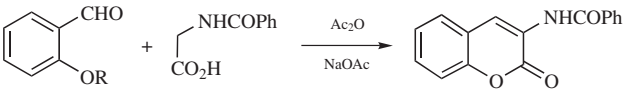
In a similar manner, an intramolecular Friedel–Crafts reaction of 2-aryl-4-(2-thienylidine)-5(4*H*)-oxazolones **600** has been reported and, in this case, cyclization and decarboxylation generates thienopyridines **601** (Scheme 7.192).[892]



600 **601**

Scheme 7.192

Finally, the intramolecular ring opening of unsaturated 5(4*H*)-oxazolones derived from 2-hydroxybenzaldehyde is noteworthy. Here, the condensation of hippuric acid and 2-hydroxybenzaldehyde under classical conditions gives a 3-(acylamino)coumarin **602** directly without isolation of an intermediate oxazolone.[893] Suitably protected 2-hydroxybenzaldehyde derivatives react similarly (Scheme 7.193).[894–896]



602

Scheme 7.193

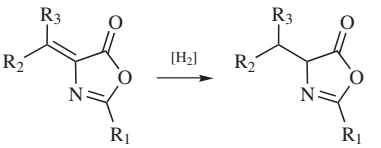
Deacetylation of 4-[(*o*-acetoxy)benzylidene]-2-phenyl-5(4*H*)-oxazolone also immediately affords **602**. The starting oxazolone was obtained by cyclodehydration of the corresponding cinnamic acid precursor or by condensation of hippuric acid with 2-acetoxybenzaldehyde in the absence of base. In examples using 2-hydroxyacetophenone, 4-methyl-3-(acylamino)coumarins are obtained.[897]

7.4.3. Reactions Involving the Exocyclic Double Bond

Classical ring-opening reactions of unsaturated oxazolones are the most well studied reactions and generate a wide variety of interesting products. However, reactions of the exocyclic double bond have also been investigated and open the way to a tremendous variety of new possibilities.

7.4.3.1. Hydrogenation

It is well known that hydrogenation of dehydroamino acid derivatives derived from ring opening of unsaturated 5(4*H*)-oxazolones affords new racemic amino acids and, in some cases, enantiomerically pure compounds. On the other hand, a number of attempts have been made to hydrogenate the double bond of the unsaturated oxazolone itself. For example, 4-benzyl-2-methyl-5(4*H*)-oxazolone was prepared from 4-benzylidene-2-methyl-5(4*H*)-oxazolone using Raney Ni as a catalyst. This process is reported to be a general procedure to prepare saturated oxazolones directly (Scheme 7.194).[898,899]

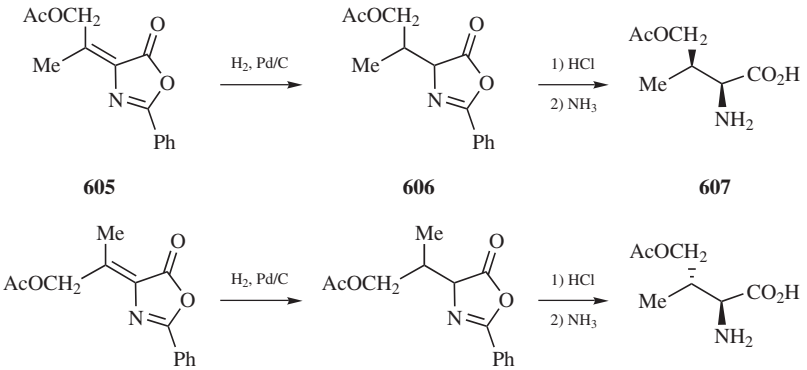


603 **604**

Scheme 7.194

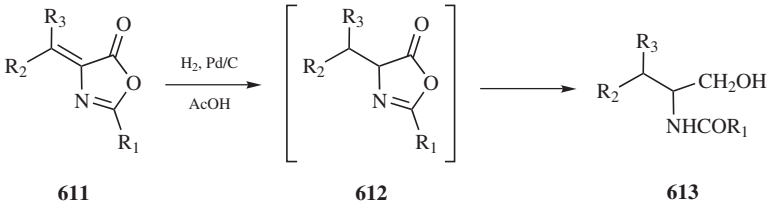
Reduction in the presence of methanolic sodium methoxide produces the corresponding *N*-acetylphenylalanine methyl ester as the final product.[900,901] Enzymatic resolution of *N*-acetylphenylalanine methyl ester then gives phenylalanine in high enantiomeric purity. Magnesium in methanol has also been used to produce nearly quantitative yields of the *N*-acetylphenylalanine methyl ester without isolation of the intermediate saturated oxazolone.[902]

Catalytic hydrogenation of the (*E*)-unsaturated oxazolone **605** and the (*Z*)-unsaturated oxazolone **608**, both derived from acetoxyacetone, affords **606** and **609** respectively. Subsequent ring opening of **606** and **609** generated erythro and threo diastereoisomers of racemic γ-hydroxyvaline acetates **607** and **610** (Scheme 7.195).[903] Further, enantioselective oxidation of the D- or L-enantiomer with D- or L-amino acid oxidase gives the corresponding α-keto acid. The unreacted enantiomer was isolated by ion exchange chromatography.



Scheme 7.195

Catalytic hydrogenation of the exocyclic double bond of several oxazolones **611**, in the presence of acetic acid, gives α-acylamino alcohols **613** via the saturated derivatives **612** (Scheme 7.196).[904] Selected examples of amino acid derivatives and amino alcohols available from reduction of unsaturated oxazolones are shown in Table 7.45 (Fig. 7.56).



Scheme 7.196

TABLE 7.45. AMINO ACID, AMINO ESTER AND AMINO ALCOHOL DERIVATIVES FROM HYDROGENATION OF UNSATURATED 5(4*H*)-OXAZOLONES

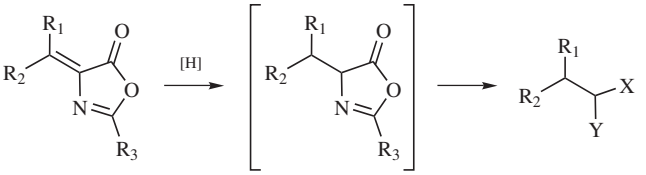


Figure 7.56

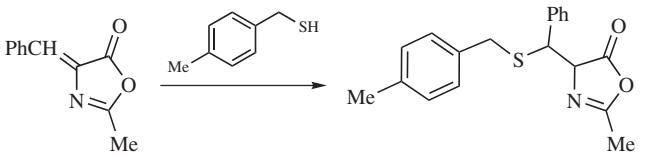
R_1	R_2	R_3	X	Y	% Yield	Reference
H	Ph	Me	CO_2Me	NHCOMe	95	900
Me	$AcOCH_2$	Ph	CO_2H	NH_2	74	903
$AcOCH_2$	Me	Ph	CO_2H	NH_2	91	903
H	4-$MeOC_6H_4$	Ph	CH_2OH	NHCOPh	50	904
H	Ph	Ph	CH_2OH	NHCOPh	60	904
Me	Me	Ph	CH_2OH	NHCOPh	60	904

7.4.3.2. Michael Reactions

Some examples of the Michael reaction on the exocyclic double bond of an unsaturated oxazolone have been discussed in previous sections. The synthesis of unsaturated 5(4*H*)-oxazolones from unsaturated 5(4*H*)-oxazolones via an addition–elimination sequence and the sequential reaction of unsaturated 5(4*H*)-oxazolones with a 1,3-bis(nucleophile) have already been considered. This section will review Michael additions exclusively and, in this respect, a wide array of nucleophiles has been studied.

Although it is well known that sulfur nucleophiles are excellent candidates for Michael reactions, they have scarcely been examined with unsaturated oxazolones. Nevertheless, 4-methyltoluene-α-thiol reacts with 4-benzylidene-2-methyl-5(4*H*)-oxazolone **614** to give **615** as a mixture of erythro and threo isomers (Scheme 7.197).[905]

Ring opening **615** to the methyl ester and separation gives rise to a procedure for the synthesis of *S*-(4-methylbenzyl)-β-phenylcysteine. Carboxypeptidase A

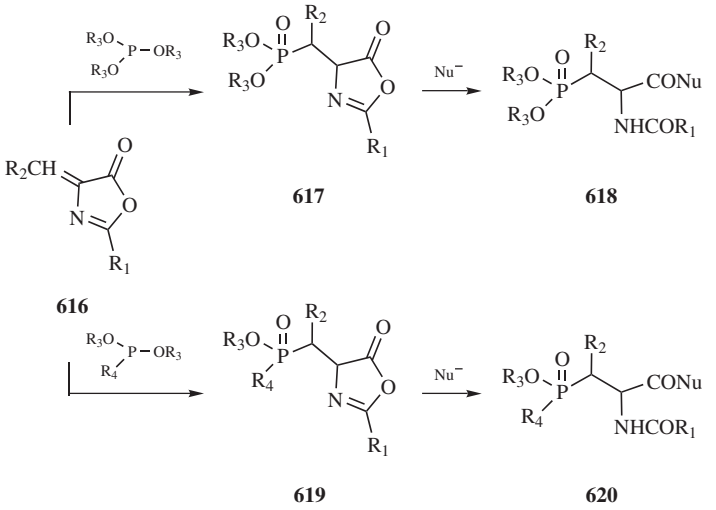


614 **615**

Scheme 7.197

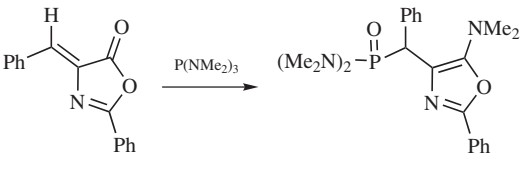
conveniently resolves the *N*-(trifluoroacetyl)- derivatives of erythro and threo *S*-(4-methylbenzyl)-β-phenylcysteine.

Organophosphorous compounds have also been used as nucleophiles with unsaturated oxazolones. Initially, Michael reaction of a trialkyl- or dialkylphosphite gives **617** or **619** that undergo subsequent ring opening to yield a 2-acylamino-3-phosphonyl-**618** or 2-acylamino-3-phosphinyl-**620** derivative of the corresponding carboxylic acid, respectively (Scheme 7.198).[906–909]



Scheme 7.198

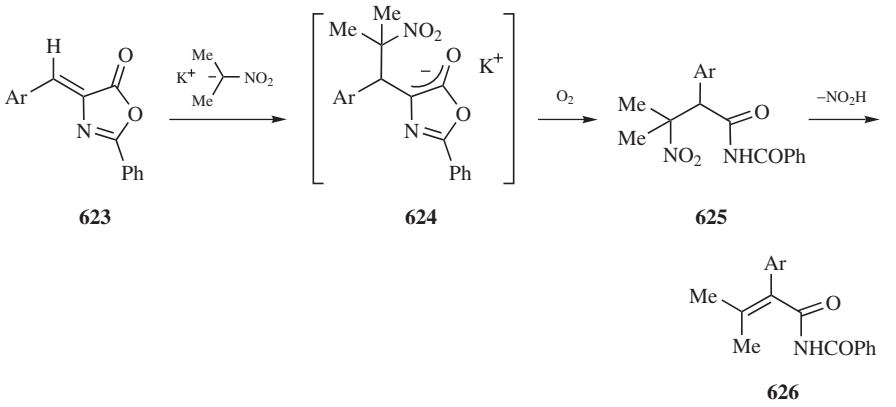
4-benzylidene-2-phenyl-5(4*H*)-oxazolone **621** reacts with hexamethylphosphorus triamide to give 4-α-[bis(dimethylamino)phosphoryl]benzyl-5-(dimethylamino)-2-phenyloxazole **622** (Scheme 7.199).[910]



Scheme 7.199

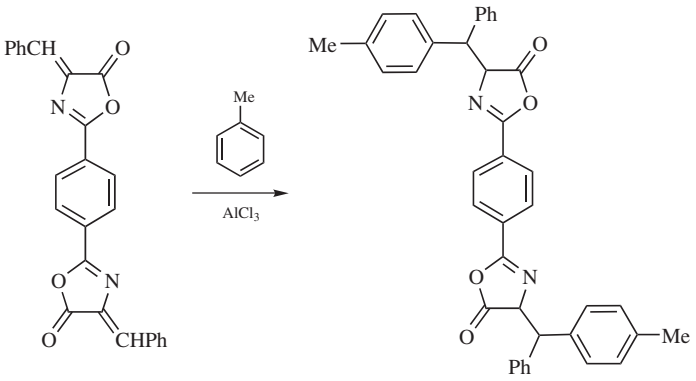
For carbon nucleophiles sequential addition of 2-potassio-2-nitropropane and oxygen to 4-arylidene-2-phenyl-5(4*H*)-oxazolones **623** has been reported (Scheme 7.200).[911] The process involves a Michael reaction of the 2-nitropropane anion followed by reaction with molecular oxygen and elimination of nitrous acid to yield 2-aryl butenoic acid imides **626**.

Previously, Friedel–Crafts alkylation of unsaturated oxazolones with xylenes leading to the ring-opened products was described in Section 7.4.2.7. In contrast,



623 **624** **625** **626**

Scheme 7.200



627 **628**

Scheme 7.201

reaction of 2,2′-(1,4-phenylene)-bis(4-phenylmethylene)-5(4*H*)-oxazolone **627** with toluene in the presence of aluminium trichloride gives the addition adduct **628** (Scheme 7.201).[912]

Sulfur ylides are among the most interesting carbon nucleophiles and their synthetic importance has been recently reviewed.[913] One especially interesting use of these ylides is their application to the synthesis of cyclopropane derivatives using unsaturated oxazolones. For example, stabilized sulfur ylides react with unsaturated oxazolones **629** via a Michael reaction to give oxazolone spirocyclopropanes **630** as shown in Scheme 7.202 and Table 7.46 (Fig. 7.57), whereas the less stabilized sulfur ylides give ring-opened products **631** as the major compounds (Scheme 7.202).[914,915]

Starting from the chiral oxazolone **632** derived from 1,2-*O*-isopropylidene-D-glyceraldehyde, diastereoselective cyclopropanation has been reported to occur with dimethyloxosulfonium methylide or (diethylamino)phenyloxosulfonium

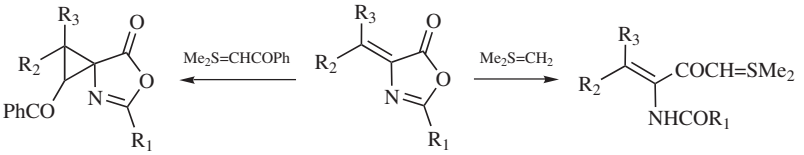
TABLE 7.46. OXAZOLONE SPIROCYCLOPROPANES FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH A STABILIZED SULFUR YLIDE[a]

Figure 7.57

R_1	R_2	R_3	% Yield
H	Ph	Ph	85
H	4-$AcOC_6H_4$	Ph	68
H	PhCH=CH	Ph	59
H	furan-2-yl	Ph	57
H	1-acetylindol-3-yl	Ph	49
Me	Me	Ph	84

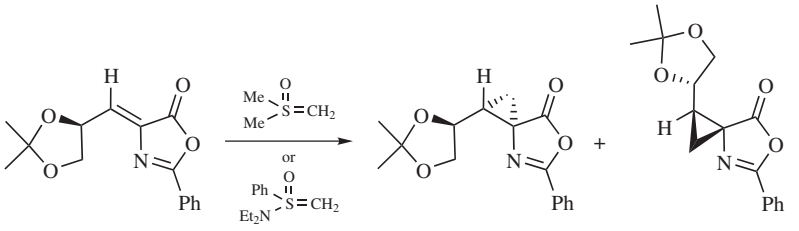
[a]Data from Ref. 914.

methylide as cyclopropanating agents (Scheme 7.203).[916] The reaction produces mixtures of *cis*- and *trans*-spirooxazolones **633** and **634**. The influence of the oxosulfonium methylide and experimental conditions on the cis/trans ratio and on cis and trans diastereoselectivities has been studied. The results are complementary to those obtained from cyclopropanation of **632** using diazomethane (see scheme 7.217). The use of chiral oxazolone **632** provides an entry to versatile precursors leading to enantiomerically pure 2-substituted-1-aminocyclopropanecarboxylic acids.



630 **629** **631**

Scheme 7.202



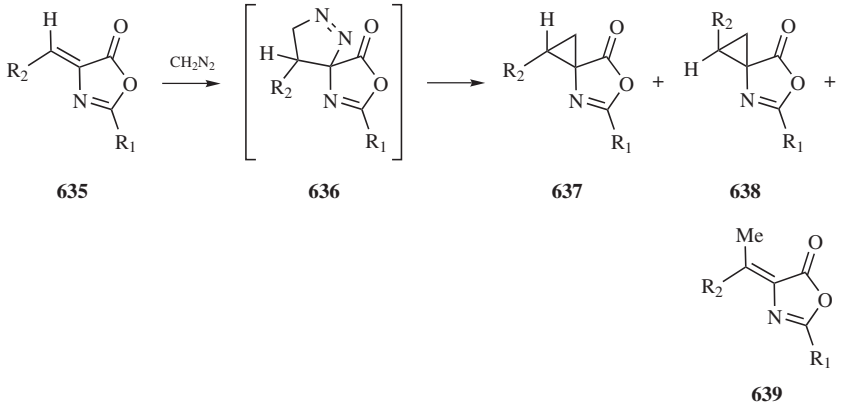
632 **633** **634**

Scheme 7.203

7.4.3.3. 1,3-Dipolar Cycloadditions

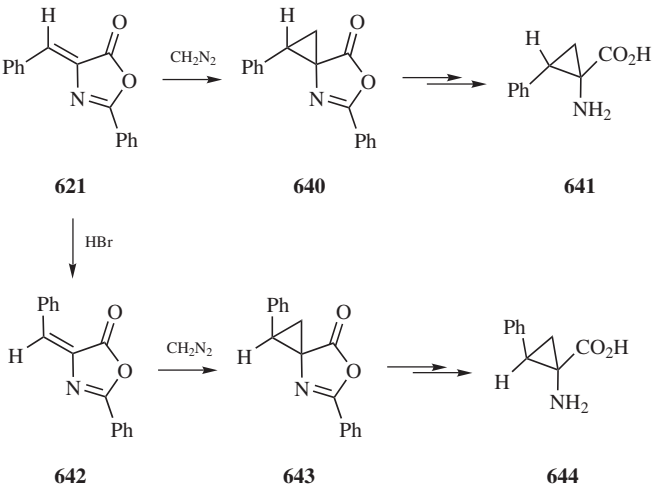
During the last two decades, the importance of the dipolarophilic nature of unsaturated 5(4*H*)-oxazolones has been widely recognized and studied with a variety of 1,3-dipoles. Among the systems studied, diazoalkanes, particularly diazomethane, are the most frequently used and have opened the way for the synthesis of aminocyclopropanecarboxylic acid derivatives.

There are a number of stereochemical considerations that have to be taken into account in this reaction. 1,3-Dipolar cycloaddition with diazoalkanes occurs to generate an intermediate spiropyrazoline **636** that, in most cases has not been isolated. The presence of EWG on the alkene moiety results in the formation of only one regioisomer of the spiropyrazoline. Two competitive processes are possible upon decomposition of the spiropyrazoline and, apart from the formation of cyclopropane derivatives **637** and **638**, homologation of the starting unsaturated 5(4*H*)-oxazolone to afford **639** is also possible. The stereochemistry of the starting oxazolone, the experimental reaction conditions and the nature and polarity of the solvent can all result in *C*-methylene insertion as the main reaction.[512] Moreover, the decomposition of pyrazolines is not a stereospecific reaction although partial retention of configuration is usually observed. Mixtures of *cis*- and *trans*-cyclopropane derivatives are obtained in which the predominant product retains the same relative configuration as the starting compound (Scheme 7.204).



Scheme 7.204

Since (*Z*)- and (*E*)-stereoisomers of unsaturated oxazolones can be obtained using appropriate isomerization procedures, cis and trans isomers of cyclopropane derivatives can be obtained in a stereoselective manner, although special care must be taken with experimental conditions to obtain the best stereoselectivity. Both racemic *cis*- and *trans*-1-amino-2-phenylcyclopropanecarboxylic acid **641** and **644** have been obtained from the corresponding (*Z*)- or (*E*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolone **621** and **642** using diazomethane. Care was taken to affect the



Scheme 7.205

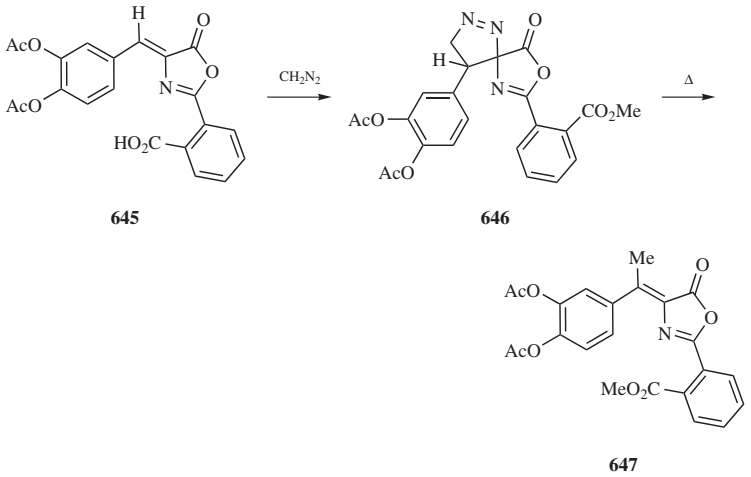
nucleophilic ring opening of the oxazolone to avoid cleavage of the cyclopropane ring (Scheme 7.205).[422]

Extension of this reaction to other 4-arylmethylene-5(4*H*)-oxazolones and a careful study of the cyclopropanation of (*Z*)-4-(ethylidene)-2-phenyl-5(4*H*)-oxazolone have also been reported.[917,918] This methodology was used to prepare cyclopropyl tyrosine and 1-amino-2-(4-hydroxyphenyl)cyclopropanecarboxylic acid.[919] However, all attempts to obtain 1-amino-2-(3,4-dihydroxyphenyl)cyclopropanecarboxylic acid, the cyclopropane analogue of DOPA via cyclopropanation of the oxazolone were unsuccessful. In this case, the intermediate spiropyrazoline **646** was isolated in excellent yield. However, pyrolysis of **646** only produced the homologated oxazolone **647** (Scheme 7.206).[920]

When 4-heteromethylene-2-phenyl-5(4*H*)-oxazolones **648** are reacted with diazomethane, a five component mixture **649**-**653** was obtained. The product ratio depends on the β-heteroatom of double bond (Scheme 7.207).[424]

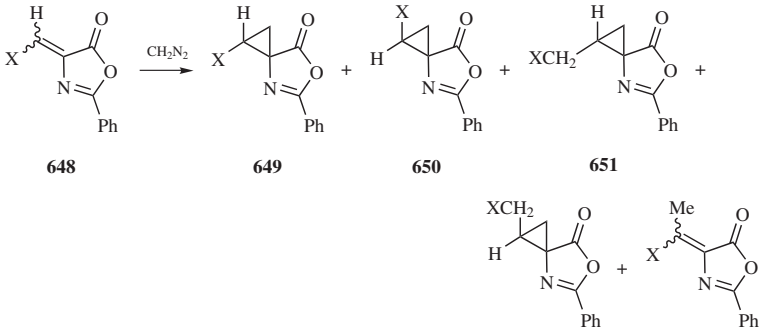
4-(Chloromethylene)-2-phenyl-5(4*H*)-oxazolone **394**[921] and 2-(acyloxymethylene)-5(4*H*)-oxazolone[424] mainly give a mixture of 2-hetero substituted spirocyclopropanes. For example, the 2-chloro derivatives **654** and **655** have been isolated and further elaborated to both stereoisomers of 1-amino-2-chlorocyclopropanecarboxylic acid **656** and **657** (Scheme 7.208).

In contrast, when the same reaction was carried out on 4-(bromomethylene)-2-phenyl-5(4*H*)-oxazolone **658** (X = Br)[922] or 4-(iodomethylene)-2-phenyl-5(4*H*)-oxazolone **658** (X = I)[424] serendipitous formation of the 2-(halomethyl)spirocyclopropanes **659** and **660** was observed. Both diastereoisomers of 2,3-methanomethionine **663** and **664** have been prepared from the isolated 2-(bromomethyl)-spirocyclopropane oxazolones, **659** and **660**, respectively. The isolated 2-(iodomethyl)spirocyclopropane oxazolones have been hydrolyzed to furnish the



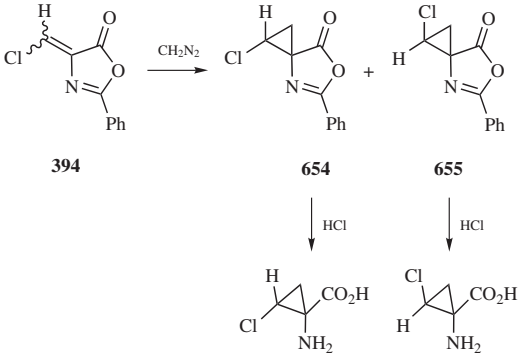
645 **646** **647**

Scheme 7.206



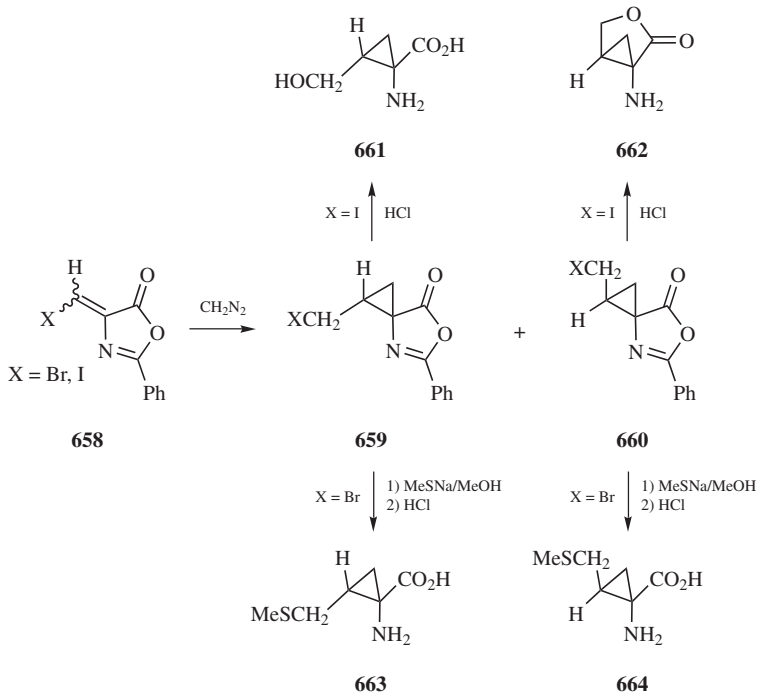
648 **649** **650** **651** **652** **653**

Scheme 7.207



394 **654** **655** **656** **657**

Scheme 7.208



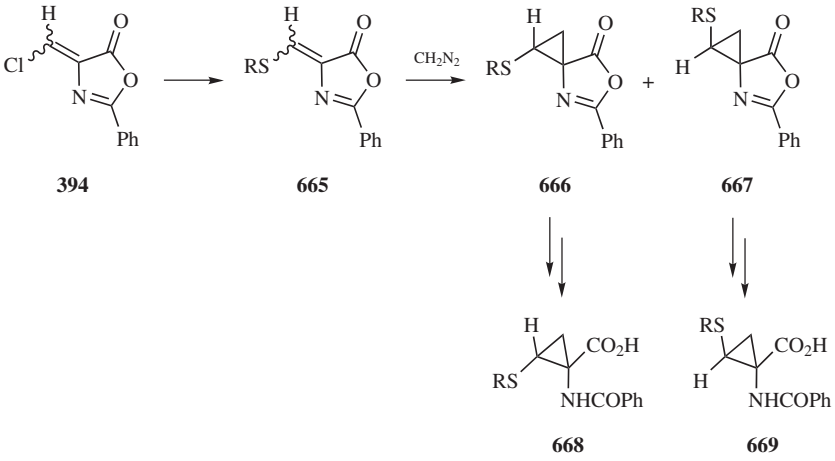
Scheme 7.209

cyclopropylhomoserine derivatives, **661** and **662**. In this case, the *trans*-cyclopropylhomoserine lactonized to **662** under the reaction conditions (Scheme 7.209).

The reaction of diazomethane with 2-phenyl-4-(sulfanylmethylene)-5(4*H*)-oxazolone **665**, readily obtained from 4-(chloromethylene)-2-phenyl-5(4*H*)-oxazolone **394**, generates the intermediate spirocyclopropane oxazolones **666** and **667**, respectively. Both **666** and **667** were independently elaborated to the 2-sulfanyl-1-aminocyclopropanecarboxylic acid derivatives **668** and **669**—a novel class of conformationally constrained masked cysteines (Scheme 7.210).[518] Representative examples of spirocyclopropane oxazolones are shown in Table 7.47 (Fig. 7.58).

Diphenyldiazomethane has also been used in 1,3-dipolar cycloadditions with 4-arylmethylene-5(4*H*)-oxazolones **670** to prepare *gem*-diphenyl-spirocyclopropane oxazolones **671**.[423,923] A number of **671** analogues were evaluated as antibacterial agents.[924] In addition, **671** derivatives were precursors for new 1-aminocyclopropanecarboxylic acid derivatives **672**, for example, 1-(benzoylamino)triphenylcyclopropanecarboxylic acid **672** (R = Ar = Ph) (Scheme 7.211).

Nitrile imines, generated *in situ* from the corresponding *N*-(phenyl)arylhydrazonoyl chlorides, react with unsaturated 5(4*H*)-oxazolones **673** to give the corresponding spiropyrazoline oxazolones **674**.[647,648,925–927] The reaction is regioselective and in each case only one regioisomeric cycloadduct is formed. The process is also stereoselective. However, some partial isomerization of an (*E*)-oxazolone to the (*Z*)



Scheme 7.210

TABLE 7.47. OXAZOLONE SPIROCYCLOPROPANES FROM 1,3-DIPOLAR CYCLOADDITION REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH DIAZOMETHANE

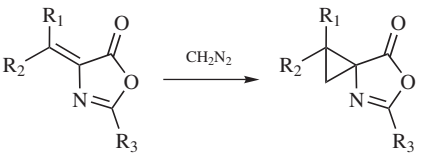
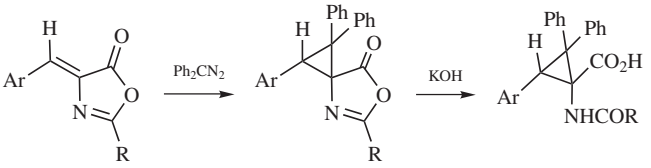


Figure 7.58

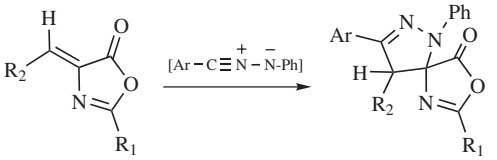
R_1	R_2	R_3	% Yield	Reference
H	Ph	Ph	45	918
Ph	H	Ph	50	918
H	4-MeC_6H_4	Ph	60	918
4-MeC_6H_4	H	Ph	40	918
H	4-$MeOC_6H_4$	Ph	55	918
4-$MeOC_6H_4$	H	Ph	45	918
H	4-ClC_6H_4	Ph	45	918
4-ClC_6H_4	H	Ph	50	918
H	3,4-$(MeO)_2C_6H_3$	2-$MeO_2CC_6H_4$	33	920
H	Cl	Ph	73 ($Z+E$)	424
H	AcO	Ph	76 ($Z+E$)	424
H	MeS	Ph	70 ($Z+E$)	518
H	PhS	Ph	73 ($Z+E$)	518
H	$PhCH_2S$	Ph	54 ($Z+E$)	518
H	Ph_3CS	Ph	67 ($Z+E$)	518
H	(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	Ph	73	933



670 **671** **672**

Scheme 7.211

isomer prior to the cycloaddition reaction has been observed. Contradictory regiochemical assignments have been made although alternative syntheses of products obtained from the cycloadducts support the regiochemistry shown in Scheme 7.212. Representative examples are shown in Table 7.48 (Fig. 7.59).



673 **674**

Scheme 7.212

TABLE 7.48. OXAZOLONE SPIROPYRAZOLINES FROM 1,3-DIPOLAR CYCLOADDITION REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH NITRILE IMINES[a]

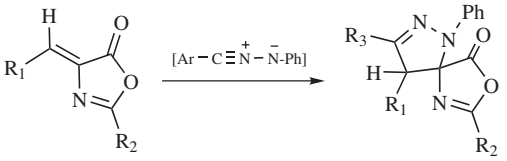
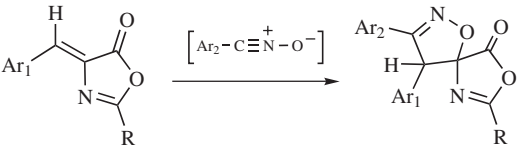


Figure 7.59

R_1	R_2	R_3	% Yield
Ph	Ph	Ph	30–70
Ph	Ph	4-MeC_6H_4	30–70
Ph	Ph	4-ClC_6H_4	30–70
4-MeC_6H_4	Ph	Ph	30–70
4-MeC_6H_4	Ph	4-MeC_6H_4	30–70
4-MeC_6H_4	Ph	4-ClC_6H_4	30–70
Ph	Ph	4-$MeOC_6H_4$	30–70

[a]Data from Ref. 927.



675 **676**

Scheme 7.213

The reaction of nitrile oxides with 4-arylmethylene-5(4*H*)-oxazolones **675** to give the corresponding spiroisoxazoline oxazolones **676** is also well known.[647,927,928] The regiochemistry of this cycloaddition reaction was initially incorrectly assigned but a careful study of the reaction showed that the regiochemistry of the 1,3-dipolar cycloaddition of nitrile oxides is the same as that observed with nitrile imines (Scheme 7.213). Examples of spiroisoxazoline oxazolones are shown in Table 7.49 (Fig. 7.60).

Both reactions have been utilized to prepare heterocyclic compounds such as pyrazoles **681** (X = *N*-Ph) and isoxazoles **681** (X = O) as shown in Scheme 7.214.[647] Starting from an unsaturated 5(4*H*)-oxazolone **677**, either a cycloaddition–ring-opening reaction sequence (**677** → **678** → **680**) or a ring-opening–cycloaddition reaction sequence (**677** → **679** → **680**) affords the same product.

TABLE 7.49. OXAZOLONE SPIROISOXAZOLINES FROM 1,3-DIPOLAR CYCLOADDITION REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES WITH NITRILE OXIDES

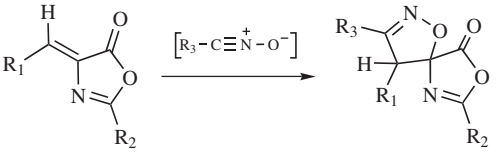
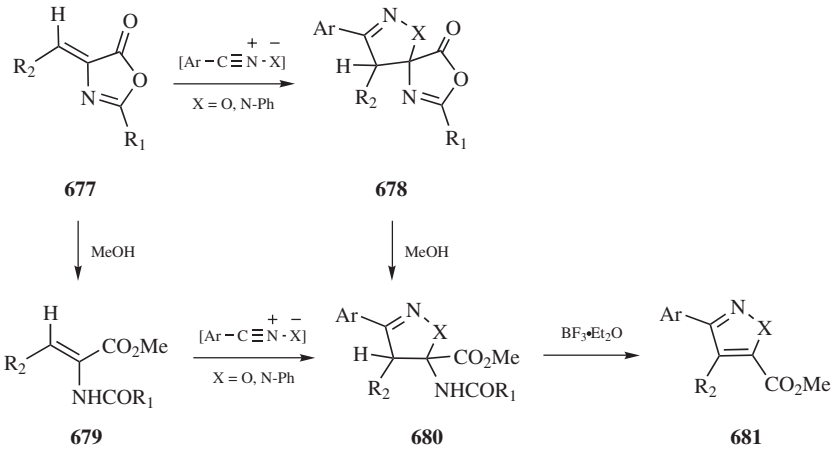


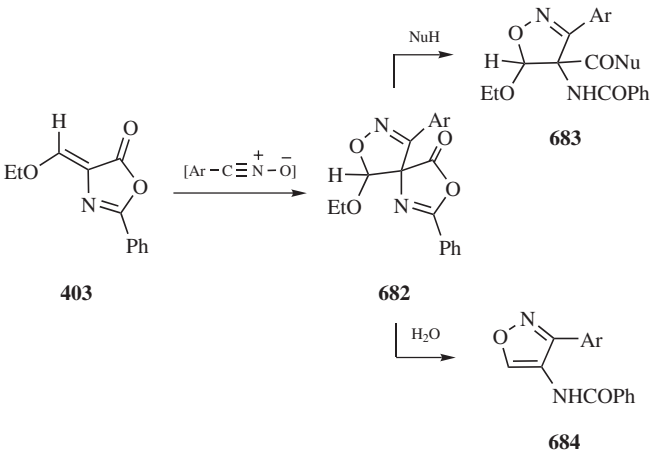
Figure 7.60

R_1	R_2	R_3	% Yield
Ph	Ph	2,4,6-$Me_3C_6H_2$	76
4-MeC_6H_4	Ph	2,4,6-$Me_3C_6H_2$	47
4-ClC_6H_4	Ph	2,4,6-$Me_3C_6H_2$	62
Ph	Ph	2,6-$Cl_2C_6H_3$	82
4-MeC_6H_4	Ph	2,6-$Cl_2C_6H_3$	80
4-ClC_6H_4	Ph	2,6-$Cl_2C_6H_3$	40

[a]Data from Ref. 928.



Scheme 7.214



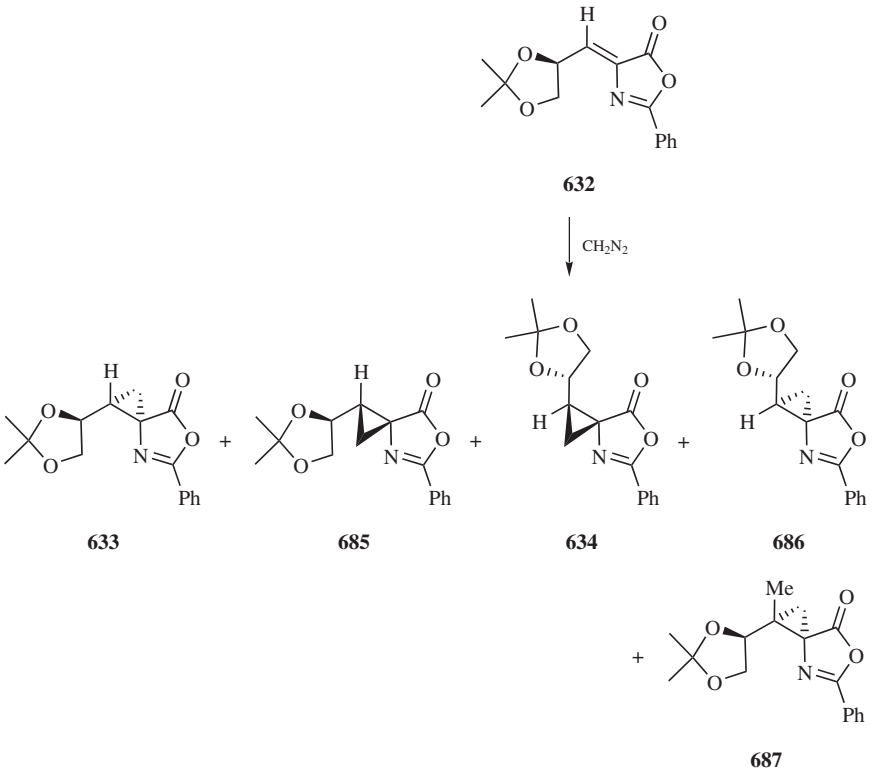
Scheme 7.215

If 4-(ethoxymethylene)-2-phenyl-5(4*H*)-oxazolone **403** is used as the dipolarophile, reaction with nitrile oxides yields cycloadducts **682** with reversed regiochemistry. Further reaction of **682** can then yield 4-aminoisoxazoline-4-carboxylic acids **683** or 4-amino-3-arylisoxazoles **684** depending on the reaction conditions (Scheme 7.215).[929]

7.4.3.4. Diastereoselective Cyclopropanations

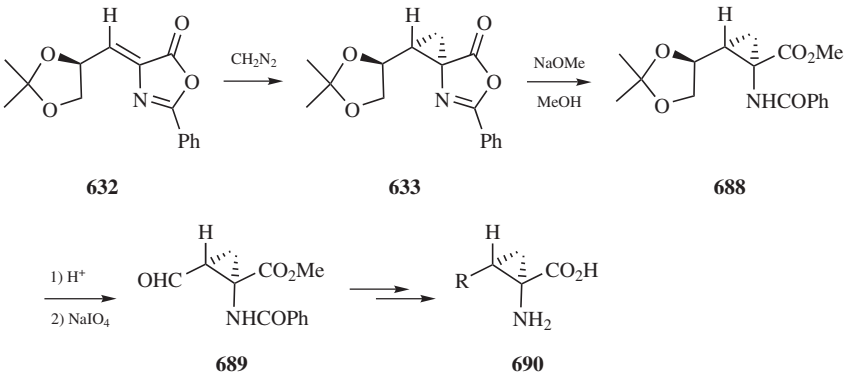
Cyclopropanation of the chiral oxazolone **632** derived from 1,2-*O*-isopropylidene-D-glyceraldehyde with diazomethane affords a mixture of five compounds.

These include the four possible diastereomeric spirocyclopropane derivatives **633**, **685**, **634**, and **686** resulting from methylene insertion into the double bond and a spirocyclopropane **687** derived from methylene insertion into the double bond of a homologated 5(4*H*)-oxazolone. The amount of **687**, the cis/trans selectivity and both the cis and trans diastereoselectivities depend on the reaction conditions. Use of nonpolar solvents avoids formation of **687**. In addition, the cis/trans selectivity and both cis and trans diastereoselectivities are very high such that the major compound **633** can be isolated in 75% yield (Scheme 7.216).[930]



Scheme 7.216

The stereochemical course of this reaction can be rationalized by considering attack of the 1,3-dipole on the $C_{\alpha\text{-Re}}$ face of the exocylic double bond. This process is in accord with the calculated energies of reactants, transition structures, and reaction intermediates at semiempirical and ab initio theory levels.[931] The major isolated compound **633** has been transformed into several interesting and enantiomerically pure cyclopropylamino acids **690** via the β-formyl intermediate **689** (Scheme 7.217).[932–934]



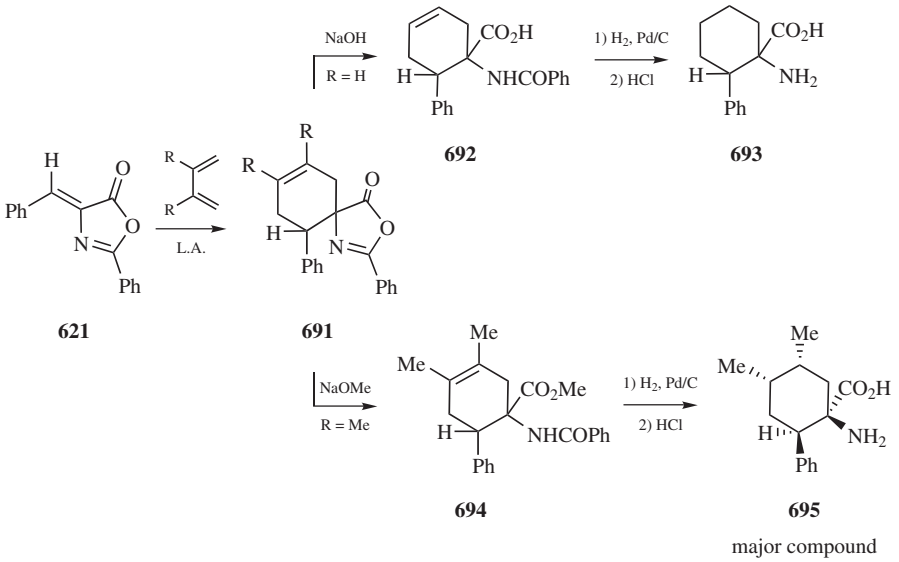
Scheme 7.217

7.4.3.5. Diels–Alder Reactions

Despite the importance and well-known reactivity of the exocyclic double bond of unsaturated oxazolones, this aspect has only recently been exploited in Diels–Alder reactions with dienes. Reaction of (*Z*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolone **621** with an excess of butadiene or 2,3-dimethylbutadiene in the presence of Lewis acid catalysts, gives the corresponding spirooxazolone adducts **691**.[935] Ring opening of **691** followed by hydrogenation and hydrolysis then leads to the synthesis of new constrained phenylalanine analogues. For example, methanolysis of the cyclohexene adduct **691** (R = Me) yields **694** that was hydrogenated to give a mixture from which the major diastereoisomer was isolated. Subsequent acid hydrolysis of this diastereoisomer then gave the corresponding stereoisomerically constrained phenylalanine analogue **695** (Scheme 7.218).

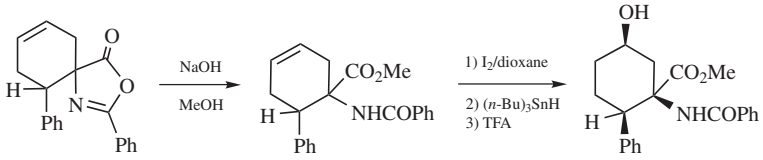
Racemic *cis*-1-amino-2-phenylcyclohexanecarboxylic acid **693** can be prepared by Diels–Alder reaction of (*Z*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolone **621** and butadiene in an analogous manner. Coupling *N-tert*-butyloxycarbonyl-L-proline with **693** yielded diastereomeric dipeptides that were separated chromatographically. The behavior of the individual dipeptides was studied as a means to effect β-turn modulation by such cyclohexane analogues of phenylalanine.[936]

In general, enantiomerically pure analogues of constrained phenylalanines with a cyclohexane skeleton have been obtained from the racemic butadiene Diels–Alder oxazolone adduct. The double bond was hydrogenated and both enantiomeric compounds were resolved using Obrecht's methodology[255,256] for resolution of quaternary amino acids. Following ring opening of the oxazolone with the (*S*)-phenylalanine cyclohexylamide, both diastereomeric dipeptides were separated and isolated by column chromatography. Subsequent hydrolysis then leads to (1*R*, 2*R*)- and (1*S*, 2*S*)-1-amino-2-phenylcyclohexane-1-carboxylic acid.[937]



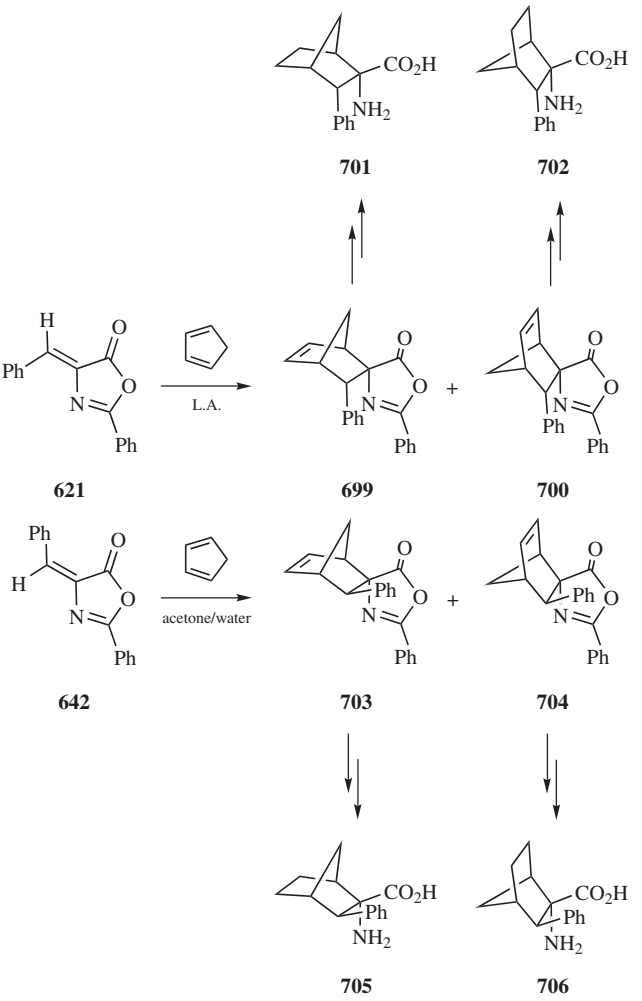
Scheme 7.218

Methanolysis of **696** followed by reaction with iodine, leads to syn γ-hydroxylation relative to the amide group. Further, deiodination and subsequent hydrolysis affords the γ-hydroxy-α-amino acid derivative **698**.[938] This interesting reaction sequence opens the way for the synthesis of hydroxy substituted constrained phenylalanines with defined stereochemistry (Scheme 7.219).



Scheme 7.219

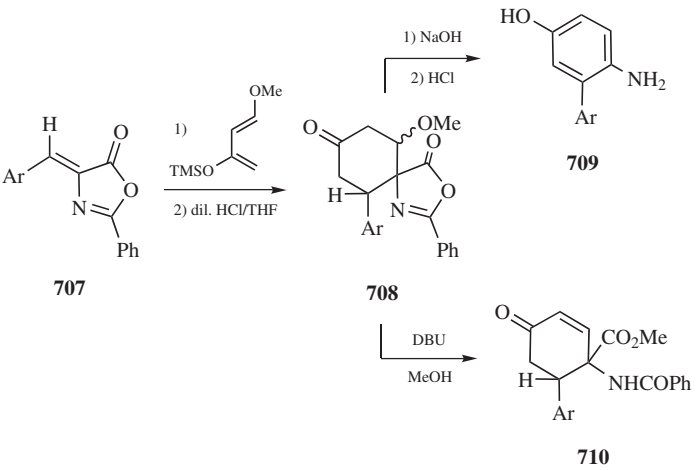
(*Z*)-4-Benzylidene-2-phenyl-5(4*H*)-oxazolone **621** also reacts with cyclopentadiene in the presence of a Lewis acid. In this case, the reaction leads to a mixture of cycloadducts **699** and **700** derived from endo and exo attack of the diene. The mixture of **699** and **700** can be separated chromatographically or simply by filtration after a typical iodolactonization reaction.[939,940] In contrast, (*E*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolone **642** gave considerable isomerization due to the presence of the Lewis acid under the same reaction conditions necessitating avoidance of these catalysts. Reaction of **642** and cyclopentadiene in mixtures of acetone–water gives the corresponding endo- and exo-cycloadducts **703** and **704** in very high yields after 6 days at room temperature.[940] Once again iodolactonization allows the separation of **703** and **704**. Each *endo*- and *exo*-cycloadduct was



Scheme 7.220

converted to the corresponding amino acid by hydrogenation of the double bond and subsequent hydrolysis (Scheme 7.220). This reaction sequence independently provides the four *d*,*l*-pairs of 2-amino-3-phenylnorbornane-2-carboxylic acids **701**, **702**, **705**, and **706** from (*Z*)- and (*E*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolones.

The Diels–Alder reaction of (*Z*)-4-arylidene-2-phenyl-5(4*H*)-oxazolone **707** and Danishefsky's diene is best conducted in toluene at reflux to produce both the endo and the exo stereoisomers of **708**.[941,942] Base treatment of the cycloadduct mixture promotes aromatization through spontaneous oxidative decarboxylation to give 3-aryl-4-benzamidophenols that are converted to 3-aryl-4-aminophenols **709** by acid



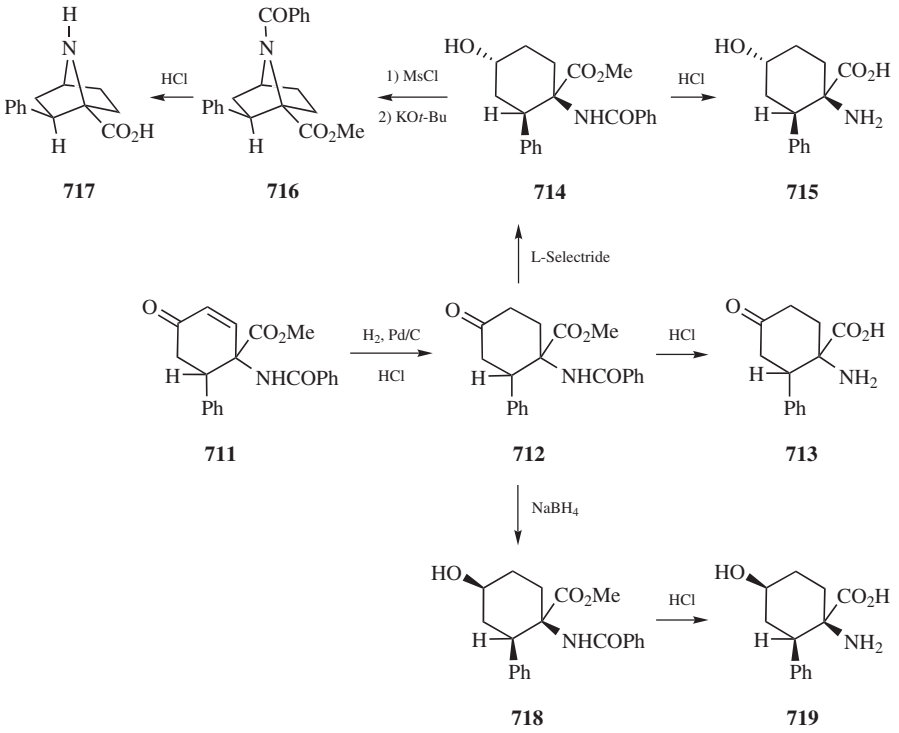
Scheme 7.221

hydrolysis.[942] On the other hand, treatment of the cycloadduct mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol leads to ring opening and elimination to produce enone **710**. Incorporation of an oxygenated functional group at C-4 renders **710** a valuable intermediate for the synthesis of δ-substituted conformationally restricted α-amino acids (Scheme 7.221).[941]

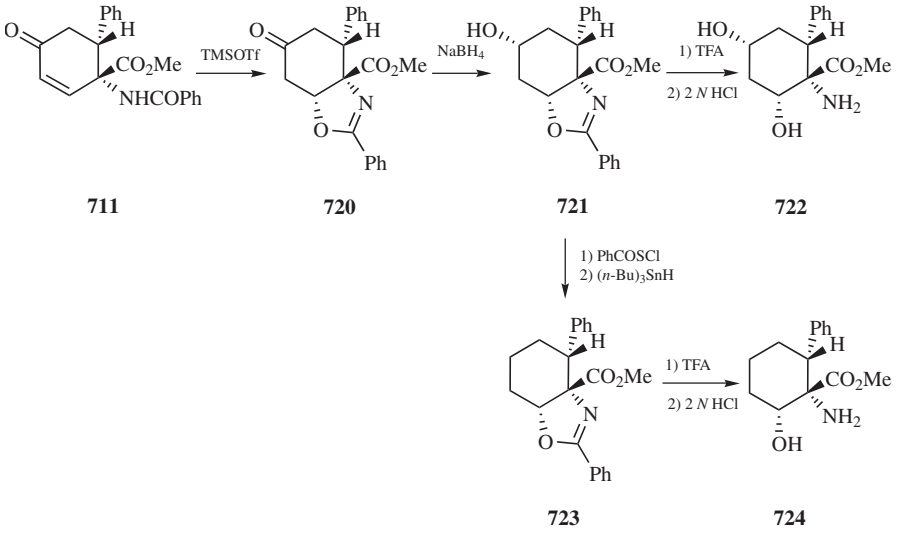
For example, hydrogenation of **711** followed by hydrolysis of the ester and benzamide gives 1-amino-4-oxo-2-phenyl-1-cyclohexanecarboxylic acid **713**.[941] Stereoselective reduction of the carbonyl group of **712** opens the way for the synthesis of new analogues of 4-hydroxy-1-aminocyclohexanecarboxylic acids **715** and **719** of defined stereochemistry.[943] In addition, **714**, the stereoisomer with trans disposed benzamide and hydroxy groups, undergoes cyclization and hydrolysis to produce 2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid **717**—a new constrained proline analogue (Scheme 7.222).[944]

Hydroxylation of **711** at C-2 can be achieved by an intramolecular conjugate addition of the benzamide to the enone system. The reaction takes place in high yield in the presence of a Lewis acid and affords direct hydroxylation with a syn relationship to the amide group via an intermediate 1,3-oxazoline (Scheme 7.223).[945]

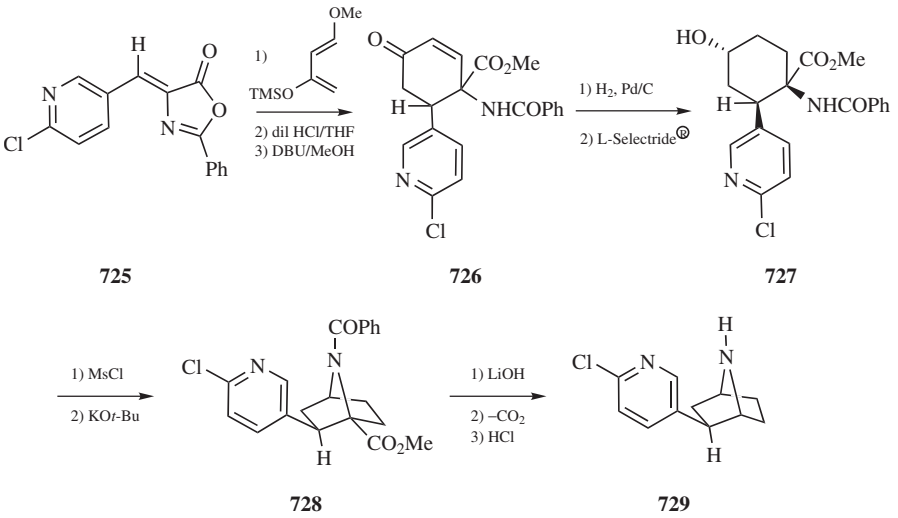
To extend this methodology, Diels–Alder reactions of several (*Z*)-4-arylidene (heteroarylidene)-2-phenyl-5(4*H*)-oxazolones with butadiene, 2,3-dimethylbutadiene, cyclopentadiene and Danishefsky's diene have been studied. This work demonstrated that the products depended on the nature of the aromatic ring and the diene used.[946] An interesting application of this methodology is the synthesis of racemic epibatidine **729**, a new alkaloid with a 7-azabicyclo[2.2.1]heptane skeleton that has proven to be a very potent analgesic. Preparation of **729** began with the Diels–Alder adduct **726** obtained from (*Z*)-4-[5′-(2′-chloropyridylmethylene)]-2-



Scheme 7.222



Scheme 7.223



725 **726** **727**

728 **729**

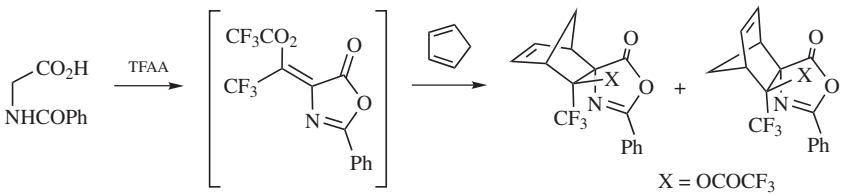
Scheme 7.224

phenyl-5(4*H*)-oxazolone **725** and Danishefsky's diene. Elaboration of **726** to **729** was accomplished readily as shown in Scheme 7.224.[947]

A number of other specific reactions have been studied. For example, Diels–Alder reactions of the unsaturated 5(4*H*)-oxazolone derived from piperonal with 2-*tert*-butyldimethylsilyloxy-1,3-butadiene, piperylene, 1-acetoxy-1,3-butadiene, and Danishefsky's diene have been described. In these cases, the results are variable and are dependent on the diene with poor yields often obtained even at high temperatures. Moreover, the stereochemical outcome of these reactions has not been determined.[948]

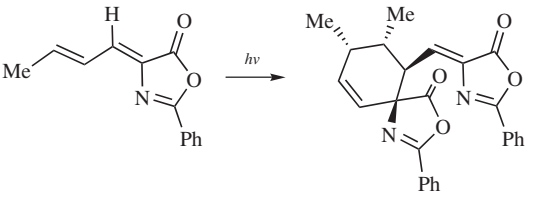
A tandem Dakin–West/Diels–Alder reaction sequence has been proposed to explain the (trifluoromethyl)bicyclo[2.2.1]heptane α-amino acid precursors **731** and **732** isolated from hippuric acid, trifluoroacetic anhydride, and cyclopentadiene (Scheme 7.225).[949]

Irradiation of 4-(but-3-enylidene)-2-phenyl-5(4*H*)-oxazolone **733** leads to the [4 + 2] adduct **734** derived from **733** acting as both a diene and a dienophile in a solid-state photo Diels–Alder reaction (Scheme 7.226).[950]



730 **731** **732**

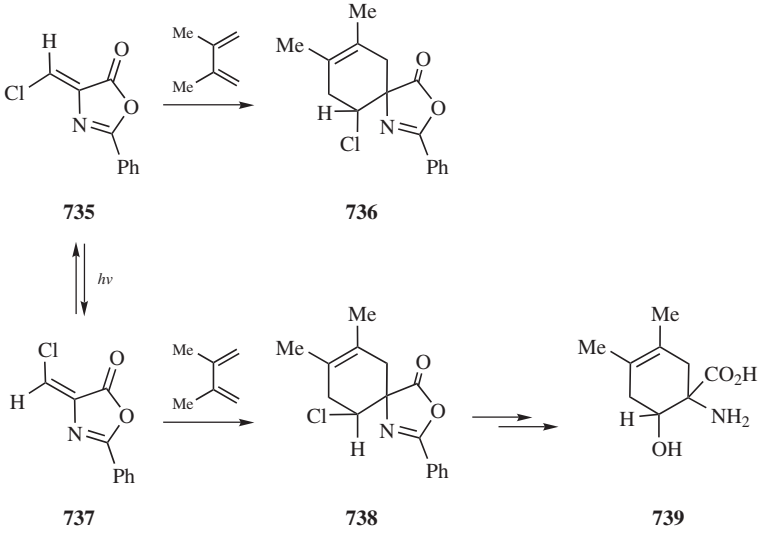
Scheme 7.225



733 **734**

Scheme 7.226

Diels–Alder reactions of 4-heteromethylene-5(4*H*)-oxazolones have been described. (*E*)-4-(Chloromethylene)-5(4*H*)-oxazolone **737** reacts with 2,3-dimethylbutadiene in the presence of ethylaluminum dichloride to afford the cycloadduct **738**. The cycloaddition reaction is characterized by high diastereoselectivity and occurs without appreciable isomerization of the dienophile. Further synthetic transformations of **738** yield 1-amino-3,4-dimethyl-6-hydroxy-cyclohex-3-enecarboxylic acid **739** (Scheme 7.227).[951] Examples of Diels–Alder reactions of acyclic dienes and unsaturated 5(4*H*)-oxazolones are shown in Table 7.50 (Fig. 7.61).



735 **736** **737** **738** **739**

Scheme 7.227

7.4.3.6. Diastereoselective Diels–Alder Reactions

(*Z*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethylene]-2-phenyl-5(4*H*)-oxazolone **632** can react as a dienophile in diastereoselective Diels–Alder reactions. Thus, **632** undergoes a thermally induced Diels–Alder reaction with cyclic dienes, for example, cyclopentadiene and cyclohexadiene, to afford a mixture of the four

TABLE 7.50. DIELS–ALDER ADDUCTS FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES AND ACYCLIC DIENES

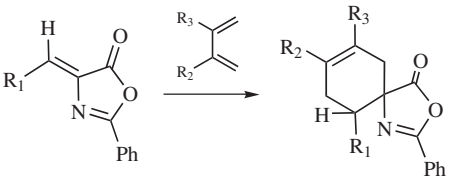
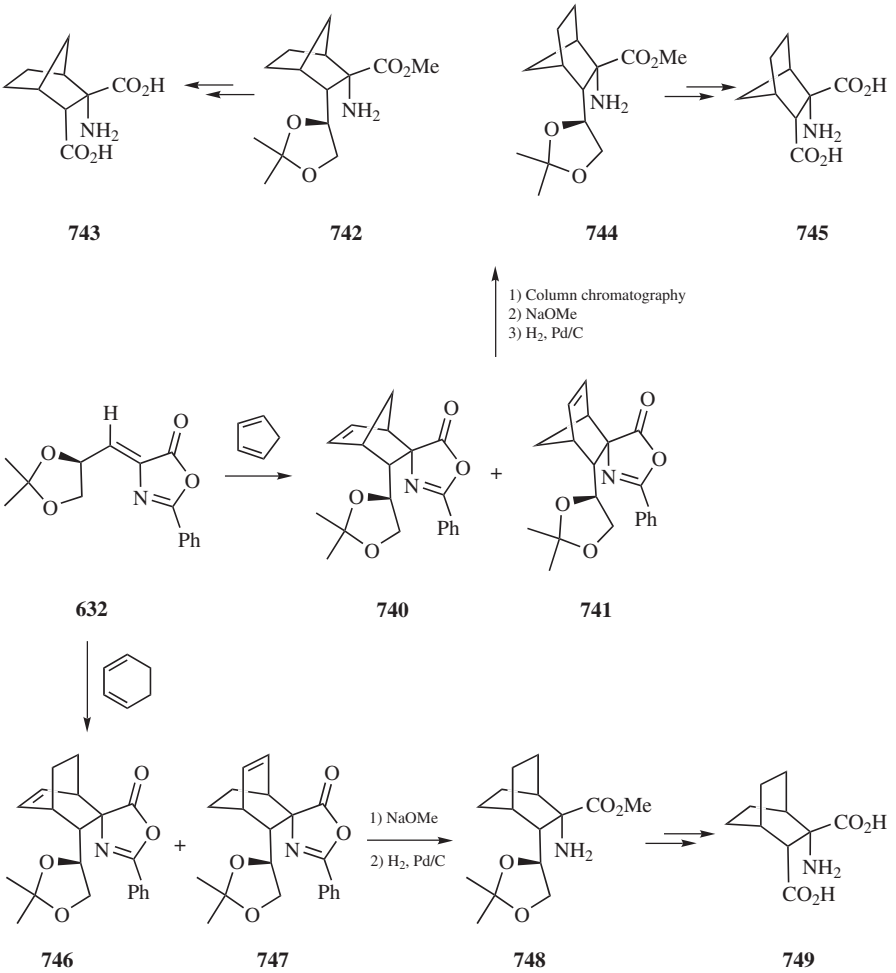


Figure 7.61

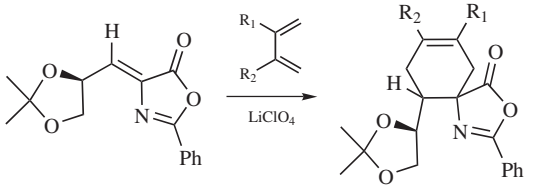
R_1	R_2	R_3	% Yield	Reference
Ph	H	H	64	935
Ph	Me	Me	91	935
4-ClC_6H_4	H	H	60	946
4-ClC_6H_4	Me	Me	75	946
2-$MeOC_6H_4$	H	H	57	946
2-$MeOC_6H_4$	Me	Me	100	946
Cl	Me	Me	70	951
Cl	Me	H	50	951
(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	H	H	92	432
(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	H	H	~100	432

possible Diels–Alder adducts.[430,432,952] In both reactions the diastereofacial selectivities are extremely high and the adduct mixture is mainly composed of one endo- and one exo-adduct. With cyclopentadiene exo-adducts **740** predominate slightly whereas reaction with cyclohexadiene shows a slight endo selectivity and endo-adduct **747** is the major compound. Solvent polarity does not have a noticeable effect on either the exo–endo selectivity or on diastereofacial selectivities at room temperature. However, if the reaction is performed at low temperature even better diastereofacial selectivities are obtained. Thermally, the reaction with cyclohexadiene is very slow although it can be accelerated by Lewis acid catalysts. Here, in some cases, the formation of cycloadducts from the (*E*)-oxazolone is also observed but use of lithium perchlorate can minimize these compounds. After isolation, the major cycloadducts have been transformed into a new class of conformationally constrained (*S*)-aspartic analogues **743**, **745**, and **749** as shown in Scheme 7.228.[953] Examples of Diels–Alder adducts from unsaturated oxazolones and cyclic dienes are shown in Table 7.51 (Fig. 7.62).

In contrast, **632** does not react or reacts very slowly in thermal Diels–Alder reactions with acyclic dienes such as butadiene, 2-methyl-1,3-butadiene, and 2,3-dimethylbutadiene. This behavior results in extensive formation of adducts derived from the (*E*)-oxazolone isomer. However, **632** and acyclic dienes do give good conversions in reasonable reaction times using lithium perchlorate, which also minimizes the formation of adducts derived from the (*E*)-oxazolone.[432] In all cases the diastereofacial selectivities are very high and additionally, reaction of **632** with 2-methyl-1,3-butadiene ($R_1 = Me$, $R_2 = H$) gives a high para-regioselectivity leading to **750** (Scheme 7.229).



Scheme 7.228



Scheme 7.229

TABLE 7.51. DIELS–ALDER ADDUCTS FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES AND CYCLIC DIENES

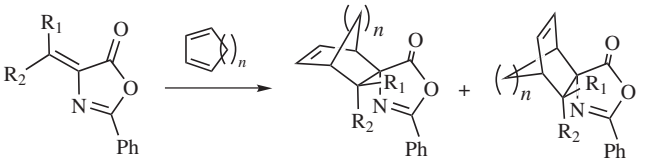


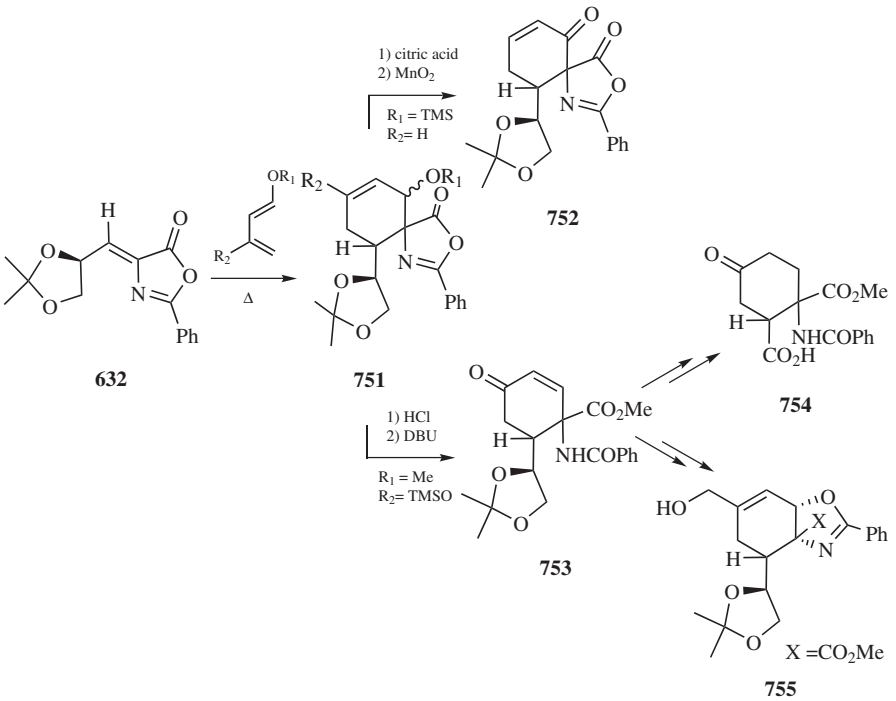
Figure 7.62

R_1	R_2	*n*	% Yield	Reference
H	Ph	1	95	939
Ph	H	1	95	939
H	4-ClC_6H_4	1	~100	946
H	4-$MeOC_6H_4$	1	50	946
H	fur-2-yl	1	70	946
H	thien-2-yl	1	71	946
H	(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	1	95	952
H	(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	2	~100	432

The chiral (*E*)-oxazolone derived from 1,2-*O*-isopropylidene-D-glyceraldehyde has also been used as a dienophile in the Diels–Alder reaction and, in this case, (*E/Z*) isomerization of the oxazolone can be avoided using heterogeneous catalysts that promote the synthesis of trans-adducts.[429]

The Diels–Alder reaction of **632** and activated dienes, such as 1-trimethylsilyloxy-1,3-butadiene and Danishefsky's diene, can be induced thermally. In both cases, adducts **751** derived from endo and exo addition are obtained. There was no endo–exo selectivity in this reaction using Danishefsky's diene. However, 1-trimethylsilyloxy-1,3-butadiene gave rise to a slight preference for exo attack and was a completely diastereoselective reaction. In both cases, further elaboration of **751** led to a single diastereoisomer, **752** and **753**, respectively, in good yields.[428,954,955] The cycloadduct from **632** and Danishefsky's diene has also been converted to highly functionalized and interesting analogues including the 1-benzamido-4-oxo-1,2-cyclohexanedicarboxylic acid 1-methyl ester **754**[955] and the tetrahydrobenzoxazole derivative **755** (Scheme 7.230; Table 7.52, Fig. 7.63).[954]

A model to rationalize the stereochemical course of the reaction has been proposed. Evaluation of the conformational energy curve derived from rotation around the (C_1—C_2) bond by AM1 semiempirical calculations shows only one deep minimum that points to the existence of a single conformation. In this conformation, which is supported by NMR studies, the $C_{\alpha\text{-Si}}$ side of the olefinic bond is shielded so that attack of the diene should come almost exclusively from the $C_{\alpha\text{-Re}}$ side as, indeed, has been observed in all cases.[952]



Scheme 7.230

TABLE 7.52. DIELS–ALDER ADDUCTS FROM REACTION OF UNSATURATED 5(4*H*)-OXAZOLONES AND ACTIVATED DIENES

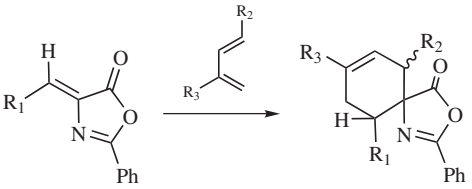
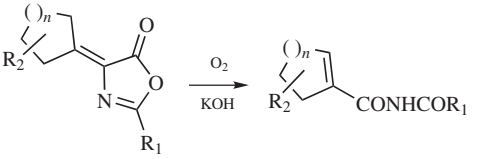


Figure 7.63

R_1	R_2	R_3	% Yield	Reference
Ph	MeO	TMSO	71	942
2-$NO_2C_6H_4$	MeO	TMSO	64	942
3-$MeOC_6H_4$	MeO	TMSO	52	942
2-$MeOC_6H_4$	MeO	TMSO	68	942
4-ClC_6H_4	MeO	TMSO	65	942
3,4-methylenedioxyphenyl	MeO	TMSO	100	948
3,4-methylenedioxyphenyl	H	TBSO	50	948
3,4-methylenedioxyphenyl	AcO	H	72	948
(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	TMSO	H	70	428
(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl	MeO	TMSO	90	955

7.4.4. Miscellaneous Reactions

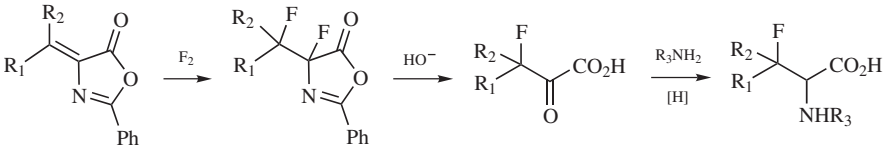
A number of other interesting reactions of unsaturated 5(4*H*)-oxazolones can not be readily classified among the characteristic reactions described in Sections 7.4.2 and 7.4.3. For example, 4-cycloalkylidene-2-phenyl(methyl)-5(4*H*)-oxazolones **756** are oxygenated in basic medium to give the cycloalkenyl imides **757**. This reaction involves a base-catalyzed isomerization, followed by oxygenation and subsequent fragmentation of an intermediate peroxide (Scheme 7.231).[956,957] Oxygen addition to 4-arylidene-5(4*H*)-oxazolones also leads to the corresponding ring-opened products.[957,958]



756 **757**

Scheme 7.231

Fluorination of unsaturated 5(4*H*)-oxazolones **758** affords the expected difluorinated derivatives **759**. Basic hydrolysis of **759** yields a β-fluoro-α-keto acid **760** that is reductively aminated to give an *erythro*-β-fluoro-α-amino acid **761** (Scheme 7.232).[959]



758 **759** **760** **761**

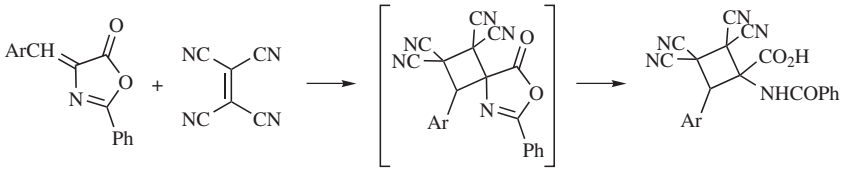
Scheme 7.232

Electrochemical reduction of 4-benzylidene-2-methyl-5(4*H*)-oxazolone to produce racemic *N*-acetylphenylalanine has been accomplished using lead and cadmium cathodes.[960]

The π-donor behavior of 4-arylmethylene-2-phenyl-5(4*H*)-oxazolones **762** with the π-acceptor tetracyanoethylene has also been studied. The initially formed charge-transfer complex is converted via intermediate **763** to a new compound for which a 2-aryl-1-benzamido-3,3,4,4-tetracyanocyclobutanecarboxylic acid **764** has been proposed on the basis of the NMR spectral data (Scheme 7.233).[961]

Charge-transfer complexes of 2-aryl-4-arylidene-5(4*H*)-oxazolones with di- and trinitrobenzene as π acceptors have also been prepared.[962]

Photoreactivities of some (*Z*)-unsaturated oxazolones **765** have been studied. The authors found that irradiation of **765** with a 450-W medium pressure mercury

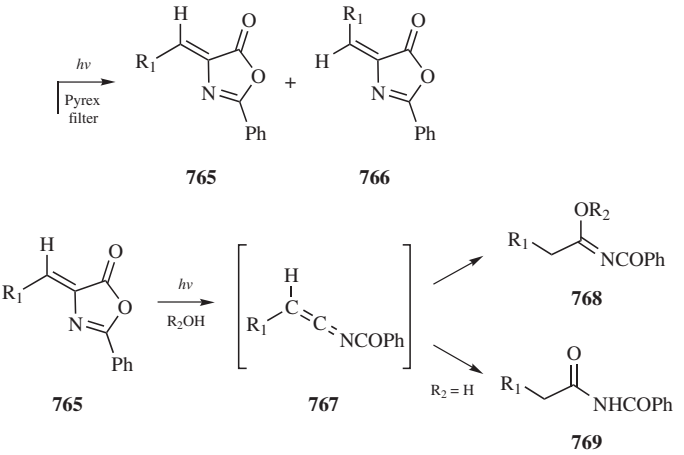


762 **763** **764**

Scheme 7.233

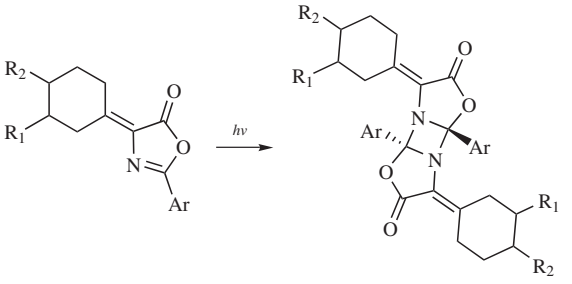
lamp and a Pyrex filter effected (*Z/E*) isomerization as the major reaction. In the absence of a Pyrex filter **765** decarbonylated to a ketenimine **767** that was trapped by protic solvents to afford *N*-acylimidates **768** and imides **769** (Scheme 7.234).[963,964]

Solid-state irradiation of 2-aryl-4-cycloalkylidene-5(4*H*)-oxazolones **770** effects photodimerization to produce centrosymmetric 1,3-diazetidines **771** in very high yields via an uncommon C—N cycloaddition (Scheme 7.235).[965]



765 **766** **765** **767** **768** **769**

Scheme 7.234



770 **771**

Scheme 7.235

Spectrometric determination of microgram levels of Zn and Cu has been achieved through complexation with unsaturated 5(4*H*)-oxazolones.[966,967] Unsaturated 5(4*H*)-oxazolones react with ethers under ultrasonic conditions to afford esters.[968] In addition, poly(5-imidazolones) with good thermal properties have been prepared from the bis(oxazolone) derived from terephthalaldehyde and primary amines[969] while new sensitizing dyes containing unsaturated 5(4*H*)-oxazolone moieties have been synthesized.[970]

7.4.5. Structural Analysis

Spectroscopic studies of series of unsaturated 5(4*H*)-oxazolones have been performed to correlate spectroscopic behavior with a characteristic substituent parameter. In this context, some authors have described little effect on the C=N and C=O IR frequencies in some 4-arylidene-2-phenyl-5(4*H*)-oxazolones by *p*-substituents on the C-4 aryl group.[971] However, other authors have reported a linear correlation of the IR frequency of the C=O group with substituent constants in some 4-arylidene-2-phenyl-5(4*H*)-oxazolones. This would be expected for a high transmission of the substituent effect through the ring.[972] Note that the carbonyl group has a two-component band in the 1768–1812-cm^{-1} region that is sensitive to conformational changes and solvent effects.[411]

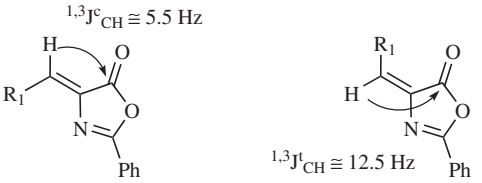
Studies of the UV–visible absorption spectra of 4-arylidene-2-phenyl-5(4*H*)-oxazolones show that the sign of the solvatochromism is substituent dependent in hydrogen-bonding solvents. On the other hand, in non-hydrogen-bonding solvents all substituents show a positive solvatochromism.[973]

Hydroxy-substituted oxazolones show an additional long-wavelength band in the visible absorption spectra in triethanolamine–acetone mixtures. Prototropic equilibrium constants at different temperatures were determined by detailed studies of this new absorption band.[973]

In measurements of absorption and fluorescence parameters for various oxazolones, the fluorescence quantum yields are usually <0.01. Oxazolones substituted with a naphthyl group or a *p*-(dimethylaminophenyl) group are exceptions.[974]

Rotational barriers about the exocyclic C—N bond of 2-aryl-4-[(*N*,*N*-dimethylamino)methylene]-5(4*H*)-oxazolones were determined by careful analysis of NMR spectral data for the methyl protons. A correlation was established between the energy barriers and Hammett's constants for substituents on the 2-aryl group. Electron-withdrawing substituents in the para position increase the barrier heights, whereas electron-donating substituents have the opposite effect.[975]

It must be borne in mind that two geometric isomers are possible for unsaturated 5(4*H*)-oxazolones. In a review published in 1975, Rao showed that in those cases where both geometric isomers had been prepared, different spectroscopic behavior was observed.[976] Different spectroscopic behaviors of the two geometric isomers have been studied further and, in some cases, the data allows configurational assignments to be made. More recent results on this subject follow.



772 **773**

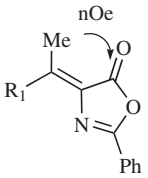
Figure 7.64. The $^{1,3}J_{CH}$ coupling constants for (*Z*)- and (*E*)-unsaturated 5(4*H*)-oxazolones.

NMR is a useful technique to determine the stereochemistry of double bonds and recently it has been applied to the configurational assignment of geometric isomers of some unsaturated 5(4*H*)-oxazolones. For example, geometric isomers can be distinguished in ^{1}H NMR by benzene-induced shifts. This technique was used to correctly assign the configuration of the (*E*, *Z*)- and (*E*, *E*)-geometric isomers of unsaturated 5(4*H*)-oxazolones prepared from (*E*)-cinnamaldehyde.[977]

The value of the long-range ^{13}C—^{1}H coupling constants between the olefinic proton and the C-5 carbonyl carbon in the fully coupled ^{13}C NMR (75 MHz) spectra can be used to assign the configuration of (*Z*)- and (*E*)-unsaturated 5(4*H*)-oxazolones because $^{1,3}J^{t}_{CH} > {}^{1,3}J^{c}_{CH}$. The coupling constants for (*Z*)-oxazolones **772** are ~5.5 Hz, whereas for (*E*)-oxazolones **773** the coupling constants are ~12.5 Hz.[978] For chiral oxazolones derived from 1,2-*O*-isopropylidene-D-glyceraldehyde these values are $^{1,3}J_{CH} = 5.5$ Hz for the (*Z*)-oxazolone and $^{1,3}J_{CH} = 12.5$ Hz for the (*E*)-oxazolone[930] (Fig. 7.64).

The stereochemistry of the double bond in 4-(α-arylethylidene)-2-phenyl-5(4*H*)-oxazolones can be determined by measurements of long-range heteronuclear selective carbon-13 {proton} nuclear Overhauser enhancements. In the (*Z*)-isomers **774**, large nuclear Overhauser enhancements are observed for the carbonyl carbon atom upon presaturation of the methyl group (Fig. 7.65). These effects are much smaller for the (*E*) isomers.[979]

Electron impact mass spectrometry is not effective to distinguish between the (*Z*) and (*E*) isomers of 4-benzylidene-2-phenyl-5(4*H*)-oxazolone and 4-(α-phenylethylidene)-2-phenyl-5(4*H*)-oxazolones because the spectra show only minor differences



774

Figure 7.65. Long-range heteronuclear selective carbon-13 {proton} nuclear Overhauser enhancements in (*Z*)-2-phenyl-4-(α-arylethylidene)-5(4*H*)-oxazolones.

in relative abundances of product ions.[980] Nevertheless, collisional spectroscopy has been applied successfully to isomer differentiation. Collisional mass spectra show clear differences for the (*Z*) and (*E*) isomers in the relative abundances of ions arising from competing fragmentations. For (*E*) isomers the $[M—CO]^+$ ion is the base peak in the spectrum, while for (*Z*) isomers the $PhCO^+$ ion is the base peak.[981]

The (*Z*) and (*E*) isomers of 4-benzylidene-2-phenyl-5(4*H*)-oxazolone and 4-(α-phenylethylidene)-2-phenyl-5(4*H*)-oxazolone also show different behavior as far as dipole moments are concerned. The solution conformation of the phenyl group relative to the degree of substitution and double bond stereochemistry has been studied by comparison of experimental and calculated values of dipole moments.[982]

The (*Z*) and (*E*) isomers of 2-aryl-4-arylidene-5(4*H*)-oxazolones show different chromatographic behavior.[983–985] In general, the relative chromatographic mobility of the (*Z*) and (*E*) isomers is dependent upon the oxazolone substituent and the chromatographic conditions.

Finally, X-ray analyses of several unsaturated oxazolones have been reported. In some cases an X-ray study has been used to determine the stereochemistry of the double bond, as for (*E*)-4-(but-2-en-1-ylidene)-2-phenyl-5(4*H*)-oxazolone,[950] (*Z*)-4-(1-ethoxyethylidene)-2-phenyl-5(4*H*)-oxazolone,[986] (*Z*)-(*N*-acetyl-4-[(2-phenyl-5-oxo-4(5*H*)-oxazolidine)methyl-^{2}*H*]-1*H*-imidazole,[987] or (*Z*)-4-(acetoxymethylene)-2-phenyl-5(4*H*)-oxazolone.[424] X-ray analyses of other 4-heteroarylmethylene-5(4*H*)-oxazolones have been reported and were directed to elucidating the structural features. For example, 4-(aminomethylene)-5(4*H*)-oxazolones show almost perfect planar arrangement of the oxazolone ring and the substituted amino group. This situation indicates the existence of extended conjugation involving the carbonyl group, the exocyclic double bond and the nitrogen atom.[505,507,988,989]

Other structural features of unsaturated-5(4*H*)-oxazolones can be deduced from crystallographic data including the effect on planarity of substituents on the exocyclic double bond. For example, 4-benzylidene-5(4*H*)-oxazolones show a completely planar conformation that favors strong electronic conjugation in both (*Z*)[990] and (*E*)[991] isomers. The same effect has been reported for other 4-arylidene-5(4*H*)-oxazolones.[992] In contrast, the presence of ortho substituents on the arylidene group force the aryl group to twist out of the plane, as seen in 2-phenyl-4-(2,4,6-trimethylbenzylidene)-5(4*H*)-oxazolone.[466]

The phenyl group of trisubstituted 4-benzylidene-5(4*H*)-oxazolones is nearly planar whereas the styryl moieties in (*Z*)-2-phenyl-4-(α-phenylethylidene)-5(4*H*)-oxazolone and *(Z)*-2-methyl-4-(α-phenylethylidene)-5(4*H*)-oxazolone show significant deviations from planarity.[993]

The X-ray crystal structure of *(Z)*-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-2-phenyl-5(4*H*)-oxazolone has been determined.[994] The analysis shows an almost planar disposition for the entire molecule with the exception of the dioxolane ring that adopts an envelope conformation. As such, the dioxolane ring is mainly situated on the *si*,*si* diastereotopic face of the olefinic bond, a situation that accounts for the observed diastereoselectivity in Diels–Alder reactions.

7.5. SUMMARY

Many aspects of the chemistry of the oxazolones have been considered in this chapter including the extensive use of these compounds as key intermediates for the synthesis of interesting and valuable products.

The synthesis of new heterocyclic structures with interesting pharmacological properties will be the objective of numerous research groups during the coming years. Oxazolones will be critical intermediates to prepare new specifically substituted heterocycles as chemists design molecules for improved pharmacological properties. For material scientists, polymerization reactions of oxazolones will be an important tool to prepare polymers with specific physical and chemical characteristics.

On the other hand, as synthetic equivalents of amino acids, unsaturated oxazolones are and will continue to be very important intermediates for the synthesis of new non-proteinogenic α-amino acids, particularly for the asymmetric synthesis of these compounds using diastereo- or enantioselective methodologies. In addition, the exocyclic double bond will continue as an important focus to build new constrained amino acids for the design of peptides with improved properties.

7.6 ADDENDUM

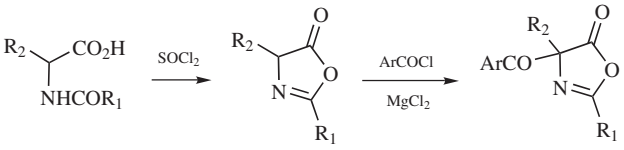
7.6.1. Saturated 5(4*H*)-Oxazolones (2-Oxazolin-5-ones)[995a]

7.6.1.1. Synthesis

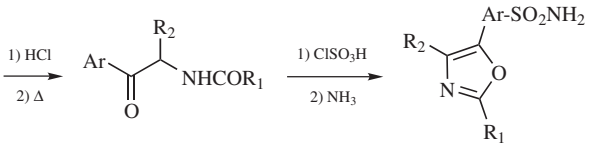
A number of recent papers have appeared in the literature related to the synthesis of saturated 5(4*H*)-oxazolones that were not yet covered in our contribution. 4-Acyl-2,4-dialkyl-5(4*H*)-oxazolones **776** have been obtained from *N*-acylglycines. Thus, cyclization of an *N*-acylglycine in the presence of thionyl chloride affords a monosubstituted 5(4*H*)-oxazolone **775**. Acylation of **775** with an aroyl chloride in the presence of magnesium chloride occurred at C-4 to produce **776**.[995b] Hydrolysis and decarboxylation of **776** gave the *N*-acylamino ketones **777** that are valuable intermediates to prepare oxazoles **778** (Scheme 7.236).

2-Benzyloxy-4-isopropyl(or 4-*tert*-butyl)-4-methyl-5(4*H*)-oxazolones **780** have been prepared from an *N*-benzyloxycarbonylamino acid **779** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC·HCl) as the cyclization agent (Scheme 7.237).[996] Treatment of **780** with tetramethylfluoroformamidinium hexafluorophosphate (TFFH) has shown that they are possible intermediates in the fluorination of α-methyl-α-alkyl amino acids by TFFH.

Several small peptides **781** possessing an N-terminal β-hydroxy acid have been obtained using the azirine–oxazolone method developed by Heimgartner.[997]

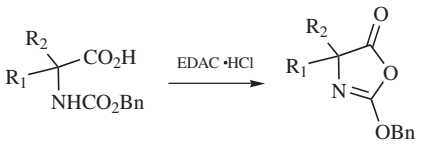


775 **776**



777 **778**

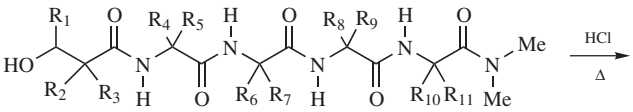
Scheme 7.236



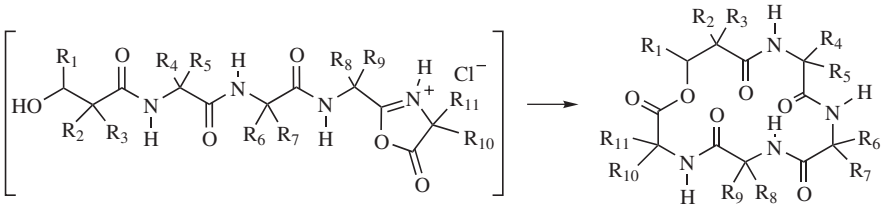
779 **780**

Scheme 7.237

Treatment of these compounds with $HCl_{(g)}$ leads to an intermediate 5(4*H*)-oxazolone **782** that, in absence of an external nucleophile, is captured intramolecularly and undergoes a ring enlargement to afford the corresponding cyclic pentadepsipeptides **783** (Scheme 7.238).



781



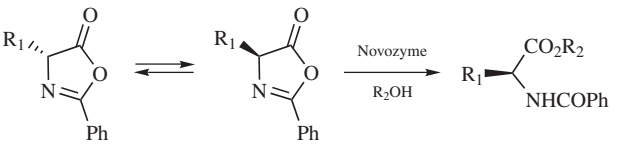
782 **783**

Scheme 7.238

7.6.1.2. Reactions

Some new ring-opening reactions of saturated 5(4*H*)-oxazolones have recently appeared in the literature. For example, the reaction of 4-substituted-4-(triphenylphosphonio)-5(4*H*)-oxazolones with methanol in the presence of DBU depends on the steric bulk of the substituent at C-4. The 5(4*H*)-oxazolones having a bulky C-4 substituent suffer ring opening whereas those having a small C-4 substituent undergo competitive substitution of the triphenylphosphonium group by methanol.[998]

Recently, *Candida antarctica* lipase B (Novozyme) has been used to develop an effective and versatile dynamic kinetic resolution of 2-phenyl-4-substituted-5(4*H*)-oxazolones **784**.[999] This catalyst tolerates a wide range of substrates that are transformed into optically active *N*-benzoylamino acid esters **785** in high yield and ee. The presence of a catalytic amount of an organic base usually increases the enantioselectivity of the reaction. However, optimal results are obtained in the absence of a base when tetrahydrofuran or acetonitrile are used as solvents (Scheme 7.239).



784 *ent*-**784** **785**

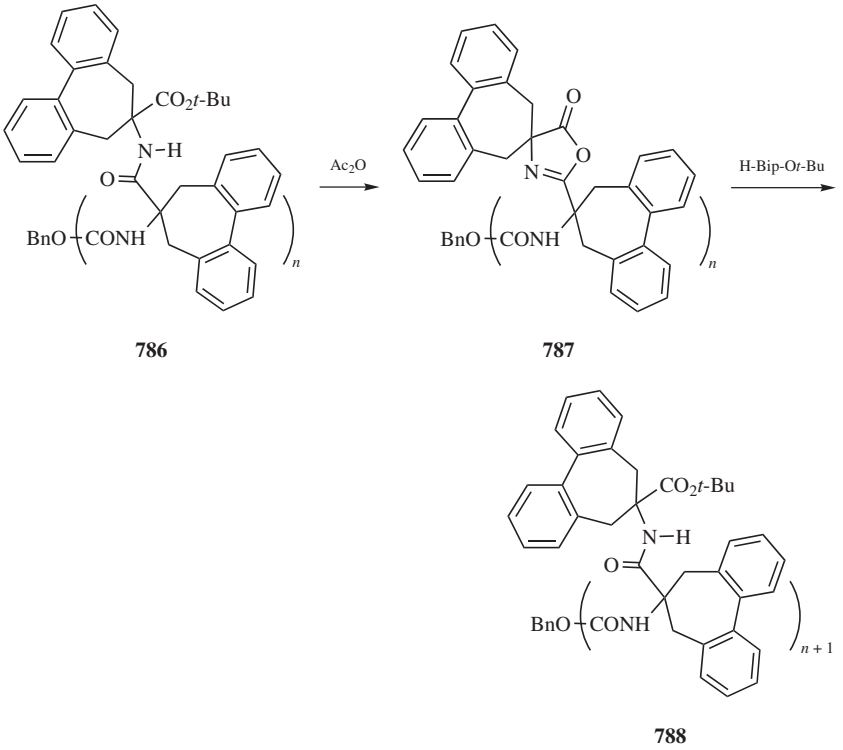
Scheme 7.239

Examples of homooligomer series of new model peptides that incorporate the α,α-disubstituted amino acid 2′,1′:1,2;1″,2″:3,4-dibenzocyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bip) have been obtained using 5(4*H*)-oxazolones **787** as key intermediates (Scheme 7.240).[1000]

N-Acylamino aromatic ketones **790** can be prepared by arylation of saturated oxazolones in the presence of Lewis acids. Cyclodehydration of **790** leads to 2,5-diaryloxazoles **791**. For example, saturated 5(4*H*)-oxazolones **789** from *N*-benzoylalanine or *N*-benzoylvaline undergo Friedel–Crafts arylation to afford substituted *N*-benzoylphenacylamines **790**. In the presence of $POCl_3$, **790** cyclizes to produce 5-aryl-2-phenyloxazoles **791** (Scheme 7.241).[1001]

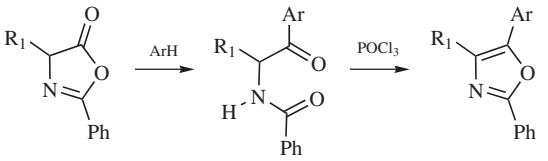
Dimerization of 4-monosubstituted-5(4*H*)-oxazolones **792** has been reported[1002] to occur in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) to give the corresponding 4,4′-bis(oxazolones) **793** (Scheme 7.242).

1,3-Dipolar cycloaddition of 4-arylmethyleneisoxazol-5-ones **794** and 2-methyl-4-phenyl-5(4*H*)-oxazolone **795** leads to pyrrole-3-carboxylic acids that have been isolated as hydroxamates **796**. The authors carried out this cycloaddition–nitrile oxide addition as a one-pot reaction (Scheme 7.243).[1003]



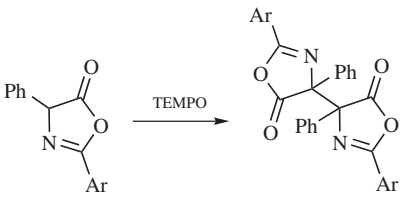
786 **787** **788**

Scheme 7.240



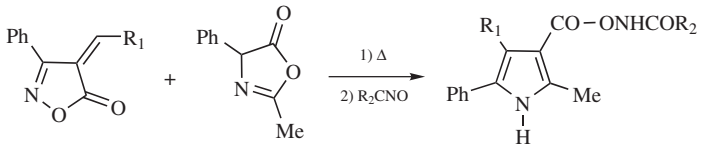
789 **790** **791**

Scheme 7.241



792 **793**

Scheme 7.242



794 **795** **796**

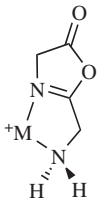
Scheme 7.243

Finally, new palladium(II) and platinum(II) complexes from 4-benzyl-4-methyl-2-phenyl-5(4*H*)-oxazolone or C_2 symmetric bis(oxazolone) ligands have been described.[1004]

7.6.1.3. Structural Analysis

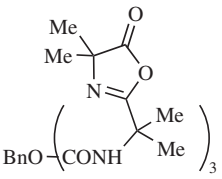
Molecular orbital calculations have been carried out on 2-(aminomethyl)-5(4*H*)-oxazolone, 2-(aminomethyl)-4-methyl-5(4*H*)-oxazolone, 2-phenyl-5(4*H*)-oxazolone, 4-methyl-2-phenyl-5(4*H*)-oxazolone and on the corresponding cations from protonation. The susceptibility to protonation of the different heteroatoms shows that in all cases protonation occurs preferentially at the ring nitrogen. In contrast, comparison of protonation and metalation of 2-(aminomethyl)-5(4*H*)-oxazolones reveals that lithium and silver cations simultaneously bind two heteroatoms, the amino group and either the ring nitrogen or oxygen. A metal cation coordinated with the two nitrogen atoms **797** is lowest energy isomer (Figure 7.66).[1005]

X-ray analysis of the saturated 5(4*H*)-oxazolone from *N*-benzyloxycarbonyl-$(Aib)_4OH$ **798** (Fig. 7.67) has been determined.[1006] The oxazolone ring is nearly planar. The conformation of the amino acid residue preceding the residue of the ring system is semiextended although the Aib_1 and Aib_2 residues are folded.



797

Figure 7.66. Proposed structure of **797** derived from metalation of 2-(aminomethyl)-5(4*H*)-oxazolones.



798

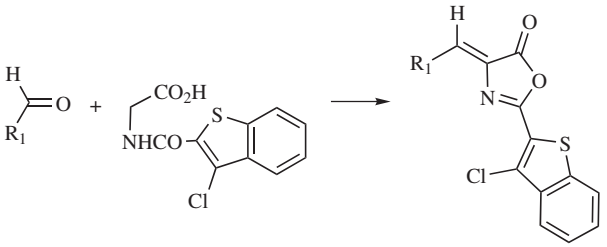
Figure 7.67. 798, A peptide oxazolone from *N*-benzyloxycarbonyl-(Aib)$_4$OH analyzed by X-ray diffraction.

7.6.2. Unsaturated 5(4*H*)-Oxazolones (2-Oxazolin-5-ones)[1007a]

7.6.2.1. Synthesis

Condensation of *N*-acylglycines with carbonyl compounds, the Erlenmeyer synthesis, continues to be exploited to prepare of a wide variety of unsaturated-5(4*H*)-oxazolones. The reaction is performed in the presence of a cyclodehydrating agent and recently bismuth(III) acetate has been evaluated in this capacity.[1007b]

Alternatively, unsaturated 5(4*H*)-oxazolones can be obtained from hippuric acid and a carbonyl compound or from the appropriate dehydroamino acid derivative using 3-(alkoxycarbonyl)benzotriazole-1-oxides as the cyclodehydrating agent.[1008] The Erlenmeyer reaction has also been used to prepare new 4-arylmethylene-2-[3-chlorobenzo[*b*]thien-2-yl]-5(4*H*)-oxazolones **800** from the appropriate *N*-acylglycine **799** and several aldehydes (Scheme 7.244).[1009] The pharmacological activity of these compounds as antibacterial and antiinflamatory agents has been studied.

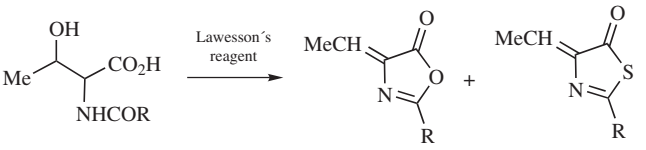


799 **800**

Scheme 7.244

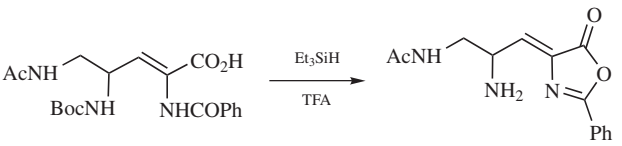
Reaction of *N*-acylthreonines with Lawesson's reagent [2,4-bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide] affords a mixture of unsaturated 5(4*H*)-oxazolones **801** and 5(4*H*)-thiazolones **802** (Scheme 7.245).[1010]

Deprotection of the α,β-didehydroamino acid **803** with TFA unexpectedly afforded the TFA salt of the 5(4*H*)-oxazolone **804** via an intramolecular cyclization (Scheme 7.246).[1011]



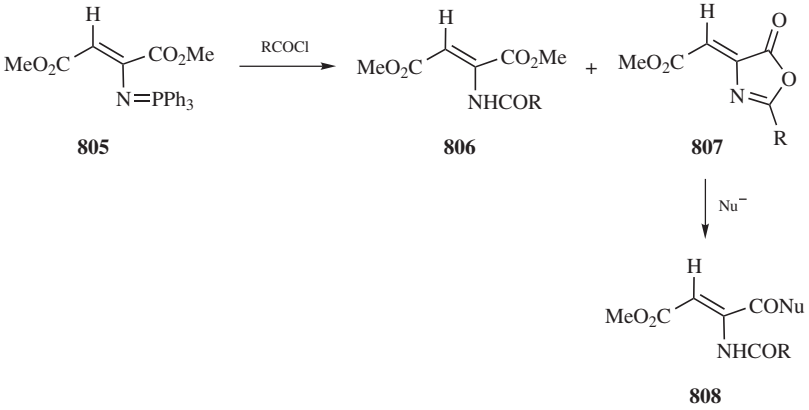
801 **802**

Scheme 7.245



803 **804**

Scheme 7.246

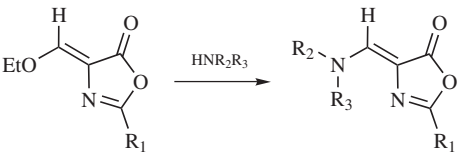


805 **806** **807** **808**

Scheme 7.247

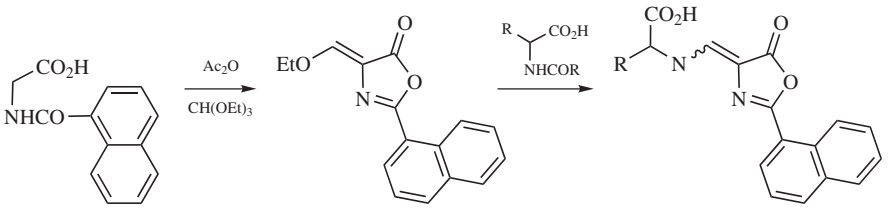
Acylation of *N*-vinyl phosphazenes **805** derived from dehydroaspartic acid esters gives *N*-acylated dehydroaspartic acid esters **806** as well as the corresponding unsaturated-5(4*H*)-oxazolones **807**. Subsequent nucleophilic ring opening of **807** affords *N*-acylated dehydroaspartic acid derivatives **808** (Scheme 7.247).[1012]

4-(Ethoxymethylene)-5(4*H*)-oxazolones are useful intermediates to prepare a variety of other 4-heteromethylene-5(4*H*)-oxazolones. In this context, 4-(ethoxymethylene)-5(4*H*)-oxazolones **809** were converted to 4-(aminomethylene)-5(4*H*)-oxazolones **810** by reaction with amines as shown in Scheme 7.248.[1013]



809 **810**

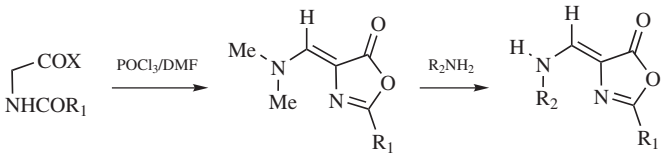
Scheme 7.248



811 **812** **813**

Scheme 7.249

For example, 4-(ethoxymethylene)-2-(1-naphthyl)-5(4*H*)-oxazolone **812**, an intermediate for fluorescent 4-(*N*-substituted-aminomethylene)-2-(1-naphthyl)-5(4*H*)-oxazolones **813**, was prepared from 1-naphthoylglycine and triethyl orthoformate.[1014] Reaction of **812** with amino acids gave the corresponding amino acid derivative **813** as a mixture of stereoisomers as shown in Scheme 7.249.



814 **815**

Scheme 7.250

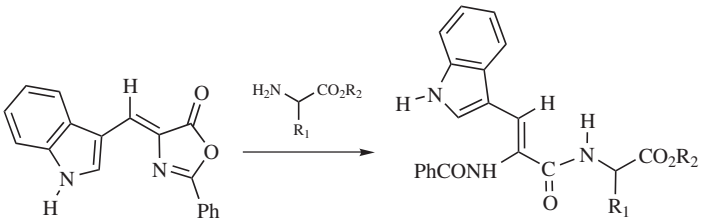
Reaction of *N*-acylamino acids with the Vilsmeier–Haack reagent leads to 2-alkyl-4-[(*N*,*N*-dimethylamino)methylene]-5(4*H*)-oxazolones **814**. The reactivity of these compounds with various nucleophiles has been studied. Primary alkylamines undergo amine exchange with **814** to afford 2-alkyl-4-[(alkylamino)methylene]-5(4*H*)-oxazolones **815** (Scheme 7.250).[1015]

7.6.2.2. Ring-Opening Reactions

The reactivity of unsaturated 5(4*H*)-oxazolones can be divided in two main categories according to the reaction site, ring-opening reactions, and reactions of the exocyclic double bond.

In the context of the nucleophilic ring-opening reactions, the mechanism of the reaction of 4-benzylidene-2-methyl-5(4*H*)-oxazolone with *n*-butylamine has been studied.[1016]

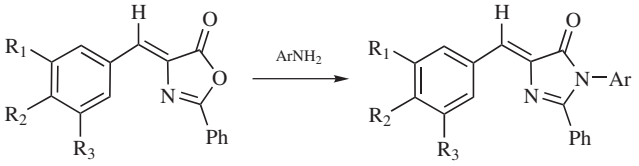
Synthetically, amino acid esters react with a 4-(indol-3-ylmethylene)-5(4*H*)-oxazolone **406** to afford dehydropeptides **816** as shown in Scheme 7.251.[1017]



406 **816**

Scheme 7.251

The synthesis and antimicrobial activity of new 1-aryl-4-arylmethylene-2-phenyl-5(4*H*)-imidazolones **818**, obtained from reaction of 4-arylmethylene-2-phenyl-5(4*H*)-oxazolones **817** and aromatic amines has been reported (Scheme 7.252).[1018]

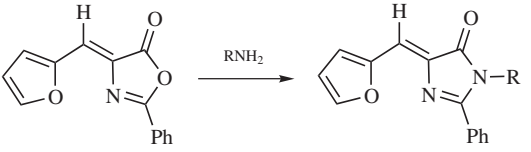


817 **818**

Scheme 7.252

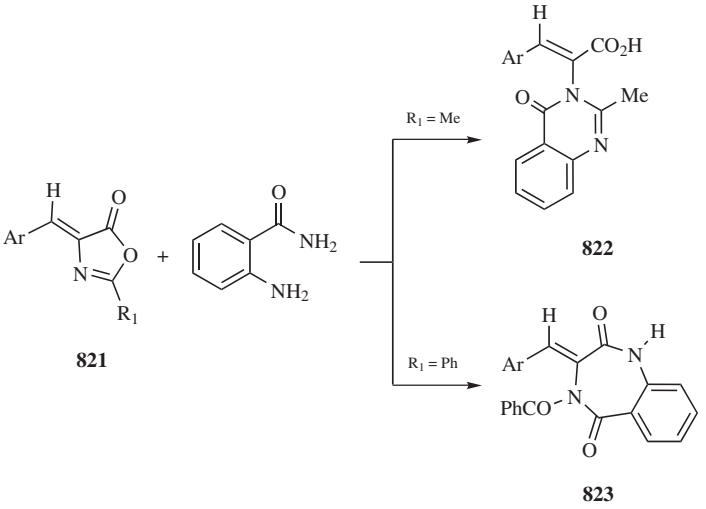
Similarly, 4-(furan-2-ylmethylene)-2-phenyl-1-substituted-5(4*H*)-imidazolones **820**, evaluated as antibacterial and antifungal agents, have been synthesized from the 4-(furan-2-ylmethylene)-2-phenyl-5(4*H*)-oxazolone **819** (Scheme 7.253).[1019]

Using 4-arylmethylene-2-phenyl-5(4*H*)-oxazolones as substrates and 2-amino-5-methyl-1,3,4-thiadiazoles as nucleophiles the synthesis of the corresponding



819 **820**

Scheme 7.253

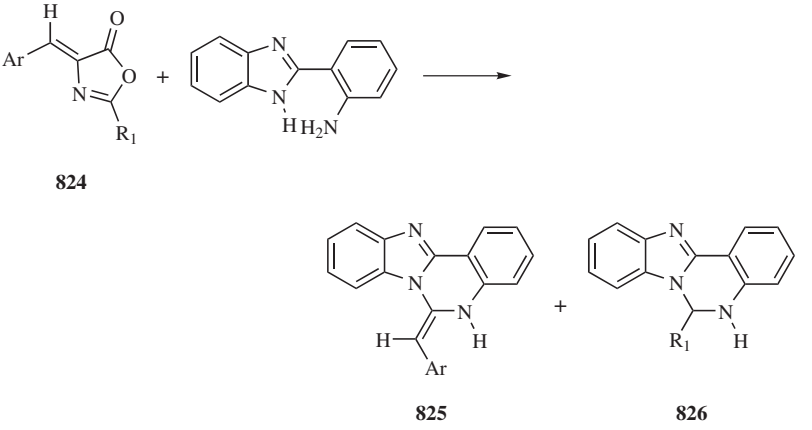


Scheme 7.254

imidazolones has been performed on solid support under microwave irradiation. Comparing the microwave-assisted reaction with conventional heating it was concluded that the microwave-assisted reaction occurs with a considerable rate enhancement and improved yields.[1020]

A new method for the synthesis of 4(3*H*)-quinazolinones **822** and 1,4-benzodiazepine-2,5-diones **823** from reaction of 4-arylmethylene-2-methyl- **821** ($R_1 = Me$) or 4-arylmethylene-2-phenyl-5(4*H*)-oxazolones **821** ($R_1 = Ph$) with *o*-aminobenzamide has also been reported (Scheme 7.254).[1021]

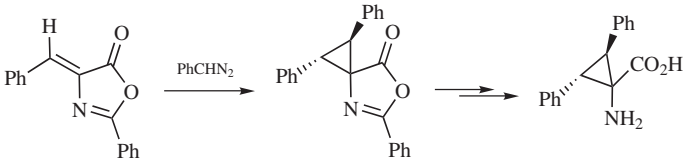
These same authors described the reaction of 4-arylmethylene-5(4*H*)-oxazolones **824** with 2-(*o*-aminophenyl)benzimidazole to produce a mixture of substituted benzimidazo[1,2-*c*]quinazolines **825** and **826** (Scheme 7.255).[1022]



Scheme 7.255

7.6.2.3. *Reactions Involving the Exocyclic Double Bond*

Recently, the cyclopropanation of (*Z*)-4-benzylidene-2-phenyl-5(4*H*)-oxazolone **621** with phenyldiazomethane was reported to give the spirocyclopropane, *rac*-**827** in very high yield.[1023] Subsequent ring opening and hydrolysis of *rac*-**827** generated *trans*-1-amino-2,3-diphenyl-1-cyclopropanecarboxylic acid, *rac*-**828** ($c_3$diPhe) (Scheme 7.256). This new, constrained phenylalanine analogue induces a γ-turn in the solid state when incorporated into model dipeptides. The enantiomers of the *N*-Boc (Boc = *tert*-butyloxycarbonyl) methyl ester of **828** have been resolved by HPLC.[1024]



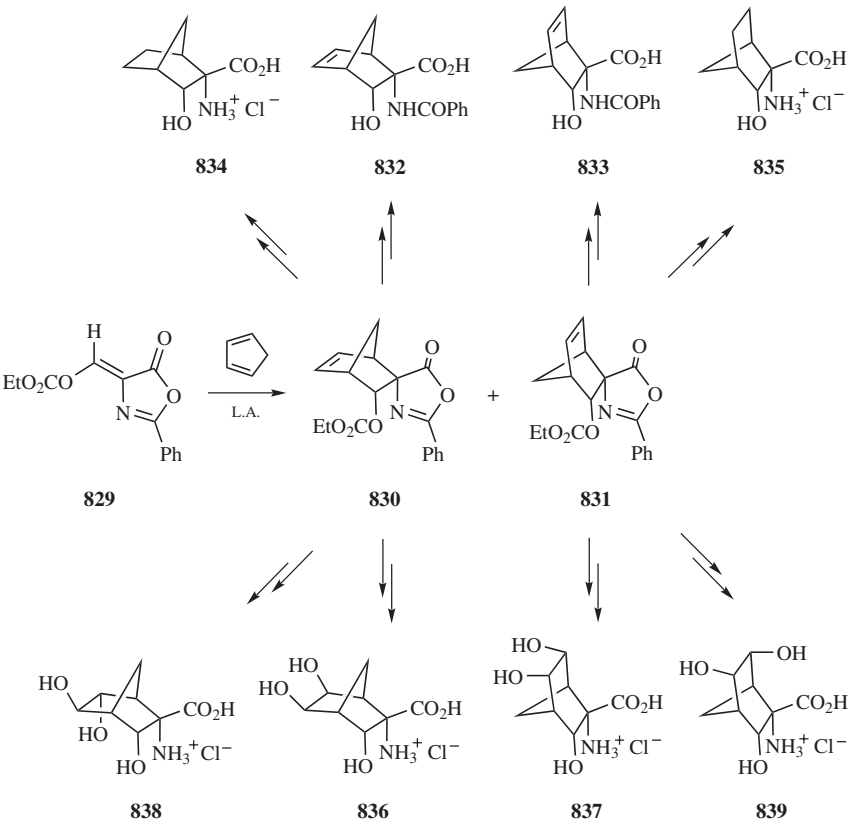
621 ***rac*-827** *rac*-**828**

Scheme 7.256

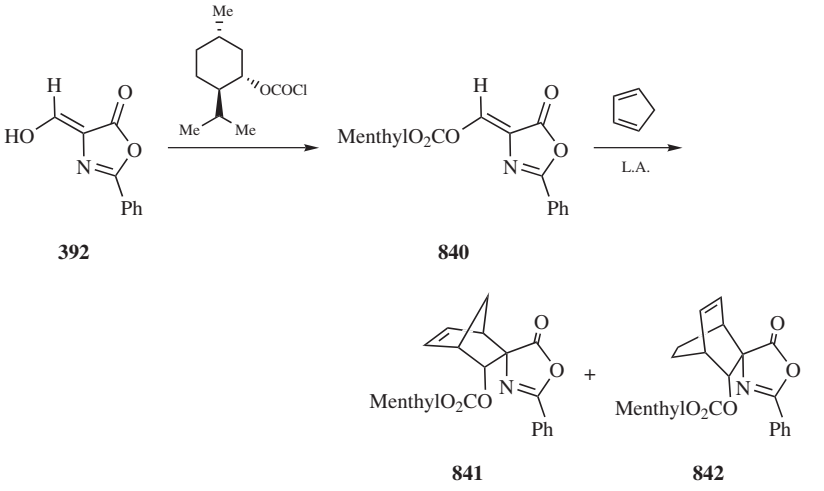
The use of 4-heteroarylmethylene- and 4-arylmethylene-5(4*H*)-oxazolones as dienophiles in the Diels–Alder reaction has been recently reviewed.[1025] More recently the reactivity of the exocyclic double bond of 4-(alkoxymethylene)-5(4*H*)-oxazolones with several dienes has been assessed. Reaction of 4-(methoxymethylene)-2-phenyl-5(4*H*)-oxazolone and 1,3-butadiene requires the presence of Et_2AlCl as a catalyst and even then the Diels–Alder cycloadduct is obtained in low yield.[1026] On the other hand, lithium perchlorate catalyzed Diels–Alder reaction between 4-[(ethoxycarbonyloxy)methylene]-2-phenyl-5(4*H*)-oxazolone **829** and cyclopentadiene is more efficient and affords a mixture of the corresponding *exo*-**830** and *endo*-**831** cycloadducts. These cycloadducts have been converted to 2-amino-3-hydroxynorbornenecarboxylic acid derivatives **832** and **833** or to 2-amino-3-hydroxynorbornanecarboxylic acids **834** and **835** after a series of careful transformations.[1027] In addition, **830** and **831** have been further elaborated to new conformationally constrained serine analogues, the polyhydroxy 2-aminonorbornanecarboxylic acids **836–839** as shown in Scheme 7.257.[1028]

Two asymmetric Diels–Alder approaches to analogues like **830** and **831** have been described. In the first case, chiral catalysts were employed for an enantioselective Diels–Alder reaction, but unfortunately, none of the chiral catalysts showed any enantioselectivity upon analysis of the reaction mixtures. Alternatively, a chiral oxazolone **840** incorporating a menthyl carbonate at C-4 was prepared and used as a dienophile with cyclopentadiene. In this case, the exo/endo ratio was 60:40 but no significant endo or exo diastereoselectivity was obtained (Scheme 7.258).[1029]

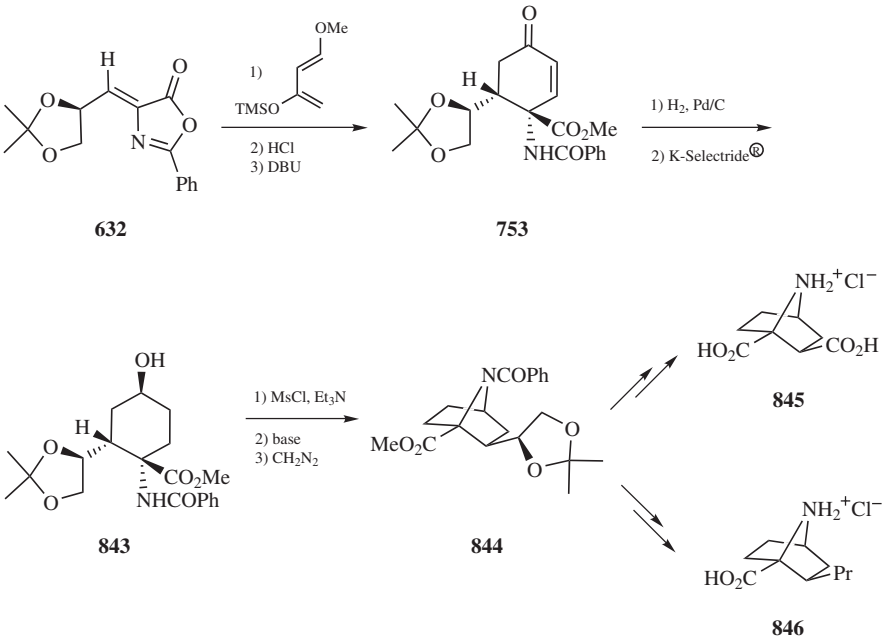
The chiral adduct **753**, obtained from the unsaturated oxazolone **632** derived from (*R*)-glyceraldehyde and Danishefsky's diene, has been conveniently elaborated to the valuable azabicyclic intermediate **844** used for the synthesis of



Scheme 7.257



Scheme 7.258



Scheme 7.259

enantiomerically pure 2-substituted 7-azabicyclo[2.2.1]heptane-1-carboxylic acids **845** and **846**, new conformationally constrained proline analogues.[1030] The key step in the construction of the 7-azabicyclo[2.2.1]heptane system was the intramolecular cyclization of the mesylate of **843** as shown in Scheme 7.259.

7.6.2.4. Structural Analysis

X-ray analysis of two new unsaturated oxazolones: 4-(ferrocenylmethylene)-2-phenyl-5(4*H*)-oxazolone[1031] and 2-phenyl-4-(4-toluidinomethylene)-5(4*H*)-oxazolone have recently been reported.[1032]

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CHAPTER 8

2-Oxazolines

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8.1. INTRODUCTION

The first oxazoline was prepared in 1884.[1] Despite an early review[2] in 1949 on the basic chemical properties of oxazolines, much of the research during the subsequent years focused on polymeric oxazolines. These polymeric oxazolines[3,4] found numerous industrial applications including surface protective coatings, as additives in gasolines and lubricating oils, as corrosion inhibitors, and as additives to textile chemicals. It was not until the early 1970s that the synthetic usefulness of oxazolines, in particular, those of 2-oxazolines (4,5-dihydro-1,3-oxazole), in organic synthesis was explored. In 1976, a review[5] of the chemistry of 2-alkyloxazolines firmly established that they are ideal reagents for the syntheses of chiral and non-chiral carboxylic acids, chiral alcohols, amino acids, aldehydes and ketones. Furthermore, the stability of the oxazoline ring to a wide variety of reagents other than mineral and Lewis acids have also made them ideally suited as a carboxylic protecting group.[6] During this period, it was also discovered that 2-aryloxazolines undergo electrophilic substitution, through directed ortho-lithiation

of the aromatic nucleus. On the other hand, aryloxazolines derived from *o*-methoxy or *o*-fluoro benzoic acids undergo nucleophilic substitution. The predictability of these reactions allowed aryloxazolines as intermediates for the construction of a variety of substituted benzenes and biphenyls, some of which can be difficult to obtain via classical methods. Extensive exploration of oxazolines in these areas continued, evidenced by the publication of a book chapter,[7] and reviews[8–14] devoted entirely to the use of oxazolines in asymmetric syntheses. Aside from such interests of oxazolines as synthetic intermediates, oxazolines are also found in a variety of marine natural products.[15,16] In particular, the oxazoline or dihydroxazole-containing lissoclinamide family of macrocyclic peptides has attracted much interest in their total syntheses.[17,18] Another important new development in oxazoline chemistry in the past 10 years or so was the application of these heterocycles as chiral ligands in a wide range of asymmetric catalytic processes.[19–23]

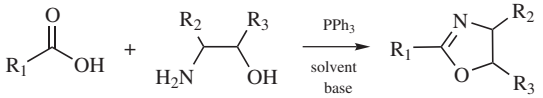
In this chapter, we will focus primarily on the literature from 1993 forward since Meyers has already comprehensively reviewed the period from 1985 to 1993–1994.[9] The discussion is divided principally into two sections, first reviewing the synthetic methods, followed by recent applications in organic syntheses. We will limit our discussion of oxazolines to synthetic applications in small molecules. In addition, given the frequency with which oxazolines are employed in chiral syntheses and natural product syntheses we have made every effort to reproduce the orientation of the oxazoline in the same manner as that reported in the original literature citation. Therefore, we have sacrificed some degree of structural consistency throughout this chapter. Benzoxazoles will not be included in this chapter. Finally, we will not be covering in detail chemical applications facilitated by bis(oxazoline) ligands in various metal-catalyzed asymmetric syntheses. The reader is referred to Chapter 9 for a comprehensive survey and review of this very important subject in asymmetric catalysis.

8.2. SYNTHESIS OF OXAZOLINES

Here, we will mention synthetic methods that are of general application. Because oxazolines are so often used as intermediates in synthesis, it is impossible to include every oxazoline that has been prepared. Instead, we will illustrate with examples the diversity of structures wherein the oxazoline ring structure is first constructed.

8.2.1. Oxazolines from Carboxylic Acids and Esters

The conceptually simple cyclodehydration of a carboxylic acid and a β-amino alcohol to an oxazoline requires harsh conditions of high temperature with azeotropic water removal (e.g., boric acid in refluxing xylene). Nonetheless, good yields of the oxazoline can be obtained if sensitive functionalities are absent.[24–26] A much milder approach has been developed by Vorbrüggen[27] where the reaction of carboxylic acids with β-amino alcohols is carried out in the



1

Scheme 8.1

presence of triphenylphosphine. The reaction is typically carried out in carbon tetrachloride (CCl_4), acetonitrile (MeCN), or hexachloroethane. The presence of a tertiary base such as triethylamine (Et_3N) or diisopropylethylamine (DIPEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or pyridine (Py), which is sometimes also used as a cosolvent, is absolutely essential to obtain a good yield of the oxazoline. Otherwise, β-chloro amide formation can be a serious side reaction. This one-pot procedure is applicable to both aliphatic and aromatic carboxylic acids. Phenols need not be protected. Selected examples are listed in Table 8.1 (Fig. 8.1; Scheme 8.1).[27–33]

A number of nonsteroidal antiinflammatory drugs (NSAID) wherein the carboxylic moiety is modified as an oxazoline have been prepared by this method.[27] These modified NSAIDs (Table 1, entries 4–6) exhibit antiinflammatory properties. However, they are less potent than their original counterparts. Importantly, they did not reduce stomach ulceration at the efficacious dose, and therefore did not present any advantage over the original NSAID.

TABLE 8.1. OXAZOLINES FROM CARBOXYLIC ACIDS

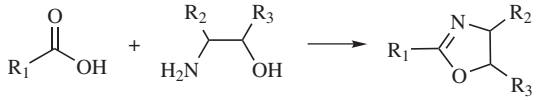


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Figure 8.1

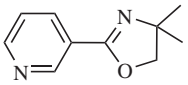
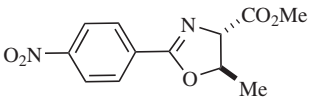
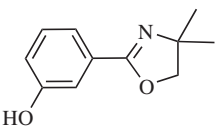
Entry	Product	% Yield	Reference
1		74	27
2		83	27
3		68	27

TABLE 8.1 (*Continued*)

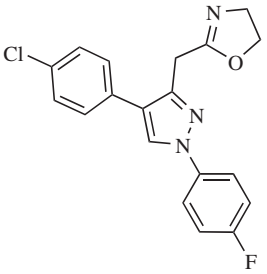
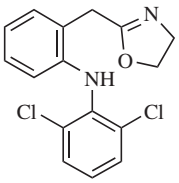
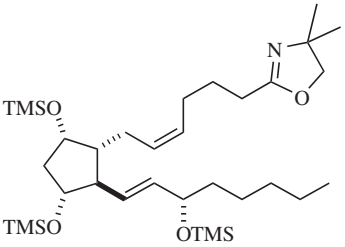
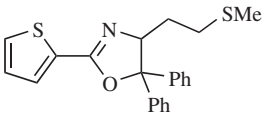
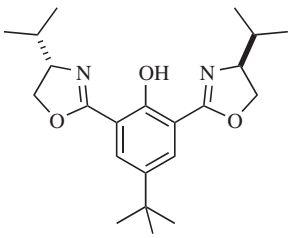
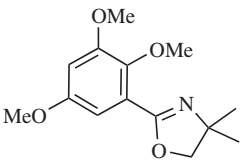
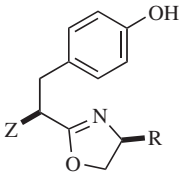
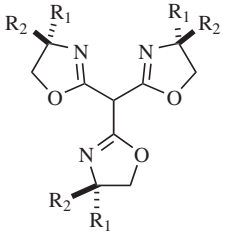
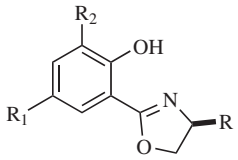
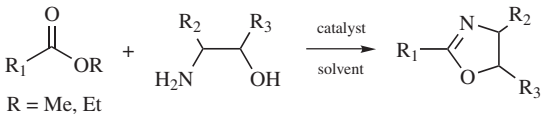
Entry	Product	% Yield	Reference
4		72	27
5		51	27
6		83	27
7		62	28
8		53	29
9		87	30

TABLE 8.1 (*Continued*)

Entry	Product	% Yield	Reference
10		R = H, Z = Bn, 60–70 R = H, Z = NHTs, 44	31
11		R_1 = H, Ph, 4-MeO–Ph R_2 = H, *i*-Pr, 4-CF_3–Ph 20–45 (4 examples)	32
12		R = Ph, *t*-Bu R_1 = NO_2, MeO R_2 = H, NO_2 19–67 (6 examples)	33

Aliphatic and aromatic carboxylic esters are also directly converted, in one step, to oxazolines using amino alcohols. As expected, harsh conditions are required for this transformation. Typically, the reaction is performed in refluxing xylene in the presence of catalytic quantities of a Lewis acid such as dibromo-[34] or dichlorodimethylstannane.[35] More recently, lanthanide chloride and samarium chloride have also been reported as useful catalysts for this one-pot transformation in refluxing toluene.[36] Representative examples are shown in Table 8.2 (Scheme 8.2).[34–36]

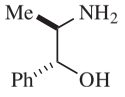
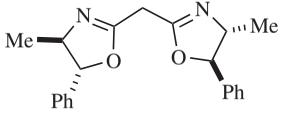
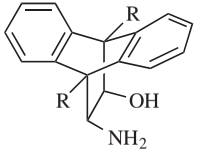
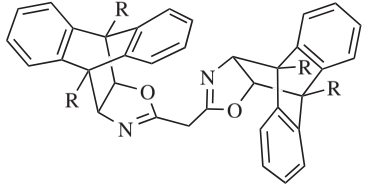
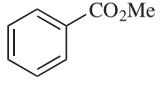
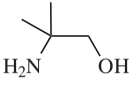
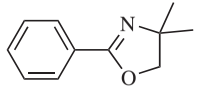
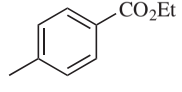
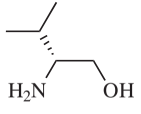
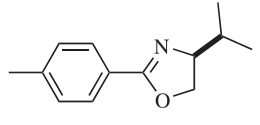
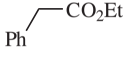
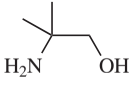
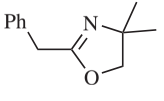
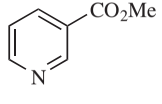
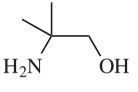
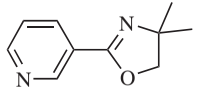
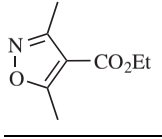
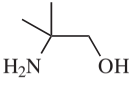
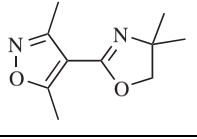
Isatoic anhydride undergoes a one-step conversion to *o*-aminophenyloxazolines **2** with amino alcohols via elimination of carbon dioxide.[37] The reaction is carried out in the presence of kaolinitic clay in refluxing chlorobenzene. These *o*-aminophenyloxazolines, in particular, those derived from chiral amino alcohols,

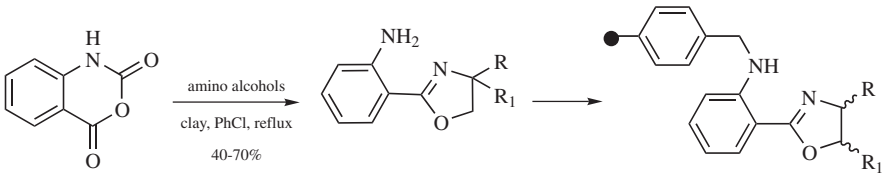


1

Scheme 8.2

TABLE 8.2. OXAZOLINES FROM CARBOXYLIC ESTERS AND AMINO ALCOHOLS

Ester	Amino Alcohol	Product	Catalyst (% Yield)	Reference
			Me_2SnBr_2 (52)	34
			Me_2SnCl_2 R = H, (97) R = Me, (94)	35
			$LaCl_3$ (82)	36
			$SmCl_3$ (54)	36
			$LaCl_3$ (75)	36
			$LaCl_3$ (64)	36
			$SmCl_3$ (82)	36



2 **3**

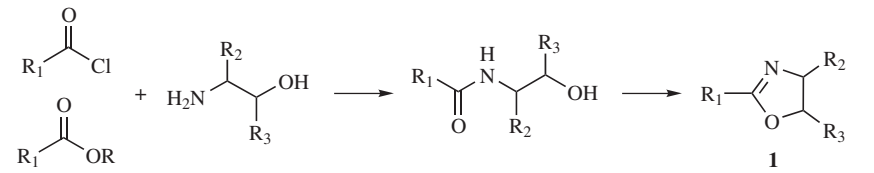
R_1 = *i*-Pr (*R*), *i*-Bu (*R*), Bn (*R*), Ph (*S*), Et(*S*); R = H;
R = R_1 = H, Me

Scheme 8.3

can be further linked to chloromethylated styrene-divinylbenzene polymer. The resulting chiral polymers **3** may find use in heterogeneous asymmetric catalytic reactions (Scheme 8.3).

8.2.2. Oxazolines from β-Hydroxy Amides

A popular approach to prepare oxazolines involves the intramolecular cylization of a β-hydroxy amide, through activation of the —OH group as a leaving group. This two-step process is widely applicable for the syntheses of structurally diverse analogues, including 2-, 4-, and 5-monosubstituted oxazolines, as well as multiply substituted oxazolines. The requisite β-hydroxy amides, commonly prepared via acylation of the appropriate amino alcohol with acid chlorides, anhydrides, and via classical peptide coupling methodology, can also be prepared through amidation with an amino alkoxide (from an amino alcohol and sodium hydride or *n*-BuLi[38–40] or methyl aluminum).[41] Naphthol has been converted to the corresponding triflate and undergoes CO insertion with valinol to give the corresponding hydroxy amide.[42] The most commonly used reagents to effect this cyclodehydration will be discussed in the following sections (Scheme 8.4).



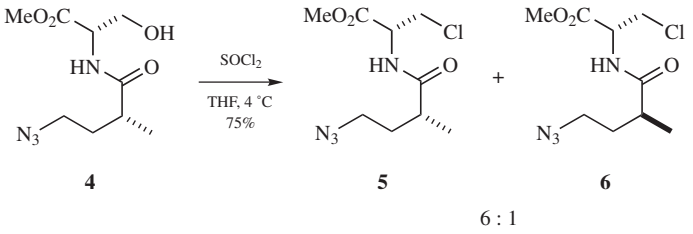
R = H, Me, Et

1

Scheme 8.4

8.2.2.1. Thionyl Chloride

Thionyl chloride ($SOCl_2$) has often been used as a dehydrating agent for primary, secondary, as well as tertiary β-hydroxy amides. With primary hydroxyl amides, the intermediate β-chloro amide can usually be isolated, which will then

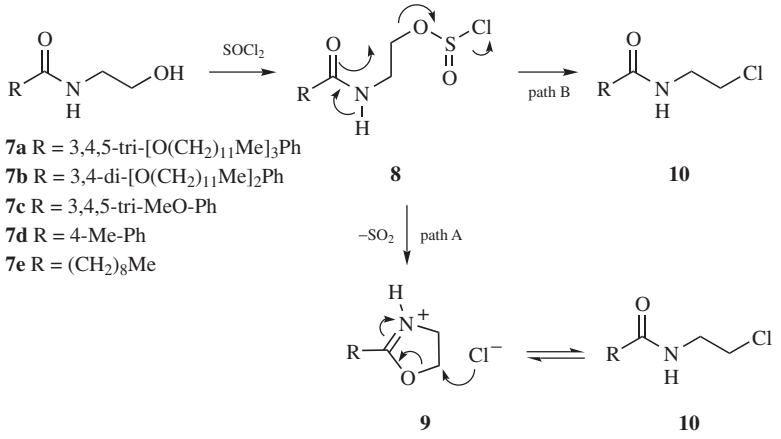


Scheme 8.5

require treatment under basic conditions to complete cyclization to the oxazoline in a separate step. Silver triflate has also been used for this purpose.[43] Representative examples are shown in Table 8.3 (Fig. 8.2).[29,30,39,40,42,44–67]

In their synthesis of (+)-calyculin A and (−)-calyculin B, Smith and co-workers observed partial epimerization when the β-hydroxy amide **4** was reacted with $SOCl_2$ despite the mild reaction conditions, 4 °C in tetrahydrofuran (THF).[43] The mechanism of this epimerization was not discussed (Scheme 8.5).

Oxazoline hydrochlorides can sometimes be isolated directly from the reaction.[68–70] Holerca and Percec investigated the mechanism for oxazoline ring formation of several primary β-hydroxy amides with $SOCl_2$ by nuclear magnetic resonance (NMR).[71] Oxazoline formation was extremely fast with amides **7a–c** and the reaction was complete within minutes at 23 °C. With amide **7e**, the reaction is sufficiently slow so that reaction intermediates can be monitored. Thus, they observed that formation of **10** was preceded by the chlorosulfite **8**. The results of this study suggest that pathway A predominates for aryl groups substituted with electron-donating groups because of the enhanced reactivity of the carbonyl group due to resonance stabilization. In these instances, β-chloro amide formation occurs via a slow chloride substitution at the 5-position of the oxazolinium ring. The proposed mechanism clarifies situations when a two-step process is needed for oxazoline ring formation using thionyl chloride (Scheme 8.6).



Scheme 8.6

TABLE 8.3. OXAZOLINES FROM PRIMARY β-HYDROXY AMIDES AND $SOCl_2$

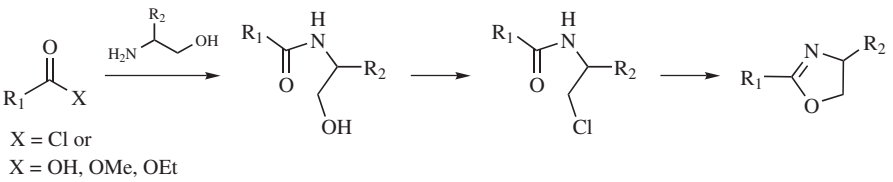


Figure 8.2

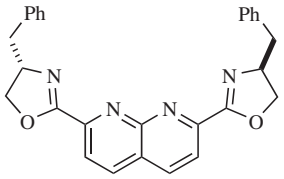
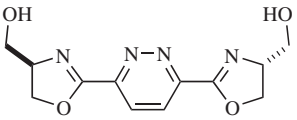
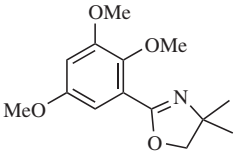
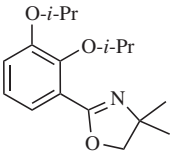
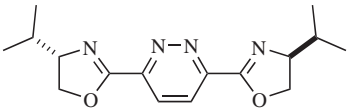
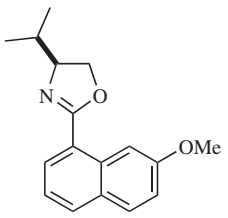
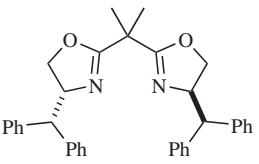
Oxazoline	Conditions	Comments	Reference
	1. $SOCl_2$, DCE, reflux; 2. NaOH, MeOH, THF, reflux 43%	Ligand preparation	29
	1. $SOCl_2$, DCE, reflux; 2. NaOH, MeOH, THF, reflux 71%	Ligand preparation	29
	$SOCl_2$; 100%	Intermediate for the synthesis of actinoidic acid, degradation product of vancomycin	30
	$SOCl_2$, rt 83% (from ester)	Intermediate for the total synthesis of dengibsin	39
	1. $SOCl_2$, CH_2Cl_2, rt; 2. *t*-BuOK, CH_2Cl_2 44% (from ester)	Ligand preparation	40
	1. $SOCl_2$, CH_2Cl_2, 0 °C; 2. MeCN, H_2O, K_2CO_3, reflux 74% (from β-trifloylamide)	Intermediate for the total synthesis of (−)-aphanorphine and (−)-eptazocine	42
	1. $SOCl_2$, reflux; 2. NaOH, MeOH, 40 °C 40%	Ligand for asymmetric Diels–Alder reaction	44

TABLE 8.3 (*Continued*)

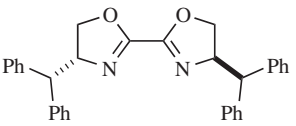
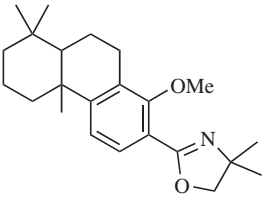
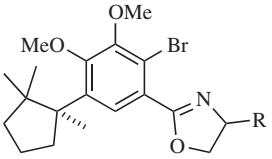
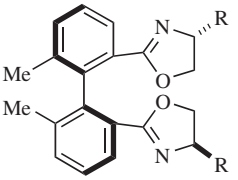
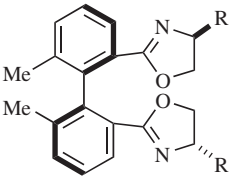
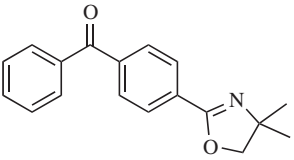
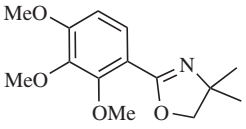
Oxazoline	Conditions	Comments	Reference
	1. $SOCl_2$, toluene, reflux; 2. NaOH, MeOH, reflux 80%	Ligand for asymmetric Diels–Alder reaction	44
	1. $SOCl_2$, rt; 2. 10% NaOH 70%	Intermediate for the total synthesis of (±)-veadeiroic acid	45
	1. $SOCl_2$, CH_2Cl_2, rt; 2. 20% K_2CO_3, MeCN, reflux R = *t*-Bu (*S*); 82% R = Ph (*S*); 83% R = *i*-Pr (*S*); 85% R = Et (*S*); 77% R = Me (*S*); 98% R = *t*-Bu (*R*); 85%	Intermediates for the total syntheses of (−)-herbertenediol, (−)-mastigophorene A, and (−)-mastigophorene B	46
	1. $SOCl_2$, CH_2Cl_2, rt; 2. K_2CO_3, MeCN/H_2O, reflux R = Ph, 86% R = *t*-Bu, 65% R = Bn, 80% R = *i*-Pr, 71%	Ligand for asymmetric allylic oxidation	47
	1. $SOCl_2$, CH_2Cl_2, rt; 2. K_2CO_3, MeCN/H_2O, reflux R = Ph, 74% R = *t*-Bu, 62% R = Bn, 79% R = *i*-Pr, 60%	Ligand for asymmetric allylic oxidation	47
	$SOCl_2$ 75%		48
	1. $SOCl_2$, 96%	Intermediate for the total synthesis of (*S*)-gossypol	49

TABLE 8.3 (*Continued*)

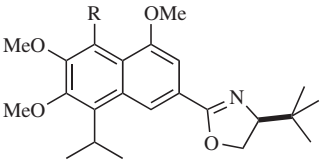
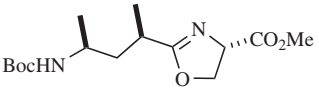
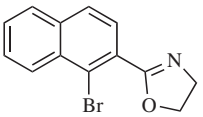
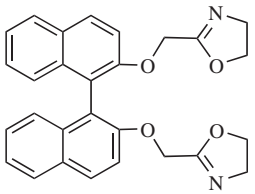
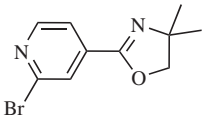
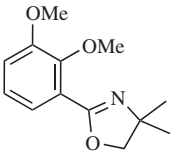
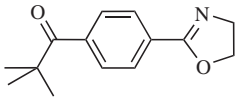
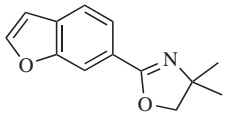
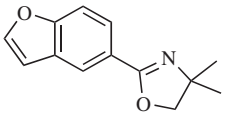
Oxazoline	Conditions	Comments	Reference
	1. $SOCl_2$ R = H, 94% R = CH_2OMe, 87%	Intermediate for the total synthesis of (*S*)-gossypol	49
	$SOCl_2$ 59%	Intermediate for the total synthesis of calyculins	50
	1. $SOCl_2$, CH_2Cl_2; 2. Et_3N, $CHCl_3$, reflux 69%	Ligand preparation	51
	1. $SOCl_2$, CH_2Cl_2, rt; 2. KF-alumina, MeCN, rt 88%	Ligand preparation	51
	$SOBr_2$ 81%		52
	$SOCl_2$, CH_2Cl_2 81–85%		53
	1. $SOCl_2$, reflux; 2. NaOH, EtOH, reflux 67%	Intermediate for the synthesis of hepatic gluconeogenesis inhibitors	54
	$SOCl_2$, rt 99%	Intermediate for the synthesis of testerone 5α-reductase inhibitors	55
	$SOCl_2$, rt 95%	Intermediate for the synthesis of testerone 5α-reductase inhibitors	55

TABLE 8.3 (*Continued*)

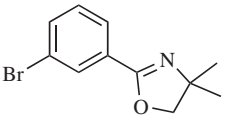
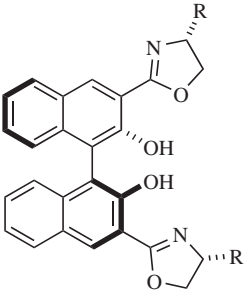
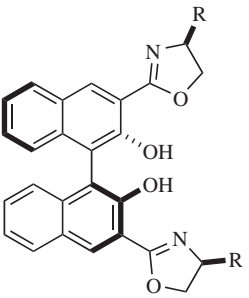
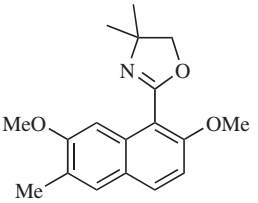
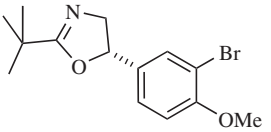
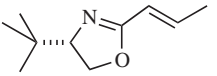
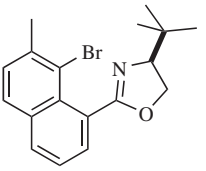
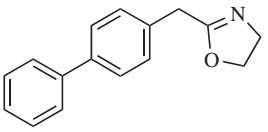
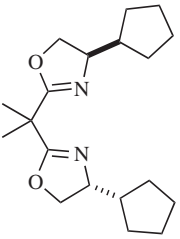
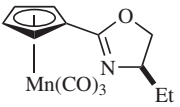
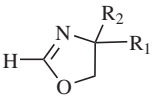
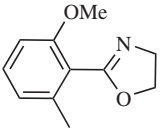
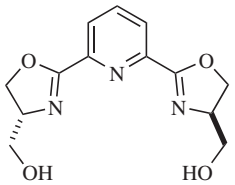
Oxazoline	Conditions	Comments	Reference
	1. $SOCl_2$; 2. NaOH 80%	Intermediate for the synthesis of RTEM-1 β-lactamase inhibitors	56
	1. $SOCl_2$, CH_2Cl_2, rt; 2. K_2CO_3, MeCN, H_2O, reflux R = Ph, 45% R = *i*-Pr, 38% R = Bn, 65%	Ligand for asymmetric 1,3-dipolar cycloaddition of nitrones	57
	1. $SOCl_2$, CH_2Cl_2, rt; 2. K_2CO_3, MeCN, H_2O, reflux R = Ph, 55% R = *i*-Pr, 55% R = Bn, 44%	Ligand for asymmetric 1,3-dipolar cycloaddition of nitrones	57
	$SOCl_2$, CH_2Cl_2 73% (from acid)	Intermediate for the total synthesis of lacinilene C-7 methyl ether	58
	$SOCl_2$ 85% (from amide)	Intermediate for the total synthesis of actinoidic acid derivatives	59
	$SOCl_2$ 54%	Intermediate for the total synthesis of (+)-α-curcumene and (+)-xanthorrhizol	60
	1. $SOCl_2$, CH_2Cl_2; rt; 2. $NaHCO_3$ 60% (from acid)		61

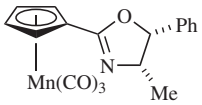
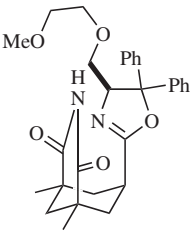
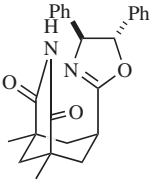
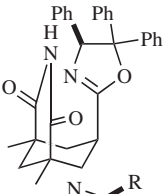
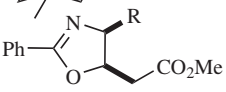
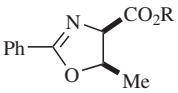
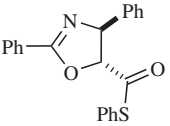
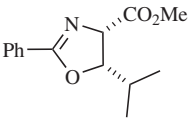
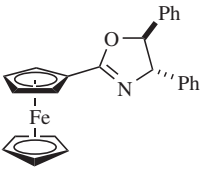
TABLE 8.3 (*Continued*)

Oxazoline	Conditions	Comments	Reference
	1. $SOCl_2$, rt; 2. NaOMe, MeOH, reflux 39% (from β-chloroamide)		62
	1. $SOCl_2$, benzene, reflux; 2. NaOH, MeOH, reflux 75% (from acid)	Ligands for asymmetric synthesis	63
	1. $SOCl_2$, 2. 20% NaOH, Et_2O 87%		64
	1. $SOCl_2$, MeCN; 2. 50% KOH 47%		65
	1. $SOCl_2$, reflux; 2. NaOH, EtOH, reflux 65% from acid (3 steps)		66
	1. $SOCl_2$, $CHCl_3$, reflux; 2. NaOH, MeOH 61% from hydroxyamide	Ligand preparation	67

For secondary β-hydroxy amides, the ring closure occurs via an S_N2 mechanism with complete inversion at carbon bearing the hydroxyl group. Thus, both cis- and trans-4,5-disubstituted oxazolines can usually be obtained reliably. Representative examples are shown in Table 8.4.[64,72–80]

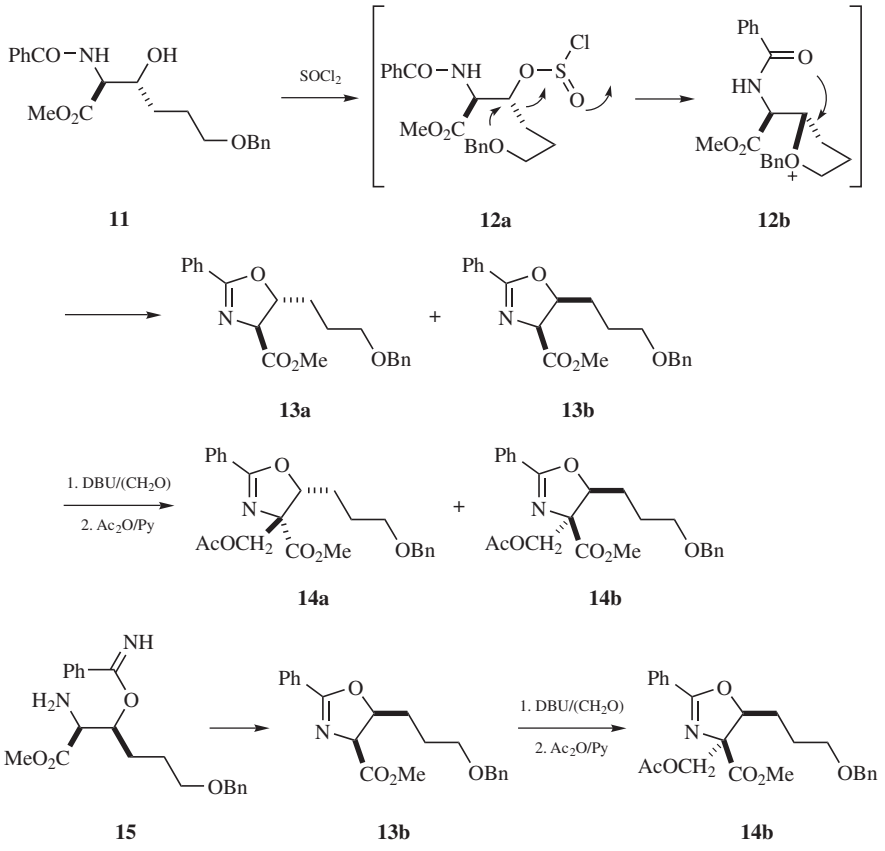
However, racemization has been reported. For example, during the total synthesis of mycestericin, Node and co-workers[81,82] reported that treatment of enantiomerically pure *threo*-benzamide **11** with $SOCl_2$ unexpectedly gave a ~1: 1 trans- and cis-mixture of oxazolines **13a** and **13b**. Consistent with this configurational assignment, further reaction with an electrophile would result in a racemic

TABLE 8.4. OXAZOLINES FROM SECONDARY AND TERTIARY β-HYDROXY AMIDES AND $SOCl_2$

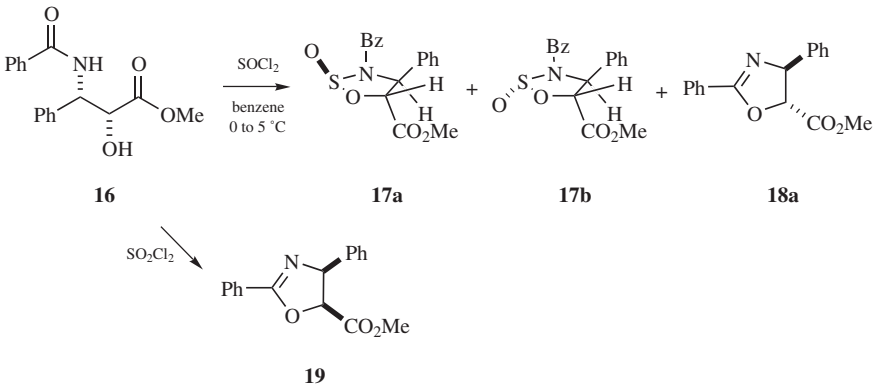
Oxazoline	Yields	Comments	References
	91%		64
	Not reported	Catalyst for enantioselective protonation	72
	92%	Catalyst for enantioselective protonation	73–75
	Not reported	Catalyst for enantioselective protonation	73
	R = *i*-Bu, 71% R = CO_2Me, 70%		76
	R = Me, 83% R = phenacyl, 44%		77
	65%	Taxol side-chain synthesis	78
		Intermediate for the total synthesis of lactacystin	79
	36%	Ligand for asymmetric hydrogenation	80

product. Indeed, reaction of the crude oxazoline mixtures with formaldehyde in the presence of DBU followed by acetic anhydride resulted in **14** with only 14% enantiomeric excess (ee). Additionally, since enantiomerically pure **14b** was obtained from enantiomerically pure oxazoline **13b** (cyclization of imidate **15** to oxazoline **13b** occurred with retention of stereochemistry), the authors concluded that the configuration at the β-hydroxy carbon atom in benzamide **11** was not completely inverted during the oxazoline forming reaction. The loss in stereoselectivity was attributed to neighboring-group participation from the benzyl ether **12** in during the cyclodehydration process (Scheme 8.7).

The reaction of the β-hydroxy amides with $SOCl_2$ can be solvent sensitive. For example, during the semisynthesis of paclitaxel from baccatin III,[83–87] the reaction of hydroxybenzamide **16** with $SOCl_2$ in benzene gave a mixture of isomeric 2-oxo-1,2,3-oxathiazolidines **17a** and **17b** together with a small amount of the *trans*-oxazoline **18a.** If a polar solvent is used, **18a** is formed as the exclusive product.[84]



Scheme 8.7



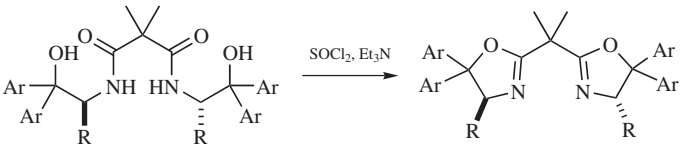
16 **17a** **17b** **18a**

19

Scheme 8.8

The expected *cis*-oxazoline **19** can be prepared using SO_2Cl_2 instead of $SOCl_2$ (Scheme 8.8).

Gibson and co-workers[88] reacted tertiary alcohol diamides with $SOCl_2$ to prepare a series of bis(oxazoline) ligands **20a–f** that are used as catalysts for asymmetric cyclopropanations. This method was preferred for preparation of **20e–f**. Use of a strong acid such as methanesulfonic acid promoted extensive elimination of water to give the corresponding enamides (Scheme 8.9).



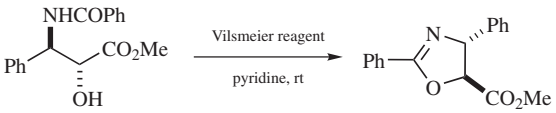
20a-f

R = *i*-Pr, *t*-Bu, Ph, Bn
Ar = 4-tolyl, 2-naphthyl

Scheme 8.9

8.2.2.2. Vilsmeier Reagent

Wuts and co-workers recently reported that the Vilsmeier reagent is superior to thionyl chloride for the cyclodehydration of primary and secondary β-hydroxy amides to prepare oxazolines, in particular, for oxazoline **18b**, which is used in Taxol synthesis (Scheme 8.10).[89] Some other examples are shown in Table 8.5 (Fig. 8.3). As expected, inversion of configuration at the alcohol bearing carbon atom is observed. Of the examples examined, serine afforded low yields due to the formation of dehydroalanine. The reaction is conveniently carried out in pyridine at room temperature. β-Chloro amides are also formed, which can be converted to the oxazoline with DBU, generally using the same mixture without isolation. The



18b

Scheme 8.10

inexpensive costs of reagents coupled with the ease of removal of byproducts have made the Vilsmeier reagent an attractive reagent for oxazoline formation.

Phosphorous oxychloride ($POCl_3$) can also be used without further activation.[90] For the synthesis of the antidepressant (*R*)-(−)-rolipram **24**, cyclization of the β-hydroxy amide **21** with $POCl_3$ gave the oxazoline intermediate **22**. Diastereoselective conjugate addition of cyanide gave the cyano derivative **23**, which was further transformed to (*R*)-(−)-rolipram (Scheme 8.11).

Unexpected oxazoline formation was observed during a study to prepare nonsedating anxiolytic 1-styrylisoquinolines **27a–h** from 2-(trifluoromethyl)arylethylamines **25a–h** under Pictet–Gams conditions ($POCl_3$ in refluxing toluene).[91] This deviation from the normal reaction pathway was hypothesized to result from the electron-withdrawing effect of trifluoromethyl group that inhibited the formation of a benzylic cation required for isoquinoline formation (Scheme 8.12).

8.2.2.3. Strong Acids

Secondary and tertiary β-hydroxy amides can be cyclized to oxazolines in the presence of strong acids such as methanesulfonic acid[92] or *p*-toluenesulfonic acid.[79] For tertiary β-hydroxy amides, elimination to the enamide can often be a competing

TABLE 8.5. OXAZOLINES FROM β-HYDROXY AMIDES USING VILSMEIER REAGENT[a]

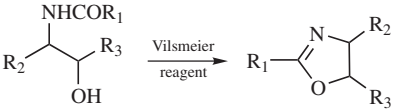
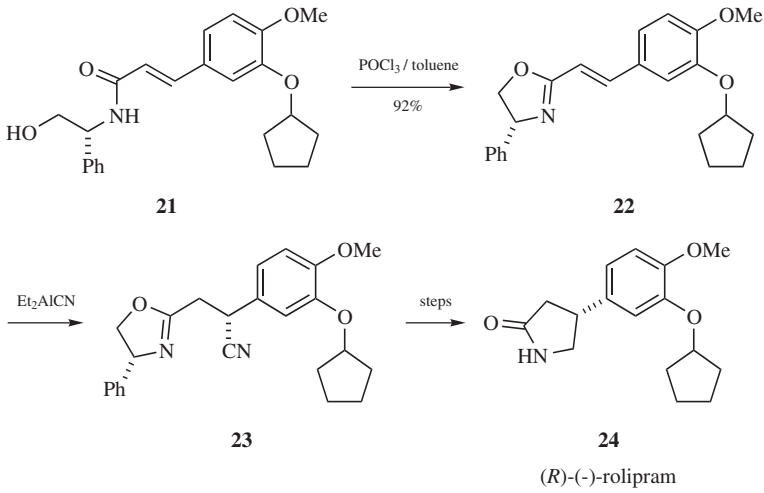


Figure 8.3

R_1	R_2	R_3	% Yield
2-(*i*-PrS)Ph	Ph	H	80
2-(PhS)Ph	Ph (*S*)	H	56
2-Br—Ph	*i*-Pr (*S*)	H	85
2-Br—Ph	Ph (*S*)	H	63
Ph	Ph (*S*)	Me (*S*)	69
Ph	Ph	CN	55
Ph	CO_2Me	H	29
2-(BocNH)—Ph	*i*-Pr (*S*)	H	71

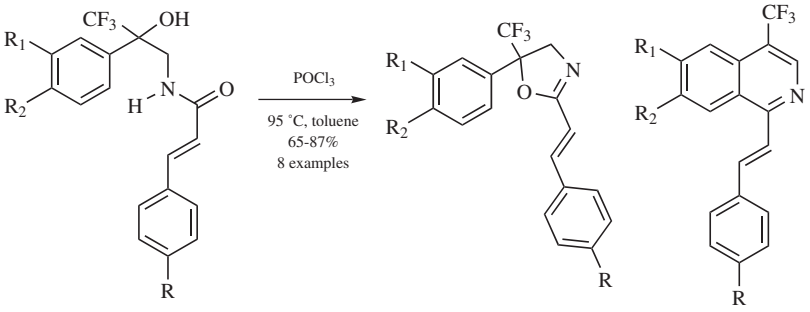
[a] Data from Ref. 89.



Scheme 8.11

side reaction.[88] Some recent examples of acid-catalyzed dehydration are shown in Scheme 8.13.

The preparation of several glucofuran[2,1-*d*]oxazolines **35** and **36** from reaction of 2-amino-2-deoxy-D-glucose **34** with HF has been described.[93] Compounds **35a** and **35b** are formed when the reaction is carried out in formic acid, whereas the orthoesters **36a–c** are formed when the reaction is carried out using anhydrides. Further reaction of **35** and **36** with methanol gives methyl glycosides. Thus, **35** and **36** may find use as potential glycosyl donors for the synthesis of 2-amino-2-deoxy sugars (Scheme 8.14).[94]

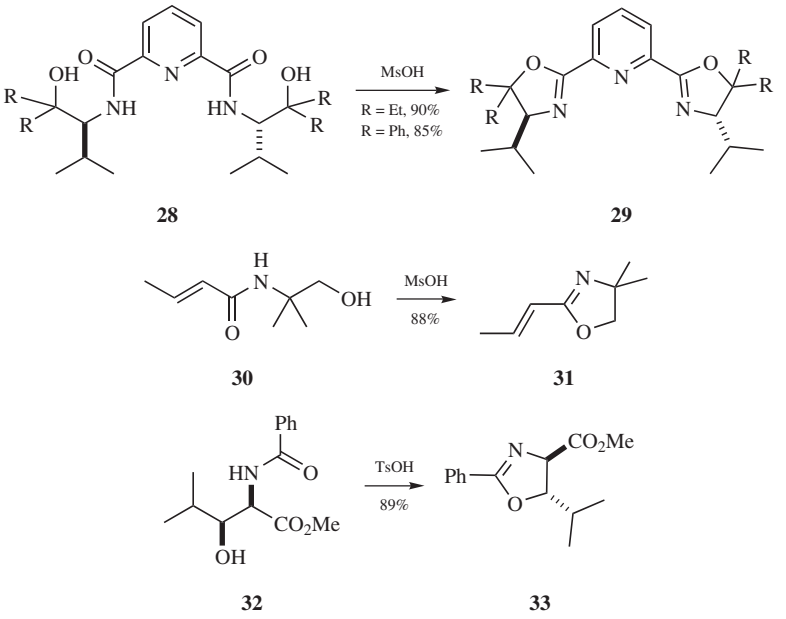


25a-h **26a-h** **27a-h**

R = H, F, CF_3, NO_2 not observed

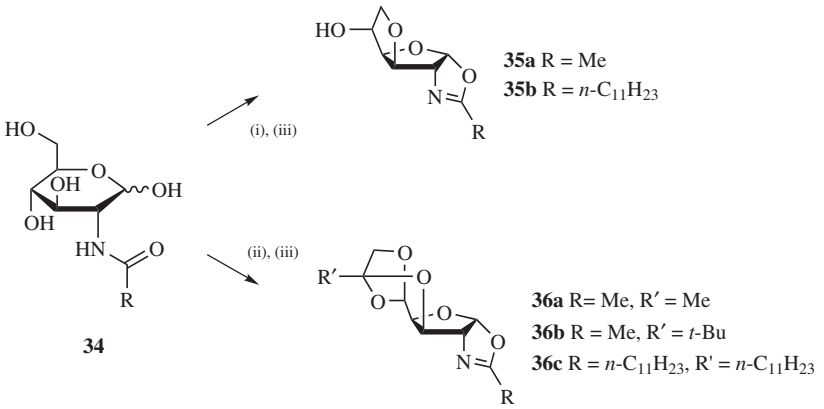
R_1 = OMe, R_2 = H or R_1,R_2 = OCH_2O

Scheme 8.12



Scheme 8.13

Deprotection of urethane-protected tertiary β-hydroxy amides **37** with trifluoroacetic acid followed by spontaneous cyclization of the liberated hydroxy amide affords oxazolines **38**.[95] The rate of deprotection is further accelerated by the addition of $CaCl_2$. Examples are shown in Table 8.6 (Fig. 8.4; Scheme 8.15).



(i) HF, 20 °C, HCO_2H
(ii) HF, −30 °C, Ac_2O, *t*-BuCOCl,or $(n\text{-}C_{11}H_{23}CO)_2O$
(iii) Et_3N

Scheme 8.14

TABLE 8.6. OXAZOLINES FROM URETHANE-PROTECTED TERTIARY β-HYDROXY AMIDES[a]

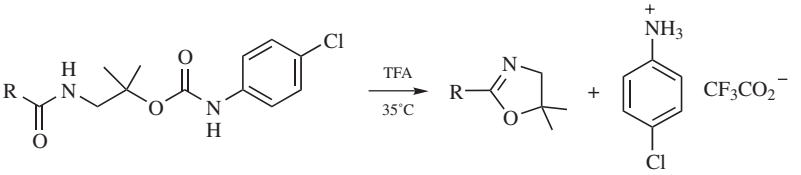
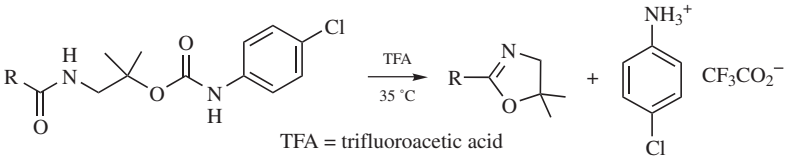


Figure 8.4

R	$T_{1/2}$ in TFA	$T_{1/2}$ in TFA/$CaCl_2$
t-Bu—	100	30
i-Pr—	165	70
$Me(CH_2)_{16}$—	225	100
CH_2=C(Me)—	60	15
PhNH—	205	95
$Me(CH_2)_2$-NH—	295	120
CH_2=C(Me)-C_6H_4-C(Me)$_2$-NH—	>450	180
EtO—	40	10
Me_2CHCH_2O—	65	15

[a] Data from Ref. 95.



TFA = trifluoroacetic acid

37 **38**

Scheme 8.15

8.2.2.4. Acetates, Mesylates, Tosylates, and Triflates

Conversion of the hydroxyl group of a β-hydroxy amide to a mesylate,[96–100] triflate,[96,101,102] or an acetate[103–108] followed by intramolecular displacement of the leaving group is a commonly employed strategy for oxazoline formation. Some examples from the recent literature are listed in Table 8.7.[41,96–123] Oxazolines prepared via cyclization to displace an acetate sometimes requires a Lewis acid such as boron trifluoride (BF_3•OEt_2)[105] or trimethylsilyl triflate (TMSOTf)[107] to improve the leaving group ability. The cyclization is expected to proceed via an S_N2 mechanism with overall inversion.

Occasionally, epimerization occurs first prior to cyclization, in which case the stereochemical outcome is a net retention. This epimerization is illustrated in the

TABLE 8.7. OXAZOLINES VIA ACETATES, MESYLATES, AND TRIFLATES

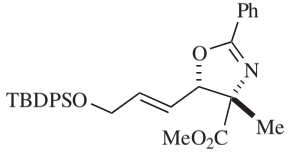
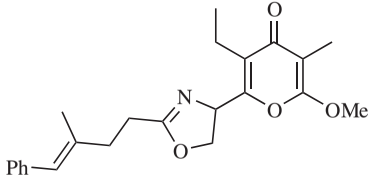
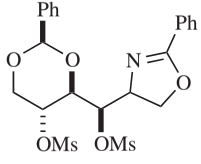
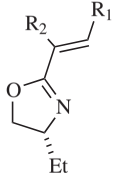
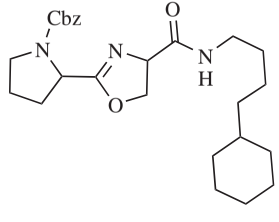
Product	Conditions (% Yield)	Comments	References
	Mesylate (99)		96
	Mesylate (95)		97
	MsCl, Et_3N, Py, CH_2Cl_2, −5 to 20 °C (93)	Intermediate for D-*erythro*-sphingnosine and 4,8-sphingadienine derivatives	109
	MsCl, Et_3N, CH_2Cl_2 $R_1 = Me$, $R_2 = H$ (74) $R_1 = Et$, $R_2 = H$ (51) $R_1 = Ph$, $R_2 = H$ (96) $R_1 = H$, $R_2 = Me$ (68) $R_1 = Ph$, $R_2 = Me$ (100)		110, 111
	1. MsCl, Et_3N; 2. K_2CO_3, acetone, reflux (96)	Intermediate for preparation of thromboxane A_2 receptor antagonist	112

TABLE 8.7 (*Continued*)

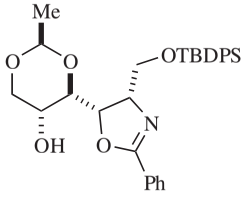
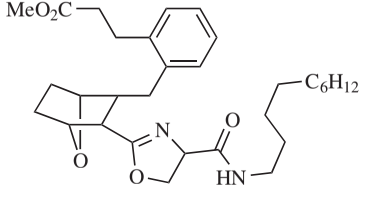
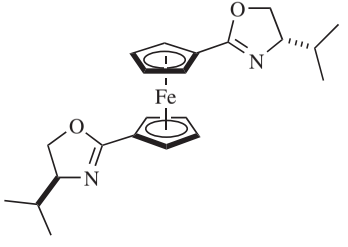
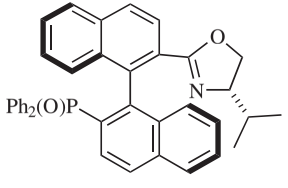
Product	Conditions (% Yield)	Comments	References
	MsCl, Py, toluene, 110 °C (85)	Intermediate for phytosphingosine-type glucosaminocerebrosides	113
	1. MsCl, Et_3N, CH_2Cl_2, 0 °C; 2. K_2CO_3, acetone, reflux (90)	Intermediate for preparation of thromboxane A_2 receptor antagonist	114
	MsCl, Et_3N (84)	Ligand preparation	115
	MsCl, DMAP, Et_3N, CH_2Cl_2 (97)	Ligand for asymmetric allylic alkylation	116

TABLE 8.7 (*Continued*)

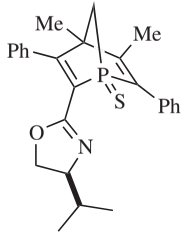
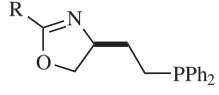
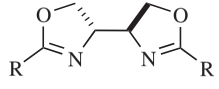
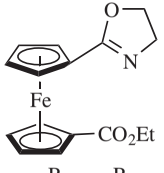
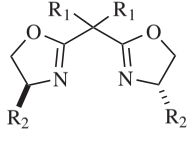
Product	Conditions (% Yield)	Comments	References
	MsCl, DMAP, Et_3N (93)	Intermediate for a ligand for asymmetric allylic alkylation and Heck reaction	117
	MsCl, DABCO, THF R = adamantyl, 3,5-di-*t*-Bu–Ph, *t*-Bu	Ligands for asymmetric allylic alkylation	118
	MsCl, Et_3N, DMF, or THF R = *t*-Bu (87) R = cyclohexyl (87) R = Ph (87) R = 2,6-di-Cl-Ph (87) R = adamantyl (82)	Ligand for asymmetric cyclopropanation	119
	MsCl, Et_3N, CH_2Cl_2, rt (62)	Ligand preparation	120
	1. MsCl, Et_3N, CH_2Cl_2; 2. MeOH, NaOH (KOH) reflux or KOAc, EtOH reflux R_1 = Et, R_2 = Bn, *i*-Pr, *t*-Bu, $PhMe_2C$, Ph_2MeC, Ph_3C (73–86) R_1 = *i*-Bu, R_2 = *t*-Bu, Ph_2MeC (77–81)	Ligand preparation	121

TABLE 8.7 (*Continued*)

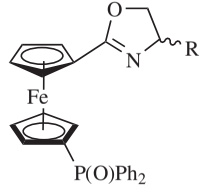
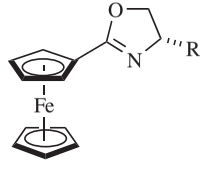
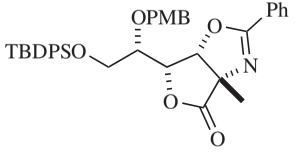
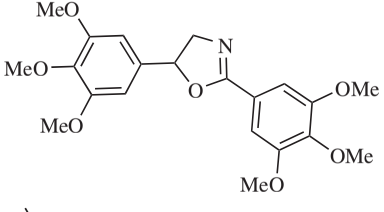
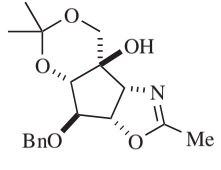
Product	Conditions (% Yield)	Comments	References
	TsCl, Et_3N, CH_2Cl_2 R = *i*-Pr (*S*), *t*-Bu (*S*), Ph (*S*), *i*-Pr (*R*), (53–60)	Ligand preparation	122
	TsCl, Et_3N, CH_2Cl_2 R = *i*-Pr (60) R = *t*-Bu (53)	Diastereoselective synthesis of chiral oxazolinylferrocene compounds	41
	Triflate (96)		96
	Triflate (59)		101
	Triflate (82)		102

TABLE 8.7 (*Continued*)

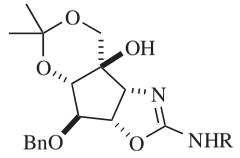
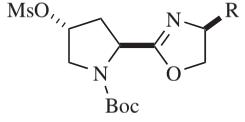
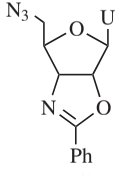
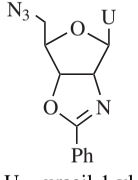
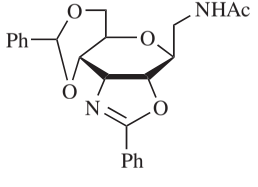
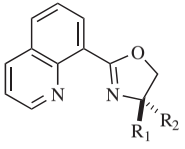
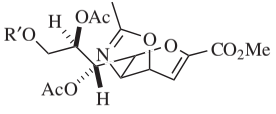
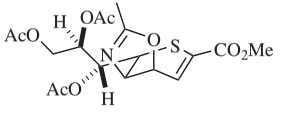
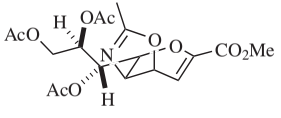
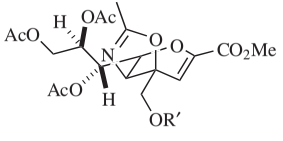
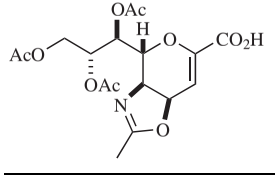
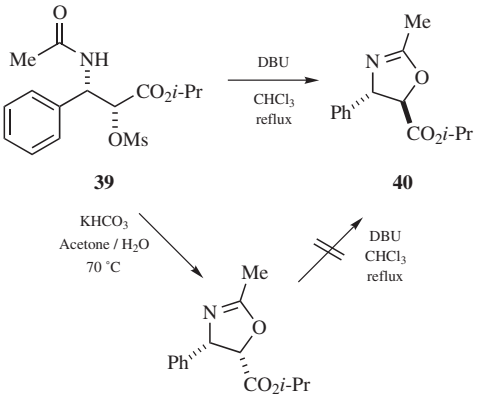
Product	Conditions (% Yield)	Comments	References
	Triflate, R = Bn (99) Triflate, R = Ph (67)		102
	Mesylate R = *i*-Pr (61) R = Ph (56) R = *i*-Bu (90)		98
 U = uracil-1-yl	Mesylate		99
 U = uracil-1-yl	Mesylate		99
	Mesylate (50)		100

TABLE 8.7 (*Continued*)

Product	Conditions (% Yield)	Comments	References
	1.MsCl, Et_3N, CH_2Cl_2, rt; 2. 5% KOH R_1 = H, Ph R_2 = H, *i*-Pr, *t*-Bu 3 examples (58–78)	Ligands for asymmetric allylic alkylation	123
 R′ = Ac, Ts	Acetate R′ = Ac (82) R′ = Ts (89)		103
	Acetate (90)		104
	Acetate $BF_3 \bullet OEt_2$ (96)		105
 R′ = Ac, Me	Acetate R′ = Ac (56) R′ = Me (60)		106
	Acetate TMSOTF (80)		107, 108

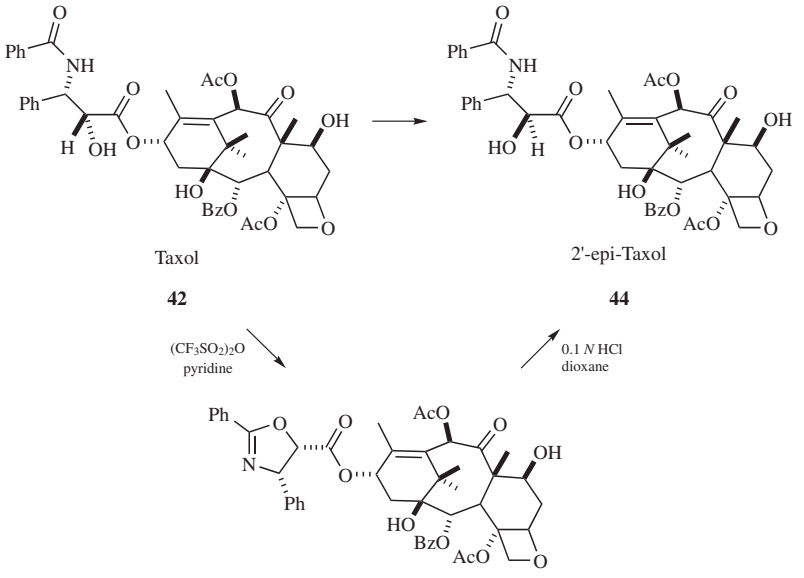


39 **40** **41**

Scheme 8.16

following example shown in Scheme 8.16.[124] Depending on the reaction conditions, either the *cis*- or *trans*-oxazoline can be formed. Since the *cis*-oxazoline **41** does not epimerize to the trans isomer **40**, the epimerization occurs first prior to ring formation.

A common strategy to invert the stereochemistry at the hydroxyl bearing carbon of an amino alcohol involves oxazoline formation with inversion followed by hydrolysis. This strategy has been applied to Taxol resulting in a practical semisynthesis of 2′-epi-Taxol **44** from Taxol **42** (Scheme 8.17).[125]

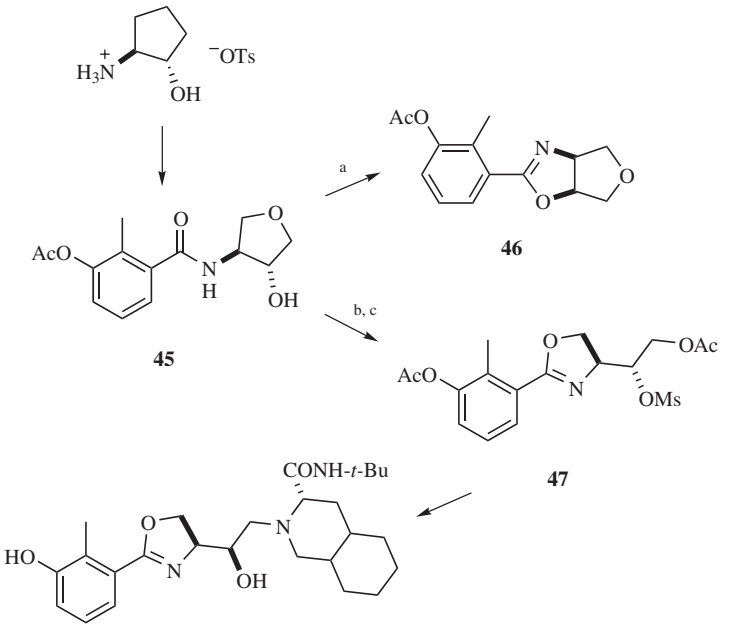


42 **44** **43**

Scheme 8.17

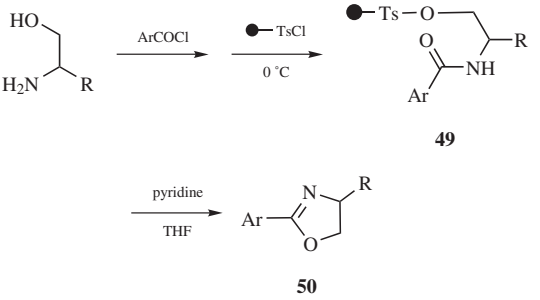
An unusual example of oxazoline formation is illustrated in the following example in which the hydroxyl moiety is masked as a tetrahydrofuran ring.[126] Depending on reaction conditions, regioselective ring closure to one of the two oxazolines can be realized. Thus, addition of methanesulfonyl chloride to a mixture of substrate and Et_3N resulted in the expected oxazoline **46**. On the other hand, addition of <1 equiv of triethylamine to a mixture of substrate and methanesulfonyl chloride, followed by acid catalysis produced oxazoline **47**. Intermediate **47**, obtained in 72% overall yield from **45**, was susequently converted to the human immunodeficiency virus (HIV)-protease inhibitor Nelfinavir® **48** (Scheme 8.18).

Similarly, tosylates can be used to prepare oxazolines in high yields.[127] An interesting application of this reaction is the use of polymer-bound tosyl chloride to facilitate high-throughput oxazoline synthesis.[128] In this case, β-hydroxy amides are captured by polymer-bound tosyl chloride at 0 °C followed by a wash step to remove excess reagents and starting materials. Exposure of the resin to a weak base such as pyridine in THF releases the oxazolines from the resin with minimal formation of elimination products. High-purity products are obtained even when the cyclization reaction is less than quantitative since unreacted starting material is polymer bound (Scheme 8.19).



a: Addition of MsCl to substrate with excess Et_3N
b: Addition of < 1 equiv of Et_3N to substrate and MsCl
c: Ac_2O and conc. H_2SO_4

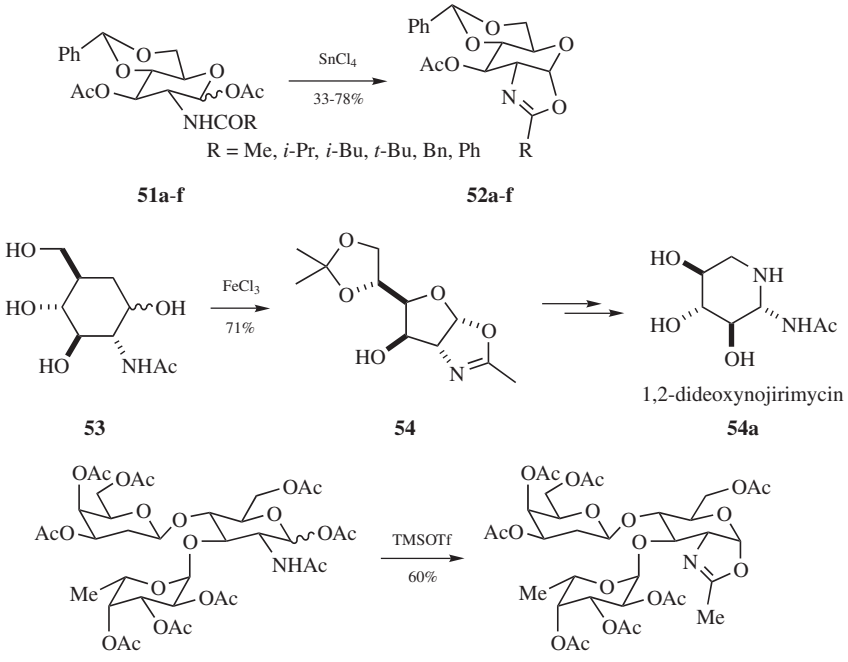
Scheme 8.18



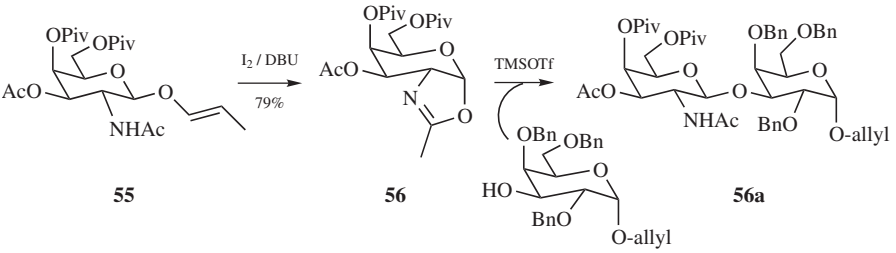
Scheme 8.19

Activation of the hydroxyl group as an acetate leaving group to promote oxazoline formation has been applied extensively in carbohydrates to afford β-glycosylation with high selectivity. A Lewis acid such as ferric chloride ($FeCl_3$),[129] tin chloride ($SnCl_4$),[130] or TMSOTf[131] is usually added to facilitate cyclization. Several recent examples are shown in Scheme 8.20. Compound **54** has been further elaborated to 1,2-dideoxynojirimycin **54a**, a potent β-*N*-acetylglycosamine inhibitor.

Colombo and co-workers[132] also developed an oxazoline glycosylation method wherein an acetate is replaced by a vinyl ether. Activation of **55** with iodine in the presence of DBU gave the oxazoline **56**. Glycosylation of **56** with a second sugar moiety using TMSOTf afforded the disaccharide **56a** in 79% yield (Scheme 8.21).



Scheme 8.20



Scheme 8.21

8.2.2.5. Burgess Reagent

Burgess reagent[133] has also been used to effect cyclodehydration of β-hydroxy amides to oxazolines. Representative examples are shown in Table 8.8.[31,43,134–144] The advantage of this reagent is that the cyclodehydration is performed under essentially neutral and mild conditions, typically in THF at room temperature or reflux.

A series of axially chiral bis(oxazolines) **58a–n** were prepared by Rippert for stereoselective cyclopropanation studies.[145] The use of Burgess reagent proved to be superior than other reagents such as $PPh_3/CCl_4/MeCN$ or $MsCl/Et_3N/CH_2Cl_2$ (Scheme 8.22).

TABLE 8.8. OXAZOLINE FORMATION USING BURGESS REAGENT

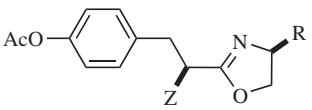
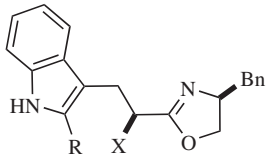
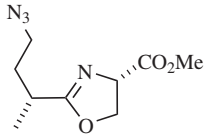
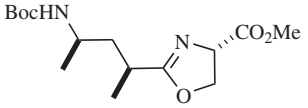
Product	Conditions (% Yields)	Comments	References
	THF, 70 °C R = Bn, Z = H (74) R = H, Z = NHBoc (67)		31, 134
	THF, 70 °C R = X = H (64) R = H, X = NHTs (54) R = Me, X = H (65)		31, 135
	THF, 55 °C (84)		43
	THF, reflux (83)	Intermediate for the total synthesis of calyculin C	136

TABLE 8.8 (*Continued*)

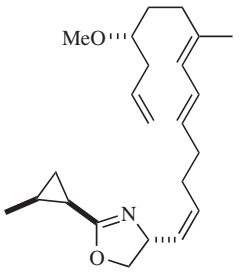
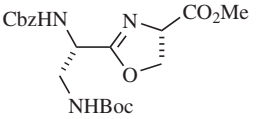
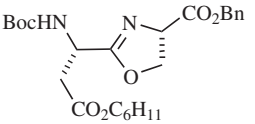
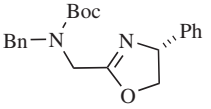
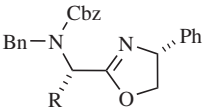
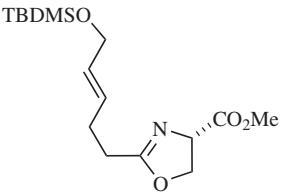
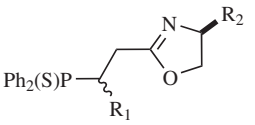
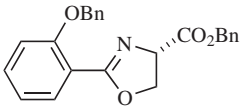
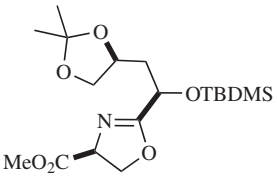
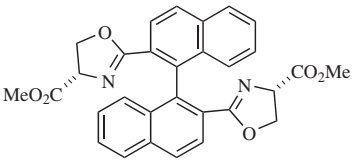
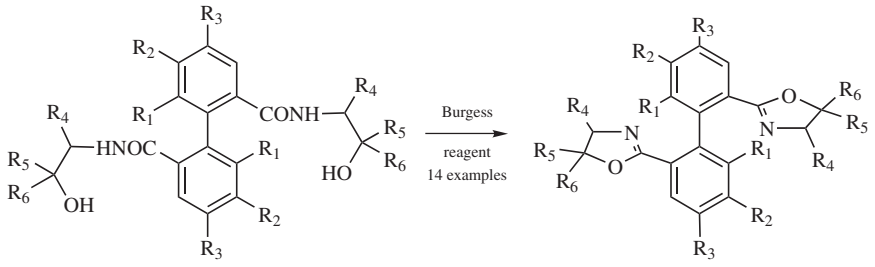
Product	Conditions (% Yields)	Comments	References
	THF, 20 °C (50)	Intermediate for the total synthesis of curacin A	137
	THF, reflux (50–67)		138
	THF, reflux (63)		138
	THF, reflux (73)	Asymmetric alkylation studies	139
	THF, reflux R = Me (74) R = Bn (43)	Asymmetric alkylation studies	139
	THF, reflux	Intermediate for the total synthesis of hennoxazole A	140
	THF, reflux R_1 = H, R_2 = Me (*S*), Bn (*S*), *i*-Pr (*S*), Ph (*S*) (31–64) R_1 = Ph (*S*), R_2 = Bn (*S*), *i*-Pr (*S*), Ph (*S*) (47–69) R_1 = Ph (*R*), R_2 = Bn (*S*), = *i*-Pr (*S*), Bn (*S*) (47–69)	Ligands for asymmetric allylic alkylation	141
	THF, reflux (66)	Intermediate for the total synthesis of mycobactin S	142

TABLE 8.8 (*Continued*)

Product	Conditions (% Yields)	Comments	References
		Intermediate for total synthesis of (−)-madumycin II	143
 *rac*	THF, reflux (56–69) (from acid)	Ligand for asymmetric diethylzinc addition to benzadehyde	144

Because of the mild and essentially neutral reaction conditions, Burgess reagent was applied for the construction of the oxazoline intermediates **60** required by Pattendon and co-workers[146,147] for their syntheses of thiangazole **61** and lissoclinamide 4 **63** (Scheme 8.23).[148]

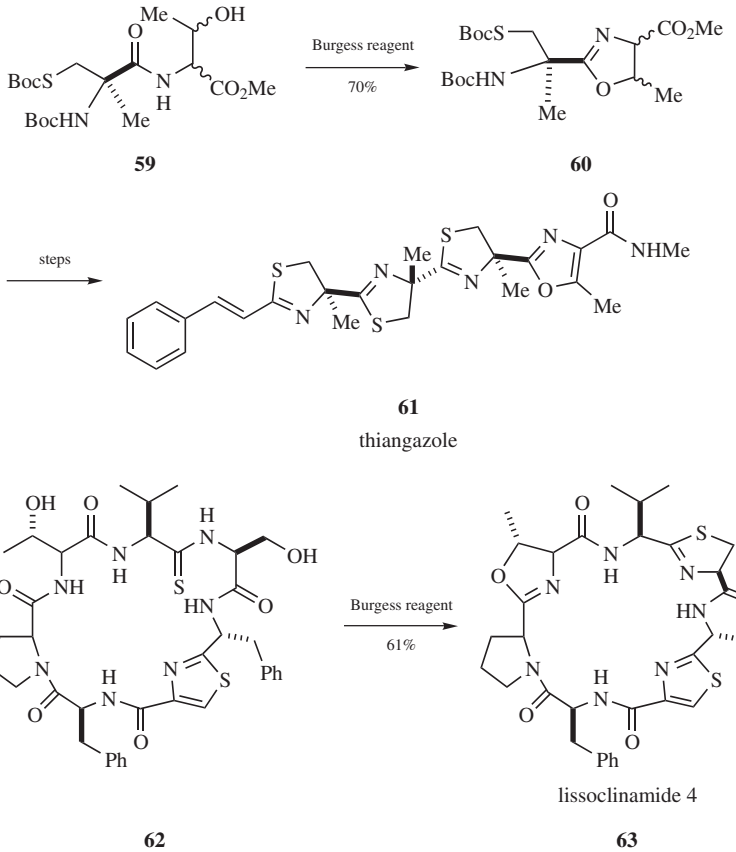
Similarly, Wipf and co-workers[149] also utilized Burgess reagent in the synthesis of lissoclinamide 7 **68**. To construct **65** with the required *allo*-threonine residue, Wipf and co-workers first prepared tripeptide **64** from natural threonine. Inversion



57a-n **58a-n**

Axial Chirality: *M*	Axial Chirality: *P*
R_1 = Me, Br	R_1 = Me, OMe, Br
R_2 = H	R_2 = H, OMe
R_3 = H, Br	R_3 = H, OMe, Br
R_4 = Me (*S*), *i*-Pr (*S*), Ph (*S*)	R_4 = Et (*S*), *i*-Pr (*S*), *t*-Bu (*S*), Ph (*S*)
R_5 = H, Ph	R_5 = H, Ph
R_6 = H, Ph	R_6 = H

Scheme 8.22

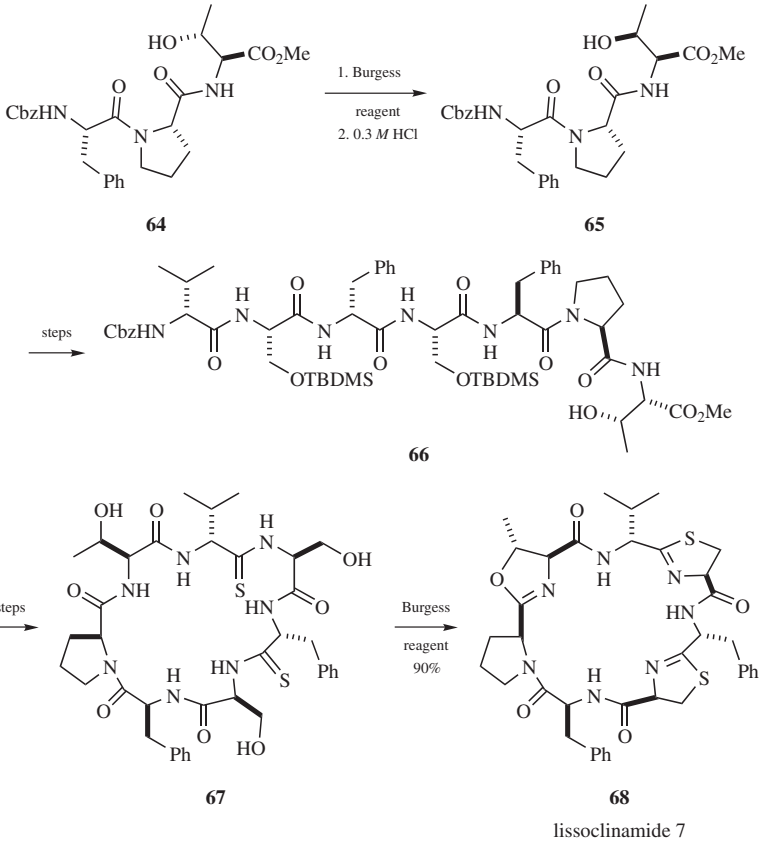


Scheme 8.23

of the hydroxyl group was accomplished through cyclization to the oxazoline followed by hydrolysis to give the tripeptide **65** containing the unnatural threonine in 80% yield.[150] The final step of the synthesis was accomplished by the global cyclization of the β-hydroxy amides and thioamides, and provided the natural product in 90% yield, without epimerization of the thiazoline fragments (Scheme 8.24).

A polymer-bound Burgess reagent has also been developed.[151] Aside from the mild, neutral cyclization conditions, this reagent also offers the advantage of a clean reaction with little epimerization and an easy work-up. Examples are listed in Table 8.9.

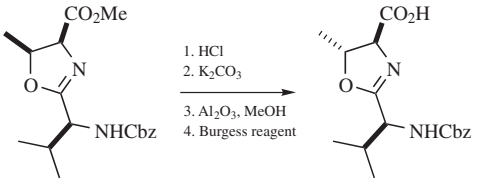
In their synthesis of the macrocyclic hexapeptide bistratamide D, Meyers and co-workers[152] prepared the *trans*-oxazoline **70** from the corresponding *cis*-oxazoline **69** through several steps, the last of which was cyclization to the oxazoline using Burgess reagent. The net outcome is inversion of the stereocenter at the 5-position of the oxazoline (Scheme 8.25).



64 **65** **66** **67** **68**

lissoclinamide 7

Scheme 8.24



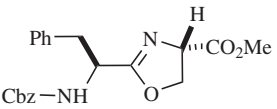
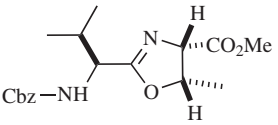
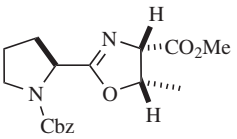
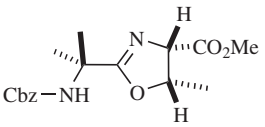
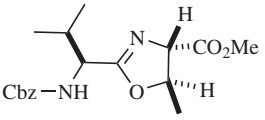
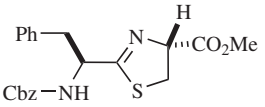
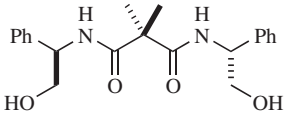
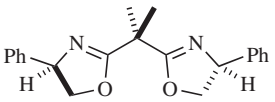
69 **70**

Scheme 8.25

8.2.2.6. Mitsunobu Reaction

The Mitsunobu reaction[153] has also been applied successfully for the preparation of oxazolines from β-hydroxy amides. This method provides an alternative to the Burgess reagent. Some recent examples are listed in Table 8.10.[154–161]

TABLE 8.9. OXAZOLINE FORMATION USING PEG-SUPPORTED BURGESS REAGENT[a]

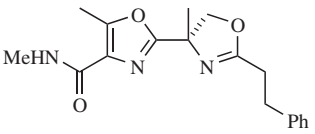
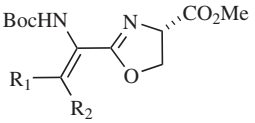
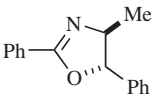
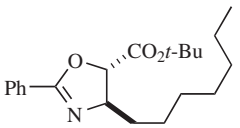
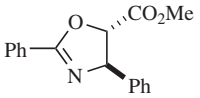
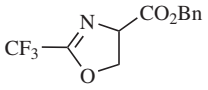
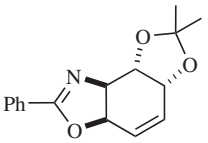
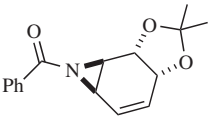
Substrate	Product	% Yield
Cbz-Phe-Ser-OMe		88
Cbz-Val-Thr-OMe		90
Cbz-Pro-Thr-OMe		85
Cbz-Aib-Thr-OMe		88
Cbz-Val-aThr-OMe		76
Cbz-Phe-ψ(CSNH)Ser-OMe		98
		80

[a] Data from Ref. 151.

Oxazoline formation under Mitsunobu conditions is very facile. As shown in the last example in Table 8.10, as much as 30% of the oxazoline is formed in addition to the desired vinylaziridine that is obtained in 64% yield.[161] Only amide groups participate in this cyclization since the oxazoline is not formed when the nitrogen is protected as a benzyloxycarbonyl (Cbz) or *tert*-butyloxycarbonyl (Boc) derivative.

Because of mild reaction conditions, this method has also been applied for a semisynthesis of paclitaxel **42** from the 10-deacetylbaccatin III derivative **71** (Scheme 8.26).[162]

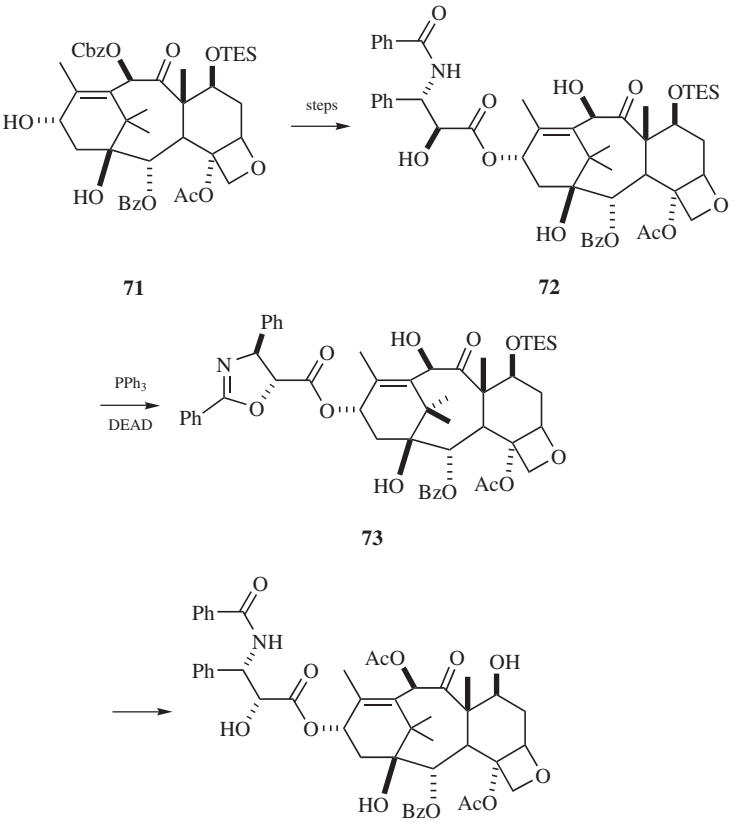
TABLE 8.10. OXAZOLINES VIA THE MITSUNOBU REACTION OF β-HYDROXY AMIDES

Product	Conditions (% Yield)	Comments	References
	PPh_3, DIAD[a] (97)	Intermediate for the synthesis of thiangazole analogues	154
	PPh_3, DEAD[b] R_1 = Me, = *i*-Pr, Ph R_2 = H, Me 4 examples (61)	Intermediates for the total synthesis of berinanamycin A, a macrocylic peptide antibiotic	155
	PPh_3, DIAD, THF, rt (74)		156
	PPh_3, DEAD, THF, rt (84)	Intermediate for the total synthesis of microginin (ACE inhibitor)	157, 158
	PPh_3, DEAD (80)	Asymmetric synthesis of homochiral *syn*- and *anti*-3-phenylisoserine	159
	PPh_3, DEAD, THF, rt (90)	Intermediate for the total synthesis of anticapsin, a naturally occuring amino acid antibiotic	160
	PPh_3, DEAD (30)	 64%	161

[a] DIAD = diisopropyl azodicarboxylate.
[b] DEAD = diethyl azodicarboxylate.

Wipf and Miller[163] reported that cyclization of threonine peptides to oxazolines under Mitsunobu conditions resulted in aziridines instead of the expected oxazolines, whereas *allo*-threonines peptides give the expected oxazolines (Table 8.11).

Oxazoline formation under Mitsunobu conditions requires that the amide substituent be in an antipepriplanar orientation to the activated hydroxyl substituent. With *allo*-threonines **77**, these groups are predisposed in such an orientation in the most stable conformation (transition state **78b**). As a result, *trans*-oxazolines **79** are easily formed. With threonines, the formation of *cis*-oxazoline **76** is disfavored because of destabilizing *gauche* interactions between the α-carboxyl



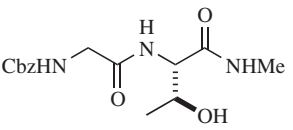
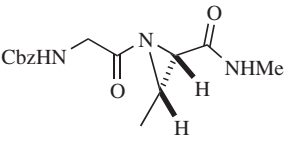
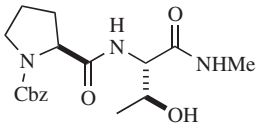
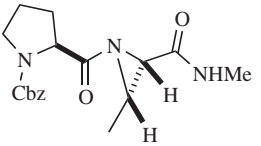
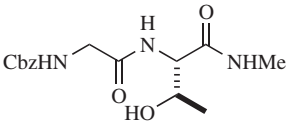
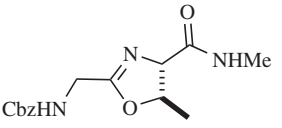
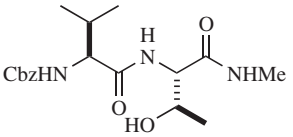
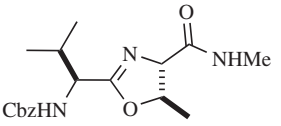
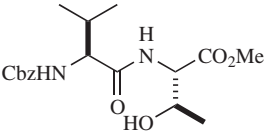
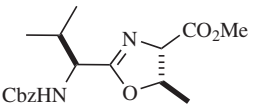
Scheme 8.26

and β-methyl groups (transition state **75b**) (Scheme 8.27). At the same time, rotation to a more stable conformation and deprotonation of **75b** by the azodicarboxylate anion **75c** present in the reaction mixture gave **75a** that is now reactive toward E_i cyclization and accounts for the formation of aziridines. Indeed, when the reaction is carried out in the presence of triethylamine hydrochloride, aziridine formation is completely suppressed since **75c** is now neutralized.

8.2.2.7. DAST and Deoxo-Fluor

Diethylaminosulfur trichloride (DAST) was first used to cyclodehydrate β-hydroxy amides in 1990 by Jones and co-workers.[164] In 1995, Lellouche and co-workers[165] showed that β-hydroxy amides react efficiently with DAST even at

TABLE 8.11. CYCLIZATION OF THREONINE AND *ALLO*-THREONINE PEPTIDES UNDER MITSUNOBU CONDITIONS[a]

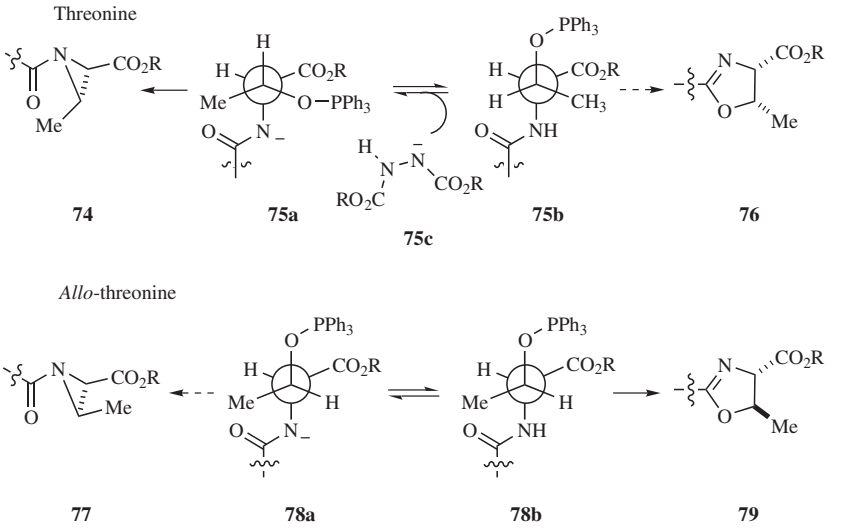
Substrate	Product	% Yield
		56
		84
		64
		83
		73

[a] Data from Ref. 163.

−78 °C in CH_2Cl_2 to afford good yields of the corresponding 2-oxazolines. Since then, it was also demonstrated that DAST is compatible with a wide range of functional groups, and good to excellent yields of the oxazoline can be obtained readily. Recent examples from the literature are shown in Table 8.12.[164–170]

Bis-(2-methoxyethyl)aminosulfur trioxide (Deoxo-Fluor) has also been used in place of DAST.[166] Deoxo-Fluor may have the advantage of increased thermal stability.[171] A comparison of the two reagents for the cyclization of several peptidyl β-hydroxy amides has been reported (Table 8.13).

In general, fluorination is not a problem. However, in some instances, DAST induced dehydration does result in a low yield of the oxazoline due to competitive fluorination.[172] For example, treatment of **80** with DAST resulted in **82**, an S_N2'



Scheme 8.27

TABLE 8.12. OXAZOLINES FROM β-HYDROXY AMIDES USING DAST

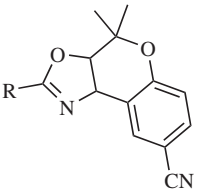
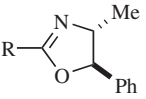
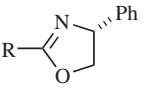
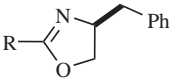
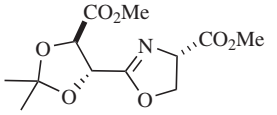
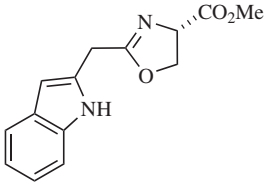
Oxazoline	Conditions (% Yields)	Comments	Reference
	CH_2Cl_2, rt R = Ph (68) R = Me (58)		164
	CH_2Cl_2, −78 °C R = Ph, *t*-Bu (62–70)		165
	CH_2Cl_2, −78 °C R = Ph, Me, *t*-Bu (57–95)		165
	CH_2Cl_2, −78 °C R = Ph, Me, *t*-Bu (76–93)		165
	CH_2Cl_2, −78 °C (53)		166
	CH_2Cl_2, −78 °C (86)		166

TABLE 8.12 (*Continued*)

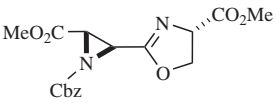
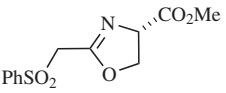
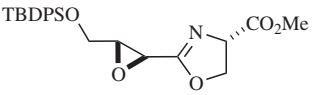
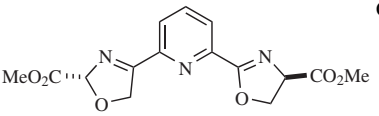
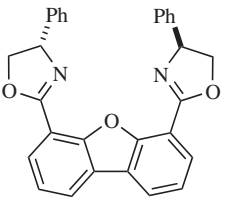
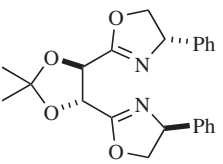
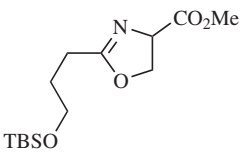
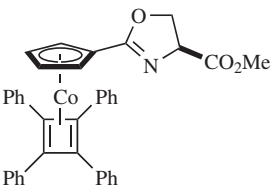
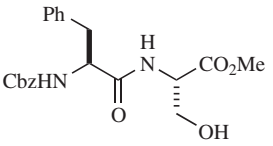
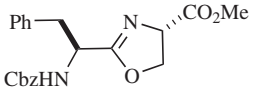
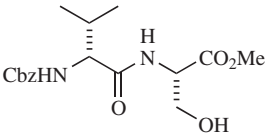
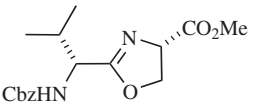
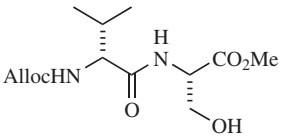
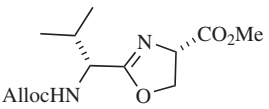
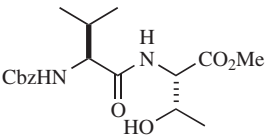
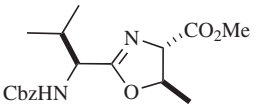
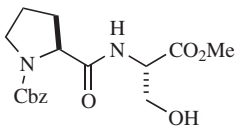
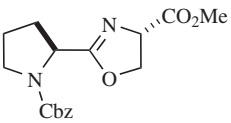
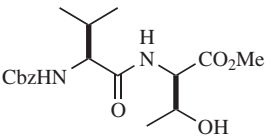
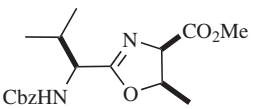
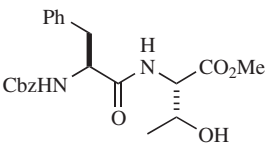
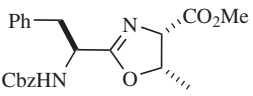
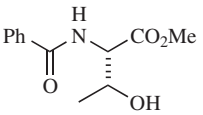
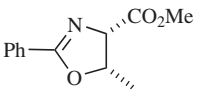
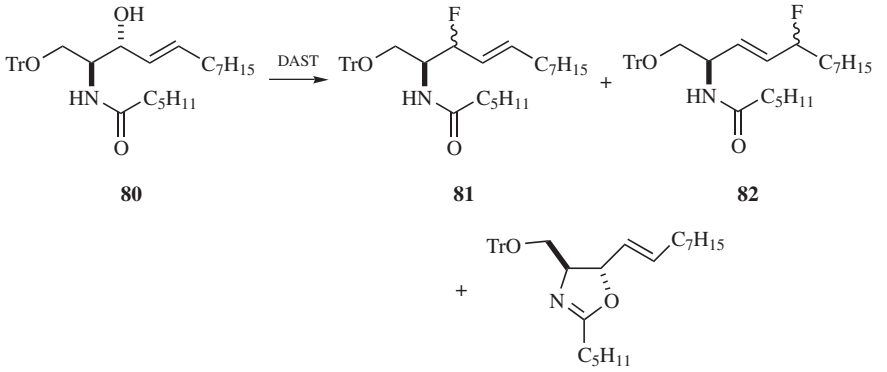
Oxazoline	Conditions (% Yields)	Comments	Reference
	CH_2Cl_2, −78 °C (90)		166
	CH_2Cl_2, −78 °C (60)		166
	CH_2Cl_2, −78 °C (73)		166
	CH_2Cl_2, −78 °C (77)		166
	CH_2Cl_2, −78 °C (61)	Catalyst for asymmetric conjugate radical addition	167
	CH_2Cl_2, −78 °C (52)	Catalyst for asymmetric cyclopropanation and aziridination	168
	CH_2Cl_2, −78 °C (78)	Intermediate for the synthesis of (−)-hennoxazole A	169
	CH_2Cl_2 (99)	Intermediate for preparation of catalyst used for asymmetric transfer of diethylzinc to benzaldehyde	170

TABLE 8.13. COMPARISION OF DAST AND DEOXO-FLUOR FOR CYCLIZATION OF PEPTIDYL β-HYDROXY AMIDES[a]

Substrate	Product[b]	Deoxo-Fluor (%)	DAST (%)
		72	86
		83	92
		80	90
		72	72
		73	92
		72	27
		61	43
		91	86

[a] Data from Ref. 166.

[b] Allyloxycarbonyl = Alloc (or AOC).



Scheme 8.28

substitution product together with **81** in preference to formation of the oxazoline **83** (Scheme 8.28).

8.2.2.8. Triphenylphosphine and Carbon Tetrachloride

β-Hydroxy amides undergo cyclodehydration to oxazolines under very mild conditions with triphenylphosphine and carbon tetrachloride. Carbon tetrabromide can also be used. The formation of the corresponding β-chloro amide is generally not a significant problem. The major disadvantage is that removal of the byproduct triphenylphosphine oxide may be difficult at times. Representative examples are shown in Table 8.14 (Fig. 8.5).[114,140,173–181]

TABLE 8.14. OXAZOLINES FROM HYDROXY AMIDES USING TRIPHENYLPHOSPHINE AND CARBON TETRACHLORIDE

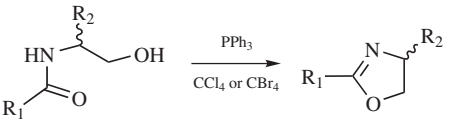


Figure 8.5

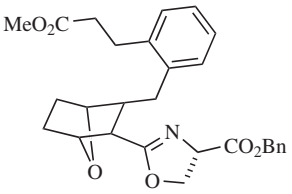
Oxazoline	Conditions (% Yield)	Comments	References
	PPh_3, CCl_4, DIPEA, MeCN, rt	Intermediate for thromboxane A_2 receptor antagonist	114

TABLE 8.14 (*Continued*)

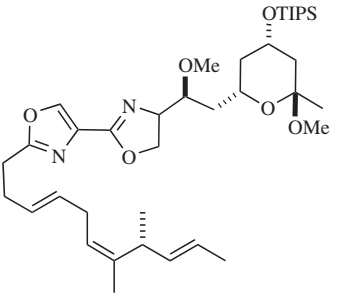
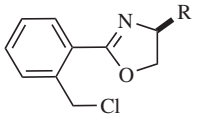
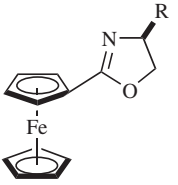
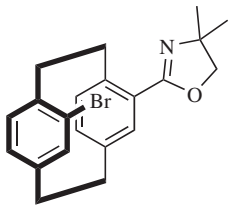
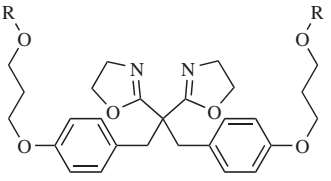
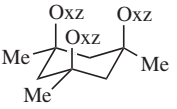
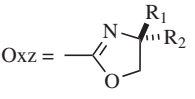
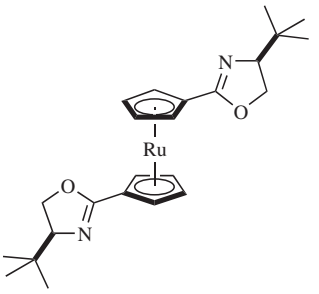
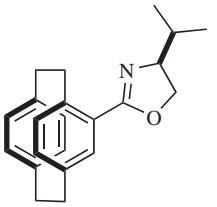
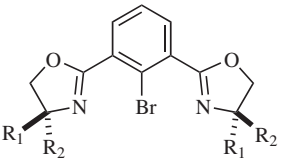
Oxazoline	Conditions (% Yield)	Comments	References
	$(BrCl_2C)_2$, PPh_3, MeCN, 2,6-di-*tert*-butyl-4-methylpyridine	Intermediate for the total synthesis of hennoxazole A	140
	PPh_3, CCl_4, Et_3N, MeCN R = *i*-Pr (52) R = Ph (70)	Intermediates for ligands for asymmetric allylic alkylation	173
	PPh_3, CCl_4, Et_3N, MeCN R = *i*-Pr (89) R = Me (83) R = H (77)	Intermediates for phosphinoferrocenyl-oxazoline–ligands for asymmetric catalysis	174, 175
	PPh_3, CCl_4, Et_3N, MeCN (97)		176
	1. PPh_3, CBr_4, THF, rt; 2. NaOH, EtOH, THF, reflux R = {3,5-bis-[O-(4-*t*-Bu)-C_6H_4)]}-C_6H_3 (96)	Catalysts for asymmetric Diels–Alder cycloaddition	177
	PPh_3, CCl_4, Et_3N, MeCN		178
	R_1 = H, R_2 = Ph (80) R_1 = Me, R_2 = H (50) R_1 = *i*-Pr, R_2 = H (81) R_1 = *t*-Bu, R_2 = H (67)		

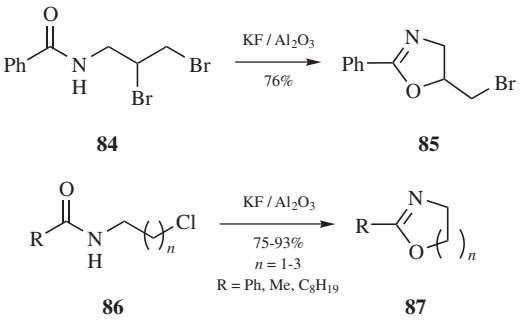
TABLE 8.14 (*Continued*)

Oxazoline	Conditions (% Yield)	Comments	References
	PPh_3, CCl_4, Et_3N, MeCN	Intermediate to catalyst for asymmetric reaction of aldehydes with organozinc reagents	179
	PPh_3, CCl_4, Et_3N, MeCN (95)	Ligand for asymmetric allylic alkylation	180
	PPh_3, CCl_4, pyridine, MeCN $R_1 = H$, $R_2 = Ph$ (48) $R_1 = Bn$, $R_2 = H$ (47)	Ligand for asymmetric allylic alkylation	181

8.2.3. Oxazolines from β-Halo Amides

The preparation of oxazolines from β-hydroxy amides and $SOCl_2$ via the corresponding β-chloro amides under basic conditions is well known and has been discussed earlier. Potassium fluoride on alumina[182,183] has been reported as a mild alternative to the aqueous or alcoholic bases that are commonly used. The reaction is typically carried out in acetonitrile or tetramethylene sulfone and moderate to good yields of oxazolines and oxazines can be obtained as shown in Scheme 8.29.

In this same study, the authors also reported isolation of oxazoline **90** in moderate yield when propenylbenzamide **88** was reacted with *N*-bromosuccinimide (NBS) in CCl_4. A radical mechanism via intermediates **89a** and **89b** has been proposed. The generality and scope of this method has not been established (Scheme 8.30).

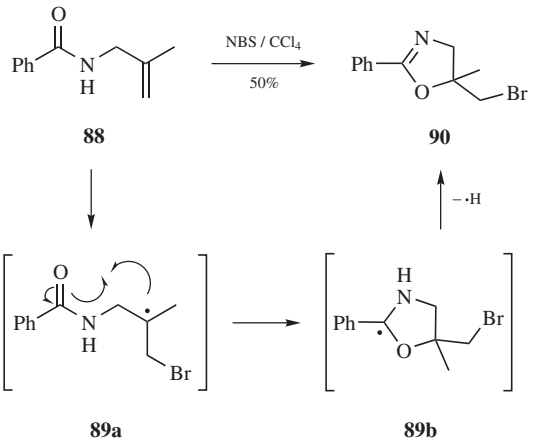


84 **85** **86** **87**

Scheme 8.29

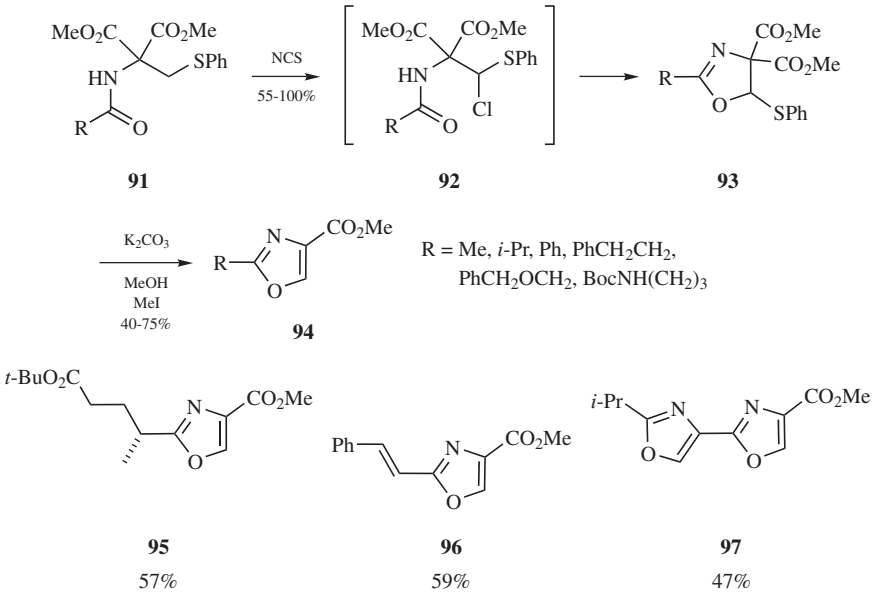
During an investigation of the synthesis of oxazole-4-carboxylates, Shapiro reported that chlorination of amino[(phenylthio)methyl]malonate derivatives **91** with *N*-chlorosuccinimide (NCS), followed by treatment with Hunig's base, afforded the oxazolines **93**. The oxazolines **93** were then converted to the respective oxazole-4-carboxylates **94–97** through decarbomethoxylation and elimination of thiophenoxide in the presence of methyl iodide. Methyl iodide traps the ejected thiophenoxide that would otherwise demethylate the oxazole-4-carboxylate (Scheme 8.31).[184]

Powerful Michael acceptors such as 2-chloro-2-cyclopropylidene acetates **98** react with carboxamides **99** to give 4-(cyclopropyl)oxazoline carboxylates **101**.[185,186] The reaction proceeds in a step-wise fashion involving first Michael addition of **99** to **98** to give an equilibrium mixture of **100a** and **100b** followed by intramolecular ring closure to the oxazoline **101**. Diastereoselectivities as high as 17:1 can be realized when substituted cyclopropylidenes (**98** $R_1 \neq H$) are employed. Examples are listed in Table 8.15 (Fig. 8.6; Scheme 8.32).



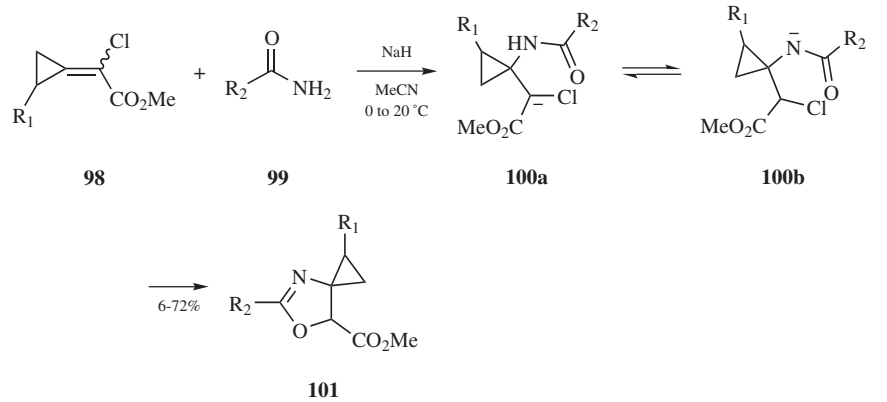
88 **90** **89a** **89b**

Scheme 8.30



Scheme 8.31

A similar reaction of vincinal aromatic or heterocyclic diamines **104** with 2-benzoylamino-3-chloropropenoic acid **102** resulted in spiro-2-oxazolines fused to a pyrazinone nucleus **108**.[187] It is believed that the enamide **102** first isomerizes to the *N*-acyl imine **103** followed by Michael addition of the diamine **104**. The resulting Michael adduct **105** cyclizes to **106** or **107** either of which leads to the same oxazoline **108**. Single-crystal X-ray confirmed the structure of **108**.[187] Unsymmetrical diamines gave two isomeric products with the predominant product



Scheme 8.32

TABLE 8.15. OXAZOLINECARBOXYLATES FROM 2-CHLORO-2-CYCLOPROPYLIDENEACETATES[a]

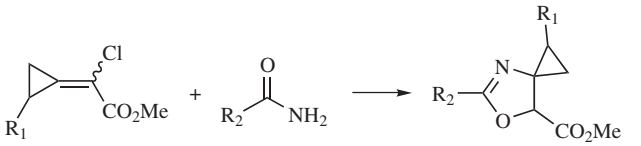


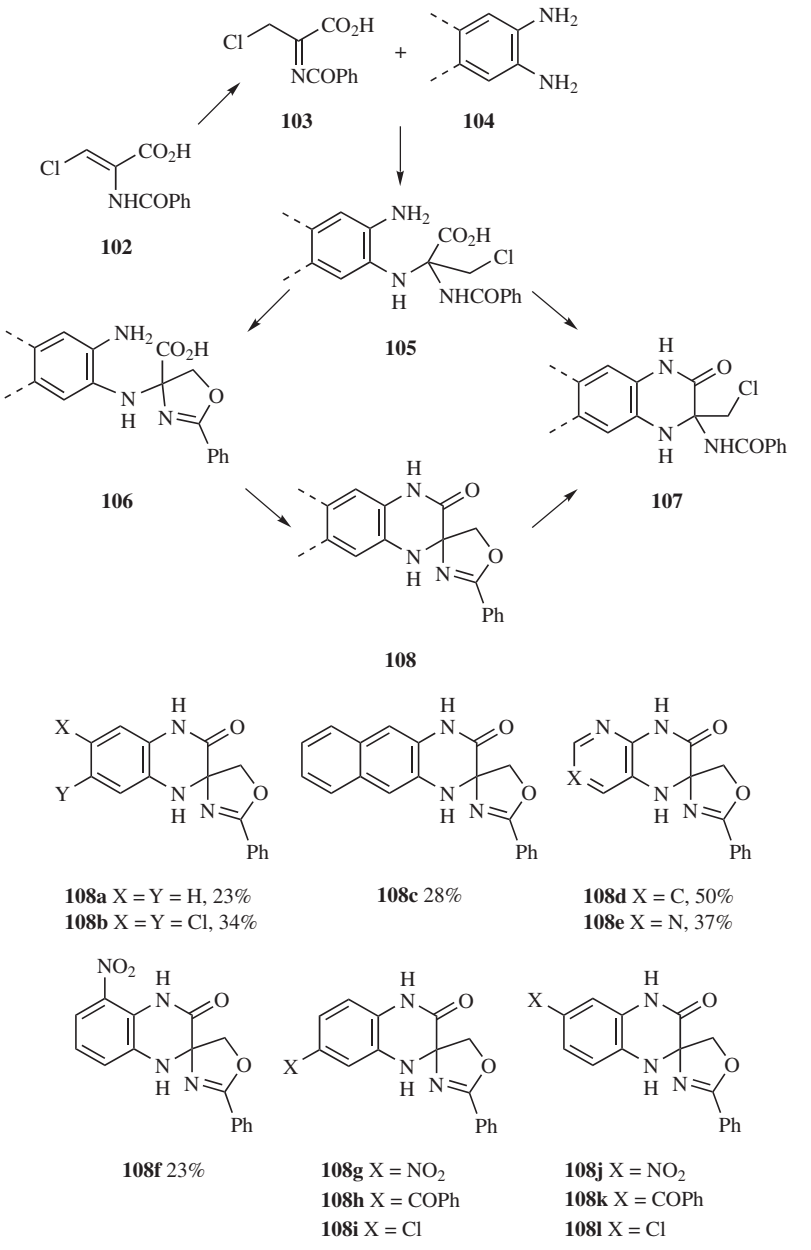
Figure 8.6

R_1	R_2	% Yield	dr
H	Ph	60	
H	3-C_5H_4N[b]	38	
H	2-C_4H_3O[c]	49	
H	4-CN—Ph	74	
H	2-Me—Ph	70	
H	3-Me—Ph	58	
H	4-Me—Ph	50	
H	3-F—Ph	75	
H	4-Br—Ph	73	
H	2-NO_2—Ph	47	
H	4-NO_2—Ph	47	
H	2-Cl—Ph	77	
H	4-Cl—Ph	68	
H	2-I—Ph	72	
H	3-I—Ph	49	
Et	Ph	56	9:1
Et	2-Me—Ph	68	17:1
Et	2-I—Ph	55	17:1
Et	4-NO_2—Ph	40	2:1
Et	3-F—Ph	46	7:1
Et	3-C_5H_4N[b]	25	5:1
CH_2CH_2OBn	4-NO_2—Ph	41	2:1
H	Me	6	
H	Et	24	
H	*n*-Pr	24	
H	*t*-Bu	25	

[a] Data from Ref. 185.
[b] Nicotinamide.
[c] Furan-2-carboxamide.

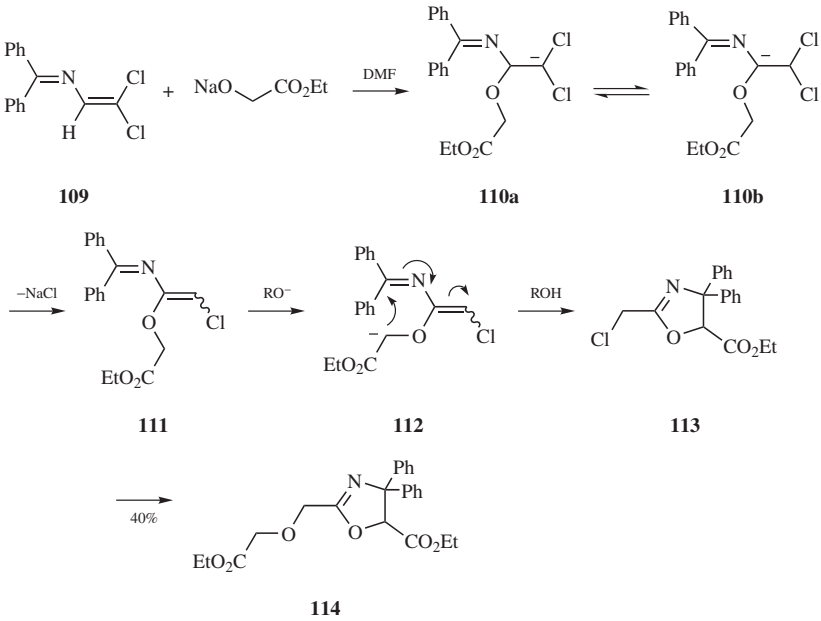
(**108g–h**) arising from initial Michael reaction of the most basic amino group (Scheme 8.33).

Similarly, Jacquot and co-workers[188] observed oxazoline formation from sodium ethyl glycolate (excess) and a 4,4-dichloro-azadiene derivative **109**. However, the generality of this reaction has not been established. The product can be rationalized according to the series of reactions shown in Scheme 8.34.



Scheme 8.33

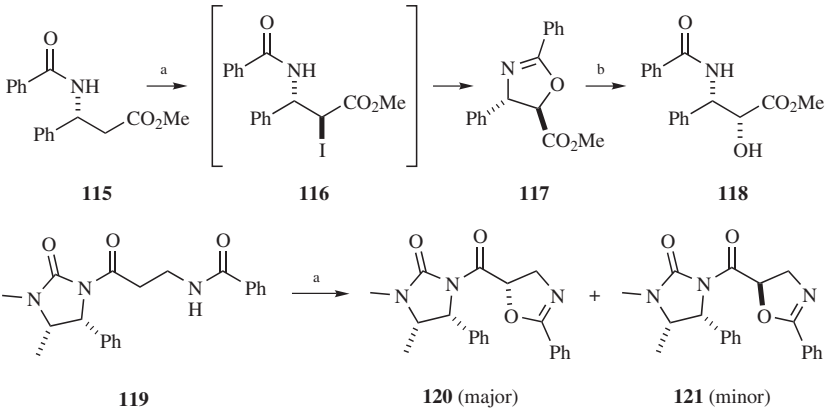
A highly stereoselective synthesis of β-amino-α-hydroxy acids from 3-benzoylamino carboxylates **115** has been developed by Cardillo and co-workers.[189,190] This one-pot procedure involves enolate formation of **115** using lithium hexamethyldisilazide followed by quenching the enolate with I_2. The iodine is



109 **110a** **110b** **111** **112** **113** **114**

Scheme 8.34

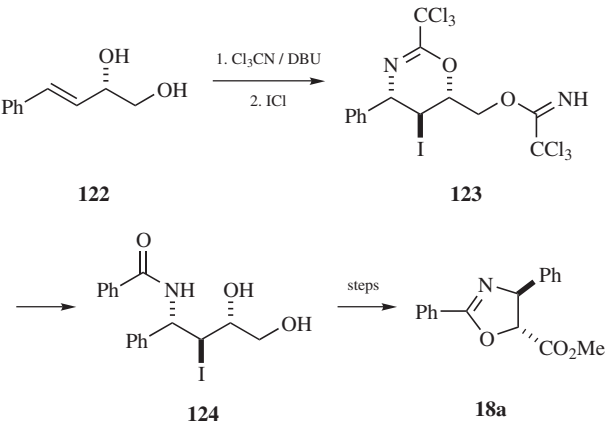
introduced from the sterically less hindered side to afford a *trans*-iodo-intermediate **116** in a 98:2 ratio. Under the reaction conditions, the intermediate iodo-compound **116** was cyclized to **117**. An alternative approach[191] based on a chiral imidazolidinone **119** has also been developed although with less impressive diastereoselectivity (60:40–85:15, depending on reaction conditions). Hydrolysis of **117** or **120** provides *anti*-β-amino-α-hydroxy acids (Scheme 8.35).



115 **116** **117** **118** **119** **120** (major) **121** (minor)

a: LiHMDS, I_2; b: 1 *M* HCl in MeOH

Scheme 8.35

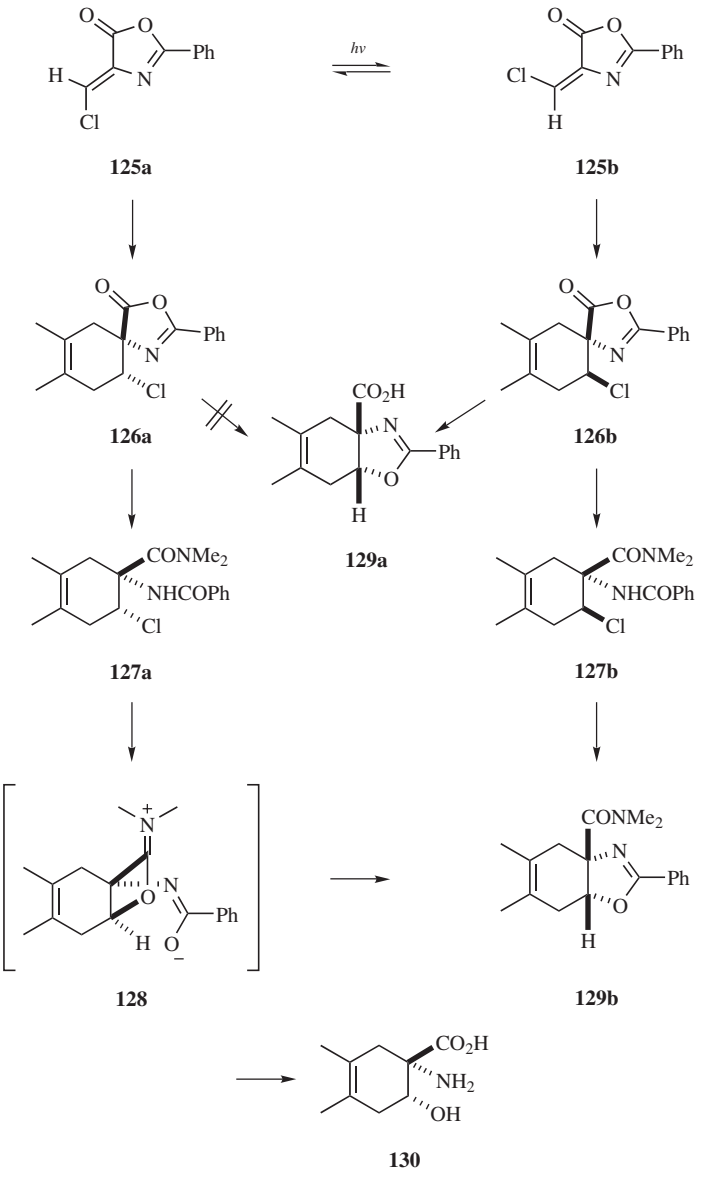


Scheme 8.36

Kang and co-workers prepared the β-halo amide arrangement required for oxazoline formation from allylic alcohols via a two-step process. For example, treatment of the allylic alcohol **122** with trichloroacetonitrile and base followed by activation of the double bond with iodine monochloride, provides **123**.[192–194] Hydrolysis of **123** gave **124** from which cyclization provided the oxazoline **18a** used for paclitaxel synthesis (Scheme 8.36).

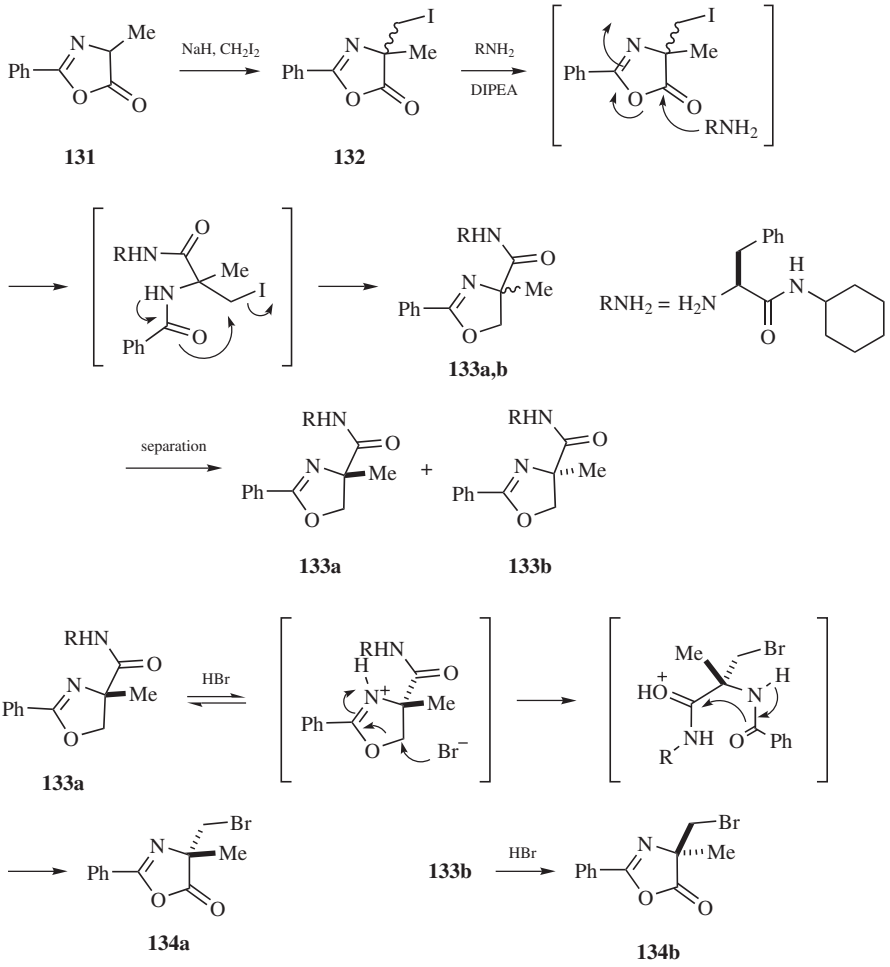
During a study of the synthesis of an α-amino-β-hydroxycyclohexenecarboxylic acid **130**, Gelmie and co-workers[195] noted that photoisomerization of the readily available (*Z*)-oxazolone **125a** gave the (*E*)-oxazolone **125b** in only ~50% yield. After chromatographic separation, **125b** was then converted to the spirooxazolone **126b**. Hydrolysis of **126b** provided the desired aminoacid **130** via oxazoline **129a**. However, the isomeric spirooxazolone **126a** could not be utilized because of incorrect stereochemistry for oxazoline formation. To circumvent the tedious separation of the two oxazolones as well as to improve the overall yield of the synthesis, the authors converted the mixture of isomeric Diels–Alder adducts **126a** and **126b** to the corresponding *N*,*N*-dimethylcarboxamides **127a** and **127b**. Now, anchimeric assistance from the *N*,*N*-dimethylcarboxamido group in the ''wrong'' isomer provided intermediate **128** with the proper stereochemistry for ring closure to produce **129b** that was hydrolyzed to **130** (Scheme 8.37).

Obrecht and co-workers found that *rac*-4-(iodomethyl)-4-methyl-2-phenyl-5(4*H*)-oxazolone **132** yields a separable mixture of diastereomeric oxazolines **133a** and **133b** upon reaction with (*S*)-Phe-cyclohexylamide.[196] After separation, each one of the diastereomeric oxazolines undergo further conversion to give optically pure (*R*)- and (*S*)-bromoazlactones **134a** and **134b** after reaction with 33% hydrogen bromide in acetic acid. Subsequent methanolysis of **134a** and **134b** allows the preparation of a wide range of (*R*)- and (*S*)-α-methylserine analogues (Scheme 8.38).



Scheme 8.37

An electrochemical method for the synthesis of a series of 4-(alkylamino)-2-phenyloxazolines **139a–f** from *N*-(2,2-dichlorovinyl)amides **135** has been reported.[197] The starting *N*-(2,2-dichlorovinyl)amide **135**, readily available from chloral and amides, undergoes facile reaction with amines to give **136**. Cathodic reduction of **136** generates chlorocarbanionic intermediates **137** and **138** that

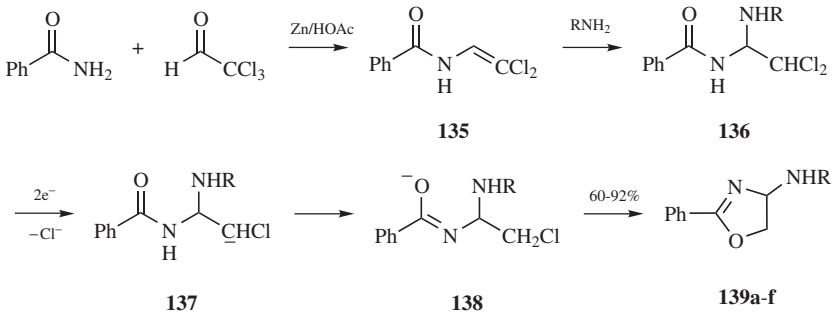


Scheme 8.38

cyclize to provide the oxazoline. Thus far, the method has only been demonstrated for 2-phenyl substituted oxazolines (Scheme 8.39).

8.2.4. Oxazolines from Nitriles

Nitriles contribute to oxazoline synthesis through several different modes of reaction. They react with amino alcohols directly to give oxazolines. In particular, trichloacetonitrile reacts with a variety of alcohols, and the resulting imidates undergo ring closure to oxazolines with proper activation or with a leaving group β to the imidate. Nitriles also participate in Ritter reactions to give oxazolines.

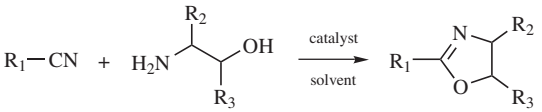


R = Bn, cyclohexyl, *i*-Pr, Bu, Me, Et

Scheme 8.39

8.2.4.1. Direct Methods

A common and effective direct approach to unsubstituted or multiply substituted oxazolines is the Lewis acid catalyzed reaction of nitriles with amino alcohols in an alcoholic or aromatic solvent (chlorobenzene) at reflux. The most common Lewis acids employed include $ZnCl_2$, $ZnBr_2$, $NiBr_2$, $CuCl_2$, and kaolinitic clay.[198] Microwave irradiation has also been reported to facilitate the transformation.[199,200] Alternatively, the condensation can be carried out in the presence of catalytic amounts of potassium carbonate. The method works well for both aliphatic and aromatic nitriles, with retention of stereochemistry. Some representative examples from the recent literature are listed in Table 8.16 (Scheme 8.40).[28,35,201–213]



Scheme 8.40

2-Heteroaryloxazolines can also form stable metal complexes that quite often can be isolated.[207]

In the absence of a catalyst, much higher temperatures are required for the reaction. For example, neat succinonitrile reacts with ethanolamine to initially give the iminoazacyclopentanediol **140** and the triol **141**, respectively. Further heating at high temperature to distill out ethanolamine effects cyclization of **140** and **141** to the bis(oxazoline) **142**.[214] Excellent yields of oxazolines can be obtained this manner (Scheme 8.41).

TABLE 8.16. OXAZOLINES FROM NITRILES AND AMINO ALCOHOLS

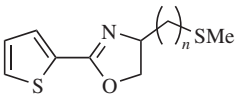
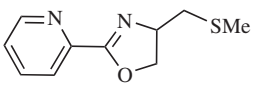
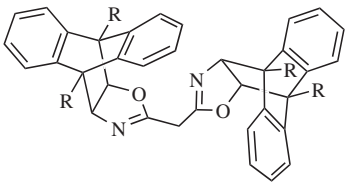
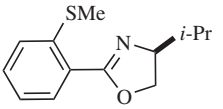
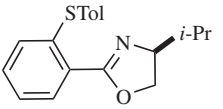
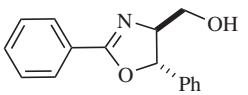
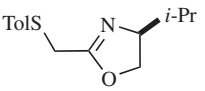
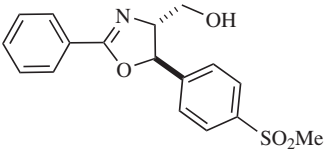
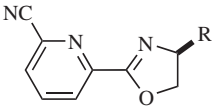
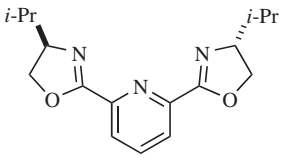
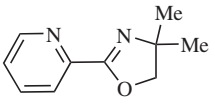
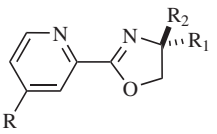
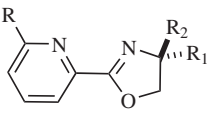
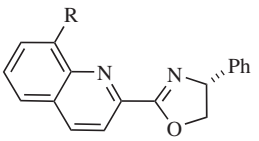
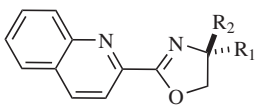
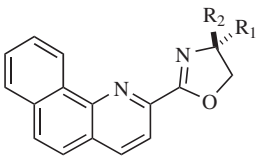
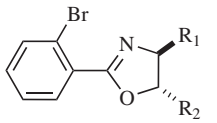
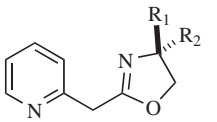
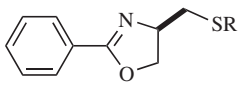
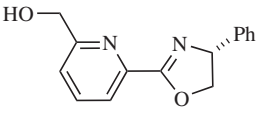
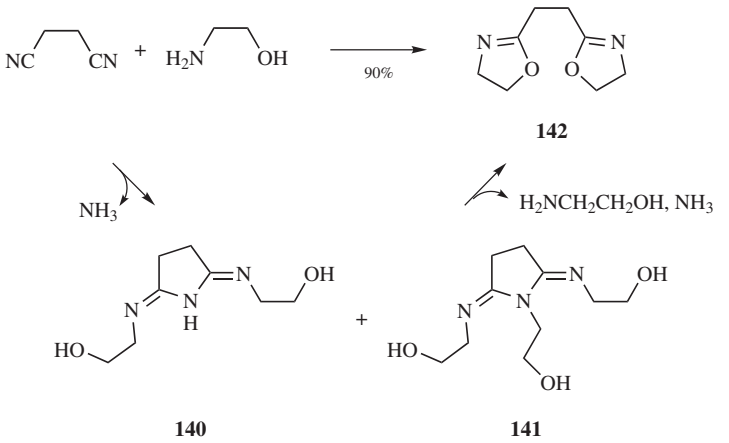
Product	Conditions (% Yield)	Comments	References
	$ZnCl_2$ $n = 1$ (67) $n = 2$ (62)		28
	$ZnCl_2$ (36)		28
	$ZnCl_2$ R = H (68) R = Me (100)		35
	$ZnCl_2$, PhCl, reflux	Diastereoselective oxidation of sulfide	201
		Diastereoselective oxidation of sulfide	202, 203
	Glycerol, ethylene glycol, cat. K_2CO_3, 115 °C (91)		204
	$ZnCl_2$, PhCl, reflux (89)	Diastereoselective oxidation of sulfide	204
	Glycerol, ethylene glycol, cat. K_2CO_3, 115 °C (94)		205
	$ZnCl_2$, PhCl, reflux R = *i*-Pr (31) R = *t*-Bu (44)	Ligand for asymmetric allylic alkylation	206
	$ZnCl_2$, PhCl, reflux (60)	Ligand for asymmetric allylic alkylation	206
	$NiBr_2$, PhCl, reflux (80)	Metal complex	207

TABLE 8.16 (*Continued*)

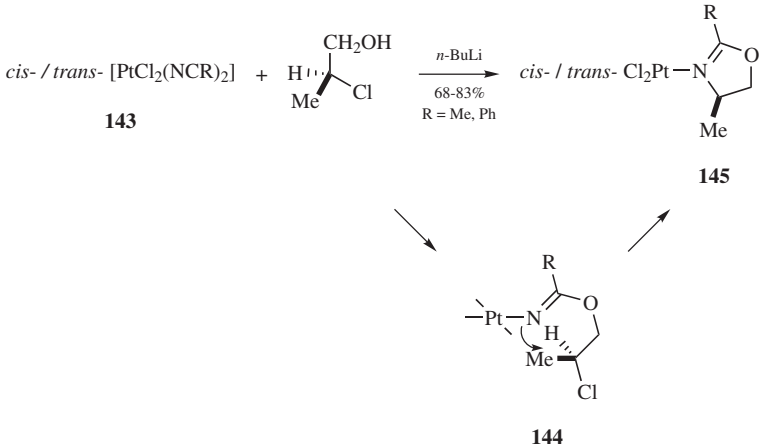
Product	Conditions (% Yield)	Comments	References
	$ZnCl_2$, PhCl, reflux R = H, Cl, OMe R_1 = H, Ph R_2 = H, *i*-Pr (30–61) (6 examples)	Ligands for asymmetric allylic alkylation	208
	$ZnCl_2$, PhCl, reflux R = 4-Me-Ph, *t*-Bu R_1 = H, Ph R_2 = H, *i*-Pr, *t*-Bu (27–64) (9 examples)	Ligands for asymmetric allylic alkylation	209
	$CuCl_2$, 100 °C, 10 mbar, neat R = H (82) R = OH (55)	Ligands for asymmetric allylic alkylation	210
	$ZnCl_2$, PhCl, reflux R_1 = H, R_2 = *i*-Pr (61) R_1 = Ph, R_2 = H (22) R_1 = H, R_2 = *t*-Bu (76)	Ligands for asymmetric allylic alkylation	209
	$ZnCl_2$, PhCl, reflux R_1 = H, R_2 = *i*-Pr (69) R_1 = Ph, R_2 = H (58)	Ligands for asymmetric allylic alkylation	209
	$ZnCl_2$, PhCl, reflux R_1 = Me; *i*-Pr; *t*-Bu; Bn; $CH_2OTBDMS$ R_2 = H, Ph (30–60) (5 examples)	Ligands for asymmetric 1,4-addition of Grignard reagents to enones	211
	$ZnCl_2$, PhCl, reflux R_1 = H, R_2 = *i*-Pr (57) R_1 = Ph, R_2 = H (42)	Ligands for asymmetric allylic alkylation	209, 212
	$ZnBr_2$, PhCN, reflux R = *t*-Bu, Bn, Me (90–95) (3 examples)	Stereoselective alkylation of sulfoxides and sulfones	213
	$CuCl_2$, 100 °C, 10 mbar, neat (44)	Ligands for asymmetric allylic alkylation	210



Scheme 8.41

cis- and *trans*-$[PtCl_2(NCR)_2]$ Nitrile complexes **143** have been reported to react with enantiomerically pure 2-chloro-1-propanol with complete inversion to give oxazoline platinum complexes **145** (Scheme 8.42).[215]

Aliphatic and aromatic nitriles are often converted to the corresponding imidates that then react with amino alcohols to provide oxazolines. This two-step process offers milder conditions. Generally, a mixture of the imidate (free base or hydrochloride) is allowed to react with the amino alcohol in a solvent (alcohols, CH_2Cl_2, $CHCl_3$) with or without a tertiary base. As expected, the cylization proceeds with retention of stereochemistry when chiral amino alcohols are used. Representative examples are shown in Table 8.17.[33,62,63,139,216–225] The ready availability of benzimidates and trimethyl orthobenzoates make them ideal surrogates for benzonitrile.[226–229]



Scheme 8.42

TABLE 8.17. OXAZOLINES FROM IMIDATES AND AMINO ALCOHOLS

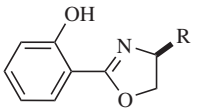
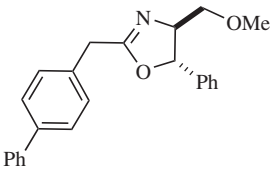
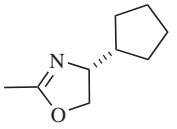
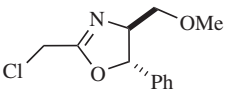
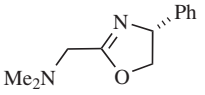
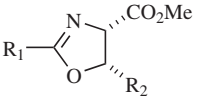
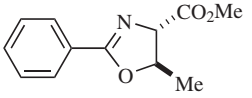
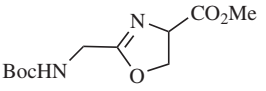
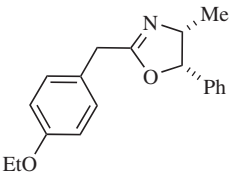
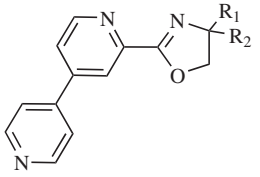
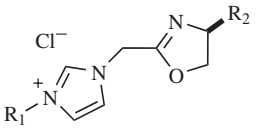
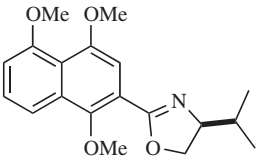
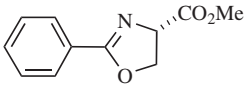
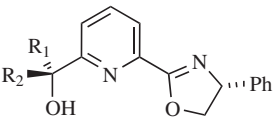
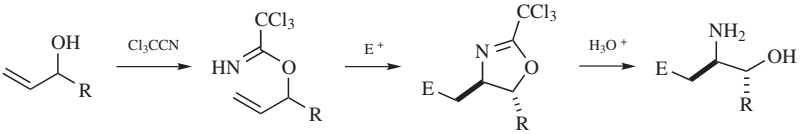
Oxazoline	Conditions (% Yield)	Comments	References
	Imidate ·HCl, IPA, reflux R = Ph, CO_2i-Pr, CO_2i-Bu, CO_2t-Bu (73)		33
	Imidate ·HCl, CH_2Cl_2, 0 °C (67)		62
	Imidate ·HCl, CH_2Cl_2, rt (70)		63
	Imidate ·HCl, Et_3N, CH_2Cl_2 (63)		139
	Imidate ·HCl, Et_3N, CH_2Cl_2 (63)		139
	Imidate ·HCl, CH_2Cl_2, Et_3N R_1 = Bn, $CH_2CH_2CH_2Ph$ R_2 = H, Me (85–90) (4 examples)		216
	Imidate ·HCl, $CHCl_3$, reflux (85)	Intermediate for oxazolines suitable to graft onto silica as chiral stationary phases	217
	Imidate free base, CH_2Cl_2, rt (80)	Intermediate for synthesis of conformationally restricted oxazole containing di- and tripeptide mimetics	218
	Imidate free base, CH_2Cl_2, pyridine, rt (99)		219
	Imidate free base, chlorobenzene, cat. HCl R_1 = H, Et, Ph R_2 = H, *i*-Pr, *i*-Bu, *t*-Bu, Bn (67–83) (6 examples)	Ligands for Rh(I)-catalyzed asymmetric hydrosilylation	220

TABLE 8.17 (*Continued*)

Oxazoline	Conditions (% Yield)	Comments	References
	Imidate free base, EtOH, cat. HCl, reflux R_1 = Me, *t*-Bu R_2 = Bn, *i*-Pr (64–72) (4 examples)	Metal complexes with rhodium and palladium	221
	Imidate ·HBF_4, DCE, reflux (67)	Intermediate for the total synthesis of (−)-*O*-methyllancistrocladine synthesis	222
	Imidate ·HCl, CH_2Cl_2, Et_3N, reflux (80)	Intermediate for the total synthesis of iminoribitol, arabinitol, xylitol, and lyxitol Intermediate for the preparation of vinyloxazolines for stereoselective nitrile oxide cycloaddition	223, 224
	Imidate free base, CH_2Cl_2, cat. H_2SO_4, reflux (91)	Intermediate for polymer supported catalyst for asymmetric allylic alkylation	225

8.2.4.2. *Indirect Methods*

Allyl alcohols readily react with trichloroacetonitrile to give the corresponding trichloroacetimidates **145**. Activation of the double bond with electrophilic reagents results in ring closure to yield oxazolines **146**. The most commonly employed electrophiles include iodine, iodine monochloride, phenylselenyl chloride, and mercuric trifluoroacetate. Other nitriles including cyanogen bromide and *N*,*N*-dimethylcyanamide can also be used. Since oxazolines readily hydrolyze to amides, the net effect of this reaction sequence is to produce β-amino alcohols **147** from an allyl alcohol. This strategy has been employed in numerous total syntheses of natural products. Examples are listed in Table 8.18 (Fig. 8.7; Scheme 8.43).[230–236]



145 **146** **147**

Scheme 8.43

TABLE 8.18. CONVERSION OF ALLYLIC ALCOHOLS TO β-AMINO ALCOHOLS VIA OXAZOLINES

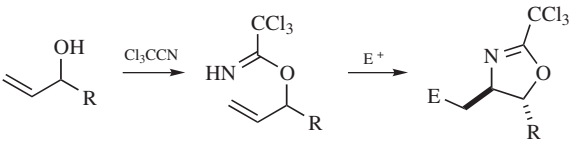
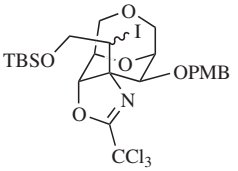
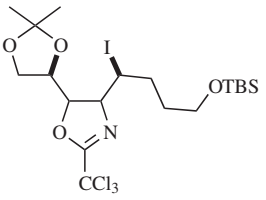
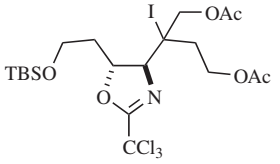
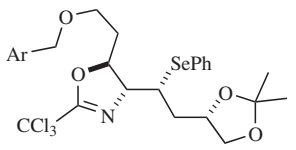
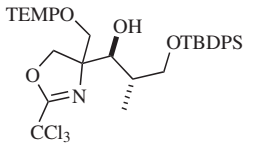
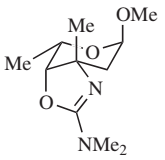
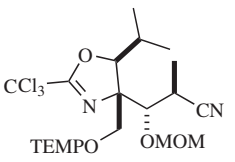
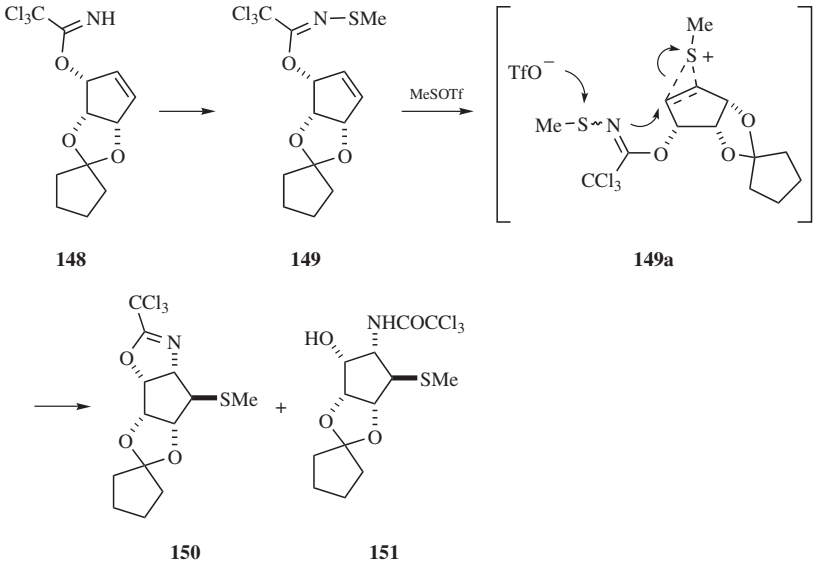


Figure 8.7

Oxazoline	Conditions (% Yields)	Comments	References
	1. Cl_3CCN / DBU 2. $I(collidine)_2ClO_4$ (86)	Intermediate for the symmetric synthesis of tetrodotoxin	230
	1. Cl_3CCN / DBU 2. IBr (85–90)	Intermediate for the asymmetric synthesis of (−)-swainsonine	231
	1. Cl_3CCN / DBU 2. I_2 (76–89)	Intermediate for the asymmetric synthesis of (−)-platynecine and (−)-hadinecine	232
	1. Cl_3CCN / DBU 2. PhSeCl (67)	Intermediate for the asymmetric synthesis of *N*-acetylneuraminic acid	233
	1. Cl_3CCN / DBU 2. $Hg(CO_2CF_3)_2$ 3. $LiBH_4$, TEMPO (73)	Intermediate for the asymmetric synthesis of (+)-lactacystin	234
	1. Me_2NCN, NaH 2. $Hg(CO_2CF_3)_2$ 3. $NaBH_4$ (96)	Intermediate for the total synthesis of methyl α-L-vancosaminide	235
	1. Cl_3CCN, DBU, EtCN 2. $Hg(CO_2CF_3)_2$, THF 3. TEMPO, $LiBH_4$ (45)	Intermediate for the asymmetric synthesis of (+)-lactacystin	236



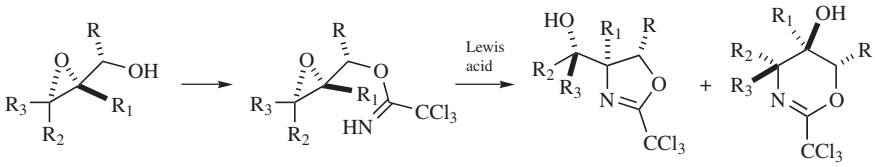
148 **149** **149a**

150 **151**

Scheme 8.44

During an investigation[237] of the total synthesis of (+)-mannostatin, reaction of the trichloroacetimidate **148** with methanesulfenyl chloride produced the *N*-sulfenylimidate **149** as the only product, presumably the result of an inductively deactivated olefin. Activation of **149** for cyclization required the super electrophilic agent methanesulfenyl triflate. Consistent with steric and ring strain considerations, the electrophile was introduced from the less-hindered face of the olefin yielding only the cis-fused oxazoline **150** together with **151** (Scheme 8.44).

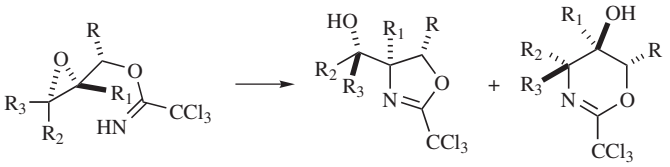
Epoxytrichloroacetimidates **153** also undergo oxazoline ring formation in the presence of a catalytic amount of Lewis acids.[238] Diethylaluminum chloride was found to be superior to boron trifluoride, which tends to further hydrolyze the oxazoline **154** to the trichloroacetamide. Generally, formation of the six-membered ring oxazine **155** is not favored, but it can be a serious side reaction if the epoxide contains substituents that stabilize the incipient cation generated prior to ring closure. Examples from this study are summarized in Table 8.19 (Fig. 8.8; Scheme 8.45).



152 **153** **154** **155**

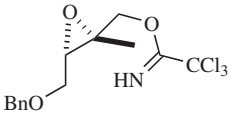
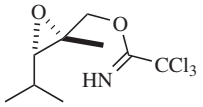
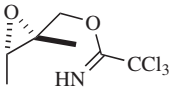
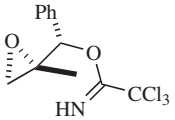
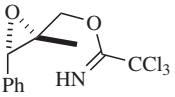
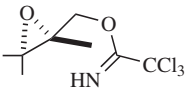
Scheme 8.45

TABLE 8.19. OXAZOLINES FROM CYCLIZATION OF EPOXYTRICHLOROACETIMIDATES CATALYZED BY DIETHYLALUMINUM CHLORIDE[a]



154 **155**

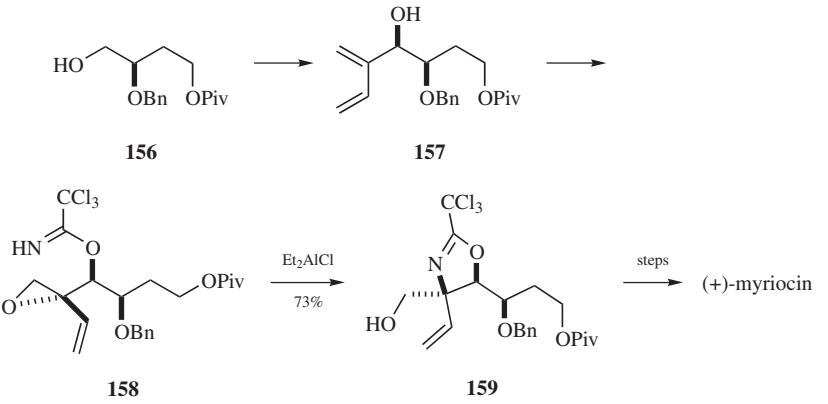
Figure 8.8

Substrate	% Yield	Oxazoline **154**	Oxazine **155**
	79	100	0
	76	100	0
	73	100	0
	54	100	0
	76	58	42
	76	25	75

[a] Data from Ref. 238.

An epoxytrichloroacetimidate was used as a key intermediate in the total synthesis of (+)-myriocin.[239] The intermediate diene **157** was constructed in several steps from **156**. Stereospecific epoxidation of **157**, followed by imidate formation gave **158**. Treatment of **158** with Et_2AlCl provided **159** for which the proper stereochemistry of the amino group is now set for the natural product (Scheme 8.46).

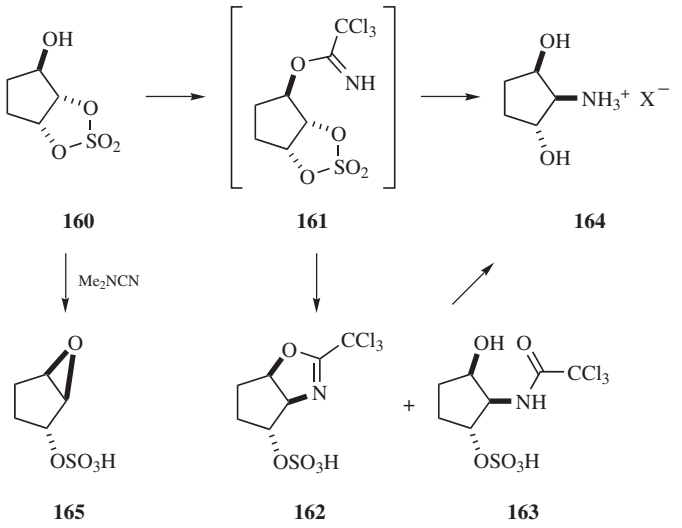
Direct displacement of a suitable leaving group α to an imidate is also known. For example, Imperiali and co-workers[240] obtained the (*syn,anti*)-2-amino-1,3-diol



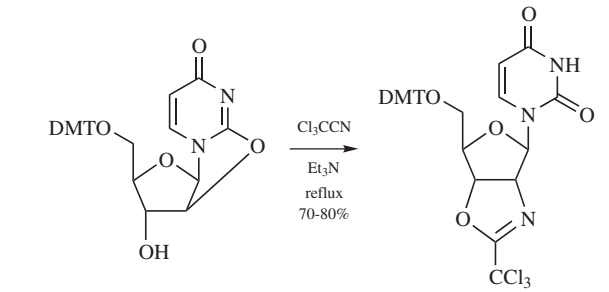
Scheme 8.46

functional group array present in aminocyclitols via a stereospecific and regiospecific ring closure of the trichloroacetimidate derived from a cyclic sulfate **160**. A large excess of trichloroacetonitrile is required to suppress the formation of the epoxide **165** that is the exclusive product using a less reactive reactive nitrile, for example, *N*,*N*-dimethylcyanamide (Scheme 8.47).

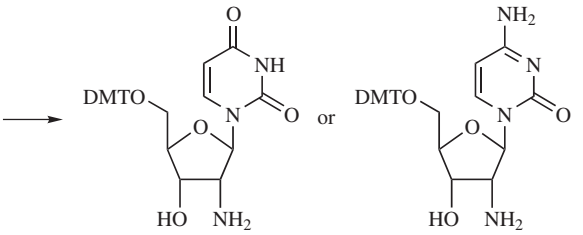
The synthesis of a 2′-amino-2′-deoxyuridine **168** and a 2′amino-2′deoxycytidine **169** from inexpensive uridine has been described. A key transformation in the synthesis is the introduction of an amino functionality via a trichloroacetimidate.[241] This approach also avoids the use of azide that is not desirable for large-scale use (Scheme 8.48).



Scheme 8.47



166 **167**

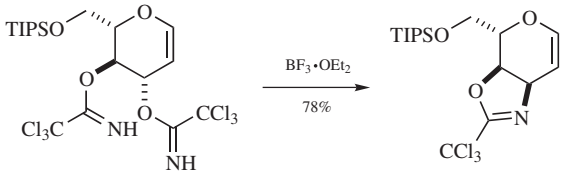


168 **169**

DMT = dimethoxytrityl

Scheme 8.48

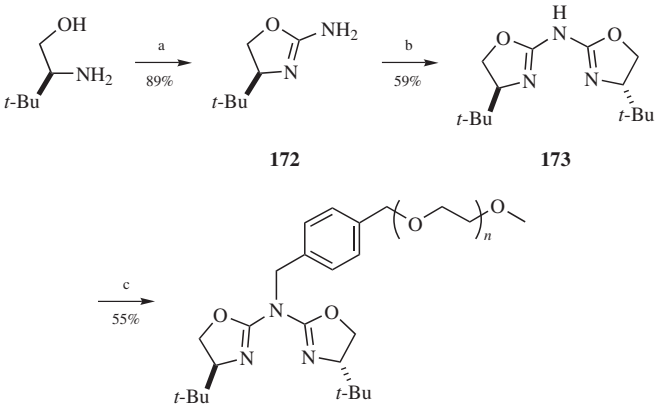
Danishefsky and co-workers described a regioselective formation of an oxazoline **171** from a bis(trichloroacetimidate) **170** in their synthesis of staurosporine.[242] The observed regioselectivity is apparently a result of a vinylogous Schmidt glycosylation (Scheme 8.49).



170 **171**

Scheme 8.49

Cyanogen bromide reacts with amino alcohols to give 2-aminooxazolines that condense in the presence of benzaldehyde and *p*-toluenesulfonic acid with loss of ammonia to give aza-bis(oxazolines) **173**.[243] Aza-bis(oxazolines) such as **173** are emerging as a new and important class of chiral ligands for asymmetric processes with the added advantage that they can be immobilized on solid supports (Scheme 8.50).



172 **173**

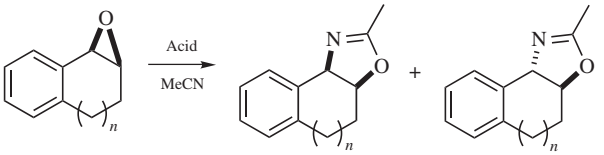
174

a: BrCN, MeOH, 0 °C; b: *p*-TsOH, PhCHO, toluene, reflux
c: *n*-BuLi, MeOPEG-Br

Scheme 8.50

8.2.4.3. Oxazolines from Ritter Reaction

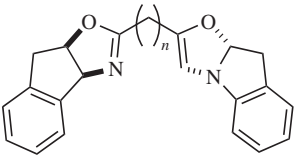
Enantiomerically pure epoxides and diols, readily available through the asymmetric epoxidation and asymmetric dihydroxylation reactions, are ideal precursors to prepare cis-amino alcohols via the Ritter reaction.[244,245] A Merck group has shown that indene oxide **175a** can be converted effectively to *cis*-1-amino-2-indanol, a key fragment of the HIV-protease inhibitor Indinavir via the *cis*-oxazoline **176a**.[246,247] The reaction is completely regiospecific and the stereochemical outcome is determined solely by the chirality at C-2. With larger rings, both cis- and trans-amino alcohols are formed (Scheme 8.51).



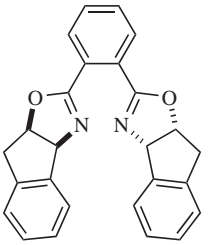
175a-c **176a-c** **177a-c**

	Acid	*cis*- / *trans*-
$n = 0$	TfOH	100:0
	MsOH	100:0
$n = 1$	TfOH	37:63
	MsOH	50:50
$n = 2$	TfOH	41:59
	MsOH	53:47

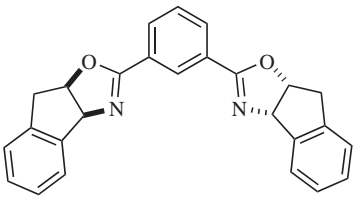
Scheme 8.51



178a n = 1, 60%
178b n = 2, 54%
178c n = 3, 63%



179 51%



180 49%

Scheme 8.52

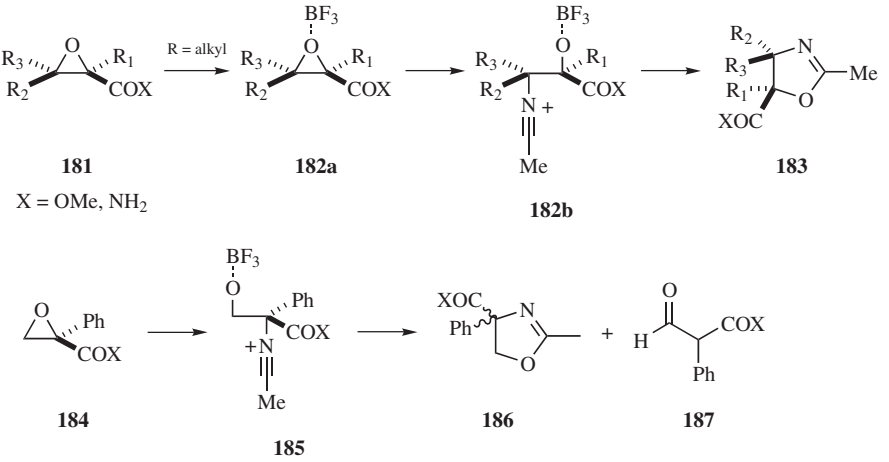
Ritter reaction of *cis*-indane-1,2-diol with other nitriles leads to C_2-symmetric bis(oxazolines) **178**–**180** that are ligands in a number of transition metal catalyzed processes (Scheme 8.52).[248]

Alkyl substituted 1,3-dioxolanes react with acetonitrile in the presence of concentrated sulfuric acid to give oxazolines. The reported yields were quite low and did not appear to be synthetically useful.[249]

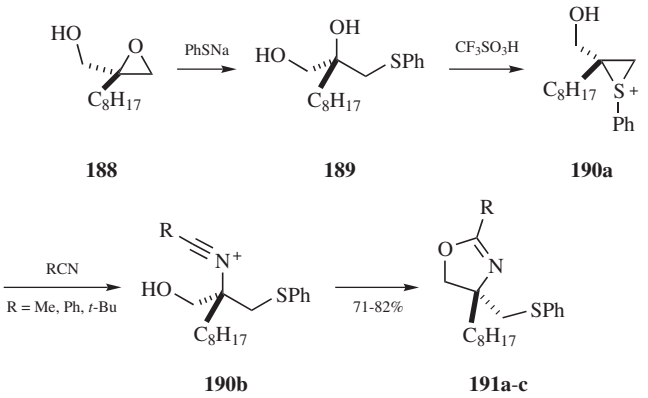
Epoxides also participate in the Ritter reaction with nitriles. An investigation of the ring opening of several alkyl-substituted glycidic esters and amides **181** showed that this transformation occurs with inversion and is completely regiospecific.[250] Esters appeared to be somewhat more reactive than amides. However, phenyl-substituted glycidic esters and amides **184** are almost totally nonstereoselective. In addition, the oxazolines **186** are isolated in low yield due to the propensity of intermediate **185** to generate an aldehyde byproduct **187** (Scheme 8.53).

Epoxides also undergo the Ritter reaction in good yields with retention of configuration via a episulfonium intermediate **190a** (double-inversion process).[251] For monosubstituted epoxides, the yields of oxazolines are lower due to nondiscriminatory attack of the nitrile on both the primary and the secondary carbon atom of the episulfonium intermediate. Complete retention of configuration is still observed despite the lower yield (Scheme 8.54).

Olefins also undergo the Ritter reaction with nitriles in the presence of diphenyl diselenide, ammonium persulfate, and trifluoromethanesulfonic acid to produce oxazolines.[252–254] When cyanamide is used, 2-aminooxazolines are obtained. The active electrophilic agent is phenylselenyl sulfate formed by oxidation of diphenylselenide with ammonium persulfate. The reaction is trans-stereospecific.



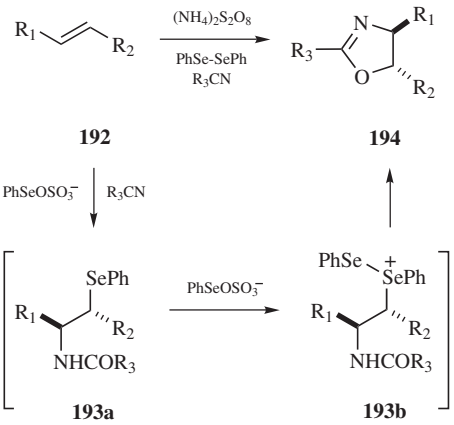
Scheme 8.53



Scheme 8.54

This reaction has been applied for the synthesis of the Taxol side chain from the *trans*-alkene (R_1 = Ph, R_2 = CH_2OAc) (Table 8.20, entry 11, Fig. 8.9; Scheme 8.55).

α-Furfuryl amides **196a–c** have been prepared via a Lewis acid catalyzed allylic substitution of furfuryl carbinol acetates **195** with nitriles via the Ritter reaction.[255] Alkyl nitriles yield the (1′*S*)-configured amides **196a–c** as the predominant products. However, reaction of **195** with benzonitrile resulted in an oxazoline **197** that was hydrolyzed to the (1′*R*)-configured amide **198**. This method of preparation of α-furfuryl amides starts with **195**, which is readily available from 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN)[256] and avoids the multi-step, low-yield synthesis via amidoalkylation of furan (Scheme 8.56).



Scheme 8.55

TABLE 8.20. OXAZOLINES FROM ALKENES[a]

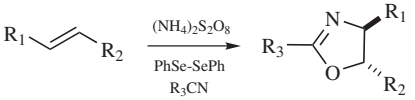


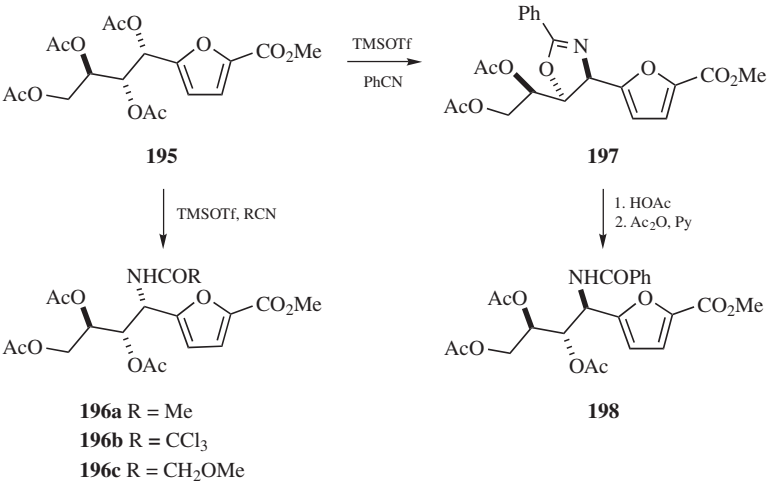
Figure 8.9

Entry	R_1		R_2	R_3	% Yield
1	Ph		H	Me	60
2	Bn		H	Me	62
3	octyl		H	Me	85
4	*n*-Pr		*n*-Pr	Me	87
5		cyclopentene		Me	60
6		cyclohexene		Me	80
7	Ph		H	NH_2	54
8	octyl		H	NH_2	45
9	*n*-Pr		*n*-Pr	NH_2	42
10	Ph		CH_2OMe	Ph	60
11	Ph		CH_2OAc	Ph	63

[a] Data from Refs. 252 and 253.

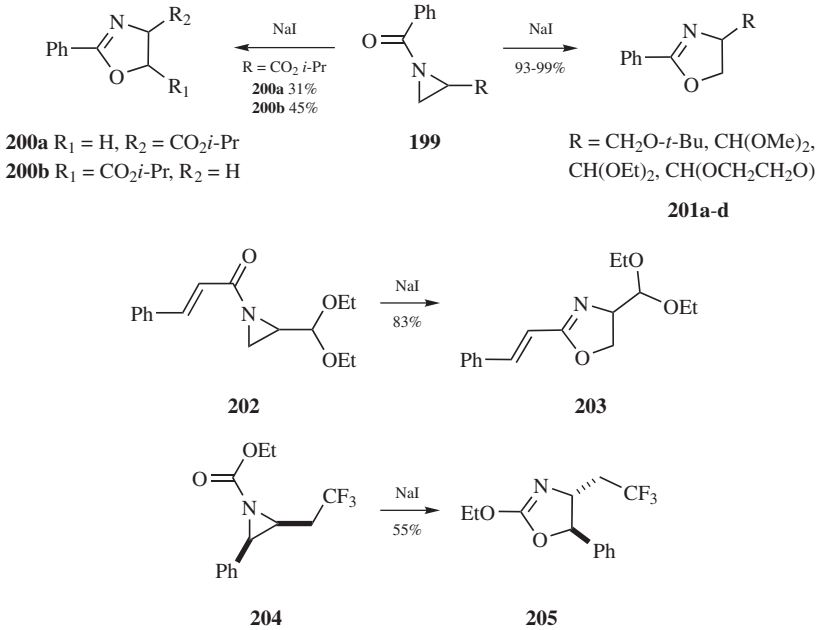
8.2.5. Oxazolines from *N*-Acylaziridines

N-Acylaziridines **199** undergo nucleophile-induced (typically by an iodide) rearrangement to oxazolines.[257,258] Excellent regiospecific ring-enlargement to a 2,4-disubstituted-oxazoline **201a–d** is observed with an alkyl substituted aziridine; on the other hand, mixtures of 2,4- and 2,5-disubstituted oxazolines **200a** and **200b**

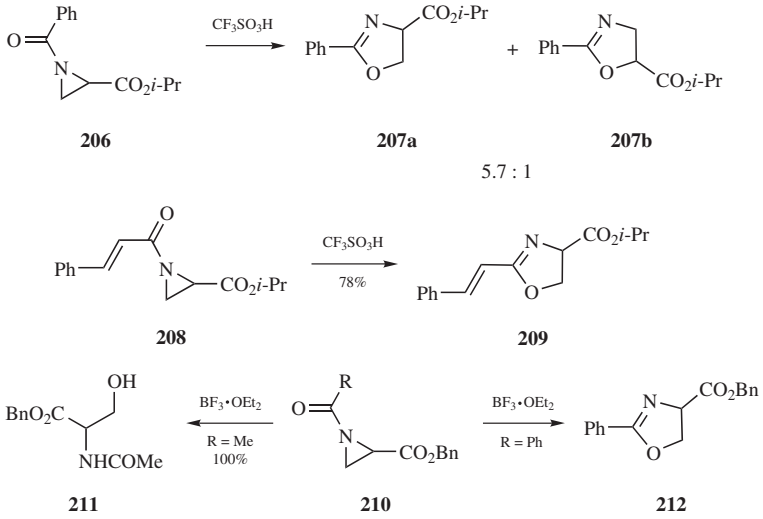


Scheme 8.56

are obtained with aziridines containing an electron-withdrawing group. A single example showed that ring enlargement occurred regiospecifically and with total inversion when a phenyl substituted aziridine **204** is subjected to rearrangement with iodide (Scheme 8.57).



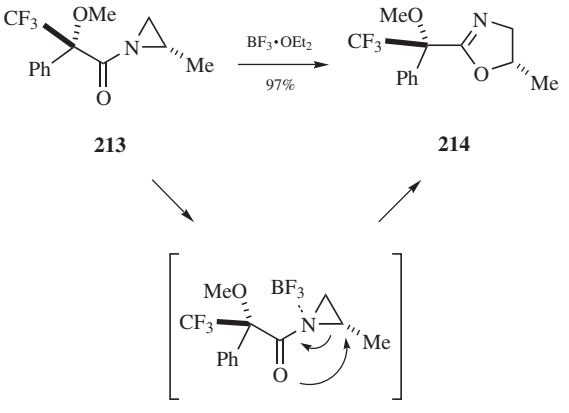
Scheme 8.57



Scheme 8.58

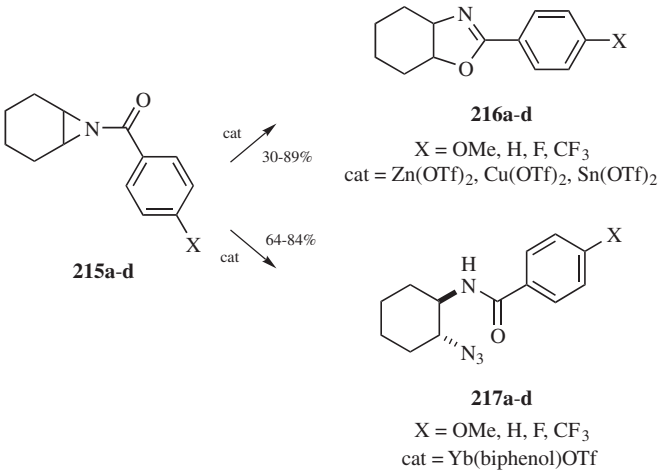
The rearrangement can also be promoted by acid.[257,259,260] Under acid catalysis, *N*-acylaziridines substituted with an electron-withdrawing group produce a 2,4-disubstituted oxazoline as the major product.[257] Borontrifluoride etherate ($BF_3 \bullet OEt_2$) has also been used successfully for an *N*-benzoyl, but not an *N*-acetyl-substituted aziridine (Scheme 8.58).[259]

Hori and co-workers studied the $BF_3 \bullet OEt_2$ catalyzed isomerization of a chiral *N*-acylaziridine **213** to the oxazoline **214**.[261] It was established that the ring expansion proceeds with retention of configuration. The authors have proposed a S_Ni mechanism for this transformation through the transition state **213a**. Ab initio molecular orbital calculations agree well with this hypothesis (Scheme 8.59).



Scheme 8.59

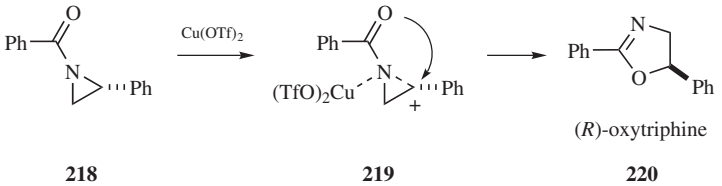
Lectka and co-workers[262] studied the ring opening of a series of *N*-acylaziridines **215a–d** to oxazolines **216a–d** promoted by Lewis acids such as $Zn(OTf)_2$, $Cu(OTf)_2$, and $Sn(OTf)_2$. Good yields of **216a–d** can be obtained, even in the presence of nucleophiles such as trimethylsilyl azide. It was further observed that the rate of reaction is increased if the phenyl ring contains electron-donating substituents. These observations are consistent with the hypothesis of N-coordination[263] with the rearrangement proceeding in a heterolytic stepwise fashion. In contrast, treatment of the same *N*-acylaziridines **215a–d** with oxophilic Lewis acids such as Yb(2,2′-biphenol)OTf in the presence of nucleophiles resulted in ring-opened products **217a–d** with incorporation of the nucleophile. In this case, rate accelerations are observed if the phenyl ring is substituted with electron-withdrawing substituents (Scheme 8.60).



Scheme 8.60

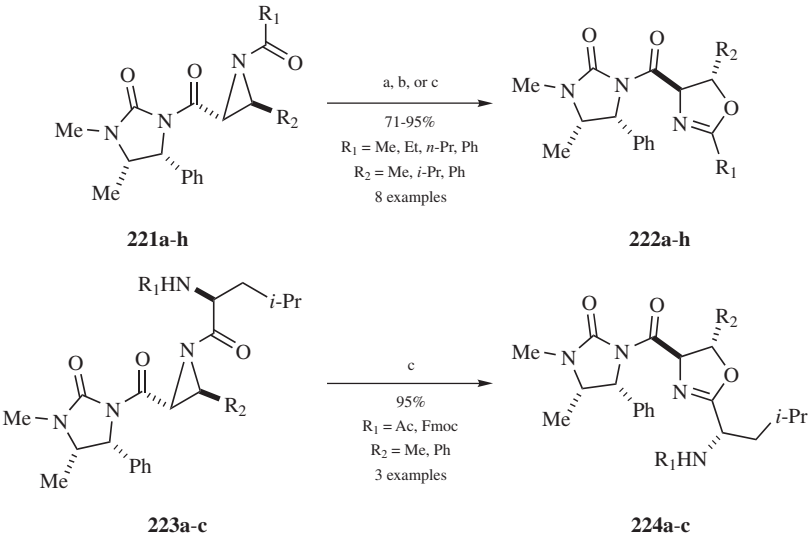
The exclusive formation of enantiomerically pure, naturally occurring (*R*)-oxytriphine **220** is indicative of an intermediate solvated tight carbocation pair **219** in the rearrangement (Scheme 8.61).[262]

Cardillo and co-workers[259,264–269] extended this rearrangement to *N*-acylaziridine-2-carboxamides. In contrast to acylated aziridine carboxylates, both the



Scheme 8.61

benzoylated and acetylated aziridinylimides rearrange spontaneously in $CHCl_3$, although acetylated derivatives are observed to be slower. The reaction is clearly acid catalyzed since addition of a stronger acid such as Amberlyst H-15 or BF_3•OEt_2 is required when the reaction is carried out in solvents such as toluene or CH_2Cl_2. The rearrangement proceeds via an S_Ni mechanism with preservation of the stereochemistry at the aziridine carbon. Finally, note that *N*-Boc protected aziridines and aziridinylimides do not rearrange to oxazolines. Instead, they ring expand to oxazolidinones in the presence of Lewis acids such as $Cu(OTf)_2$, $Zn(OTf)_2$, or BF_3•OEt_2. Magnesium bromide etherate is not an active catalyst (Scheme 8.62).[269,270]



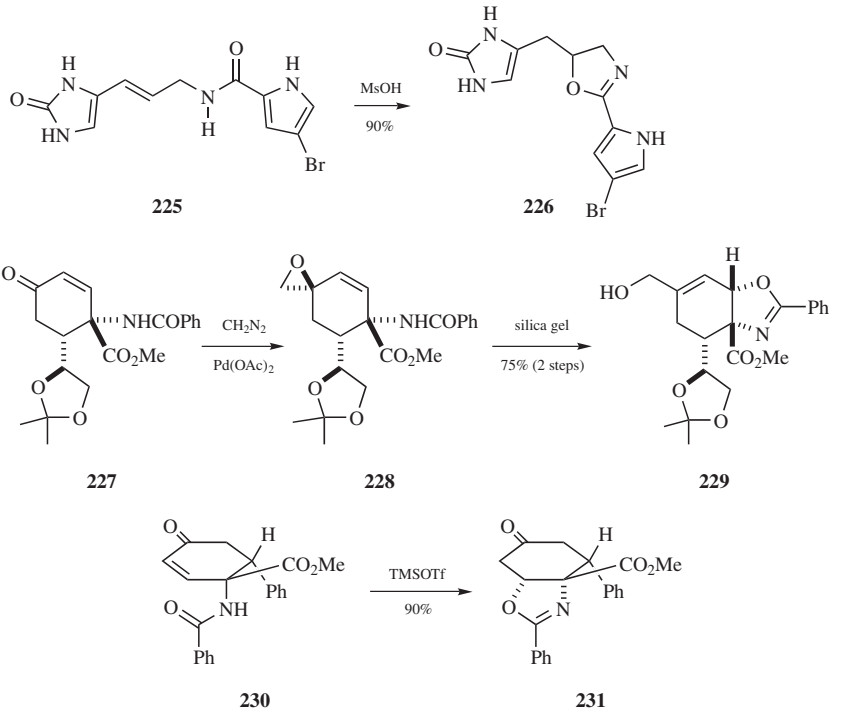
a: $CHCl_3$, reflux, b: Amberlyst H-15, toluene, reflux, c: CH_2Cl_2, BF_3 •OEt_2, −78 ˚C

Scheme 8.62

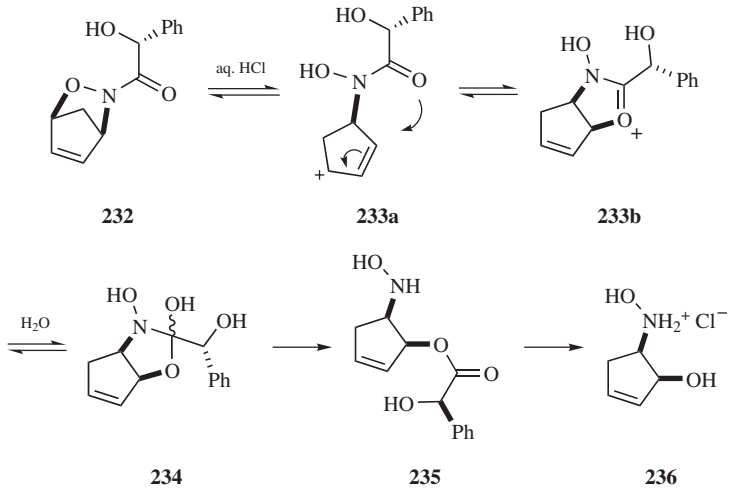
8.2.6. Oxazolines from Allyl amides (Enamides)

Allyl amides (enamides), for example, **225**, **228**, and **230** cyclize to oxazolines, for example, **226**, **229**, and **231** when the double bond is activated by an electrophile. The double bond can also be conjugated to a ketone, or present as an allylic epoxide. Reagents commonly used to promote the cyclization include acids,[271] iodine,[272,273] selenium reagents,[274,275] and trimethylsilyl triflate (Scheme 8.63).[276]

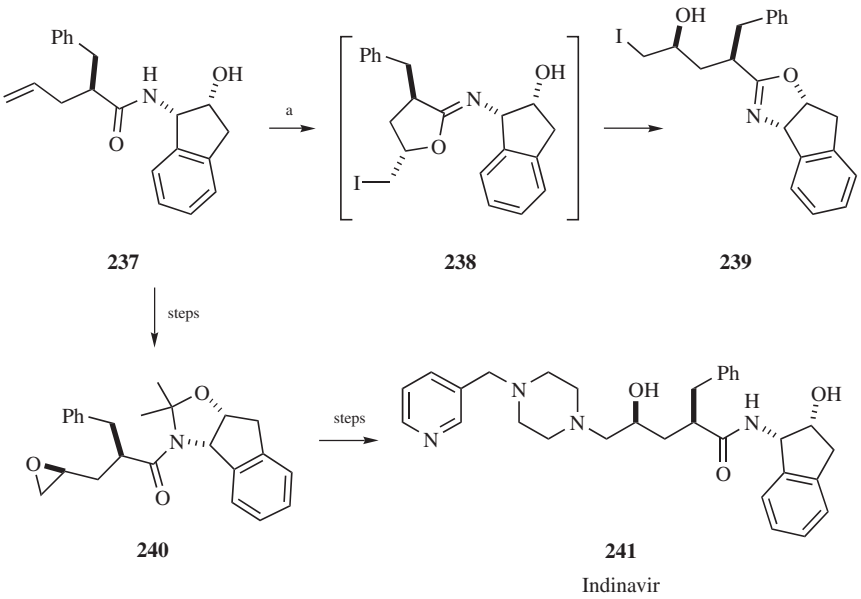
An interesting transformation of a conformationally restrained allyl amide **232** to an α-hydroxy-cyclopentenyl hydroxylamine **236** has been reported.[277] The mechanism is thought to involve a series of reversible reactions leading ultimately to **234**, which fragments irreversibly to **235**. Hydrolysis of the ester accounts for the observed product **236** (Scheme 8.64).



Scheme 8.63



Scheme 8.64



a: *N*-iodosuccinimide; IPAc; aqueous $NaHCO_3$

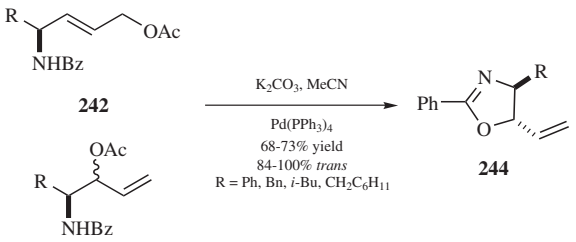
Scheme 8.65

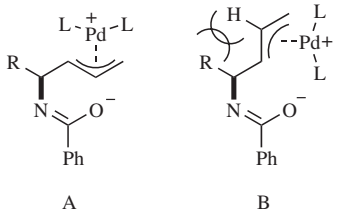
During an investigation[278] of the utility of epoxide **240** as an intermediate in the synthesis of the HIV protease inhibitor Indinavir **241**, it was found that the amino alcohol **237** must first be protected prior to iodination. Without protection, the iodination of the unsaturated amide **237** gave the unstable oxazoline **239** in 83% yield (Scheme 8.65).

Benzamido allylic acetates **242** and **243** undergo palladium-catalyzed cyclization to oxazolines. Excellent yields and very high diastereoselectivity is observed for the conversion of several acyclic primary and secondary benzamido allylic acetates to *trans*-5-vinyl substituted oxazolines **244**.[279,280] The diastereoselectivity of the reaction is determined by the the steric interactions between the R group and the hydrogen of the π-allylpalladium complex in the transition state. *trans*-Oxazolines are obtained since transition state A is favored over transition state B (Scheme 8.66).

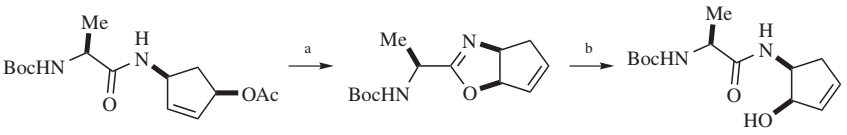
An interesting application of this methodology is the preparation of a *cis*-1,2-aminocyclopentenol derivative **247** (Scheme 8.67).[281]

Oxazoline formation from 5-vinyloxazolidinones promoted by palladium (0) is also known.[282] Oxidative insertion of palladium with loss of CO_2 results in a pair of equilibrating π-allyl palladium complexes. The stereochemistry of the vinyl group is therefore not important. Ring closure from the thermodynamically more stable transition state accounts for the trans-isomer as the major product. Depending on the exact substitution, diastereoselectivities ranging from 2.5:1 to 16:1 can be obtained (Scheme 8.68).



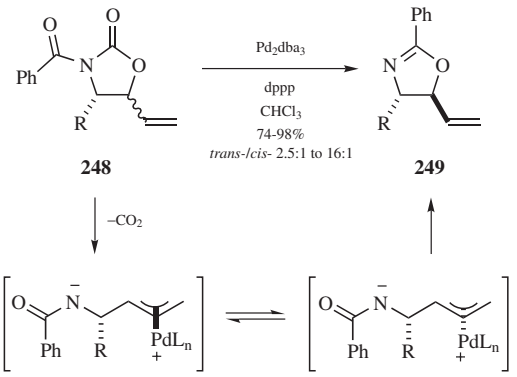


Scheme 8.66



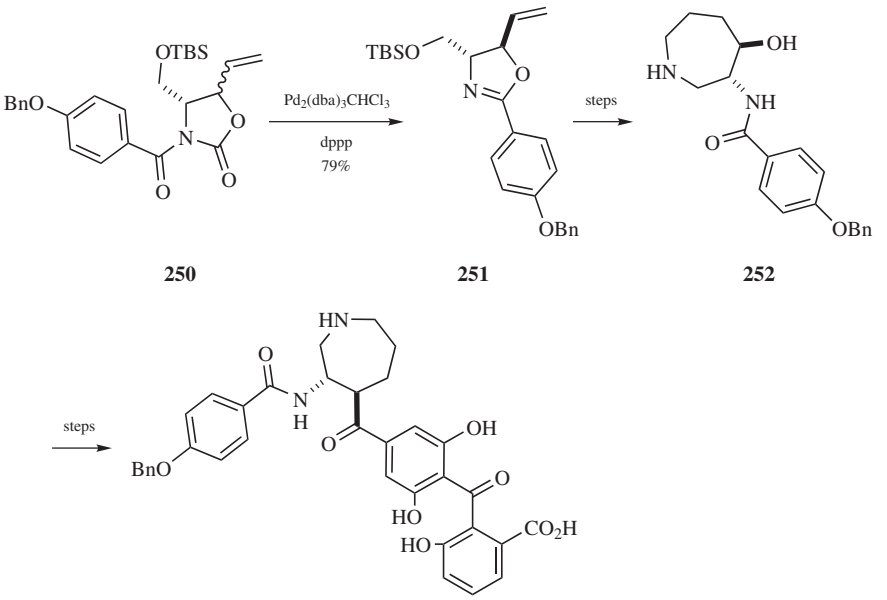
a: NaH, cat $Pd(PPh_3)_4$, DMF
b: 1 *N* HCl

Scheme 8.67



R = Me, Ph, Bn, CH_2CH_2SMe, $CH_2CH_2OTBDMS$

Scheme 8.68

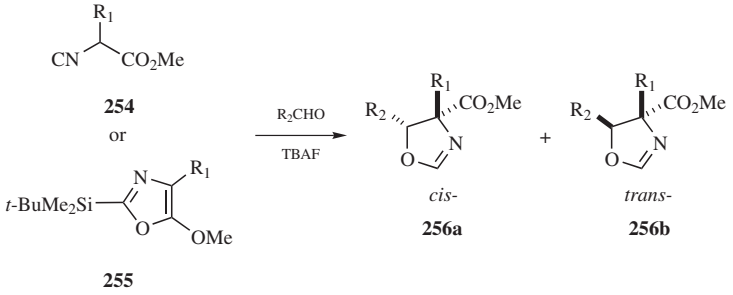


Scheme 8.69

This reaction was utilized to establish the vincinal amino alcohol stereochemistry required for the construction of key intermediates **251** and **252** for the synthesis of the natural product balanol **253** (Scheme 8.69).[283,284]

8.2.7. Oxazolines from Isonitriles

Oxazolines **256a** and **256b** are produced when α-isocyanoesters **254** react with aromatic aldehydes in the presence of catalytic or stoichiometric quantities of



Scheme 8.70

TABLE 8.21. OXAZOLINES FROM α-ISOCYANOESTERS[a]

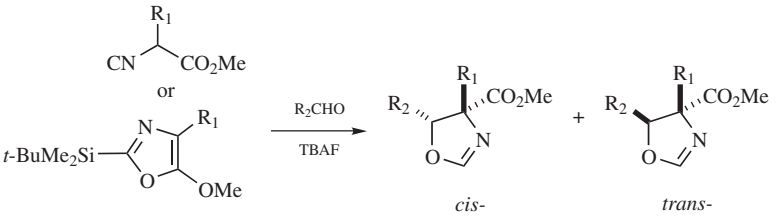
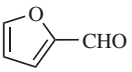
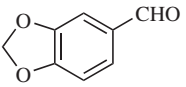


Figure 8.10

R_1	R_2CHO	% Yield	cis/trans
Me		80	75 : 25
Me		79	88 : 12
Me	EtCHO	0	
t-Bu	PhCHO	77	100 : 0
Me	MeCHO	81	62 : 38
H	PhCHO	51	4 : 96

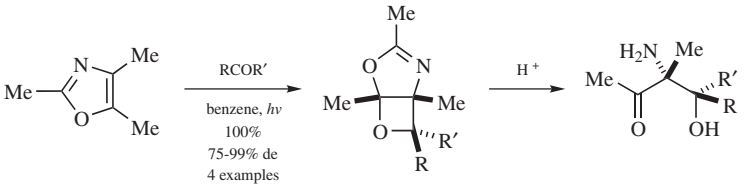
[a] Data from Ref. 285.

tetrabutylammonium fluoride.[285] 5-Methoxy-4-substituted-2-(*tert*-butyldimethylsilyl)oxazoles **255**, latent α-isocyanoesters react similarly, except that at least a stoichiometric amount of fluoride is required for the desilylation. The cis/trans-ratio is dependent on the bulkiness of the substituent at the α-carbon of the isocyanoester. Selected examples are summarized in Table 8.21 (Fig. 8.10; Scheme 8.70).

8.2.8. Oxazolines from Cycloadditions

8.2.8.1. [2 + 2] Cycloadditions

2,4,5-Trimethyloxazole **257** undergoes photochemically induced [2 + 2] cycloaddition with aromatic and aliphatic aldehydes to provide bicyclic oxazolines **258** with excellent regiochemical and stereochemical control.[286] Diastereoselectivities from 75–99% can be achieved, which is the first reported example of a Paterno-Büchi[287,288] reaction involving an oxazole. The oxetane cycloadducts can be hydrolyzed to α-amino-β-hydroxy ketones. Other oxazoles have not been evaluated to determine if they undergo the photochemical cycloaddition (Scheme 8.71).



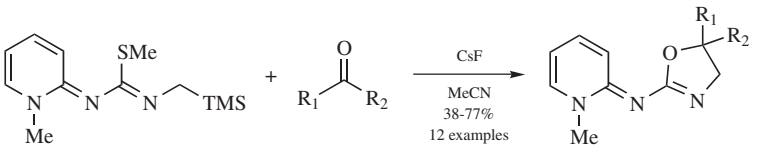
257 **258** **259**

R	Et	*t*-Bu	Ph	Ph
R′	H	H	H	CO_2Me

Scheme 8.71

8.2.8.2. [3 + 2] Cycloadditions

Azomethine ylides undergo a formal [3 + 2] cycloaddition with carbonyl compounds to provide oxazolines. Thioimidates, in particular, are effective as ylide precursors. For example, Kohra and co-workers reported that the thioimidate **260**, upon activation with cesium fluoride, reacts with aromatic aldehydes and diarylketones to provide oxazolines **261** in modest to good yields.[289] Aliphatic aldehydes and simple ketones are unreactive (Scheme 8.72).



260 **261**

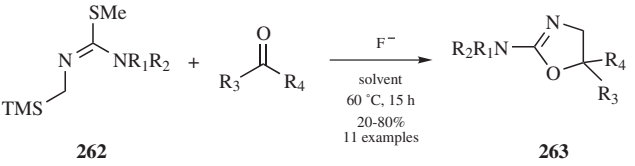
R_1 = Ph, substituted-Ph, 1-naphthyl, 2-thienyl, 3-pyridyl, cinnamoyl

R_2 = H, Ph

Scheme 8.72

For *N*-(trimethylsilylmethyl)-*S*-methylisothioureas **262**, cycloaddition with carbonyl compounds results in 2-aminooxazolines **263**.[290,291] Aliphatic and aromatic aldehydes and ketones can be employed successfully. However, reaction with ketones appears to be poor. Ylide generation with CsF is the method of choice although TBAF and KF have also been used but with lower yields. A polar solvent such as MeCN, DMF, or hexamethylphosphoric triamide (HMPA) is required for a succesful reaction (Scheme 8.73).

N-(Methylthiomethylmethylene)glycinate derivatives, for example, **264**, also undergo cycloaddition with benzaldehyde in the presence of DBU to provide *cis*- and *trans*-2-oxazolines **265a** and **265b**, respectively (Scheme 8.74).[292]

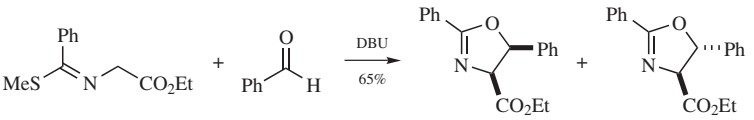


262 **263**

R_1, R_2 = $(CH_2)_5$, $(CH_2)_4$
R_1 = R_2 = Et
R_1 = Ph, R_2 = Me

R_3 = Ph, 4-Cl-Ph, 4-CF_3-Ph, 4-MeO-Ph, styryl, *i*-Pr, pentyl
R_4 = H, Me

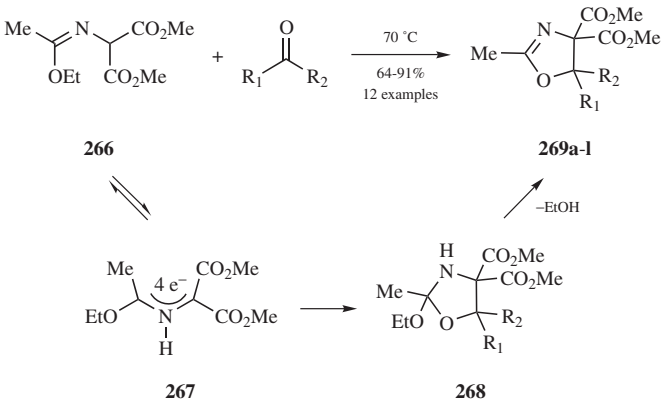
Scheme 8.73



264 **265a** **265b**

Scheme 8.74

Bazureau and co-workers[293–295] reported that imididate **266** reacts with carbonyl compounds to provide good yields of oxazolines **269a–l** as the only product. Only one of the two possible regioisomers is formed. Exclusive formation of the 5-regioisomer is consistent with FMO calculations based on the assumption that the reaction proceeds via an azomethine ylide intermediate **267**. The azomethine ylide is formed via a thermal 1,2-prototropy and can be trapped by aromatic aldehydes or diethyl ketooxalate. Aryl alkyl ketones and dialkyl ketones are unreactive. Aliphatic aldehydes have not been evaluated extensively in this study. Interestingly, when the reaction is carried out in an ionic liquid such as 1-ethyl-3-methylimidazolium tetrafluoroborate, significant rate enhancements and improved yields of the cycloadduct are obtained (Scheme 8.75).[296]



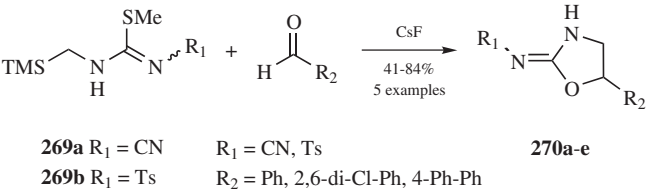
266 **269a-l**

267 **268**

R_1 = Ph, 2-furyl, 2-pyridyl, styryl, 2-CHO-Ph, 3-CHO-Ph, *i*-Pr, CO_2Et
R_2 = H, CO_2Et,

Scheme 8.75

N-Cyano- and *N*-(*p*-toluenesulfonyl)-*N*'-(trimethylsilylmethyl)-*S*-methylisothioureas **269a** and **269b** have also been utilized as synthetic equivalents of azomethine ylides.[290] Reaction of **269a** and **269b** with aromatic aldehydes and aryl ketones, in the presence of CsF, gives 2-iminooxazolines **270a–e** in modest-to-good yield. These 2-iminooxazolines apparently are stable to isolation and do not isomerize to 2-aminooxazolines (Scheme 8.76).



269a R_1 = CN
269b R_1 = Ts

R_1 = CN, Ts
R_2 = Ph, 2,6-di-Cl-Ph, 4-Ph-Ph

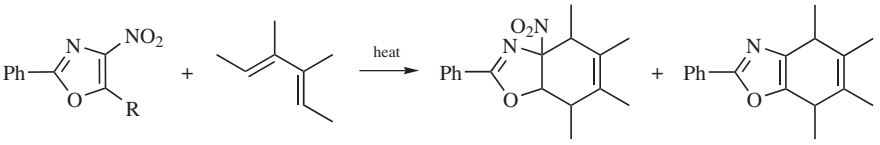
270a-e

Scheme 8.76

5-Alkoxyoxazoles undergo Lewis acid catalyzed reaction with a variety of aldehydes to give a mixture containing *trans*-2-oxazoline-4-carboxylates predominately. The reader is directed to a thorough review of this chemistry recently published by Suga.[297]

8.2.8.3. [4 + 2] Cycloadditions

4-Nitro-2-phenyloxazole **271a** undergoes Diels–Alder [4 + 2] cycloaddition with both electron-rich and electron-poor dienophiles to give an oxazoline **273** that may not be isolable due to the facile aromatization to a fused oxazole **274**.[298,299] Examples are shown in Table 8.22 (Scheme 8.77).



271a
R = H

272

273

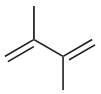
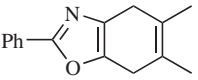
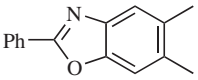
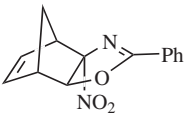
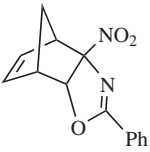
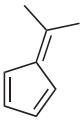
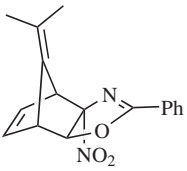
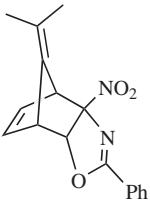
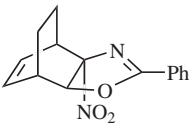
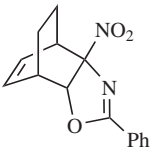
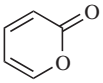
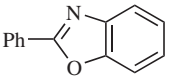
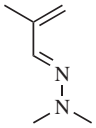
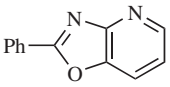
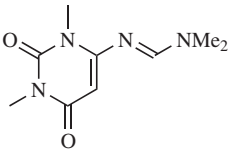
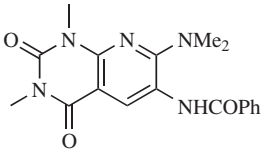
274

Scheme 8.77

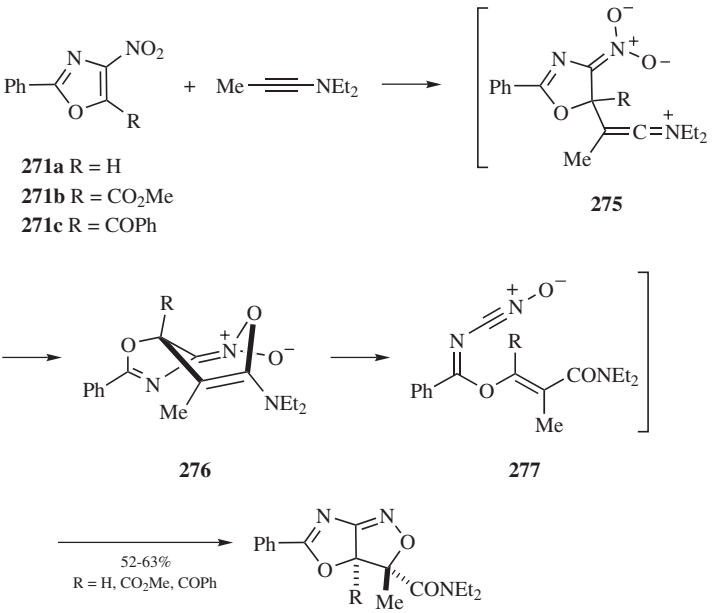
Nitrooxazoles **271a–c** also react with electron-rich ynamines to yield isoxazolines.[300] The proposed reaction mechanism involves the Michael addition of the ynamine to give **275**, followed by rearrangement to a nitrile oxide **277**. Intramolecular 1,3-dipolar cycloaddition of **277** accounts for the exclusive cis stereochemistry observed in the products **278a–c** (Scheme 8.78).

Unlike ynamines, ethyl vinyl ether requires the more electron-deficient 4-nitro-2-phenyl-5-oxazolecarboxylic acid methyl ester **271b** for reaction to occur. The initial [4 + 2] cycloadduct **279** undergoes further reaction with ethyl vinyl ether to give the tricyclic oxazoline **280** in 76% yield (Scheme 8.79).

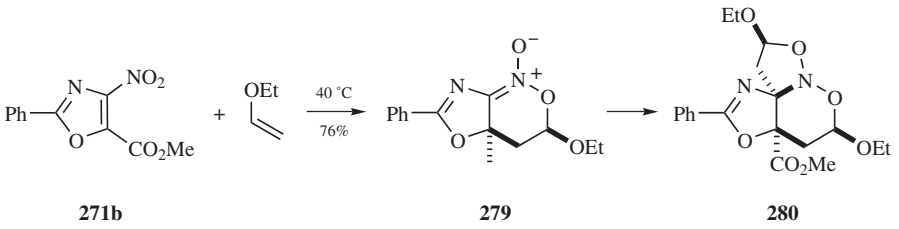
TABLE 8.22. OXAZOLINES FROM [4 + 2] CYCLOADDITIONS[a]

Diene	Products		Conditions
	 71%	 13%	110 °C
	 19%	 66%	40 °C
	 53% (products not separable)		40 °C
	 30%	 33%	110 °C
	 21%		150 °C
	 29%		55 °C
	 67%		25 °C

[a] Data from Ref. 299.



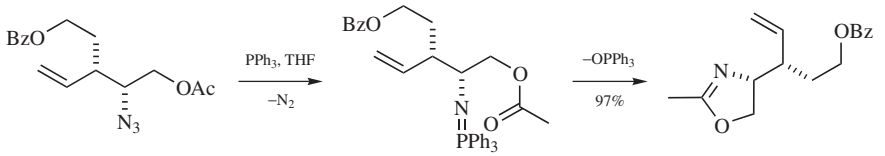
Scheme 8.78



Scheme 8.79

8.2.9. Miscellaneous Methods

The Staudinger-aza-Wittig[301] cyclization methodology for imine formation can also be applied to the synthesis of oxazolines under essentially neutral conditions.[302] Thus, an azido ester such as **281** reacts with triphenylphosphine to give the oxazoline **283** in excellent yield. There was no evidence for cyclization at the benzoate presumably because cyclization to a five-membered ring is faster than



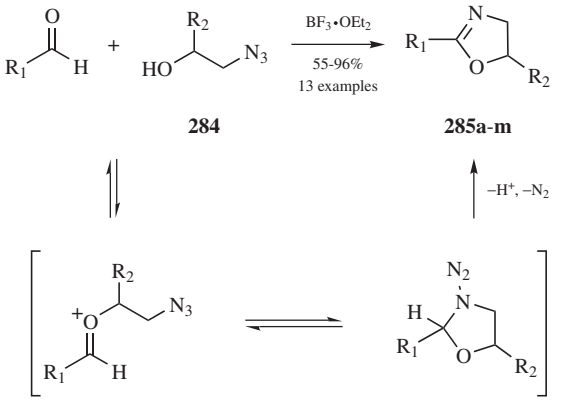
281 **282** **283**

Scheme 8.80

cyclization to a seven-membered ring. The generality and scope of this reaction apparently has not been fully explored to date (Scheme 8.80).

Oxazolines **285a–m** are also produced when 1,2-azido alcohols **284** are subjected to a variety of Lewis acids. In particular, boron trifluoride etherate was the most effective.[303] The reaction works well with electron-rich and electron-deficient aromatic aldehydes and aliphatic aldehydes. However, ketones are unreactive and α,β-unsaturated aldehydes gave only a modest yield of the oxazoline. The mechanism is believed to proceed via initial hemiketal formation and subsequent dehydration to generate an oxonium ion **286a** that is captured by intramolecular attack of the azide to give the cyclic aminal **286b**. Elimination of H^+ and N_2 from **286b** then gives the oxazolines **285a–m** in modest to excellent yield (Scheme 8.81).

S-Ethenylsulfimines **287** react with amides to yield 2-substituted-oxazolines **289**.[304] The reaction proceeds via initial Michael addition of an amide anion to **287** to give **288** that collapses to the oxazoline. The reaction is typically carried out at room temperature or 50 °C in THF, 1,2-dimethoxyethane (DME), or even MeCN using NaH as the base. Aryl, heteroaryl, and aliphatic amides can be used and the yields of **289** are modest to excellent (Scheme 8.82).



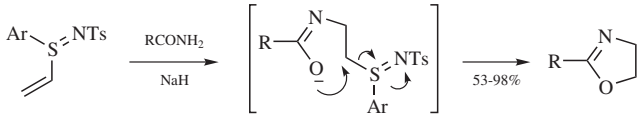
284 **285a-m**

286a **286b**

R_1 = Ph, 4-NO_2-Ph, 4-MeO_2C-Ph, 4-MeO-Ph, Bn, *t*-Bu, pentyl

R_2 = H, Ph

Scheme 8.81

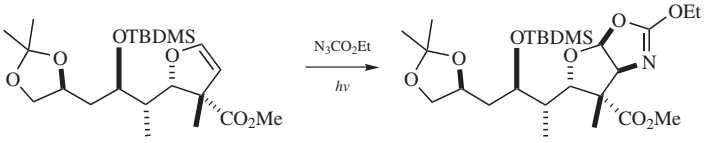


287 **288** **289**

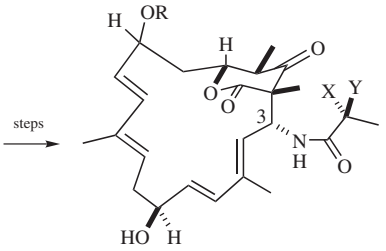
Ar = Ph, 4-Me-Ph

R = Ph, 4-Me-Ph, 2-Me-Ph, 4-Cl-Ph, 3-Cl-Ph, 4-pyridyl, Me, Et

Scheme 8.82

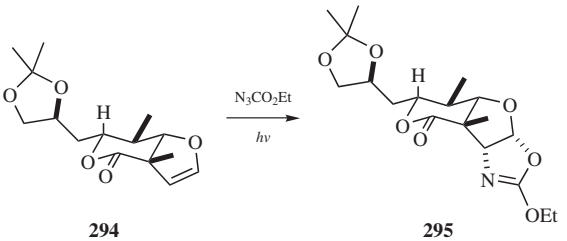


290 **291**

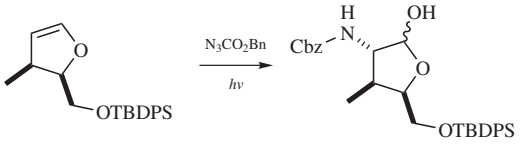


293

lankacidin C: X,Y = O, R = H
lankacidin A: X,Y = O, R = Ac
lankacidinol: X = H, Y = OH, R = H
lankacidinol A: X = H, Y = OH, R = Ac

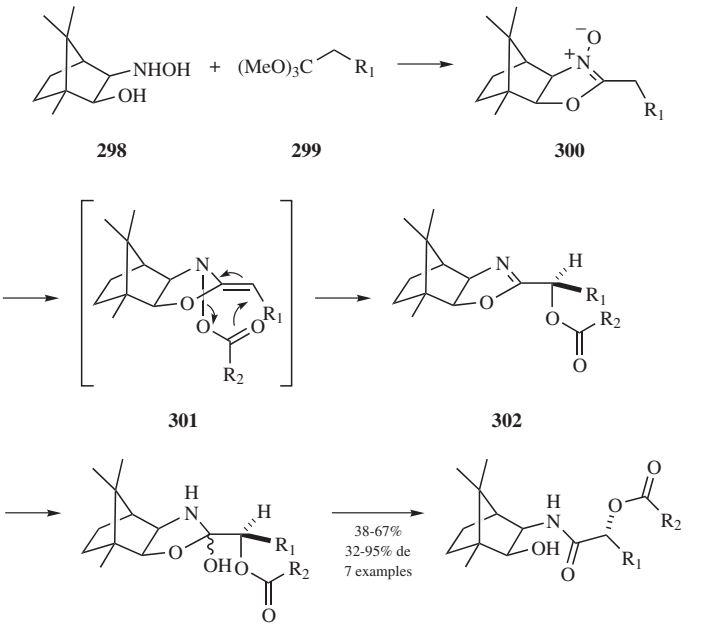


294 **295**



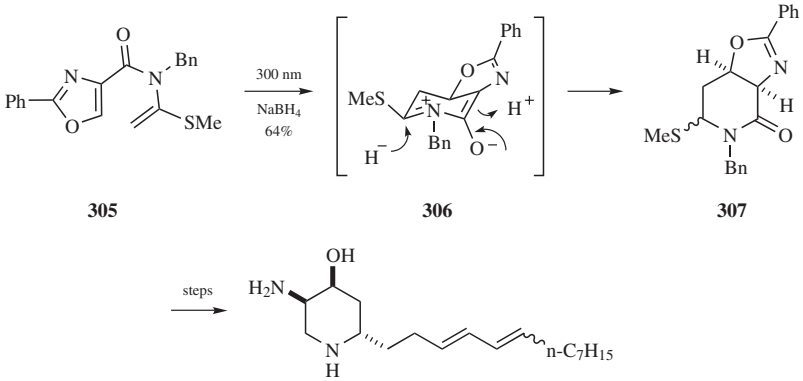
296 **297**

Scheme 8.83



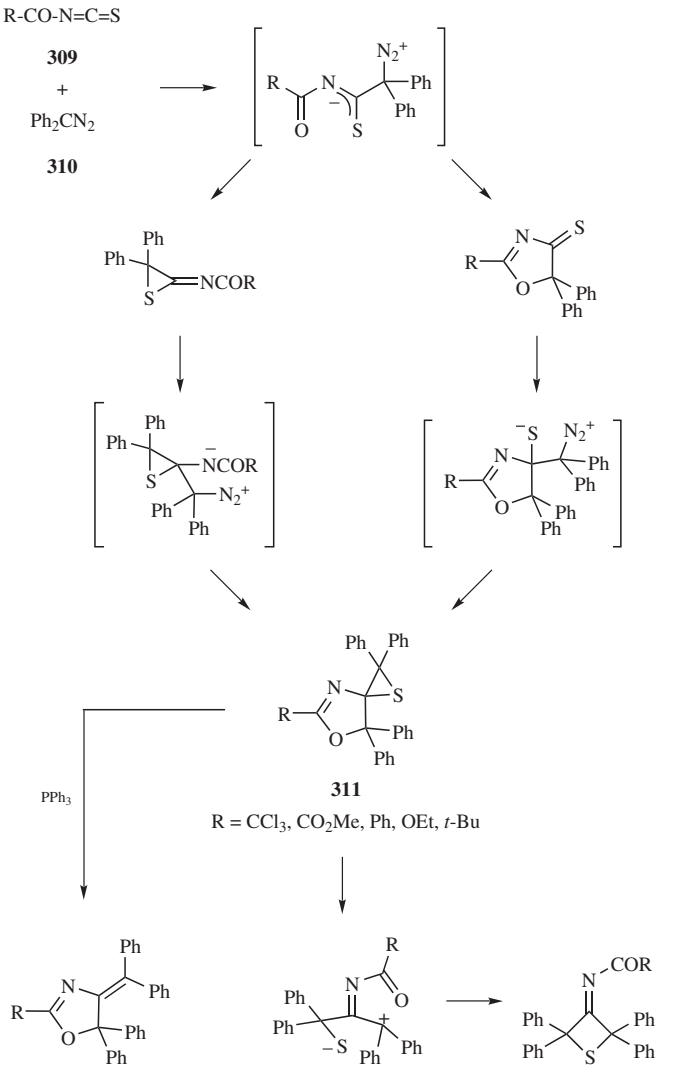
Scheme 8.84

In their synthesis of lankacidin antibiotics,[305] Williams and co-workers utilized an insertion reaction of an azidoformate-derived acylnitrene on the electron-rich dihydrofuran **290** to introduce the sterically hindered C-3 amino appendage in the macrocyclic framework. The oxazoline formation is totally stereospecific with the



pseudodistomin A

Scheme 8.85



Scheme 8.86

acylnitrene approaching the olefin from the less-hindered β-face. In contrast, using the lactonized substrate **294**, the reaction occurred unexpectedly from the α-face to give **295**. During this study, the authors also examined benzyl azidoformate as the source of the acyl nitrene. Even with the simple dihydrofuran **296**, a high diastereoselectivity was observed (Scheme 8.83, p. 414).

Langlois and co-workers[306] developed a stereoselective hetero-Claisen rearrangement of camphor-based oxazoline *N*-oxides **300**, available from hydroxylaminoisoborneol **298** and orthoesters **299**. The rearrangement, initiated by acylation of

the oxazoline *N*-oxide, provided 2-(α-acyloxy)oxazolines **302** that spontaneously hydrolyzed to **304**. The stereoselectivity observed is consistent with an intermediate (*Z*)-keteneaminal **301** in which the [3,3]-sigmatropic rearrangement occurs from the α-face (Scheme 8.84, p. 415).

4-Acyl-2-phenyloxazole derivatives undergo a reductive photocyclization in the presence of sodium borohydride to generate a bicyclic oxazoline with a cis-fused pyridinone ring **307**. The stereochemistry of the product is consistent with hydride attack from the less hindered surface of the cyclic intermediate **306**. The oxazoline containing pyridinone is a key intermediate used for the synthesis of pseudodistomins **308** (Scheme 8.85, p. 415).[307]

Spirocyclic oxazolines **311** are produced in 37–67% yield from acylisothiocyanates **309** and an excess of diphenyldiazomethane **310**.[308] The proposed mechanism for product formation is indicated in Scheme 8.86. The reaction has also been demonstrated for 2-diazofluorene. There are no reports for aliphatic diazo compounds.

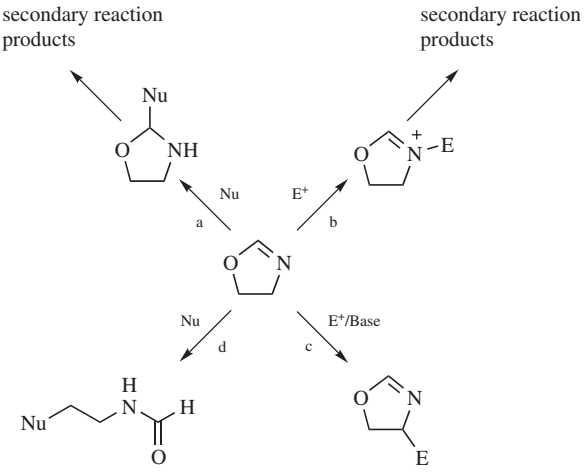
8.3. REACTIONS AND APPLICATIONS

Oxazolines can participate in a diverse range of reactions. Other than the oxygen atom, each position of the oxazoline ring is capable of some type of electrophilic or nucleophilic reaction (Scheme 8.87). The 2-position is susceptible to nucleophilic attack ultimately resulting in ring-opened products (pathway a). The ring-opened product can then undergo further reaction or rearrangement depending on the nucleophile. The nitrogen atom can undergo electrophilic reactions including oxidation, alkylation, and salt formation (pathway b). The 4-position is acidic and can be deprotonated and undergo typical carbanion chemistry (pathway c). The 5-position is susceptible to nucleophilc attack also leading to ring-opened products (pathway d). Reactions may also occur at a remote site of a molecule that can be influenced by the oxazoline ring. Examples of such reactions include those wherein an oxazoline acts as an activating group, directing group, or as a chiral auxilliary. Oxazolines are also used extensively as chiral catalysts in stereoselective synthesis. This section will focus on a discussion of mononuclear oxazolines. A comprehensive discussion of the syntheses and reactions of chiral bis(oxazolines) is found in Chapter 9.

8.3.1. Nucleophilic Reactions

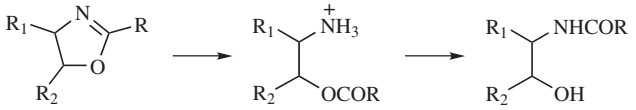
8.3.1.1. Hydrolysis

Hydrolysis is undoubtedly the most common nucleophilic reaction at the 2-position. It is generally used to unmask the hydroxy amide or amino alcohol after synthetic manipulations on the oxazoline ring are completed. Hydrolysis under

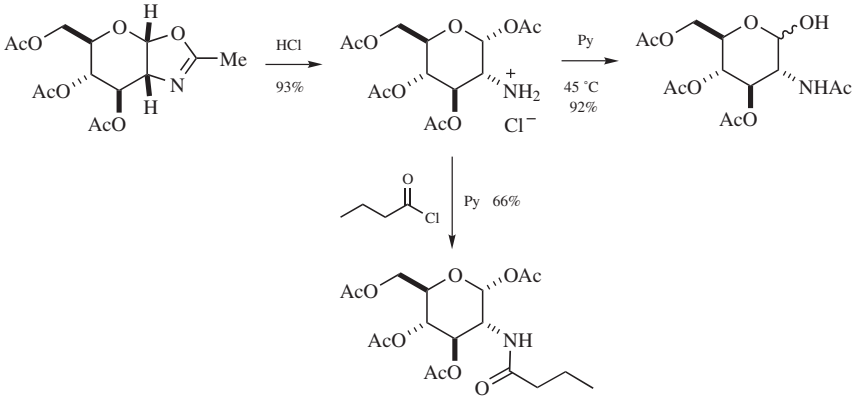


Scheme 8.87

strongly acidic conditions gives the amino alcohol. However, the reaction can be stopped at an intermediate stage if it is carried out under mild conditions. For example, the initially formed amino ester can be isolated or trapped in certain cases although it is more commonly rearranged to the hydroxy amide, typically under mildly basic conditions (Schemes 8.88 and 8.89).[309] The configuration of the oxazoline at the 4 and 5-positions is normally retained under the hydrolysis conditions as shown in Scheme 8.89. Selected examples are shown in Table 8.23.[157–159,185,191,195,230,231,239,241,250,264,268,271,273,281,284,286,310–312]



Scheme 8.88



Scheme 8.89

TABLE 8.23. HYDROLYSIS OF OXAZOLINES

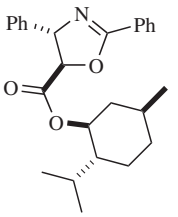
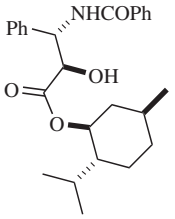
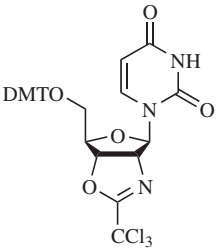
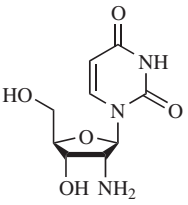
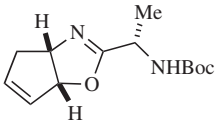
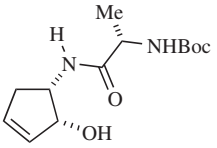
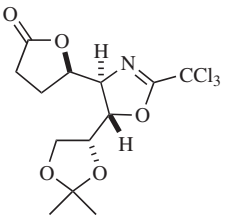
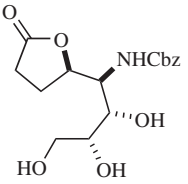
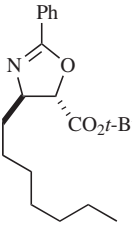
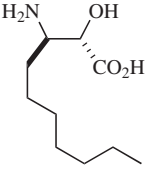
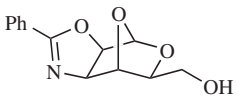
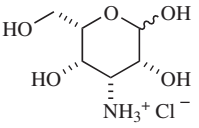
Entry	Oxazoline	Hydrolysis Conditions	Product/Yield	Reference
1		(1) 1 *N* HCl, MeOH/THF, reflux (2) aq. $NaHCO_3$	 80%	310
2	 DMT = dimethoxytrityl	80% HOAc, rt	 84%	241
3		1 *N* HCl	 67%	281
4		TFA/water, rt	 90% (after Cbz protection)	231
5		(1) 6 *N* HCl, reflux (2) Dowex 50 × 8–200	 92%	157, 158
6		2.5 *N* HCl, reflux	 90%	311

TABLE 8.23 (*Continued*)

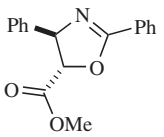
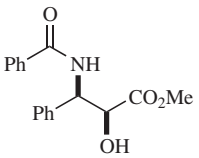
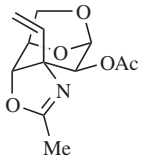
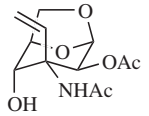
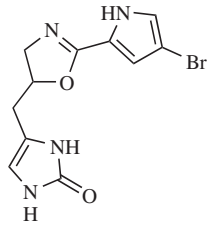
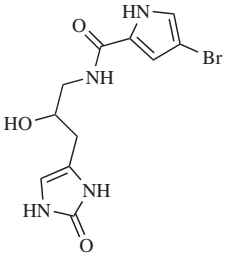
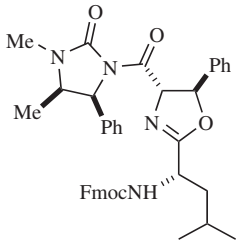
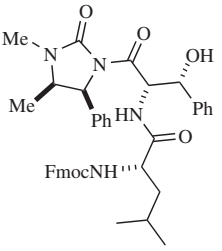
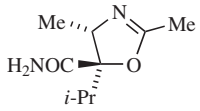
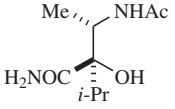
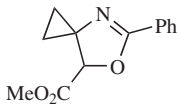
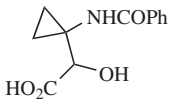
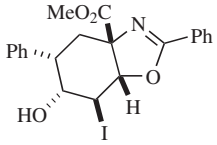
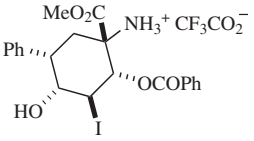
Entry	Oxazoline	Hydrolysis Conditions	Product/Yield	Reference
7		(1) 0.5 *N* HCl/MeOH (2) aq. $NaHCO_3$	 88%	159
8		(1) 1 *N* HCl/THF (2) aq. $NaHCO_3$	 64% (after acetylation)	230
9		(1) 5% HCl, reflux (2) NaOH	 85%	271
10		$BF_3{\cdot}OEt_2$, water/ CH_2Cl_2, piperidine	 65%	268
11		$BF_3{\cdot}OEt_2$, water or wet $CHCl_3$, rt, 1 week	 100%	250
12		1 *N* HCl, 100 °C	 70% after benzoylation	185
13		TFA, THF/water, 80 °C	 82%	273

TABLE 8.23 (*Continued*)

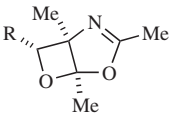
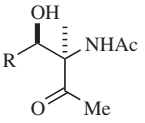
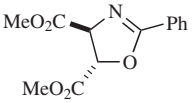
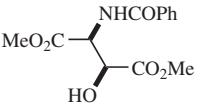
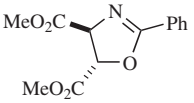
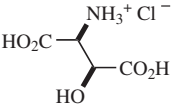
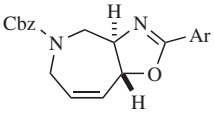
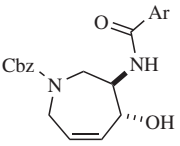
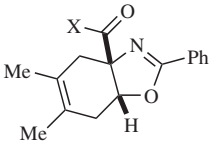
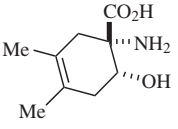
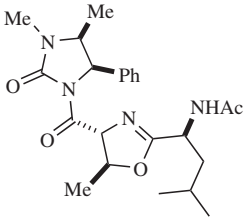
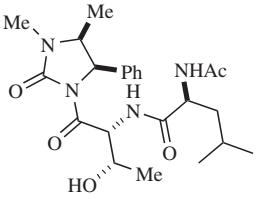
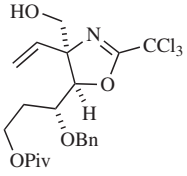
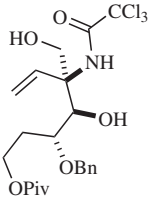
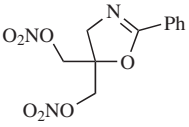
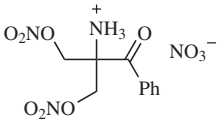
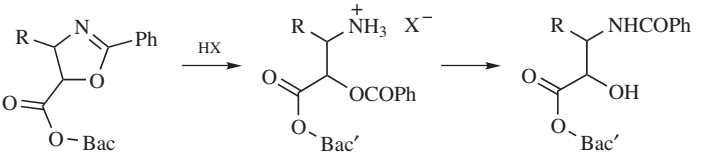
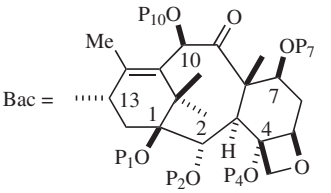
Entry	Oxazoline	Hydrolysis Conditions	Product/Yield	Reference
14	 R = Et, *t*-Bu, Ph	Water/EtOAc, rt		286
15		0.1 *N* HCl/THF, rt	 70%	191
16		6 *N* HCl, reflux	 95%	191
17	 Ar = 4-BnO-Ph-	(1) 2 *N* HCl/THF, rt (2) Et_3N/MeOH, rt	 72%	284
18	 X = MeO, NMe_2	(1) 20% HCl/EtOH (2) Propylene oxide	 50–52%	195
19		TsOH/MeOH/ water, rt	 95%	264
20		1 *N* HCl/THF	 100%	239
21		57% HNO_3, 20 °C	 96%	312

TABLE 8.24. UNMASKING THE SIDE-CHAIN OF TAXOL ANALOGUES BY ACID HYDROLYSIS[a]



312 **313**



Scheme 8.90

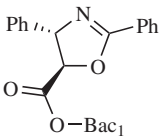
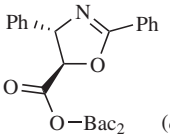
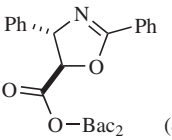
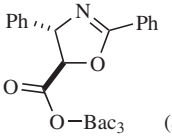
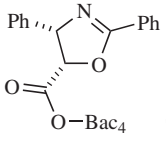
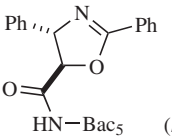
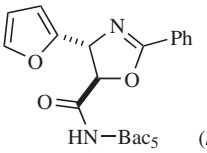
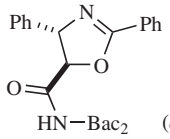
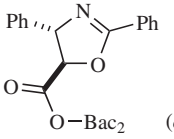
Entry	Oxazoline	Hydrolysis Conditions	Product	% Yield	References
1	 (*b*)	(1) 1 *N* HCl/MeOH/THF, rt (2) aq. $NaHCO_3$	**313**	93	310, 313
2	 (*c*)	(1) 0.1 *N* HCl, MeOH, 60–80 °C (2) aq. $NaHCO_3$	**313**[d]	80	78, 162, 314
3	 (*c*)	(1) 1 *N* HCl/MeOH, rt (2) aq. $NaHCO_3$	**313**[d]	95	310
4	 (*e*)	(1) 0.1 *N* HCl/EtOH, 95 °C (2) aq. $NaHCO_3$	**313**	75	314
5	 (*f*)	0.1 *N* HCl/dioxane, 50 °C,	**312**[g]	84	125

TABLE 8.24 (*Continued*)

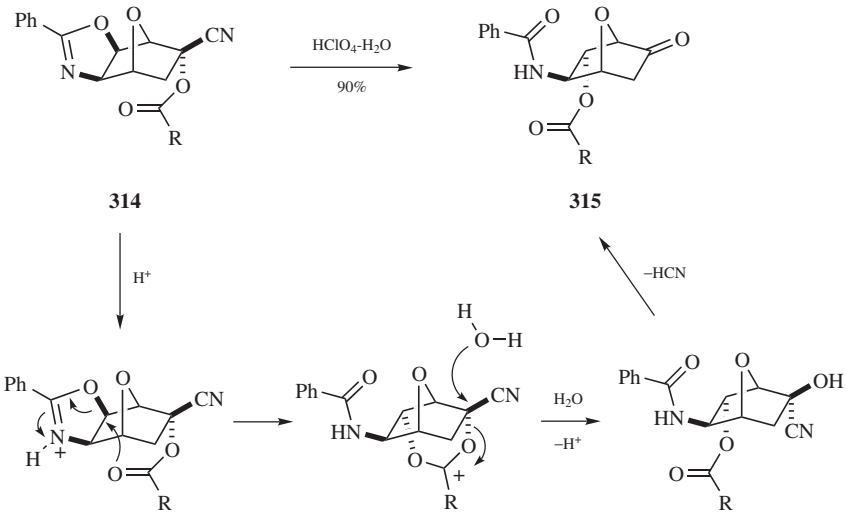
Entry	Oxazoline	Hydrolysis Conditions	Product	% Yield	References
6	 (*h*)	(1) 1 *N* HCl/MeOH/THF, 5 °C (2) aq. $NaHCO_3$	**313**[d]	61	86
7	 (*h*)	(1) 1 *N* HCl /MeOH/THF, 5 °C (2) aq. $NaHCO_3$	**313**[d]	39	86
8	 (*c*)	(1) 1 *N* HCl/MeOH/THF, 5 °C (2) aq. $NaHCO_3$	**313**[d]	50	86
9	 (*c*)	0.1 *N* HCl, 95 °C	**313**[d]	75	85

[a] Groups P_1-P_{10} denote protecting groups at 1–10 positions, respectively.
[b] Bac_1: $P_1 = H$, $P_2 = Bz$, $P_4 = P_{10} = Ac$, $P_7 = 2,2,2$-trichloro-*t*-butoxycarbonyl.
[c] Bac_2: $P_1 = H$, $P_2 = Bz$, $P_4 = P_{10} = Ac$, $P_7 =$ triethylsilyl.
[d] The silyl protective groups on the baccatin core structure were removed under reaction conditions.
[e] Bac_3: $P_1 = H$, $P_2 = Bz$, $P_4 = Ac$, $P_7 = P_{10} = 2,2,2$-trichloroethoxycarbonyl.
[f] Bac_4: $P_1 = H$, $P_2 = Bz$, $P_4 = P_{10} = Ac$, $P_7 = H$.
[g] A solution of **312** in methylene chloride isomerized to **313** at room temperature after 20 h.
[h] Bac_5: $P_1 =$ dimethylsilyl, $P_2 = Bz$, $P_4 =$ methoxycarbonyl, $P_7 =$ triethylsilyl, $P_{10} = Ac$.

Partial hydrolysis of an oxazoline to produce the hydroxy amide was used extensively in the synthesis of Taxol analogues (Table 8.24; Scheme 8.90).[78,85,86,125,162,310,313,314] It is noteworthy that a solution of the amino ester salt **312** isomerized to **313** after prolonged standing at room temperature (entry 5).[125]

Vogel and co-workers reported an interesting oxazoline hydrolysis during which the ester group in **314** migrated to give **315**.[311] Although the authors did not discuss the mechanism for the migration, the product likely results from anchimeric assistance of the 2-amido ester to give an intramolecular nucleophilic substitution at the 5-position rather than typical attack at the 2-position (Scheme 8.91).

Alvarez-Ibarra and co-workers reported oxidative hydrolysis of 2-thio substituted oxazolines (Scheme 8.92).[315,316] Presumably, the reaction proceeds through a



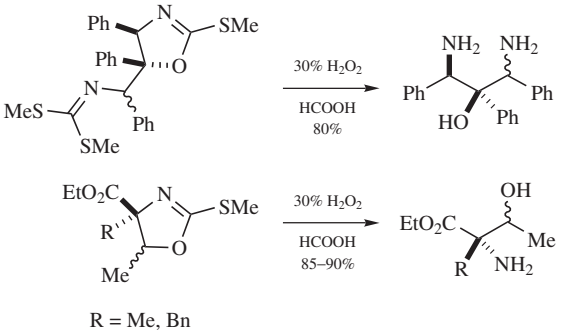
Scheme 8.91

sulfoxide or sulfone intermediate that is more reactive for hydrolysis. This appears to be a general method to hydrolyze 2-thiooxazolines.

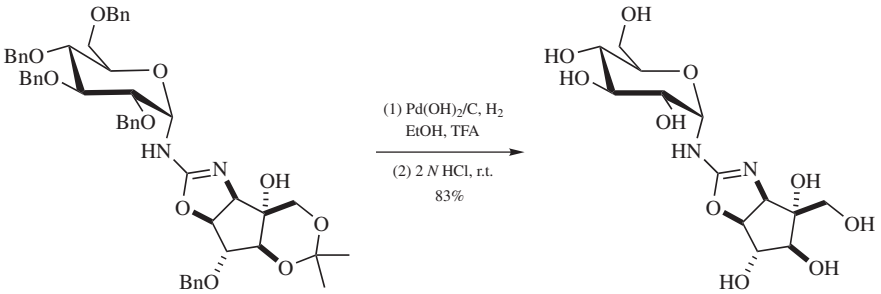
In general, 2-amino-substituted oxazolines are more resistant to acid hydrolysis. For example, the 2-aminooxazoline moiety in the protected azasugar **316** was preserved during acid cleavage of a ketal in the final step of a trehazolin synthesis (Scheme 8.93).[102]

Oxazolines are generally resistant to basic hydrolysis. For example, the ester in the spirocyclic oxazoline ester **317** was quantitatively hydrolyzed under basic conditions to afford the corresponding acid **318** (Scheme 8.94).[185]

However, oxazolines can be completely hydrolyzed using strongly basic conditions. For example, Giuliano and Smith hydrolyzed the 2-aminooxazoline **319** with

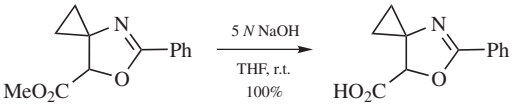


Scheme 8.92



316 trehalamine

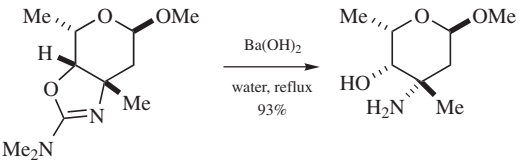
Scheme 8.93



317 **318**

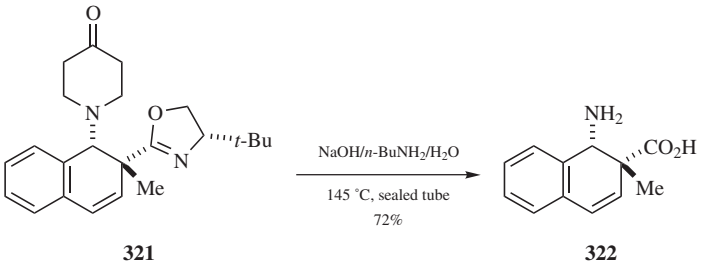
Scheme 8.94

aqueous barium hydroxide at reflux and isolated the amino alcohol **320** in excellent yield (Scheme 8.95).[235] Meyers and Shimano reported an efficient basic hydrolysis of oxazoline **321** to the amino acid **322** (Scheme 8.96).[317] In this case, *N*-butylamine was used to scavenge divinyl ketone produced from the piperidinone moiety.



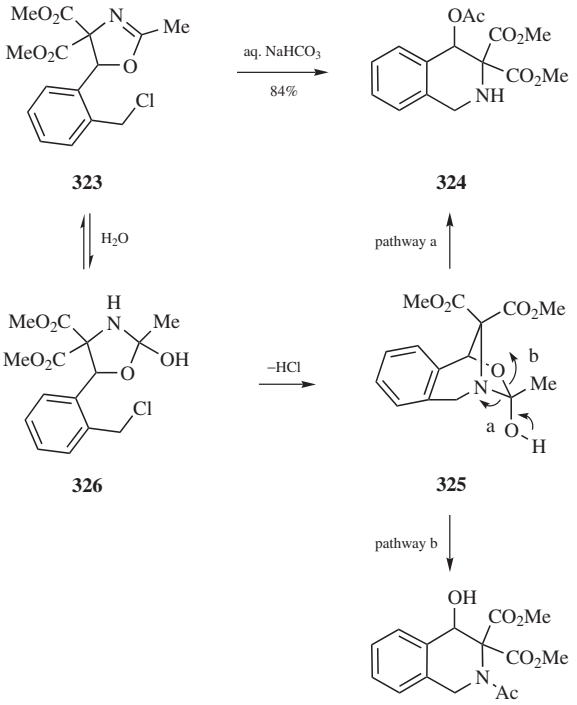
319 **320**

Scheme 8.95



321 **322**

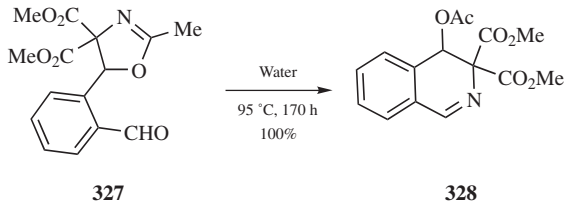
Scheme 8.96



Scheme 8.97

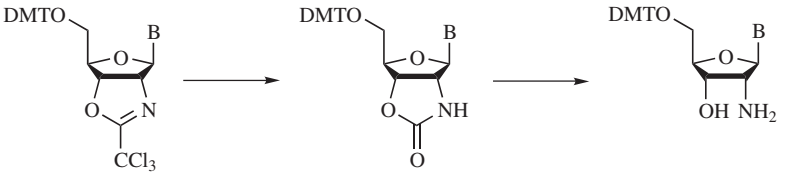
Bazureau and co-workers reported an unusual hydrolysis of the tetrasubstituted oxazoline **323**. In this case, **323** was unstable and hydrolyzed quickly to the tetrahydroisoquinoline amino ester **324** under mildly basic conditions (Scheme 8.97).[295] Although the authors did not discuss the reaction mechanism, it is possible that the facile hydrolysis is facilitated by the formation of the bicyclic intermediate **325** produced via intramolecular trapping of **326**.

The same group also reported an analogous reaction wherein the oxazoline **327** hydrolyzed under neutral conditions to give the dihydroisoquinoline **328** (Scheme 8.98).[294,295] In contrast, with a meta-substituted aldehyde, the oxazoline was stable under the same reaction conditions, which suggests that an intramolecular mechanism is operative and is consistent with the above analysis.



Scheme 8.98

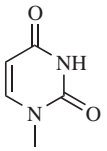
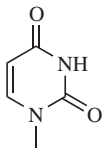
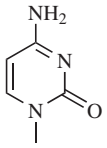
TABLE 8.25. HYDROLYSIS OF OXAZOLINE **329** UNDER BASIC CONDITIONS[a]



329 **330** **331**

DMT = dimethoxytrityl

Scheme 8.99

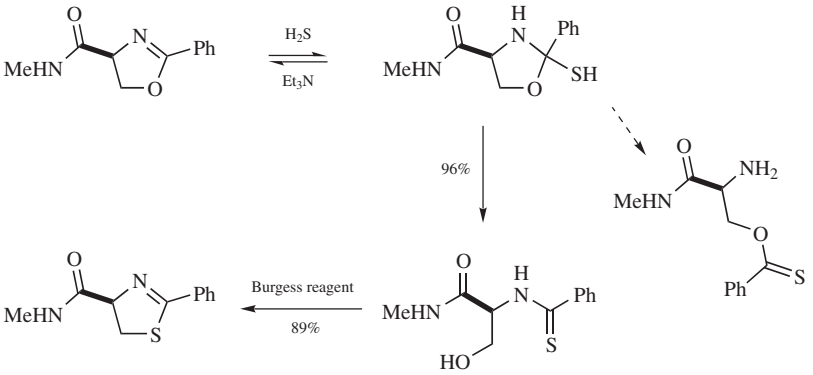
Entry	Base (B)	Hydrolysis Conditions	% Yield (Product)
1		2.7 *N* NaOH/dioxane, reflux, 10 h	58 (**330**), 8 (**331**)
2		6 *N* NaOH/EtOH, reflux, 16 h	79 (**331**)
3		aq. Cs_2CO_3/EtOH, reflux, 18 h	94 (**331**)

[a] Data from Ref. 241.

In a special case, basic hydrolysis of 2-(trichloromethyl)oxazolines **329** gave the oxazolidinone **330** or the amino alcohol **331** depending on the reaction conditions as shown in Table 8.25 (Scheme 8.99). Formation of **330** is presumably the result of facile displacement of the trichloromethyl leaving group.

8.3.1.2. Substitution at the 2-Position by Other Nucleophiles

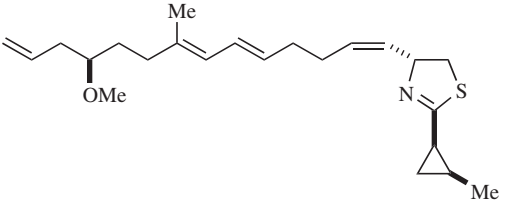
Other nucleophiles are known to attack the 2-position of oxazolines. Wipf and co-workers developed a general method to convert oxazolines to thiazolines by thiolysis followed by cyclodehydration (Scheme 8.100).[154,318] Initial attack of hydrosulfide at the 2-position of the oxazoline occurs under either acidic or



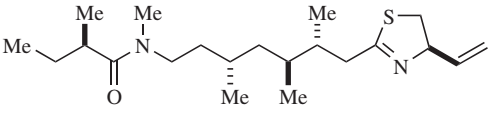
Scheme 8.100

moderately basic conditions. The authors found that presence of a base (triethylamine) was crucial to prevent the isomeric ring opening of the initial intermediate. Racemization at the labile amino acid α-carbon atom is usually minimal except in the case of *cis*-4,5-disubstituted-oxazolines under prolonged reaction conditions. This strategy was successfully applied for the total syntheses of curacin A[137,319,320] and kalkitoxin (Fig. 8.11).[321]

The reaction generally tolerates steric hindrance at the 2-exocyclic position as well as at the 4- and 5-positions. However, the reaction rate was found to be sensitive to steric effects. Thus, thiolysis of a threonine-derived oxazoline **332** was considerably slower than that for the corresponding serine-derived oxazoline **333** (Scheme 8.101).[318] The rate difference could be exploited to selectively convert a serine-derived oxazoline to a thioamide in the presence of a threonine-derived oxazoline.

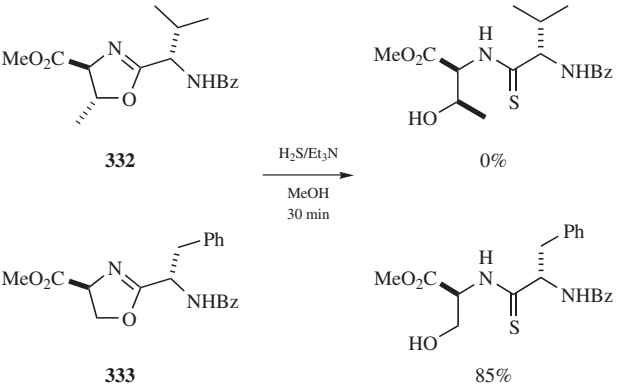


curacin A



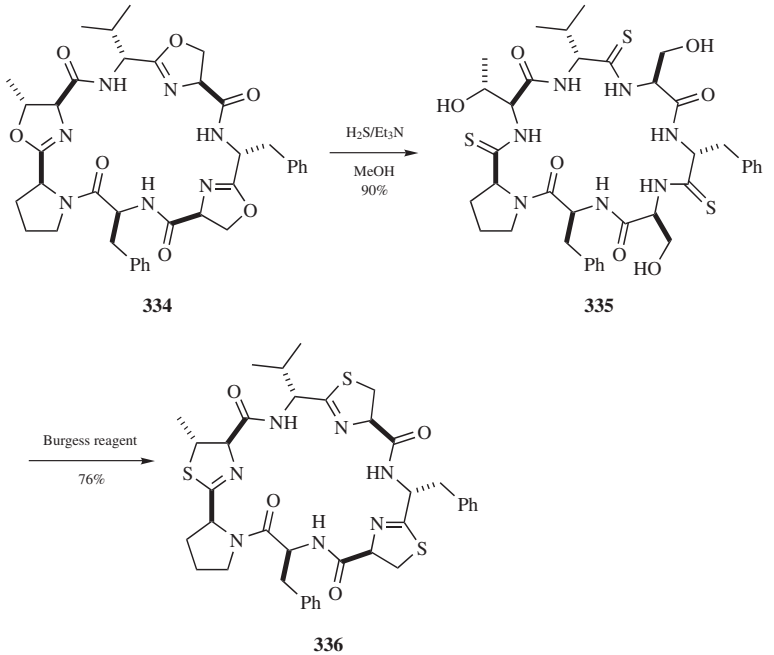
kalkitoxin

Figure 8.11. Curacin A and kalkitoxin.



Scheme 8.101

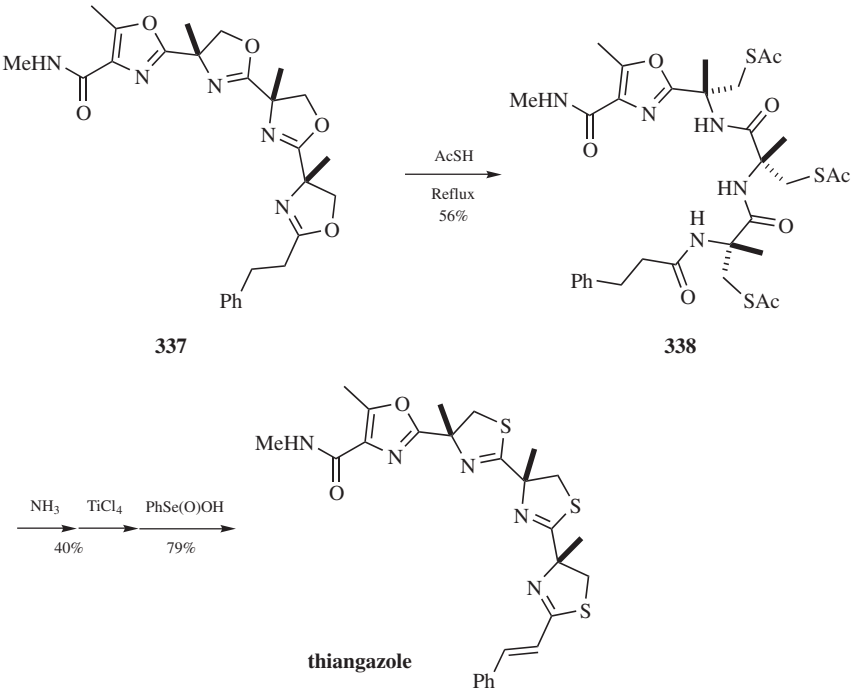
However, this strategy failed when applied to the synthesis of the cyclopeptide lissoclinamide 7. Here, the serine-derived oxazoline moiety could not be selectively thiolyzed in the presence of the threonine-derived oxazoline in the cyclopeptide **334**.[149] The authors attributed this lack of chemoselectivity to the increased stability and thus reduced reactivity, of the serine-derived oxazoline in the macrocyclic scaffold. All three oxazoline moieties reacted under the prolonged reaction conditions to give the trithio cyclopeptide **335** (Scheme 8.102). The structure of **335** was confirmed by conversion to the tristhiazoline cyclopeptide **336**.



Scheme 8.102

8.3.1.3. Nucleophilic Substitution at the 5-Position

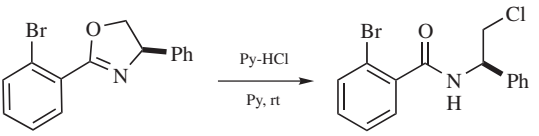
Nucleophilic attack at the 5-position of an oxazoline normally proceeds under acidic conditions. For example, in their total synthesis of thiangazole, Wipf and co-workers used thiolacetic acid to convert the trisoxazoline **337** to the S-protected cysteine derivative **338** that was further elaborated to thiangazole through aminolysis, cyclodehydration, and oxidation (Scheme 8.103).[154] This approach complements the thioamide method to prepare thiazolines.[149,154]



Scheme 8.103

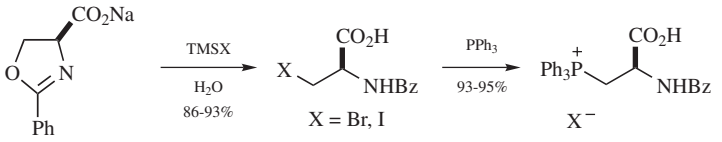
Such nucleophilic ring-opening reactions may be carried out under mild conditions. For example, Wuts and co-workers cleanly converted the 2,4-diaryloxazoline **339** to the chloro amide **340** using pyridine hydrochloride (Py·HCl) at room temperature (Scheme 8.104).[89] Jugé and co-workers also reported mild ring opening of the oxazoline carboxylate salt **341** using HBr or HI generated *in situ* from the corresponding trimethylsilyl halide (Scheme 8.105). The resulting 2-halomethyl amino acids **342** were converted to the corresponding phosphonium salts **343**.[322]

Nucleophilc attack becomes a more facile process when the 5-position is activated by an electron-donating group. This strategy has been used extensively in glycoside synthesis, whereby an anomeric oxazoline is used as a glycopyranosyl



339 **340**

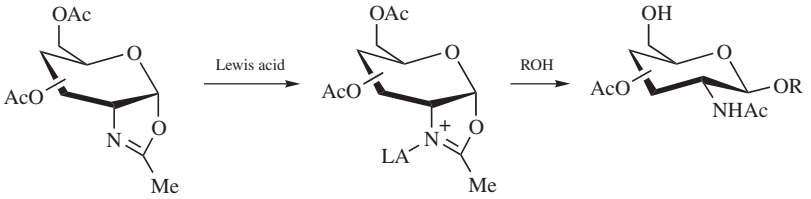
Scheme 8.104



341 **342** **343**

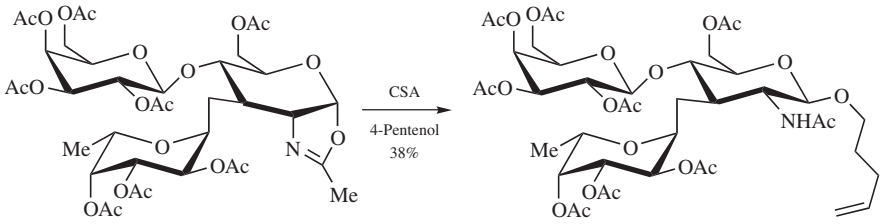
Scheme 8.105

donor (Scheme 8.106).[94] This reaction is promoted by acid and usually results in configurational inversion at the 5-position. A major advantage of this procedure is that the ring-opened product directly incorporates the desired *N*-acetyl function.



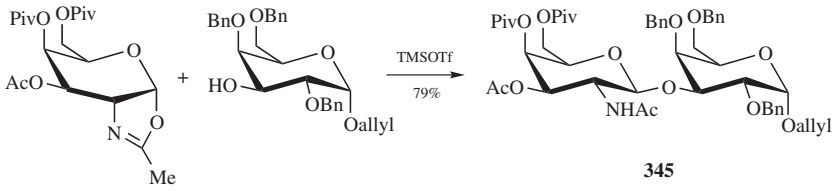
Scheme 8.106

This method works very well for reactive glycosyl acceptors such as primary alcohols. It can be carried out without affecting other acid sensitive functionalities including acetonides[129] and even orthoesters.[93] Nishimura and co-workers successfully employed this method to prepare the trisaccharide monomer **344** (Scheme 8.107).[131] After deprotection, the product was copolymerized with acrylamide to give a biologically interesting glycoprotein model.



344

Scheme 8.107



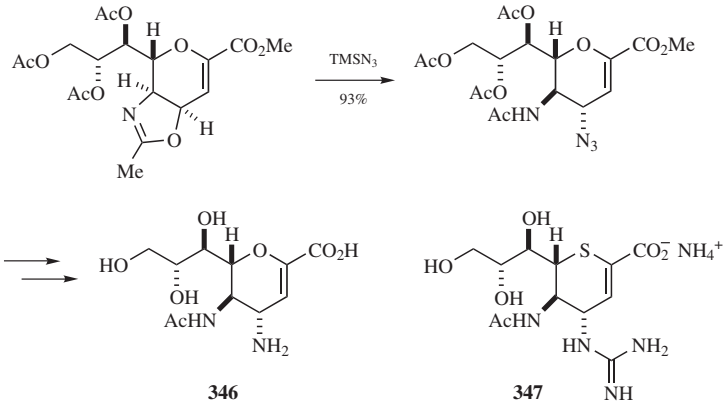
345

Scheme 8.108

Less reactive alcohols (e.g., secondary alcohols) usually give lower yields.[94] However, Colombo and co-workers obtained a good yield of the disaccharide **345** using this method (Scheme 8.108).[132]

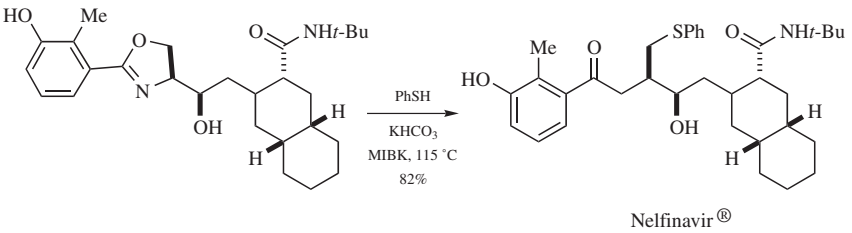
Other useful nucleophiles for this type of substitution include azide and thiolacetic acid. Glaxo researchers utilized such a strategy in their synthesis of the neuraminic acid analogue **346** (Scheme 8.109).[108] Itzstein and co-workers used a similar strategy to synthesize a thio analogue of neuraminic acid **347**[104] and reported that thiolacetic acid was also a suitable nucleophile.[105]

Base-catalyzed nucleophilic attack at the 5-position is rare although it can be an efficient process under appropriate conditions. For example, in the synthesis of acquired immune deficiency syndrome (AIDS) drug Nelfinavir®, a base-catalyzed thiolysis reaction was used in the final step (Scheme 8.110).[126,323] The solvent,



346 **347**

Scheme 8.109

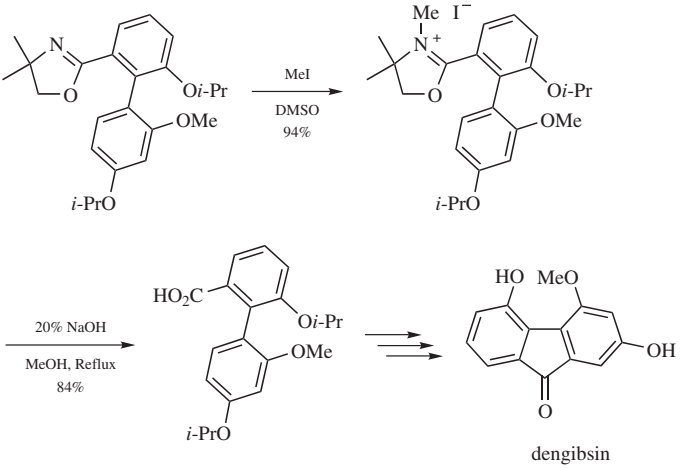


Scheme 8.110

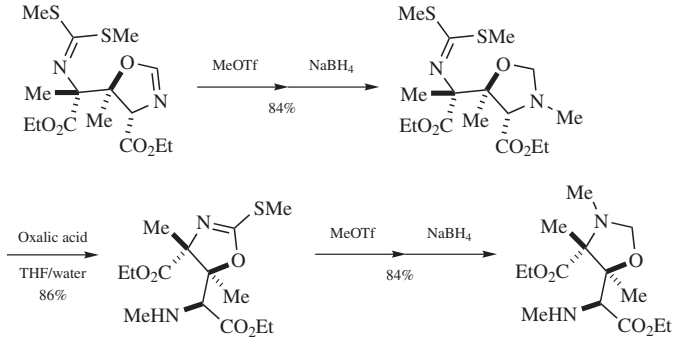
methyl isobutyl ketone (MIBK), as well as the choice of base was found to be critical to minimize side products.

8.3.2. N-Alkylations

The oxazoline nitrogen is a nucleophile and reacts with a variety of electrophiles. Alkylation leads to iminium salts.[324,325] Meyers' group developed the strategy of initial N-alkylation to activate the oxazoline for mild hydrolysis and reduction.[9] Holenca and Persec have firmly established that the hydrolysis proceeds through a nucleophilic attack at the 2-position of the oxazolinium salt.[71] Reactions of an oxazolinium salt have been used extensively in organic synthesis involving oxazolines. For example, Jones and Ciske hydrolyzed an *N*-methyloxazolinium iodide in their dengibsin synthesis (Scheme 8.111).[324] Alvarez-Ibarra and co-workers reduced an intermediate *N*-methyloxazolinium triflate to prepare oxazolidine **348** (Scheme 8.112).[326,327]

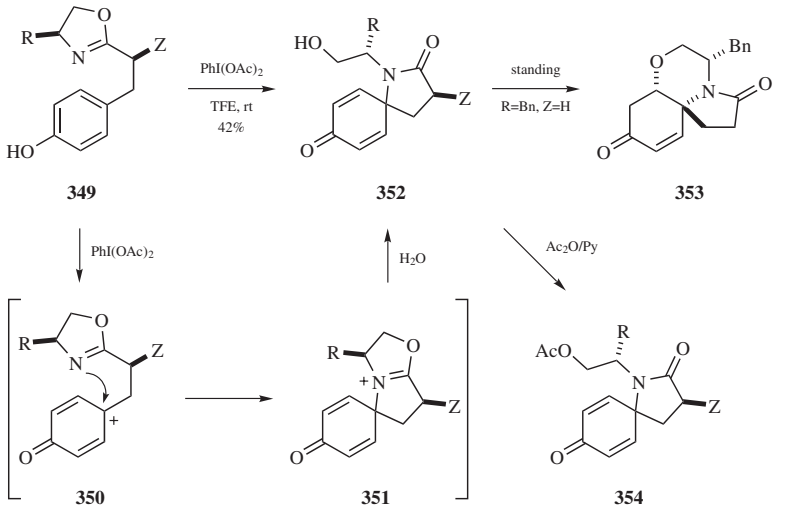


Scheme 8.111



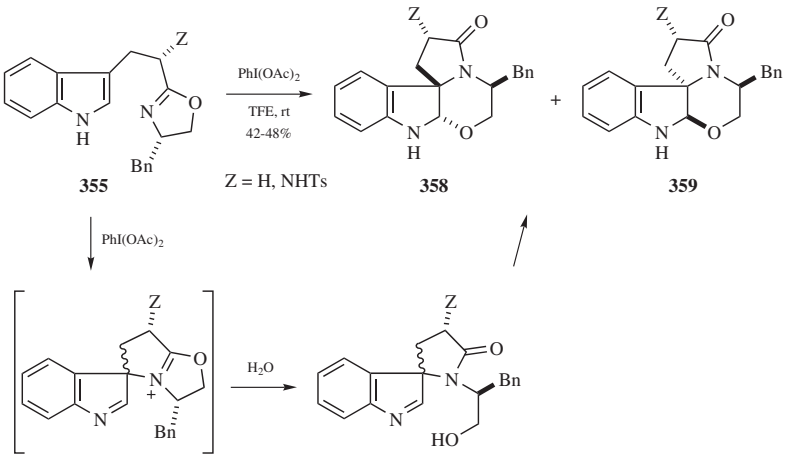
Scheme 8.112

Ciufolini and co-workers designed a clever strategy to prepare azaspirocyclic building blocks.[31,134,135] The key step in their strategy is the intramolecular trapping of the carbocation **350**, generated from oxidation of the phenol **349**, by the oxazoline nitrogen atom (Scheme 8.113).[31,134] Hydrolysis of the resulting oxazolinium ion **351** gives the spirocycle **352**, which undergoes spontaneous Michael addition to produce the tricyclic compound **353** as a single isomer. Alternatively, the initial spirocycle **352** can be trapped as an acetate, **354**. A similar cyclization occurs when the indole oxazoline **355** is oxidized (Scheme 8.114). In this case, a 1:1 mixture of diastereomers **358** and **359** was obtained.[31,135]



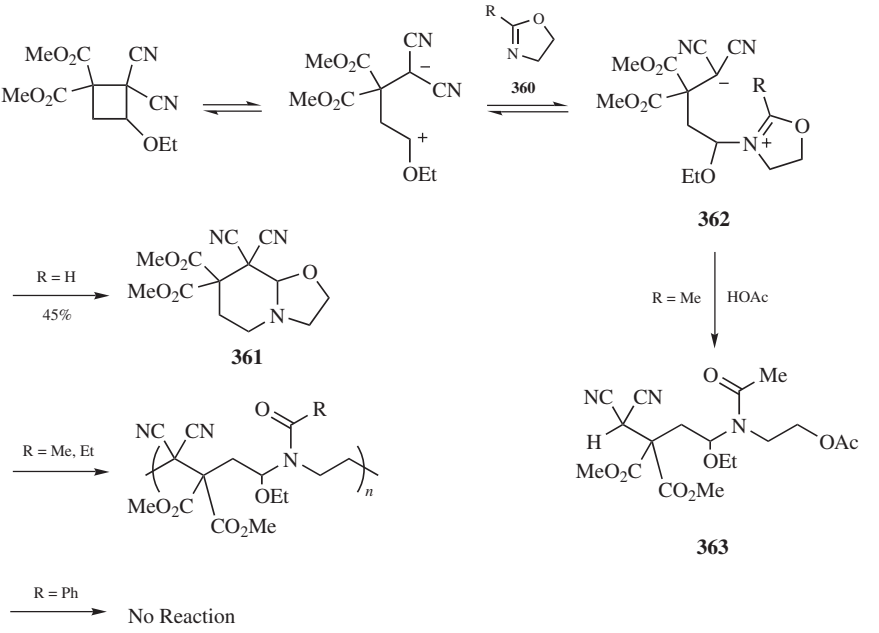
R = H, Bn; Z = H, NHTs

Scheme 8.113



Scheme 8.114

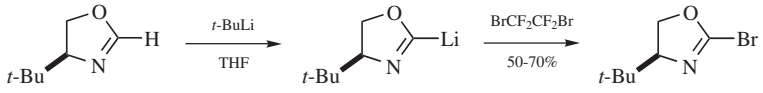
Yokozawa reported that the 2-substituent strongly affects the reactivity of a 2-substituted-oxazoline **360** with dimethyl 2,2-dicyano-3-ethoxy-1,1-dicarboxylate as shown in Scheme 8.115. Thus, oxazoline itself, **360** (R = H), gave the annulated bicyclic product **361** that resulted from collapse of the zwitterionic intermediate **362**, whereas simple 2-alkyloxazolines, **360** (R = Me, Et), gave an alternating (1:1) copolymer. 2-Phenyloxazoline, **360** (R = Ph), was unreactive under the reaction conditions.[328] The zwitterionic intermediate **362** (R = Me) was trapped by acetic acid to give the open-chain adduct **363** that resulted from nucleophilic ring opening at the 5-position of the oxazolinium zwitterion.



Scheme 8.115

8.3.3. Proton Abstractions

Proton abstraction at the 2-position is rare and requires strongly basic conditions. For example, Meyers and Novacheck used *tert*-butyllithium to deprotonate **364** in their preparation of the 2-bromooxazoline **365** (Scheme 8.116).[329] Interestingly,

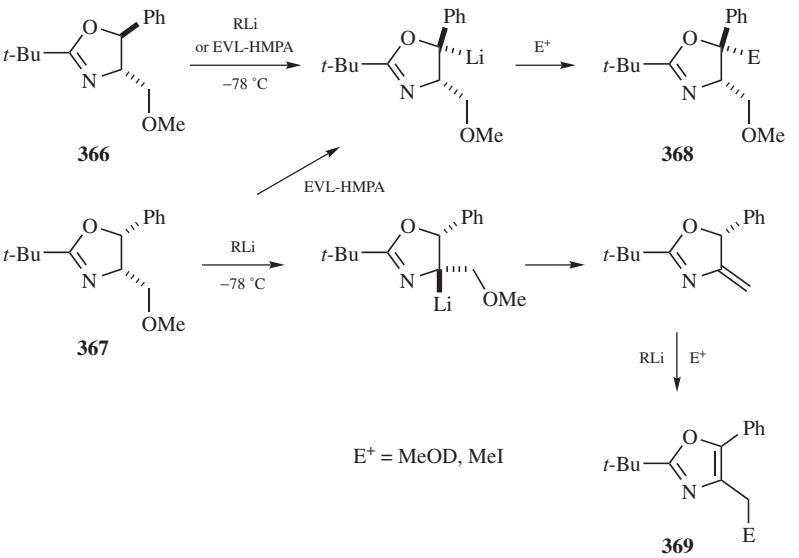


364 **365**

Scheme 8.116

deprotonation at the 4-position was not competitive in this case, probably due to the steric hindrance from the *tert*-butyl group. Cross-coupling reactions of **365** with stannanes are described in Section 8.3.13. It is noteworthy that triflation of the corresponding oxazolidinone gave only the *N*-Tf-oxazolidinone.

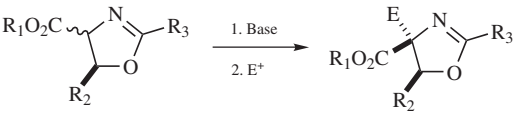
Meyers and Shimano discovered the unusual deprotonation behavior of ethoxyvinyllithium–HMPA complex (EVL–HMPA) for the deprotonation of the *trans*-oxazoline **366** and the *cis*-oxazoline **367**. The EVL–HMPA complex is prepared by deprotonation of ethyl vinyl ether with *tert*-butyllithium in THF followed by addition of HMPA. Reaction of the *trans*-oxazoline **366** with both the EVL–HMPA complex and conventional alkyllithium reagents (RLi) resulted in deprotonation at the benzylic 5-position. In contrast, deprotonation of **367** occurred at the 4-position with an alkyllithium reagent RLi, whereas benzylic deprotonation predominated with the EVL–HMPA complex (Scheme 8.117).[330] The authors proposed that EVL–HMPA complexes with the 5-phenyl substituent prior to deprotonation.



Scheme 8.117

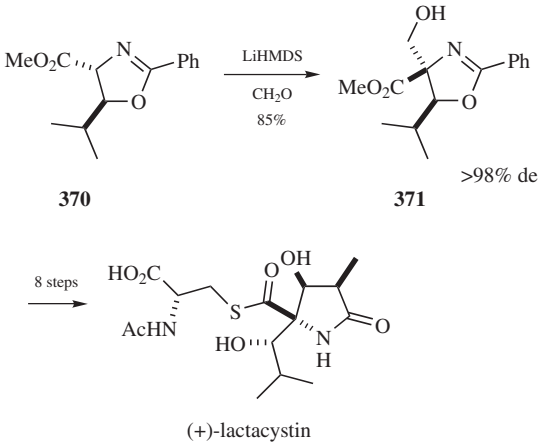
Deprotonation at an activated 4-position has been employed extensively in asymmetric synthesis, which is the key step in the Seebach protocol for the preparation of α-alkyl amino acids.[331] The existing alkyl group at the 5-position acts as a directing group for the alkylation and is oriented trans to the new alkyl group (Scheme 8.118). This reaction provides an efficient methodology for normally difficult stereoselective construction of a quaternary chiral center.

Several groups employed this strategy for the synthesis of lactacystin analogues, an important class of nonprotein neurotrophic factors. For example, in their total



Scheme 8.118

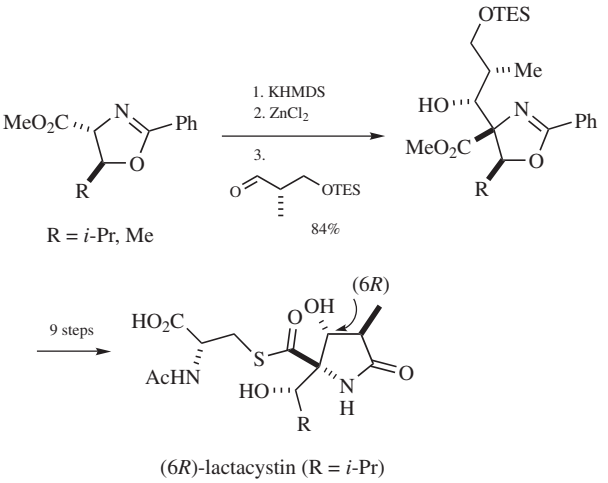
synthesis of (+)-lactacystin, Omura, Smith, and co-workers used this method to construct the key quaternary chiral center (Scheme 8.119).[227,229] Here, deprotonation of the oxazoline-4-carboxylic acid ester **370** with LiHMDS followed by reaction with formaldehyde gave the alcohol **371** in good yield with excellent diastereoselectivity (>98% de). Using a milder base (DBU), Node, Kajimoto, Wong, and co-workers also demonstrated the utility of this method in their synthesis of mycestericin D.[81,82]



Scheme 8.119

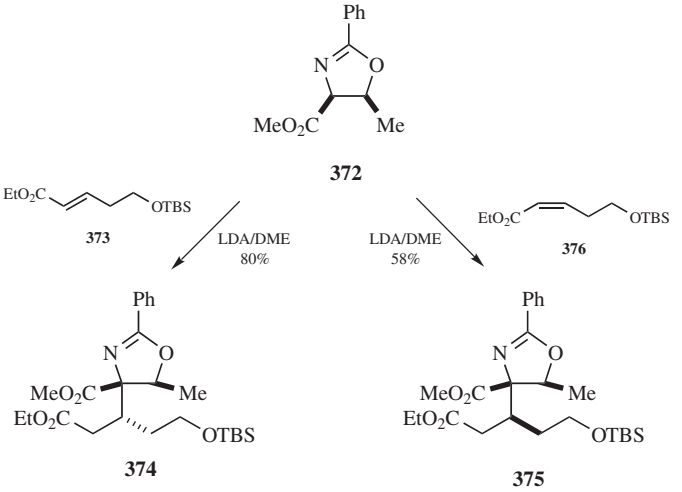
An additional chiral center results using a prochiral electrophile, for example, an aldol reaction with an aldehyde. The stereochemistry at the new chiral center can be controlled following traditional aldol condensation methods. For example, Corey and Choi used a zinc oxazoline enolate in their synthesis of (6*R*)-lactacystin (Scheme 8.120).[332] The authors proposed that, depending on the enolate geometry, either a chair [for the (*Z*) enolate] or a boat [for the (*E*) enolate] six-membered transition state may be responsible for the preferred stereochemistry at the new chiral center bearing the hydroxy group. Adams and co-workers used a similar strategy in their total synthesis of *clasto*-lactacystin β-lactone.[79]

A stabilized 4-oxazoline enolate can also undergo highly stereoselective Michael addition. Overman and co-workers studied this reaction in their synthesis of sarains A–C. Thus, deprotonation of the oxazoline **372** with LDA at −78 to −65 °C followed by reaction with the trans-ester **373** gave a single diastereomer of



Scheme 8.120

oxazoline **374** by NMR. The other diastereomeric oxazoline **375** was obtained in high selectivity albeit lower yield from reaction using the cis-ester **376** (Scheme 8.121).[333] A chelated transition state model was proposed to rationalize the high diastereoselectivity (Fig. 8.12). The olefin approaches the enolate from the opposite face of the neighboring 5-methyl group. The organizational role of the lithium ion in the transition state is supported by the observation that substantially lower selectivity was obtained when HMPA was present.



Scheme 8.121

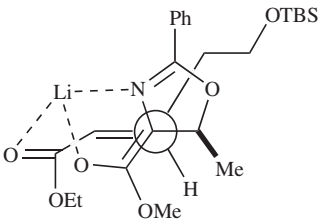
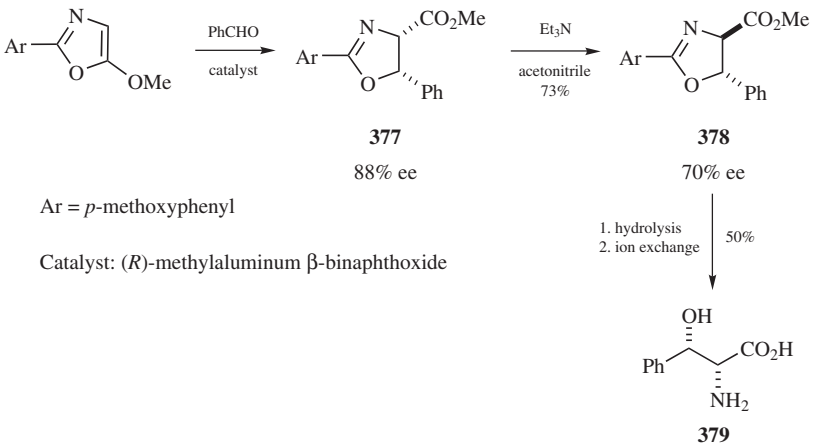


Figure 8.12. Chelated transition state model.

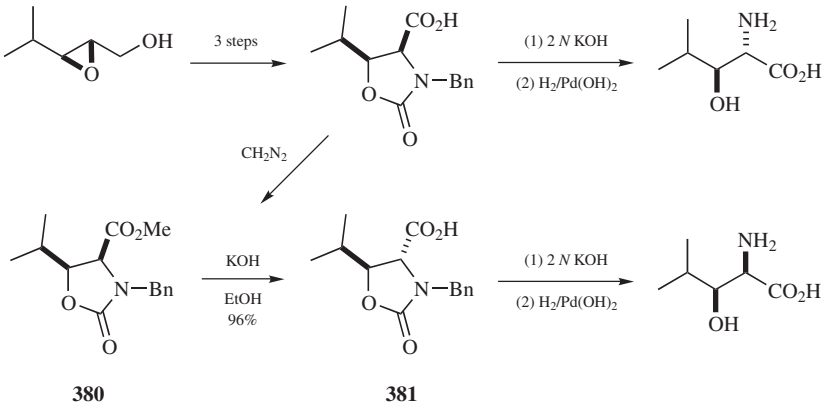
The facile proton abstraction of activated oxazolines offers a convenient method to convert cis oxazolines to the thermodynamically more stable trans isomer. Suga, Ibata, and co-workers took advantage of this property to correctly determine the stereochemistry for the oxazoline obtained from the [3 + 2] cycloaddition of 5-methoxy-2-(*p*-methoxyphenyl)oxazole with benzaldehyde (Scheme 8.122).[334,335] The cis-oxazoline **377** (88% ee) was converted to the trans-oxazoline **378** (70% ee) using triethylamine. A two-step sequence then converted **378** to β-phenylserine **379** thus confirming the cis stereochemistry of **377**.

Proton abstraction and epimerization of activated oxazolines is comparable to a similar epimerization known for oxazolidinones. For example, Omura and Smith reported an elegant synthesis of all four stereoisomers of 3-hydroxyleucine from (*E*)-4-methyl-2-penten-1-ol (Scheme 8.123).[227,336a] One of the key steps was the efficient epimerization of the cis-oxazolidinone ester **380** to the trans-oxazolidinone acid **381** during saponification.

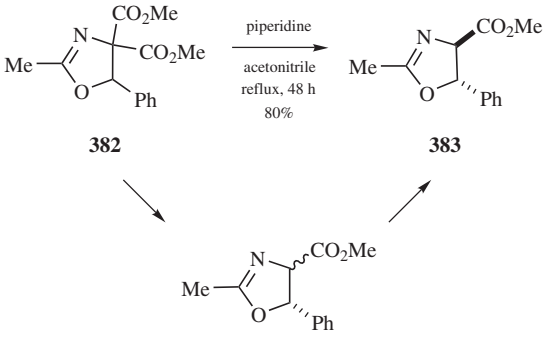
Finally, Bazureau and co-workers reported an interesting decarbomethoxylation reaction of the 4,4-oxazolinedicarboxylic acid diester **382**. The ester group cis to the neighboring 5-phenyl substituent in **382** was selectively removed to produce the trans-monoester **383**.[294] However, considering the reaction conditions, the product



Scheme 8.122



Scheme 8.123



Scheme 8.124

is likely the result of equilibration of an initial cis/trans mixture **384** to the thermodynamically more stable trans product **383** (Scheme 8.124).

8.3.4. Oxidations

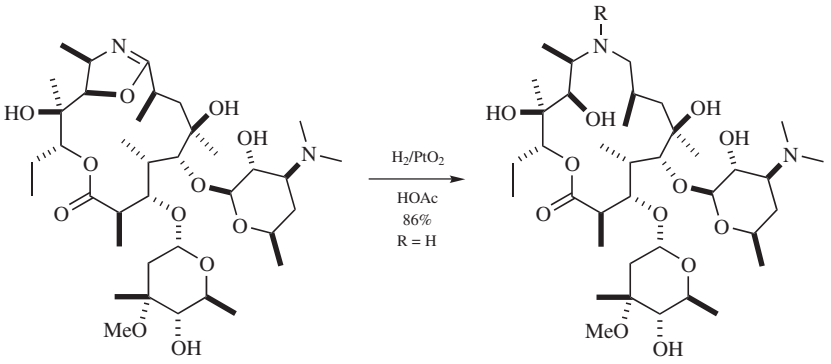
Oxazolines are oxidized to the corresponding oxazoles by a variety of oxidants. The reader should consult Chapter 1, Part A of this series[336b] for detailed discussions and examples.

8.3.5. Reductions

Oxazolines are reduced to oxazolidines that are usually reduced further to amino alcohols. For example, hydrogenation of the oxazoline **385** was an important step in

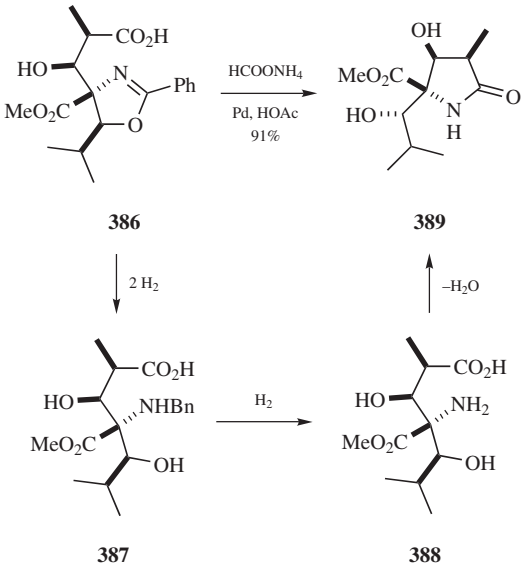
the semisynthesis of azithromycin (Scheme 8.125).[337] In contrast, traditional catalytic hydrogenolysis of oxazoline **386** was unsuccessful, whereas catalytic-transfer hydrogenation proved to be quite efficient (Scheme 8.126).[227,229] Presumably, **386** initially gives the benzylamino alcohol **387** that undergoes hydrogenolysis to the amino alcohol **388**. Cyclization of **388** *in situ* then gives the desired lactam **389**.

The reduction can be stopped at the benzylamino alcohol stage using an appropriate reducing agent. For example, in their general strategy to prepare pseudodistomins, Naito and co-workers reduced the bicyclic oxazoline **390** to the



385 azithromycin (R = Me)

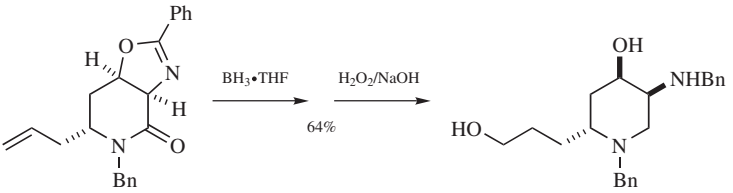
Scheme 8.125



386 **389**

387 **388**

Scheme 8.126



390 **391**

Scheme 8.127

benzylamino alcohol **391** using borane (Scheme 8.127).[307] Oxazolines are stable to lithium aluminum hydride (LAH) at low temperature[217] but they can be reduced to alkylamino alcohols using LAH under more forcing conditions (60 °C, THF).[334]

8.3.6. Oxazolines as Protecting Groups

Oxazolines have been extensively used as masking groups for either amino alcohols or carboxylic acids. This application has been thoroughly reviewed in Greene's popular monograph[6] and is evident throughout this chapter. Therefore, it is not repeated further here.

8.3.7. Oxazolines as Activating Groups

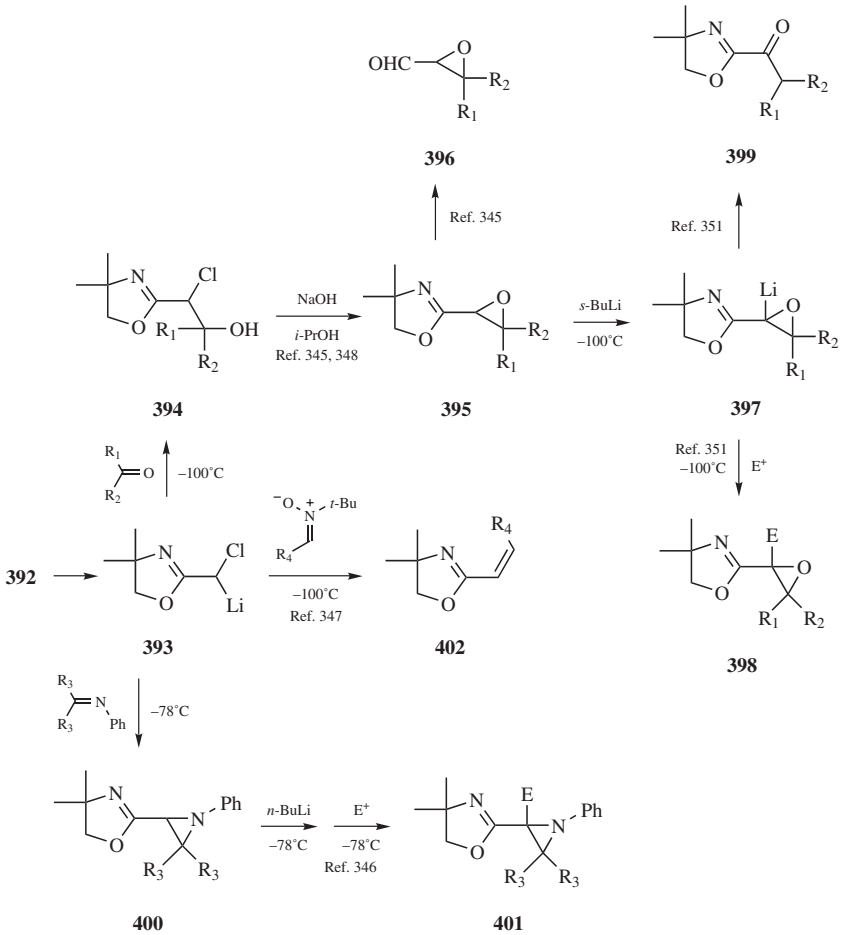
The oxazoline ring acts as an electron-withdrawing group for a substituent at the 2-position. Thus, the α-protons of a 2-alkyloxazoline exhibit some acidity and can be abstracted by a base. A 2-alkenyloxazoline can be viewed as a masked acrylic acid derivative and is capable of undergoing Michael addition and Diels–Alder reactions. These reactions can often be carried out stereoselectively using a chiral oxazoline. Other types of chiral auxilliaries, most notably oxazolidinones, are also very effective for these types of applications. However, they are outside the scope of this chapter. The discussion in this section will focus on the new developments with oxazolines.

8.3.7.1. α-Proton Abstraction

The carbanion generated by α-proton abstraction of a 2-alkyloxazoline is capable of typical enolate chemistry. Thus, the carbanion was found to react with nitriles to give an enamine,[338] with formate esters to give an aldehyde that can be trapped,[339] with chiral sulfinate esters to give chiral sulfoxides,[204] and with alkylating agents.[26,51] A carbamate-protected aminomethyl chiral oxazoline was deprotonated and alkylated with diastereoselectivities up to 92% de.[139]

The proton abstraction typically requires strong bases although weaker bases can be employed if the α-carbon is substituted with an additional activating group, such as an aryl group.[340] Deprotonation of chiral arylmethyloxazolines followed by alkylation gave modest levels of diastereoselection (up to 60% de).[341] Deprotonation of appropriately substituted 2-(allyloxymethyl)oxazolines resulted in stereoselective [2,3]-Wittig rearrangement.[342–344] Ion pair acidities of 2-biphenylmethyl oxazolines have been calculated.[62] Experimental data indicated that the anion–metal ion pairs studied did not aggregate in THF.

Florio's group published an interesting series of reports detailing the application of 2-(chloromethyl)oxazolines in organic synthesis.[345–351] Deprotonation of 2-(chloromethyl)-4,4-dimethyloxazoline **392** yields a carbanion **393** that undergoes a wide variety of synthetically useful reactions (Scheme 8.128). Thus, quenching **393** with a carbonyl compound at −100 °C gave chlorohydrins **394** that can be



Scheme 8.128

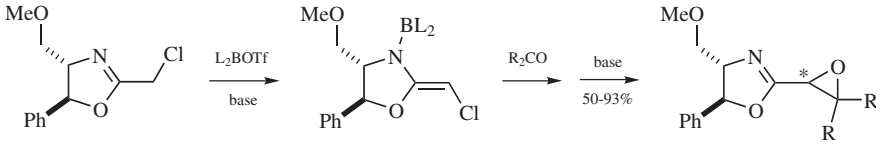
converted to the 2-oxazoline substituted epoxides **395** upon treatment with a base.[345] Further, the oxazoline-epoxide **395** can be converted to an epoxy aldehyde **396**.[345] If the oxazoline-epoxide **395** is deprotonated, the resulting carbanion **397** can be trapped with an electrophile to give a tetrasubstituted epoxide **398**. Alternatively, in the absence of an electrophile, upon warming to room temperature, **397** rearranges to the ketone **399**.[351]

Trapping **393** with a Schiff base derived from aniline gave an *N*-phenylaziridine **400**.[346] Deprotonation of **400** followed by quenching with an electrophile produced the tetrasubstituted-*N*-phenylaziridine **401**, analogous to the conversion of **395** to **398**.[346]

Most interestingly, reaction of **393** with nitrones gave a 2-(*cis*-alkenyl)-substituted oxazoline **402**. A chelation-based transition state model was proposed to rationalize this unusual cis selectivity.[347] The 2-(trans-alkenyl)-substituted oxazoline can be obtained using the analogous des-chloro lithiated 2-alkyloxazoline.[347]

A chloromethyllithium species substituted with a chiral oxazoline moiety gives an epoxide with modest levels of diastereoselection (up to 33% de) using a symmetrical ketone.[348] However, higher levels of diastereoselection were obtained using boron azaenolates.[349,350] Thus, treatment of the chiral 2-(chloromethyl) oxazoline **403** with a dialkylboron triflate gave the (*Z*)-boron azaenolate **404** (Scheme 8.129). Reaction of **404** with ketones followed by base treatment gave the desired epoxide **405** in good yields. For aromatic ketones and 9-BBNOTf the (*R*) configuration was obtained in the newly created chiral center. However, the stereochemistry was reversed if Bu_2BOTf was used. For aliphatic ketones, Bu_2BOTf was found to give better selectivities than 9-BBNOTf although the relative configuration of the new chiral center was unchanged. The absolute configuration in the case of aliphatic ketones was not reported. A titanium azaenolate of **403** was also found to give **405** in good yields (50–75%) and selectivities (76–96% de) from aliphatic ketones. However, it gave poor selectivities with aromatic ketones (0–50% de).[350]

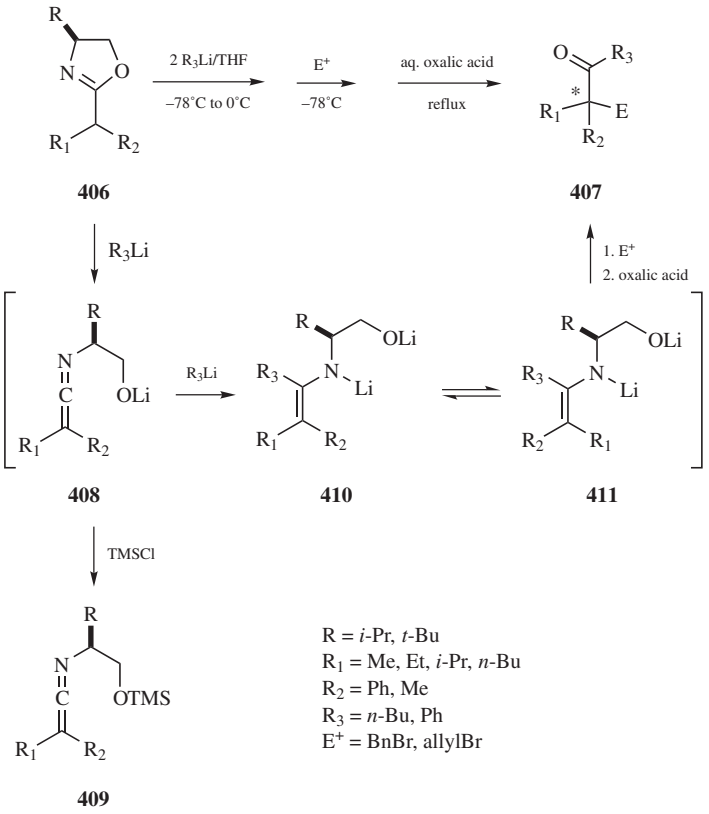
Meyers and co-workers recently reported a ketenimine rearrangement that has been applied to the synthesis of ketones containing a chiral α-quaternary carbon. As



403 **404** **405**

L_2B = 9-BBN, R = Ar: Selectivity = 70-96% de *(R)*
L_2B = Bu_2B, R = Ar: Selectivity = 64-88% de (*S*)
L_2B = 9-BBN, R = alkyl: Selectivity = 33-40% de (NR)
L_2B = Bu_2B, R = alkyl: Selectivity = 80-94% de (NR)

Scheme 8.129



Scheme 8.130

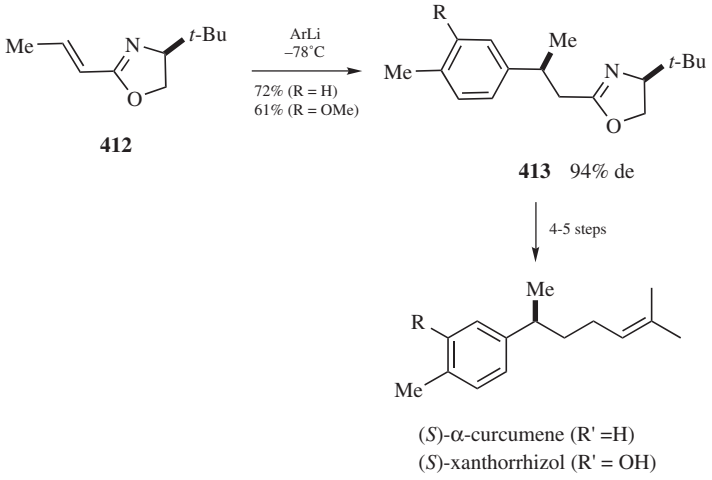
shown in Scheme 8.130, deprotonation of a 2-alkyloxazoline **406** by an alkyl or aryllithium reagent followed by trapping with an electrophile gave the desired ketone **407** in good yields (50–75%) and enantioselectivities (35–87% ee).[352] The selectivity was independent of the configuration at the α-carbon in **406** since both isomers gave the same diastereomeric mixture of ketenimines **408** that were trapped with TMSCl to give the *O*-TMS ketenimine derivative **409**. The authors reported that equilibration of the enamine species **410** and **411** as well as the facial discrimination determined the stereochemical outcome. The choice of THF as the solvent was critical to achieve high selectivities. The absolute configuration of the products was not reported.

8.3.7.2. Michael Additions of 2-Alkenyloxazolines

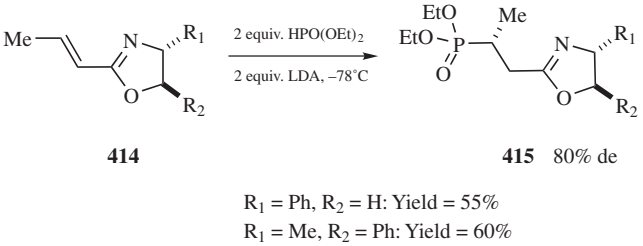
The use of oxazolines as chiral auxiliaries for asymmetric Michael additions has yielded mixed results. For example, Langlois' group reported modest diastereoselectivities (up to 60% de) for cyanide addition to a number of chiral

α,β-unsaturated oxazolines using diethylaluminium cyanide.[90,353,354] On the other hand, Meyers' group capitalized on their earlier successes using a *tert*-leucine-based oxazoline auxilliary and applied this methodology to their asymmetric syntheses of (+)-α-curcumene and (+)-xanthorrhizol. Thus, reaction of an aryllithium with the chiral oxazoline **412** gave the desired adducts **413** with excellent selectivities (Scheme 8.131).[60] Ultimately, **413** (R = H or OMe) were converted to (+)-α-curcumene and (+)-xanthorrhizol, respectively, in 4–5 steps. However, the yields of **413** were markedly dependent on the method of generation of the lithium reagent. Thus, for **413** (R = H), the best yield was obtained when the lithium reagent was prepared by direct metalation of *p*-bromotoluene with excess lithium in ether followed by filtration to remove insoluble material. Alternatively, for **413** (R = OMe), the low solubility of the lithium reagent necessitated the preparation by transmetalation of the corresponding bromide using *tert*-butyllithium.

More recently, Quirion and co-workers reported good diastereoselectivities (up to 80% de) for addition of diethyl phosphite to the chiral oxazolines **414** (Scheme 8.132).[355] The absolute stereochemistry of the products was not confirmed. The phosphonate **415** can be converted to biologically important β-amidophosphonates by known methods.



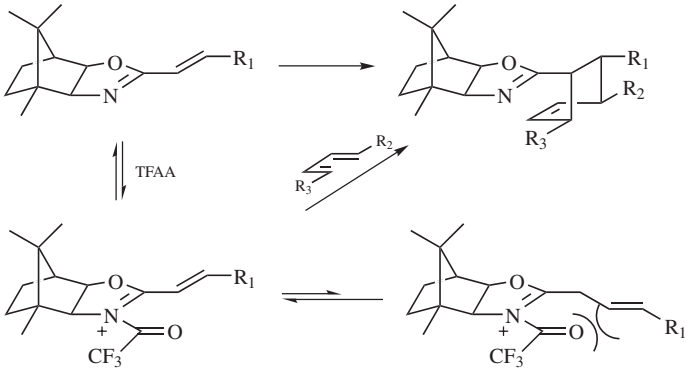
Scheme 8.131



Scheme 8.132

8.3.7.3. Diels–Alder Reactions of 2-Alkenyloxazolines

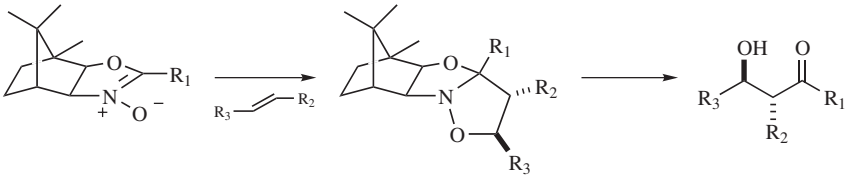
New developments in this area from Langlois' group are primarily and generally on the development of the asymmetric version of these reactions. Most of the reactions employed camphor-derived 2-alkenyloxazolines as dienophiles (Scheme 8.133). In many cases, these reactions were carried out in the presence of trifuoroacetic anhydride to activate the alkene by complexation at the oxazoline nitrogen as well as to limit the number of reactive conformations. The reader should consult the recent and extensive reviews of this chemistry by Langlois.[12,13]



Scheme 8.133

8.3.8. Dipolar Cycloadditions of Oxazoline *N*-Oxides

An oxazoline *N*-oxide is a versatile dipole and can react with a variety of dipolarophiles (Scheme 8.134). Langlois' group has been very active in this area and has made extensive use of the *N*-oxides of camphor-derived oxazolines for these reactions. The initial adduct can be converted to the anti aldol product after hydrolysis and hydrogenolysis. This subject has been thoroughly reviewed by Langlois,[12–14] most recently in 2000.[14]



Scheme 8.134

8.3.9. Oxazolines as Directing Groups for Aromatic Reactions

Oxazoline-directed aromatic substitution and addition reactions provide synthetic chemists with powerful tools for the construction of complex aromatic compounds. Since the last authoritative review by Meyers,[9] these technologies have matured and found widespread applications in organic synthesis. While there has been somewhat limited methodological research in this area in the intervening years, one particularly exciting new development is the diastereoselective ortho-metalations directed by chiral oxazolines. Sections 8.3.9.1–8.3.9.3 will discuss these new developments as well as new synthetic applications of these reactions.

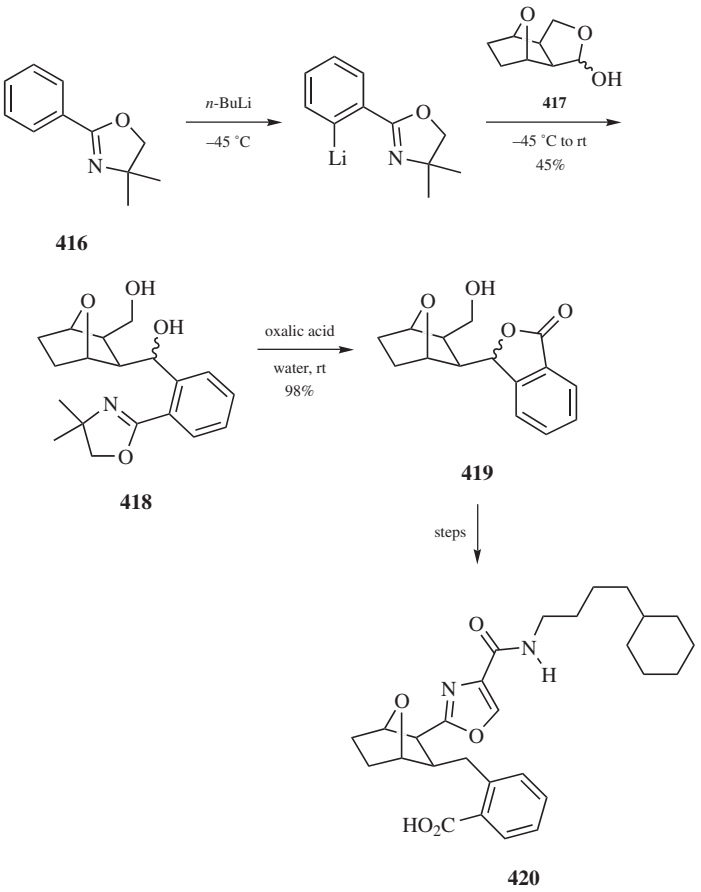
8.3.9.1. Metalation and Electrophilic Substitutions

Since the discovery in 1975 by Gschwend[356] and Meyers[356a] the oxazoline-directed aromatic ortho-metalation protocol has been used extensively in organic synthesis. A variety of electrophiles have been reacted with the active aryl metal species to prepare a diverse array of aromatic structures. In a traditional application of this methodology, Misra and co-workers used ortho-lithiation and subsequent reactions in their synthesis of a thromboxane A_2 receptor antagonist **420** (Scheme 8.135).[114] Lithiation of excess 4,4-dimethyl-2-phenyloxazoline **416** (3 equiv) was performed in THF at –45 °C. After reaction with the lactol **417**, the resulting oxazoline **418** was hydrolyzed under mild conditions to give the corresponding acid (not shown) that was cyclodehydrated under the reaction conditions to the lactone **419**. Further elaboration of **419** then gave the desired target **420**.

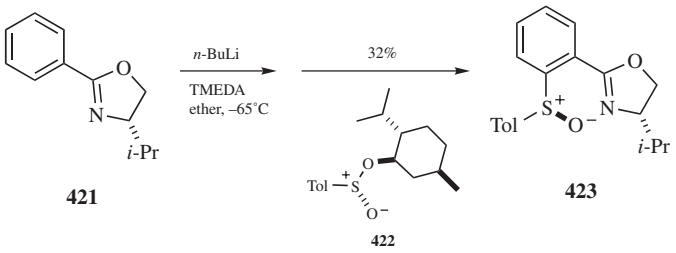
Williams and co-workers reacted an aryllithium intermediate, generated from metalation of the oxazoline **421**, with menthyl toluenesulfinate **422** to prepare an authentic aryl-substituted chiral sulfoxide (Scheme 8.136).[203,204] The sulfoxide configuration was inverted during the displacement reaction. Similarly, Uemura and co-workers prepared chiral oxazolinyl aryl sulfides in good yields using disulfides as the electrophile.[357] Using diarylphosphinyl halides as the electrophile, Pfaltz and co-workers prepared chiral phosphinooxazolines in good yields via the same metalation methodology.[358,359]

Benzylic deprotonation occurs under normal lithiation conditions when both ortho-positions are occupied. Interestingly, Thomas and co-workers were able to deprotonate a benzylic proton in the presence of an ortho proton (Scheme 8.137).[66] Thus, metalation of 2-(2-methylphenyl)oxazoline **424** produced a benzylic lithium species that reacted with a Cbz-protected leucinal **425** to give a modest yield of the iminolactone diastereomers **426** and **427** together with the expected alcohols **428** and **429**. The mixture of **426–429** was efficiently hydrolyzed to give the lactones **430** and **431**.

The authors then applied this strategy in their total synthesis of the anti-ulcer compound AI-77-B (Scheme 8.138). It is noteworthy that the ortho-methoxy group

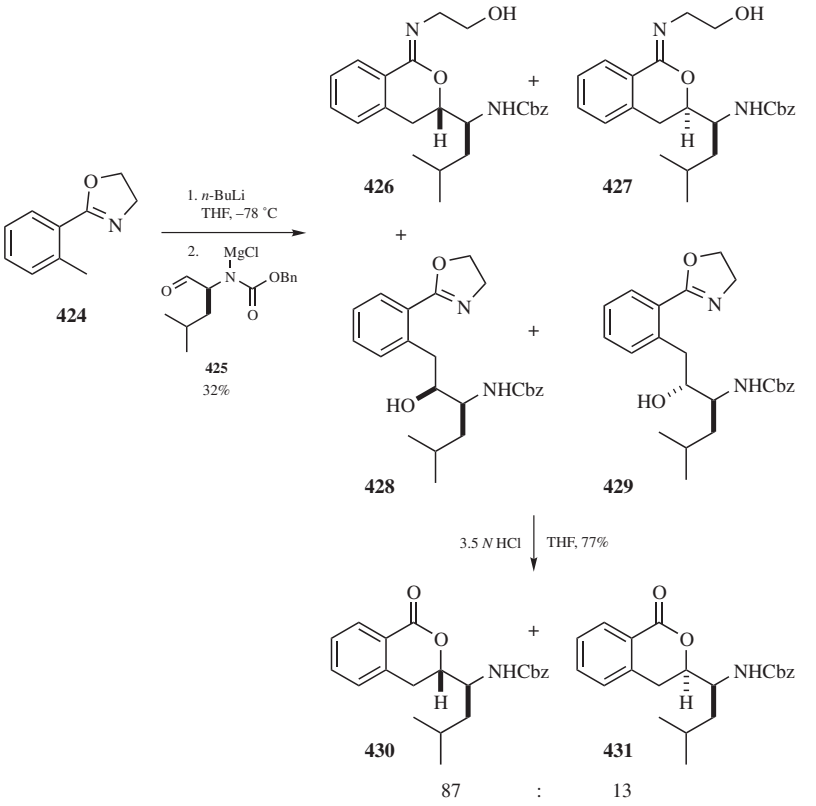


Scheme 8.135

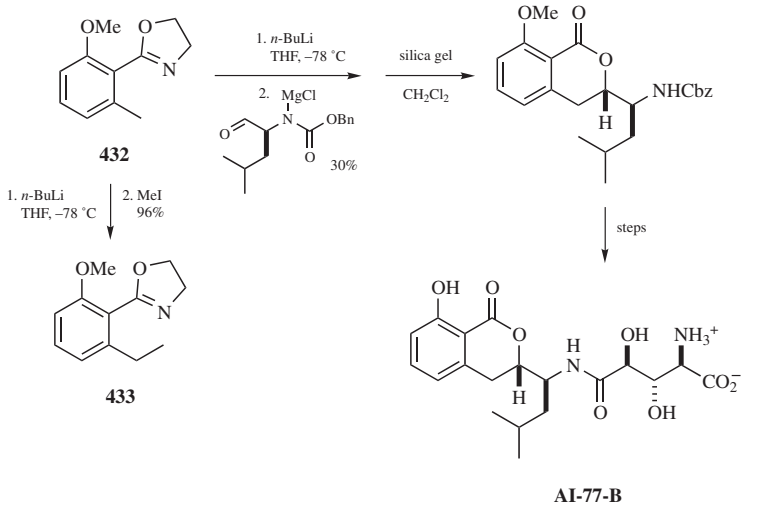


Scheme 8.136

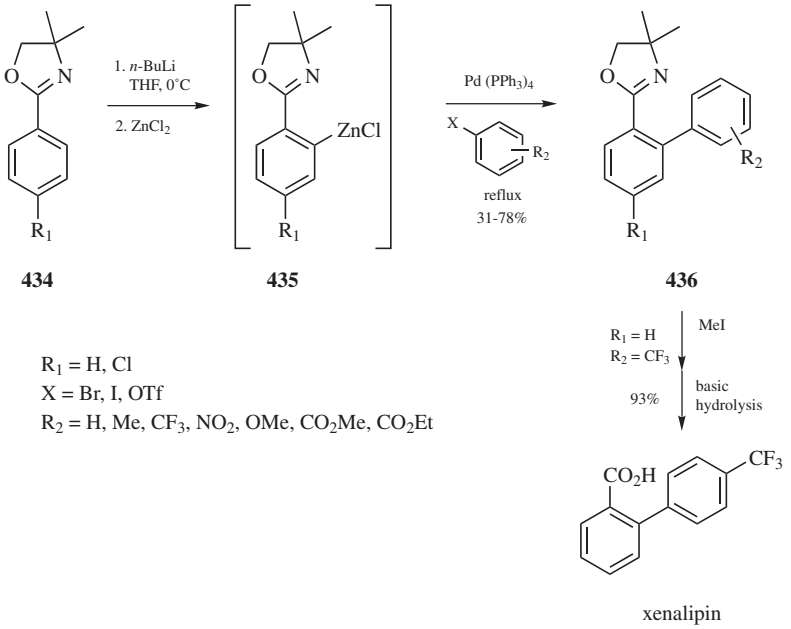
of **432** did not interfere with the lithiation and the subsequent electrophilic reaction. For example, methylation of the benzyllithium species prepared from **432** gave the expected ethyl homologue **433** in excellent yield. In comparison with the oxazoline-directing group, the authors found that an ethyl ester yielded unreliable results, especially on scale-up.



Scheme 8.137



Scheme 8.138



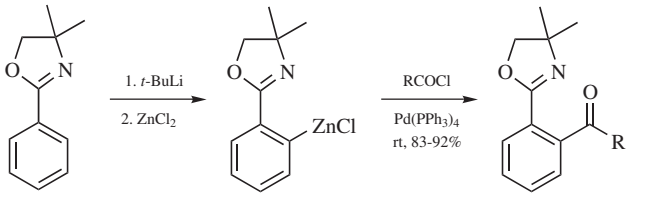
434 **435** **436**

R_1 = H, Cl
X = Br, I, OTf
R_2 = H, Me, CF_3, NO_2, OMe, CO_2Me, CO_2Et

Scheme 8.139

Pfizer workers took advantage of both the oxazoline-directed metalation and Negishi's cross-coupling methodology to devise a new approach to prepare biaryls (Scheme 8.139).[360] The initially formed lithium species from **434** was converted to the organozinc reagent **435**. Subsequent cross-coupling of **435** with aryl halides or triflates gave the biaryls **436**. The reaction is more efficient for electron-deficient aryl iodides and triflates. Aryl bromides tend to react slower and gave lower yields. Other ortho-directing groups, such as amides, can be used in place of oxazoline, but they are not as easily converted to other functional groups. The hypolipidemic agent, xenalipin, was efficiently prepared by hydrolysis of **436** ($R_1 = H$, $R_2 = CF_3$) after quaternization with methyl iodide.

Evans and co-workers employed a similar approach to prepare aryl ketones. Direct acylation of an aryllithium species by acyl halides is usually complicated by the competitive secondary reactions of the newly formed ketones. Although these ketones can be prepared using other acyl equivalents, such as esters or amides, the reaction conditions have to be carefully controlled. To circumvent these difficulties, Evans and co-workers devised an alternative approach wherein the aryllithium from metalation of an oxazoline was converted to the corresponding arylzinc species by transmetalation. The more tolerant organozinc reagent **437** was then reacted with acid chlorides under the Negishi cross-coupling conditions to afford the corresponding ketones **438** (Scheme 8.140).[361] Internal chelation of **437** with the oxazoline nitrogen atom reduces the reactivity and necessitates the use of excess



416 **437** **438**

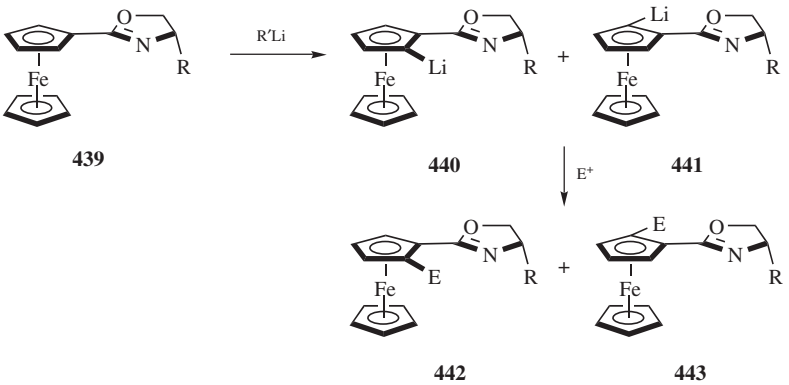
R = Ph, cyclopentyl, methallyl

Scheme 8.140

437 to obtain synthetically useful yields of **438**. There was no reaction in the absence of the palladium catalyst.

Bidentate ferrocene ligands containing a chiral oxazoline substituent possess both planar chiral and center chiral elements and have attracted much interest as asymmetric catalysts.[362,363] However, until recently, preparation of such compounds had been limited to resolution. In 1995, four groups simultaneously communicated their results on the asymmetric synthesis of these structures using an oxazoline-directed diastereoselective lithiation (Scheme 8.141).[175,364–366] When a chiral oxazolinylferrocene **439** was metalated with butyllithium and the resulting aryllithium species trapped with an electrophile, diastereomer **442** was favored over **443**. The structure of the major diastereomer **442** was confirmed, either by conversion to a compound of known stereochemistry[365] or by X-ray crystallography of the product itself[175] or of the corresponding palladium complex.[366]

Subsequent studies revealed the scope and generality of this reaction that has been employed extensively for the synthesis of chiral ferrocenyloxazoline ligands.[41,174,367,368] Selected examples are listed in Table 8.26 (Scheme 8.142).[41,174,364,365,368–374] Sammakia and Latham optimized the reaction conditions



439 **440** **441** **442** **443**

Scheme 8.141

TABLE 8.26. LITHIATION OF OXAZOLINYLFERROCENE **439** AND TRAPPING WITH ELECTROPHILES[a]

439 **442**

Scheme 8.142

Entry	R, R′	E^+	Lithiation Conditions	dr	% Yield	References
1	Me, *n*-Bu	TMSCl	TMEDA/Et_2O, 0 °C	>50 : 1	72	174
2	Me, *s*-Bu	Ph_2PCl	Et_2O, −78 °C	8 : 1	25	364
3	CH_2OMe, *s*-Bu	TMSCl	THF, −78 °C, ramp to 0 °C	4 : 1	NR	365
4	CH_2SMe, *s*-Bu	TMSCl	THF, −78 °C, ramp to 0 °C	3 : 1	NR	365
5	CH_2OTBS, *s*-Bu	TMSCl	THF, −78 °C, ramp to 0 °C	2 : 1	NR	365
6	CH_2OCH_2OMe, *s*-Bu	TMSCl	THF, −78 °C, ramp to 0 °C	4 : 1	NR	365
7	Bn, *s*-Bu	TMSCl	THF, −78 °C, ramp to 0 °C	3 : 1	NR	365
8	Bn, *s*-Bu	Ph_2PCl	Et_2O, −78 °C	14 : 1	56	364
9	Ph, *s*-Bu	TMSCl	THF, −78 °C, ramp to 0 °C	6 : 1	NR	365
10	Ph, *s*-Bu	Ph_2PCl	Et_2O, −78 °C	>199 : 1	55	364
11	Ph, *s*-Bu	Ph_2CO	THF, −78 °C	NR	34	370
12	*i*-Pr, *n*-Bu	$C_2Cl_4Br_2$	TMEDA/ether, −78 °C	single isomer	94	369
13	*i*-Pr, *s*-Bu	TMSCl	TMEDA/hexane, −78 °C, ramp to 0 °C	>500 : 1	94	368
14	*i*-Pr, *s*-Bu	Ph_2PCl	Et_2O, −78 °C	39 : 1	77	364
15	*i*-Pr, *s*-Bu	PhSeSePh	Et_2O, −78 °C	39 : 1	54	364

TABLE 8.26 (*Continued*)

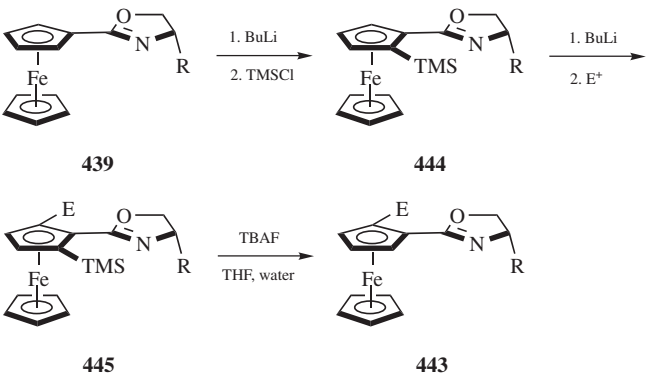
Entry	R, R′	E^+	Lithiation Conditions	dr	% Yield	References
16	*i*-Pr, *s*-Bu	MeI	Et_2O, −78 °C	39 : 1	58	364
17	*s*-Bu, *s*-Bu	Ph_2PCl	Et_2O, −78 °C	24 : 1	58	364
18	*t*-Bu, *s*-Bu	TMSCl	TMEDA/hexane, −78 °C, ramp to 0 °C	>500 : 1	NR	368
19	*t*-Bu, *s*-Bu	Ph_2PCl	Et_2O, −78 °C, ramp to 0 °C	13 : 1	65	41
20	*t*-Bu, *n*-Bu	Bu_3SnCl	TMEDA/hexane, −78 °C, ramp to 0 °C	>99 : 1	99	41
21	*t*-Bu, *s*-Bu	PhSSPh	THF, −78 °C, ramp to 0 °C	32 : 1	81	41, 371
22	*t*-Bu, *n*-Bu	CO_2	Et_2O, rt	NR	83	41
23	*t*-Bu, *s*-Bu	DMF	THF, −78 °C, ramp to 0 °C	NR	73	41
24	*t*-Bu, *s*-Bu	Ph_2CO	THF, −78 °C	27 : 1	87	372, 373
25	*t*-Bu, *s*-Bu	Se	THF, −78 °C	NR	69 (after oxidation to diselenide)	374

[a] Not reported: NR.

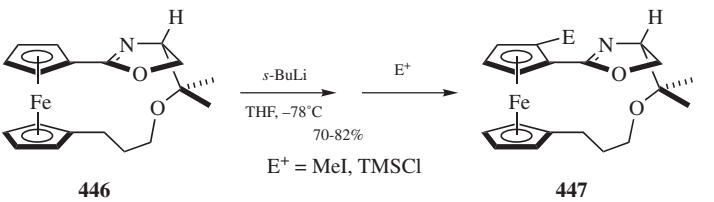
and found that the highest diastereoselectivity (>500:1, entry 13) was obtained using *sec*-butyllithium as the base, hexane as the solvent, and TMEDA as the additive.[368] Ahn and co-workers also observed sensitivities of the reaction toward solvent, base and temperature.[41] Low yields could often be attributed to incomplete lithiation, over-lithiation (using *tert*-butyllithium as the base), or decomposition of the ferrocenyllithium reagent itself.

The minor diastereomer **443** can be prepared by further reaction of the silylferrocene **444**. Thus, lithiation of **444** followed by trapping of the intermediate silylferrocenyllithium (not shown) with an electrophile gives **445**. Desilylation of **445** then gives **443** (Scheme 8.143).[41,174,175]

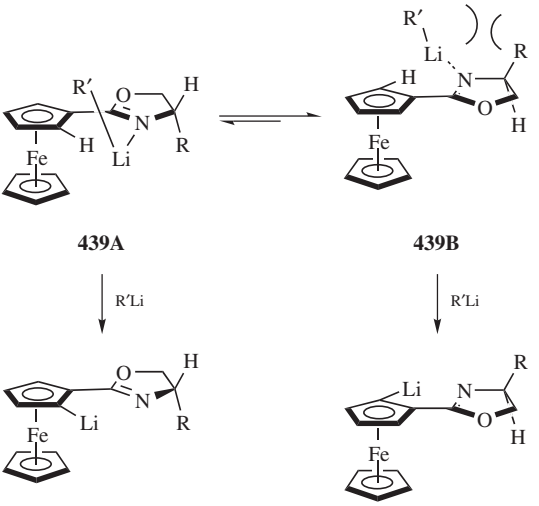
Both Richards[175] and Sammakia[127] proposed working models to account for the diastereoselectivity. In an elegantly designed study, Sammakia and Latham convincingly demonstrated that the nitrogen atom is responsible for the directive effect of the oxazoline (Scheme 8.144).[127,368] Thus, when the conformationally constrained oxazolinylferrocene **446** was metalated using *sec*-butyllithium in THF followed by trapping with methyl iodide or TMSCl, only one diastereomer, **447** was detected by chiral HPLC and NMR. The structure of **447** (E = Me) was determined by X-ray crystallography and was found to contain the methyl group syn to the oxazoline nitrogen. These results suggest that the nitrogen atom of the oxazoline must be responsible for the directive effect.



Scheme 8.143



Scheme 8.144



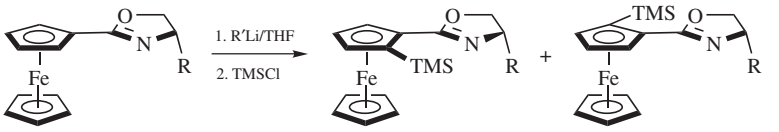
Scheme 8.145

Based on the above findings, Sammakia and Latham proposed a model to explain the origin of the diastereoselective lithiation (Scheme 8.145).[127] They suggested that the stereoselectivity should be determined by the interaction between the oxazoline substituent and the metalating reagent. The ferrocenyloxazoline exists in an equilibrium of two rotamers **439A** and **439B**. Rotamer **439A** is disfavored due to the steric interaction between the oxazoline substituent and the bottom cyclopentadienyl ring. The butyllithium reagent, presumably bulky due to its association with ligands, preferentially approaches the reaction site from the relatively open top face. Even though rotamer **439A** is less populated, it is more reactive toward lithiation because the top face is less sterically congested. The Curtin–Hammett principle dictates the predominance of the product from rotamer **439A**.

This model would predict higher selectvities for bulkier lithium reagents. Experimental data (Table 8.27; Scheme 8.146) supports this prediction. An unexpectedly lower selectivity was obtained when *tert*-butyllithium was used to metalate *tert*-butyl-substituted oxazolinylferrocene. In this particular case, the authors suggested that the reaction may proceed via oxygen directed or a nondirected pathway.

Similarly, oxygen-directed metalation was thought to be responsible for the low diastereoselectivity observed in the lithiation of the *trans*-4,5-diphenyloxazolinylferrocene **449** (Scheme 8.147).[367,375] Alternatively, factors other than the unlikely oxygen-directed lithiation may be operative in this case. Since the populations of the rotamers **449A** and **449B** should be nearly equal because of the pseudo C_2 symmetry present in **449**, the product ratio is determined solely by the reactivities of the two rotamers. For a nitrogen-directed lithiation, the top face of **449A** should still be relatively unhindered compared with that of **449B**. However, the top face of **449A** is more sterically congested than the top face of a mono-substituted

TABLE 8.27. LITHIATION OF OXAZOLINYLFERROCENE **439** AND TRAPPING WITH TMSCl[a]



439 **444** **448**

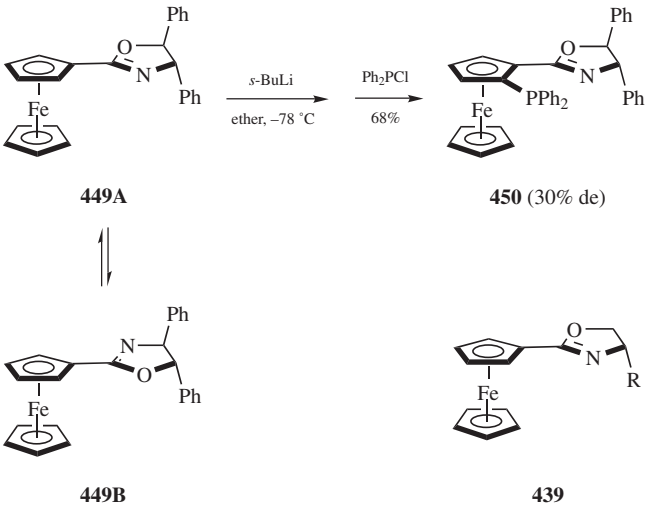
Scheme 8.146

Entry	R	R′	Selectivity (**444/448**)
1	*i*-Pr	*n*-Bu	3:1
2	*i*-Pr	*s*-Bu	8 : 1
3	*i*-Pr	*t*-Bu	16 : 1
4	*t*-Bu	*n*-Bu	6 : 1
5	*t*-Bu	*s*-Bu	36 : 1
6	*t*-Bu	*t*-Bu	6 : 1

[a] Data from Ref. 127.

oxazolinylferrocene, (e.g., **439**) due to the presence of the 5-phenyl group. This explains the lower selectivity observed in **449** in comparison with **439**.

Dilithiation of a C_2-symmetric bis(oxazoline)-substituted ferrocenes as well as biaryls provides a versatile method for preparation of C_2-symmetric tetradentate ligands. This reaction was originally described in 1995 by Park, Ahn, and coworkers.[366] The same group[376] and others have further expanded this reaction to



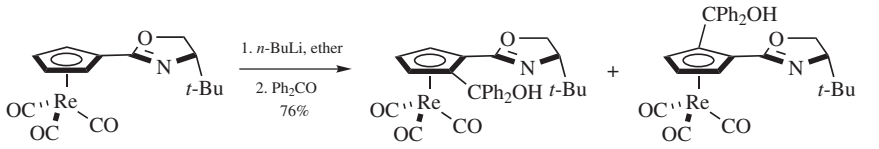
449A **450** (30% de)

449B **439**

Scheme 8.147

prepare a variety of tetradentate ligands.[115,144,179,377] Examples of C_2-symmetric tetradentate ligands are described in Chapter 9.

Bolm and co-workers expanded the diastereoselective lithiation to include the η^5-cyclopentadienylrhenium(I) tricarbonyl oxazoline complex **451** (Scheme 8.148).[378] The selectivity was determined to be 9:1 favoring diastereomer **452**. The structure of **452** was determined by crystallography. Interestingly, lithiation of **451** with *sec*-butyllithium resulted in the formation of nucleophilic addition products.



451 **452** **453**

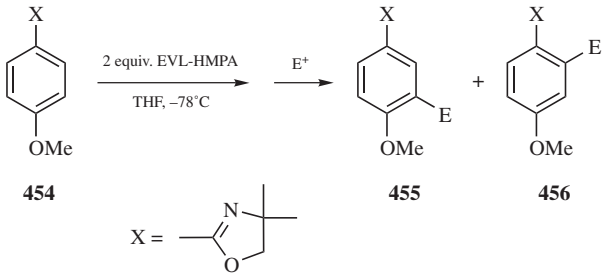
Scheme 8.148

Metalation of arenes substituted with both an oxazoline and a methoxy group with a simple alkyllithium reagent usually effects lithiation at positions ortho to the oxazoline, that is, the oxazoline is a much stronger directing group than the methoxy group. However, Meyers and Shimano discovered that the regiochemistry can be dramatically altered using ethoxyvinyllithium complexed with HMPA (EVL–HMPA).[379] Oxazoline-substituted methoxyarenes were lithiated at the position ortho to the methoxy group when treated with excess EVL–HMPA. Indeed, even the more powerful directing group, diisopropyl carboxamide (—CON*i*-Pr_2) was not competitive with a methoxy group when EVL–HMPA was used as the base. The results from a variety of arenes demonstrated that this methodology is quite general (Table 8.28; Scheme 8.149).

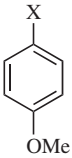
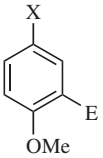
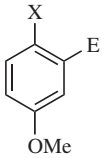
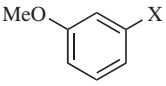
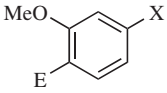
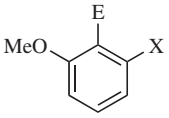
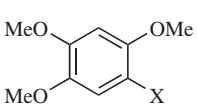
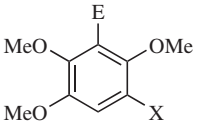
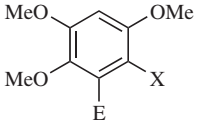
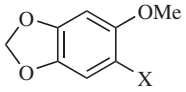
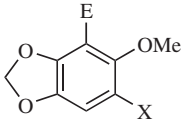
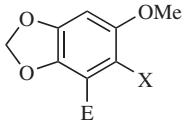
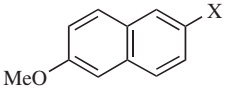
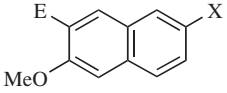
The authors concluded that an oxazoline group was necessary to activate an arene for this type of metalation since reactions with anisole and 1,3-dimethoxybenzene were slower even at higher temperature (−56 °C). The reaction may be kinetically controlled since the expected regiochemistry was observed when the reaction was carried out at 0 °C. The reaction of the oxazoline-substituted naphthalene (Table 8.28, entry 5) represents the first example of lithiation in such a system. Simple alkyllithium reagents only undergo addition to the naphthalene ring (see Section 8.3.9.3). The authors suggest that steric effects created by a large cluster of EVL and HMPA may be responsible for this unexpected regioselectivity.

Although lithiation remains the most frequently used metalation reaction, there have been a number of new reports of direct palladation of aryloxazolines. For example, Smoliakova and co-workers prepared the dimeric palladium complex **457** by direct reaction of $Pd(OAc)_2$ with 2-phenyloxazoline in the presence of NaOAc/HOAc (Scheme 8.150).[380] The dimeric complex **457** was converted to the monomeric triphenylphosphine complex **458** for which the X-ray crystal structure was determined. A similar reaction sequence was observed for naphthalenes.[381] Muller

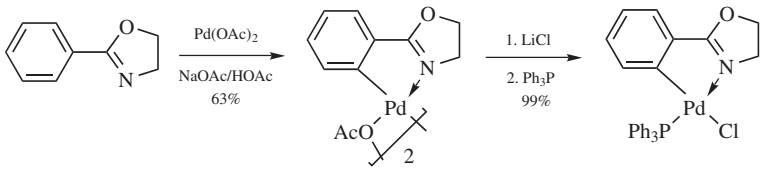
TABLE 8.28. LITHIATION OF ARENES BY EVL–HMPA[a]



Scheme 8.149

Entry	Oxazoline **454**	Major Product (**455**) E^+: % Yield	Minor Product (**456**)[b]	**455/456**[b]
1		 MeI : 96; DMF : 89		>99 : 1
2		 MeOD : 98; MeI : 88; $(CH_2O)_n$: 72		>93 : 7
3		 MeI : 97; $ClCO_2Et$: 92		>99 : 1
4		 MeI : 97		>99 : 1
5		 MeI : 93	NR	NR

[a] Data from Ref. 379.
[b] Not reported = NR.

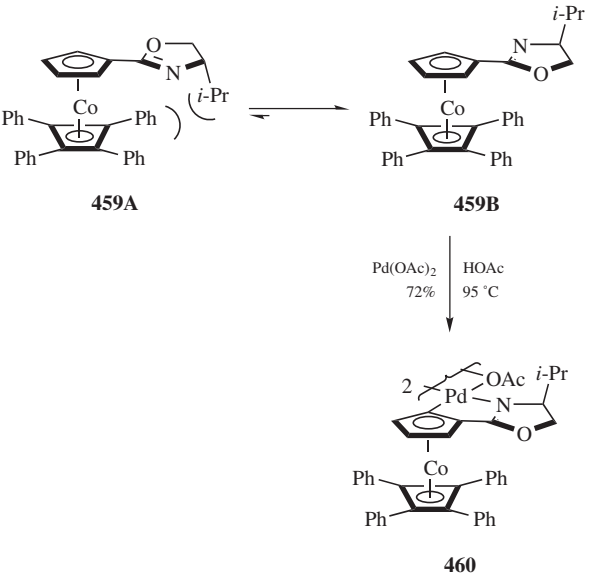


457 **458**

Scheme 8.150

and co-authors comprehensively reviewed the coordination chemistry of oxazolines in 1999 in which they discussed this type of cyclopalladation reaction in more detail.[20]

More recently, Richards and Stevens reported a diastereoselective cyclopalladation of the oxazoline-substituted $(\eta^5\text{-}C_5H_5)(\eta^4\text{-}C_4Ph_4)Co$ **459**.[382] Although this compound resisted lithiation under various conditions, it reacted readily with palladium acetate to form a single diastereomeric cyclopalladation product **460**. The configuration of **460** is the opposite to that obtained in the ferrocene lithiation (see above) and was confirmed by nOe analysis. The authors attributed the diastereoselectivity to the instability of rotamer **459A** due to the severe steric interaction between the isopropyl group and the $(\eta^4\text{-}C_4Ph_4)$ phenyl substituents. The reaction proceeds only through rotamer **459B** to give the observed product (Scheme 8.151).



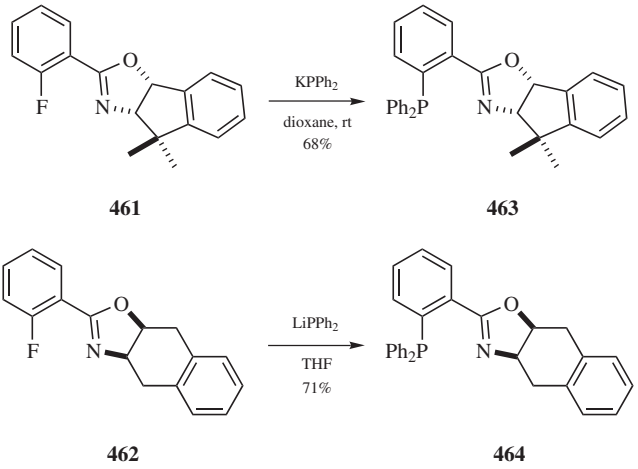
459A **459B**

460

Scheme 8.151

8.3.9.2. Nucleophilic Substitutions

It is well known that ortho-methoxy and ortho-fluoroaryloxazolines undergo facile nucleophilic substitution reactions using a variety nucleophiles.[8,9] Although a methoxy group is more commonly used as the leaving group for economic reasons, fluoride is sometimes used as the leaving group to avoid side reactions of the methoxy group, such as demethylation.[383] Two groups used the 2-(*ortho*-fluorophenyl)oxazolines **461**[384] and **462**[385] to prepare the tricyclic phosphinooxazoline ligands **463** and **464** (Scheme 8.152). These ligands were then employed in palladium-catalyzed enantioselective allylic substitution reactions.



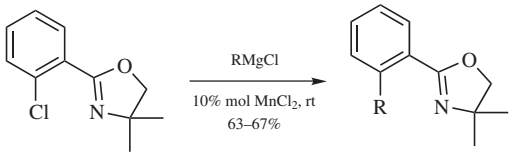
461 **463**

462 **464**

Scheme 8.152

Although 2-(*ortho*-chlorophenyl)-4,4-dimethyloxazoline **465** does not react with a Grignard reagent under normal conditions, Cahiez recently reported that the substitution occurred in the presence of a catalytic amount of manganese chloride (10% mol) to give the substitution product **466** in acceptable yield (Scheme 8.153).[386] The reaction mechanism has not yet been defined.

One of the most useful aspects of the oxazoline-directed aromatic substitution is the synthesis of biaryls. This method nicely complements other well-known biaryl



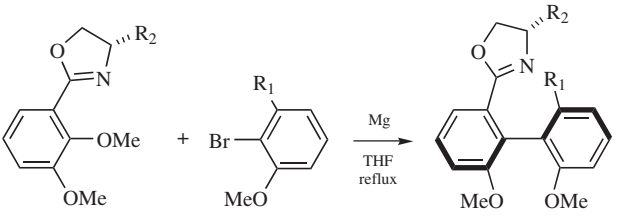
465 **466**

Scheme 8.153

syntheses, such as the Suzuki coupling.[387,388] For example, Zhu and co-workers applied oxazoline-directed aromatic substitution methodology in their synthesis of a protected actinoidic acid, a vancomycin substructure.[30,59] Meyers' group has perfected the experimental procedure to prepare unsymmetrical biaryls[53] and reported a general synthesis of pyrrolophenanthridine alkaloids,[389] such as oxoassoanine,[390] pratosine, hippadine, kalbretorine, and ungeremine, using this method.

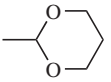
However, a more exciting application of this reaction is the oxazoline-directed synthesis of axially chiral biaryls. The oxazoline system not only activates the ortho-methoxy group for nucleophilic displacement but also determines the stereochemical outcome of the reaction. This provides a convenient method for the introduction of axial-chirality. Meyers' group continues their earlier lead on this subject with reports of the stereoselective synthesis of tetrasubstituted biphenyls.[391,392] Selected examples are shown in Table 8.29 (Scheme 8.154). The best diastereoselectivities were obtained when R_1 in the bromide **468** is a noncomplexing group (entries 5–8). Indeed, the opposite stereoisomer is obtained when R_1 can complex with magnesium (entries 1, 3–4). Surprisingly, the selectivity is not very sensitive to the 4-substituent of the oxazoline (entries 6–7).

TABLE 8.29. OXAZOLINE-DIRECTED STEREOSELECTIVE SYNTHESIS OF BIPHENYLS[a]

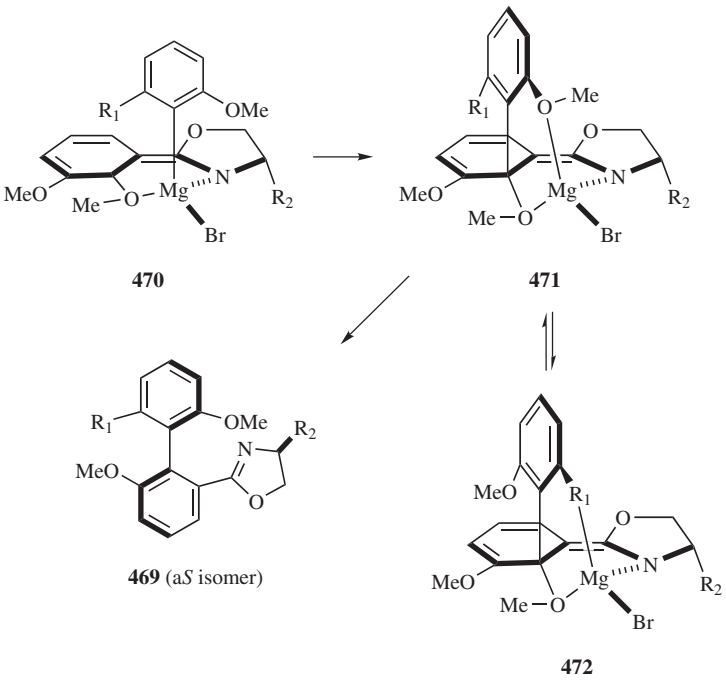


467 **468** **469**

Scheme 8.154

Entry	**468** (R_1)	**467** (R_2)	**469** % Yield	% de (Configuration)
1		*i*-Pr	90	60 (a*R*)
2		*i*-Pr	78	20 (a*S*)
3	CH_2OBn	*i*-Pr	80	16 (a*R*)
4	CH_2OMe	*i*-Pr	75	20 (a*R*)
5	Me	*i*-Pr	79	80 (a*S*)
6	CH_2OTBS	*i*-Pr	73	86 (a*S*)
7	CH_2OTBS	*t*-Bu	67	84 (a*S*)
8	CH_2OTIPS	*i*-Pr	70	86 (a*S*)

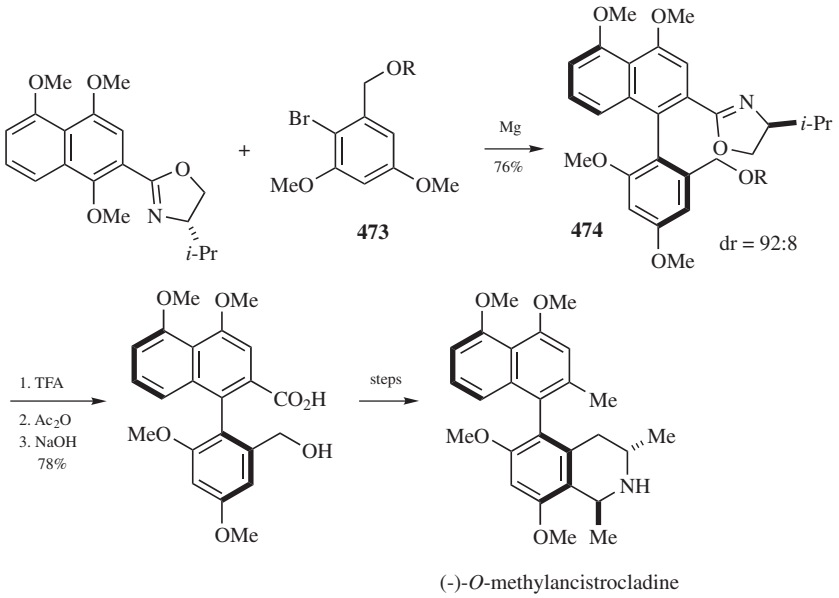
[a] Data from Ref. 391.



Scheme 8.155

A chelation-based mechanism was proposed to rationalize the observed diastereoselectivity (Scheme 8.155). Initially, the Grignard reagent approaches the oxazolinylarene from the opposite face of the 4-R_2-oxazoline substituent to give the pre-reaction complex **470**. Subsequent aryl migration results in the intermediate adduct **471** in which the methoxy group of the Grignard reagent, the methoxy leaving group and the oxazoline nitrogen are all chelated with magnesium. These control elements determine the stereochemical outcome of this reaction. Obviously, the stereoselectivity suffers when the R_1 group can compete with the methoxy group to complex with magnesium and forms the isomeric complex **472**.

This interpretation of the reaction mechanism prompted Rizzacasa and Leighton[393] to reinvestigate and improve an earlier synthesis of (−)-*O*-methylancistrocladine reported by Sargent and Rizzacasa.[394] Undesired chelation near the reaction center of the Grignard reagent generated from bromide **473** was blocked by TBS protection (R = TBS, Scheme 8.156).[393] This strategy was quite successful since the diastereoselectivity of the product biaryl **474** was improved to 92:8. An analogous reaction in the previous synthesis produced a **474** analogue (dr = 69:31) when the CH_2OR moiety was a chelating cyclic acetal.[394] Further elaboration of **474** should then lead to (−)-*O*-methylancistrocladine. The same group also reported similar synthetic approaches to (+)-dioncophylline C[395] and (+)-*O*-methylancistrocline[396] (Fig. 8.13).



Scheme 8.156

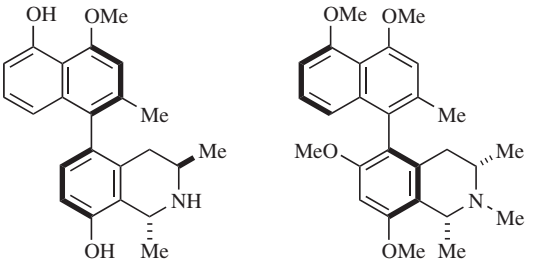
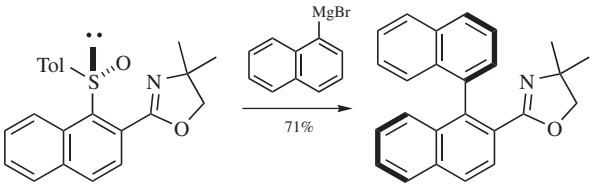


Figure 8.13. (+)-Dioncophylline C and (+)-*O*-methylancistrocline.

Although the axial stereochemistry is controlled by the chiral oxazoline, Baker and Sargent reported that a chiral sulfoxide can also introduce axial chirality while acting as a leaving group (Scheme 8.157).[397,398] However, this reaction does not proceed via the typical S_NAr mechanism, but rather through an initial attack of the Grignard reagent at the sulfur center.[399,400] Modest atropisomeric selectivity for the binaphthyl **476** was obtained by reaction of sulfoxide **475** with 1-naphthylmagnesium bromide. The authors also reported better atropisomeric selectivities using an ester or an amide as the activation group.[398]

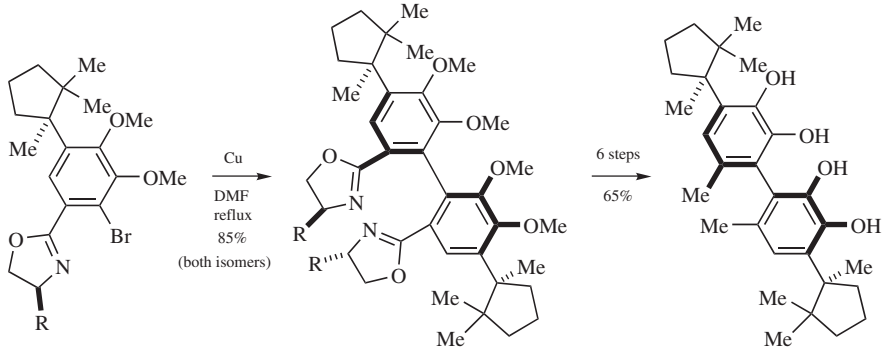
The Ullmannn coupling[401,402] of aromatic halides does not require activation but the presence of a chiral oxazoline group on the haloarene allows the selective introduction of axial chirality into the biaryl product. This constitutes an important



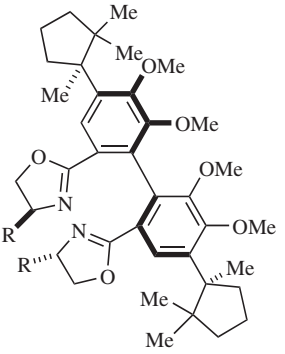
476 **475** (60% ee)

Scheme 8.157

method to prepare chiral biaryl-based bisoxazolines (see also Chapter 9). A significant portion of Meyers' 1998 review on chiral oxazolines was devoted to this subject so only a recent example will be discussed here. In their asymmetric synthesis of mastigophorene, Meyers and Degnan studied the steric effect of the oxazoline substituent in **477** on the diastereoselectivity of the biaryl **478a** (Scheme 8.158).[46] The selectivity was thermodynamically controlled since the two diastereomers interconvert at the reaction temperature. The stability of the



477 **478a** (a*S* isomer) (-)-mastigophorene A



478b (a*R* isomer)

Scheme 8.158

TABLE 8.30. DIASTEREOSELECTIVITY IN ULLMANN COUPLING REACTIONS (SCHEME 8.158)[a]

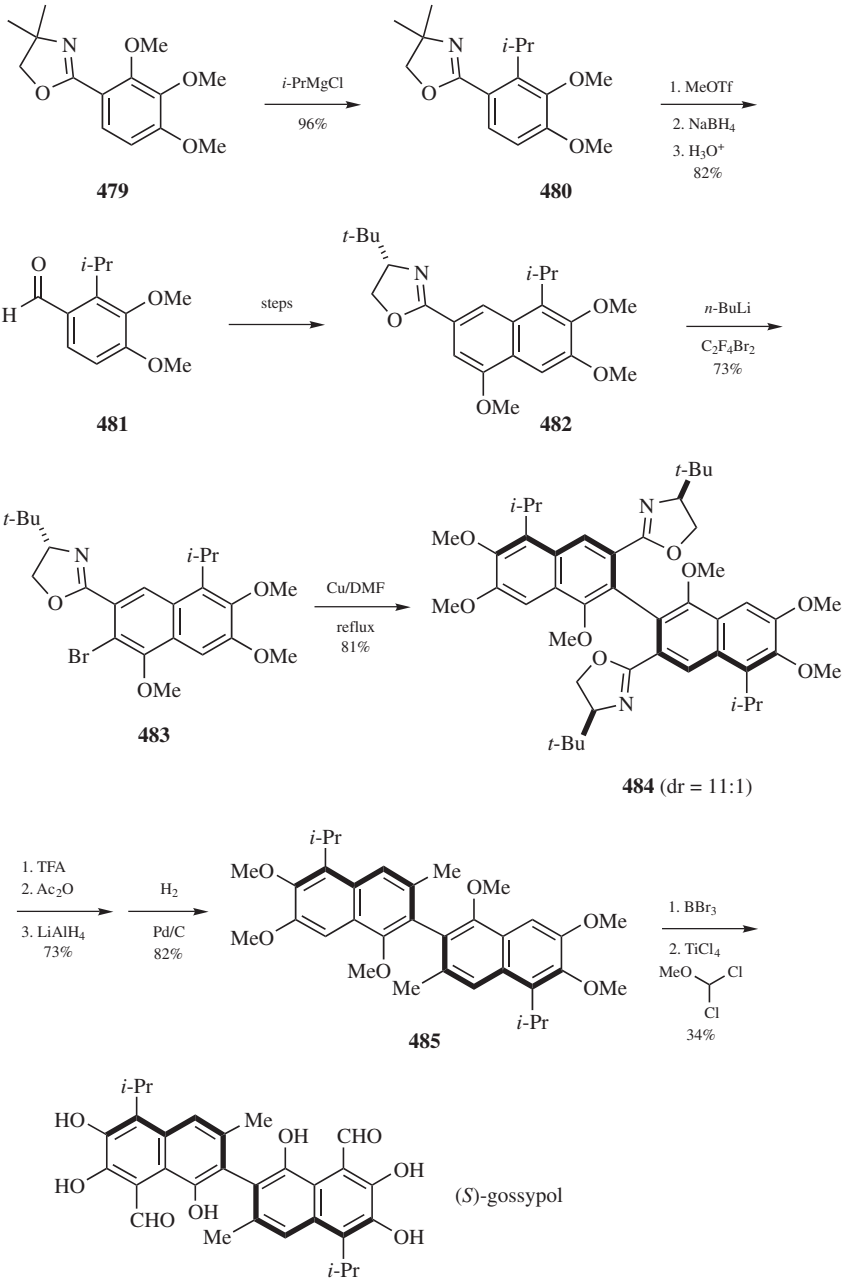
Entry	**477** (R)	dr (**478a/478b**)
1	*t*-Bu	3 : 1
2	Ph	4 : 1
3	*i*-Pr	6.4 : 1
4	Et	7.1 : 1
5	Me	7.2 : 1

[a] Data from Ref. 46.

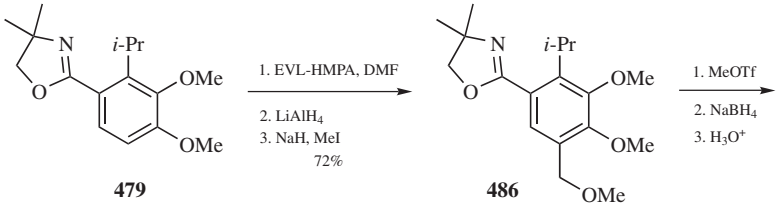
copper-product chelation complex determines the stereochemical outcome. Interestingly, the smallest oxazoline substituent **477** (R = Me) gave the best diastereoselectivity (Table 8.30, entry 5). The authors rationalized these unexpected results in terms of minimization of interaction between the R group and the arene. The biaryl **478a** was subsequently converted to (−)-mastigophorene A in six steps.

It is most appropriate to conclude this subsection with an elegant demonstration of oxazoline-directed aromatic reactions by Meyers' group. Meyers and Willemsen took full advantage of the reactions described in this section in their asymmetric total synthesis of (*S*)-gossypol.[49] The initial synthesis (Scheme 8.159) included a Grignard displacement of an ortho-methoxy group of 4,4-dimethyl-2-(2,3,4-trimethoxyphenyl)oxazoline **479** to produce **480**. After N-methylation, reduction and hydrolysis converted **480** to the key 2,3,4-trisubstituted benzaldehyde **481**. After construction of the naphthalene ring, a *tert*-butyloxazoline was incorporated to direct the subsequent lithiation and Ullmann coupling. Lithiation occurred at the 3-position of **482** rather than the 1-position presumably due to the steric hindrance of the neighboring isopropyl group. Stereoselective Ullmann coupling of the bromide **483** gave the desired binaphthyl **484** in an 11:1 diastereomeric ratio. Removal of the bisoxazolines required hydrolysis to an intermediate bis-(amino ester) that was then sequentially acetylated, reduced, and hydrogenated to give the binaphthyl **485**. Further eleboration of **485** then gave (*S*)-gossypol in two steps.

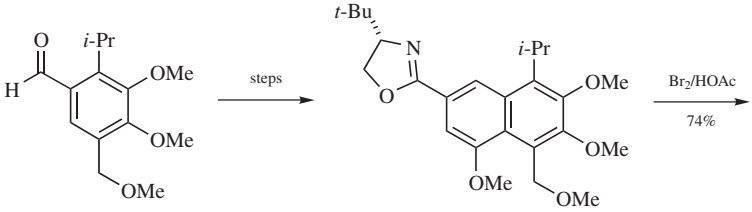
The authors redesigned their synthesis and incorporated the formyl group at an earlier step to overcome the unsatisfactory yield for this reaction at a late stage in their first synthesis. Now, taking advantage of an earlier discovery from their group (see Section 8.3.9.1), they were able to selectively lithiate **479** ortho to the methoxy group with EVL–HMPA (Scheme 8.160). The resulting intermediate lithio species (not shown) was converted to the oxazoline **486** in three steps. Similar to their initial synthesis, **486** was now converted to the 2,3,4,5-tetrasubstituted benzaldehyde **487** from which the naphthalene ring of **488** was constructed followed by incorporation of the *tert*-butyloxazoline ring. Bromination of **488** gave the bromide **489** that was subjected to the Ullmann coupling. The authors noted that this Ullmann coupling required a high concentration of the reactants to achieve a high diastereoselectivity in the binaphthyl product **490**. Reductive oxazoline cleavage in **490** gave **491** that was then elaborated to (*S*)-gossypol in good yield.


479
i-PrMgCl
96%
480
1. MeOTf
2. NaBH4
3. H3O+
82%
481
steps
482
n-BuLi
C2F4Br2
73%
483
Cu/DMF
reflux
81%
484 (dr = 11:1)
1. TFA
2. Ac2O
3. LiAlH4
73%
H2
Pd/C
82%
485
1. BBr3
2. TiCl4
34%
(S)-gossypol

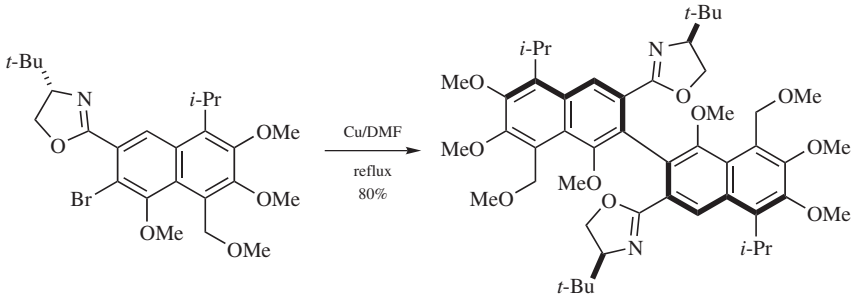
Scheme 8.159



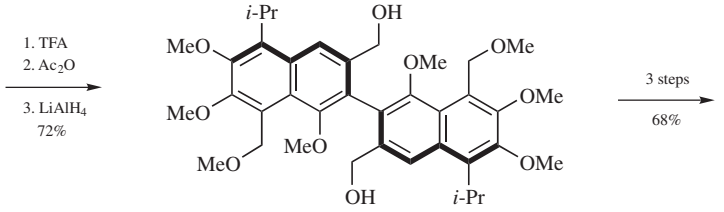
479 **486**



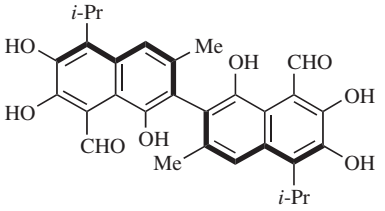
487 **488**



489 **490** (dr = 17:1)



491



(*S*)-gossypol

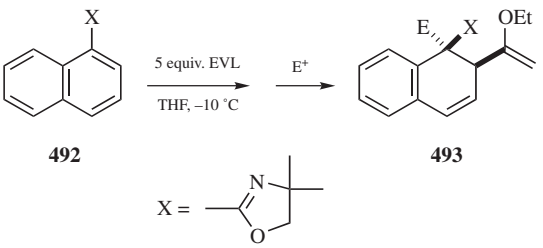
Scheme 8.160

8.3.9.3. Nucleophilic Additions

Oxazoline-directed conjugate addition of nucleophiles to a naphthalene nucleus is one of the most useful methods to prepare dihydronaphthalenes. Since Meyers' last comprehensive review,[9] the focus has been directed to stereoselective synthesis of these important compounds. Meyers' laboratory has continued their preeminence in this field and has expanded the scope and applications of this reaction.

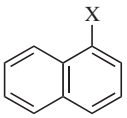
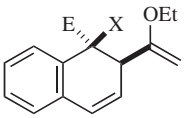
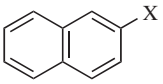
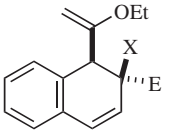
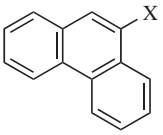
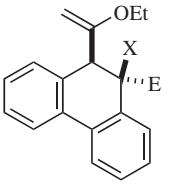
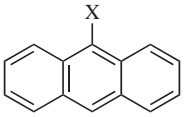
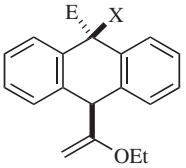
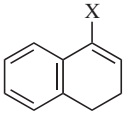
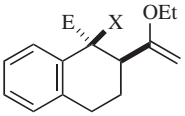
Ethoxyvinyllithium (EVL) is an effective lithiation agent at low temperatures (−78 °C) in the presence of HMPA (see Section 8.3.9.1). However, in the absence of HMPA, it reacts like a normal lithium reagent and cleanly adds to oxazolinylnaphthalenes at higher temperatures (−10 °C). Thus, addition of EVL to 4,4-dimethyl-2-(1-naphthyl)oxazoline **492** generates an intermediate carbanion (not shown) that is alkylated to afford **493**, usually as a single diastereomer (dr > 100:1) (Scheme 8.161).[403] The resulting vinyl ether in **493** can be easily converted to the corresponding methyl ketone. This reaction is applicable to oxazoline substituted anthracene and phenanthrene rings as well (Table 8.31).

In their syntheses of key intermediates **496** and **498** required for (−)-aphanorphine and (−)-eptazocine respectively, Meyers' group used a lithiosilane as a surrogate for LiH in the initial conjugate addition (Scheme 8.162).[222,404] As expected, the lithiosilane adds to the starting oxazolinylnaphthalene **494** from the face opposite to the bulky isopropyl group. Methylation of the intermediate carbanion then occurs on the face opposite to the bulky silyl group to produce the tandem adduct **495**. The use of ether in the solvent mixture was critical to achieve the high diastereoselectivity. It was assumed that the low complexation ability of ether affords some rigidity and order in the transition state. Given the steric demands of the silyl group, it is not surprising that the minor diastereomer arose from the isomeric silyl addition but still coupled with trans-methylation. Subsequent conversion of **495** to **496** and **498** was straightforward. The stereochemistry of the saturated oxazoline **498** was confirmed by X-ray crystallography. Degnan and Meyers recently expanded the utility of this reaction using a silyl group as an oxygen or nitrogen surrogate via Tamao oxidation[405] and chemical modifications.[406]



Scheme 8.161

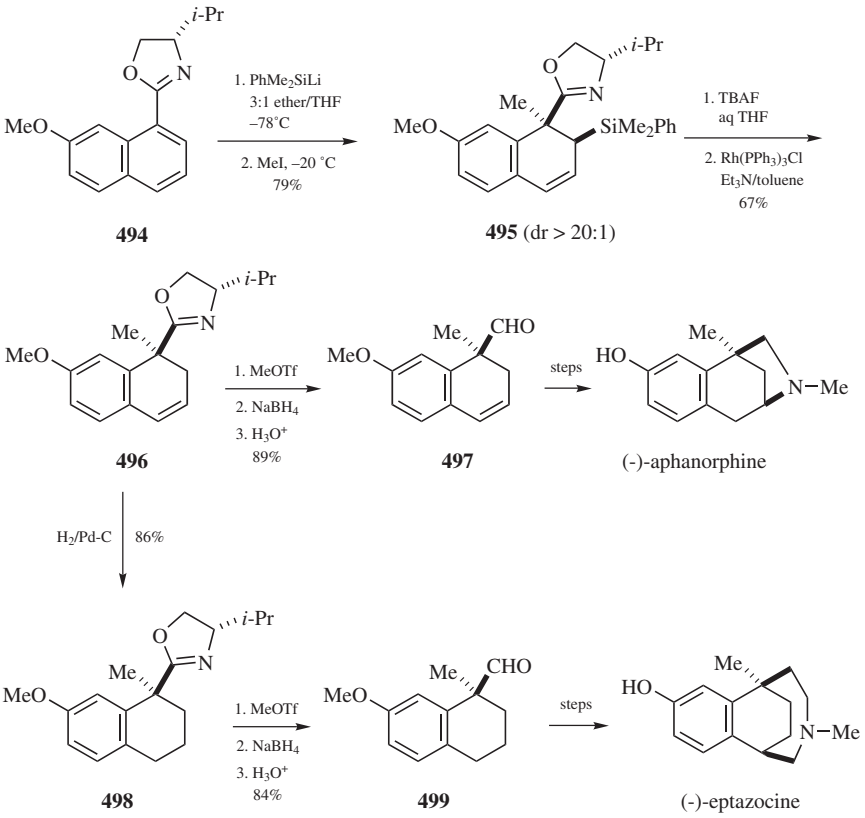
TABLE 8.31. DIASTEREOSELECTIVE CONJUGATE ADDITIONS OF EVL[a]

Entry	Substrate	Product	E, % Yield
1			Me, 50
2			Me, 98
3			Me, 98 allyl, 98
4			Me, 97
5			Me, 66

[a] Data from Ref. 403.

Meyers and Shimano further expanded the scope of this methodology to include lithium amides as the nucleophile.[317,407] The authors meticulously optimized the reaction conditions and determined the scope of the amide addition. Selected examples are listed in Table 8.32 (Scheme 8.163). The best results were obtained when THF was used as the solvent together with a stoichiometric amount of HMPA, relative to the lithium amide. The reaction was quite sensitive to the steric demand of the amide. Thus, lithium diethylamide give no product whereas lithium methyl *n*-pentylamide and lithium piperidide gave efficient reaction. Primary amides also failed to react.

Unlike analogous reactions with a carbon nucleophile, the initial attack of the lithium amide was reversible. A strong piece of supporting evidence was the exclusive formation of the butyl addition product **504** when *n*-butyllithium was added after initial formation of the aza enolate **505** (Scheme 8.164). The reaction outcome is therefore heavily dependent on the secondary reaction with the



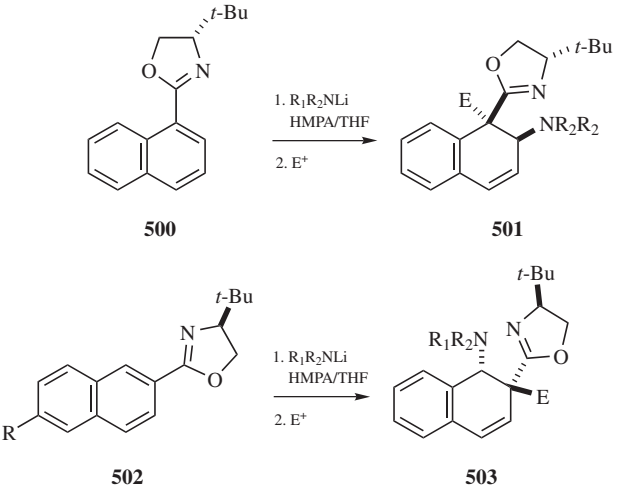
Scheme 8.162

electrophile that renders the overall reaction irreversible. Consequently, strong electrophiles readily trap the intermediate carbanion whereas weak electrophiles only lead to recovery of the starting material after work up (Table 8.32, entry 8).

The authors proposed a chelating transition state model to explain these results (Fig. 8.14). The thermodynamically more stable intermediate resulting from initial lithium amide addition should have the amino group on the face opposite to the bulky *tert*-butyl group. Due to the same steric effect, the HMPA ligand should also occupy a position on the β face. The electrophile approaches the enolate from the α face and gives the trans product. For bulky amines, either the aza enolate does not form due to severe steric hindrance or the aza enolate is inactive for the same reason.

The utility of this reaction was demonstrated by converting the initial adduct **506** to a β-amino acid **509** and ultimately the β-lactam **510** (Scheme 8.165). It is noteworthy that the oxazoline ring in **506** was stable to cold concentrated HCl and the oxazoline ring in **507** was stable to hot caustic. However, the authors also noted

TABLE 8.32. ADDITION OF LITHIUM AMIDES TO OXAZOLINYLNAPHTHALENES[a]



Scheme 8.163

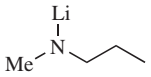
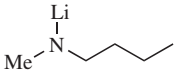
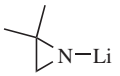
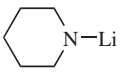
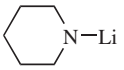
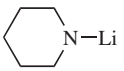
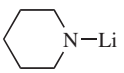
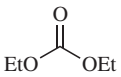
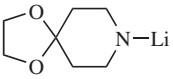
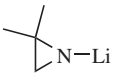
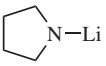
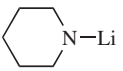
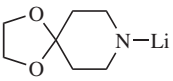
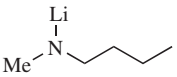
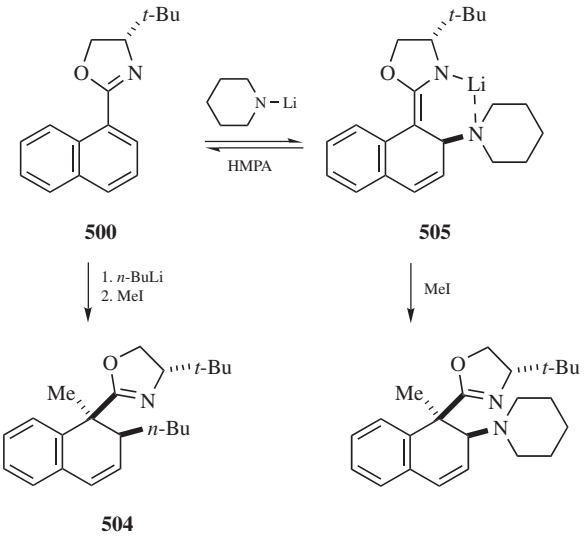
Entry	Oxazoline	R_1R_2NLi	Electrophile	% Yield	dr
1	**500**	Me_2NLi	MeI	94	98.5 : 1.5
2	**500**		MeI	93	>99 : 1
3	**500**		MeI	93	>99 : 1
4	**500**		MeI	0	
5	**500**		MeI	95	>99 : 1
6	**500**		AllylBr	92	>99 : 1
7	**500**		BnBr	67	>99 : 1
8	**500**			0	

TABLE 8.32 (*Continued*)

Entry	Oxazoline	R_1R_2NLi	Electrophile	% Yield	dr
9	**500**		MeI	96	>99 : 1
10	**502** (R = H)	Me_2NLi	MeI	91	97.5 : 2.5
11	**502** (R = H)		MeI	0	
12	**502** (R = H)		MeI	94	>99 : 1
13	**502** (R = H)		MeI	94	>99 : 1
14	**502** (R = H)		MeI	94	>99 : 1
15	**502** (R = OMe)		MeI	90	>99 : 1

[a] Data from Ref. 407.



Scheme 8.164

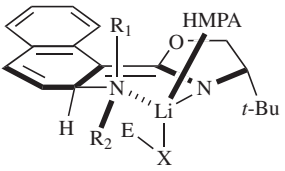
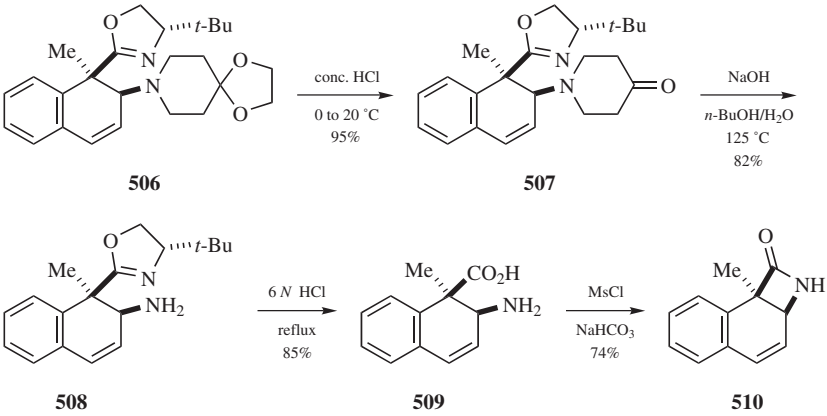


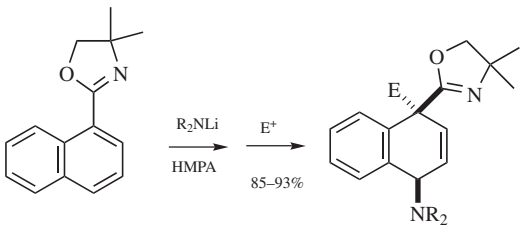
Figure 8.14. Chelating transition state model for addition of lithium amides to oxazolinylnaphthalenes.



Scheme 8.165

that the oxazoline ring in **506** is hydrolyzed to a hydroxy amide using 1 *N* HCl at room temperature. No explanation was given for this unusual behavior.

The same authors later reported that although sterically hindered lithium dialkylamides do not react under the normal conditions, they do undergo an unusual 1,6-addition to the oxazolinylnaphthalene **511** in the presence of excess HMPA (8–10 equiv).[408] These reactions are also diastereoselective to afford the trans tandem adduct as the major product (Scheme 8.166). A dimeric lithium



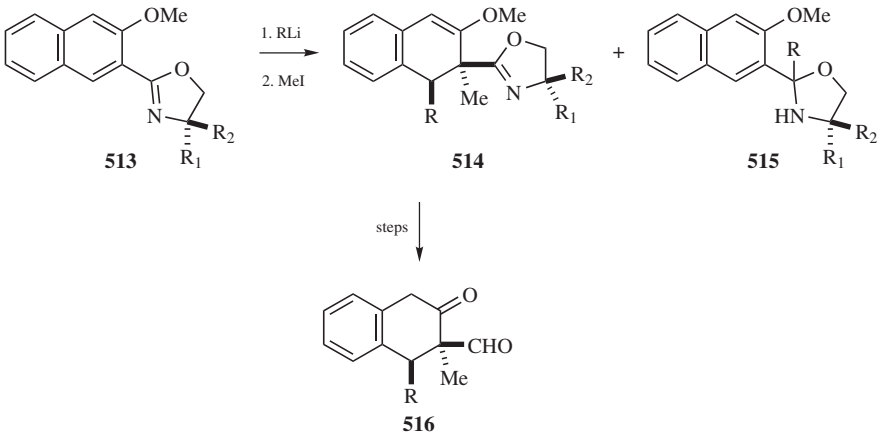
60-97% de

R = Bn, allyl; E^+ = MeI, MeOTf, BnBr, allylBr

Scheme 8.166

amide–HMPA complex was postulated to rationalize these results in view of the earlier findings (see above). Adduct **512** has been converted to useful δ-amino acid derivatives.

More recently, Meyers and Kolotuchin reported that nucleophilic addition to the 1-position of the 3-methoxy-(2-oxazolinyl)naphthalene **513** is preferred over methoxy group displacement.[409] The reaction works well and as expected for RLi (R = *n*-Bu, *sec*-Bu, and Ph). However, 1,2-addition to **513** to give the oxazolidine **515** predominates for RLi (R = Me, *tert*-Bu, and $PhMe_2Si$) (Scheme 8.167). When **513** contained a chiral oxazoline (R_1 = *tert*-Bu, R_2 = H), a single diastereomer of **514** was obtained in moderate yields (56 and 60% for R = *n*-Bu and Ph, respectively). Standard oxazoline chemistry and functional group manipulations were used to convert **514** to a variety of useful, chiral tetralones **516**.



Scheme 8.167

The absence of methoxy group displacement was rationalized in the following manner. Initial nucleophilic addition to the 3-position leads to an intermediate, **517**, in which the aromaticity of both rings was destroyed whereas addition to the 1-position gives an intermediate **518**, which retains the aromaticity of one benzene ring (Fig. 8.15).

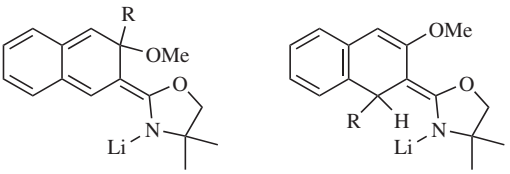


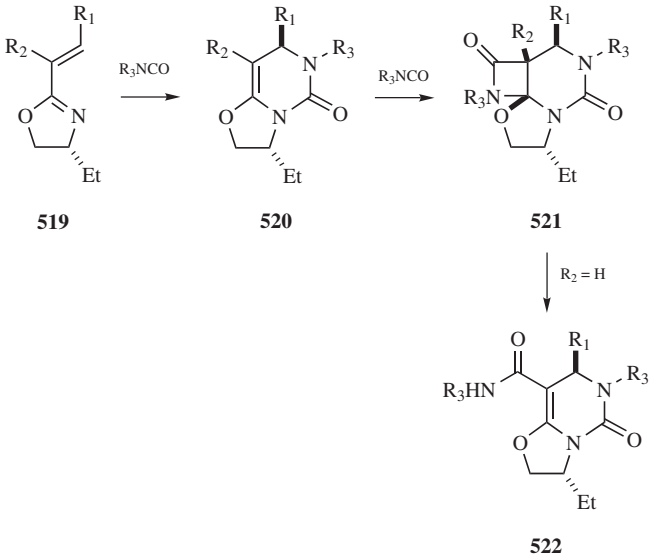
Figure 8.15. Proposed intermediates for nucleophilic addition to 3-methoxy-(2-oxazolinyl)naphthalene.

8.3.10. Oxazolines as Chiral Directing Groups

Discussions of oxazolines as chiral directing groups are included in the previous sections under the appropriate reaction classifications. Meyers has already published a recent review of chiral oxazolines (1998) that focused primarily on their use in aromatic reactions and Ullmann coupling reactions in particular.[11] The examples of oxazolines as chiral directing groups described in this section will include reactions that are not discussed in any previous section of this chapter.

Elliott and co-workers reported an asymmetric hetero-Diels–Alder reaction using a chiral 2-(alkenyl)oxazoline **519** as the enophile.[110,111,410] Initial addition of the isocyanate to **519** gives the bicyclic [4 + 2] adduct **520**. Depending on the substituents, **520** can undergo a [2 + 2] cycloaddition with a second molecule of an isocyanate to generate the tricyclic compound **521**. For $R_2 = H$, **521** ring opens to give the tetrahydrooxazolopyrimidinecarboxamide **522** (Scheme 8.168). Selected examples are summarized in Table 8.33.

In all cases, the initial addition to generate **520** was diastereospecific, that is, the isocyanate always adds to **519** from the face opposite to the 4-ethyl substituent of the oxazoline. In the cases wherein **521** was isolated (Entries 17–20 from Table 8.33), the stereochemistry of the two additional chiral centers from the secondary [2 + 2] cycloaddition was controlled by the chiral center formed during the initial reaction, that is, the isocyanate reacts with **520** from the opposite face of the neighboring R_1 group. For $R_1 = H$, $R_2 = Me$, **519** reacted with an arylisocyanate ($R_3 = Ar$) to give tricyclic adducts **521a** and **521b** as a 1.7:1 mixture of diastereomers (Entries 18–20). For $R_1 = Ph$, $R_2 = Me$, **519** reacted with phenylisocyanate



519 **520** **521** **522**

Scheme 8.168

TABLE 8.33. HETERO-DIELS–ALDER REACTION OF CHIRAL 2-ALKENYLOXAZOLINES (SCHEME 8.168)[a]

Entry	R_1, R_2	R_3	Time (h)	Temperature (°C)	Product (% Yield)
1	Me, H	Ph–	48	25	**522** (58)
2	Me, H	4-Br-Ph–	24	25	**522** (61)
3	Me, H	4-O_2N-Ph–	21	25	**522** (62)
4	Me, H	4-MeO-Ph–	120	25	**522** (65)
5	Me, H	4-Me-PhSO_2–	0.5	25	**522** (66)
6	Et, H	Ph–	46	25	**522** (53)
7	Et, H	4-Br-Ph–	1.25	150	**522** (69)
8	Et, H	4-O_2N-Ph–	1	150	**522** (71)
9	Et, H	4-MeO-Ph–			**522** (trace)
10	Et, H	4-Me-PhSO_2–	0.5	25	**522** (90)
11	Ph, H	Ph–	1	150	**522** (76)
12	Ph, H	4-Br-Ph–	1	150	**522** (59)
13	Ph, H	4-O_2N-Ph–	1	150	**522** (74)
14	Ph, H	4-MeO-Ph–	1	150	**522** (10)
15	Ph, H	4-Me-PhSO_2–	0.5	25	**522** (94)
16	Ph, Me	Ph–	30	60	**520** (62)
17	Ph, Me	Ph–	24	150	**521** (26)
18	H, Me	Ph–	65	150	**521** (81)
19	H, Me	4-Br-Ph–	18	150	**521** (42)
20	H, Me	4-MeO-Ph–	25	150	**521** (0–70)
21	H, Me	4-O_2N-Ph–			**521** (0)
22	H, Me	4-Me-PhSO_2–	1	25	**520** (98)
23	Ph, Me	4-Me-PhSO_2–	1	25	**520** (75)

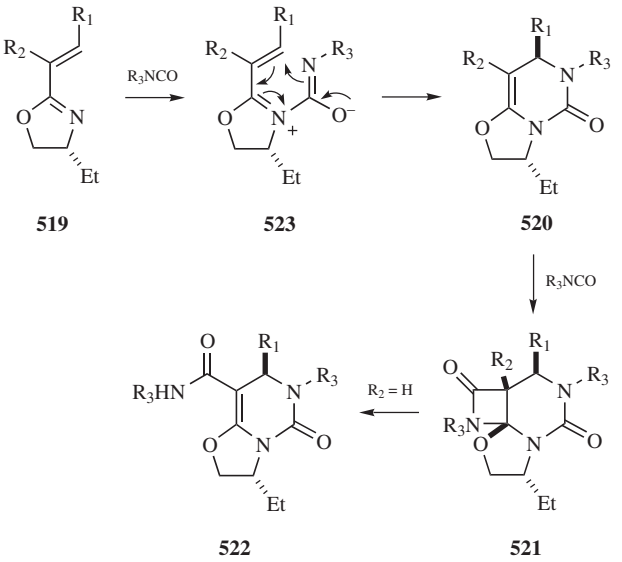
[a] Data from Ref. 111.

($R_3 = Ph$) to give **521** as a single diastereomer although the yield was low (entry 17).

The reaction rate depends on the electronic nature of the substituent (R_3) on the isocyanate. Isocyanates with electron-withdrawing groups react faster than those with electron-donating groups. The reaction is also sensitive to the steric bulk on the isocyanate and the oxazoline. Thus, neither *tert*-butyl- nor benzylisocyanate react under the conditions examined. 4,4-Dimethyl-2-(2-propenyl)oxazoline was unreactive, even under forcing conditions. The authors proposed a stepwise mechanism involving a 1,3-dipolar intermediate **523** to rationalize these results (Scheme 8.169). Computational studies by the same group also supported this mechanism.[410] The authors suggested that the asymmetric induction may originate from the reduction of the steric interaction between the isocyanate oxygen atom and the ethyl group during the cyclization of **523**.

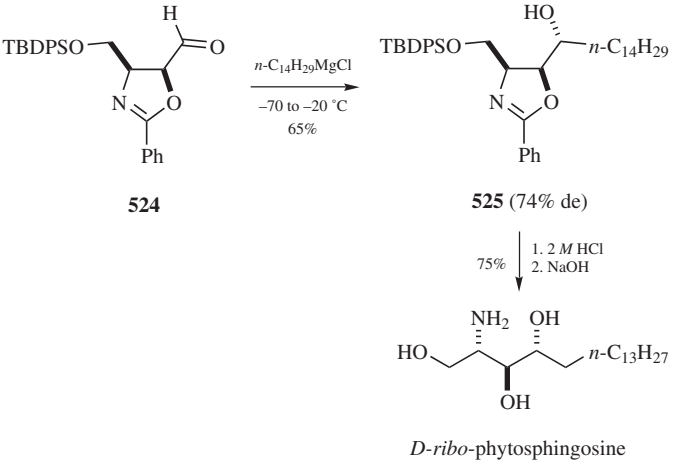
Murakami and Taguchi utilized a diastereoselective Grignard addition to a substituted-chiral oxazoline aldehyde **524** (Scheme 8.170) in an improved stereoselective synthesis of D-*ribo*-phytosphingosine.[113] The good stereoselectivity observed for **525** can be rationalized by a Felkin–Ahn transition state model although a chelation control mechanism could not be ruled out.

In an effort to demonstrate the interesting concept of a catalytic chiral auxilliary, Williams and co-workers showed that the oxazoline-substituted acrylate ester **526**

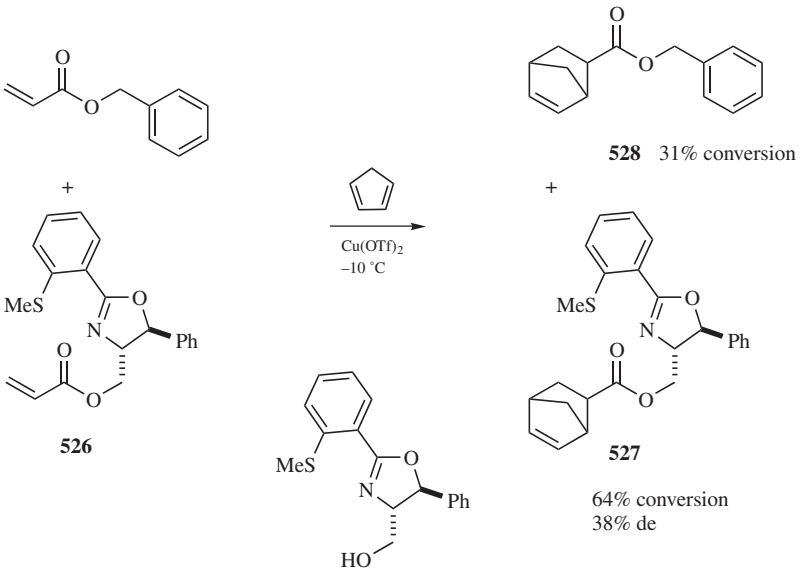


Scheme 8.169

gave modest levels of diastereoselectivity as well as rate acceleration in a Diels–Alder reaction using cyclopentadiene in competition studies with benzyl acrylate (Scheme 8.171).[411] Their strategy relied on a rapid transesterification of **527** with benzyl alcohol to give **528** as the final product. Furthermore, transesterification of the oxazoline alcohol **529** with benzyl acrylate to give **526** had to be equally rapid to support the catalytic cycles.



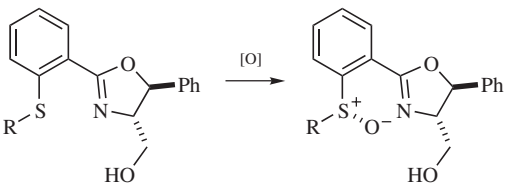
Scheme 8.170



Scheme 8.171

This same group also devised a stereoselective oxidation of sulfides **530** using a chiral oxazoline as the directing group (Scheme 8.172).[203,204] The sulfoxides **531** were obtained in good yields (up to 90%) and selectivities (up to 94% de) using *t*-BuOOH/Ti(*i*-PrO)$_4$ or *m*-CPBA as the oxidant. The authors found that a free hydroxy group in **530** was necessary to achieve high selectivities. Thus, a TIPS protected derivative of **530** gave a much lower selectivity for the sulfoxide with the opposite configuration. The sulfoxide configuration was determined by X-ray crystallography or by authentic synthesis. The oxazoline–sulfoxide ligands **531** were used to examine electronic effects in catalytic allylic substitutions.[412]

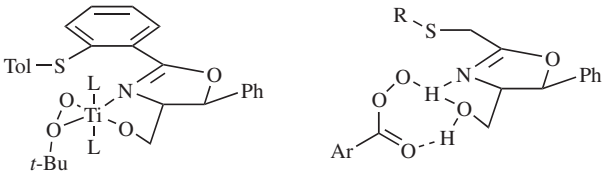
The authors proposed transition state models **532** and **533** to account for the diastereoselectivities observed in metal-catalyzed and *m*-CPBA oxidations, respectively (Fig. 8.16). The organization as well as directing role of the hydroxy group is



530 **531**

R = Me, Tol

Scheme 8.172

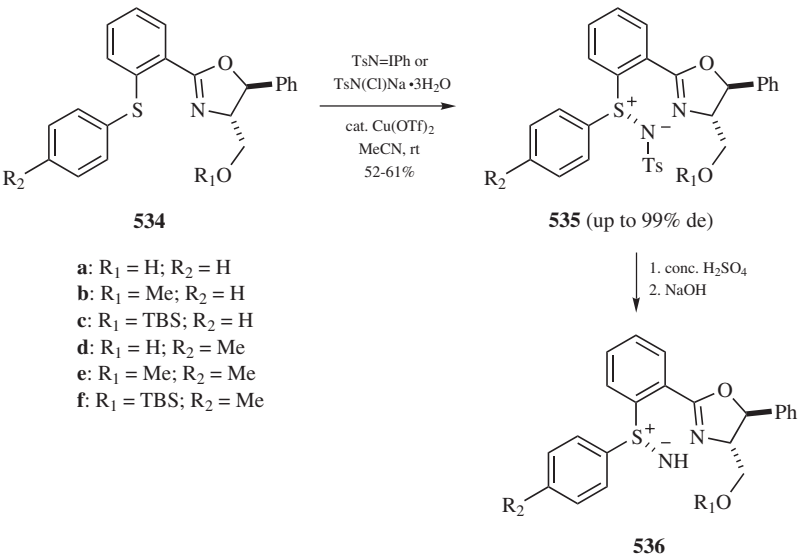


532 **533**

Figure 8.16. Transition state models for oxidations.

fairly obvious based on the models. Model **533** also explains the strong solvent dependence of the selectivity when the oxidation is carried out with *m*-CPBA. Solvents with strong hydrogen bonding capabilities disrupt the intramolecular hydrogen bonding resulting in lower selectivities.

Uemura and co-workers applied similar principles for their copper-catalyzed sulfimidation of diaryl sulfides (Scheme 8.173).[357,413,414] The reaction was carried out in the presence of a copper(II) salt using either tosyliminophenyliodane (TsN=IPh) or *N*-chloro-*p*-toluenesulfonamide (Chloramine-T) sodium salt as the imidation reagent. A diaryl sulfide **534** was imidated to give the *N*-tosylsulfimides **535** in modest yield with excellent diastereoselectivity (up to 99% de). In this case, however, a chiral 4-(methoxmethyl)oxazoline directing group gave better results than the corresponding 4-(hydroxymethyl)oxazoline analogue. The tosyl group of **535** was hydrolyzed to afford the sulfimides **536** that were used as chiral ligands in catalytic allylic substitutions.[357]



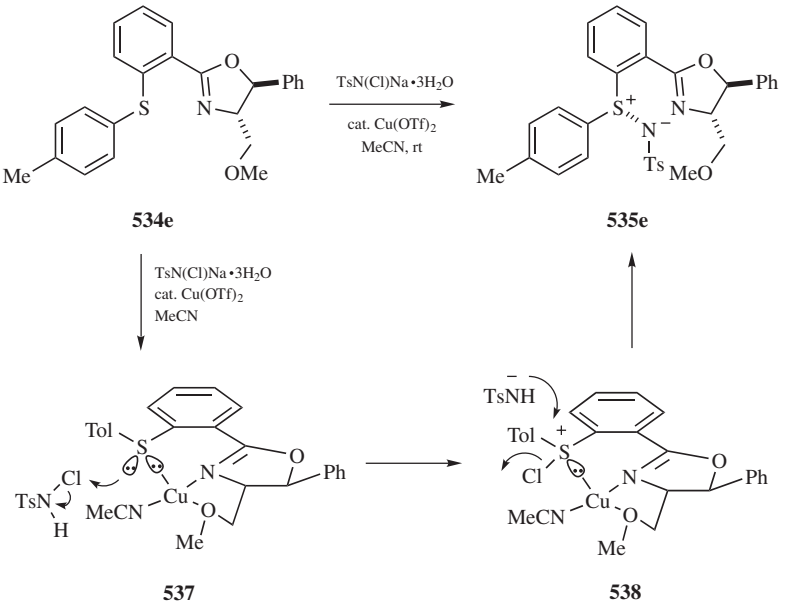
534

a: R_1 = H; R_2 = H
b: R_1 = Me; R_2 = H
c: R_1 = TBS; R_2 = H
d: R_1 = H; R_2 = Me
e: R_1 = Me; R_2 = Me
f: R_1 = TBS; R_2 = Me

535 (up to 99% de)

536

Scheme 8.173



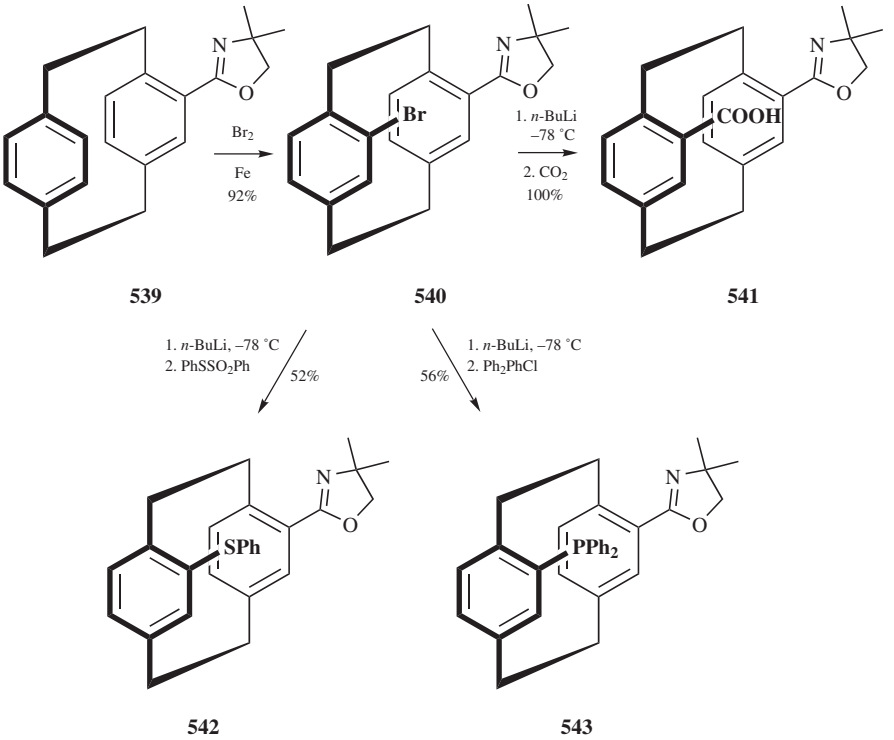
Scheme 8.174

The authors proposed a working mechanism to explain the diastereoselectivities (Scheme 8.174). Thus, the prereaction complex **537** reacts with the Chloramine-T to yield an intermediate chlorosulfonium ion **538**. Further reaction of **538** with toluenesulfonamide anion effected a configurational inversion to give the observed product.

Very recently, Pelter and co-workers showed that oxazolines were a strong Ψ-geminal directing group, characteristic of all carbonyl compounds in reactions of cyclophanes.[176] Thus, bromination of the oxazolinylcyclophane **539** gave exclusively the Ψ-geminal bromide **540** in excellent yield (Scheme 8.175). The bromide **540** served as a precursor to potential bidentate ligands, such as the acid **541**, the phenyl sulfide **542** and diphenylphosphine **543**.

8.3.11. Oxazolines as Ligands in Asymmetric Catalysis

The use of chiral oxazolines as ligands for catalytic asymmetric synthesis is undoubtedly the most important development in oxazoline chemistry. Compared with other ligands, oxazolines offer the advantage of being easily accessible from chiral amino alcohols that are, in turn, readily available from a chiral pool of amino acids. There have been numerous reports on this exciting use of oxazolines during the last 10 years. Many of the ligands studied to date contain at least two oxazoline units. The synthesis and reactions of bis(oxazolines) are discussed in detail in Chapter 9; the discussions in this section are limited to mononuclear oxazolines.

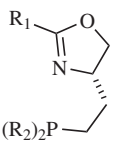


Scheme 8.175

There are many excellent reviews on asymmetric catalysis. Prominent among these reviews are two recently published books. One is a three volume work published in 1999 and edited by Jacobsen, Pfaltz, and Yamamoto.[362] The other was published in 2000 and edited by Ojima.[363] Moreover, Lemaire and co-authors have extensively reviewed nitrogen-containing ligands for asymmetric catalysis in 2000.[415] Pfaltz reviewed the use of chiral heterocycles in asymmetric catalysis.[23] These books and reviews provide a comprehensive discussion and examination of various catalytic asymmetric reactions and encompass the topic of this section. Additionally, Pfaltz and Helmchen specifically reviewed the use of phosphinooxazoline ligands, one of the most frequently used subclasses of mononuclear oxazolines, in asymmetric synthesis for the literature up to 2000.[21] Therefore, the discussions here are intended to be a brief overview of recent developments (1999–2001) in this very active and fruitful research area. This section is organized to show the diversity of oxazoline structures as well as the type of catalytic reactions in which they function as useful ligands. For a more detailed treatment of catalytic process as well as earlier literature references, the reader is directed to the aforementioned comprehensive reviews.

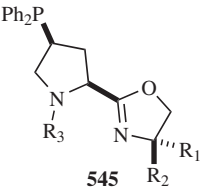
8.3.11.1. Oxazoline Ligands

Mononuclear oxazolines useful for asymmetric catalysis are generally bidentate ligands that can be classified into the following four basic catagories: phosphino-oxazolines (PhosOx, Figs. 8.17–8.19), pyridine-oxazolines (PyrOx, Fig. 8.20) including the quinoline-oxazolines, sulfide-oxazolines (SulfOx, Fig. 8.21), selenide-oxazolines (SelOx, Fig. 8.22), and hydroxy-oxazolines (HydrOx, Fig. 8.23). Additional coordinating groups can be added to these basic classes of ligand structures and can sometimes provide enhanced levels of selectivity. The coordination chemistry of oxazolines has been reviewed extensively by Muller and co-authors covering the literature up to 1999.[20] Unless otherwise warranted, the coordination chemistry is generally not discussed in this section.



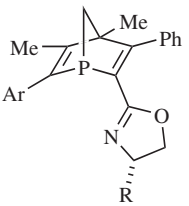
544

a: R_1 = *t*-Bu; R_2 = Ph
b: R_1 = Ph; R_2 = Ph
c: R_1 = adamantyl; R_2 = Ph
d: R_1 = 3,5-di-*t*-Bu-Ph; R_2 = Ph
e: R_1 = Tr; R_2 = Ph
f: R_1 = 3,5-di-*t*-Bu-4-MeO-Ph; R_2 = Ph
g: R_1 = 9-anthracyl; R_2 = Ph
h: R_1 = 2-EtO-1-naphthyl; R_2 = Ph
i: R_1 = Me; R_2 = Ph
j: R_1 = *t*-Bu; R_2 = *o*-Tol
k: R_1 = Ph_2CH; R_2 = Ph
l: R_1 = Ph_2CH; R_2 = *o*-Tol
m: R_1 = Ph_2MeCH; R_2 = *o*-Tol



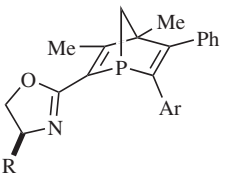
545

a: R_1 = *i*-Pr; R_2 = H; R_3 = Boc
b: R_1 = *t*-Bu; R_2 = H; R_3 = Boc
c: R_1 = Ph; R_2 = H; R_3 = Boc
d: R_1 = H; R_2 = *i*-Pr; R_3 = Boc
e: R_1 = H; R_2 = Ph; R_3 = Boc
f: R_1 = H; R_2 = CO_2Me; R_3 = Boc
g: R_1 = R_2 = Me; R_3 = Boc
h: R_1 = *i*-Pr; R_2 = H; R_3 = Fmoc
i: R_1 = *i*-Pr; R_2 = H; R_3 = Cbz
j: R_1 = *i*-Pr; R_2 = H; R_3 = Piv
k: R_1 = *i*-Pr; R_2 = H; R_3 = Ac
l: R_1 = *i*-Pr; R_2 = H; R_3 = *i*-Pr_2NCO



546

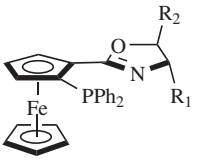
a: R = *i*-Pr; Ar = Ph
b: R = *t*-Bu; Ar = Ph
c: R = *i*-Pr; Ar = 9-phenanthryl
d: R = *i*-Pr; Ar = 9-anthracyl



547

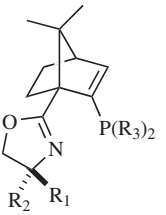
a: R = *i*-Pr; Ar = Ph
b: R = *t*-Bu; Ar = Ph
c: R = *i*-Pr; Ar = 9-phenanthryl
d: R = *i*-Pr; Ar = 9-anthracyl

Figure 8.17. PhosOx ligands.



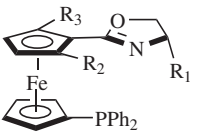
548

a: R_1 = *i*-Pr; R_2 = H
b: R_1 = *t*-Bu; R_2 = H
c: R_1 = Bn; R_2 = H
d: R_1 = Ph; R_2 = H
e: R_1 = R_2 = Ph



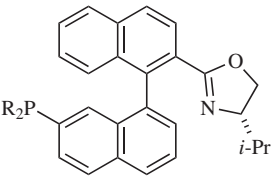
549

a: R_1 = *i*-Pr; R_2 = H; R_3 = Ph
b: R_1 = *t*-Bu; R_2 = H; R_3 = Ph
c: R_1 = Ph; R_2 = H; R_3 = Ph
d: R_1 = *t*-Bu; R_2 = H; R_3 = cyclohexyl
e: R_1 = H; R_2 = *i*-Pr; R_3 = Ph



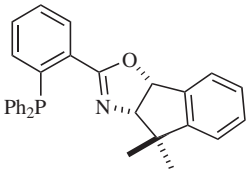
550

a: R_1 = *i*-Pr; R_2 = H; R_3 = H
b: R_1 = Bn; R_2 = H; R_3 = H
c: R_1 = *t*-Bu; R_2 = H; R_3 = H
d: R_1 = Ph; R_2 = H; R_3 = H
e: R_1 = Bn; R_2 = TMS; R_3 = H
f: R_1 = Bn; R_2 = H; R_3 = Me
g: R_1 = Bn; R_2 = H; R_3 = TMS
h: R_1 = Ph; R_2 = H; R_3 = TMS
i: R_1 = Ph; R_2 = Me; R_3 = H

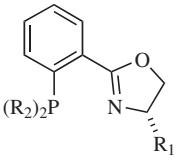


551

a: R = Ph; a*S* isomer
b: R = Ph; a*R* isomer
c: R = 3,5-di-Me-Ph; a*R* isomer



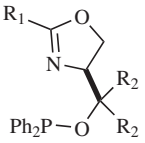
552



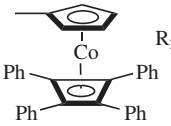
553

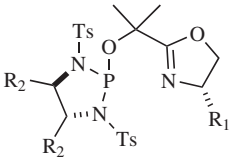
a: R_1 = *i*-Pr; R_2 = Ph
b: R_1 = Ph; R_2 = Ph
c: R_1 = *t*-Bu; R_2 = Ph
d: R_1 = CH_2*t*-Bu; R_2 = Ph
e: R_1 = *t*-Bu; R_2 = *o*-Tol
f: R_1 = *i*-Pr; R_2 = *i*-Pr
g: R_1 = *t*-Bu; R_2 = *i*-Pr
h: R_1 = *i*-Pr; R_2 = *t*-Bu
i: R_1 = *i*-Pr; R_2 = cyclohexyl
j: R_1 = *t*-Bu; R_2 = cyclohexyl
k: R_1 = Ph; R_2 = Ph

Figure 8.18. PhosOx ligands.



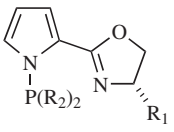
554

a: R_1 = Ph; R_2 = H
b: R_1 = adamantyl; R_2 = H
c: R_1 = ferrocenyl; R_2 = H
d: R_1 = pentaphenylferrocenyl; R_2 = H
f: R_1 =  R_2 = H
g: R_1 = ferrocenyl; R_2 = *i*-Pr
h: R_1 = ferrocenyl; R_2 = *i*-Bu
i: R_1 = ferrocenyl; R_2 = Bn
j: R_1 = 3,5-di-*t*-Bu-Ph; R_2 = Bn



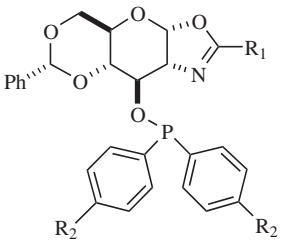
556

a: $R_1 = R_2$ = Ph
b: R_1 = *t*-Bu; R_2 = Ph
c: R_1 = *t*-Bu, R_2, $R_2 = (CH_2)_4$



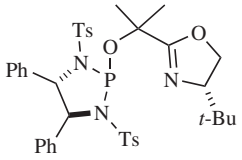
559

a: R_1 = *i*-Pr; R_2 = Ph
b: R_1 = *t*-Bu; R_2 = Ph
c: R_1 = *t*-Bu; R_2 = *o*-Tol
d: R_1 = *t*-Bu; R_2 = cyclohexyl

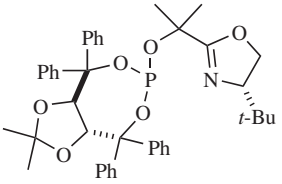


555

a: R_1 = Me; R_2 = H
b: R_1 = Bn; R_2 = H
c: R_1 = Ph; R_2 = H
d: R_1 = *i*-Pr; R_2 = H
e: R_1 = *i*-Bu; R_2 = H
f: R_1 = *t*-Bu; R_2 = H
g: R_1 = Me; $R_2 = CH_2NEt_2Me^+$

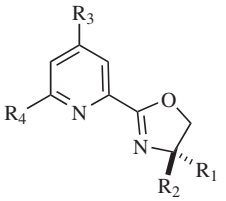


557



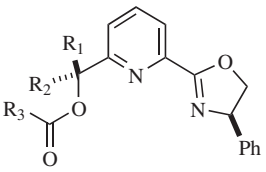
558

Figure 8.19. PhosOx ligands.



560

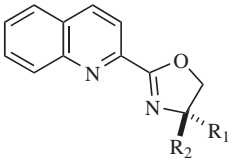
a: R_1 = *i*-Pr; R_2 = H; R_3 = H; R_4 = H
b: R_1 = H; R_2 = Ph; R_3 = H; R_4 = H
c: R_1 = *i*-Pr; R_2 = H; R_3 = Cl; R_4 = H
d: R_1 = *i*-Pr; R_2 = H; R_3 = OMe; R_4 = H
e: R_1 = H; R_2 = Ph; R_3 = Cl; R_4 = H
f: R_1 = H; R_2 = Ph; R_3 = OMe; R_4 = H
g: R_1 = *i*-Pr; R_2 = H; R_3 = H; R_4 = Me
h: R_1 = *t*-Bu; R_2 = H; R_3 = H; R_4 = Me
i: R_1 = *t*-Bu; R_2 = H; R_3 = OMe; R_4 = Me
j: R_1 = *t*-Bu; R_2 = H; R_3 = H; R_4 = H



561

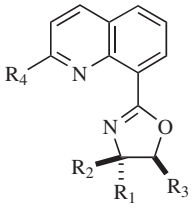
a: R_1 = H; R_2 = H; R_3 = CH_2CH_2COTG
b: R_1 = H; R_2 = *t*-Bu; R_3 = CH_2CH_2COTG
c: R_1 = *t*-Bu; R_2 = H; R_3 = CH_2CH_2COTG
d: R_1 = H; R_2 = H; R_3 = Ph

TG = TentaGel Resin



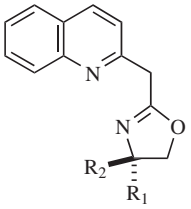
562

a: R_1 = *i*-Pr; R_2 = H
b: R_1 = H; R_2 = Ph
c: R_1 = *t*-Bu; R_2 = H



563

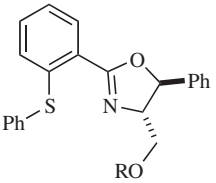
a: R_1 = *i*-Pr; R_2 = H; R_3 = H; R_4 = H
b: R_1 = H; R_2 = Ph; R_3 = H; R_4 = H
c: R_1 = *t*-Bu; R_2 = H; R_3 = H; R_4 = H
d: R_1 = H; R_2 = Bn; R_3 = H; R_4 = H
e: R_1 = *i*-Pr; R_2 = H; R_3 = Ph; R_4 = H
f: R_1 = CH_2SiPh_2t-Bu; R_2 = H; R_3 = Ph; R_4 = H
g: R_1 = Bn; R_2 = H; R_3 = H; R_4 = Me
h: R_1 = *i*-Pr; R_2 = H; R_3 = H; R_4 = Me
i: R_1 = Ph; R_2 = H; R_3 = H; R_4 = Me
j: R_1 = *t*-Bu; R_2 = H; R_3 = H; R_4 = Me
k: R_1 = Bn; R_2 = H; R_3 = H; R_4 = *n*-Bu
l: R_1 = Bn; R_2 = H; R_3 = H; R_4 = *i*-Bu
m: R_1 = *t*-Bu; R_2 = H; R_3 = H; R_4 = *i*-Bu
n: R_1 = Me; R_2 = H; R_3 = H; R_4 = H
o: R_1 = Bn; R_2 = H; R_3 = H; R_4 = H
p: R_1 = Ph; R_2 = H; R_3 = H; R_4 = H



564

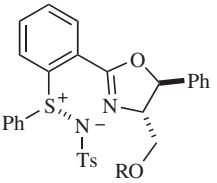
a: R_1 = *i*-Pr; R_2 = H
b: R_1 = H; R_2 = Ph
c: R_1 = *t*-Bu; R_2 = H

Figure 8.20. PyrOx ligands.



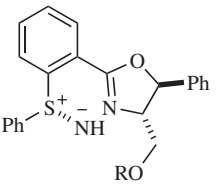
534

a: R = H
b: R = Me
c: R = TBS



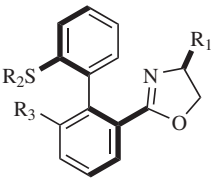
535

a: R = H
b: R = Me
c: R = TBS



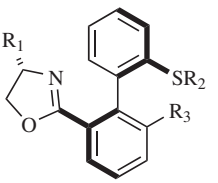
536

a: R = H
b: R = Me
c: R = TBS



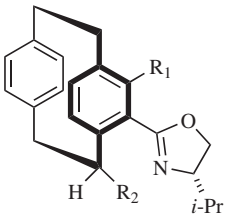
565

a: R_1 = *i*-Pr; R_2 = Me; R_3 = OMe
b: R_1 = *i*-Pr; R_2 = *i*-Pr; R_3 = OMe
c: R_1 = *t*-Bu; R_2 = Me; R_3 = OMe
d: R_1 = *t*-Bu; R_2 = *i*-Pr; R_3 = OMe
e: R_1 = *i*-Pr; R_2 = Me; R_3 = H
f: R_1 = *t*-Bu; R_2 = Me; R_3 = H
g: R_1 = *i*-Pr; R_2 = *i*-Pr; R_3 = H



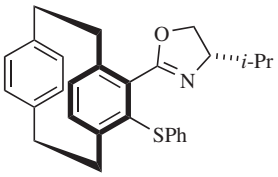
566

a: R_1 = *i*-Pr; R_2 = Me; R_3 = OMe
b: R_1 = *i*-Pr; R_2 = *i*-Pr; R_3 = OMe
c: R_1 = *t*-Bu; R_2 = Me; R_3 = OMe
d: R_1 = *t*-Bu; R_2 = *i*-Pr; R_3 = OMe
e: R_1 = *i*-Pr; R_2 = Me; R_3 = H
f: R_1 = *t*-Bu; R_2 = Me; R_3 = H
g: R_1 = *i*-Pr; R_2 = *i*-Pr; R_3 = H



567

a: R_1 = SPh; R_2 = H
b: R_1 = H; R_2 = SPh

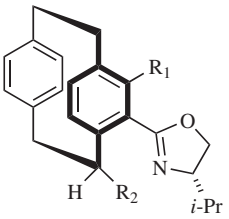


568

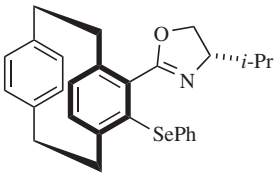
Figure 8.21. SulfOx ligands.

8.3.11.2. Allylic Substitution Reactions

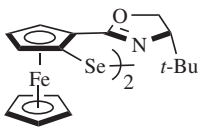
The subject of catalytic asymmetric allylic alkylations has been thoroughly and systematically reviewed by Trost and Van Vranken in 1996.[416] Much of the recent literature was reviewed by Pfaltz and Lautens in 1999[417] and by Trost and Lee in 2000.[418] Many mononuclear oxazoline ligands have been successfully employed in



569



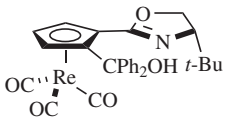
570



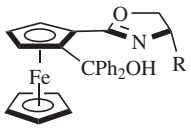
571

a: R_1 = SePh; R_2 = H
b: R_1 = H; R_2 = SePh

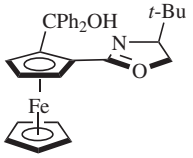
Figure 8.22. SelOx ligands.



452

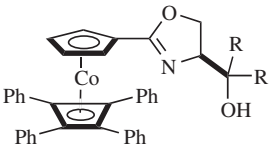


572

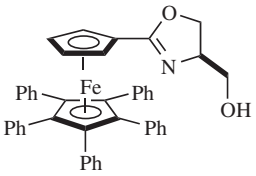


573

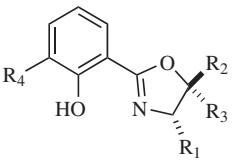
a: R = *t*-Bu
b: R = Ph



574



575

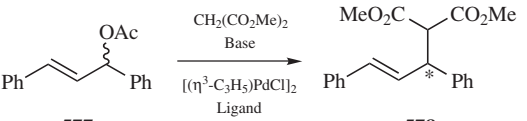


576

a: R_1 = Ph, R_2 = Ph, R_3 = H; R_4 = H
b: R_1 = Ph, R_2 = H, R_3 = Ph; R_4 = H
c: R_1 = Ph, R_2 = Ph, R_3 = H; R_4 = *t*-Bu
d: R_1 = Ph, R_2 = H, R_3 = Ph; R_4 = *t*-Bu
e: R_1 = Ph, R_2 = H, R_3 = H; R_4 = *t*-Bu
f: R_1 = Bn, R_2 = H, R_3 = H; R_4 = *t*-Bu

Figure 8.23. HydrOx ligands.

palladium catalyzed allylic substitution reactions. Despite the shortcomings (see below), asymmetric allylic substitution of racemic diphenylallyl acetate **577** using dimethyl malonate (Scheme 8.176) has been a standard reaction used by many researchers to evaluate new chiral ligands. The performance of selected ligands in this reaction is summarized in Table 8.34.[98,117,118,123,180,208,209,225,357,413,419–429] Table 8.34 is organized to show a generic ligand structure and the ligand that gave the best results, whether optimized or not.



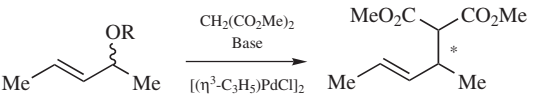
Scheme 8.176

Since the enantioselectivity of this reaction is known to be sensitive to the solvent, base, counterion, and source of catalyst,[416–418] one should be cautious in comparing results from different groups. Many groups observed some cooperative effect in the selectivity when additional chirality is present in the ligand. In cases wherein the new chiral elements exert opposite chiral induction (noncooperative), the directive effect of the oxazoline ligand often dominates except in the cases of chiral bridgehead phosphines **546** and **547.** Here, the chirality of the phosphine was shown to be more important (entry 3).[117] Although axial diastereomers **565e** and **566e** exist as an equilibrium mixture in solution, only **566e** complexes with palladium (entry 18).[429] A similar phenomenon was observed for the diastereomers **565f** and **566f**. It is not surprising that this was not observed for **565g** and **566g** considering the higher rotation barrier. The origins of enantioselection can be understood through structural analysis by X-ray crystallography[419–421,430] and solution NMR.[118,420,421] Other soft nucleophiles, such as acetylacetone (ligands **555g** and **551b**),[424] dimethyl methylmalonate (ligand **555g**),[424] benzylamines (ligand **555g**),[420,424] and silyl enolates (ligand **544**),[419] gave similar selectivities.

TABLE 8.34. PALLADIUM-CATALYZED ALKYLATION OF DIPHENYLALLYL ACETATE WITH DIMETHYL MALONATE

Entry	Ligand	Best Ligand	**578** % Yield	% ee	References
1	**544a–d**	**544a**, **544d**	95	98 (*R*)	118, 419
2	**545a–l**	**545a**	100	30 (*S*)	98
3	**546a–d**, **547a–d**	**546a**	100	94 (*S*)	117
4	**551b**	**551b**	99	91 (*R*)	420, 421
5	**551c**	**551c**	99	97 (*R*)	421
6	**554**	**554a**, **c**	>95 (conv.)	90 (*S*)	422
7	**555a–f**	**555a**	100	96 (*S*)	423
8	**555g**	**555g**	95	92 (*S*)	424
9	**556a–c-558**	**556a**	100 (conv.)	88 (*S*)	425
10	**559a–d**	**559a**	100 (conv.)	72 (*S*)	426
11	**560a–i**	**560i**	94	93 (*S*)	208, 427
12	**561a–d**	**561a**	60–100	80 (*R*)	225
13	**562a–c**	**562c**	93	92 (*S*)	209, 427
14	**563a–f**	**563c**	94	77 (*S*)	123, 427
15	**563g–m**	**563j**	79	78 (*R*)	428
16	**564a–c**	**564b**	88	78 (*S*)	427
17	**534a–c-536a–c**	**536b**	99	90 (*S*)	413, 357
18	**565a–g**, **566a–g**	1 : 1 **565e/566e**	93	82 (*S*)	429
19	**567**, **568**	**567b**	98	94 (*S*)	180
20	**569**, **570**	**569b**	98	93 (*S*)	180

TABLE 8.35. PALLADIUM-CATALYZED ALKYLATION OF DIMETHYLALLYL ACETATE AND DIMETHYLALLYL *tert*-BUTYLCARBONATE WITH DIMETHYL MALONATE



579

a: R = Ac
b: R = Boc

580

Scheme 8.177

Entry	**579** (R)	Ligand	Best Ligand	**580** % Yield[a]	% ee	Reference
1	Ac	**536b**	**536b**	63	49 (NR)	357
2	Boc	**544**	**544f**	77	82 (*R*)	118, 419
3	Boc	**554**	**554f**	>95 (conv.)	70 (*S*)	422

[a] Not reported: NR.

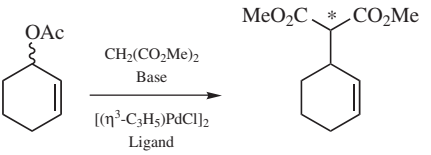
At least two groups examined the issue of catalyst recycle by using polymer-bound[225] or water-soluble ligands.[424]

Although a diphenylallyl system serves as a good starting point to evaluate chiral ligands, Burgess and Hou suggested that the smaller dimethylallyl system, generated from **579**, should be used as a more stringent test for ligand performance.[118] Selected examples are listed in Table 8.35 (Scheme 8.177).[118,357,419,422] As expected, the enantioselectivities using **579** dropped in comparison with those obtained using the diphenylallyl system **577**. It is important to note that the best ligand for the diphenylallyl system may not necessarily give the best selectivity for the dimethylallyl system.

A number of groups have also studied alkylation in cyclic allyl systems. Selected examples of reations using 3-acetoxycyclohexene **581** are listed in Table 8.36 (Scheme 8.178).[98,419,425,426,431] Although the proline-based PhosOx ligands **545** did not give good selectivities in reactions with **577** (Table 8.34, entry 2), here using **581** the selectivity with **545a** was reasonable (Table 8.36, entry 2). Gilbertson and co-workers studied the effects of substrate ring size on the ligand performance and found that **545** gave best selectivities (up to 90%) using 3-acetoxycyclopentene as the substrate.[98] Interestingly, good selectivity (80% ee) was still obtained when the PhosOx ligand contained an achiral oxazoline moiety (e.g. **545g**). The authors attributed the effect of substrate ring size and the lack of good selectivities in the diphenylallyl system to the small size of the chiral pocket around the catalytic center.

When unsymmetrical allylic substrates are used, two regioisomers are produced. Monosubstituted allyl substrates react primarily at the unsubstituted terminus to give an achiral linear product (Scheme 8.179).[432] However, Pfaltz and co-workers were able to reverse the regioselectivity and obtain the more highly substituted

TABLE 8.36. PALLADIUM-CATALYZED ALKYLATION OF 3-ACETOXYCYCLOHEXENE WITH DIMETHYL MALONATE



581 **582**

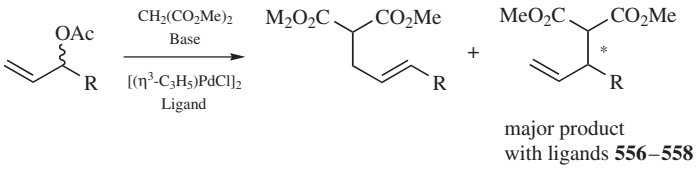
Scheme 8.178

Entry	Ligand	Best Ligand	**582** % Yield	% ee	References
1	**544a–d**	**544d**	95	79 (*S*)	419
2	**545a**	**545a**	93	80 (*S*)	98, 431
3	**556–558**	**556b**	100 (conv.)	71 (*R*)	425
4	**559**	**559b**	91 (conv.)	41 (*R*)	426

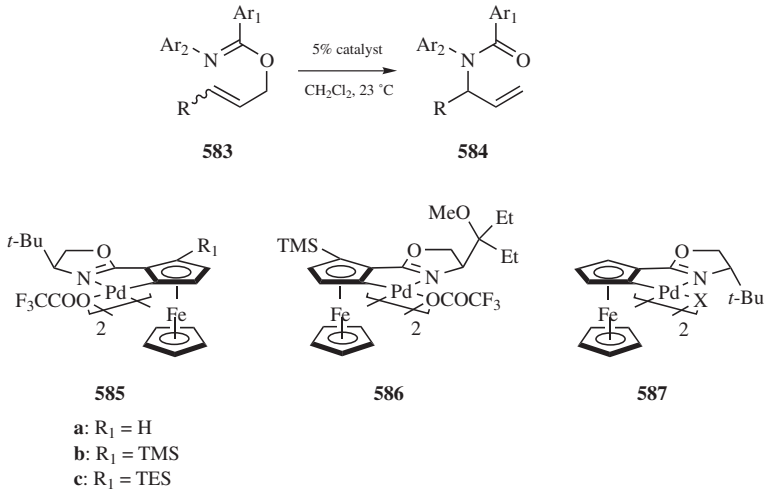
product enatioselectively using ligands **556–558**.[425] More recently, the same group reported a selective preparation of either regioisomer using enantiomers of the catalyst as well as enantiomerically enriched disubstituted substrates.[433]

This alkylation reaction is generally carried out using a palladium catalyst although other metals can be effective as well.[416–418] Williams and co-workers recently reported the use of zero-valent platinum complexes as catalysts.[430,434] When the PhosOx ligand **553a** was used, the enantioselectivities were inferior to results obtained using the corresponding palladium complex. Additionally, the selectivities were sensitive to excess ligand. The authors concluded that the platinum complex is hemilabile, that is, the complex can accept an additional ligand resulting in a loss of chelation. It is noteworthy that the X-ray crystal structures of the $PtCl_2$(**553a**) and $PdCl_2$(**553a**) complexes were very similar.

Overman's group improved their earlier versions of chiral catalysts for the rearrangement of allylic imidates **583** to the amides **584** (Scheme 8.180).[435] High selectivities were obtained using cyclopalladated catalysts bearing ferrocenyloxazoline moieties **585–587**. These catalysts were conveniently prepared by oxidative insertion of Pd(0) to oxazoline-substituted ferrocenyl iodides. The iodide complex was inactive and was converted to the active trifluoroacetate complex using silver trifluoroacetate. The enatioselectivities were generally 75–95% ee although most reactions took more than a day to complete. Not surprisingly, the olefin configuration as well as the chiral catalyst determines the product stereochemistry. The



Scheme 8.179

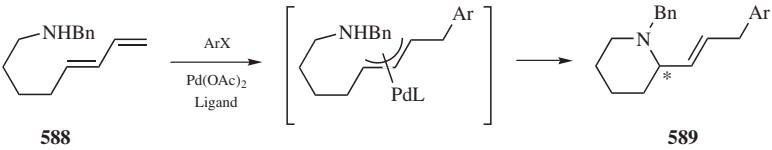


Scheme 8.180

rearrangement is sensitive to the electronic nature of the aryl groups. Imidates with electron-withdrawing aryl groups react much slower than imidates with electron-donating aryl groups. Similarly, reaction of trichloroacetimidates is too slow to be of any practical use. The best results to prepare the (*R*) isomer of **584** (96% ee, 89–97% yield) were obtained using the (*Z*) alkene **583** (R = *i*-Bu, Ar_1 = Ph or *o*-Tol, Ar_2 = 4-MeO—Ph) and catalyst **585b**.

While intramolecular allylic substitution is a straightforward and attractive strategy for construction of carbocycles, there are surprisingly few reports on the asymmetric variant of this cyclization.[416–418] Helmchen and Flubacher have reported a Heck-induced enantioselective intramolecular allylic amination reaction of **588** to produce the 2-substituted piperidine derivative **589** (Scheme 8.181).[436] Selectivities as high as 80% were obtained with sterically hindered aryl triflates (Ar = 2,6-di-Me—Ph) using the PhosOx ligand **553b**. However, the reaction was exceedingly slow and required 10 days to complete.

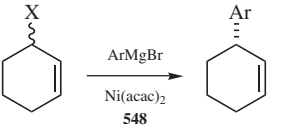
Allylic substitution using hard nucleophiles proceeds through a different mechanism.[416–418] Instead of attacking the allyl group of the π allyl–metal complex, hard nucleophiles attack the metal first and the product is subsequently formed by reductive elimination. Nickel(0) complexes have often been used for this purpose. Reports of good enantioselectivities in this type of reaction are limited.



X = I, OTf; Ar = Ph, 2,6-di-Me-Ph; Ligand = **553b**, **c**

Scheme 8.181

Uemura and co-workers recently reported their success using ferrocene-based PhosOx ligands.[437,438] Reactions using an arylboronic acid as the nucleophile gave good yields with various allylic substrates although enantioselectivities were moderate (up to 53% ee).[437] Better results were obtained using an aryl Grignard reagent as the nucleophile.[438] While acyclic substrates gave low selectivities (<40% ee), cyclohexenyl substrates **590** gave better results (Scheme 8.182). The best selectivity for the (*S*) isomer of **591** (95% ee) was obtained with 3-phenoxycyclohexene (X = OPh) as the substrate, 2-naphthylmagnesium bromide (Ar = 2-naphthyl) as the nucleophile, and **548a** as the ligand. The PhosOx ligand **553a** was less effective than **548**, which demonstrated the importance of planar chirality in this reaction. Unlike the reaction with an aryl boronic acid as the nucleophile, the Grignard reagent produced a significant amount of biaryl as the byproduct. The biaryl byproduct was thought to arise from reduction of the Ni(II) precatalyst by the Grignard reagent generating an active Ni(0) species.



590 **591**

X = OAc, OCO_2Me, OMe, OPh, OH, Br

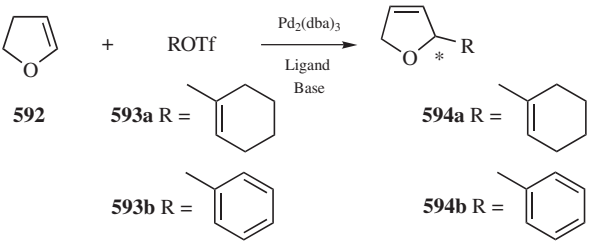
Scheme 8.182

8.3.11.3. Heck Reactions

The Heck reaction is a synthetically powerful reaction wherein a carbon–carbon bond is formed between two sp^2 hybridized carbon atoms.[439] The syn nature of the addition of vinyl–aryl palladium species to carbon–carbon double bond precludes a syn β-hydride elimination for cyclic olefins. As a result, a new chiral center is formed. Shibasaki and Vogl provided a comprehensive review of this subject in 1999.[440] Overman and Donde reviewed the intramolecular version of this reaction in 2000.[441] Pfaltz and co-authors specifically reviewed this reaction using PhosOx ligands.[442]

Although BINAP has been proven the most effective ligand system for the asymmetric Heck reaction,[440,441] it promotes double bond migration resulting in mixtures of isomers when the engery differences between the isomers are small. In 1996, Pfaltz and co-workers first demonstrated that chiral PhosOx ligands are very effective for highly enantioselective as well as regioselective Heck reactions.[443,444] Subsequent research by several groups expanded the structural diversity of the PhosOx ligands leading to some improvements in catalyst activity although selectivities have not yet surpassed the selectivity (99% ee) achieved using by Pfaltz's best ligand, the *tert*-leucinol-based PhosOx **553c**. The Heck reaction of dihydrofuran **592** and cyclohexenyl triflate **593a** or phenyl triflate **593b** has been

TABLE 8.37. ASYMMETRIC INTERMOLECULAR HECK REACTION



Scheme 8.183

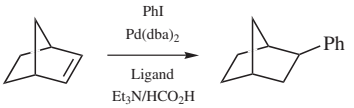
Entry	Ligand	Triflate	Best Ligand	**594a** % Yield	**594b** % Yield	% ee	References
1	**545a**,**b**,**d**,**l**	**593a**	**545a**	99 (conv.)		86 (*S*)	98, 445
2	**546a–d**, **547a–d**	**593a**	**546b**	91		93 (*R*)	117
3	**549a–e**	**593a**	**549b**	100 (conv.)		94 (*R*)	446
4	**550a–i**	**593b**	**550g**		75	92 (*R*)	447
5	**551a**,**b**	**593b**	**551a**		65	88 (*R*)	448
6	**551b**,**c**	**593b**	**551c**		84	86 (*S*)	421
7	**552**	**593a**	**552**	91		98 (*R*)	449
8	**555a–f**	**593b**	**555b**		100	96 (*R*)	450

chosen by many researchers as a model to evaluate the efficiency of the chiral ligands. Selected examples are listed in Table 8.37 (Scheme 8.183).[98,117,421,445–450]

The stereochemistry of the oxazoline usually determines the stereochemical outcome of this reaction. However, this rule does not apply when planar or axial chirality is involved and exceptions have been described. For example, an exception is the proline-based ligand **545** wherein the chirality of the oxazoline was found unimportant.[98,445] Another exception is the ferrocene-based ligand **550** in which the planar chirality is the major factor that determines the stereochemical outcome of the reaction.[447] Still another exception is the binaphthyl-based PhosOx **551** wherein the axial chirality dominates. This result was consistent with structural analysis by X-ray crystallography.[448] And it is perhaps not very surprising considering the similarity of the binaphthyl-based PhosOx ligands to the powerful BINAP ligands. The low tendency of PhosOx-palladium catalysts to promote double-bond migration permits a wide variety of cycloalkenes and triflates to be used for this reaction.[95,421,445,446,449,450] Both reaction rates and regioselectivities as well as enantioselectivities are sensitive to the base as well as the solvent used in the reaction.[98,445,446] The origin of the enantioselectivity was investigated using NMR analysis and X-ray crystallography.[421,448,450] It is noteworthy that crotyl alcohol has been coupled with phenyl triflate **593b** to give moderate yields (up to 54%) of β-phenylbutanal although the enantioselectivity was low (up to 17% ee).[450]

The Heck reaction yields the final product through a β-hydride elimination whereas hydroarylation or hydrovinylation generates the final product via a reductive elimination. Nonetheless, both reactions share a common first step, that is, addition of an aryl or a vinyl palladium species to an alkene, and thus are briefly discussed here. Norbornene **595** is the most studied alkene to evaluate an the

asymmetric version of this reaction.[440] Zhou and co-workers recently reported their results using the PyrOx ligands **563** (Scheme 8.184).[451] *exo*-2-Phenylnorbornane **596** was produced exclusively with the best enantioselectivity (74% ee) obtained using **563a**.



595 **596**

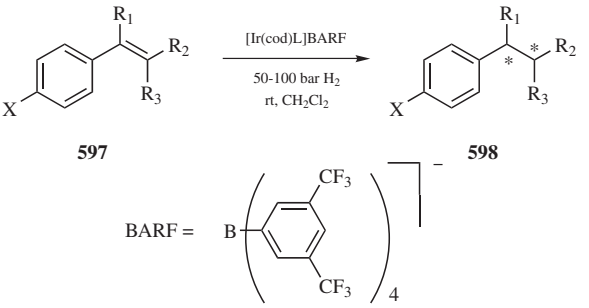
Ligand = **563a**, **c**, **n**-**p**

Scheme 8.184

8.3.11.4. Hydrogenation Reactions

Enantioselective hydrogenation reactions have received the most attention and success in asymmetric catalysis over the years. Historically, high selectivities were achieved primarily with functionalized substrates using Rh(I) or Ru(II) complexes containing chiral diphosphine ligands. Recent advances in this area include the enantioselective hydrogenation of nonfunctionalized substrates and the proliferation of other ligands including oxazolines. This subject has been frequently and systematically reviewed. For example, Noyori and co-authors provided a comprehensive review of asymmetric hydrogenation of various substrates in 2000.[452] For a more detailed examination on the reaction with specific substrates, the reader is referred to the following reviews contained in the book edited by Jacobsen, Pfaltz, and Yamamoto: Brown's chapter on the hydrogenation of functionalized alkenes,[453] Halterman's chapter on the reaction with nonfunctionalized alkenes,[454] the chapter by Noyori and Ohkuma on carbonyl substrates,[455] and the chapter by Blaser and Spindler on imino substrates.[456] This subsection is intended to be a brief overview of recent advances using mononuclear oxazoline ligands.

Mononuclear oxazolines are among the most effective ligands for enantioselective hydrogenation of nonfunctionalized alkenes.[454] The styrene substrate **597** is one of the most studied nonfunctionalized alkenes used to evaluate the efficiency of new chiral ligands (Scheme 8.185). Selected examples of enatioselective hydrogenation of **597** using iridium catalysts are shown in Table 8.38.[359,425,426,457–459]



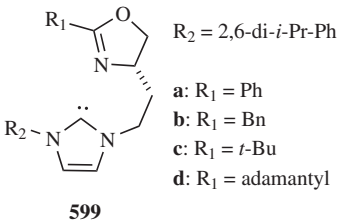
597 **598**

Scheme 8.185

TABLE 8.38. ASYMMETRIC HYDROGENATION OF STYRENES **597** (SCHEME 8.185)

Entry	**597** (X, R_1, R_2, R_3)	Best Ligand	Conditions	**598** % Yield	% ee	Reference
1	H, Me, Ph, H	**544l**	0.2% cat., 50 bar, 2 h	99	95 (*S*)	457
2	H, Me, Ph, H	**553j**	1% cat., 50 bar, 2 h	>99 (conv.)	99 (*R*)	359
3	H, Me, Ph, H	**554g**	0.1% cat., 50 bar, 2 h	100 (conv.)	97 (*R*)	458
4	H, Me, Ph, H	**554j**	0.4% cat., 50 bar, 2 h	100 (conv.)	98 (*R*)	458
5	H, Me, Ph, H	**556c**	4% cat., 100 bar, 2 h	15 (conv.)	94 (*R*)	425
6	H, Me, Ph, H	**558**	4% cat., 100 bar, 2 h	100 (conv.)	75 (*R*)	425
8	H, Me, Ph, H	**599d**	0.2% cat., 50 bar, 2 h	99	98 (*S*)	459
9	MeO, Me, Ph, H	**544l**	0.2% cat., 50 bar, 2 h	99	93 (*S*)	457
10	MeO, Me, Ph, H	**553j**	1% cat., 50 bar, 2 h	>99 (conv.)	99 (*R*)	359
11	MeO, Me, Ph, H	**557**	4% cat., 100 bar, 2 h	57 (conv.)	92 (*R*)	425
12	MeO, Me, Ph, H	**558**	4% cat., 100 bar, 2 h	98 (conv.)	62 (*R*)	425
13	MeO, Me, Ph, H	**599d**	0.6% cat., 50 bar, 2 h	99	97 (*S*)	459
14	MeO, Me, Me, H	**544a**	0.6% cat., 50 bar, 2 h	90	80 (*S*)	457
15	MeO, Me, Me, H	**553e**	0.3% cat., 50 bar, 2 h	>99 (conv.)	61 (*R*)	359
16	MeO, Me, Me, H	**554i**	0.1% cat., 50 bar, 2 h	100 (conv.)	96 (*R*)	458
17	MeO, Me, Me, H	**557**	4% cat., 100 bar, 2 h	100 (conv.)	85 (*R*)	425
18	MeO, Me, Me, H	**559d**	1% cat., 50 bar, 2 h	100 (conv.)	75 (*R*)	426
19	MeO, Me, Me, H	**599d**	0.6% cat., 50 bar, 2 h	99	91 (*S*)	459
20	MeO, Me, Et, H	**599d**	0.6% cat., 50 bar, 2 h	94	84 (NR)	459
21	MeO, Me, H, Me	**544a**	0.6% cat., 50 bar, 2 h	70	75 (*R*)	457
22	MeO, Me, H, Me	**554g**	0.4% cat., 50 bar, 2 h	100 (conv.)	85 (*R*)	458

23	MeO, Me, H, Me	**558**	4% cat., 100 bar, 2 h	100 (conv.)	90 (*S*)	425
24	MeO, Me, H, Me	**559d**	1% cat., 50 bar, 2 h	100 (conv.)	70 (*S*)	426
25	MeO, Me, H, Me	**599d**	1% cat., 50 bar, 2 h	95	78 (*R*)	459
26	H, Me, CO_2Et, H	**553i**	1% cat., 50 bar, 2 h	86 (conv.)	81 (*R*)	359
27	H, Me, CO_2Et, H	**554h**	0.5% cat., 50 bar, 2 h	100 (conv.)	90 (*R*)	458
28	H, Me, CO_2Et, H	**556c**	4% cat., 100 bar, 2 h	32 (conv.)	91 (*R*)	425
29	H, Me, CO_2Et, H	**558**	4% cat., 100 bar, 2 h	100 (conv.)	75 (*R*)	425
30	H, Me, CO_2Et, H	**559c**	1% cat., 50 bar, 2 h	99 (conv.)	92 (*R*)	426
31	Cl, Me, Ph, H	**553j**	1% cat., 50 bar, 2 h	99 (conv.)	99 (*R*)	359
32	Cl, Me, Ph, H	**558**	4% cat., 100 bar, 2 h	52 (conv.)	78 (*R*)	425
33	H, H, CH_2OAc, Me	**544a**	0.5% cat., 50 bar, 2 h	53	72 (NR)	457
34	H, H, CH_2OAc, Me	**544b**	0.5% cat., 50 bar, 2 h	95	57 (NR)	457
35	H, H, CH_2OH, Me	**544i**	1% cat., 50 bar, 2 h	80	67 (NR)	457
36	H, H, CH_2OH, Me	**599d**	1% cat., 50 bar, 2 h	99	93 (NR)	459
37	MeO, Et, H, H	**544a**	0.3% cat., 50 bar, 2 h	99	44 (*R*)	457
38	MeO, Et, H, H	**554j**	0.1% cat., 1 bar, 2 h	100 (conv.)	88 (*S*)	458
39	MeO, Et, H, H	**599d**	0.3% cat., 50 bar, 2 h	91	31 (*R*)	459
40	H, Et, H, H	**544a**	0.3% cat., 50 bar, 2 h	99	40 (*R*)	457
41	MeO, Me, Me, Me	**553d**	2% cat., 50 bar, 2 h	99 (conv.)	81 (NR)	359



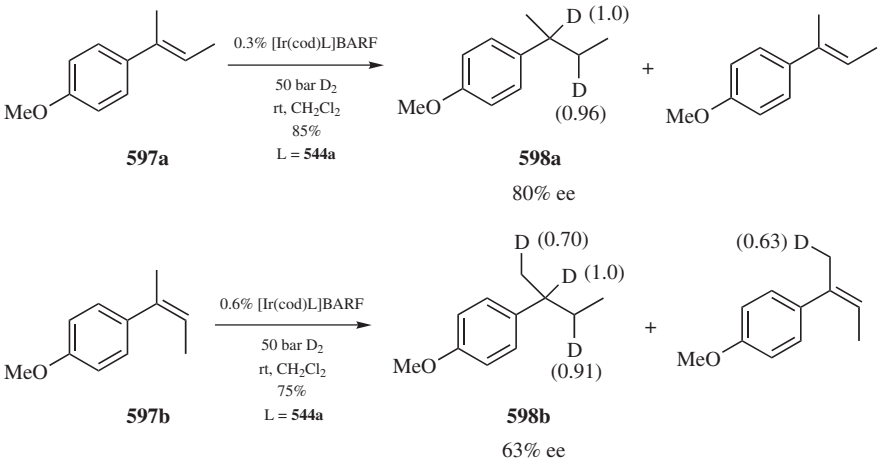
599

Figure 8.24. Oxazoline-carbene ligands.

The relationship between selectivity vs. ligand topography was determined for some ligands based on the x-ray crystal structure of the corresponding iridium complexes.[426,457,458] The structures of the respective oxazoline-carbene ligands **599a–d** are shown in Figure 8.24.[459]

In a number of thoughtfully designed and carefully executed experiments, Burgess and co-workers demonstrated that double-bond migrations are competitive with hydrogenation in at least some of the reactions using an iridium complex.[457] For example, deuteration of (*E*)-2-(4-methoxyphenyl)-2-butene **597a** gave the expected deuterated product **598a** with deuterium detected only at the carbon atoms of the double bond and recovered **597a** that was completely undeuterated (Scheme 8.186). In contrast, deuterium scrambling was observed from deuteration of (*Z*)-2-(4-methoxyphenyl)-2-butene **597b** and the recovered **597b** showed deuterium incorporation into the α-methyl group. Interestingly, no double-bond migration or isomerization in the recovered styrene was observed in the latter reaction.

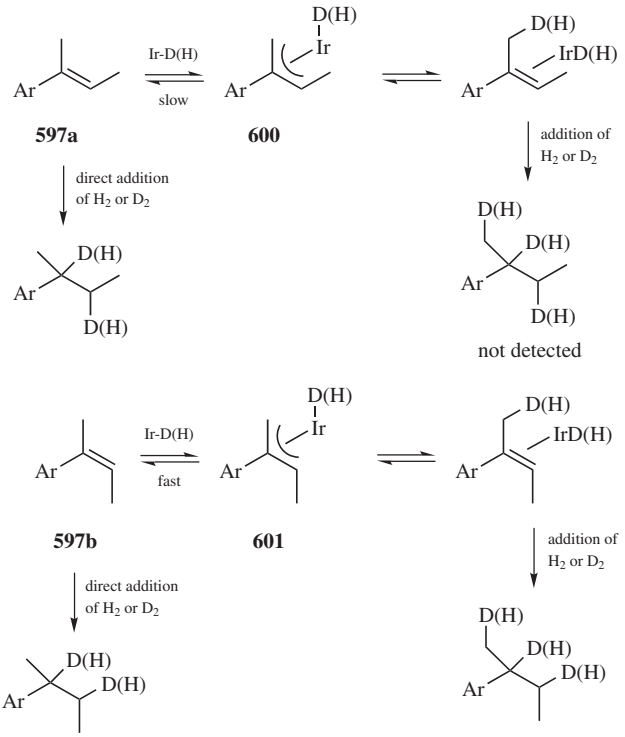
The authors proposed the mechanism in Scheme 8.187 to account for these results. It was suggested that the π-allyl complex **600** produced from **597a** was less



597a **598a** 80% ee

597b **598b** 63% ee

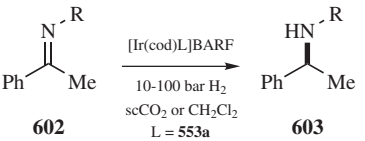
Scheme 8.186



Scheme 8.187

stable than the π-allyl complex **601** prepared from **597b**. Therefore, formation of **600** and further reaction does not compete with the direct addition reaction to **597a**. However, formation of complex **601** may be sufficiently competitive to allow deuterium scrambling. The possibility of double-bond migration adds some degree of difficulty to the design of ligands for this type of hydrogenation reaction. Using a similar method, this group also demonstrated that double-bond migration is less prevalent in reactions using the new oxazoline-carbene ligands **599a–d**.[459]

In an effort to develop an environmentally friendly process, Pfaltz and coworkers employed supercritical carbon dioxide as the solvent for the hydrogenation of imines **602a,b** to produce the α-methylbenzylamines **603a,b** (Scheme 8.188).[460] Thus, the Ir(I)-**553a** complex exhibited high activity for the hydrogenation of **602a** in supercritical CO_2 and produced **603a** with an enantioselectivity similar to that obtained in CH_2Cl_2. The authors also demonstrated successful reaction using the recycled catalyst. However, they cautioned that supercritical CO_2 should not be regarded simply as a ''nonpolar substitute solvent''. For example, hydrogenation of **602b** did not exceed 30% conversion in supercitical CO_2 even at prolonged reaction times or with higher catalyst loadings whereas the same reaction in CH_2Cl_2 went to completion within normal reaction time.



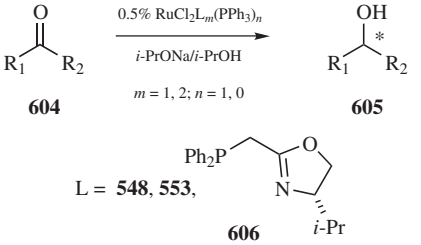
602 **603**

a: R = Ph
b: R = Bn

a: R = Ph
b: R = Bn

Scheme 8.188

TABLE 8.39. ENANTIOSELECTIVE TRANSFER HYDROGENATION OF KETONES



604 **605**

L = **548**, **553**,

606

Scheme 8.189

Entry	**604** (R_1, R_2)	Best Catalyst	% Yield	% ee	Reference
1	Ph, Me	$RuCl_2$(**548a**)PPh_3	94 (conv.)	>99.6 (*R*)	467
2	Ph, Me	$RuCl_2$(**548d**)PPh_3	95 (conv.)	72 (*R*)	467
3	Ph, Me	$RuCl_2$(**553a**)PPh_3	43 (conv.)	55 (*R*)	467
4	Ph, Me	$RuCl_2$(**606**)$_2$	96	72 (*R*)	461
5	Ph, Et	$RuCl_2$(**548d**)PPh_3	99 (conv.)	>99.7 (*R*)	467
6	Ph, *n*-Bu	$RuCl_2$(**548d**)PPh_3	99 (conv.)	98.7 (*R*)	467
7	Tol, Me	$RuCl_2$(**548a**)PPh_3	98 (conv.)	>99.3 (*R*)	467
8	4-F-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	97.3 (*R*)	467
9	4-Cl-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	98.7 (*R*)	467
10	4-Br-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	>99.3 (*R*)	467
11	3-Me-Ph, Me	$RuCl_2$(**548a**)PPh_3	98 (conv.)	>99.9 (*R*)	467
12	3-F-Ph, Me	$RuCl_2$(**548a**)PPh_3	98 (conv.)	>99.6 (*R*)	467
13	3-Cl-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	>99.7 (*R*)	467
14	3-Br-Ph, Me	$RuCl_2$(**548a**)PPh_3	77 (conv.)	>99.7 (*R*)	467
15	2-Me-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	>99.9 (*R*)	467
16	2-F-Ph, Me	$RuCl_2$(**548a**)PPh_3	92 (conv.)	96.6 (*R*)	467
17	2-Cl-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	>99.7 (*R*)	467
18	2,4-di-Me-Ph, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	>99.9 (*R*)	467
19	2-furyl, Me	$RuCl_2$(**548a**)PPh_3	66 (conv.)	95 (*R*)	467
20	*t*-Bu, Me	$RuCl_2$(**548a**)PPh_3	81 (conv.)	>99 (*S*)	467
21	cyclohexyl, Me	$RuCl_2$(**548a**)PPh_3	68 (conv.)	52 (*S*)	467
22	cyclohexyl, Me	$RuCl_2$(**548d**)PPh_3	31 (conv.)	66 (*S*)	467
23	*n*-hexyl, Me	$RuCl_2$(**548a**)PPh_3	99 (conv.)	26 (*S*)	467

PhosOx ligands were also effective for ruthenium (II)-catalyzed transfer hydrogenation of alkyl ketones **604** (Scheme 8.189). Both Pfaltz's and Uemura's groups examined the complexation of PhosOx ligands with ruthenium (II) using spectroscopic techniques including X-ray crystallography.[461,462] These studies showed that ligand **606** forms geometric isomers of hexacoordinated $RuCl_2L_2$ complexes,[461] whereas ligand **548** forms one major diastereomer of the pentacoordinated complex $RuCl_2LPPh_3$.[462] These complexes, $RuCl_2$(**606**)$_2$ and $RuCl_2$(**548**)PPh_3 were used in transfer hydrogenation of ketones by *i*-PrOH, an enantioselective version of the Meerwein–Ponndorf–Verley reduction.[463–466]

Interestingly, both groups found that mixtures of isomeric complexes can be used in place of isomerically pure complexes without a significant loss in selectivity.[461,462] The data in Table 8.39[461,467] indicates that extremely high selectivities were obtained using ferrocene-based PhosOx ligands **548a,d**.[467] The fact that ligand **553a** (entry 3) gave poorer conversion and selectivity with acetophenone than ligand **548a** (entry 1) suggests the importance of the planar chirality in **548**. Additionally, modest-to-excellent selectivities were also obtained with the refractory alkyl methyl ketones (entries 20–22). Kinetic resolution of racemic aryl methyl carbinols can be also achieved using the ferrocene-based PhosOx ligands (yields up to 49% and ee's up to 99.8%).[467]

8.3.11.5. Additions of Dialkylzincs to Aldehydes

Asymmetric addition of a dialkylzinc reagent to an aldehyde, catalyzed by a Lewis base or a Lewis acid, is a viable alternative to enantioselective reduction of ketones as means to prepare enantiomerically enriched alcohols like **605** and **608**.[468] The HydrOx ligands are among the most effective Lewis bases for this addition reaction. The asymmetric induction results from complexation of the ligand with the dialkylzinc reagent prior to reaction with the aldehyde. Previously, it was established that phenyl addition proceeds overwhelmingly when an alkyl phenylzinc reagent is used.[469] Table 8.40 (Scheme 8.190) summarizes selected recent examples of asymmetric additions of alkylzinc reagents to a variety of aliphatic, aromatic, and heterocyclic aldehydes **607**.[170,374,378,470,471] Bolm and coauthors suggested that the ferrocenyloxazoline diselenide itself, **571** may serve as a precatalyst and that the active catalytic species may be the alkyl zinc selenide resulting from reaction of **571** and a dialkylzinc reagent.[374]

A linear correlation between the ee of the ferrocene ligand **572b** and ee of the product has been established.[370,472] However, there is a remarkable nonlinear effect observed[473,474] for the addition of dimethylzinc to benzaldehyde when employing a diastereomeric mixture of the HydrOx ligands **572a** and **573**.[472] Thus, 1-phenylethanol was produced in 95% ee even when a 50:50 mixture of **572a** and **573** was used. This discovery suggests that the diasteromeric mixture generated by preparation of these ligands may be useful as an asymmetric catalyst without tedious separation of the individual diastereomers.

TABLE 8.40. ASYMMETRIC ADDITION OF DIALKYLZINC REAGENTS TO ALDEHYDES

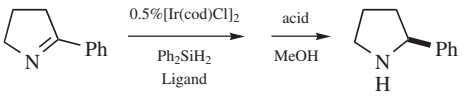
607 **608**

Scheme 8.190

Entry	**607** (R_1)	Dialkylzinc (R_2, R_3)	Ligand	L mol%	% Yield **608**	% ee	References
1	Me	Ph, Ph	**572a**	5	94	75 (*S*)	470
2	hexyl	Ph, Et	**452**	2	>80	74 (*S*)	378
3	$Ph(CH_2)_2$	Ph, Et	**452**	2	>80	76 (*S*)	378
4	$Ph(CH_2)_2$	Ph, Ph	**572a**	5	91	50 (*S*)	470
5	(*E*)-styryl	Ph, Et	**452**	2	>80	88 (*R*)	378
6	(*E*)-styryl	Ph, Et	**572a**	10	97	90 (*S*)	471
7	Bn	Ph, Et	**572a**	10	82	83 (*S*)	471
8	*i*-Pr	Ph, Et	**572a**	10	75	91 (*S*)	471
9	*t*-Bu	Ph, Et	**571**	5	85	65 (*S*)	374
10	*t*-Bu	Ph, Et	**572a**	10	68	94 (*S*)	471
11	*t*-Bu	Ph, Ph	**572a**	5	99	56 (*S*)	470
12	Ph	Et, Et	**574a**	10	>90 (conv.)	68 (*R*)	170
13	Ph	Et, Et	**574b**	10	>90 (conv.)	54 (*R*)	170
14	Ph	Et, Et	**574c**	10	>90 (conv.)	8 (*R*)	170
15	Ph	Et, Et	**575**	10	>90 (conv.)	75 (*R*)	170
16	Tol	Ph, Et	**452**	2	>80	85 (*R*)	378
17	Tol	Ph, Et	**571**	5	80	76 (*R*)	374
18	Tol	Ph, Et	**572a**	10	86	98 (*R*)	471
19	4-Cl–Ph	Ph, Et	**452**	2	>80	96 (*R*)	378
20	4-Cl–Ph	Ph, Et	**571**	5	85	84 (*R*)	374
21	4-Cl–Ph	Ph, Et	**572a**	10	86	97 (*R*)	471
22	4-Cl–Ph	Ph, Ph	**572a**	10	92	90 (*R*)	470
23	4-Cl–Ph	Ph, Ph	**572a**	5	99	82 (*R*)	470
24	4-Cl–Ph	Ph, Ph	**572b**	10	99	88 (*R*)	470
25	2-Br–Ph	Ph, Et	**452**	2	>80	83 (*R*)	378
26	2-Br–Ph	Ph, Et	**571**	5	65	77 (*R*)	374
27	2-Br–Ph	Ph, Et	**572a**	10	64	91 (*R*)	471
28	2-Br–Ph	Ph, Ph	**572a**	5	98	31 (*R*)	470
29	4-MeO–Ph	Ph, Et	**572a**	10	82	98 (*R*)	471
30	3-MeO–Ph	Ph, Et	**452**	2	>80	93 (*R*)	378
31	3-MeO–Ph	Ph, Et	**572a**	10	99	96 (*R*)	471
32	2,4,6-tri-Me–Ph	Ph, Et	**452**	2	>80	80 (*R*)	378
33	4-Ph–Ph	Ph, Et	**571**	5	86	85 (*R*)	374
34	4-Ph–Ph	Ph, Et	**572a**	10	98	97 (*R*)	471
35	1-naphthyl	Ph, Ph	**572a**	5	99	28 (*R*)	470
36	2-naphthyl	Ph, Et	**571**	5	96	76 (*R*)	374
37	2-naphthyl	Ph, Et	**572a**	10	70	96 (*R*)	471
38	ferrocenyl	Ph, Ph	**572a**	5	89	>96 (*R*)	470
39	2-furyl	Ph, Et	**452**	2	>80	95 (*R*)	378
40	2-furyl	Ph, Et	**572a**	10	99	95 (*R*)	471
41	2-pyridyl	Ph, Ph	**572a**	5	98	3 (*R*)	470

8.3.11.6. Hydrosilylation Reactions

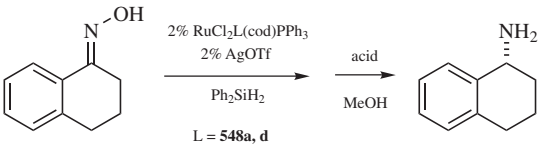
Nishiyama and Itoh reviewed asymmetric hydrosilylation and related reactions in 2000.[475] Although a number of catalytic systems are known to be very effective for the asymmetric hydrosilylation of ketones, reports of efficient catalysts for the analogous reaction with imines are limited.[476] Uemura and co-workers recently reported that ferrocene-based PhosOx **548** were effective ligands for iridium-catalyzed hydrosilylation of imines (Scheme 8.191).[477] The best results for 2-phenyl-1-pyrroline **609** were obtained using **548d** [>95% yield of (*S*)-2-phenyl-pyrrolidine **610**, 88% ee]. PhosOx **553a** also proved to be an effective catalyst and afforded **610** in comparable yield and ee. Ruthenium(II) catalysts gave similar results, but a rhodium(I) catalyst did not perform as well. Interestingly, the X-ray crystal structure of [Ir(**548a**)(cod)]BF_4 was very similar to that determined for [Rh(**548a**)(cod)]BF_4 (cod = 1,5-cyclooctadiene).



609 Ligand = **548**, **553a** **610**

Scheme 8.191

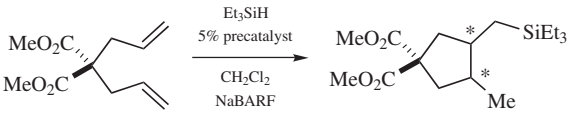
The same group also reported ruthenium-catalyzed asymmetric hydrosilylation of ketoximes (Scheme 8.192).[478] With (*E*)-3,4-dihydro-1(2*H*)-naphthalenone oxime **611**, the best results were obtained with PhosOx **548d** to afford (*R*)-1-aminotetralin **612** in 65% yield and 83% ee. Addition of AgOTf was somewhat beneficial to improve both the selectivities and yields. Although the authors did not elaborate on the role of AgOTf, it presumably activates the catalyst by removing a chloride resulting in a more effective cationic species.



611 **612**

Scheme 8.192

Palladium-catalyzed enantioselective hydrosilylation of carbon–carbon double bonds is well known.[479] Widenhoefer's group recently extended this reaction to cyclization of functionalized 1,6-dienes. The PyrOx ligands were excellent ligands for this reaction, and comparative evaluations of ligand performance for the hydrosilylation-cyclization of dimethyl diallylmalonate **613** have been reported (Scheme 8.193).[480,481] The trans-isomer of **614** is the preferred product and



613 **614**

Precatalyst = PdCl(Me)(**560**)

Scheme 8.193

diastereomeric excesses are usually >95%. The best enantioselectivity was obtained at −40 °C using the PyrOx ligand **560j** that gave the (*R*, *R*) isomer of **614** in 89% yield and 91% ee. A wide range of silanes and dienes can be used in this reaction with satisfactory results.[481] Employing disiloxanes such as pentamethyldisiloxane ($HSiMe_2OTMS$)[482] or 1-*tert*-butyl-3,3-dimethyl-1,1-diphenyldisiloxane ($HSiMe_2OTBDPS$)[483] in place of triethylsilane permits facile incorporation of a silyl-protected alcohol into **614**.

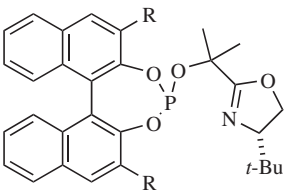
8.3.11.7. Michael Addition Reactions

Asymmetric Michael additions have been reviewed by Tomioka and Nagaoka in 1999[484] and Kanai and Shibasaki in 2000.[485] Reasonable enantioselectivities were obtained using PhosOx and Sulfox ligands. Pfaltz and Escher recently examined the use of the binaphthyl-based phosphite-oxazoline ligands **615–618** (Fig. 8.25) for the addition of diethylzinc to cyclic enones **619**.[486] The results of the enantioselective Michael addition are shown in Table 8.41 (Scheme 8.194). These same ligands were also evaluated in the Michael addition of diethylzinc to (*E*)-4-phenyl-3-buten-2-one **621** (Scheme 8.195). Ligand **615f** (a*S*) gave the best results and afford the (*S*) enantiomer of 4-phenyl-2-hexanone **622** in 99% yield and 87% ee.

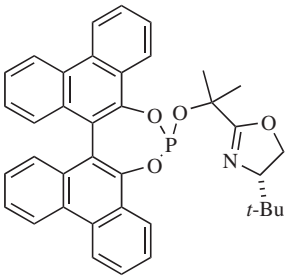
Williams' group observed low enantioselectivities for the Michael addition of a prochiral nucleophile, ethyl 2-cyanopropionate **623**, to methyl vinyl ketone **624** catalyzed by chiral platinum complexes (Scheme 8.196).[487] The NMR analysis indicated that these cationic Pt complexes act as Lewis acids toward nitriles. The X-ray crystal structure as well NMR analysis showed that the solvent ligand that is readily displaced by an organic substrate is situated cis to the nitrogen donor in the Pt complex and, therefore, is in a ''chiral pocket'' created by the oxazoline ring.

8.3.11.8. Cyclopropanation Reactions

Catalytic asymmetric cyclopropanations via carbene transfer to alkenes were reviewed by Singh and co-workers in 1997,[488] Doyle and Protopopova in 1998,[489] and mostly recently by Doyle in 2000.[490] The reaction can be catalyzed by copper,[491] rhodium,[492] and other metals.[493] Bis(oxazolines) are known to be among the most effective ligands for this cyclopropanation reaction (see Chapter 9).

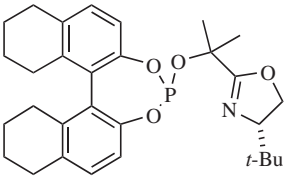


615

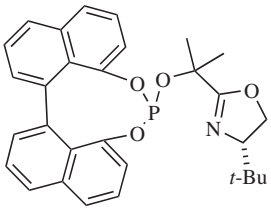


616

a: R = H
b: R = Me
c: R = Ph
d: R = 4-Ph-Ph
e: R = 2,4,6-tri-Me-Ph
f: R = 3,5-di-*t*-Bu-Ph



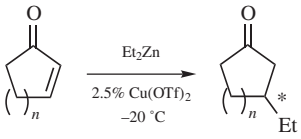
617



618

Figure 8.25. Binaphthyl-based phosphite-oxazoline ligands.

TABLE 8.41. ASYMMETRIC MICHAEL ADDITIONS TO CYCLIC ENONES[a]



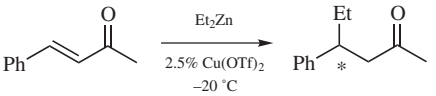
619 **620**

Ligand = **615**-**618** (a*S* and a*R* isomers)

Scheme 8.194

Entry	**619** (n)	Best Ligand	% Yield[b]	% ee
1	1	**615d** (a*R*)	41	94 (*R*)
2	2	**618** (a*R*)	69	90 (*R*)
3	2	**615b** (a*R*)	96	90 (*R*)
4	3	**616** (a*S*)	97	94 (NR)

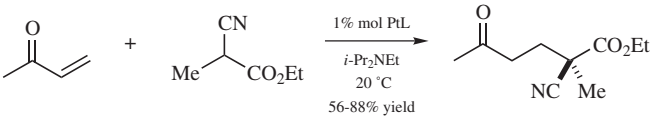
[a] Data from Ref. 486.
[b] Not reported: NR.



621 **622**

Ligand = **615**-**618** (a*S* and a*R* isomers)

Scheme 8.195



624 **623** **625**

16-25% ee

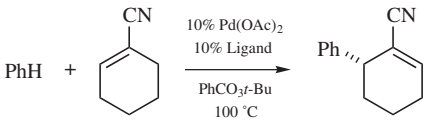
PtL = PtR(**553a**)$(CH_2Cl_2)^+$ BF_4^- , R = Me, Ph

Scheme 8.196

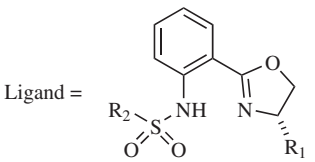
Mononuclear oxazolines have been less studied. Moderate enantioselectivities (up to 60%) were obtained using PyrOx as ligands for the copper(I)-catalyzed carbene-transfer reaction of ethyl diazoacetate to styrene.[494,495] However, the diastereoselectivities (cis/trans) in these reactions were generally poor.

8.3.11.9. Miscellaneous Catalytic Reactions

Mikami and co-workers reported the first examples of an asymmetric Fujiwara–Moritani reaction,[496] which is generally catalyzed by chiral Pd(II) complexes (Scheme 8.197).[497] Reaction of 1-cyano-1-cyclohexene **626** with benzene gave



626 **627** (40-49%)



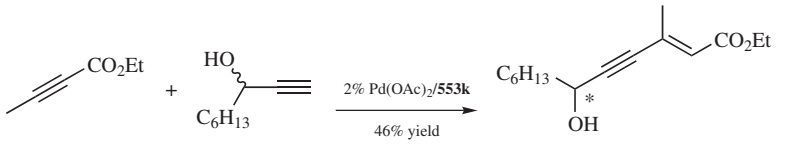
628

a: R_1 = *i*-Pr; R_2 = Tol
b: R_1 = *i*-Pr; R_2 = CF_3
c: R_1 = *t*-Bu; R_2 = CF_3
d: R_1 = *i*-Pr; R_2 = C_4F_9
e: R_1 = *i*-Pr; R_2 = 3,5-di-CF_3-Ph

Scheme 8.197

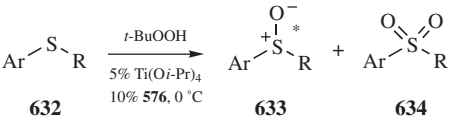
(6*R*)-6-phenyl-1-cyano-1-cyclohexene **627**. The optimum reaction conditions produced **627** in 25% yield and 44% ee using **628b** as the ligand.

Pfaltz and Lücking reported that alkyne couplings can be catalyzed efficiently by palladium–PhosOx catalysts.[498] High yields (up to 95%) were obtained for homocouplings of alkynes under solvent-free conditions. More interestingly, using an enantiomerically pure ligand effected kinetic resolution of racemic propargylic alcohols. For example, when ethyl 2-butynoate **629** was cross-coupled with a racemic propargyl alcohol **630** (2.2 equiv) in the presence of the PhosOx ligand **553k**, the eneynol **631** was obtained in 46% yield and 53% ee (Scheme 8.198).



Scheme 8.198

Recently, Feng and co-workers reported an asymmetric sulfide oxidation[499,500] catalyzed by titanium complexes bearing HydrOx ligands, for example, **576** (Scheme 8.199).[501] Enantioselectivities approached a level of synthetic utility for oxidation of aryl alkyl sulfides **632** although the yields of the sulfoxide **633** were poor due to overoxidation to the sulfone **634**. The overoxidation is especially significant for reactions with high enantioselectivity.



13–68% yield
0-96% ee

Ar = Ph, 4-Br-Ph-, 4-Me-Ph-, py; R = Me, Et, Bn

Scheme 8.199

8.3.12. Polymeric Oxazolines

Oxazolines undergo polymerization upon exposure to a variety of cationic initiators such as strong Lewis acids or strong protic acids. Copolymerization between different oxazolines of defined composition can be carried out in a random manner or in a controlled fashion resulting in block polymers. Alternatively, oxazolines can also be grafted onto other types of polymers. It is beyond the scope of this chapter to review in detail this enormous and important subject. Instead, the

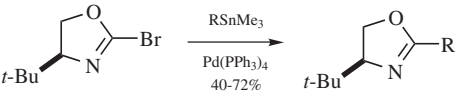
reader is referred to several excellent reviews that deal with polymerization of oxazolines.[502–508]

Polymeric oxazolines have diverse industrial applications and are used as amphiphilic copolymer membranes, as ink-receptive layers for ink-jet recording sheets, and as molded castings for solid rocket fuel motors. Polymeric oxazolines can be found as fiber binders in polymer composite materials, as components of interpenetrating polymer networks, as thermoset and powder coating cross-linking agents, and as glass fiber coatings. In addition, polymeric oxazolines are precursors to multifunctional cyclophosphazenes used as novel photoinitiators, are chain extenders or blend compatibilizers to modify elongation, viscosity, and impact strength of polymer blends, and are precursors for hyperbranched polyether–polyamide dendrimers.

Polymeric oxazolines have also been used as vehicles for controlled drug release[509,510] and DNA transfection,[511] as polymeric micelles, which serve as carriers for drug transport (e.g., paclitaxel),[512] and as formulation additives for controlled-release of insecticides.[513]

8.3.13. Miscellaneous Reactions

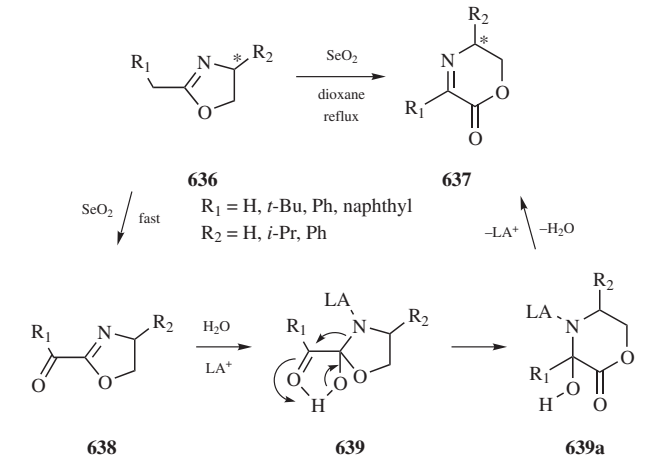
Achiral 2-stannyloxazolines are known to undergo Stille coupling with aromatic halides.[9] However, Stille couplings with chiral 2-halooxazolines were not reported until Meyers and Novachek prepared the requisite 2-bromooxazoline **365** (see Scheme 8.116) and successfully coupled **365** with a variety of alkynyl and alkenylstannanes to afford chiral 2-substituted oxazolines **635** in reasonable yields (Scheme 8.200).[329]



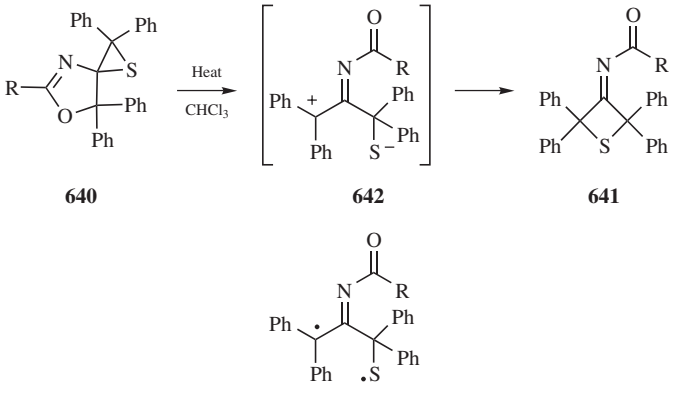
365 **635**

Scheme 8.200

Molinski and Shafer reported a novel synthesis of 1,4-oxazinones **637** by SeO_2-promoted oxidative rearrangement of 2-alkyloxazolines **636** (Scheme 8.201).[514] The best yields were obtained when R_1 was H, *t*-Bu, or aryl (60–94%). The yield was low (33%) when R_1 is *i*-Pr and no desired product was obtained when $R_1 = Me$. More interestingly, the stereochemical integrity of the oxazoline was preserved during the reaction. For $R_1 = H$, oxazinone **637** is a ''chiral glycine'' synthon and is useful for asymmetric synthesis of amino acids. The same group later corrected the mechanism proposed in the original paper. After careful kinetic and labeling studies, the authors proposed a mechanism involving rearrangement of intermediate **639** (Scheme 8.201).[515]



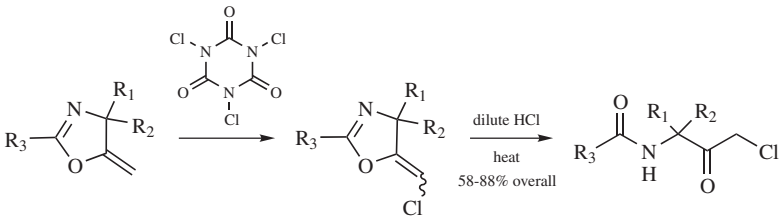
Scheme 8.201



Scheme 8.202

In a special case, the spirocyclic oxazoline **640** was found to be unstable and undergoes rearrangement to the thietane *N*-acylimine **641** (Scheme 8.202).[308,516] A zwitterionic intermediate **642** was proposed to account for the formation of **641**. A biradical **643** is also a possible intermediate for this rearrangement.

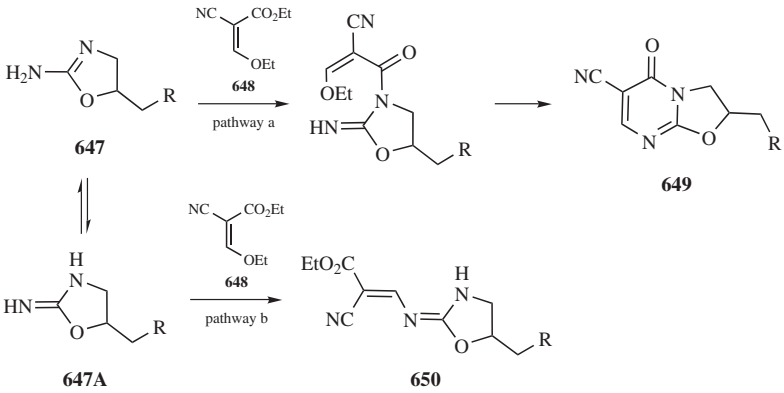
The C=C bond in a 5-(alkylidene)oxazoline **644** is activated for electrophilic reactions similar to that in analogous vinyl acetates. Rohm & Haas researchers exploited this property to prepare chloromethyl ketone fungicides **646** (Scheme 8.203).[517] The overall process constitutes an indirect chlorination of α-amido ketones since the 5-(vinylidene)oxazolines were prepared from α-amido ketones.



644 **645** **646**

R_1 = alkyl, aryl; R_2, R_3 = alkyl

Scheme 8.203



647 **649**

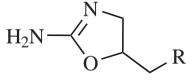
647A **650**

Scheme 8.204

In a series of papers, Jarry and co-workers demonstrated the utility of a 2-aminooxazoline **647** (Fig. 8.26) to prepare bicyclic heterocycles. This oxazoline undergoes annulation reactions with bifunctional electrophiles to give triazinones or pyrimidinones. Selected examples are summarized in Table 8.42.[518–522]

The structures of many of the products were confirmed by X-ray crystallography. The ring nitrogen of **647** is known to be more nucleophilic, and thus the initial reaction occurs there normally. This finding is consistent with the product distributions seen for entries 1 and 3. However, acyclic products were also observed when ethoxycarbonyl isocyanate (entry 2) or ethyl 3-ethoxy-2-cyanoacrylate **648** (entries 4 and 6) were used as electrophiles. These acyclic products appear to result from initial reaction with the 2-amino group. Based on a semiempirical computational study, the authors proposed dual pathways for the reaction of **647** with **648** to explain the cyclized and acyclic products (Scheme 8.204).[521] Thus, the cyclic product was proposed to arise from initial attack by the ring nitrogen (pathway a) whereas the azadiene arose from initial attack by the 2-amino group (pathway b).

TABLE 8.42. REACTION OF **647** WITH BIFUNCTIONAL ELECTROPHILES



647

Figure 8.26

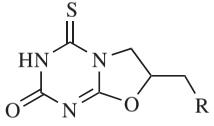
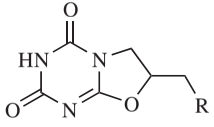
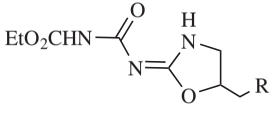
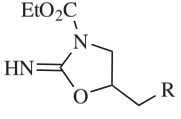
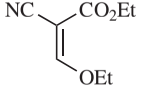
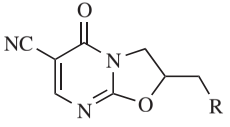
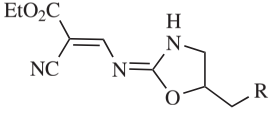
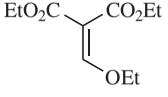
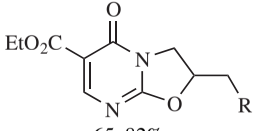
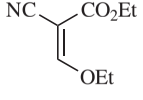
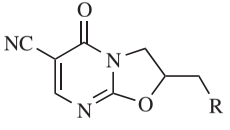
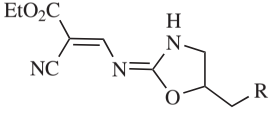
Entry	**647** (R)	E^+ (Conditions)	Cyclic Product	Acyclic Product	Reference
1	Cl, alkoxy, aryloxy, 2° amino	EtO_2CNCS $CHCl_3$, rt	 53–84%	None	518
2	*t*-BuO, ArO	EtO_2CNCO CH_2Cl_2, 0 °C to rt	 32–37%	 17–23%	519
3	MeO, PhO	EtO_2CCl Et_3N, acetone, rt	None	 68–71%	520

TABLE 8.42 (*Continued*)

Entry	**647** (R)	E^+ (Conditions)	Cyclic Product	Acyclic Product	References
4	PhO	 **648**	 46%	 41%	521
5	*t*-Bu, 2° amino		 65–82%	None	522
6	2° amino	 **648**	 43–49%	 37–39%	522

8.4. SUMMARY

2-Oxazolines continue to find numerous applications in organic synthesis. Since the last review by Meyers in 1994, new reagents have been introduced and new methods for their preparation have been uncovered. The popularity of this ring system in organic synthesis has grown due to the well-understood chemical behavior. The use of oxazolines in directed metalation reactions to construct complex molecules or as protecting groups is ubiquitous throughout the literature. Chiral oxazolines, readily accessible from a large pool of chiral amino alcohols, have been widely employed as auxiliaries in asymmetric syntheses. For example, an important extension in the area of aromatic substitution of aryloxazolines is the development of symmetrical, unsymmetrical and axially chiral biaryl synthesis. Similarly, oxazoline-directed nucleophilic additions to naphthalenes as a synthetic method for the preparation of dihydronaphthalenes have also expanded to include asymmetric versions with excellent stereochemical controls.

Another significant development in oxazoline chemistry is the application of oxazoline-containing ligands for asymmetric catalysis, such as palladium-catalyzed allylic substitutions, Heck reactions, hydrogenations, dialkylzinc additions to aldehydes, and Michael reactions. The discovery of diastereoselective metalation of chiral ferrocenyloxazolines has further expanded the availability of chiral ligands for metal-catalytic reactions.

Other applications of oxazolines have also been discovered. Anomeric oxazolines have now emerged as useful glycosyl acceptors in the glycosylation of sugars. 2-Alkenyloxazolines have been found to undergo asymmetric Michael addition and hetero-Diels–Alder reactions. Further explorations in these areas of oxazoline chemistry will undoubtedly continue and the list of new applications will grow.

Acknowledgments

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CHAPTER 9

Chiral Bis(oxazolines)

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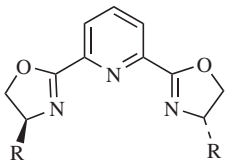
9.1. INTRODUCTION

As we have seen in the preceding chapters, oxazoles, and oxazolines come in many different forms and have shown numerous useful applications. In this chapter, we will discuss the chiral C_2-symmetric bis(oxazoline). This category of oxazolines has become a powerful tool in the realm of synthetic organic chemistry. The past several decades have seen impressive advances in synthetic medicinal agents for treatment of complex human diseases. Such progress has been fueled by the discovery and development of asymmetric processes since many therapeutic agents often possess multiple asymmetric centers. It is now regulation that these agents be prepared in an enantiomerically pure form. Thus, there has been a major emphasis on the synthesis of organic molecules having defined stereochemistry with a certain degree of predictability. The introduction of chiral C_2-symmetric bis(oxazoline) ligands in asymmetric synthesis has greatly enhanced this skill and led to many improvements in a variety of asymmetric organic transformations.

9.2. BIS(OXAZOLINE) LIGANDS

In 1989, the first bis(oxazoline) ligands were introduced by Nishiyama and coworkers.[1–2] These bis(oxazolinylpyridines), also called ''py-box'' ligands **1** were originally used for the enantioselective hydrosilylation of ketones (Fig. 9.1).

The bis(oxazoline) ligand bu-box **2** was introduced the following year by Masamune.[3] The effectiveness of this ligand was demonstrated in the cyclopropanation reaction of styrene with ethyl diazoacetate. Subsequently, 1991 led to several additions to the library of available bis(oxazoline) ligands. Some of these ligands include those introduced by Evans[4] **3** and Masamune[5] **4**, **5** that were utilized in cyclopropanation reactions. Corey[6] investigated Diels–Alder reactions using the phe-box ligand **6**, while ligand **7**, introduced by Helmchen,[7] was employed in hydrosilylation and transfer hydrogenation reactions. The remainder of the decade



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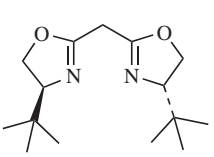
1b R = *i*-Pr
1c R = *t*-Bu
1d R = *i*-Bu



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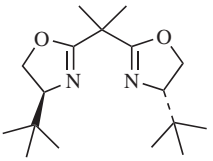

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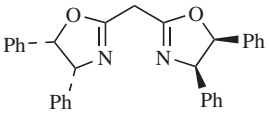

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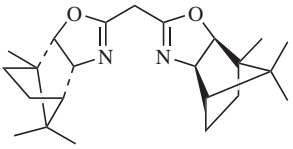

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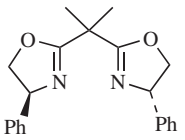

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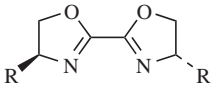

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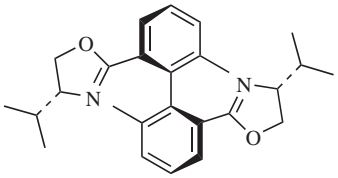
7b R = *i*-Pr
7c R = *t*-Bu



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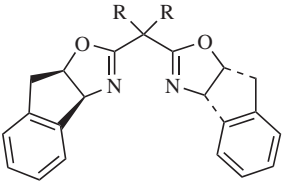

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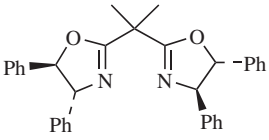
9b R = Me



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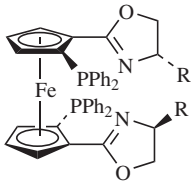
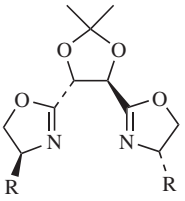
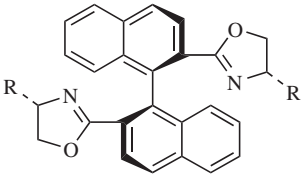


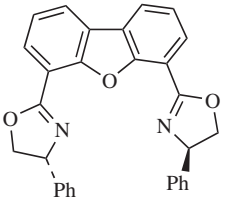
11a R = *i*-Pr
11b R = *t*-Bu



12a R = Ph
12b R = *i*-Pr
12c R = *t*-Bu



13a R = Ph
13b R = *i*-Pr
13c R = *t*-Bu



14

Figure 9.1. Bis(oxazoline) ligands.

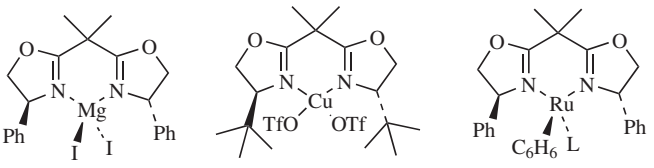
saw the introduction of additional ligands by Corey[8] **8** (cyclopropanation), Ghosh[9] and Davies[10] **9** (Diels–Alder), Desimoni[11] **10** (Diels–Alder), Ikeda[12] **11** (allylic substitution), Andersson[13] **12** (cyclopropanation), Hayashi[14] **13** (cyclopropanation), and Curran[15] **14** (Diels–Alder). This small sampling of bis(oxazoline) ligands and their related reactions demonstrates the power and versatility of this type of ligand in organic synthesis.

9.3. BIS(OXAZOLINE)-METAL COMPLEXES

Bis(oxazoline) ligands are generally used in conjunction with a metal cation that is coordinated by the nitrogen atoms of the ligand. The geometry of this complex controls the stereoselectivities observed in the various reactions involving them. Bis(oxazoline)–metal complexes exhibit a number of notable features. These include (1) the presence of a C_2-symmetric axis that reduces the number of possible transition states, (2) a metal complex that is conformationally constrained, and (3) a metal center in close proximity to the ligand donor that imposes a strong steric bias on the metal center.

9.3.1. Geometry of Ligand–Metal Complexes

Many different ligand–metal complexes have been used as catalysts for a variety of organic transformations.[16] These complexes are formed *in situ* by stirring the bis(oxazoline) ligand with various metal salts [CuOTf, $Cu(OTf)_2$, $Ni(ClO_4)_2 \bullet 6H_2O$, MgI_2, etc.]. Some of the most commonly used metals are copper, magnesium, and ruthenium. It has been proposed by Corey and Ishihara that the magnesium(II) complex of the phe-box ligand **15** adopts a tetrahedral geometry around the metal.[17] In contrast, Evans and co-workers have speculated that the copper(II) complex of the bu-box ligand **16** adopts a square-planar geometry about the metal center, as shown in Figure 9.2.[4] The difference between these two conformations, tetrahedral



15
tetrahedral

16
square planar

17a L = OH_2
17b L = NH_3
17c L = NH_2Me
17d L = NH_2Bu
tetrahedral

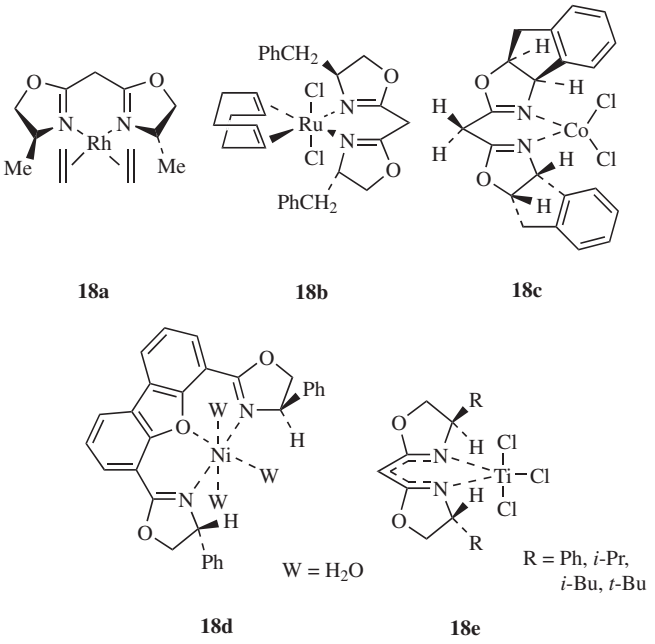
Figure 9.2. Bis(oxazoline)–metal complexes.

and square planar, leads to reversal of enantioselectivity, particularly in the Diels–Alder reaction.[4,17]

One of the most studied ligand–metal complexes is the bis(oxazoline)–ruthenium(II) complex.[18–23] Kurasowa and co-workers proposed that the aqua and amine complexes of bis(oxazoline)–ruthenium(II) **17a–d** also adopt a tetrahedral geometry about the metal center.[21,22] These are only a few of many examples of the complexes formed between a variety of transition metals and bis(oxazoline) ligands that have been studied.[16]

9.3.2. X-ray Crystal Structure

Various X-ray crystal structures of metal–ligand complexes provided evidence of the geometry of the complexes in the solid state, even though the structure of these complexes may differ in solution. The first crystal structure of a bis(oxazoline)–metal complex was determined in 1994 by Brown and co-workers.[24] This group crystallized and elucidated the structure of *N*,*N*-bis-[2-((4*S*)-(methyl)-1,3-oxazolinyl)]methane-bi(η^2ethene)rhodium(I), **18a**, as depicted in Figure 9.3. The key features of this crystal structure include the C_2-axis of symmetry, the axial positions of the methyl groups and the orientation of the ethene molecules, orthogonal to the complexation square plane. In 1995, Woodward and co-workers were able to crystallize and determine the structure of benzylbis(oxazoline) with ruthenium



18a **18b** **18c**

18d **18e**

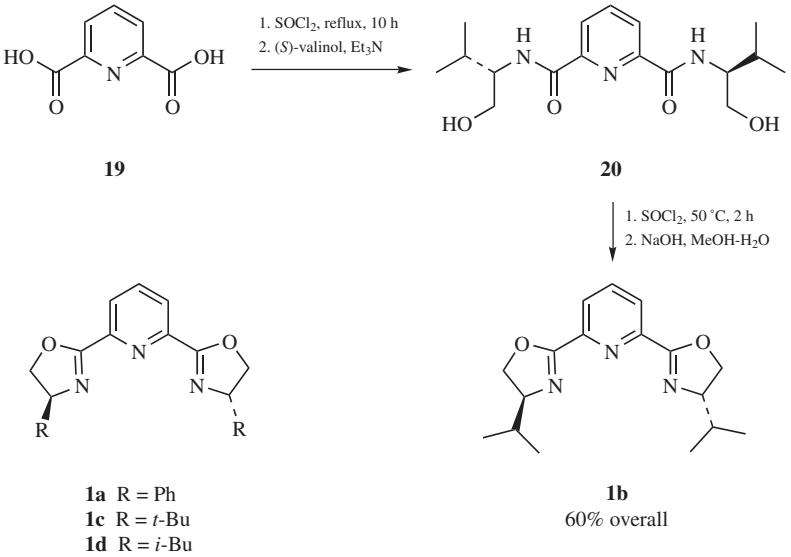
Figure 9.3. Bis(oxazoline)–metal crystal structures (two-dimensional representation).

and cyclooctadiene **18b**.[20] Ghosh and co-workers determined the structure of indabox **9a** with cobalt **18c**.[16] Kanemasa and Curran resolved the cationic aqua complex of DBF-box **18d**.[15] A number of structures of titanium–bis(oxazoline) complexes **18e** have been determined by Singh through various spectroscopic techniques.[23]

Other ligand–metal complexes whose crystal structures have been determined include the complex of *i*-pr-box with tungsten tetracarbonyl,[20] Corey's phe-box ligand complexed to ruthenium,[19,21,22] along with several Nishiyama-type py-box ligands coordinated to palladium[25,26] and molybdenum.[27]

9.4. SYNTHESIS OF BIS(OXAZOLINE) LIGANDS

Optically active natural and unnatural amino acids as well as various cyclic amino alcohols have been utilized in the synthesis of a wide variety of bis(oxazoline) ligands. As previously mentioned, the first bis(oxazoline) ligands, py-box **1a–d**, were synthesized by Nishiyama and co-workers in 1989.[1,2] The common material for their syntheses was pyridine 2,6-dicarboxylic acid **19**. Conversion of **19** to the acid chloride was achieved by treatment with thionyl chloride, as illustrated in Figure 9.4. This was followed by condensation with (*S*)-valinol in the presence of triethylamine. Conversion of the resulting bis(amidodiol) **20** to py-box-*ip* **1b** was achieved by sequential treatment of **20** with thionyl chloride at 50 °C followed by cyclization with aqueous sodium hydroxide in methanol to afford py-box-*ip* **1b** in 60% overall yield. The same synthetic scheme can be used to obtain the other



19 **20**

1a R = Ph
1c R = *t*-Bu
1d R = *i*-Bu

1b
60% overall

Figure 9.4. Synthesis of py-box-*ip* ligand **1b**.

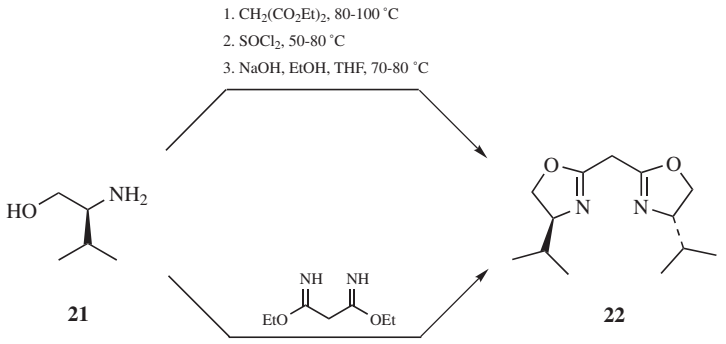


Figure 9.5. Synthesis of *i*-pr-box ligand **22**.

isomer and the ligands containing different functionalities on the bis(oxazolines) (structures **1a**, **1c**, and **1d**) by altering the amino alcohol used.

Masamune and co-workers reported that *i*-pr-box **22** can also be obtained from (*S*)-valinol by a similar strategy (see above).[3] Thus, **21** was reacted with diethylmalonate and the resulting diamide was treated with thionyl chloride followed by sodium hydroxide in a mixture of ethanol and tetrahydrofuran (THF) to yield *i*-pr-box **22** (Fig. 9.5). The synthesis of *i*-pr-box **22** can also be achieved directly by treatment of **21** with diethyl iminomalonate in the presence of triethylamine.[5]

Evans and co-workers synthesized bu-box **3** starting from commercially available (*S*)-*tert*-leucine.[4] Lithium aluminum hydride reduction of (*S*)-*tert*-leucine afforded the amino alcohol **23** which, as shown in Figure 9.6, was acylated with dimethylmalonyl dichloride **24** to provide the corresponding bis(amidodiol) **25** in

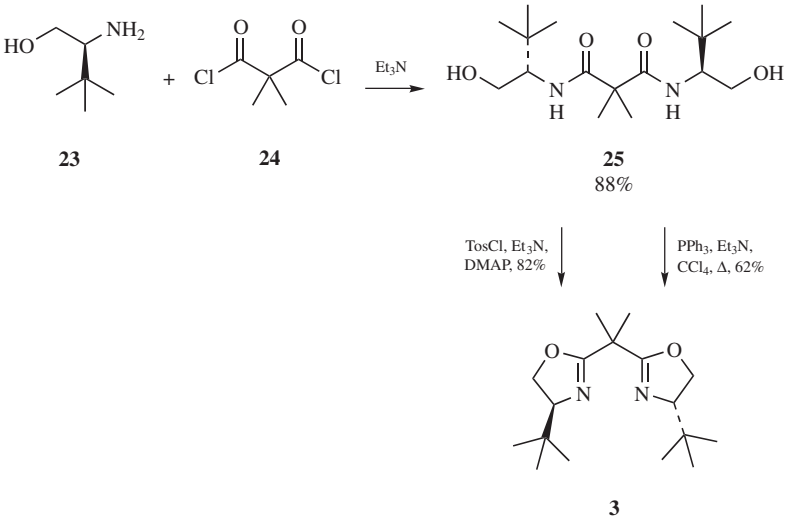


Figure 9.6. Synthesis of bu-box ligand **3**.

88% yield. Cyclization was achieved by treatment with triphenylphosphine and triethylamine in carbon tetrachloride followed by heating to yield bu-box **3** in 62% yield.

In 1998, Evans published an improved synthesis of bu-box **3** starting from the same amino acid.[28] The updated synthesis began with sodium borohydride–iodine reduction to afford amino alcohol **23** followed again by treatment with dimethylmalonyl dichloride **24** to afford **25** in 88% yield (from **23**). Cyclization was achieved by treatment of **25** with toluenesulfonyl chloride and triethylamine in the presence of a catalytic amount of dimethylaminopyridine to afford bu-box **3** in 82% yield (Fig. 9.6).

Corey and Ishihara's synthesis of phe-box ligand **29** began with the trifluoroacetyl derivative of (*S*)-phenylglycine **26**. Treatment of **26** with methylmagnesium iodide, as shown in Figure 9.7, followed by potassium hydroxide in methanol afforded amino alcohol **27** in 88% yield (2 steps).[17] This was then acylated with dimethylmalonyl dichloride **24** and triethylamine followed by cyclization using methanesulfonic acid at reflux to afford phe-box ligand **29** in 78% yield.

Two other synthetic approaches to ring closure can be illustrated with Masamune's protocol[3] for the construction of ligand **31** and Desimoni's protocol[11] for the construction of the structurally related ligand **10** (Fig. 9.8). Thus, starting from bisamide **30**, Masamune and co-workers effected ring closure through treatment with dichlorodibutylstannane in refluxing xylene to afford bis(oxazoline) **31**. Desimoni's protocol called for treatment of **30** first with methanesulfonyl chloride and triethylamine in dichloromethane followed by heating with aqueous sodium hydroxide in ethanol. This yielded the isomeric bis(oxazoline) **10**.

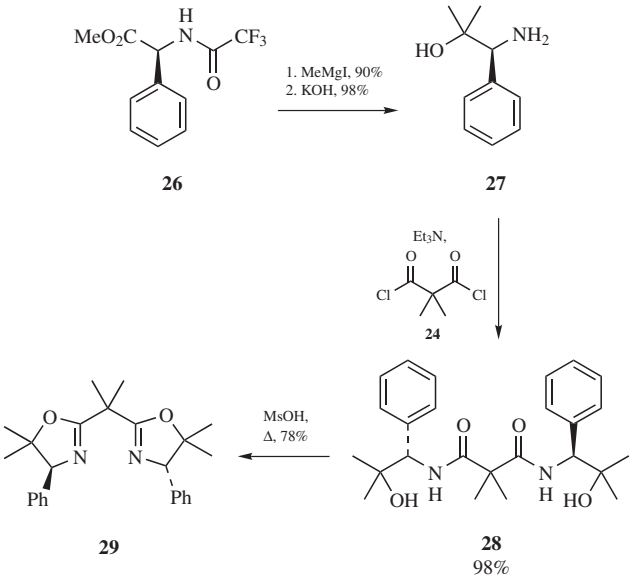


Figure 9.7. Synthesis of phe-box ligand **29**.

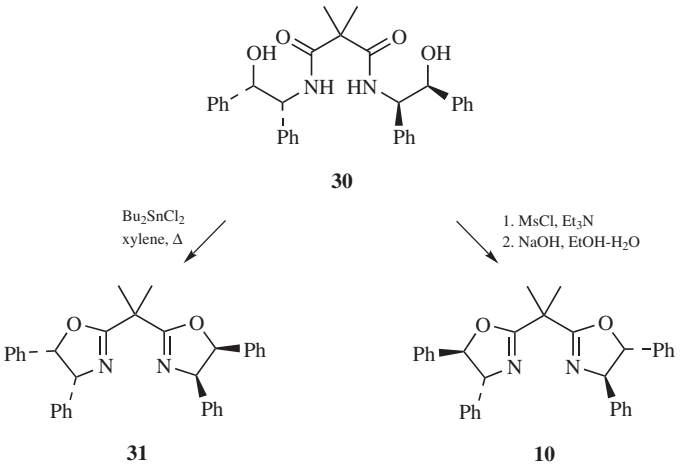


Figure 9.8. Synthesis of tetraphenyl bis(oxazoline) ligands **31** and **10**.

The constrained bis(oxazolines) **9a** and **9b** can be constructed beginning with malononitrile **32** as shown by Ghosh and co-workers.[9] Thus, treatment of **32** with anhydrous hydrochloric acid in dioxane, as shown by Lehn and co-workers,[29] yielded imidate salt **33** (Fig. 9.9). Condensation of the imidate salt with commercially available (1*S*,2*R*)-1-aminoindan-2-ol afforded the conformationally constrained bis(oxazoline) inda-box **9a**. Alkylation at the bridging methylene of **9a** was carried out by Davies and co-workers.[30] Treatment of **9a** with lithium diisopropylamide followed by alkylation with methyl iodide afforded **9b**. Alternatively, alkylation with diiodoalkanes incorporated ring systems at the bridging position (structures **34a–d**).

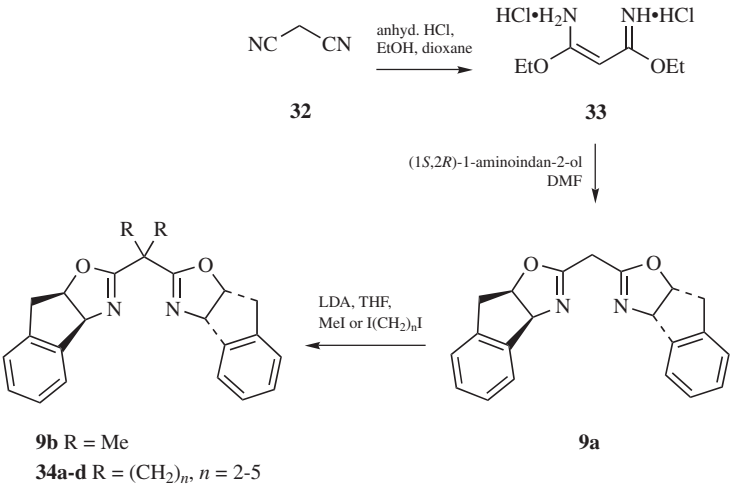


Figure 9.9. Synthesis of inda-box ligands **9a,b** and **34a–d**.

9.5. CARBON–CARBON BOND-FORMING REACTIONS

Chiral C_2-symmetric bis(oxazoline) ligands have become very important in organic synthesis since their introduction in 1989. They have allowed chemists control over the stereochemical outcome of many different types of reactions. Their utility in many carbon–carbon bond forming reactions is especially well documented.

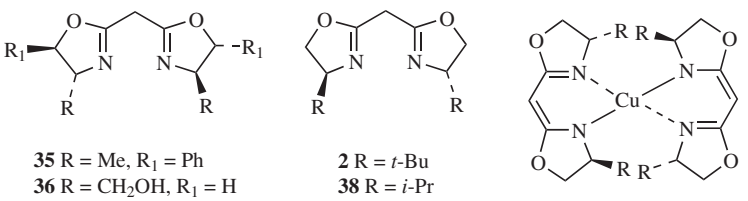
9.5.1. Cyclopropanation

One of the many carbon–carbon bond-forming reactions that have been studied using the chiral C_2-symmetric bis(oxazoline) ligands is the cyclopropanation reaction. This reaction has been extensively studied by many independent research groups.

9.5.1.1. Stryene and Ethyl Diazoacetate

Of the cyclopropanation reactions studied, the reaction between styrene and ethyl diazoacetate has become the benchmark for determining the utility of a bis(oxazoline) ligand in cyclopropanations. In 1990, Masamune and co-workers introduced several bis(oxazoline) ligands including **2** and **35–40** as catalysts for the cyclopropanation of styrene with ethyl diazoacetate.[3] The reactive species in these reactions were determined to be the bis(oxazoline) dimers of type **2a** and **38a–40a**, as shown in Figure 9.10.

This complex was generated by treatment of ligand **2**, for example, with *n*-butyllithium followed by addition of 0.5 equiv of copper(II) chloride. This species was purified by column chromatography and used in 1 mol % (relative to ethyl diazoacetate) in the reaction between styrene (3 equiv) and ethyl diazoacetate (1 equiv). The results of these experiments are summarized in Table 9.1 (Fig. 9.11). As can be seen from these results, the yields range from 72–88%, the trans/cis ratios are all approximately equal (∼70:30), but the enantioselectivities for the isomers



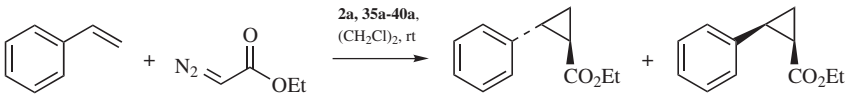
35 R = Me, R_1 = Ph
36 R = CH_2OH, R_1 = H
37 R = Et, R_1 = H

2 R = *t*-Bu
38 R = *i*-Pr
39 R = Ph
40 R = Bn

2a, 38a-40a

Figure 9.10. Masamune's bis(oxazoline)-Cu(II) complexes.

TABLE 9.1. MASAMUNE'S Cu(II)-BIS(OXAZOLINE)-CATALYZED CYCLOPROPANATION[a]



41 **42** **43** **44**

Figure 9.11

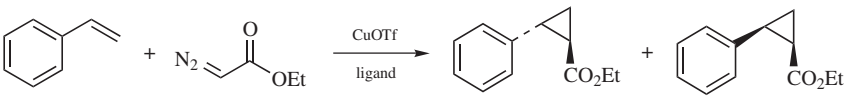
Ligand	Isolated % Yield	trans/cis (**43**:**44**)	trans (**43**) ee (config)	cis (**44**) ee (config)
35a	78	71:29	28% (1*S*,2*S*)	30% (1*S*,2*R*)
36a	88	75:25	48% (1*S*,2*S*)	36% (1*S*,2*R*)
37a	78	72:28	19% (1*S*,2*S*)	31% (1*S*,2*R*)
38a	72	71:29	46% (1*R*,2*R*)	31% (1*R*,2*S*)
39a	76	71:29	36% (1*R*,2*R*)	15% (1*R*,2*S*)
40a	81	70:30	60% (1*R*,2*R*)	52% (1*R*,2*S*)
2a	80	75:25	90% (1*R*,2*R*)	77% (1*R*,2*S*)

[a]Data from Ref. 3.

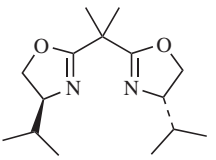
are best with the complex derived from the bulky bu-box ligand **2a** ($ee = 90\%$ for the trans isomer and 77% for the cis).

In 1991, Evans and co-workers employed CuOTf-derived complexes of bis-(oxazoline) ligands **2**, **3**, **7b**, **38**, and **45** in the same cyclopropanation reaction of

TABLE 9.2. EVAN'S Cu(I)-BIS(OXAZOLINE)-CATALYZED CYCLOPROPANATION



41 **42** **43** **44**



45

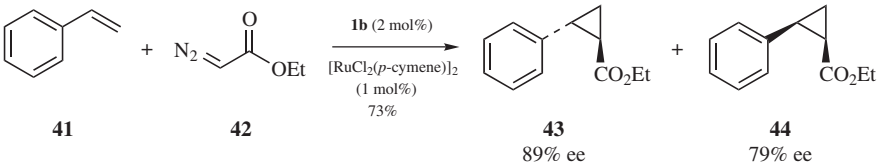
Figure 9.12

Ligand	trans/cis (**43**:**44**)	trans (**43**) ee (config)	cis(**44**) ee (config)
2	77:23	98% (1*R*,2*R*)	93% (1*R*,2*S*)
3	73:27	99% (1*R*,2*R*)	97% (1*R*,2*S*)
7b	66:34	3% (1*R*,2*R*)	8% (1*R*,2*S*)
38	64:36	64% (1*R*,2*R*)	48% (1*R*,2*S*)
45	69:31	49% (1*R*,2*R*)	45% (1*R*,2*S*)

[a]Data from Ref. 4.

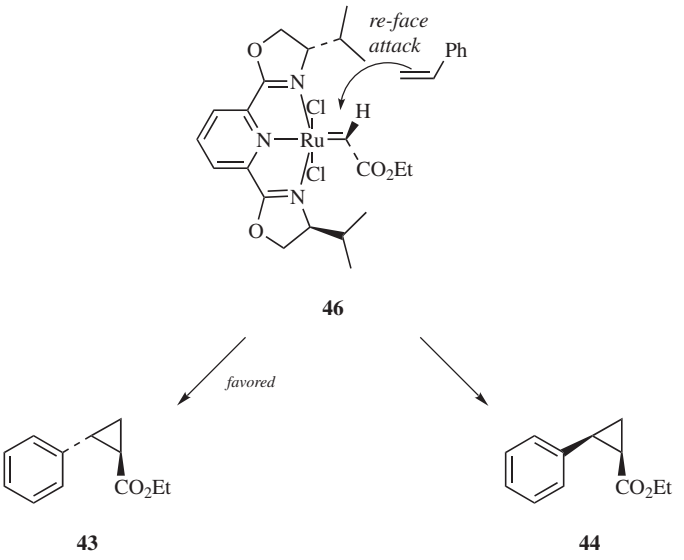
styrene and ethyl diazoacetate.[4] The active catalyst was prepared by mixing bis(oxazoline) and CuOTf in a 1:1 ratio. It has been shown that the bulky bu-box ligands **2** and **3** provided the best selectivities, for both trans/cis ratio and enantioselectivity (Table 9.2). Evans ligand **3** containing the geminal methyl groups exhibited a slight improvement in enantioselectivities over Masamune's bu-box **2**. These results show that the presence of a six- rather than five-membered metal chelating species (**3** vs. **7b**), the presence of geminal methyl groups to prevent enolization (**3** vs. **2**) and the bulky *tert*-butyl groups (**3** vs. **45**) are optimal for cyclopropanation using this type of bis(oxazoline) ligand (Fig. 9.12).

Other types of bis(oxazoline) ligands have been tested using the reaction of styrene and ethyl diazoacetate. Of note is Nishiyama's py-box-*ip* ligand **1b**, which was used in 2 mol% and with $[Ru(II)Cl_2(p\text{-cymene})]_2$ as a metal source.[31,32] The best result from these conditions was a yield of 73%, trans/cis ratio of 91:9 with a trans enantiomeric excess (ee) of 89% and a cis ee of 79%, as shown in Figure 9.13. The selectivity observed in Nishiyama's reaction can be explained by the following model, shown in Figure 9.14.[31,32] This model shows the ligand–metal–substrate



41 **42** **43** 89% ee **44** 79% ee

Figure 9.13. Nishiyama's Ru(II)-py-box-*ip* catalyzed cyclopropanation.



43 **44**

Figure 9.14. Transition state for cyclopropanation using Ru(II)-py-box-*ip*.

complex of py-box-*ip* **1b** with ruthenium(II) chloride and diazoacetate. The orientation of the styrene attacking from the *re*-face is controlled by the isopropyl substituent on the ligand favoring the formation of product **43** containing the *trans*-(1*R*,2*R*) stereochemistry.

Table 9.3 contains a sampling of various other bis(oxazoline) ligands that have been used in the cyclopropanation reaction of styrene with ethyl diazoacetate (Table 9.3, Fig. 9.15).[33–40]

9.5.1.2. Styrene and Other Diazoacetates

Many ligands have also been evaluated with other alkyl diazoacetates. Of note are the sterically demanding diazoacetate esters, such as *tert*-butyl and menthyl diazoacetates (Table 9.4, Fig. 9.16). Masamune and co-workers examined bu-box ligand **2a** using styrene with both *l*-(−)-menthyl and *d*-(+)-menthyl diazoacetates.[3] It has been shown that the use of these sterically more demanding diazoacetates led to higher selectivities for both trans/cis isomers and enantioselectivities (trans/cis = 86:14; trans = 98% ee; cis = 96% ee for *l*-(−)-menthyl diazoacetate). Evans[4] and Nishiyama[31] investigated their ligands, **3** and **1b**, respectively, with *tert*-butyl diazoacetate. Evans reported a yield of 75%, trans/cis ratio of 81:19, trans ee of 96% and cis ee of 93%. Nishiyama's py-box-*ip* ligand **1b** exhibited similar results (trans/cis = 97:3; trans = 94% ee; cis = 85% ee).

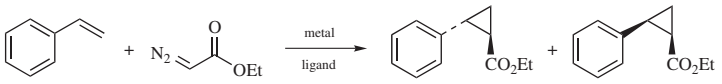
9.5.1.3. Miscellaneous Cyclopropanations

Cyclopropanations using bis(oxazoline) catalysts are not limited to reactions of styrene; many different types of olefins can be used in cyclopropanations. The work of Masamune and co-workers included an example using 2,3,3-trimethylbutene with his bu-box complex **2a** and *l*-(−)-menthyl diazoacetate.[3,5] The product was obtained in 60% yield, trans/cis ratio of 95:5, trans ee of 80% and cis ee of 91%.

Silyl enol ethers can also be used in the cyclopropanation reaction. Reissig showed that the reaction between methyl diazoacetate **53** and various enol ethers **52a–c** using bu-box ligand **3** proceeded in moderate yields, as shown in Table 9.5 (Fig. 9.17*a*), with trans/cis ratios up to 97:3 and ee between 32 and 49%.[35] Pfaltz showed that cyclic enol ethers can be used as well.[41] Cyclopentenyl enol ether **55** proceeded with methyl diazoacetate **53** and bu-box ligand **3** to afford the cyclopropanation products in 56% yield, a trans/cis ratio of 27:73, trans ee of 87% and cis ee of 92% (Fig. 9.17*b*, p. 544).

Intramolecular cyclopropanations are also well documented in the literature. It has been shown by Koskinen and co-workers that the cyclopropanation of diazomalonate **57**, illustrated in Figure 9.18, using benzyl bis(oxazoline) **40** and copper(I) triflate afforded lactone **58** in 73% yield and 32% ee.[36] Nishiyama and co-workers showed that cyclopropanations of diazoacetates **59a–c** proceeded in yields ranging from 79–93% and 24–86% ee (Table 9.6, Fig. 9.18, p. 544).[32]

TABLE 9.3. CYCLOPROPANATIONS USING VARIOUS METALS AND LIGANDS

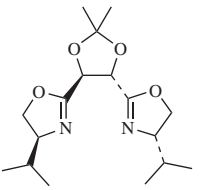


41 **42** **43** **44**

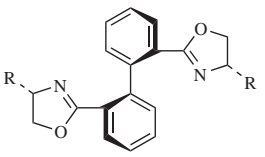
Figure 9.15*a*

Ligand	% Yield	trans/cis (**43**:**44**)	trans (**43**) ee (config)	cis (**44**) ee (config)	Reference
12b[a,c]	76	70:30	84% (1*R*,2*R*)	65% (1*R*,2*S*)	33
47[a,c]	85	70:30	84% (1*R*,2*R*)	85% (1*R*,2*S*)	34
13a[a,d]	43	67:33	55% (1*R*,2*R*)	57% (1*R*,2*S*)	14
13b[a,d]	58	60:40	62% (1*R*,2*R*)	61% (1*R*,2*S*)	14
13c[a,d]	59	59:41	87% (1*R*,2*R*)	86% (1*R*,2*S*)	14
12a[a,c]	64	80:20	38% (1*R*,2*R*)	21% (1*R*,2*S*)	37
48a[a,c]	72	74:26	49% (1*R*,2*R*)	59% (1*R*,2*S*)	38
48b[a,c]	69	68:32	74% (1*R*,2*R*)	84% (1*R*,2*S*)	38
49[b,c]	51	90:10	60% (1*S*,2*S*)		39
50a[a,c]	83	62:38	75% (1*R*,2*R*)	85% (1*R*,2*S*)	40
50b[a,c]	70	75:25	69% (1*R*,2*R*)	66% (1*R*,2*S*)	40
50c[a,c]	85	70:30	18% (1*R*,2*R*)	17% (1*R*,2*S*)	40
50d[a,c]	69	71:29	36% (1*R*,2*R*)	28% (1*R*,2*S*)	40
50e[a,c]	91	65:35	57% (1*R*,2*R*)	51% (1*R*,2*S*)	40
50f[a,c]	85	66:34	64% (1*R*,2*R*)	60% (1*R*,2*S*)	40

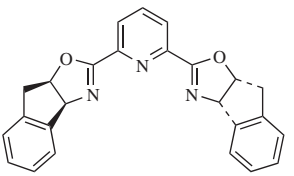
[a]Metal = CuOTf.
[b]Metal = $[RuCl_2(p\text{-cymene})]_2$.
[c]A 1 mol% catalyst.
[d]A 2 mol% catalyst.



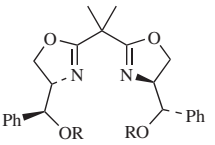
47



48a R = *i*-Pr
48b R = *t*-Bu



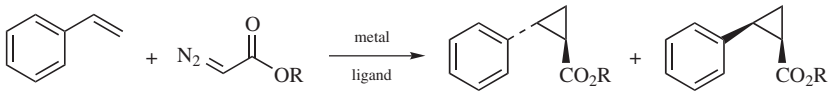
49



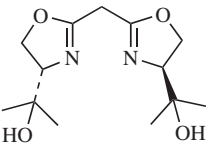
50a R = COPh
50b R = H
50c R = COMe
50d R = Me
50e R = Bn
50f R = $SiMe_2t$-Bu

Figure 9.15*b*. Cyclopropanation ligands.

TABLE 9.4. CYCLOPROPANATION OF DIAZOACETATE ESTERS



41 **42** **43** **44**

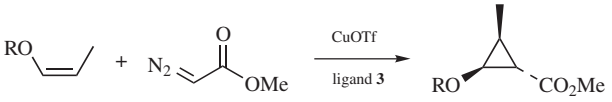


51

Figure 9.16

Metal	Ligand	R	% Yield	trans/cis (**43**:**44**)	trans (**43**) ee (config)	cis (**44**) ee (config)	Reference
$CuCl_2$	**2a**	*l*-menthyl	72	86:14	98% (1*R*,2*R*)	96% (1*R*,2*S*)	3
$CuCl_2$	**2a**	*d*-menthyl	71	84:16	98% (1*R*,2*R*)	80% (1*R*,2*S*)	3
CuOTf	**3**	*t*-Bu	75	81:19	96% (1*R*,2*R*)	93% (1*R*,2*S*)	4
CuOTf	**3**	BHT	85	94:6	99% (1*R*,2*R*)		4
CuO*t*-Bu	**51**	*d*-menthyl	-	83:17	90% (1*S*,2*S*)	90% (1*S*,2*R*)	33, 34
Ru	**1b**	*d*-menthyl	85	95:5	86% (1*R*,2*R*)	95% (1*R*,2*S*)	31
Ru	**1b**	*l*-menthyl	87	95:5	95% (1*R*,2*R*)	76% (1*R*,2*S*)	31
Ru	**1b**	*t*-Bu	81	97:3	94% (1*R*,2*R*)	85% (1*R*,2*S*)	31

TABLE 9.5. CYCLOPROPANATION OF ENOL ETHERS[a]

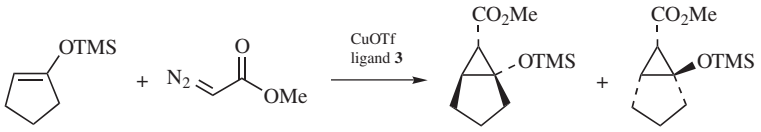


52a R = Bu **53** **54a-c**
52b R = *i*-Pr
52c R = $SiMe_3$

Figure 9.17*a*

R	% Yield	trans (1α, 2β, 3β)/ cis (1α, 2α, 3α)	trans % ee
Bu	48	90:10	32
i-Pr	54	97:3	40
$SiMe_3$	39	97:3	49

[a]Data from Ref. 35.

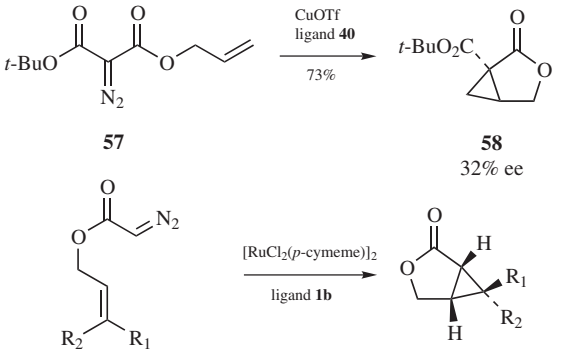


55 **53** 56% yield, **56a:56b** = 27:73 **56a** 87% ee **56b** 92% ee

Figure 9.17*b*. Cyclopropanation of a cyclic enol ether.

The power of chiral C_2-symmetric bis(oxazolines) in cyclopropanation reactions has also been exhibited in total synthesis. One example is Corey and co-workers' synthesis of sirenin **63** using bis(oxazoline) ligand **8** (Fig. 9.19).[8] They showed that the intramolecular cyclopropanation of diazo derivative **61** proceeded in 77% yield and with 90% ee. Shibasaki and co-workers constructed prostratin **67** through the intermediate cyclopropane **66**, also shown in Figure 9.19. Using bis(oxazoline) ligand **64** and copper(I) triflate-derived catalyst, compound **66** was prepared in 70% yield and 92% ee from diazo derivative **65**.[42]

TABLE 9.6. INTRAMOLECULAR CYCLOPROPANATIONS[a]



57 **58** 32% ee

59a R_1 = Ph, R_2 = H
59b R_1 = H, R_2 = Ph
59c R_1 = R_2 = Me

60a R_1 = Ph, R_2 = H
60b R_1 = H, R_2 = Ph
60c R_1 = R_2 = Me

Figure 9.18

Product	% Yield	% ee
60a	93	86
60b	79	24
60c	91	76

[a]Data from Ref. 32.

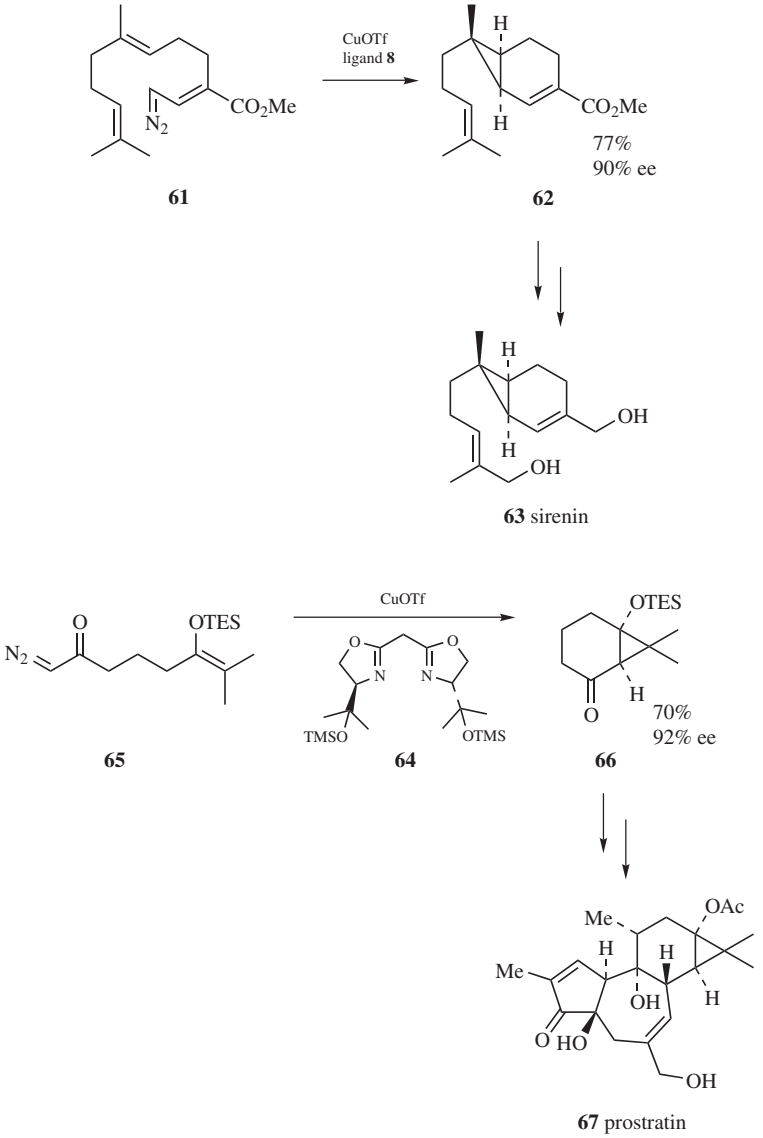


Figure 9.19. Natural product syntheses using cyclopropanations.

9.5.2. Diels–Alder Reactions

The Diels–Alder reaction is one of the most powerful reactions in organic synthesis. It allows the formation of up to four contiguous chiral centers in one reaction. Asymmetric Diels–Alder reactions,[43] in particular catalytic asymmetric Diels–Alder reactions,[16,44] have become very important because they allow

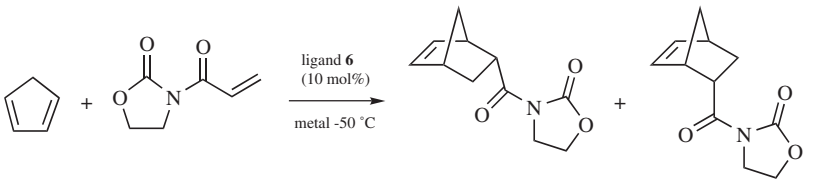
chemists to construct these chiral centers in an efficient and stereopredictable manner.

9.5.2.1. Cyclopentadiene and 3-Acryloyl-1,3-oxazolidin-2-one

Metal complexes of bis(oxazoline) ligands are excellent catalysts for the enantioselective Diels–Alder reaction of cyclopentadiene and 3-acryloyl-1,3-oxazolidin-2-one. This reaction was most commonly utilized for initial investigation of the catalytic system. The selectivity in this reaction can be twofold. Approach of the dienophile (in this case, 3-acryloyl-1,3-oxazolidin-2-one) can be from the endo or exo face and the orientation of the oxazolidinone ring can lead to formation of either enantiomer (*R* or *S*) on each face. The ideal catalyst would offer control over both of these factors leading to reaction at exclusively one face (endo or exo) and yielding exclusively one enantiomer. Corey and co-workers first experimented with the use of bis(oxazoline)–metal complexes as catalysts in the Diels–Alder reaction between cyclopentadiene **68** and 3-acryloyl-1,3-oxazolidin-2-one **69**;[6] the results are summarized in Table 9.7 (Fig. 9.20). For this reaction, 10 mol% of various iron(III)-phe-box **6** complexes were utilized at a reaction temperature of −50 °C for 2–15 h. The yields of cycloadducts were ∼85%. The best selectivities were observed when iron(III) chloride was used as the metal source and the reaction was stirred at −50 °C for 15 h. Under these conditions the facial selectivity was determined to be 99:1 (endo/exo) with an endo ee of 84%.

Corey and co-workers subsequently examined the stereochemical outcome by using substituted phe-box ligand **29** in the same reaction.[17] Complexes of iron(III) and magnesium(II) were investigated (Table 9.8, Fig. 9.21). It has been shown that

TABLE 9.7. COREY'S DIELS–ALDER REACTION USING Fe(III) HALIDES[a]



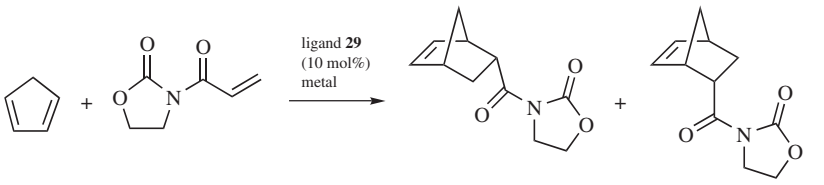
68 **69** **70** (*endo R*) **71** (*endo S*)

Figure 9.20

Metal	Time (h)	% Yield	endo/exo	endo ee (config)
$FeCl_2I$	15	85	97:3	80% (*R*)
$FeCl_3$	15		99:1	84% (*R*)
FeI_3/I_2	2	95	96:4	82% (*R*)

[a]Data from Ref. 6.

TABLE 9.8. COREY'S DIELS–ALDER REACTION USING Fe(III) OR Mg(II) SALTS[a]



68 **69** **70** (*endo R*) **71** (*endo S*)

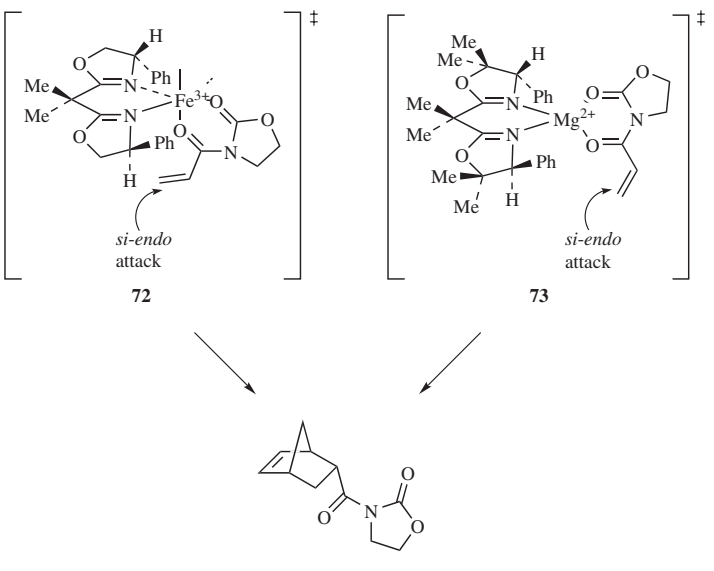
Figure 9.21

Metal	Time (temp)	% Yield	endo/exo	endo ee (config)
FeI_3	19 h (−50 °C)	87	95:5	85% (*R*)
$MgCl_2$	24 h (−80 °C)	82	97:3	91% (*R*)
$Mg(SbF_6)_2$	3 h (−80 °C)	84	98:2	91% (*R*)

[a]Data from Ref. 17.

the use of magnesium(II) led to improved selectivities (up to 98:2 endo/exo with 91% endo ee for the 2*R* isomer). Furthermore, ligand–metal complexes prepared from MgI_2 and one equivalent of iodine as a cocatalyst or 2 equiv of $AgSbF_6$ furnished similar endo enantioselectivity (91% ee).

The observed selectivities for these reactions led to their proposed transition states. The rationalized model for iron chelation (**72**, Fig. 9.22) shows that iron



72 **73**

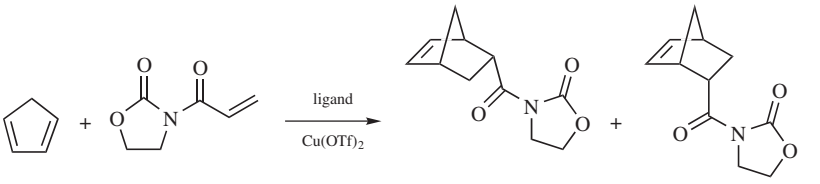
70

Figure 9.22. Corey–Ishihara transition state.

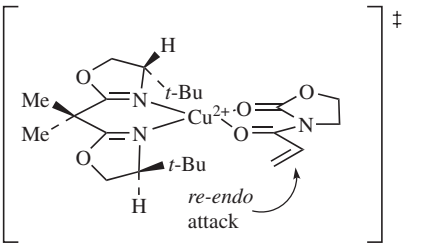
binds in an octahedral complex with the oxazolidinone occupying one axial and one equatorial position on the metal, which is sterically favored over the other possibility of the oxazolidinone binding to both axial positions (binding to both equatorial positions leads to the (2*S*) adduct, which is not the observed product).[6] The magnesium chelation model **73** shows the metal chelating in a tetrahedral complex leading, as in the iron reactions, to the major product with endo facial selectivity and enantioselectivity for the (2*R*) isomer.[17]

In 1993, Evans and co-workers examined phe-box **6**, *i*-pr-box **45**, and bu-box **3** ligands in the Diels–Alder reaction of cyclopentadiene **68** and 3-acryloyl-1,3-oxazolidin-2-one **69** using a weak Lewis acid such as copper(II) triflate.[45] The results are summarized in Table 9.9. The reaction was carried out between −50 and −78 °C for 3–18 h and achieved selectivities of up to 98:2 (endo/exo) with an endo ee of >98% (using bu-box **3**). Interestingly, the enantiomer produced in these reactions was the (2*S*) configuration, compared to the (2*R*) isomer obtained with iron(III) and magnesium(II) as reported by Corey.[6,17] This observed stereochemistry was explained by the chelation model of the copper(II) complex **74** (Fig. 9.23)

TABLE 9.9. CuOTf-MEDIATED DIELS–ALDER REACTION[a]



68 **69** **70** (*endo R*) **71** (*endo S*)



74

Figure 9.23

Ligand	Time (temp)	% Yield	endo/exo	endo ee (config)
6	3 h (−50 °C)	92	95:5	30% (*S*)
45	3 h (−50 °C)	93	96:4	58% (*S*)
3	18 h (−78 °C)	86	98:2	>98% (*S*)

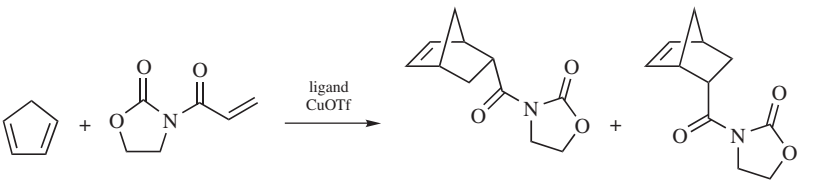
[a]Data from Ref. 45.

in which the copper binds with square-planar geometry in relation to the ligand and oxazolidinone. This leads to *re*-face approach of the diene and (2*S*) configuration of the product.

Ghosh and co-workers have also demonstrated that the Cu(II)-bis(oxazoline) complexes of conformationally constrained inda-box ligands **9a** and *ent*-**9a** are excellent catalysts for the enantioselective Diels–Alder reaction.[9] Using copper(II) triflate as the metal source, the reaction resulted in selectivities up to >99:1 endo/exo ratio with endo ee up to 99% (2*R* isomer), as shown in Table 9.10 (Fig. 9.24). Of particular interest, Cu(II)-phe-box ligand **6**-derived catalyst complex exhibited considerably lower enantioselectivity (30%).[45] Furthermore, they have shown that the use of Mg(II) as the chelating metal resulted in a reversal of stereochemistry [up to 98:2 endo/exo and 61% endo ee for the (2*S*) isomer]. Davies also showed that the use of copper(II) triflate with his structurally related inda-box ligands **9b** and **34a** led to similar selectivities.[10]

Desimoni and co-workers were able to produce either enantiomer (2*R* or 2*S*) of the Diels–Alder cycloadduct using the same isomer of phe-box ligand *ent*-**6** under different reaction conditions (Fig. 9.25, Table 9.11).[46,47] They found that when using magnesium(II) perchlorate as the metal source, the reaction produced cycloadduct in >98% yield with an endo/exo ratio of 93:7 and an endo ee of 70% for the (2*S*) isomer. In contrast, when magnesium(II) perchlorate was used in the presence of 2 equiv of water, the reaction afforded the cycloadduct again in >98% yield with an endo/exo ratio of 93:7, but in this instance, the endo ee was 65% for the (2*R*) isomer. This selectivity difference was explained by a change in

TABLE 9.10. INDA-BOX-MEDIATED DIELS–ALDER REACTION

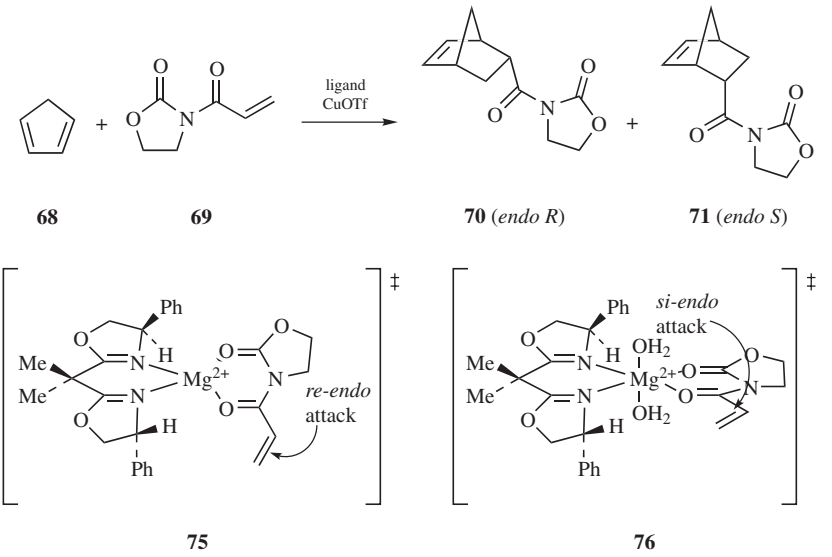


68 **69** **70** (*endo R*) **71** (*endo S*)

Figure 9.24

Ligand	Metal	Time (temp)	% Yield	endo/exo	endo ee (config)	Reference
ent-**9a**	Cu (50 mol%)	6 h (−78 °C)	78	>99:1	97% (*R*)	9
ent-**9a**	Cu (8 mol%)	8 h (−78 °C)	94	>99:1	98% (*R*)	9
9a	Cu (8 mol%)	8 h (−78 °C)	98	>99:1	94% (*S*)	9
ent-**9a**	Cu (4 mol%)	8 h (−78 °C)	90	>99:1	99% (*R*)	9
ent-**9a**	Mg (100 mol%)	7 h (−78 °C)	81	98:2	61% (*S*)	9
ent-**9a**	Mg (10 mol%)	7 h (−78 °C)	76	95:5	34% (*S*)	9
9b	Cu	– (−65 °C)		130:1	92% (*S*)	10
34a	Cu	– (−70 °C)		96:1	98% (*S*)	10

TABLE 9.11. DIELS–ALDER REACTION USING ANHYDROUS AND HYDRATED Mg(II)



68 **69** **70** (*endo R*) **71** (*endo S*)

75 **76**

Figure 9.25

Ligand	Metal	Temperature °C	% Yield	endo/exo	endo ee (config)	Reference
ent-**6**	$Mg(ClO_4)_2$	−50	>98	93:7	70% (*S*)	46
ent-**6**	$Mg(ClO_4)_2 \bullet 2H_2O$	−50	>98	93:7	65% (*R*)	47

the chelation geometry about the magnesium in the presence of water. In the absence of water, the metal chelated in a tetrahedral geometry, shown in structure **75**, as previously mentioned, allowing for *re*-face approach of the diene and the formation of the product containing the (2*S*) isomer.[17] In the presence of water, the chelation geometry about the metal became octahedral, as shown in structure **76**, thus favoring *si*-face approach of the diene and the formation of the product containing the (2*R*) isomer.

Interestingly, Ghosh and co-workers showed that when using copper(II) perchlorate hydrates $[Cu(ClO_4)_2 \bullet 6H_2O]$, the observed stereochemistry of the cycloadduct did not change as compared to the use of copper(II) triflate, as shown in Figure 9.26.[48] This suggests that the metal–ligand–substrate complex in the presence or absence of water remained square planar when using copper(II).

Kanemasa, Curran, and co-workers did an extensive study on the metal and counterion effects in the Diels–Alder reaction using the DBF-box ligand **14**.[15,49] Their results are summarized in Table 9.12 (Fig. 9.27). It has been shown that, for this ligand, the optimal conditions were use of nickel(II) perchlorate at −40 °C for 14 h leading to 96% yield of cycloadduct in a ratio of 97:3 (endo/exo) with >99% endo ee.

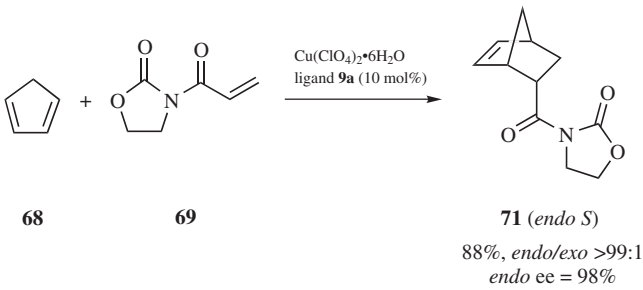


Figure 9.26. Diels–Alder reaction using a Cu(II)-aqua complex.

TABLE 9.12. DBF-BOX-MEDIATED DIELS–ALDER REACTION

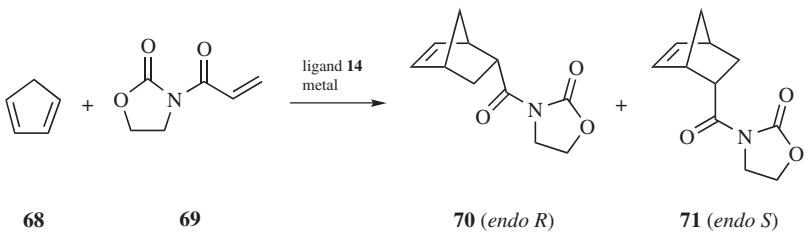


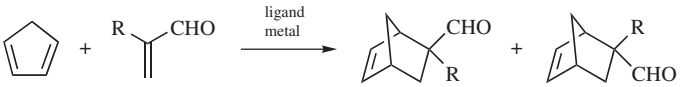
Figure 9.27

Metal	Time (temp)	% Yield	endo/exo	endo ee (config)	Reference
$Mn(ClO_4)_2$	2 h (r.t.)	91	89:11	64% (*S*)	49
$Fe(ClO_4)_2$	48 h (−40 °C)	90	99:1	98% (*S*)	49
$Co(ClO_4)_2•6H_2O$	48 h (−40 °C)	97	97:3	99% (*S*)	49
$Ni(ClO_4)_2•6H_2O$	14 h (−40 °C)	96	97:3	>99% (*S*)	49
$Ni(ClO_4)_2$	24 h (−40 °C)	100	95:5	96% (*S*)	49
$Cu(ClO_4)_2 + 3H_2O$	15 h (−40 °C)	99	97:3	96% (*S*)	49
$Zn(ClO_4)_2 + 3H_2O$	15 h (−40 °C)	99	96:4	97% (*S*)	49
$MgBr_2$	1 h (r.t.)	99	89:11	41% (*S*)	15
MgI_2	2 h (r.t.)	89	91:9	70% (*S*)	15
$MgBr_2$, I_2	1 h (r.t.)	96	90:10	69% (*S*)	15
$Mg(OTf)_2$	10 h (r.t.)	93	88:12	25% (*S*)	15
$Mg(ClO_4)_2$	10 h (−40 °C)	100	97:3	91% (*S*)	15
$Mg(ClO_4)_2 + 3H_2O$	48 h (−40 °C)	68	96:4	48% (*S*)	15

9.5.2.2. Various Dienes and Dienophiles

Diels–Alder reactions involving bis(oxazoline) ligands are not limited to the reaction between cyclopentadiene and 3-acryloyl-1,3,-oxazolidin-2-one; they can be used with a wide variety of dienes and dienophiles. Evans demonstrated the utility of py-box ligand **1d** in the reaction between cyclopentadiene **68** and various

TABLE 9.13. DIELS–ALDER REACTIONS WITH SUBSTITUTED ACROLEINS[a]



68

77a R = H
77b R = Br
77c R = Me
77d R = Ph
77e R = Cl

78a R = H
78b R = Br
78c R = Me
78d R = Ph
78e R = Cl

79a R = H
79b R = Br
79c R = Me
79d R = Ph
79e R = Cl

Figure 9.28

Dienophile	Ligand	Metal	Time (temp)	endo/exo	% ee
77a	**1d**	$Cu(SbF_6)_2$	18 h (−20 °C)	94:6	85
77b	**1d**	$Cu(OTf)_2$	60 h (−40 °C)	3:97	87
77b	**1d**	$Cu(SbF_6)_2$	12 h (−78 °C)	2:98	96
77c	**1d**	$Cu(OTf)_2$	120 h (−20 °C)	4:96	85
77c	**1d**	$Cu(SbF_6)_2$	8 h (−40 °C)	3:97	92
77d	**3**	$Cu(OTf)_2$	24 h (rt)	90:10	99
77d	**3**	$Cu(SbF_6)_2$	24 h (rt)	91:19	96
77e	**3**	$Cu(OTf)_2$	24 h (rt)	93:7	53
77e	**3**	$Cu(SbF_6)_2$	24 h (rt)	86:14	95

[a]Data from Ref. 50.

substituted acroleins **77a–e**.[50] These results, summarized in Table 9.13 (Fig. 9.28), included yields up to 96% with endo/exo ratios up to 94:6 and 2:98 and ee up to 99%.

Ghosh's[9,48] and Kanemasa's groups[49] examined their ligands **9**, *ent*-**9** and **14**, respectively, in the Diels–Alder reactions of oxazolidinones **80a–d** and cyclopentadiene **68**. Their results are summarized in Table 9.14 (Fig. 9.29).

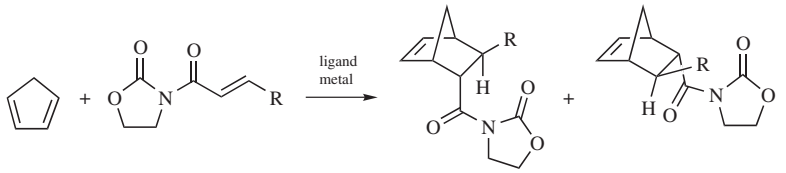
There are also several other examples of bis(oxazoline)–metal complex catalyzed Diels–Alder reactions of cyclopentadiene and other unsaturated esters.[16,51,52] The corresponding cycloadducts were isolated in yields up to 92% with endo/exo ratios up to >99:1 and ee up to >95% (Table 9.15, Fig. 9.30).

9.5.2.3. Bis(oxazoline)-Mediated Diels–Alder Reactions in Total Synthesis

Evans has utilized Cu(II)-bis(oxazoline)-mediated Diels–Alder reactions as the key step in several total syntheses. In 1996, Evans and co-workers used bu-box ligand **3** in the intramolecular Diels–Alder reaction of oxazolidinone **87** to form cycloadduct **88** enantioselectively, as shown in Figure 9.31.[53] Compound **88** was subsequently converted to (-)-isopulo'upone **89**.

Diels–Alder reaction of furan **90** and 3-acrylol-1,3-oxazolidin-2-one **69** was effectively carried out with Cu(II)-bu-box **3**-derived complex. The corresponding

TABLE 9.14. DIELS–ALDER REACTIONS OF *N*-ACYL OXAZOLIDINONES



68

80a R = Me
80b R = Ph
80c R = CO_2Et
80d R = *n*-Pr

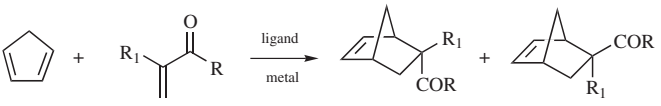
82a R = Me
82b R = Ph
82c R = CO_2Et
82d R = *n*-Pr

81a R = Me
81b R = Ph
81c R = CO_2Et
81d R = *n*-Pr

Figure 9.29

Dienophile	Ligand	Metal	Time (temp)	% Yield	endo/exo	endo ee (config)	Reference
80a	*ent*-**9a**	Cu	26 h (0 °C)	84	92:8	94% (*R*)	9
80a	*ent*-**9a**	Mg	48 h (0 °C)	76	92:8	55% (*S*)	9
80b	*ent*-**9a**	Cu	72 h (r.t.)	78	80:20	35% (*S*)	9
80c	*ent*-**9a**	Cu	8 h (−45 °C)	75	93:7	94% (*S*)	9
80a	**14**	$Ni(ClO_4)_2 \bullet 3H_2O$	20 h (r.t.)	90	92:8	93% (*S*)	49
80d	**14**	$Ni(ClO_4)_2 \bullet 3H_2O$	72 h (r.t.)	100	93:7	94% (*S*)	49
80a	**9a**	$Cu(ClO_4)_2 \bullet 6H_2O$	36 h (−30 °C)	85	95:5	99% (*S*)	48
80c	**9a**	$Cu(ClO_4)_2 \bullet 6H_2O$	7 h (−78 °C)	95	92:8	92% (*R*)	48

TABLE 9.15. DIELS–ALDER REACTIONS WITH VARIOUS DIENOPHILES

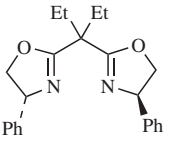


68

84a R = OEt, R_1 = COPh
84b R = OEt, R_1 = SPh
84c R = OCH_2CF_3, R_1 = SPh
84d R = CO_2Me, R_1 = Ph

85
endo

86
exo



83

Figure 9.30

Dieneophile	Ligand	Metal	% Yield	endo/exo	endo ee (config)	Reference
84a	**83**	MgI_2	88	>99:1	87% (*R*)	51
84b	**6**	$CuBr_2/AgSbF_6$	92	15:1	>95% (*S*)	52
84c	**6**	$CuBr_2/AgSbF_6$	92	13:1	>95% (*S*)	52
84d	**14**	$Mg(ClO_4)_2$	75	86:14	30% (*R*)	16
84d	**14**	$Cu(SbF_6)_2$	50	94:6	68% (*R*)	16

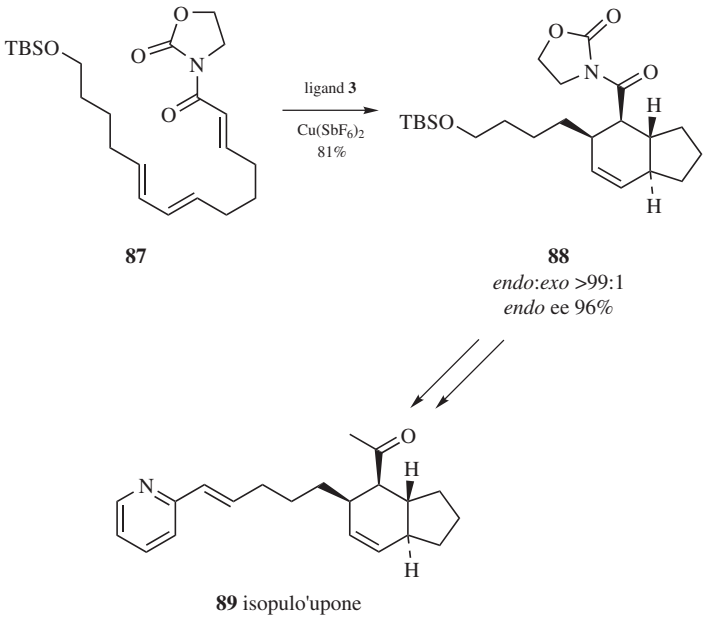


Figure 9.31. Synthesis of isopulo'upone via a Diels–Alder reaction.

cycloadduct **91** was obtained in 97% ee. This cycloadduct was converted to *ent*-shikimic acid **92** as shown in Figure 9.32.[54] Similarly, cyclocondensation of diene **93** with oxazolidinone **69** formed the cycloadduct **94** (endo ee 98%), which was transformed into *ent*-Δ^1-tetrahydrocannabinol **95**.[55]

Another example of a bis(oxazoline)–metal complex catalyzed reaction in total synthesis was illustrated by Murai and co-workers in the construction of a precursor for the synthesis of azadirachtin **97**.[56] The cycloadduct **71** was obtained in 99% ee and 97% yield (Fig. 9.33).

9.5.3. Hetero-Diels–Alder and Ene Reactions

The addition of olefins to aldehydes can take place via an ene reaction. As shown in Figure 9.34, reaction of methylenecyclohexene **98** with ethyl glyoxylate **99** forms the ene product **100**. Evans and co-workers showed that such an ene reaction can be carried out enantioselectively by utilizing bis(oxazoline)–metal complexes. Examples of ene products with yields up to 99% and ee up to 97% are summarized in Table 9.16 (Fig. 9.34).[57]

Using a diene, the reaction can proceed through the ene pathway as above, or through the hetero-Diels–Alder pathway. For example, the condensation of 2,3-dimethyl-1,3-butadiene **103** with glyoxylate esters **99**, **104**, and **105** can proceed to form either a hetero Diels–Alder cycloadduct **106** or an ene product **107** (Fig. 9.35).

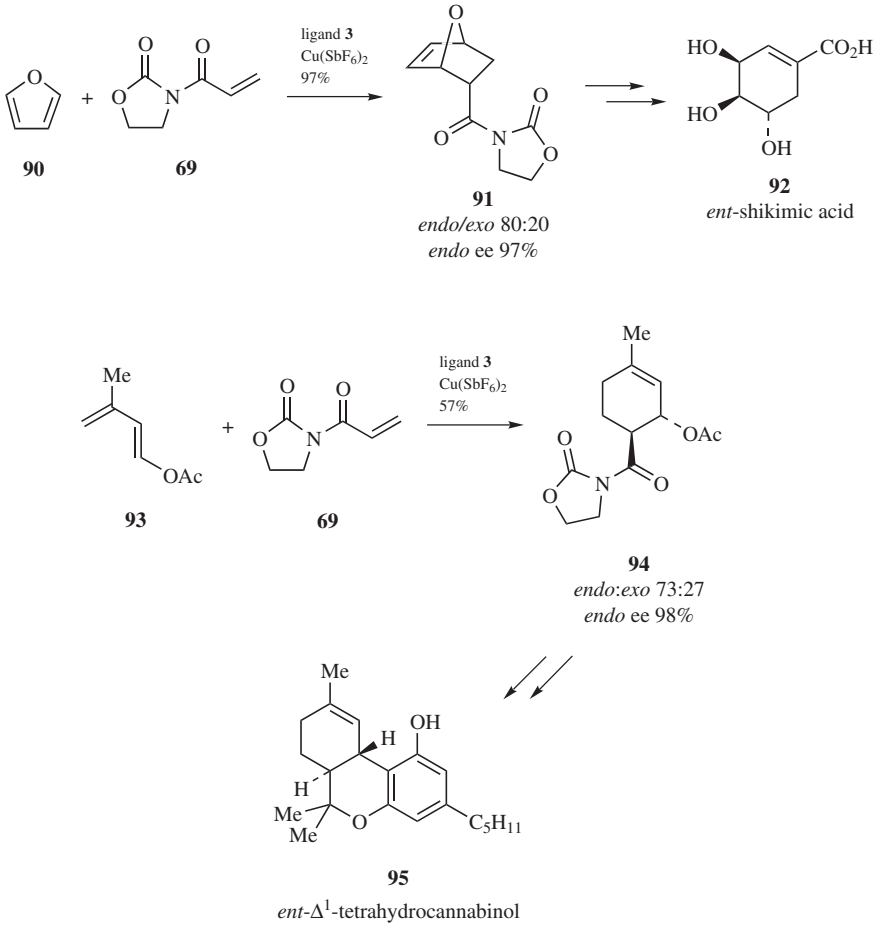


Figure 9.32. Natural product syntheses using Diels–Alder reactions.

Jørgensen and co-workers showed that in the presence of bu-box ligand **3** complexed with copper(II) triflate or phe-box ligand *ent*-**6** complexed with copper(II) triflate, the above reaction proceeded in a combined yield of up to 86% with product ratios (**106**:**107**) varying from ~1:2 to 2:1 and ee between 77 and 95% for either product (Table 9.17, Fig. 9.35*a*).[58–62]

It has been shown that complete selectivity for the hetero-Diels–Alder cycloadduct **109** (100% endo, 60% ee) can be achieved in the hetero-Diels–Alder reaction of 1,3-cyclohexadiene **108** and ethyl glyoxylate **99** using *ent*-**6** and copper(II) triflate derived catalyst complex. Another interesting reaction introduced by Jørgensen and co-workers was the reaction between 1,3-cyclohexadiene **108** and diethyl ketomalonate **110** to form cycloadduct **111** in 76% yield with an ee of 84% (Fig. 9.35*b*, p. 558).[63]

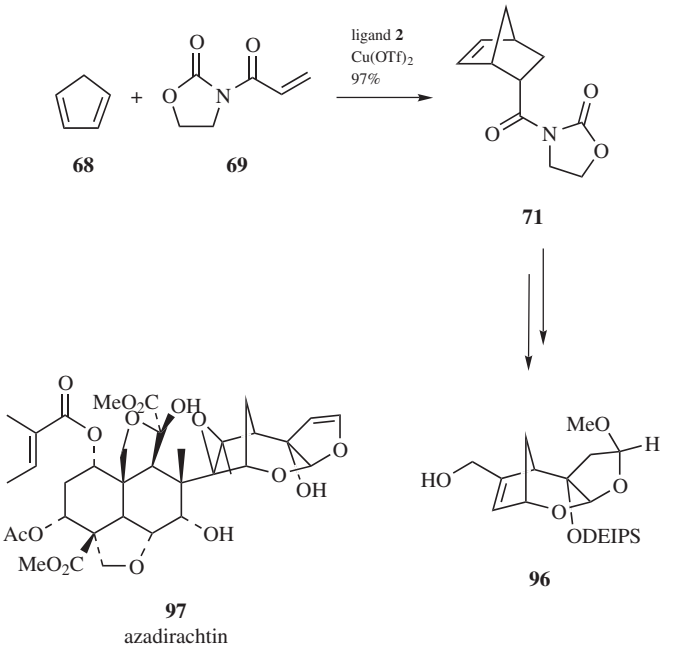


Figure 9.33. Synthetic study toward azadirachtin.

TABLE 9.16. ENANTIOSELECTIVE ENE REACTIONS OF ETHYL GLYOXYLATE[a]

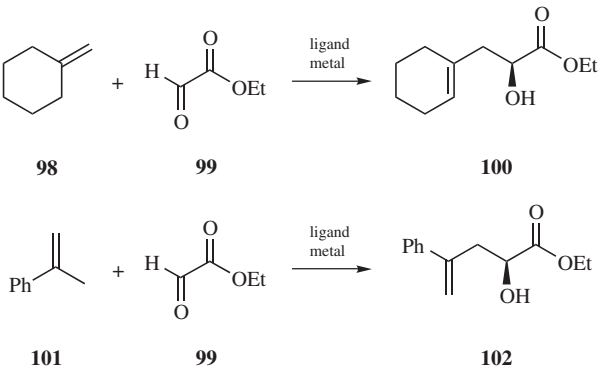
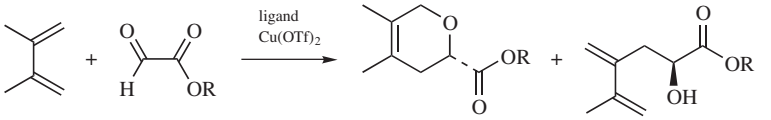


Figure 9.34

Alkene	Ligand	Metal	% Yield **100**	% Yield **102**	ee (config)
98	**3**	$Cu(SbF_6)_2$	90		97% (*S*)
98	**6**	$Cu(OTf)_2$	99		87% (*R*)
101	**3**	$Cu(SbF_6)_2$		97	93% (*S*)
101	**6**	$Cu(OTf)_2$		99	89% (*R*)

[a]Data from Ref. 57.



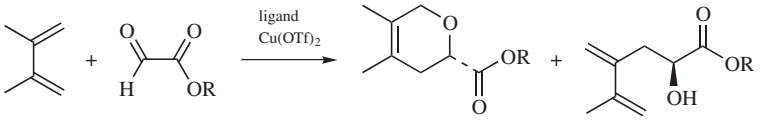
103 **99** R = Et, **104** R = Me, **105** R = *i*-Pr **106** **107**

Figure 9.35

Activated dienes such as Danishefsky's diene **112** can also be used in the hetero-Diels–Alder reaction with alkyl glyoxylates. Ghosh and co-workers showed that this reaction proceeded to form cycloadducts **113a,b** in yields up to 76% and ee up to 70% using either bu-box **3**, phe-box **6** or inda-box *ent*-**9a**.[64] The results are summarized in Table 9.18 (Fig. 9.36).

Subsequently, Jørgensen and co-workers carried out reactions using Danishefsky's diene **112** and α-keto esters **114a–d** to afford cycloadducts **115a–d** in yields up to 95% with ee up to 99% (Table 9.19, Fig. 9.37*a*).[65]

TABLE 9.17. ENANTIOSELECTIVE HETERO-DIELS–ALDER AND ENE REACTION PRODUCTS[a]



103 **99** R = Et, **104** R = Me, **105** R = *i*-Pr **106** **107**

Figure 9.35*a*

Ligand	R	Temperature (°C)	**106** yield (ee)	**107** yield (ee)	**106**:**107**
3	Me	20	25% (90%)	39% (85%)	1:1.6
3	Et	20	20% (85%)	36% (83%)	1:1.8
3	*i*-Pr	20	12% (77%)	12% (83%)	1:1
ent-**6**	Me	20	36% (81%)	50% (85%)	1:1.4
ent-**6**	Et	20	31% (83%)	50% (88%)	1:1.6
ent-**6**	*i*-Pr	20	31% (87%)	40% (90%)	1:1.3
3	Et	20	20% (85%)	36% (83%)	1:1.8
3	Et	−30	5% (95%)	4% (94%)	1:0.8
ent-**6**	Et	20	31% (83%)	50% (88%)	1:1.6
ent-**6**	Et	0	22% (85%)	32% (89%)	1:1.5
ent-**6**	Et	−30	13% (85%)	7% (90%)	1:0.6

[a]Data from Ref. 58.

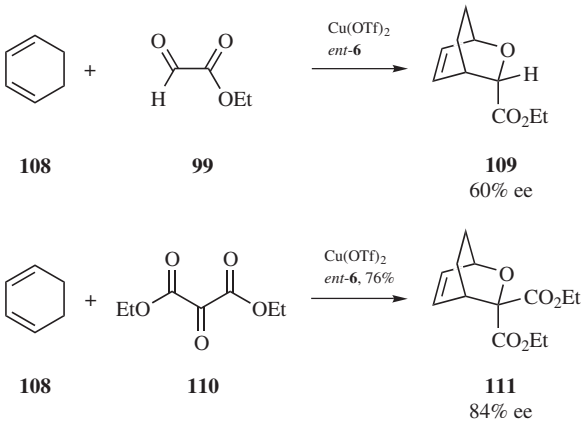


Figure 9.35*b*. Hetero-Diels–Alder reactions.

Whiting's group performed an aza-Diels–Alder condensation using Danishefsky's diene **112** and methyl α-[(4-methoxyphenyl)imino]acetate **116**, which afforded the tetrahydropyridone **117** in 67% yield and 92% ee (Fig. 9.37*b*).[66]

Enantioselective hetero-Diels–Alder reactions of α,β-unsaturated acyl phosphonates and enol ethers have been reported by Evans in 1998.[67,68] As depicted in Figure 9.38*a*, cyclocondensation of dienes **118a** and **118b** with enol ethers **119a–c**

TABLE 9.18. HETERO–DIELS–ALDER REACTION OF DANISHEFSKY'S DIENE WITH GLYOXYLATE ESTERS[a]

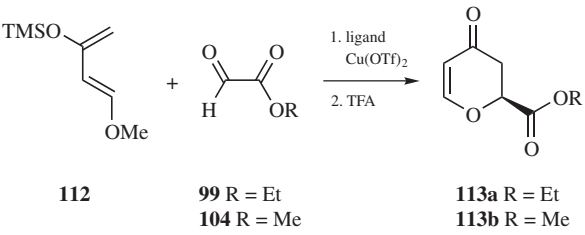
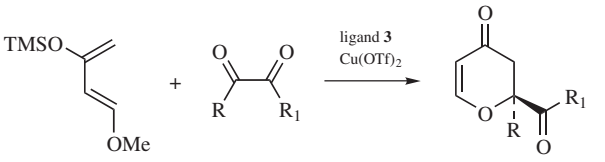


Figure 9.36

Ligand	R	Time (temp)	% Yield **113a** or **113b**	ee (config)
6	Et	9 h (−78 °C)	27	44% (*S*)
6	Me	9 h (−78 °C)	40	47% (*S*)
3	Et	8 h (−78 °C)	42	17% (*R*)
3	Me	9 h (−78 °C)	37	2% (*R*)
ent-**9a**	Et	9 h (−78 °C)	70	72% (*S*)
ent-**9a**	Me	9 h (−78 °C)	67	70% (*S*)
ent-**9a**	Et	9 h (rt)	76	50% (*S*)

[a]Data from Ref. 64.

TABLE 9.19. ENANTIOSELECTIVE HETERO-DIELS–ALDER REACTIONS USING DANISHEFSKY'S DIENE[a]



112

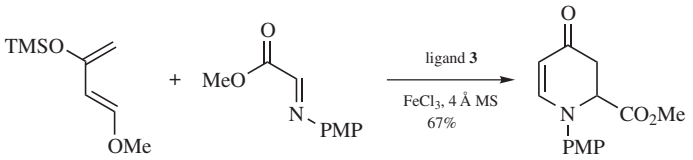
114a R = Me, R_1 = OEt
114b R = Me, R_1 = OMe
114c R = Ph, R_1 = OEt
114d R = Me, R_1 = Me

115a R = Me, R_1 = OEt
115b R = Me, R_1 = OMe
115c R = Ph, R_1 = OEt
115d R = Me, R_1 = Me

Figure 9.37*a*

Ketone	Time (temp)	% Yield	% ee
114a	8 h (r.t.)	85	92
114a	30 h (−40 °C)	78	99
114b	23 h (r.t.)	95	91
114c	20 h (r.t.)	77	77
114d	60 h (−40 °C)	90	94

[a]Data from Ref. 65.



112 **116** **117**
92% ee

PMP = *p*-methoxyphenyl

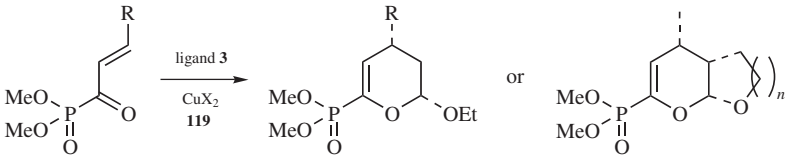
Figure 9.37*b*. Hetero-Diels–Alder reaction of imines.

afforded the cycloadducts **120a–d** in up to >99:1 endo/exo ratio with yields up to 98% and selectivities as high as 99% (ee). Selected examples are presented in Table 9.20 (Fig. 9.38*a*).

Ghosez and co-workers also presented a hetero-Diels–Alder reaction using a hetero-atom-containing diene **121** and the oxazolidinone **80a** in the presence of bu-box **3** complexed with copper(II) triflate to afford the cycloadduct **122** in 80% yield (>99:1 exo/endo, 95% ee) as shown in Figure 9.38*b*.[69]

Bis(oxazoline)-mediated hetero-Diels–Alder reactions have also been utilized in total synthesis. For example, Ghosh and co-workers used inda-box **9a** in the construction of a key intermediate for the synthesis of laulimalide **123**, a potent

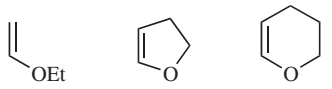
TABLE 9.20. ENANTIOSELECTIVE HETERO-DIELS–ALDER REACTIONS OF α,β-UNSATURATED ACYL PHOSPHONATES



118a R = Me
118b R = OEt

120a R = Me
120b R = OEt

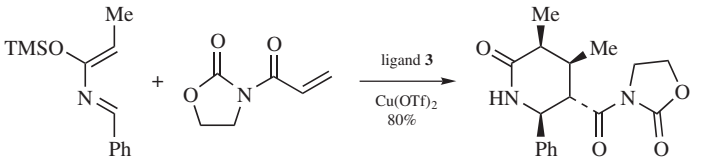
120c $n = 1$
120d $n = 2$



119a **119b** **119c**

Figure 9.38*a*

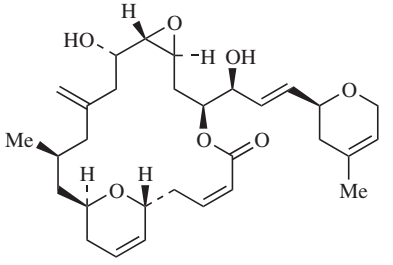
R	Vinyl Ether	X	% Yield	% ee	Reference
Me	**119a**	OTf	89	99	67
OEt	**119a**	SbF_6	98	97	68
Me	**119b**	OTf	91	95	67
Me	**119c**	SbF_6	55	92	67



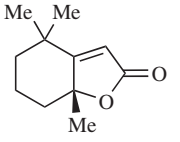
121 **80a**

122
95% ee

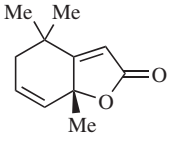
Figure 9.38*b*. Hetero-Diels–Alder reactions with aza dienes.



123
laulimalide



124
(*R*)-dihydroactinidiolide



125
(*R*)-actinidiolide

Figure 9.39. Natural products via enantioselective hetero-Diels–Alder reactions.

antitumor agent.[70] Jørgensen and co-workers have also utilized this reaction in the syntheses of (*R*)-dihydroactinidiolide **124** and (*R*)-actinidiolide **125** as illustrated in Figure 9.39.[71]

9.5.4. 1,3-Dipolar Cycloadditions

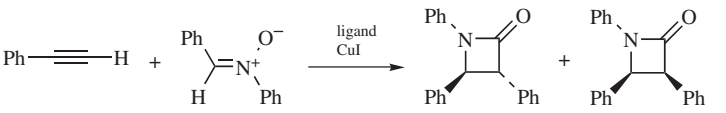
Lewis acid catalyzed 1,3-dipolar cycloadditions of olefins and nitrones are useful synthetic transformations that have the potential of defining up to three contiguous chiral centers. Presumably, such reactions can also be catalyzed by chiral Lewis acids derived from metal–bis(oxazoline) complexes.

Miura and co-workers attempted the cyclization of phenylacetylene **126** with (*Z*)-α,*N*-diphenylnitrone **127** to form β-lactams **128** and **129** in the presence of *i*-pr-box **45** and copper(I) iodide or bu-box **3** and copper(I) iodide, as shown in Figure 9.40 (Table 9.21).[72] When the ligands were used in catalytic amounts, precipitation of the copper acetylide was observed and virtually no cycloadduct was formed. However, when the reaction was carried out using 1 equiv of ligand and copper(I) iodide, the trans cycloadduct **128** was formed in up to 54% yield and 68% ee.

The Jørgensen[73–76] and Desimoni[77] groups have also carried out bis(oxazoline)-metal complex-catalyzed 1,3-dipolar cycloadditions with nitrones. Cycloaddition of α,β-unsaturated oxazolidinones such as **69**, **80a**, and **130** with nitrone **127** in the presence of phe-box ligands **6** and *ent*-**6** provided quantitative yields of cycloadducts. Selectivities of up to 100:0 endo/exo ratio and corresponding endo ee as high as 82% were achieved (Table 9.22, Fig. 9.41*a*).

Similarly, cycloaddition of ethyl vinyl ether **119** and **133** afforded an excellent yield of **134** and **135** as shown in Figure 9.41*b*.[76]

TABLE 9.21. 1,3-DIPOLAR CYCLOADDITION OF PHENYLACETYLENE[a]



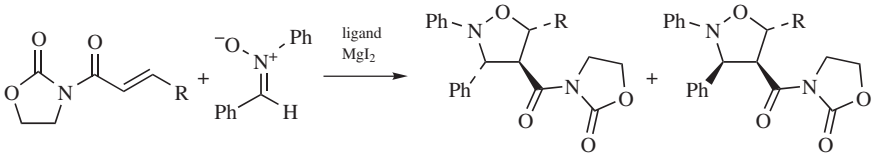
126 **127** **128** **129**

Figure 9.40

Ligand	Ligand/CuI	% Yield	trans % ee
45	1:0.1	45	40
45	1:1	54	68
3	1:1	53	67

[a]Data from Ref. 72.

TABLE 9.22. ENANTIOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF α,β-UNSATURATED OXAZOLIDINONES AND NITRONES



69 R = H
80a R = Me
130 R = *n*-Pr

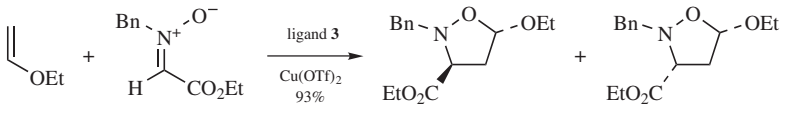
127

131a R = H
131b R = Me
131c R = *n*-Pr

132a R = H
132b R = Me
132c R = *n*-Pr

Figure 9.41*a*

Alkene	Ligand	Additive	endo/exo	endo % ee	Reference
80a	**6**		84:16	75	73
130	**6**		>95:5	82	73
80a	*ent*-**6**	4 Å MS	96:4	79	73
80a	*ent*-**6**	H_2O	94:6	73	74
69	*ent*-**6**	4 Å MS	73:27	82	75
69	*ent*-**6**		100:0	48	75
69	*ent*-**6**	H_2O	90:10	36	75
80a	*ent*-**6**		97:3	46	77



119

133

endo/exo = 84:16

134
endo
89% ee

135
exo

Figure 9.41*b*

9.5.5. Allylic Substitutions

Pfaltz and co-workers have done substantial work in the area of allylic substitution reactions involving bis(oxazoline) ligands.[33,78,79] The substitution reaction of racemic 1,3-diphenylallyl acetate **136** with the anion of dimethylmalonate in the presence of 1–2 mol% palladium-bis(oxazoline) complex afforded enantiomerically enriched diethyl (*E*)-(1,3-diphenylallyl)malonate **137**, as shown in Figure 9.42.

The results from various palladium complexes derived from bis(oxazoline) ligands *ent*-**45**, **139**, and **140** were examined using the above reaction and are

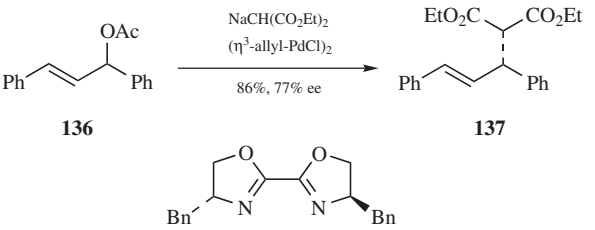


Figure 9.42. Palladium-catalyzed allylic malonate substitution.

shown in Table 9.23 (Fig. 9.43*a*). The substitution product **137** was obtained in yields of up to 99% and ee up to 97%.

Pfaltz's group also investigated ligand **139** in the reaction involving the asymmetric allylic acetate **141**. A substitution ratio (**142a/142b**) of 93:7 was observed in this case and both products were obtained as pure enantiomers (Fig. 9.43*b*).

Ikeda and co-workers examined ferrocene-based ligands **11a** and **11b** in the same allylic substitution reaction of racemic acetate **136** (Fig. 9.44, Table 9.24).[12] This catalytic system resulted in quantitative yield of **137** with ee of 96 and 99%, respectively.

TABLE 9.23. ENANTIOSELECTIVE SUBSTITUTION OF 1,3-DIPHENYLALLYL ACETATE WITH DIETHYLMALONATE

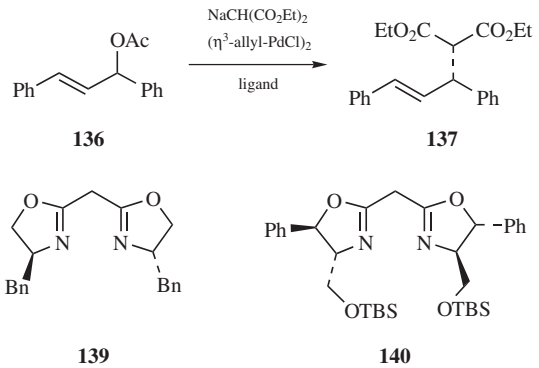
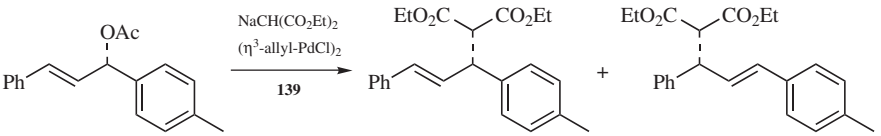


Figure 9.43*a*

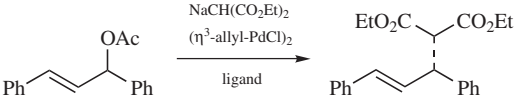
Ligand	Solvent	% Yield	% ee	Reference
139	THF	85	76	78
139	THF/Et_2O	99	84	78
139	CH_2Cl_2	97	88	78
ent-**45**	THF	94	94	79
140	THF	94	97	79



141 **142a** 93% **142b** 7%

Figure 9.43*b*

TABLE 9.24. FERROCENE-BOX–MEDIATED ENANTIOSELECTIVE SUBSTITUTION OF 1,3-DIPHENYLALLYL ACETATE WITH DIETHYLMALONATE[a]



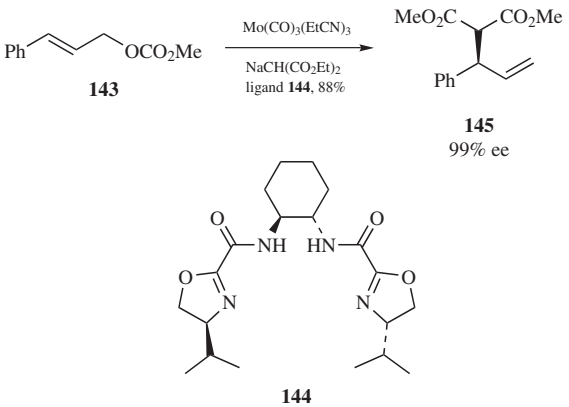
136 **137**

Figure 9.44

Ligand	% Yield	% ee
11a	100	96
11b	100	99

[a]Data from Ref. 12.

An interesting allylic substitution reaction of (*E*)-cinnamyl methyl carbonate **143** has been examined by Pfaltz's group.[80] The use of a molybdenum complex of ligand **144** resulted in **145** in 88% yield with an ee of 99% [for the (*R*) isomer] (Fig. 9.45).



143 **145** 99% ee

144

Figure 9.45. Molybdenum-mediated allylic substitution.

9.5.6. Mukiayama Aldol

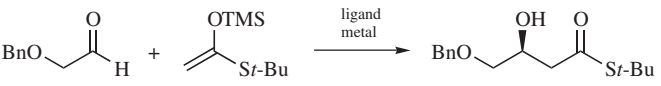
Mukiayama aldol reactions between silyl enol ethers and various carbonyl containing compounds is yet another reaction whose stereochemical outcome can be influenced by the presence of bis(oxazoline)–metal complexes. Evans has carried out a great deal of the work in this area.[81–85] In 1996, Evans and co-workers reported the copper(II)- and zinc(II)-py-box (**1a–c**) catalyzed aldol condensation between benzyloxyacetaldehyde **146** and the trimethylsilyl enol ether [(1-*tert*-butylthio)vinyl]oxy trimethylsilane **147**.[81,82,85] Complete conversion to aldol adduct **148** was achieved with enantiomeric excesses up to 96% [using copper(II) triflate]. The use of zinc as the coordination metal led to consistently lower selectivities and longer reaction times, as shown in Table 9.25 (Fig. 9.46).

In 1997, Evans reported on the aldol reaction using the same enol ether **147** with a variety of glyoxylates and pyruvates using tin triflate and copper triflate. [83,84] As shown in Table 9.26 (Fig. 9.47*a*), reaction of several pyruvates using bu-box ligand **3** complexed with copper(II) triflate afforded yields of up to 99% with selectivities up to 96% (ee) for adduct **150**.[84]

Evans also investigated the aldol condensation between methyl pyruvate **151** and several different substituted enol ethers **152**, again using bu-box **3** and copper(II) triflate. These reactions achieved selectivities up to 98:2 (syn/anti) with syn ee up to 98% and yields up to 96% (Table 9.27, Fig. 9.47*b*).[84]

Another type of aldol condensation using cyclic enol ethers was demonstrated by Yamamoto and co-workers in which the condensation of tributyl (1-cyclohex-ene-1-yloxy)stannane **154** with benzaldehyde proceeded in 74% yield, as shown in Figure 9.48.[86] The ratio of anti product **155** to syn product **156** was 36:64 with an anti ee of 84% (Fig. 9.48).

TABLE 9.25. MUKAIYAMA ALDOL REACTION OF BENZYLOXYACETALDEHYDE AND A TRIMETHYLSILYL ENOL ETHER[a]



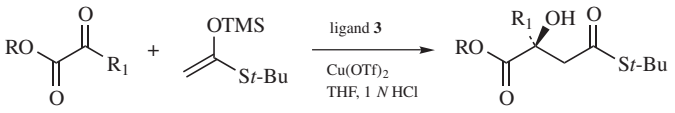
146 **147** **148**

Figure 9.46

Ligand	Metal	% ee
1a	$Cu(OTf)_2$	96
1b	$Cu(SbF_6)_2$	85
1c	$Cu(SbF_6)_2$	9
1a	$Zn(OTf)_2$	40
1b	$Zn(SbF_6)_2$	36
1c	$Zn(SbF_6)_2$	18

[a]Data from Ref. 81.

TABLE 9.26. ENANTIOSELECTIVE ALDOL REACTION MEDIATED BY Bu-BOX[a]



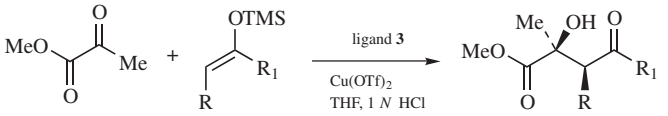
149 **147** **150**

Figure 9.47*a*

R	R_1	% Yield	% ee
Me	Me	99	96
Bn	Me	99	95
t-Bu	Me	99	91
Me	Et	94	84
Me	*t*-Bu	94	94
Et	*i*-Pr	36	84

[a]Data from Ref. 84.

TABLE 9.27. Cu(II)-Bu-BOX-MEDIATED MUKAIYAMA ALDOL REACTIONS[a]

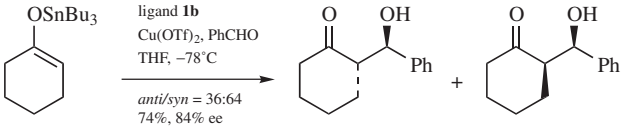


151 **152** **153**

Figure 9.47*b*

R	R_1	Enol Geometry	syn/anti	% Yield	% ee
Me	*t*-BuS	*Z*	94:6	96	96
Me	*t*-BuS	*E*	95:5	88	98
Me	EtS	*Z*	94:6	90	93
Me	EtS	*E*	98:2	91	98
i-Bu	EtS	*Z*	90:10	88	93

[a]Data from Ref. 84.



154 **155** *anti* **156** *syn*

Figure 9.48. Cu(II)-py-box-mediated Mukaiyama aldol reaction.

9.5.7. Conjugate Addition

9.5.7.1. Free Radical Conjugate Addition

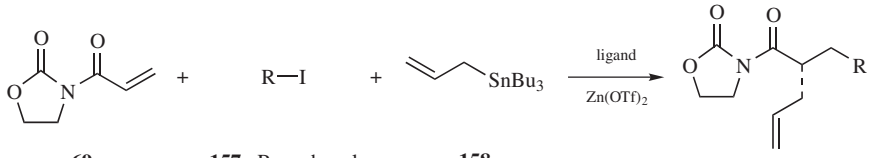
Stereocontrolled free radical conjugate additions have been studied using C_2-symmetric bis(oxazoline)–metal complexes. The most common reaction used to study the effectiveness of these ligands in free radical conjugate additions is the reaction of alkyl iodides, electron-deficient alkenes and allyltributyl stannane. Thus, using this reaction, Porter and co-workers have studied bis(oxazoline) ligands **6** and *ent*-**6**.[87,88] Stoichiometric amounts of these ligands complexed with zinc(II) triflate were employed in the reaction of iodocyclohexane **157a** or *tert*-butyliodide **157b** and 3-acryloyl-1,3-oxazolidin-2-one **69** in the presence of allyltributyl stannane **158**. The results are summarized in Table 9.28 (Fig. 9.49). The corresponding addition products **159a** and **159b** were obtained in up to 92% yield with ee up to 90%.

Sibi's group studied a similar reaction using ligands **9b**, **34a–c**, and **161** with iodides **157b** and **157c**, tributyltin hydride **160** and *N*-crotonyl oxazolidinone **80a** or *N*-cinnamoyl oxazolidinone **80b**.[89,90] As shown in Table 9.29 (entries 7 and 9), the inda-box ligands exhibited optimum results with yields up to 92% and selectivities up to 93% (ee). The use of the ligand–metal complexes in catalytic amounts led to lower yields and enantioselectivities (Fig. 9.50).[89]

9.5.7.2. Michael Addition

Another type of conjugate addition reaction in which bis(oxazoline)–metal complexes have been used is the Michael addition reaction. Early work in this

TABLE 9.28. PHE-BOX-MEDIATED FREE RADICAL CONJUGATE ADDITION[a]



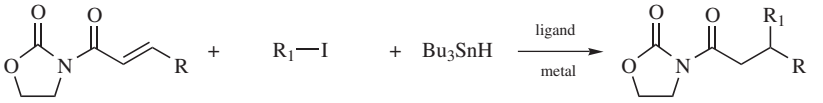
69 **157a** R = *c*-hexyl, **157b** R = *t*-Bu **158** **159a** R = *c*-hexyl, **159b** R = *t*-Bu

Figure 9.49

Ligand	R	Solvent	% Yield	ee (config)
6	*c*-hexyl	CH_2Cl_2	62	50% (*S*)
6	*c*-hexyl	ether	61	80% (*S*)
6	*t*-Bu	pentane/CH_2Cl_2	78	88% (*S*)
ent-**6**	*t*-Bu	pentane/CH_2Cl_2	92	90% (*R*)

[a]Data from Ref. 87.

TABLE 9.29. ENANTIOSELECTIVE FREE RADICAL CONJUGATE ADDITIONS TO α,β-UNSATURATED *N*-ACYL OXAZOLIDINONES

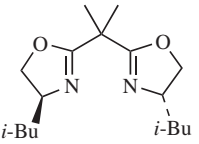


80a R = Me
80b R = Ph

157b R_1 = *t*-Bu
157c R_1 = *i*-Pr

160

162a R = Me, R_1 = *t*-Bu
162b R = Ph, R_1 = *i*-Pr



161

Figure 9.50

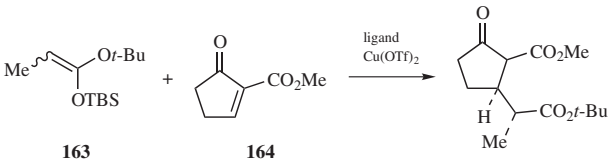
Entry	Ligand (mol%)	Metal	R	R_1	% Yield	ee (config)	Reference
1	**161** (1.0)	MgI_2	Ph	*i*-Pr	88	82% (*R*)	89
2	**161** (0.5)	MgI_2	Ph	*i*-Pr	86	79% (*R*)	89
3	**161** (0.2)	MgI_2	Ph	*i*-Pr	86	67% (*R*)	89
4	**161** (1.0)	$Zn(OTf)_2$	Me	*t*-Bu	90	82% (*S*)	89
5	**161** (0.2)	$Zn(OTf)_2$	Me	*t*-Bu	71	70% (*S*)	89
6	**9b** (1.0)	MgI_2	Ph	*i*-Pr	88	89% (*R*)	90
7	**34a** (1.0)	MgI_2	Ph	*i*-Pr	88	93% (*R*)	90
8	**34b** (1.0)	MgI_2	Ph	*i*-Pr	90	82% (*R*)	90
9	**34c** (1.0)	MgI_2	Ph	*i*-Pr	92	82% (*R*)	90

area met with limited success. Bernardi and Scolastico, for example, attempted the Michael addition of the silyl enol ether **163** to 2-methoxycarbonylcyclopent-2-enone **164**.[91] These reactions resulted in only moderate yields and poor enantioselectivity (Table 9.30, Fig. 9.51).

A number of subsequent Michael reactions catalyzed by bis(oxazoline)–metal complexes however, proceeded with improved enantioselectivity.[92–97] For example, Michael reactions of **166a** and **166b** and oxazolidinone **80a** using Cu(II)–bis(oxazoline) **3** provided products **167a** and **167b** in high ee as shown in Figure 9.52*a*.[92,93] Conjugate additions of *O*-benzylhydroxylamine **169** to α,β-unsaturated pyrazole derivatives **168a–c** have been shown to proceed with good enantioselectivities and isolated yields (Table 9.31, Fig. 9.52*a*).[94]

Michael addition of ethylacetoacetate **171** to nitroalkenes, for example, β-nitrostyrene **172** also proceeded with excellent enantioselectivities.[95] Evans reported the Cu(II)-bis(oxazoline) catalyzed Michael addition of methylthio enolsilane **174** to the fumarate derivative **80c** to provide **175** in 98% ee as shown in Figure 9.52*b*.[95,96]

TABLE 9.30. POLAR CONJUGATE ADDITION REACTION[a]



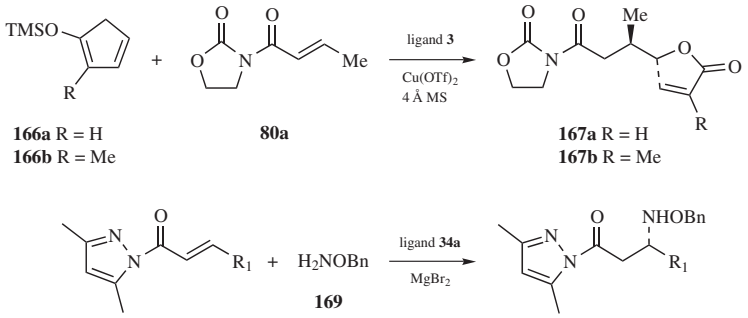
163 **164** **165**

Figure 9.51

Ligand	% Yield	% ee
2	40	0
6	50	33
4	50	43

[a]Data from Ref. 91.

TABLE 9.31. BIS(OXAZOLINE)-MEDIATED CONJUGATE ADDITIONS



166a R = H
166b R = Me

80a

167a R = H
167b R = Me

168a R_1 = Me
168b R_1 = Et
168c R_1 = Bn

169

170a R_1 = Me
170b R_1 = Et
170c R_1 = Bn

Figure 9.52*a*

Product	% Yield	anti/syn	% ee	Reference
167a	89	8.5:1	95	92
167b	95	24:1	91	92
170a	87		88	94
170b	84		88	94
170c	57		70	94

9.5.8. Allylation and Cyanohydrin Formation

Stereoselective addition to aldehydes is another powerful tool in organic chemistry. Two very specific types of this reaction include allylation of aldehydes and cyanohydrin formation. These are both reactions that can benefit from the use of chiral bis(oxazoline) ligands.[98,99,100–102] Two examples are summarized in Figure 9.53.

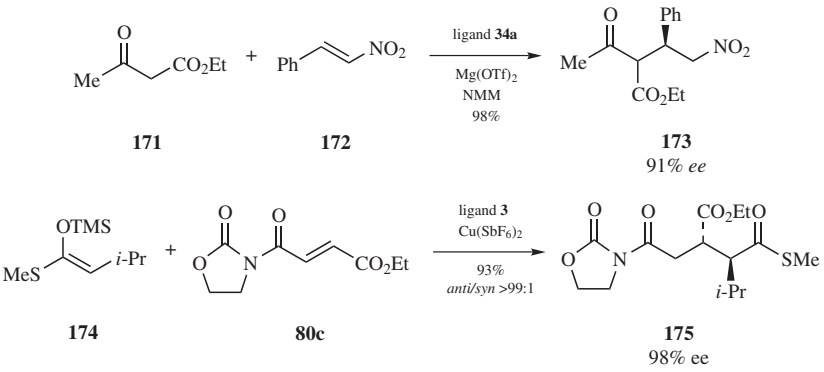


Figure 9.52*b*

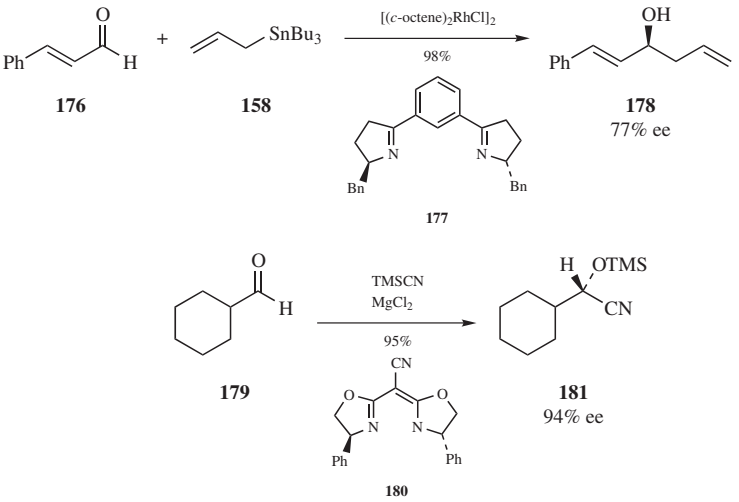


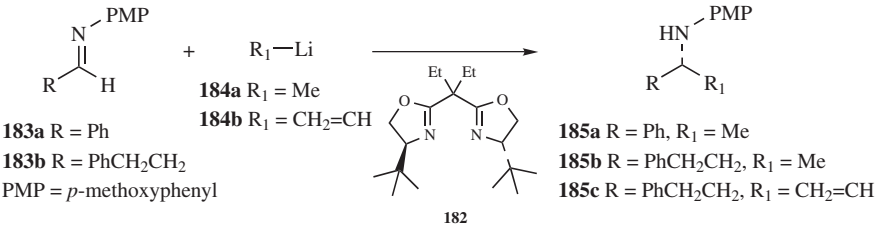
Figure 9.53. Nucleophilic additions to aldehydes.

9.5.9. Alkylation of Imines and Oximes

Stereoselective addition to carbonyl groups is a powerful tool in organic synthesis and has received a great deal of attention. Addition to imines can be equally as powerful, but has received much less attention. Denmark and co-workers first introduced the use of bis(oxazoline) ligands in the addition reactions of imines.[103,104] The most successful ligand has been the modified bu-box ligand **182**. This ligand was used both stoichiometrically and catalytically in the reaction between various imines and several alkyllithium species. Selected examples are summarized in Table 9.32 (Fig. 9.54).

Nakamura and co-workers used *i*-pr-box ligand **22** stoichiometrically for the addition of alkyl zinc reagents **186a–c** to cyclic imines **187a** and **187b**.[105] This

TABLE 9.32. ASYMMETRIC ADDITION TO IMINES[a]



183a R = Ph
183b R = $PhCH_2CH_2$
PMP = *p*-methoxyphenyl

182

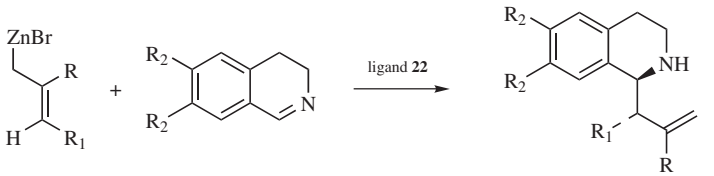
185a R = Ph, R_1 = Me
185b R = $PhCH_2CH_2$, R_1 = Me
185c R = $PhCH_2CH_2$, R_1 = CH_2=CH

Figure 9.54

mol% **182**	R	R_1	% Yield	% ee
1.0	Ph	Me	95	75
1.0	$PhCH_2CH_2$	Me	96	91
1.0	$PhCH_2CH_2$	CH_2=CH	95	89
0.1	Ph	Me	98	68
0.2	$PhCH_2CH_2$	Me	81	82
0.2	$PhCH_2CH_2$	CH_2=CH	82	82

[a]Data from Ref. 103.

TABLE 9.33. ENANTIOSELECTIVE ADDITION OF ALLYLZINC REAGENTS TO CYCLIC IMINES[a]



186a R = H, R_1 = H
186b R = Me, R_1 = H
186c R = H, R_1 = Ph

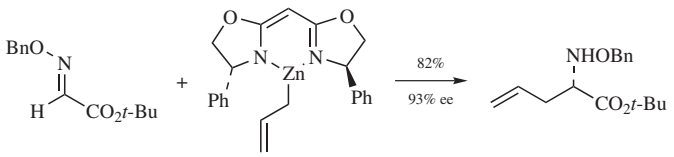
187a R_2 = H
187b R_2 = OMe

188a R = H, R_1 = H, R_2 = H
188b R = H, R_1 = H, R_2 = OMe
188c R = Me, R_1 = H, R_2 = OMe
188d R = H, R_1 = Ph, R_2 = OMe

Figure 9.55*a*

R	R_1	R_2	% Yield	% ee
H	H	H	72	95
H	H	OMe	90	95
Me	H	OMe	96	97.5
H	Ph	OMe	92	77

[a]Data from Ref. 105.



189 **190** **191**

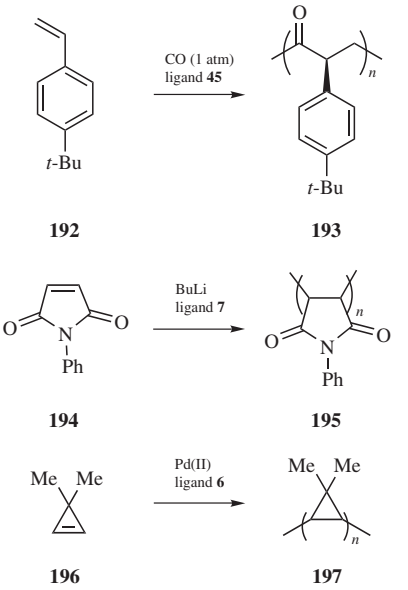
Figure 9.55*b*

process led to the 1,2,3,4-tetrahydroisoquinolines **188a–d** in yields up to 96% with enantioselectivities up to 97.5% (Table 9.33, Fig. 9.55*a*).

Hanessian's group investigated the addition reactions of oximes using bis(oxazoline) ligand *ent*-**39**.[106] As shown in Figure 9.55*b*, reaction of the α-oximino ester **189** and alkyl zinc reagent **190** afforded the homoallylic hydroxyl amine **191** in 82% yield with an enantioselectivity of 93% ee.

9.5.10. Asymmetric Polymerization

Bis(oxazoline) ligands have also been used to produce polymers containing main chain chirality. Some examples include those by Wagner and co-workers in which *i*-pr-box **45** is used to mediate the copolymerization of *tert*-butylstyrene **192** with carbon monoxide to achieve a polymer of type **193** with stereoregularity up to 98%,[107,108] Oishi and co-workers' polymerization of *N*-substituted maleimides **194**[109–111] and Risse and co-workers' polymerization of substituted cyclopropenes **196**[112] are shown in Figure 9.56.



192 **193**

194 **195**

196 **197**

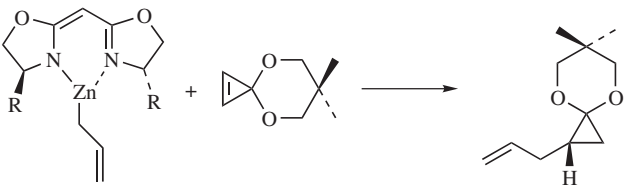
Figure 9.56. Bis(oxazoline)-mediated chiral polymerizations.

9.5.11. Miscellaneous Carbon–Carbon Bond-Forming Reactions

Bis(oxazoline) ligands have been shown to be useful in the many carbon–carbon bond-forming reactions previously listed. They have also been used in a myriad of other carbon–carbon bond-forming reactions. For example, Nakamura and co-workers used bis(oxazoline) ligands *ent*-**2**, *ent*-**22**, and *ent*-**39** in ligand-induced enantioselective allylzincation.[113] This reaction consisted of the transformation of the cyclopropenone acetal **198** into allylic cyclopropanone acetal **199** in yields ranging from 73 to 90% with selectivities from >98:2 for the isomer shown to 1:99 (Fig. 9.57).

Ukaji and co-workers employed bis(oxazoline) ligands in the asymmetric bis(alkoxycarbonylation) reaction of homoallylic alcohols.[114] One example of this reaction, the conversion of homoallylic alcohol **200** to its carbonylation product **201**, is illustrated in Figure 9.58. This reaction proceeded in 78% yield with an ee of 50%.

Bis(oxazoline) ligands have also been used to mediate the [2,3]-Wittig rearrangements of allylic ethers. Nakai and co-workers demonstrated the rearrangement of (*Z*)-crotyl benzyl ether **202** using *tert*-butyllithium and bis(oxazoline) ligand **203** to form a mixture of erythro **204a** and threo **204b** rearrangement

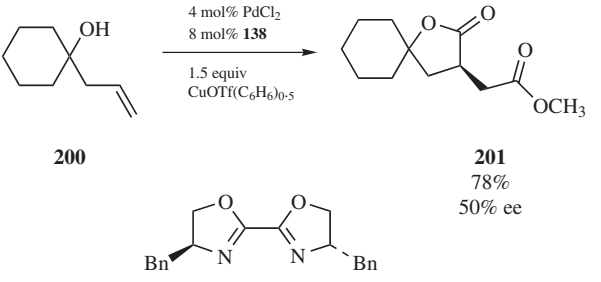


ent-**2** R= *t*-Bu
ent-**22** R= *i*-Pr
ent-**39** R= Ph

198

199
73-90%
from >98:2
to >1:99

Figure 9.57. Allylzincation.



200

201
78%
50% ee

138

Figure 9.58. Bis(alkoxycarbonylation).

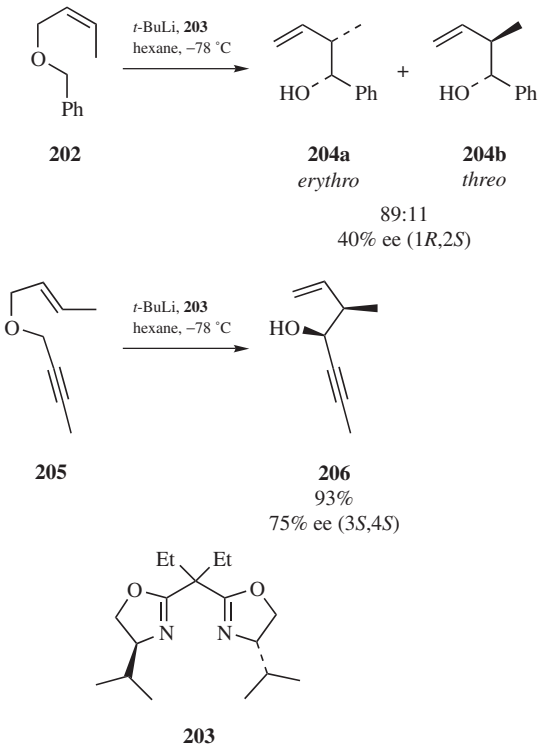


Figure 9.59. [2,3]-Wittig rearrangement.

products.[115] The reaction conditions favored the formation of erythro product **204a** in a ratio of 89:11 with 40% ee for the (1*R*,2*S*) isomer (Fig. 9.59). Under the same reaction conditions, (*E*)-crotyl propargylic ether **205** was converted into homoallylic alcohol **206** in >90% yield [93:7 erythro, 75% ee for (3*S*, 4*S*) isomer].

Allene annulation is yet another reaction in which bis(oxazoline) ligands are used for asymmetric induction.[10,116,117] One example, shown in Figure 9.60, is the reaction of *N*-tosyl-2-iodoaniline **207** with 1,2-undecadiene. This reaction proceeds

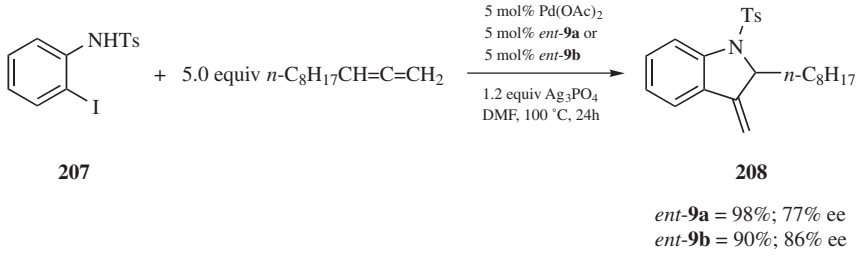


Figure 9.60. Allene annulation.

in the presence of inda-box ligands *ent*-**9a** or *ent*-**9b** to afford the annulation product **208** in 98% (77% ee) and 90% (86% ee) yields, from *ent*-**9a** or *ent*-**9b**, respectively.

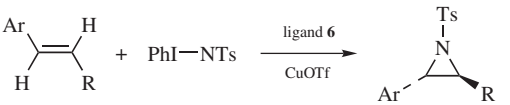
Other reactions that have been attempted using bis(oxazoline) ligands for chiral induction include the synthesis of chiral fullerenes[118] and C—H insertion reactions,[119] which met with moderate success. Also, [2+2] photocycloaddition[120] and Meerwein arylation[121] have been attempted, but both of these led to low enantioselectivities.

9.6. AZIRIDINATION AND EPOXIDATION

Aziridination and epoxidation of olefins are very important transformations in organic synthesis. Attempts to carry out these reactions enantioselectively by using bis(oxazoline)–metal catalysts have been reported. Evans and co-workers investigated aziridination of cinnamate esters **209a–e** using [*N*-(*p*-toluenesulfonyl)imino]phenyl-iodinane **207** and copper(I) triflate coordinated to several bis(oxazoline) ligands including phe-box **6**.[122,123] The results are summarized in Table 9.34 (Fig. 9.61).

Jacobsen's group carried out the conversion of (*E*)-*N*-benzylideneaniline **211** to aziridines **212a** and **212b** (Fig. 9.62).[124] Knight and co-workers examined the aziridination of styrene **41** using [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane **207**.[37,125] Jørgensen's group investigated the conversion of the α-imino esters **214a** and **214b** to aziridines **216a** and **216b**.[126] However, Waegell and co-workers attempted the epoxidation of *trans*-stilbene **217** with moderate success (Fig. 9.62).[127]

TABLE 9.34. AZIRIDINATION OF CINNAMATE ESTERS[a]



209 **207** **210**

Figure 9.61

Ar	R	% Yield	% ee
Ph	CO_2Me	63	94
Ph	CO_2Ph	64	97
Ph	CO_2CMe_3	60	96
β-Naphthyl	CO_2Me	73	96
α-Naphthyl	CO_2Me	76	95

[a]Data from Ref. 122.

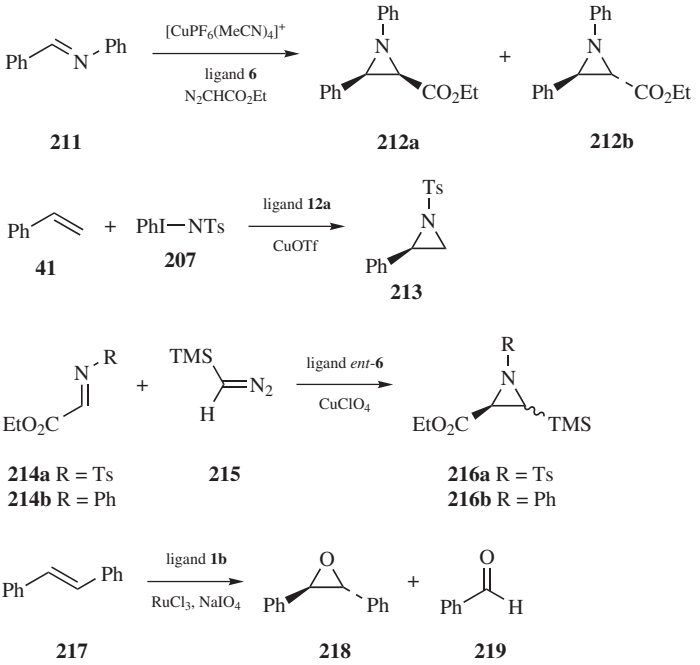


Figure 9.62. Bis(oxazoline)-mediated aziridinations and epoxidation.

9.7. SULFIMIDATION

Uemura and co-workers discovered that prochiral sulfides react with [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane **207** in the presence of bis(oxazoline) ligands to form the corresponding chiral sulfimides.[128–130] For example, (*E*)-cinnamyl phenyl sulfide **220** reacted with **207** in the presence of copper(I) triflate and *ent*-**6** to form the chiral sulfimide **221** in 80% yield (58% ee) as shown in Figure 9.63.

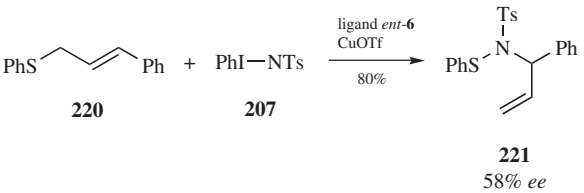


Figure 9.63. Bis(oxazoline)-mediated sulfimidation.

9.8. ALLYLIC OXIDATION

Oxidation of olefin containing molecules at the allylic position is yet another important synthetic transformation. There are many examples of oxidation of cyclic olefins including those by Pfaltz's group.[131] These reactions consisted of the oxidation of cyclic olefins **222a–c** by *tert*-butyl perbenzoate in the presence of the copper(I) complexes of ligands **1b**, **3**, **6**, and **45**. The corresponding benzoates **223a–c** were obtained in yields up to 84% with selectivities up to 84% (ee) (Table 9.35, Fig. 6.64).

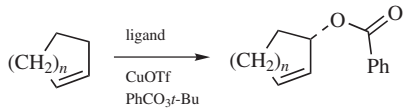
Other examples of this type of reaction include those conducted by Andrus and co-workers using the copper(I) complex of ligand **224** in the allylic oxidation of cyclohexene.[132] As shown in Figure 9.65, this reaction afforded the oxidation product, (1*S*)-2-cyclohexen-1-yl 4-nitrobenzoate **225** in 76% yield and 73% ee. Clark and co-workers also experimented with the allylic oxidation of cyclohexene using inda-box *ent*-**9b** to afford the oxidation product, (1*S*)-2-cyclohexen-1-yl benzoate, **223b** in 76% yield (71% ee).[133]

9.9. REDUCTIONS

9.9.1. Hydrosilylation

Reductive hydrosilylations of ketones using chiral C_2-symmetric bis(oxazolines) as catalysts have been studied by many different groups.[1,2,7,134–139] Nishiyama and

TABLE 9.35. BIS(OXAZOLINE)-MEDIATED ALLYLIC OXIDATION[a]



222a $n = 1$
222b $n = 2$
222c $n = 3$

223a $n = 1$
223b $n = 2$
223c $n = 3$

Figure 9.64

n	Ligand	% Yield	% ee
1	**45**	66	82
1	**3**	61	84
1	**6**	84	71
2	**45**	69	64
2	**3**	64	77
2	**6**	77	67
2	**1b**	80	71
3	**45**	75	74

[a]Data from Ref. 131.

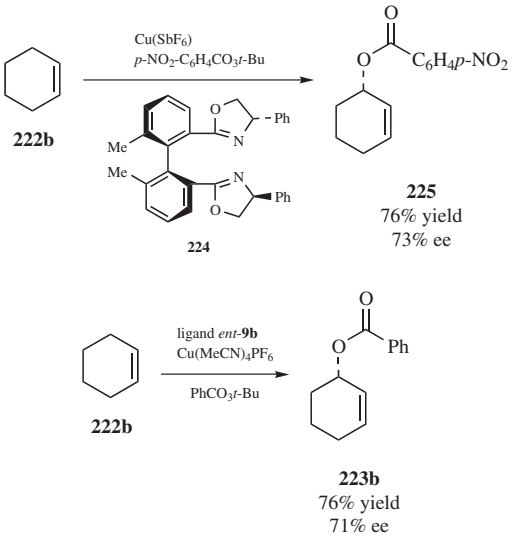


Figure 9.65. Allylic oxidations of cyclohexene.

co-workers used the orignal bis(oxazolines), especially py-box-*ip* **1b**, for the reduction of many ketones.[1,134–136] Acetophenone **226** was one of the most common ketones used in these reactions. They used the rhodium complex of ligand **1b** as the catalyst and diphenylsilane as the reducing agent to afford (*S*)-1-phenylethanol **227** (Fig. 9.66). Depending on the Lewis acid additive used, **227** was produced in up to 96% yield and up to 94% ee (Table 9.36).

Nishiyama and co-workers also used several cyclic ketones in the hydrosilylation reaction.[135] For example, 2-methylcyclohexanone **228** was reduced to form a

TABLE 9.36. HYDROSILYLATION OF ACETOPHENONE[a]

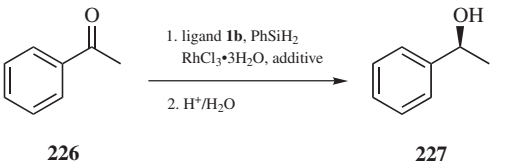


Figure 9.66

Additive	% Yield	% ee
none	0	
BF_3•OEt_2	90	82
AgOTf	96	89
$AgBF_4$	91	94

[a]Data from Ref. 1.

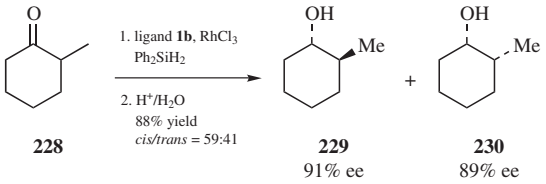


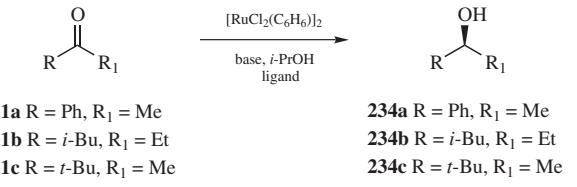
Figure 9.67. Hydrosilylation of methylcyclohexanone.

mixture (41:59) of *trans*-2-methylcyclohexanol **229** and *cis*-2-methylcyclohexanol **230** in a combined yield of 88%. The selectivities of the products were 91% (ee) for the trans alcohol **229** and 89% (ee) for the cis alcohol **230**, as shown in Figure 9.67.

9.9.2. Transfer Hydrogenation

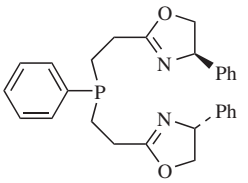
Another asymmetric reduction using bis(oxazoline) ligands is the transfer hydrogenation reaction studied by Zhang and co-workers.[140,141] The transfer hydrogenation reaction of many different ketones including **231a–c** have been examined. These ketones were reduced using isopropanol in the presence of the ruthenium complex of bis(oxazoline) ligands **232** or **233**. The reaction yields varied widely (up to 100%) and selectivities (up to 97% ee) as summarized in Table 9.37 (Fig. 9.68).

TABLE 9.37. BIS(OXAZOLINE)-MEDIATED TRANSFER HYDROGENATION OF KETONES

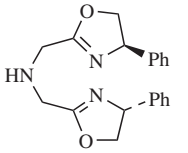


231a R = Ph, R_1 = Me
231b R = *i*-Bu, R_1 = Et
231c R = *t*-Bu, R_1 = Me

234a R = Ph, R_1 = Me
234b R = *i*-Bu, R_1 = Et
234c R = *t*-Bu, R_1 = Me



232



233

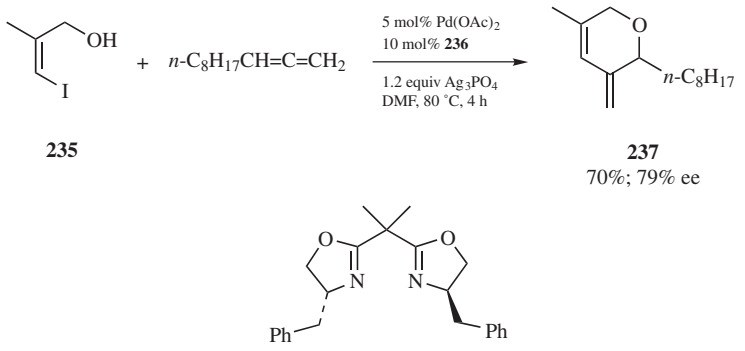
Figure 9.68

R	R_1	Ligand	% Yield	% ee	Reference
Ph	Me	**232**	72	79	140
i-Bu	Et	**232**	100	63	140
t-Bu	Me	**232**	85	92	140
Ph	Me	**233**	91	97	141

9.10. MISCELLANEOUS REACTIONS

Many examples of the use of chiral C_2-symmetric bis(oxazoline) ligands have been presented here. Other examples include their use in various heteroannulations, one of which is shown in Figure 9.69. Here, the vinyl iodide, (*Z*)-3-iodo-2-methyl-2-propen-1-ol, **235** is condensed with 1,2-undecadiene to form the 3-methylene-2*H*-pyran derivative **237**.[142] When this reaction was run in the presence of 10 mol% of bis(oxazoline) ligand **236** complexed with palladium(II), **237** was produced in 70% yield with 79% ee.

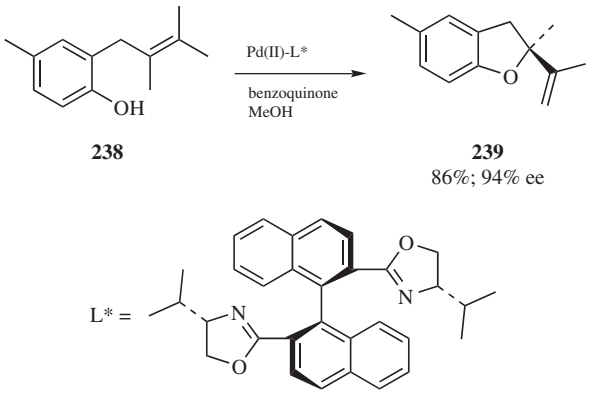
Bis(oxazoline) ligands have also been used in Wacker-type cyclizations.[143] For example, the phenolic derivative **238** was cyclized in the presence of ligand **13b** complexed with palladium(II) to yield the 2,3-dihydrobenzofuran **239** in 86% yield with an ee of 94% (Fig. 9.70).



235 **237** 70%; 79% ee

236

Figure 9.69. Heteroannulation example.



238 **239** 86%; 94% ee

13b

Figure 9.70. Wacker-type cyclization.

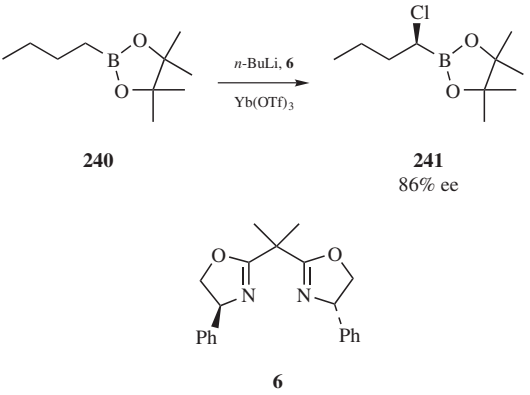
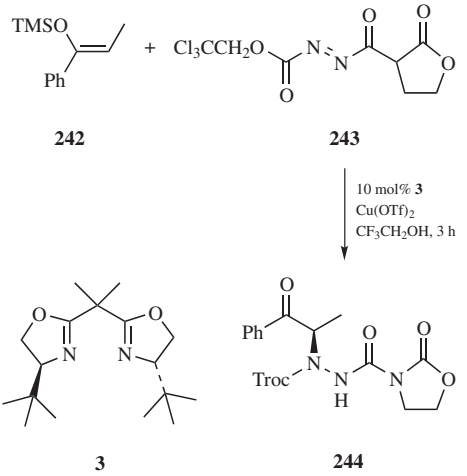


Figure 9.71. Synthesis of (α-chloroalkyl)boronates.

Yet another use for bis(oxazoline) ligands is in the synthesis of (α-chloroalkyl) boronates.[144] As shown in Figure 9.71, the alkylboronate **240** was converted to the α-chloro derivative **241** in 86% ee through the use of ytterbium(III) triflate-complexed phe-box **6**.

Enantioselective amination of enolsilanes has also benefited from the use of bis(oxazoline) lignads.[145] For example, (*Z*)-1-phenyl-1-(trimethylsilyloxy)-1-propene, **242** was condensed with **243** using copper(II) triflate-complex bu-box ligand **3** to afford **244** in 95% yield (99% ee) as shown in Figure 9.72.

Bis(oxazoline) ligands have also been employed in the catalytic enantioselective aza-Claisen rearrangement of allylic imidates,[146] chirality recognition in the determination of the ee of 1,1′-bi-2-naphthol,[147] and the enantioselective formation of double and triple helicates.[148]



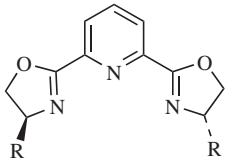
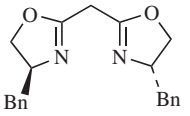
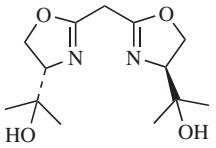
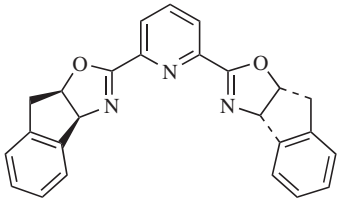
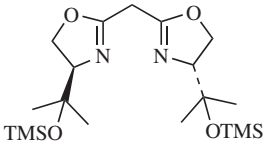
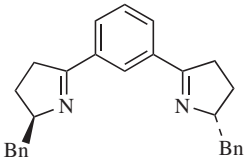
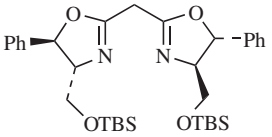
Troc = 2,2,2-trichloroethoxycarbonyl

Figure 9.72. Enantioselective amination of enolsilanes.

9.11. CONCLUSION

As evident in this chapter, metal complexes of chiral bis(oxazoline) ligands are versatile catalysts for a wide variety of asymmetric transformations. An extensive list of applications has been presented in this chapter. Since the first report of the synthesis of a chiral C_2-symmetric bis(oxazoline) by Nishiyama in 1989, innumerable articles dealing with design, synthesis, and applications of bis(oxazoline) ligands have appeared in the literature. Many new catalytic systems have been devised by employing a variety of metals, counterions and ligands designed from natural and unnatural amino acids or amino alcohols. An impressive level of enantioselectivities, isolated yields, and catalytic efficiencies have been achieved in many cases. The effectiveness of these catalysts and the overall importance of enantio- and diastereoselection in synthesis, especially in this pharmaceutical age, insures that chiral C_2-symmetric bis(oxazoline) ligands will be an important part of organic synthesis for years to come (Table 9.38).

TABLE 9.38. BIS(OXAZOLINE) LIGANDS

Ligand	References	Ligand	References
	1, 2		33, 77, 78
R = Ph R = *i*-Pr R = *t*-Bu R = *i*-Bu			33, 34
	39		42
	98, 99		33, 77, 78

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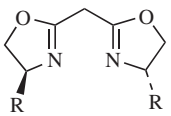
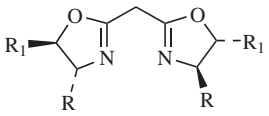
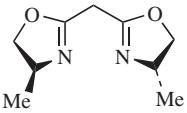
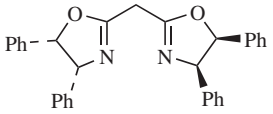
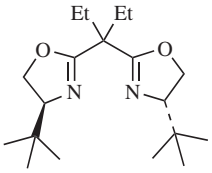
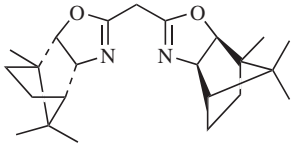
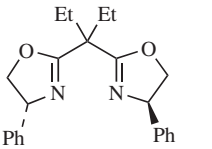
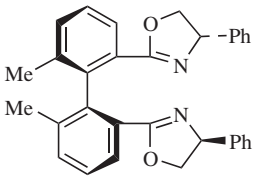
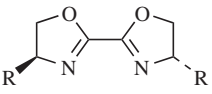
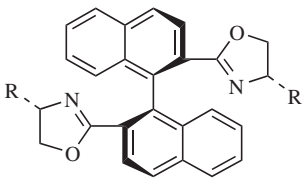
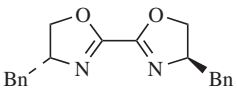
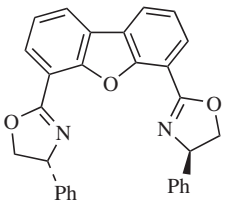
 R = *t*-Bu R = *i*-Pr R = Ph R = Bn	3	 R = Me, R_1 = Ph R = CH_2OH, R_1 = H R = Et, R_1 = H	3
	24		5
	103, 104		5
	51		132
 R = Ph R = *i*-Pr R = *t*-Bu	7	 R = Ph R = *i*-Pr R = *t*-Bu	14
	33, 77, 78		15

TABLE 9.38 (*Continued*)

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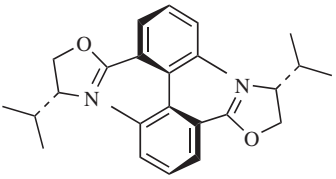
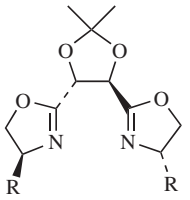
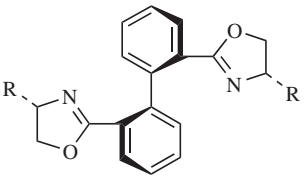
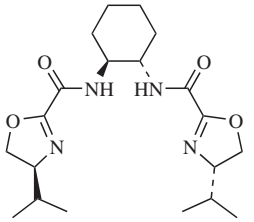
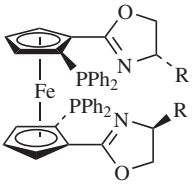
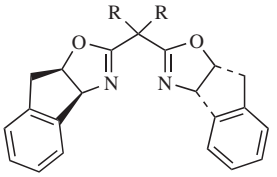
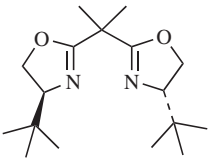
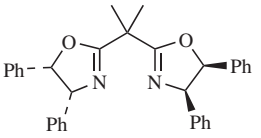
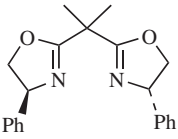
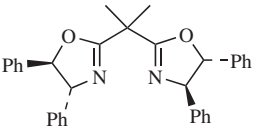
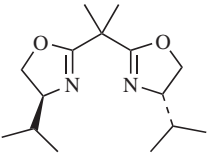
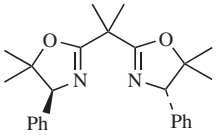
	8	 R = Ph R = *i*-Pr R = *t*-Bu	13
 R = *i*-Pr R = *t*-Bu	38		80
 R = *i*-Pr R = *t*-Bu	12	 R = H R = Me	9 (R = H) 10 (R = Me)
	4		3
	6		11
	4		17

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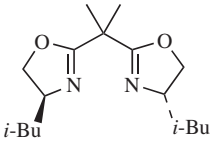
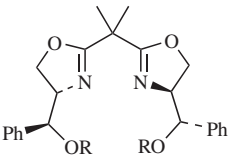
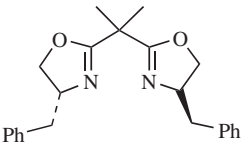
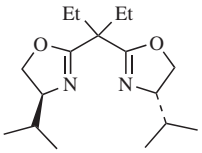
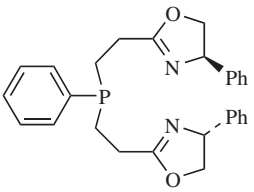
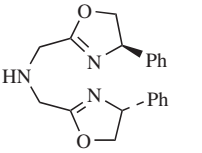
	89, 90	 R = COPh R = H R = COMe R = Me R = Bn R = SiMe$_2$*t*-Bu	40
	142		115
	140, 141		140, 141

9.12. ADDENDUM

Chemistry involving chiral C_2-symmetric bis(oxazoline) catalysts remains an exciting and dynamic field, which is evidenced by the number of publications concerning their use since the completion of this chapter. The recent manuscripts deal with a variety of aspects in this field. Some highlights of this research include the use of bis(oxazoline) catalysts in the Mukaiyama-Michael reaction of alkylidene malonates and enolsilanes by Evans and co-workers.[149] One example of this reaction shown in Figure 9.73 depicts the reaction of the enolsilane [(1-*tert*-butylthio)vinyl]oxy trimethylsilane **245** with dimethyl benzylidenemalonate **246**. The reaction is catalyzed by 10 mol% of complexed bu-box ligand **3** in a mixture of 2,2,2-trifluoroethanol, toluene and methylene chloride at −78 °C and produced the corresponding thioester **247** in 91% yield with 93% ee. Evans also investigated the use of bis(oxazolines) in the catalysis of carbonyl-ene reactions with glyoxylate and pyruvate esters,[150] the cycloadditions of silyl ketenes[151] and further investigated their utility in hetero Diels–Alder reactions.[152]

Another recent example of the use of chiral C_2-symmetric bis(oxazoline) ligands is the work by Mamai and co-workers.[153] This group studied the cyclopropanation reaction of oxazolidinones **80a** and **80b** using diphenylsulfonium isopropylide **248**,

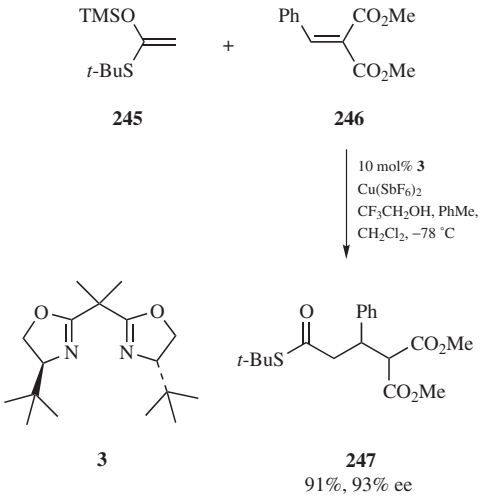
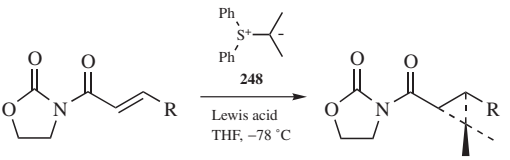


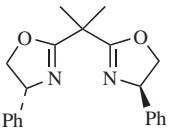
Figure 9.73. Enantioselective Mukaiyama–Michael addition of enolsilanes.

TABLE 9.39. CYCLOPROPANATIONS WITH SULFUR YLIDES[a]



80a R = Me
80b R = Ph

249a R = Me
249b R = Ph

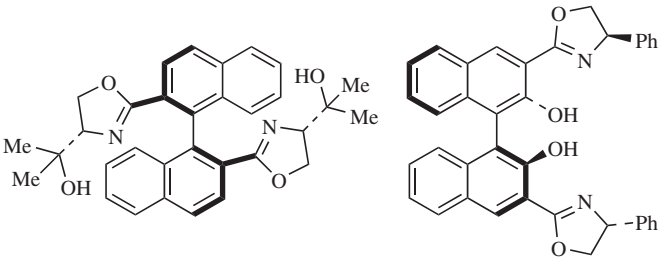


***ent*-6**

Figure 9.74

Substrate	Lewis Acid	equiv	% Yield	% ee
80a	$Zn(OTf)_2$	1	63	95
80a	$ZnBr_2$	1	60	93
80a	$Sn(OTf)_2$	1	60	81
80a	MgI_2	1	66	46
80a	$Zn(OTf)_2$	0.75	65	82
80a	$Zn(OTf)_2$	0.75	63	55
80b	$Zn(OTf)_2$	1	69	36
80b	MgI_2	1	70	14

[a]Data from Ref. 153.



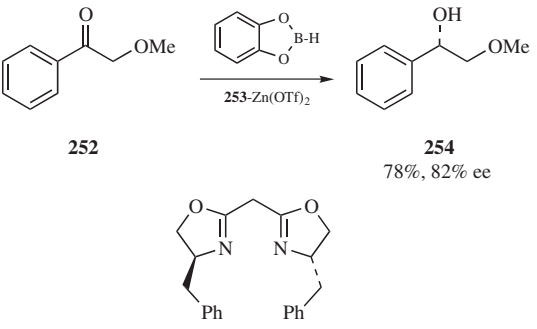
250 **251**

Figure 9.75. Biaryl bis(oxazolines).

as shown in Figure 9.74. The reaction afforded cyclopropane derivatives **249a** and **249b** in yields ranging from 60 to 70% and ee as high as 95% (Table 9.39, Fig. 9.74).

Many other groups further studied the utility of bis(oxazolines) including Ikeda's use of biaryl bis(oxazolines) such as **250** (Fig. 9.75) in the zinc-catalyzed asymmetric alkylation of benzaldehyde with diethylzinc.[154] This reaction proceeded in yields up to 92% with ee up to 88%. Kodama and co-workers used a biaryl bis(oxazoline) ligand, namely, [1,1′-]binaphthalenyl-2,2′-diol (BINOL)-box **251**, in the lanthanide-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones to alkenes.[155]

Bandini and co-workers studied the zinc triflate-bis(oxazoline)-catalyzed reduction of α-alkoxy-ketones with catecholborane.[156] The example in Figure 9.76 shows the reduction of α-methoxyacetophenone **252**. 1-Phenyl-2-methoxyethanol **254** was isolated in 78% yield and 82% ee.



252 **254**
78%, 82% ee

253

Figure 9.76. Reduction of α-alkoxy-ketones.

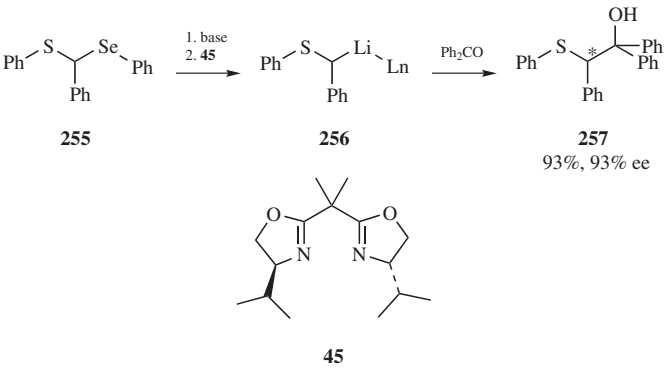


Figure 9.77. Addition of an α-thioorganolithium reagent to aldehydes.

Nakamura and co-workers examined the use of bis(oxazolines) in the addition of α-thioorganolithiums to various aldehydes.[157] One example, shown in Figure 9.77, produced the corresponding hydroxysulfide **257** in 93% yield with an ee of 93%.

Glos and co-workers introduced the aza-bis(oxazolines) **258** and **259** (Fig. 9.78) as a new class of chiral C_2-symmetric bis(oxazoline) ligands.[158] These catalysts were used in various reactions such as enantioselective allylic substitution and cyclopropanation; it was also shown that these new catalysts could easily be tethered to a polymeric support, as shown in structure **259**, allowing for facile recovery of the catalyst. There have been other examples of bis(oxazoline) ligands immobilized on solid supports and their use in catalysis.[159–162] These methods have shown mixed results.

Another new use for chiral bis(oxazolines) is the Friedel–Crafts reaction of aromatic and heteroaromatic compounds. Jørgensen and co-workers found that the

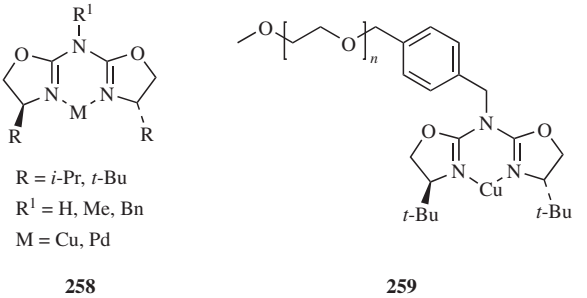
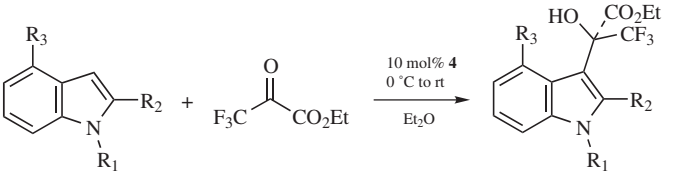
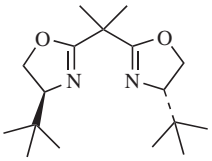


Figure 9.78. Aza-bis(oxazolines).

TABLE 9.40. BIS(OXAZOLINE)-MEDIATED FRIEDEL–CRAFTS REACTIONS OF INDOLES[a]



260 **261** **262**



3

Figure 9.79

R_1	R_2	R_3	% Yield	% ee
Me	H	H	94	89
H	H	H	93	83
Me	Me	H	88	94

[a]Data from Ref. 163.

use of bu-box **3** with copper(II) triflate catalyzed the condensation of various indoles **260** with ethyl trifluoropyruvate **261**.[163] This condensation afforded a chiral hydroxy-trifluoromethyl ester substituent in the 3-position of the indole ring in yields up to 94% with ee ranging from 83 to 94% (Table 9.40, Fig. 9.79).

Inda-box *ent*-**9a** has been used recently in the production of the natural product (−)-malyngolide **265**.[164] The key step of the synthesis by Ghosh and Shirai, as shown in Figure 9.80, is the hetero-Diels–Alder reaction of Danishefsky's diene **112** and α-ketoester **263** to afford the pyranone derivative **264** in 77% yield and 47% ee that was converted into (−)-malyngolide in several additional steps. The preparation of different pyranones was investigated using different α-ketoesters.

The selected examples shown above, together with numerous others, represent an extension of the vast amount of information regarding chiral C_2-symmetric bis(oxazolines) and their uses in asymmetric transformations. The utility and importance of this chemistry continues to be demonstrated as more applications for these complexes are discovered.

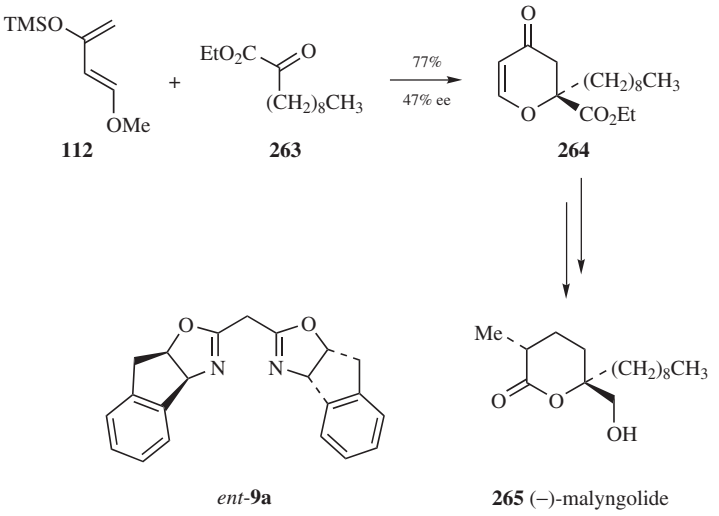


Figure 9.80. Synthesis of (−)-malyngolide.

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Author Index

The entries in this index refer to the chapter number (boldface) and the reference number.

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Subject Index

General oxazolone and oxazoline substitution patterns are described in the text although entries in an associated table may be more specific in accordance to the examples from the original literature. For instance, a table of 4,5-diphenyl-2(3*H*)-oxazolones can be referred to in the text as 4,5-disubstituted 2(3*H*)-oxazolones. Tables of oxazolones and oxazolines that incorporate multiple substitution patterns or functional groups are titled with a general designation as 2(3*H*)-oxazolones, 5(2*H*)-oxazolones, saturated 5(4*H*)-oxazolones, unsaturated 5(4*H*)-oxazolones, and oxazolines. The individual entries in a table are not included in the index. *Italicized* page numbers refer to tables.

Alphabetized lists of the general classes and exact names of oxazolones, oxazolines and bis(oxazolines) follow the subject index. The list of general classes of oxazolones, oxazolines and bis(oxazolines) includes all classes described in the text or tables as either starting materials or products. The entries in these lists are sorted and arranged in accordance with the sort order rules defined in Microsoft Word. The subject index is cross-referenced wherever possible to facilitate locating a general substitution pattern, a synthetic method or a reaction.

For example, using a ketone as a starting material, the general classes of compounds that can be prepared include **2(3*H*)-oxazolones**, **3-aryl-5-*tert*-butyl-2(3*H*)-oxazolones**, **3-aryl-5-phenyl-2(3*H*)-oxazolones**, **4-(alkylthio)-5(2*H*)-oxazolones**, **4-(arylthio)-5(2*H*)-oxazolones**, **4-alkoxy-5(2*H*)-oxazolones**, **4,5-diphenyl-2(3*H*)-oxazolones**, **4,5-diphenyl-2(3*H*)-oxazol-2-thiones**, and **5(2*H*)-oxazolone *N*-oxides**, which are identified as bolded entries.

Additionally, all of these bolded entries are included alphabetically in the list of general classes of compounds that follows the subject index. Here, for example, the entry for 2(3*H*)-oxazolones lists all pages that discuss 2(3*H*)-oxazolones and will direct one not only to the pages that use ketones as a starting material but to other synthetic methods or reactions as well.

A table index follows the subject index.

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Oxazolines

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Oxazolones

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