

Science of Synthesis

Organometallics

Compounds of Group 1 (Li ... Cs)

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Thieme

Dedicated To:

*All chemists mesmerized by the
utter beauty of methyllithium sparks.*

*All those who nurture perseverance
and collaboration of minds.*

Our parents, our children, and theirs.

All students, past, present, and future.

And to the indomitable Krista Voigt.

Volume 8: Compounds of Group 1 (Li...Cs)

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8.2.4 **Product Subclass 4: Sodium–Oxygen Compounds**

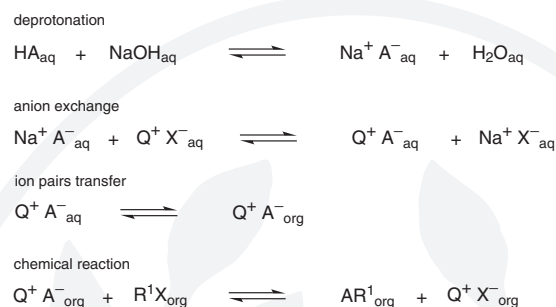
A. Jończyk and A. Kowalkowska

Applications of Product Subclass 4 in Organic Synthesis

8.2.4.1 **Sodium Hydroxide**

Sodium hydroxide is a hygroscopic substance which exhibits both basic as well as nucleophilic properties and is used for the generation of organic anions and dihalocarbenes, and for hydrolysis of esters, among many other reactions. These reactions can be carried out under conventional conditions or, more conveniently and efficiently, under conditions of phase-transfer catalysis (PTC).^[1–7] Different forms of solid sodium hydroxide (pellets, beads, flakes) are commercially available, as well as a 50% aqueous solution, widely applied in phase-transfer-catalyzed reactions. Phase-transfer catalysis is used to carry out reactions of electrophiles with anions in the form of alkali metal salts (commercially available alkali metal cyanides, azides, carboxylates, etc.) or anions generated from compounds with acidic properties (HA) by means of a suitable base, usually sodium hydroxide. Under the latter circumstances, the two-phase reacting system consists of an aqueous solution or solid sodium hydroxide (the basic phase) and of the anion precursor and the electrophile dissolved in an organic solvent [the organic phase (org)]. Organic substrates can be dissolved in aprotic solvents of low polarity (e.g., benzene, dichloromethane). The reactions are catalyzed by means of compounds capable of forming lipophilic ion pairs with anions, such as the quaternary onium salts, Q^+X^- (often tetraalkylammonium salts), crown ethers, or poly(ethylene glycol)s and their ethers. The basicity of the aqueous phase is adjusted with respect to the acidity of the compound which is to be deprotonated. Reactions of relatively strong acids such as thiols, phenols, and 1,3-dicarbonyl compounds with electrophiles, e.g. alkylating agents, are usually carried out in the presence of dilute aqueous sodium hydroxide. In these cases, the anion formation takes place in the aqueous phase and the newly generated anion pairs with the sodium cation. Na^+A^- cannot enter into the nonpolar organic phase because it lacks lipophilic properties. Since the reacting species (the anion and the electrophile) are located in two immiscible phases, the reaction cannot proceed or occurs at a low rate. The catalyst Q^+X^- can dissolve to some extent in the aqueous phase or, in the case of highly lipophilic catalysts, resides only in the organic phase. In the first case, the ion exchange between the ion pair Na^+A^- and the catalyst occurs in the aqueous phase and the lipophilic ion pairs Q^+A^- thus formed easily migrate into the organic phase, in which a chemical reaction leads to the formation of the product and regeneration of the catalyst (Scheme 1).

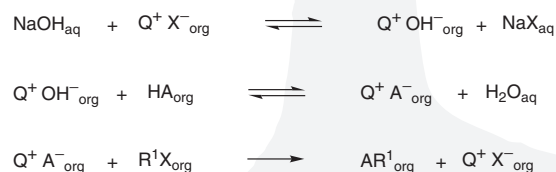
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Scheme 1 Phase-Transfer-Catalyzed Reaction in the Presence of a Moderately Lipophilic Catalyst Q^+X^- 

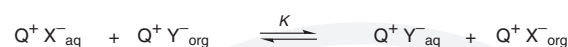
However, highly lipophilic salts Q^+X^- , which are practically insoluble in the aqueous phase, are also efficient phase-transfer catalysts. In this case, the anion exchange between the two anion pairs Na^+A^- and Q^+X^- , dissolved respectively in the aqueous and the organic phases, takes place at the interphase (int) as shown in Scheme 2.

Scheme 2 Phase-Transfer-Catalyzed Generation of Ion Pairs in the Presence of a Lipophilic Catalyst Q^+X^- 

The alkylation of compounds which are relatively weak acids requires concentrated aqueous solution or solid sodium hydroxide. When a concentrated aqueous base is used, deprotonation cannot occur in the aqueous phase since the strong salt-out effect precludes dissolution of the anion precursor in this phase. One possible solution to this problem lies in the formation of the lipophilic Q^+OH^- at the interphase. After migration into the organic phase, the quaternary ammonium hydroxide effects deprotonation of the acid and the resulting ion pair Q^+A^- undergoes alkylation (this mechanistic pathway is described as extraction of the OH^- into the organic phase; Scheme 3).

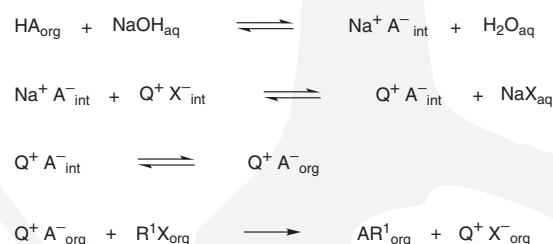
Scheme 3 Phase-Transfer-Catalyzed Reaction with Hydroxide Ion Extracted into the Organic Phase

The rate of phase-transfer-catalyzed alkylation is determined by the concentrations of R^1X and of the reacting anion in the organic phase; the latter depends on the concentration of OH^- . Regarding the concentration of Q^+OH^- in the organic phase, it should be noted that the lipophilicity of anions such as Cl^- , Br^- , or I^- , introduced with the catalyst or formed during the alkylation stage, should be taken into account. Lipophilicity increases in the series $OH^- < SO_4^{2-} < F^- < Cl^- < CN^- < Br^- < I^- < ClO_4^- < SCN^-$, and hydrophilicity increases in the opposite direction in the same series. For a given Q^+ , the equilibrium constant K of anion exchange between phases depends roughly on their hydration energy (the solvation energy of anions in the organic phase may be neglected), which is particularly high for anions having small radii or bearing more than one negative charge (Scheme 4).

Scheme 4 Equilibrium Constant K for Anion Exchange between Phases

Thus, in the presence of lipophilic anions, the concentration of weakly lipophilic OH^- in the organic phase is negligibly low. Therefore, the mechanism with extraction of Q^+OH^- into the organic phase^[8] is valid in processes in which halide anions are not involved, such as during isotope exchange in CH acids,^[9] carbanion oxidation with oxygen,^[9] or alkene isomerization^[10] catalyzed by tetrabutylammonium hydrogen sulfate. In the case of this catalyst, the counter anion HSO_4^- undergoes reaction with sodium hydroxide to form one of the most hydrophilic anions, namely SO_4^{2-} . In view of the foregoing, alkyl iodides can be expected to be poor alkylating agents since the lipophilic iodide anions inhibit the reaction. This conclusion is true when alkylating CH acids of $pK_a \geq 22$ (measured in dimethyl sulfoxide), but in the case of CH acids of $pK_a \leq 16$ –17 (measured in dimethyl sulfoxide), alkyl iodides can be safely used. The inhibiting effect of I^- is explained by the unfavorable equilibrium for formation of Q^+A^- in the presence of I^- , and by the decrease of the effective concentration of OH^- at the interphase resulting from the adsorbed I^- .^[11] The undesired effect of the iodide anions is avoided when alkylation with alkyl iodides is carried out using equimolar amounts of HA and Q^+X^- , usually tetrabutylammonium hydrogen sulfate. Typically, such reactions are performed in the presence of aqueous sodium hydroxide in dichloromethane (extractive alkylation). Alternatively, the organic phase with dissolved ion pairs is separated (the solvent may be replaced) and treated with an alkyl iodide (ion-pair extraction).^[12]

According to another, much more often encountered and commonly accepted mechanistic pathway, the HA compound is deprotonated by sodium hydroxide at the interphase.^[3,6,7,13] The anion pairs are formed in low concentration and stay at the interphase. The salt-out effect of the concentrated aqueous sodium hydroxide and the lack of lipophilic properties do not allow the anion pairs to enter either into the aqueous or the organic phase. Anion exchange with the catalyst which occurs at the interphase produces the lipophilic anion pairs Q^+A^- , which leave the interphase and are alkylated in the organic phase with concomitant regeneration of the catalyst, Q^+X^- . The processes with participation of the latter are repeated until one or all of the reagents are consumed (Scheme 5).

Scheme 5 Phase-Transfer-Catalyzed Reactions with Anions Generated at the Interphase

In spite of the low concentration of Q^+A^- in the organic phase, which cannot exceed that of the catalyst (usually $\leq 5\%$ of the amount of HA), the rates of phase-transfer-catalyzed processes are high. The reason is the high concentration of the electrophilic substrate, the purely ionic character of the bond in the ion pairs Q^+A^- , and the weak solvation of A^- in the nonpolar organic phase.

Compared to traditional methodologies, phase-transfer catalysis offers significant advantages: elimination of organic solvents, avoidance of dangerous and expensive bases, high selectivity, yield, and purity of products, as well as simplicity of procedures.

for references see p 1117

8.2.4.1.1

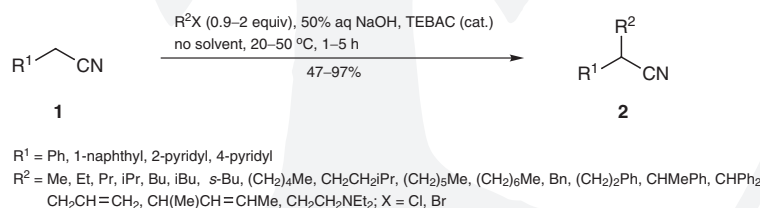
Method 1:
Generation and Reactions of Carbanions

The use of sodium hydroxide and a phase-transfer catalyst allows alkylation of CH acids of $pK_a \leq 24$ ^[7], or isotopic exchange with acids of $pK_a \leq 38$.^[9] Addition of a dipolar aprotic solvent (dimethyl sulfoxide, hexamethylphosphoric triamide) to the system often increases the reaction rate and the yield.^[6] Mixtures of solid sodium hydroxide and potassium carbonate show increased efficiency as bases; furthermore, such mixtures facilitate stirring because they prevent formation of sticky mixtures with the generated water, which happens when solid sodium hydroxide is used.^[14] The use of solid potassium carbonate or potassium hydroxide (aqueous solution or solid) with a phase-transfer catalyst sometimes gives better results than with sodium hydroxide. Phase-transfer-catalyzed reactions have been reviewed^[15] and are also included in a review on nitrile-stabilized carbanions.^[16]

8.2.4.1.1.1

Variation 1:
Reactions of Carbanions with Alkylating Agents

Phase-transfer-catalyzed alkylation of phenylacetonitrile (**1**, $R^1 = \text{Ph}$) with alkyl halides,^[17–21] haloacetates,^[22] chloroacetonitrile^[23] and other chloroalkanenitriles,^[24] α -chloro ethers,^[25] nitrobenzyl chlorides,^[26] or alkyl chain dihalo compounds^[27–31] occurs in high yield to give nitriles **2** (Scheme 6). 2-Substituted derivatives of phenylacetonitrile undergo reaction with alkyl halides,^[21] chloroalkanenitriles,^[24] α -chloro ethers,^[25] nitrobenzyl chlorides,^[26] haloacetates,^[32] dihaloalkanes,^[33] halonitrobenzenes,^[34,35] chloronitropyridines,^[36] their *N*-oxides,^[37] or chloro-substituted nitrogen heterocycles.^[38,39] Diphenylacetonitrile undergoes reaction with alkyl halides,^[40] haloacetates,^[32] chloroalkanenitriles,^[24] α -chloro ethers,^[25] nitrobenzyl chlorides,^[26] dihaloalkanes,^[33] halonitrobenzenes,^[34,35] chloronitropyridines,^[36] their *N*-oxides,^[37] or chloro-substituted nitrogen heterocycles^[38,39] under phase-transfer catalysis to form mono- and/or disubstituted products, usually in high yield (Scheme 6). Alkylation of 1-naphthyl- or 1-naphthyl(phenyl)acetonitrile^[41] and pyridylacetonitriles^[42] is also efficiently carried out under phase-transfer catalysis.

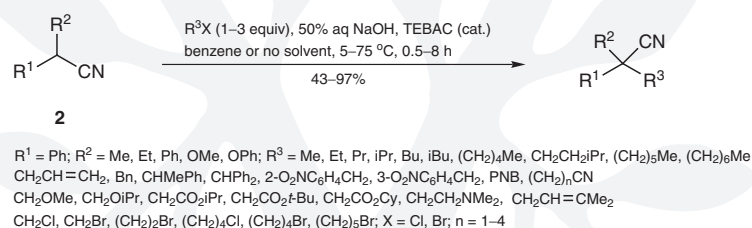
Scheme 6 Phase-Transfer-Catalyzed Alkylation of Arylacetonitriles^[19,20,41,42]

Typically, these processes are carried out in the presence of 50% aqueous sodium hydroxide and benzyltriethylammonium chloride as the catalyst. Chlorides or bromides (provided excess of aqueous base is used) are suitable alkylating agents, but the use of iodides is not recommended.^[1,2,11]

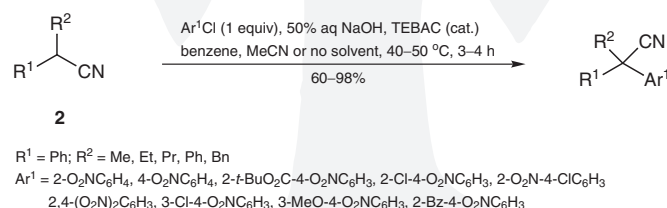
High-yield monoalkylation of arylacetonitriles is usually observed (Scheme 6), unless the monoalkyl derivative is a stronger acid than the starting CH acid. Thus, reaction of phenylacetonitrile with esters of haloacetic acids (with secondary or preferably tertiary alcohols)^[22] affords significant amounts of dialkylated products,^[22] while the use of chloroacetonitrile^[23] or nitrobenzyl chlorides^[26] results in the formation of these products exclusively. With an excess of active alkylating agents, at elevated temperature, dialkylated products are formed in very high yield.^[21] When substituent effects increase dramatically

the acidity of the alkylated phenylacetonitrile (e.g., **2**, $R^1 = \text{Ph}$; $R^2 = 4\text{-O}_2\text{NC}_6\text{H}_4$), its anion forms an unreactive ion pair with Q^+ and the process is arrested.^[34] A special procedure for isolation of monoalkylated nitriles **2** ($R^1 = \text{Ph}$; $R^2 = \text{Me, Et, CH}_2\text{CH}=\text{CH}_2$) from the reaction mixtures is available.^[43] Alkylation of phenylacetonitrile with α -chloro ethers affords substituted glutaronitriles; simple alkylated products result from 2-phenylalkanenitriles.^[25] Displacement of chloride in *gem*-dihalocyclopropanes substituted with a *tert*-butoxycarbonyl, phenylsulfonyl,^[44] or phenyl^[45] group by carbanions from **2** ($R^1 = \text{Ph}$; $R^2 = \text{Ph, alkyl}$), generated under phase-transfer-catalyzed conditions, gives the corresponding *gem*-disubstituted cyclopropanes^[44] or 2-substituted 1-phenylcyclopropenes,^[45] respectively, via elimination–addition pathways. Similarly, 1,2-disubstituted methylenecyclopropanes are synthesized from 1,1-dichloro-2-(chloromethyl)cyclopropane.^[46] Phase-transfer-catalyzed alkylation^[47–49] or nitroarylation^[47] of phenylacetonitrile and its 2-substituted derivatives is realized with dibenzo-18-crown-6 as a catalyst,^[47] with polystyrene-bound Q^+X^- ,^[48] and also under microwave irradiation.^[49] Phase-transfer catalysis is a convenient method for alkylation of phenylacetonitrile substituted at C2 with an alkoxy (**2**, $R^1 = \text{Ph}$; $R^2 = \text{OR}^3$)^[50,51] or a dimethylamino group (**2**, $R^1 = \text{Ph}$; $R^2 = \text{NMe}_2$);^[52] in the latter case, a mixture of concentrated aqueous and solid sodium hydroxide is used (Schemes 7 and 8).

Scheme 7 Phase-Transfer-Catalyzed Alkylation of Phenylacetonitrile Derivatives^[21,24–26,32,33,40,50]

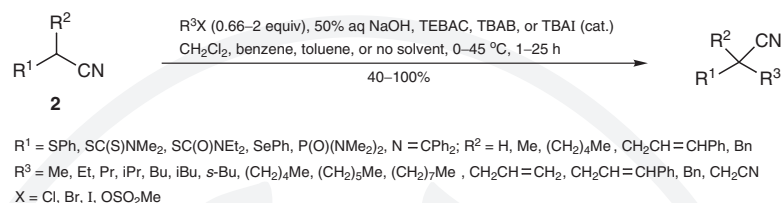


Scheme 8 Arylation of Phenylacetonitrile Derivatives by Nucleophilic Aromatic Substitution^[35]



Aliphatic nitriles are not strong enough CH acids to be alkylated under the conditions of phase-transfer catalysis, but nitriles **2** substituted with sulfur,^[53–56] selenium,^[57] or phosphorus,^[58–60] as well as with two heteroatoms (e.g., **2**, $R^1 = \text{OPh}$; $R^2 = \text{SMe}^{[61]}$), easily enter into the reaction (Scheme 9). In the case of diethyl (cyanomethyl)phosphonate,^[58,59] an equimolar amount of Q^+X^- is used. Alkylated sulfur-substituted acetonitriles are useful substrates for the synthesis of ketones,^[54] functionalized nitriles,^[55] or α -sulfanylalkanoic acid esters.^[56] Alkylation of the glycine Schiff base **2** ($R^1 = \text{N}=\text{CPh}_2$) is accomplished with mono-^[62] and dihaloalkanes^[63] in high yield under standard phase-transfer conditions.

for references see p 1117

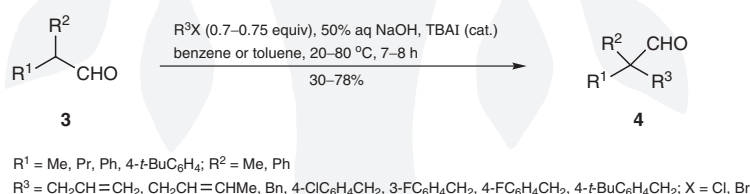
Scheme 9 Phase-Transfer Alkylation of Heteroatom-Substituted Nitriles^[53–57,60,62]

Phase-transfer reactions of methylene nitriles with aliphatic dihalo compounds allow the synthesis of cyclic products.^[27–31,41,53–55,57,59,63] The use of 1-bromo-2-chloroethane is recommended for cyclopropanation of arylacetonitriles,^[28] but dibromoalkanes give better results in the synthesis of larger rings.^[27]

2-Benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (isoquinoline Reissert compound) undergoes efficient alkylation with alkyl bromides,^[64] chloronitrobenzenes,^[64,65] benzyl halides,^[64–66] chloronitropyridines,^[36] and 9-chloroacridine.^[39] Sonication improves yields and shortens the reaction times.^[65] The products are useful precursors of 1-substituted isoquinolines.^[39,64]

1-Substituted benzyl isocyanides^[67,68] and 9-fluorenyl isocyanide^[68] also undergo alkylation under phase-transfer conditions. The products of nitrobenzylation of benzhydryl and 9-fluorenyl isocyanide undergo elimination of the isocyanide group, with formation of the corresponding alkenes.^[67,68]

Methine aldehydes **3** ($R^1 = R^2 \neq H$) are alkylated with active alkylating agents (methyl, allyl, and benzyl halides) under phase-transfer catalysis to yield the products **4** (Scheme 10).^[69,70] In the case of 2-ethylhexanal, competitive C- and O-alkylation is observed.^[69] Direct dibenzylation at C2 of phenylacetaldehyde affords the products in 19–29% yield.^[70]

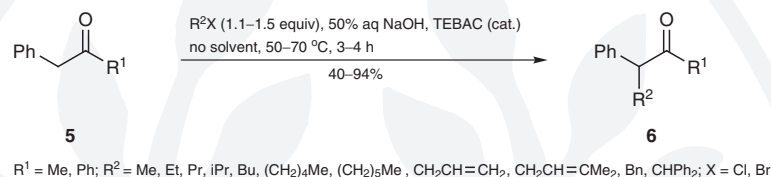
Scheme 10 Phase-Transfer Alkylation of Methine Aldehydes^[69,70]

α,β -Disubstituted α,β -unsaturated aldehydes undergo phase-transfer alkylation, giving the corresponding α,α -disubstituted β,γ -unsaturated products.^[70] A similar result is observed in the reactions of methylene aldehydes with alkylating agents, which take place with formation of aldol products followed by elimination of water to give α,β -unsaturated aldehydes, which finally undergo deconjugative alkylation.^[70–72]

The ease of ketone alkylation under phase-transfer catalysis is highly dependent upon their acidity. When sodium hydroxide and a phase-transfer catalyst are used, α -aryl substituted ketones are obtained in the best yield and selectivity.^[73] Thus, benzyl ketones such as phenylacetone (**5**, $R^1 = Me$)^[74–76] and 1,2-diphenylethanone (**5**, $R^1 = Ph$),^[77,78] 1-acenaphthenone,^[79] 3,4-dihydronaphthalen-2(1*H*)-one,^[80] 2-arylcyclohexanones,^[81] and anthrone^[82] undergo alkylation in the presence of aqueous sodium hydroxide and either Q^+X^- , 18-crown-6,^[81] or α -phosphoryl sulfoxides and sulfones^[76] as the catalyst, giving the products **6**, usually in good yield (Scheme 11). The accessibility of the positive nitrogen center in Q^+ is the decisive factor determining the rate of methylation of 1,2-diphenylethanone with dimethyl sulfate, as well as the ratio of C/O substitution.^[78] Alkylation of 1-phenylacetone and 1,2-diphenylethanone with α -chloro ethers gives O-deriva-

tives in moderate yield.^[83] Alkyl benzyl ketones undergo facile monoalkylation,^[74,76] but in the case of cyclic ketones, dialkylation decidedly prevails.^[79,80] Phase-transfer nitroarylation of α -alkyl-substituted phenylacetones is aided by the addition of small amounts of dimethyl sulfoxide, whereas 1,1-diphenylacetone and 4-nitrohalobenzenes give only O-substituted products.^[84] Anthrone treated with an excess of allyl or propargyl bromides gives the 10,10-disubstituted products, while 10-propargylanthrone gives mainly O-alkyl derivatives, i.e. 9-alkoxy-10-propargylanthracenes.^[82]

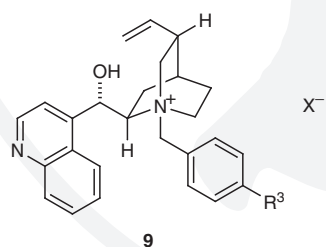
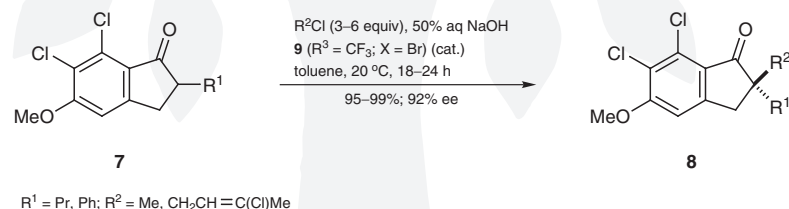
Scheme 11 Phase-Transfer Alkylation of Benzyl Ketones^[74,77]



The reaction of benzyl ketones with dibromoalkanes gives rather complex mixtures. This is due to the difficulty in substituting both benzylic hydrogens and the ambident nature of the enolate anions. However, phase-transfer cyclopropanation of benzyl ketones with 1,2-dibromoethane occurs in reasonable yields of ca. 50%.^[75,77,79] Alkylation of 1,3-diphenylacetone with 1,2-dibromoethane^[85] or 1,3-diarylacetones with 1,3-dibromopropane^[86] affords a benzylidenedihydrofuran derivative (via C- then O-substitution) or 2,6-diaryl-cyclohexanones (via C1/C3 substitution), respectively.

Alkylation of derivatives of 2-phenyl-^[87–89] or 2-propylindan-1-one **7**^[89] or 1-methyl-3,4-naphthalen-2(1*H*)-one^[90] with haloalkanes^[87–89] or 1,5-dihalopentanes^[90] in the presence of concentrated aqueous sodium hydroxide, with N-alkylated *Cinchona* alkaloids **9** as catalysts, leads to formation of the expected products **8** with moderate to high enantiomeric excess (Scheme 12).

Scheme 12 Phase-Transfer Asymmetric Alkylation of 2-Substituted Indan-1-ones^[87–89]

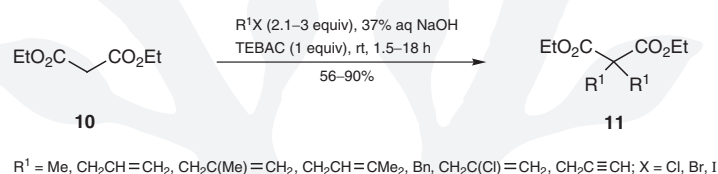


Dialkyl ketones, alkyl aryl ketones, and cycloalkanones undergo reactions with reactive alkylating agents, affording mixtures of mono-, di-, and polyalkylated products in yields scarcely exceeding 50%.^[73] A predominance of dibenzylation of acetophenone from a solvent-free phase-transfer reaction is attributed to π – π interaction in the transition state of the benzylation of the monosubstituted derivative.^[91]

for references see p 1117

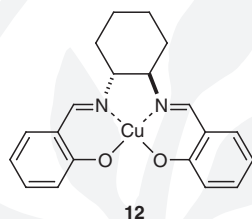
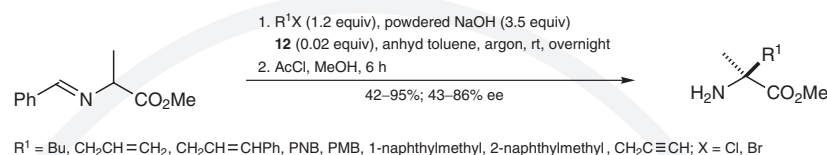
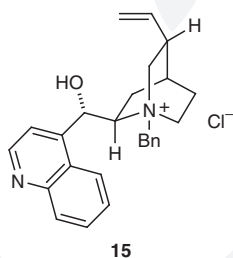
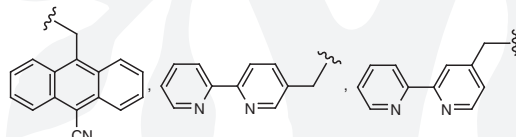
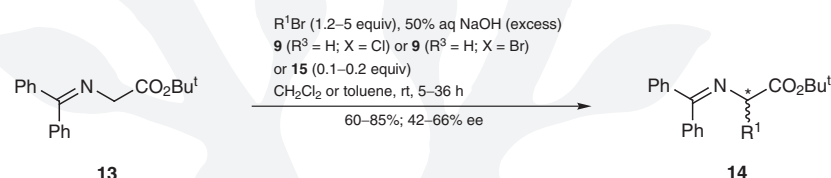
Methyl or ethyl esters of malonic acid,^[92] α -arylalkanecarboxylic acids,^[92,93] and α -phenylbutyrolactone^[93] undergo cleavage under concentrated aqueous sodium hydroxide and phase-transfer conditions. However, the reaction of equimolar amounts of diethyl malonate (**10**) and benzyltriethylammonium chloride in the presence of 12.5 M sodium hydroxide with reactive alkylating agents (methyl, allyl, benzyl, and propargyl halides) leads to the formation of the corresponding dialkylated esters **11** in high yields (Scheme 13).^[94] An extractive alkylation technique is applied in the quantitative synthesis of ethyl diethylmalonate.^[12] The approaches mentioned above require large amounts of Q^+X^- ; on the other hand, di-*tert*-butyl malonate, and *tert*-butylphenyl- and diphenylacetates are alkylated with mono- and dihaloalkanes under typical phase-transfer conditions, affording the expected mono- and/or disubstituted products. Dialkylation and cycloalkylation of di-*tert*-butyl malonate is easily accomplished with an excess of the alkylating agent.^[92] The enhanced acidity of (π -aryl)tricarboxylchromium complexes of methyl α -phenylcarboxylates and related compounds avoids competitive hydrolysis under phase-transfer conditions and produces the alkylated products, often in quantitative yield.^[93] *tert*-Butyl isocyanacetate undergoes alkylation under phase-transfer catalysis with allyl or benzyl halides.^[95]

Scheme 13 Phase-Transfer-Catalyzed Dialkylation of Diethyl Malonate^[94]



The alkylation of Schiff bases derived from esters of α -amino acids under phase-transfer conditions with an equimolar^[96,97] or catalytic^[97] amount of Q^+X^- , followed by hydrolysis of the products thus formed, is a convenient method for preparation of various amino acids.

Alkylation of Schiff bases in the presence of chiral catalysts {such as chemically modified *Cinchona* alkaloids,^[98–110] TADDOL [(4*R*,5*R*)- or (4*S*,5*S*)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol],^[111] NOBIN (enantiopure 2-hydroxy-2'-amino-1,1'-binaphthyl),^[112] metal-salen complexes (e.g., **12**, Scheme 14),^[113,114] or N-spiro C_2 -symmetric quaternary ammonium bromides^[115]} affords the enantiomerically enriched products.^[109,116] Alternatively, phase-transfer alkylation of a glycine-derived Schiff base having an ester chiral auxiliary, in the presence of tetrabutylammonium hydrogen sulfate, affords the corresponding products in modest diastereomeric excess.^[117] Reactions involving a benzophenone imine **13** afford the alkylated products in good chemical yields and reasonable enantiomeric excess (higher enantiomeric excess is observed in reactions carried out in the presence of potassium or cesium hydroxide and *Cinchona* alkaloids N-substituted with a 9-anthracenylmethyl group^[109,116] or other Q^+X^- as catalysts^[116]). Inversion of enantioselectivity is noticed during phase-transfer benzylation of **13** with a *Cinchonidinium* salt **15** as the catalyst: in the presence of sodium hydroxide, the *R*-enantiomer of the product predominates, while potassium hydroxide gives the *S*-enantiomer **14** ($R^1 = Bn$) (Scheme 15).^[110] Efficient asymmetric catalytic processes are accomplished using both N- and O-alkylated *Cinchona* alkaloids;^[109,116] formation of O-derivatives may take place in situ during the alkylation reaction.^[98,103]

Scheme 14 Phase-Transfer-Catalyzed Asymmetric Alkylation of *N*-Benzylidenealanine Methyl Ester^[113]**Scheme 15** Phase-Transfer-Catalyzed Asymmetric Alkylation of the Benzophenone Imine of Glycine *tert*-Butyl Ester^[199,101,105,106,108]

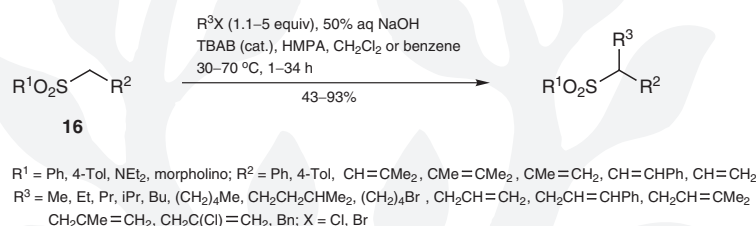
Alkylation of 1,3-dicarbonyl compounds (e.g., ethyl cyanoacetate, acetoacetate, malonate) is carried out in the presence of dilute aqueous sodium hydroxide and equimolar amounts of tetrabutylammonium hydrogen sulfate, in dichloromethane (extractive alkylation).^[12]

1,3-Disubstituted 2*H*-indol-2-ones undergo alkylation^[118] and nitroarylation^[119] in the presence of concentrated aqueous sodium hydroxide, a catalyst Q^+X^- , and small amounts of dimethyl sulfoxide. Alkylation of *N*-substituted 2*H*-indol-2-ones has little practical value since mixtures of mono- and dialkylated products result unless dihaloalkanes are used. In the latter case, three- and five-membered cycloalkanespiro-3-(2*H*-indol-2-ones) are obtained in good yields.^[118]

for references see p 1117

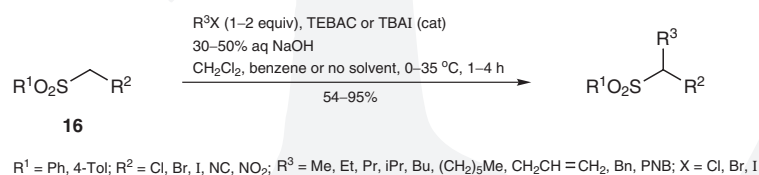
Alkyl sulfones and sulfonamides are insufficiently acidic to undergo alkylation under phase-transfer conditions. However, phase-transfer catalysis provides a convenient means to carry out alkylation of benzyl sulfones **16** ($R^2 = \text{Ph}$),^[120] 2- and 4-nitrobenzyl sulfones,^[121] 1-phenylmethanesulfonamides,^[120] halomethyl^[122,123] and dihalomethyl aryl sulfones,^[122] chloro- and dichloromethanesulfonamides,^[124] allyl^[125–127] and α -chloroallyl aryl sulfones (Scheme 16).^[128] The rate of alkylation of benzyl sulfones and sulfonamides,^[120] [(chloromethyl)sulfonyl]morpholine,^[124] and some allylic sulfones^[125,127] is accelerated by the addition of small amounts of hexamethylphosphoric triamide. 2,1-Benzisothiazole 2,2-dioxides (benzosultams) undergo arylation at C3 with 4-fluoronitrobenzene in the presence of powdered sodium hydroxide in dimethyl sulfoxide.^[129]

Scheme 16 Phase-Transfer-Catalyzed Alkylation of Benzyl and Allyl Sulfones and Sulfonamides^[120,127]



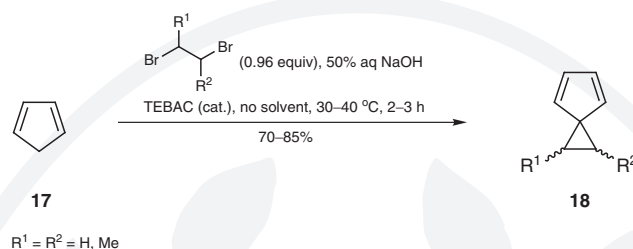
The combination of the sulfonyl group with another electron-withdrawing group, e.g. methylsulfonyl,^[130] phenylsulfonyl,^[131] phenylsulfonyl,^[131,132] cyano-, ethoxycarbonyl-,^[133] (ethoxycarbonyl)vinyl-,^[134] isocyano-,^[135–140] or nitro-,^[141] gives CH acids **16** which can be conveniently alkylated under phase-transfer catalysis (Scheme 17). In the case of diethyl [(phenylsulfonyl)methyl]phosphonate, the extractive alkylation technique is successfully applied.^[142,143] The products of these reactions are used in many important transformations; particularly useful are derivatives of tosylmethyl isocyanide,^[135] which can be used for the preparation of heterocyclic compounds,^[135] ketones,^[137] sex pheromones,^[139] [3.3]heterophanes,^[138] and *anti*-[3.3]metacyclophanes.^[140]

Scheme 17 Phase-Transfer-Catalyzed Alkylation of Heteroatom-Substituted Sulfones^[122,123,136,141]



Methylene sulfones substituted with aryl,^[121] vinyl,^[127] iodo,^[123] phenylsulfonyl,^[131,132] phenylsulfonyl,^[131] cyano,^[133] ethoxycarbonyl,^[133] or isocyano^[137] groups afford cyclic products under phase-transfer catalysis conditions using alkylating reagents.

Phase-transfer catalysis is successfully applied in the alkylation of cyclopentadiene (**17**) (Scheme 18),^[144–147] indene,^[148] and fluorene^[149] and in the nitrobenzylation and/or nitroarylation of 1,3-diphenylindene and 9-phenylfluorene.^[150] Alkylation of **17** with monohaloalkanes gives complex mixtures of products and thus is not useful,^[144] but the use of 1,2-dihaloalkanes^[144–146] or 1,4-dibromobutane^[147] affords the corresponding spiro products, e.g. **18**, in good yields.

Scheme 18 Phase-Transfer-Catalyzed Cycloalkylation of Cyclopentadiene with Dihaloalkanes^[145]

Alkylation of indene leads initially to the formation of 1-alkyl derivatives, which undergo isomerization to the 3-substituted products. The use of 1,4-dibromobutane gives spiro[cyclopentane-1,1'-indene].^[148] Fluorene is the weakest cyclopentadiene hydrocarbon; its phase-transfer-catalyzed alkylation is aided by dimethyl sulfoxide.^[149]

α -Substituted benzylamines are synthesized via a three-step procedure: preparation of *N*-benzylidenebenzylamine, its phase-transfer-catalyzed alkylation, and subsequent hydrolysis of the products.^[151] Aryl iodides and bromides undergo coupling with mono-substituted alkynes in the presence of aqueous sodium hydroxide and poly(ethylene glycol) as the phase-transfer catalyst, under microwave irradiation, or without transition-metal catalysts (Sonogashira-type reaction).^[152] Fischer carbene complexes undergo alkylation under phase-transfer conditions with iodomethane, allyl and benzyl halides, or (*Z*)-1,4-dibromobut-2-ene, giving the products in 50–80% yield. Complexes with a methylene group are usually monoalkylated.^[153]

1,2-Diphenyloctan-1-one [6, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = (\text{CH}_2)_5\text{Me}$]; **Typical Procedure:**^[77]

A mixture of ketone **5** ($\text{R}^1 = \text{Ph}$; 9.8 g, 0.05 mL), 1-bromohexane (9.08 g, 7.7 mL, 0.055 mol), 50% aq NaOH (13.5 mL), and TEBAC (0.15 g) was stirred at 50–60 °C for 4 h. After cooling, the mixture was diluted with H_2O , the solid product was collected by filtration, washed with H_2O , and crystallized; yield: 10.8 g (77%); 58–59 °C (MeOH).

***tert*-Butyl 3-(2,2'-Bipyridin-5-yl)-*N*-(diphenylmethylene)alaninate** (**14**, $\text{R}^1 = 2,2'$ -Bipyridin-5-ylmethyl); **Typical Procedure:**^[101]

To the soln of ester **13** (150 mg, 0.5 mmol) and (8*S*,9*R*)-(-)-*N*-benzylcinchonidinium chloride (**15**; 21 mg, 0.05 mmol) in CH_2Cl_2 (9 mL) was added 50% aq NaOH (0.8 mL) and a soln of 5-(bromomethyl)-2,2'-bipyridine (160 mg, 0.64 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 24 h at rt, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (5 mL), and the combined organic phases were evaporated. The residue was purified by flash chromatography (hexane/EtOAc 5:1 containing 0.5% Et_3N); yield: 197 mg (85%, 66% ee).

8.2.4.1.1.2

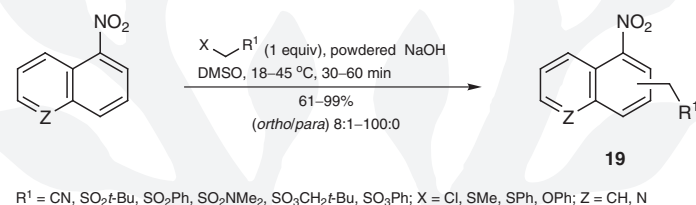
Variation 2:
Reactions of Carbanions with Aromatic Nitro Compounds

Carbanions bearing a leaving group (halogen, arylsulfanyl, aryloxy, dialkyl dithiocarbonate), generated from the corresponding CH acids by bases, undergo reaction with carbocyclic^[154–156] and heterocyclic^[157] nitroarenes according to the vicarious nucleophilic substitution (VNS) pathway. The process consists of the formation of a σ^{H} complex which then undergoes a base-mediated elimination. Acidification of the product thus formed affords nitroarenes substituted at the 2- or 4-position with respect to the nitro group. Products of the vicarious nucleophilic substitution (VNS) reaction, i.e. compounds *ortho* substituted to the nitro group, are useful substrates for the synthesis of heterocyclic compounds.^[157]

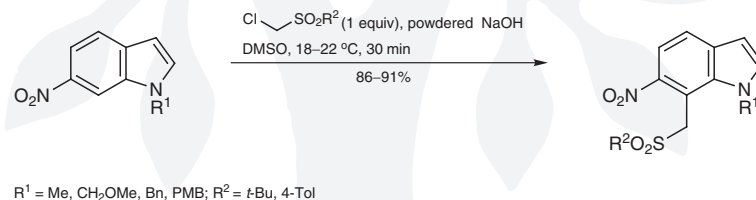
for references see p 1117

This process is often realized using powdered sodium hydroxide in dimethyl sulfoxide^[61,158–171] or liquid ammonia;^[158,161] typical phase-transfer catalysis conditions are not suitable but an ion-pair extraction technique has been applied in some cases.^[158] The vicarious nucleophilic substitution (VNS) reaction allows the functionalization of nitrobenzene^[161,163] and of nitronaphthalene,^[161] as well as of nitroquinoline^[164] derivatives with α -(cyanoalkyl)^[161,163,164] or α -[(alkoxycarbonyl)alkyl]^[161] groups, nitrobenzene,^[162,163,169] nitronaphthalene,^[165] nitroquinoline,^[164] nitroindole,^[166] and nitrobenzofuroxan^[167] derivatives with an α -(sulfonylalkyl) group; and nitrobenzene and nitronaphthalene derivatives with a (phenylsulfinyl)methyl group;^[158] as well as nitro aromatic compounds with other functional groups, e.g. to give **19** (Schemes 19 and 20).^[61,159,160] Quaternary ammonium salts are particularly useful reagents for the introduction of N,N-disubstituted carbamoylmethyl groups into aromatic nitro compounds.^[170] An intramolecular variant of the VNS reaction leads to the formation of five-, six-, and seven-membered benzosultam derivatives.^[168]

Scheme 19 Vicarious Nucleophilic Substitution Functionalization of 1-Nitronaphthalene and 5-Nitroquinoline^[159,161,164,165]



Scheme 20 Vicarious Nucleophilic Substitution Functionalization of 6-Nitroindole Derivatives^[166]



1-Nitronaphthalenes **19** (Z = CH); General Procedure:^[165]

To a stirred suspension of powdered NaOH (50 mmol) in DMSO (5–10 mL), a soln of the aromatic nitro compound (5 mmol) and CH acid (5 mmol) in DMSO (3–5 mL) was added dropwise at 18–22 °C (with external cooling when necessary). The reaction was stirred for 0.5–1 h and the mixture was then poured into dil HCl (ca. 150 mL). The solid products were collected by filtration, washed with H₂O, and dissolved in EtOAc, CHCl₃, or CH₂Cl₂. Oily products were extracted with the same solvents. The solns were washed with H₂O, dried (Na₂SO₄), and concentrated. Crude products were crystallized or purified by column chromatography; yield: 61–99%.

8.2.4.1.1.3

Variation 3:

Reactions of Carbanions with Heteroelectrophiles

Reactions of nucleophiles, including carbanions, with suitable heteroelectrophiles lead to the generation of new carbon–halogen, carbon–sulfur, or carbon–nitrogen bonds (X-phile reactions^[172]).

Phase-transfer-catalyzed reactions of CH acids with carbon tetrachloride, hexachloroethane, or trichloro(phenyl)methane lead to chlorinated products which, depending upon the structure of both substrates, undergo further reaction as nucleophiles, electrophiles, or can be isolated.^[173,174] 2-Substituted (including 2-methoxy) derivatives of phenylacetonitrile, trichloroethene (via a vinyl anion),^[175] benzyl and benzal chlorides,^[176] alkyl phenylacetates (with concomitant hydrolysis), alkyl and benzyl sulfones,^[177] and sulfonamide^[120] lead to the formation of chlorinated products with carbon tetrachloride. On the other hand, 2-(dialkylamino)phenylacetonitriles with tetrachloro- or trichloro(phenyl)methane give the corresponding products substituted at C2 with the trichloro or the dichloro(phenyl)methyl group, respectively. These products are formed by addition of chloro carbanions to the highly electrophilic iminium salts generated from the chlorinated aminonitriles.^[178] Phase-transfer-catalyzed reaction of phenylacetonitrile with carbon tetrachloride affords (*E*)-dicyanostilbene by a chlorination–alkylation–elimination pathway.^[179]

Sodium hydroxide–dimethylformamide is another base–solvent system used for efficient chlorination or bromination of aryl methyl sulfones with perhalomethanes.^[180] α -Mono- or dichlorination of allylic sulfones under phase-transfer catalysis conditions is highly dependent upon the tetrachloromethane or hexachloroethane to sulfone ratio (Scheme 21);^[125,128,181] with excess of hexachloroethane, benzosultams afford the 3,3-dichloro derivatives in good yields.^[182] Sulfones possessing α - and α' -hydrogen atoms treated with carbon tetrachloride in the presence of sodium hydroxide and a phase-transfer catalyst give alkenes^[177,183] via Ramberg–Bäcklund reaction (see Section 8.2.4.1.6). Phenyl vinyl sulfone undergoes reaction with alcohols and carbon tetrachloride to afford 2-alkoxy-1,1-dichloro sulfones by trapping the transient α -sulfonyl carbanion with the chlorinating agent.^[184] A phase-transfer-catalyzed reaction of *tert*-butyl methyl ketone (3,3-dimethylbutan-2-one) with carbon tetrachloride leads to the formation of pivalic acid (96% yield)^[177] via the haloform reaction, but benzyl methyl^[185] or alkyl phenyl ketones^[178,186] give mixtures of products in rather low yield, unless chloroform is added to the mixture. Under these conditions, 2-alkyl-1-phenyl-1-(trichloromethyl)oxiranes are isolated in 50–60% yield.^[178] Enolate anions generated from enol esters under phase-transfer catalysis conditions undergo chlorination with carbon tetrachloride, then the trichloromethyl anion is added; the products thus formed undergo cyclization to the trichloromethyl-substituted oxiranes in low yields (ca. 20%).^[187]

Scheme 21 Phase-Transfer-Catalyzed Chlorination of CH Acids^[175–177,181]

$\text{R}^1\text{CH(R}^2\text{)X}^1 \xrightarrow{\text{ZCCl}_3, 50\% \text{ aq NaOH, catalyst}} \text{R}^1\text{CH(R}^2\text{)X}^2\text{Cl}$									
R ¹	R ²	X ¹	Z	Equiv ZCCl ₃	Catalyst	Conditions ^a	X ²	Yield (%)	Ref
Ph	Me	CN	Cl	8	TEBAC	20 °C, 1.5 h	CN	78	[175]
3-Tol	Cl	Cl	Cl	4	DTMAC ^b	reflux, 4 h	Cl	87	[176]
SO ₂ Ph	CH=CM ₂	H	CCl ₃	1	TBAB	CH ₂ Cl ₂ , 20–25 °C, 1 h	H	71	[181]
SO ₂ Ph	CH=CM ₂	H	CCl ₃	2.1	TBAB	CH ₂ Cl ₂ , 20–45 °C, 1 h	Cl	96	[181]
Ph	CO ₂ <i>t</i> -Bu	H	Cl	20	TEBAC	no solvent, 48 h	Cl	68	[177]

^a All reactions are carried out in the presence of 50% aq NaOH.

^b Dodecyltrimethylammonium chloride.

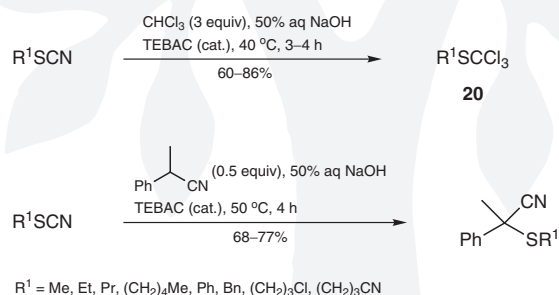
for references see p 1117

Processes which involve reactions of carbanions generated in situ from chlorinated CH acids with electrophiles, are synthetically important. They comprise phase-transfer-catalyzed reactions of carbon tetrachloride or hexachloroethane with aldehydes (usually aromatic ones) and fluorene,^[188] arylacetonitriles,^[178] or allylic sulfones,^[128] leading to substituted oxiranes, with phenylacetonitrile and electrophilic alkenes giving substituted cyclopropanes,^[178] and with allylic sulfones, alkylating agents, or electrophilic alkenes, affording alkylated sulfones^[128] (see Sections 8.2.4.1.1.4 and 8.2.4.1.1.6). Alternatively, monochlorinated intermediates are generated by phase-transfer-catalyzed equilibration of dichlorinated CH acids with nonchlorinated CH acids which are then allowed to react in situ with electrophiles.^[128,171]

Relatively acidic hydrocarbons such as acetylene can be chlorinated with carbon tetrachloride under phase-transfer catalysis conditions.^[189] The CH bonds in aliphatic and alicyclic hydrocarbons are brominated,^[190,191] chlorinated,^[191] or iodinated^[191,192] by carbon tetrabromide, tetrachloride, tetraiodide, or triiodomethane. Chlorination and bromination are carried out under typical phase-transfer catalysis conditions; however, iodination does not require any catalyst. In cases involving cyclic hydrocarbons, the reactions proceed in good yields and with high selectivity, e.g. halogenation of monosubstituted cubane leads to the preferential formation of 1,3-dihalogenated derivatives.^[191] Radicals and radical anions are involved in these processes.^[190–192]

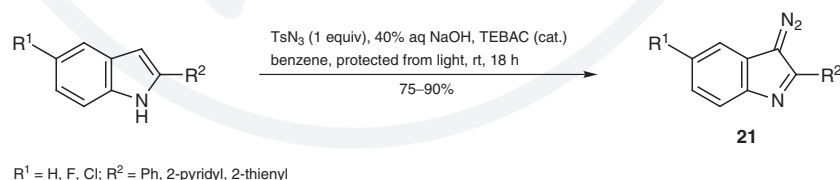
Thioalkylation of phenylacetylene,^[189] 2-substituted phenylacetonitrile,^[193] and chloroform^[193,194] is carried out with thiocyanates under phase-transfer catalysis conditions, e.g. to give **20** (Scheme 22). Alternatively, reactions of the analogous nitriles with elemental sulfur and alkyl halides lead to similar results. This process is aided by small amounts of dimethyl sulfoxide and, in addition to sulfonylated nitriles, affords polysulfides (mainly disulfides).^[195]

Scheme 22 Phase-Transfer-Catalyzed Sulfenylation of CH Acids with Thiocyanates^[193]



Transfer of the diazo group to CH-acidic compounds relies upon the use of tosyl azide under phase-transfer catalysis conditions.^[196,197] Application of this process to indoles substituted at C2 gives 3-diazo-3*H*-indoles **21** (Scheme 23).^[198] Similarly, 2,4,6-triisopropylbenzenesulfonyl azide is used in the synthesis of cyclic diazo ketones.^[199]

Scheme 23 Phase-Transfer-Catalyzed Synthesis of 3-Diazo-3*H*-Indoles^[198]



Benzyl Trichloromethyl Sulfide (20, R¹ = Bn); Typical Procedure:^[193]

To a vigorously stirred mixture of benzyl thiocyanate (29.8 g, 0.2 mol), CHCl₃ (72 g, 0.6 mol), and TEBAC (0.5 g, ca. 0.002 mol), 50% aq NaOH (40 mL, 0.75 mol) was added portionwise (slightly exothermic reaction). The temperature rose to 40 °C and stirring was continued at 40 °C for 3–4 h. The mixture was diluted with H₂O, the phases were separated, the aqueous phase was extracted with CHCl₃, and the combined organic extracts were washed with H₂O, dried, and evaporated. The residue was purified by distillation under reduced pressure and the solidified distillate was recrystallized; yield: 38.6 g (80%); bp 128–129 °C/7 Torr; mp 37–39 °C.

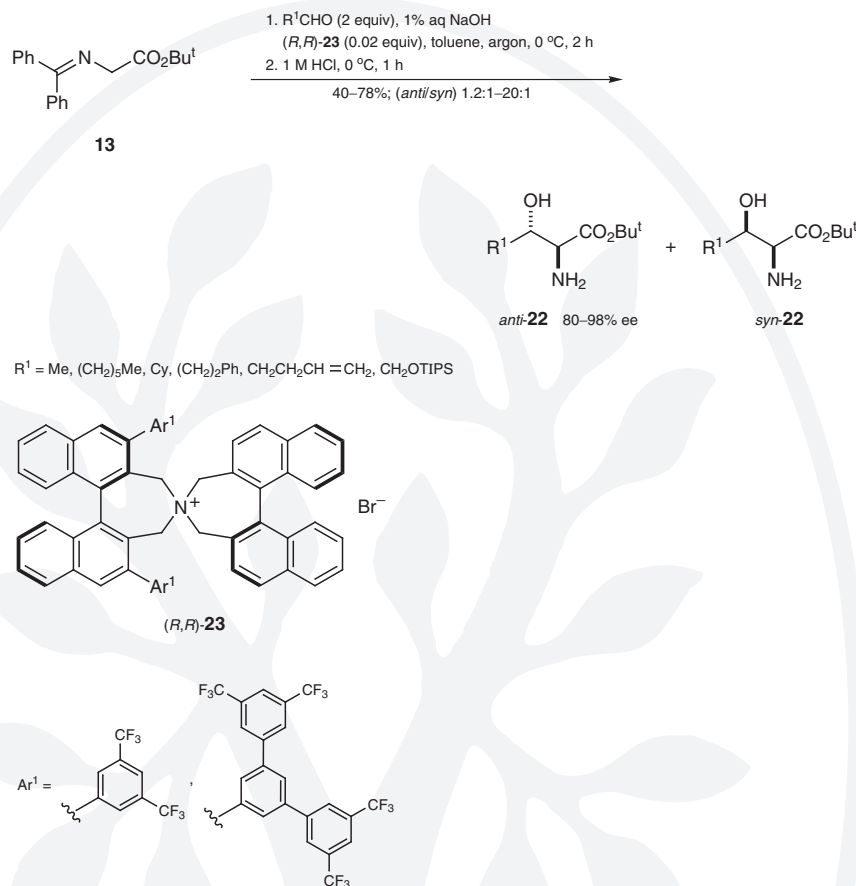
8.2.4.1.1.4

Variation 4:**Reactions of Carbanions with Carbonyl Compounds, Nitroso Compounds, and Imines**

Carbanions generated by treatment of various CH acids with bases undergo reaction with aldehydes or ketones to give β -hydroxy-substituted products which often readily undergo elimination of water to give the corresponding α,β -unsaturated carbonyl compounds (aldol-type condensations).^[200,201] The process is often carried out in the presence of dilute or concentrated aqueous solutions of sodium hydroxide;^[1,4,15,200,201] the hydroxide is sometimes used in catalytic amounts and addition of a phase-transfer catalyst usually enhances the rate and yield.^[202–205] Reactive carbonyl compounds such as methylene aldehydes or ketones often give complicated mixtures of products due to competing Michael addition or polycondensation and other reactions.

Aliphatic nitriles are not prone to condensation with aromatic aldehydes in the presence of sodium hydroxide; however, arylacetonitriles undergo this reaction to give α,β -unsaturated nitriles in good yield.^[16] In such cases, poly(ethylene glycol)s^[202] or tetrabutylammonium bromide^[203] are used as catalysts. When this reaction is carried out with a catalytic amount of calix[4]arene containing a (trimethylammonio)methyl group on the upper rim, the α,β -unsaturated nitriles formed are accompanied by products arising from the Michael addition of the starting nitriles to the unsaturated products.^[204] However, both indene and acetophenone give the corresponding benzylidene derivatives on reaction with benzaldehyde in yields of ca. 90%. Inverse phase-transfer catalysis for these reactions has been suggested.^[204] Under typical phase-transfer catalysis conditions, fluorene and indene form benzylidene (or arylidene) derivatives in low and high yields, respectively.^[203] Acyclic and cyclic ketones, arylacetonitriles, phenylsulfonylacetonitrile, and indene undergo reaction with benzaldehyde in the presence of dilute sodium hydroxide, with or without anionic or cationic surfactants or typical phase-transfer catalysts, affording aldol products and/or unsaturated derivatives, often in high yield. Cationic surfactants favor formation of the latter products.^[205] Condensation of *N*-(diphenylmethylene)-aminoacetonitrile with aromatic aldehydes (33% aqueous sodium hydroxide and benzyltriethylammonium chloride as a catalyst or a 4% aqueous solution of this base with dimethyl sulfoxide) is employed in the synthesis of 4-aryl-2-aza-3-cyano-1,1-diphenylbuta-1,3-dienes.^[206] Upon treatment with aldehydes under phase-transfer catalysis conditions, the benzophenone Schiff base of glycine *tert*-butyl ester **13** gives the aldol products **22** (Scheme 24).^[207,208] In the presence of *N*-benzylcinchoninium chloride, the products are obtained in good yield and moderate diastereomeric excess,^[207] while the use of the enantiomerically pure, C₂-symmetrical, chiral quaternary ammonium salt **23** as the phase-transfer catalyst gives, in general, good yields, high *syn/anti* diastereoselectivity, and enantiomeric excess values up to 98%.^[208]

for references see p 1117

Scheme 24 Phase-Transfer-Catalyzed Asymmetric Aldol Condensation of the Benzo-phenone Imine of Glycine *tert*-Butyl Ester with Aldehydes^[208]

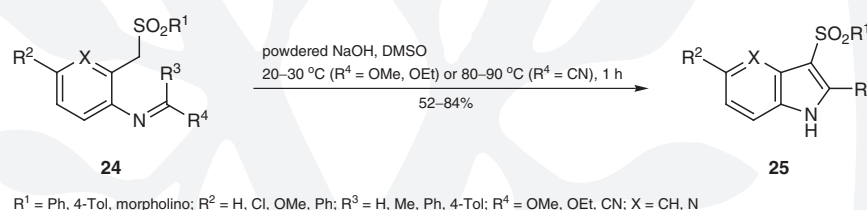
Phase-transfer-catalyzed reaction of 2-phenylalkenenitriles with vinyl acetate leads to products equivalent to formal addition of carbanions to C1 of the vinyl group.^[43,209] These products are formed via addition of the nitrile carbanion to the carbonyl group of acetaldehyde (from saponification of the vinyl ester), followed by transesterification of vinyl acetate.^[210] Condensation of *N*-acyl-1,2-dihydroisoquinaldonitriles with aldehydes (also with acetaldehyde generated in situ from vinyl acetate^[209]) and ketones in the presence of 50% aqueous sodium hydroxide gives esters of 1-isoquinolylmethanols, which are hydrolyzed, directly or in a separate step, to the corresponding methanols;^[211–213] in the case of ketones, the process is accelerated by the use of benzyltriethylammonium chloride as catalyst.^[211] Carbanions from adducts of 1-phenylalkyl isocyanides with aromatic and aliphatic aldehydes undergo cyclization to give substituted dihydrooxazoles, useful precursors of β -amino alcohols.^[214] Cyclization also occurs during phase-transfer-catalyzed condensation of 2-(2-acetoxyethyl)-2-methylcyclobutanone with acetone, which is the key step in the synthesis of (\pm)-grandisol and (\pm)-lineatin.^[215] Typical phase-transfer catalysis conditions (50% sodium hydroxide, benzyltriethylammonium chloride catalyst) are applied in the condensation of *N*-benzylidenebenzylamine with aromatic aldehydes (the products are easily cleaved to give substituted aminoethanols)^[216] and arylacetonitriles with substituted nitrosobenzenes.^[217] Depending upon conditions, the latter process gives either α -(arylimino)arylacetonitriles and/or 1-anilino-1,2-diaryl-2-cyanoethenes.^[217] Benzyltriethylammonium chloride catalyst and 50% aqueous sodium hydroxide is a convenient system for condensation of sulfones and sulfonamides with aromatic

aldehydes.^[218] Condensation of dimethyl sulfone with 2 equivalents of benzaldehyde, catalyzed by benzyltriethylammonium chloride, gives 3,5-diphenyl-1,4-oxathiane *S,S*-dioxide in yields up to 60%.^[219] In the presence of catalytic amounts of sodium hydroxide, under microwave irradiation, anthracenone undergoes reaction with aromatic aldehydes to afford 10-(arylmethylene)anthracenones,^[220] while benzene-1,4-dicarbaldehyde undergoes reaction with aryl methyl ketones to give substituted 1,4-bis(oxopropenyl)benzenes.^[221]

Methyl group(s) in heterocyclic compounds (2-methylbenzoxazole, 2-methylbenzothiazole,^[222] 4-methyl- and 4,6-dimethylpyrimidines, methyl- and 2,5-dimethylpyrazines, and 3-methylpyridazine^[223]) undergo deprotonation under phase-transfer catalysis conditions, generating the corresponding carbanions which enter into reaction with aromatic aldehydes, to give the corresponding alcohols and/or unsaturated products.

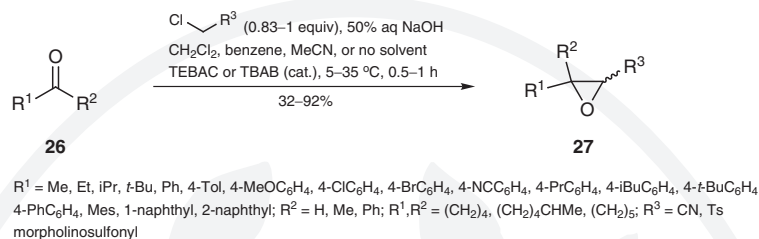
Intramolecular addition of carbanions generated from benzyl sulfones or sulfonamides **24** with the sodium hydroxide–dimethyl sulfoxide system to *ortho*-arylimino,^[224] -imidate,^[225] or -cyanoimino^[226] functionalities proceeds with subsequent elimination of sulfinic acid, methanol, ethanol, or hydrogen cyanide, respectively, and leads to 3-sulfonyl-substituted indoles **25** (Scheme 25).^[224–226] Under similar conditions, 2-(phenylamino)-3-sulfonylindoles are obtained by direct cyclization of benzyl sulfones *ortho*-substituted with the carbodiimide functionality.^[226]

Scheme 25 Synthesis of 3-Sulfonylindole and Indole-3-Sulfonamide Derivatives^[225,226]

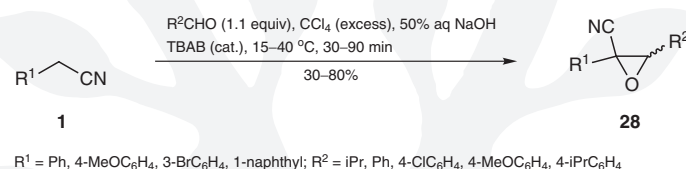


Synthetically important are phase-transfer-catalyzed Darzens-type condensations^[227] of carbonyl compounds **26** (usually aromatic aldehydes) with α -chloronitriles (carried out in the presence of Q^+X^- ,^[228–234] chiral ammonium salts,^[235] octopus compounds,^[236] or crown ethers^[47,81]), *tert*-butyl α -chlorocarboxylates,^[229,237] chloromethyl^[122,238–240] and α -chloroallyl sulfones,^[128] chloromethanesulfonamides,^[124,241] including *N*-substituted sulfonamides containing a chiral handle,^[241] and phenacyl chloride^[242,243] (in the presence of *N*-benzylquininium chloride^[242] or chiral crown ethers^[243]). These reactions lead to the formation of oxiranes **27** substituted with the corresponding electron-withdrawing groups (Scheme 26). The reaction, carried out in the presence of a chiral catalyst, gives the products in low^[235,242] or moderate enantiomeric excess.^[243] Darzens condensation of nitriles and esters with aromatic aldehydes yields the oxiranes as mixtures of stereoisomers (in the case of sulfones and sulfonamides, one stereoisomer with *trans* aryl and sulfonyl groups). Condensation of 2-chlorophenylacetonitrile with benzaldehyde carried out in the presence of benzyltriethylammonium chloride or dibenzo-18-crown-6 or without any catalyst leads to a different stereochemical outcome.^[230]

for references see p 1117

Scheme 26 Synthesis of Oxiranes by Phase-Transfer-Catalyzed Darzens-Type Condensations^[122,124,228,233,234,239]

α -Halo-substituted nitriles and esters are unpleasant compounds (lachrymators). To avoid separate preparation, they are synthesized by reaction of the corresponding CH acids **1** with perchloroalkanes under phase-transfer catalysis conditions and then allowed to react in situ with carbonyl compounds to give the substituted oxiranes **28** in good yield (Scheme 27).^[178] A similar approach is also applied for the reactions of fluorene^[188] or allylic sulfones.^[128]

Scheme 27 Phase-Transfer-Catalyzed Darzens-Type Condensation of In Situ Generated α -Chloronitriles with Aldehydes^[178]**3-tert-Butyloxirane-2-carbonitrile (27, R¹ = *t*-Bu; R² = H; R³ = CN); Typical Procedure:**^[234]

A mixture of 50% aq NaOH (20 mL) and TEBAC (0.45 g, 2 mmol) was vigorously stirred while a mixture of chloroacetonitrile (7.55 g, 0.1 mol) and pivalaldehyde (9.5 g, 0.11 mol) was added dropwise at 10–15 °C (ice-water bath) during 15–20 min. The mixture was stirred for 30 min, diluted with H₂O (100 mL), and extracted with Et₂O (3 × 30 mL). The combined organic phases were washed with H₂O, dried (MgSO₄), and evaporated. The residue was distilled under reduced pressure to give the product as a mixture of diastereomers (6:5); yield: 10.0 g (80%); bp 64 °C/14 Torr.

cis-2,3-Diphenyloxirane-2-carbonitrile (28, R¹ = R² = Ph); Typical Procedure:^[178]

A soln of BnCN (2.34 g, 0.02 mol) and PhCHO (2.12 g, 0.022 mol) in CCl₄ (5 mL) (**CAUTION: toxic**) was added dropwise to a vigorously stirred mixture of 50% aq NaOH (15 mL), CCl₄ (15 mL), and TBAB (0.1 g) at 20 °C. The mixture was stirred for 1 h and diluted with H₂O. The organic products were extracted with CH₂Cl₂ (2 ×), and the combined organic extracts were washed with H₂O, dried (Na₂SO₄), and evaporated to dryness. The residue was purified by crystallization; yield: 3.54 g (80%); mp 69–70 °C (MeOH).

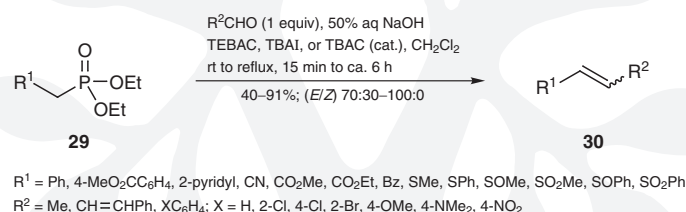
8.2.4.1.1.5

Variation 5:**Alkenation by the Horner–Wadsworth–Emmons Reaction**

The base-mediated condensation of the esters of alkylphosphonic acids with carbonyl compounds is a convenient method for the preparation of alkenes (the Horner–Wadsworth–Emmons reaction).^[244,245] When alkylphosphonic esters (usually diethyl) which are substituted with an aryl or an electron-withdrawing group are used, the Horner–Wadsworth–Emmons reaction can be conveniently carried out under phase-transfer catalysis conditions. The majority of the Horner–Wadsworth–Emmons alkenation reactions are

performed under phase-transfer catalysis (Scheme 28),^[58,142,246–253] but diethyl methylphosphonate substituted with sulfur, cyano, carbonyl,^[254] or alkoxycarbonyl^[251,254] (together with benzyloxy- or *tert*-butoxycarbonylamino^[255]) groups and bisphosphonate^[254] undergo reaction with aromatic aldehydes without added catalysts to afford the corresponding alkenes **30** in good yields. However, in at least some cases, the starting phosphonates **29** are able to catalyze the reactions.^[76,254] The phase-transfer-catalyzed Horner–Wadsworth–Emmons reaction is usually carried out with aromatic aldehydes, but aliphatic aldehydes,^[142,246,252,255] as well as α,β -unsaturated ones^[246,248,252,254,255] and also acetone^[246] and alkyl phenyl ketones,^[250] may be used. The reaction of 3- and 4-acetoxy-substituted benzaldehydes with triethyl phosphonoacetate in the presence of 50% aqueous sodium hydroxide in dichloromethane at 0–5 °C leads to the formation of 3- and 4-hydroxycinnamic acids, whereas 2-hydroxy acids are obtained from the reaction of 2-acetoxybenzaldehydes with triethyl phosphonoacetate in a solid base–tetrahydrofuran system.^[251] Alkenes bearing electron-withdrawing groups are often formed as mixtures of *E*- and *Z*-isomers, but bulky substituents [sulfonyl, diethoxyphosphoryl,^[247,254] [(alkoxycarbonyl)amino](ethoxycarbonyl)methyl]^[255] present in the phosphonate afford either the pure *E*-isomers, a high *E/Z* ratio,^[247,254] or a high *Z/E* ratio^[255] of the products. The nature of the solvent,^[249] and in particular the structure of the catalyst,^[247,249] affect the stereochemical outcome to some extent. In a few cases, solid potassium hydroxide^[250] or sodium methoxide,^[253] both in tetrahydrofuran, give better results than typical phase-transfer catalysis conditions.

Scheme 28 Synthesis of Alkenes by Phase-Transfer-Catalyzed Horner–Wadsworth–Emmons Reactions^[246,247,250,253]



(*E,E*)-1-Phenyl-4-(2-pyridyl)buta-1,3-diene (30, $\text{R}^1 = 2\text{-Pyridyl}$; $\text{R}^2 = \text{CH=CHPh}$);

Typical Procedure:^[246]

A soln of phosphonate **29** ($\text{R}^1 = 2\text{-pyridyl}$) (8.0 g, 35 mmol) and (*E*)-cinnamaldehyde (4.63 g, 35 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred two-phase system consisting of CH_2Cl_2 (35 mL), 50% aq NaOH (20 mL), and TBAI (0.7 g). The mixture was refluxed for ca. 3 h. The organic layer was separated, washed with H_2O (5 mL), dried (MgSO_4), and evaporated. The residue was purified by crystallization; yield: 4.9 g (68%); mp 121–123 °C (petroleum ether).

8.2.4.1.1.6

Variation 6: Reactions of Carbanions with Electrophilic Alkenes

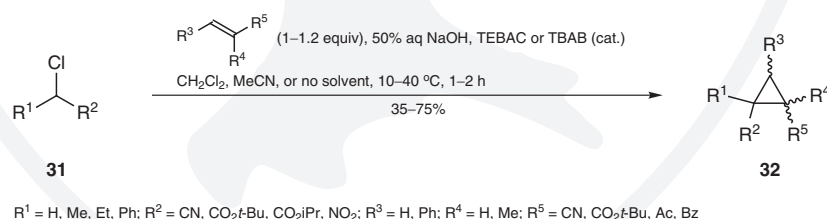
Addition of CH acids to electrophilic (electron-poor) alkenes is usually carried out in the presence of various bases (the Michael reaction),^[16,256–258] including sodium hydroxide. In the latter case, phase-transfer catalysts accelerate the reaction and usually increase the yield. Phase-transfer catalysis is particularly useful when the intermediate anion (the adduct) can undergo cyclization, i.e. when the starting CH acids possess a good leaving group at the carbanionic center. Under phase-transfer catalysis conditions, (methylsulfanyl)(phenoxy)acetone nitrile,^[61] ketones (acenaphthenone,^[79] 2-arylcyclohexanone^[81]), and α -chloroalkyl sulfones^[128] undergo reaction to form simple Michael adducts with acrylonitrile, alkyl acrylates, or vinyl sulfones, often in high yields. In cases involving methylene CH acids, e.g. acenaphthenone,^[79] disubstituted products are easily produced.

for references see p 1117

Concentrated aqueous sodium hydroxide with benzyltriethylammonium chloride as the catalyst (and less frequently, dilute aqueous sodium hydroxide in dimethyl sulfoxide) are used for the addition of anions generated from *N*-benzylidenebenzylamine^[151,259,260] or *N*-(diphenylmethylene)(arylmethyl)amines^[261,262] to acrylonitrile,^[151] cinnamionitriles,^[259] alkyl cinnamates,^[260] or chalcones (1,3-diphenylprop-2-en-1-ones),^[261,262] and anions from *tert*-butyl phenylacetate to cinnamionitrile or alkyl cinnamates.^[263] Reactions of *N*-benzylidenebenzylamine result in the formation of pyrrolidine derivatives.^[259,260] Concentrated (60%) aqueous base and benzyltriethylammonium chloride catalyst is required for the reaction of substituted methylpyrazoles with chalcones and aromatic aldehydes.^[264] In the latter case, arylidenepyrazoles (products of aldol-type reaction) enter into the Michael addition with methylpyrazole.^[264] The nitro group makes a double bond particularly electron deficient; hence, addition of various CH acids to 3-nitro-2-enopyranosides^[265,266] or *C*-(3-nitromethyl)hexofuranose derivatives^[267] can be carried out in dilute aqueous sodium hydroxide solution with tributylhexadecylphosphonium bromide^[265,266] or tetrabutylammonium bromide^[267] as the catalyst. Electrophilic alkenes from aldol-type condensations enter into in situ Michael reactions, e.g. during water-soluble calixarene-catalyzed condensation of phenylacetone nitrile with aromatic aldehydes, carried out in the presence of 5 M aqueous sodium hydroxide. Under similar conditions, the yield of the Michael adducts from the reactions of arylacetone nitriles and ketones with α,β -unsaturated nitriles and ketones are significantly increased when calixarenes are used as the catalysts.^[204]

Phase-transfer catalysis provides a convenient means for the preparation of electrophilic cyclopropanes **32** from α -chloronitriles,^[268,269] α -chloro esters,^[268,270,271] and α -chloronitroalkanes **31**,^[272] or diethyl bromomalonate,^[273,274] with α,β -unsaturated nitriles,^[268,269,272,273] esters,^[268,271] aldehydes,^[273,274] ketones,^[270,273] phosphonium salts, and phosphonates (Scheme 29).^[273] Preparation of cyclopropanes is also carried out by a two-step procedure involving isolation of the Michael adducts and cyclization.^[268,272] The cyclopropanes are usually produced as mixtures of *cis/trans* isomers, but pure *cis*-2-phenylcyclopropyl ketones^[270] and *trans*-cyanonitrocyclopropanes are also observed.^[272] In reactions of α -chloronitriles with unsaturated nitriles^[269] and isopropyl α -chlorophenylacetate with *tert*-butyl acrylate,^[271] the stereochemistry of the products is controlled by the presence of the catalyst. A quite general and highly efficient method for the preparation of 1-arylcyclopropane-1-carbonitriles, which are additionally substituted at C2 with an electron-withdrawing group, consists of the reaction of [(α -cyanoaryl)methyl]- or [(α -cyanovinyl)methyl]trimethylammonium salts with electrophilic alkenes, carried out in the presence of 50% aqueous sodium hydroxide in dichloromethane^[275] (see Section 8.2.4.1.4.2).

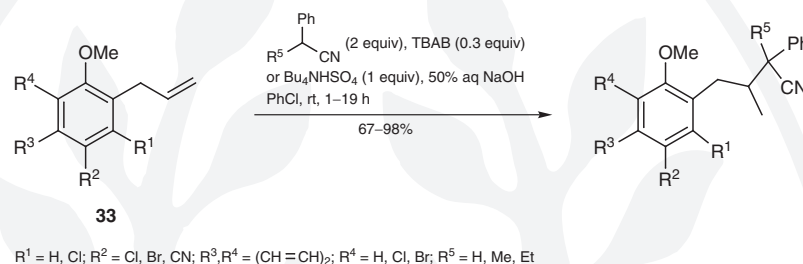
Scheme 29 Cyclopropanes by Phase-Transfer-Catalyzed Reactions of α -Chloro-Substituted CH Acids with Electrophilic Alkenes^[268,270,272]



A one-pot reaction of phenylacetone nitrile with carbon tetrachloride and acrylonitrile or *tert*-butyl acrylate performed under phase-transfer catalysis conditions produces the corresponding cyano(phenyl)cyclopropanes in ca. 50% yield, via (2-chlorophenyl)acetone nitrile, generated in situ.^[178] 2-Benzoyl-1,2-dihydroisoquinaldonitrile undergoes reaction with electrophilic alkenes under phase-transfer-catalyzed conditions, providing 1-(2-electron-withdrawing group substituted) and/or 1-(2-benzoyl 2-electron-withdrawing group

substituted) alkylisoquinolines.^[276] Poorly activated alkenes, such as the ring-substituted 2-propenylanisoles (or their precursors, 2-allylanisoles **33**)^[277] and (*E*)-1,2-dichloroethene,^[278] undergo addition reactions under phase-transfer catalysis conditions with phenylacetonitrile^[277] and its 2-substituted derivatives (Scheme 30).^[277,278] In the case of (*E*)-1,2-dichloroethene, the intermediate adducts undergo elimination of hydrogen chloride to afford the β -chlorovinylated products in good yield.^[278]

Scheme 30 Phase-Transfer-Catalyzed Reactions of 2-Arylalkanenitriles with Substituted 2-Allylanisoles^[277]



***tert*-Butyl 2-Cyano-2-methylcyclopropanecarboxylate (32, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{CN}$; $\text{R}^3 = \text{R}^4 = \text{H}$; $\text{R}^5 = \text{CO}_2t\text{-Bu}$); Typical Procedure:**^[268]

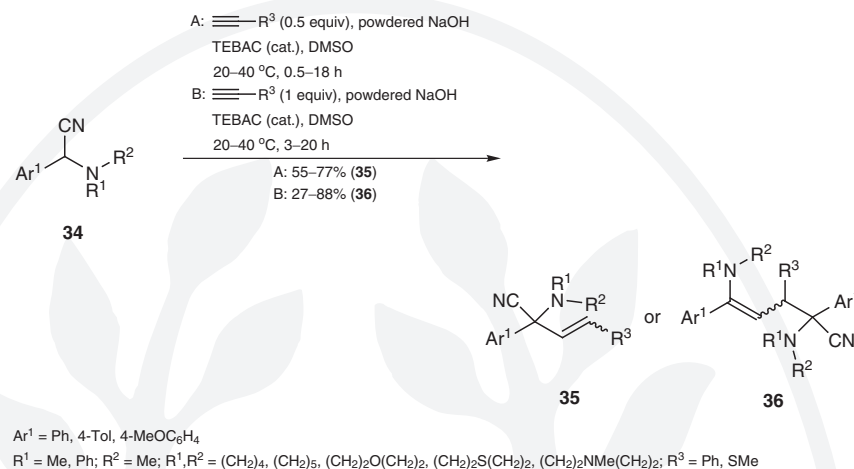
To a stirred mixture of 50% aq NaOH (20 mL) and TEBAC (0.4 g), a soln of 2-chloropropanenitrile (8.95 g, 0.1 mol) and *tert*-butyl acrylate (15.4 g, 0.12 mol) was added dropwise at 35–40 °C (exothermic reaction). After the addition was complete, stirring was continued for 1 h at about 25 °C. The mixture was diluted with H_2O , extracted with benzene (**CAUTION: carcinogen**), and the combined organic extracts were washed with brine, dried (MgSO_4), and evaporated. The residue was purified by distillation under reduced pressure to give the product as a mixture of *cis*- and *trans*-isomers (*trans/cis* 76:24); yield: 12.14 g (67%); bp 110–113 °C/16 Torr; the *trans*-isomer was isolated by fractional distillation; bp 108–109 °C/15 Torr; the *cis*-isomer was isolated by crystallization; mp 63–65 °C (hexane).

8.2.4.1.1.7

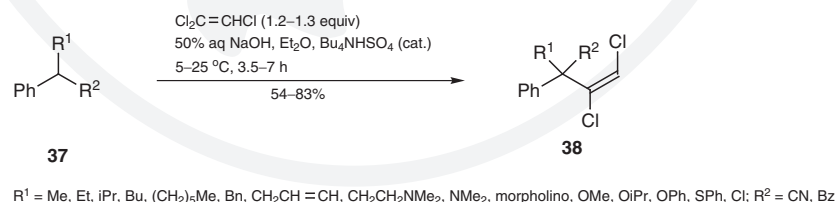
Variation 7: Reactions of Carbanions with Alkynes

Reactions of carbanions, generated from methine CH acids, with alkynes leads to the formation of their vinylated products. In the case of methylene CH acids, more complex processes take place. Phase-transfer-catalyzed addition of 2-phenylalkanenitriles to acetylene and its derivatives is usually carried out in dimethyl sulfoxide in the presence of powdered potassium hydroxide and benzyltriethylammonium chloride as a catalyst,^[279] but sodium hydroxide is occasionally used for this purpose. The powdered sodium hydroxide–dimethyl sulfoxide– Q^+X^- system is used for vinylation of 2-substituted *N*-(benzylidene)glycinonitriles with acetylene, phenyl- and ethoxyacetylene,^[280] or 2-(*N*-morpholino)phenylacetonitrile with acetylene.^[281] Reaction of arylacetonitriles **34**, substituted at C2 with different amino groups, with acetylene furnishes substituted 1,3-dienamines.^[281] Carbanions from these CH acids undergo addition to phenyl-, (methylsulfonyl)-, and methoxyacetylenes^[282] or 1-phenyl- or 1-(methylsulfonyl)prop-1-yne^[283] resulting in the formation of the corresponding vinylated compounds **35** and/or the products **36** of the reaction of 2 equivalents of the alkyne with 1 equivalent of the nitrile (Scheme 31). The ratio of these two kinds of products depends upon the basicity of the amine, i.e. the concentration of the ammonium salts which are in equilibrium with the aminonitriles, but the conditions also affect the reaction outcome.^[282,283]

for references see p 1117

Scheme 31 Reactions of 2-(Dialkylamino)arylacetonitriles with Monosubstituted Acetylenes^[282]

Chloro- and dichloroacetylene exhibit electrophilic properties and explode in contact with oxygen or air but can be stabilized by formation of complexes with diethyl ether.^[284] Fortunately, both of these chlorinated alkynes can be generated under phase-transfer catalysis conditions from safe precursors and can undergo reaction in situ with carbanions.^[285] Thus, the reaction of 2-substituted phenylacetonitriles with 1,1-dichloroethene [or (*Z*)-1,2-dichloroethene] in the presence of concentrated aqueous sodium hydroxide, with tetrabutylammonium hydrogen sulfate as the catalyst in a diethyl ether/cyclohexane mixture, leads to the formation of alkynenitriles in good yield. The reaction takes place via a *trans* addition of the nitrile carbanions to the in situ generated chloroacetylene, giving initially the *Z*-chlorovinyl derivatives, followed by elimination of hydrogen chloride.^[286] In a similar fashion, these nitriles give phenyl- or (phenylsulfanyl)ethynyl derivatives via the 1,1-dichloro-2-phenyl- or 1,1-dichloro-2-(phenylsulfanyl)ethene intermediates.^[287] Dichloroacetylene is conveniently generated from trichloroethene by means of 50% aqueous sodium hydroxide and benzyltriethylammonium chloride^[288] or dimethyl sulfoxide.^[289] When allowed to react in situ with the anions generated from 2-phenylalkanenitriles^[290] and α -substituted benzyl ketones **37** or phenylacetaldehydes,^[291] it leads to the formation of dichlorovinyl products **38** (Scheme 32). Enolates from aldehydes afford O-substituted products, the divinyl ethers.^[291] Anions generated from *N*-arylformamides under phase-transfer catalysis conditions undergo reaction with trichloroethene (via dichloroacetylene) to give mixtures of enamidines and pyrrole-2,5-diylidenediamines in high total yield.^[292]

Scheme 32 Phase-Transfer-Catalyzed Dichlorovinylolation of Nitriles and Ketones with Trichloroethene^[290,291]

(E)-3,4-Dichloro-2-methoxy-2-phenylbut-3-enenitrile (38, R¹ = OMe; R² = CN);

Typical Procedure:^[290]

A stirred mixture of methoxy(phenyl)acetonitrile (2.94 g, 20 mmol), 50% aq NaOH (4.0 mL), and Bu₄NHSO₄ (1.0 g, 3.0 mmol) was cooled to 5–10°C. Then, a soln of 1,1,2-trichloroethene (3.15 g, 24 mmol) in Et₂O (2.7 mL) was added at 5–10°C over 30 min. The mixture was stirred at 5–10°C for 4 h, carefully diluted with H₂O (20 mL), and the phases were separated. The aqueous phase was extracted with benzene (2 × 10 mL) (**CAUTION: carcinogen**), the combined organic phases were washed with H₂O (2 × 10 mL), and dried (MgSO₄), and evaporated to dryness. The residue was purified by distillation; yield: 3.15 g (65%); bp 108°C/0.5 Torr.

8.2.4.1.1.8

**Variation 8:
Isomerization and Isotopic Exchange**

These processes do not produce lipophilic inorganic anions and take place by extraction of Q⁺OH[−] into the organic phase.^[8] The isomerization of allylbenzene to a mixture of *Z*- and *E*-1-phenylprop-1-enes is realized using 50% aqueous sodium hydroxide and a catalyst, Q⁺X[−].^[10] Under similar conditions, substituted 2-allylanisoles undergo rearrangement to *E*-2-propenylanisoles.^[277] Propargyl sulfides undergo isomerization to allenic compounds by dilute aqueous sodium hydroxide and tetrabutylammonium hydrogen sulfate catalyst.^[293] Alkylation of indene under typical phase-transfer catalysis conditions leads to 3-alkyl derivatives as the result of isomerization of the initially formed 1-alkyl derivatives.^[148]

A variety of CH acids, including aliphatic ketones,^[294,295] dichloromethane,^[296] 1-alkylindenes (isomerization accompanies H–D exchange),^[297] fluorene,^[297] diazomethane,^[298] and thiazoles^[299,300] are deuterated using a sodium deuteroxide–phase-transfer catalyst system. To reach a high degree of deuterium incorporation, the process should be repeated a few times,^[294–296,298] and even compounds of p*K*_a as high as 38 enter a slow isotopic exchange.^[9,301] Pinacol, used together with tetraalkylammonium hydrogen sulfate, enhances phase-transfer-catalyzed H–D exchange of CH acids with p*K*_a ≤ 27.^[302] Measurements of isotopic exchange rates reveal that γ-halo and γ-trimethylammonium substituents increase the kinetic CH acidity of alkanenitriles and sulfones.^[303]

8.2.4.1.2

**Method 2:
Generation and Reactions of Heteroanions**

Phase-transfer catalysis is a useful method for the synthesis of ethers and sulfides via reactions of the corresponding heteroanions with alkylating agents.^[1,15] The high nucleophilicity of S-anions assures a very high yield of sulfides. Amines cannot be deprotonated by sodium hydroxide but alkylation of aromatic amines can be catalyzed to some extent by Q⁺X[−]; however, the origin of this effect is obscure.^[1] Activation of the N–H bond by a neighboring electron-withdrawing group facilitates the generation of N-anions and their alkylation. The heteroanion formation is also possible using dialkyl phosphites under phase-transfer catalysis conditions (Michaelis–Becker reaction).

8.2.4.1.2.1

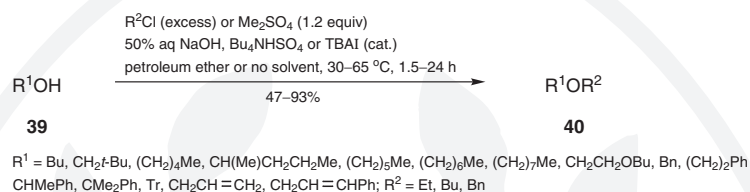
**Variation 1:
Reactions of O-Anions**

Attempted preparation of alcohols by phase-transfer-catalyzed solvolysis of alkyl halides leads to ethers as the main products because the alcohols formed initially undergo deprotonation and alkylation.^[304] For efficient alkylation of alcohols, a concentrated aqueous solution or solid sodium hydroxide is required. Phase-transfer-catalyzed methylation (by dimethyl sulfate)^[305] or alkylation (by alkyl chlorides)^[306] of alcohols **39** gives ethers **40** in

for references see p 1117

high yield (Scheme 33). Of the tetrabutylammonium salts tested as catalysts, the most efficient is the hydrogen sulfate and the least is the perchlorate, with the results for the iodide lying in between.^[306]

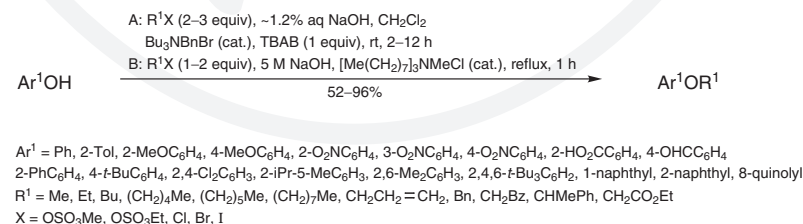
Scheme 33 Phase-Transfer-Catalyzed Synthesis of Dialkyl Ethers^[305,306]



Under phase-transfer catalysis conditions, acid-labile hemiketals undergo methylation with iodomethane in yields exceeding 95%,^[307] while benzyl alcohol undergoes reaction to displace one bromine in 1,4-dibromobutane in 88% yield.^[308] Dimethylation of chiral 1,2-disubstituted ethane-1,2-diols takes place in yields of 93–95%.^[309] An analogous process occurs when poly(ethylene glycol)s (except for the parent diol and diethylene glycol) are treated with excess chloromethane or dimethyl sulfate in the presence of powdered sodium hydroxide in benzene.^[310] On the other hand, 50% aqueous sodium hydroxide is used without a quaternary catalyst (Q^+X^-) in monoalkylation^[311] or monobenzylation,^[312] of poly(ethylene glycol)s; evidently the diols or their ethers act as catalysts. The addition of tetrabutylammonium salts does not alter the reaction rate.^[311] The efficient monobenzylation of symmetrical diols occurs in the presence of powdered sodium hydroxide and 15-crown-5 in tetrahydrofuran.^[313] The hydrophilic properties of polyols (e.g., pentaerythritol^[314,315] or carbohydrates^[316,317]) does not preclude their etherification by phase-transfer catalysis, but special conditions have to be fulfilled (e.g., a large excess of sodium hydroxide is required). In cases involving slowly reacting alcoholates, the formation of symmetrical ethers (by solvolysis of the alkyl halides to the corresponding alcohols and subsequent alkylation) competes with the formation of the nonsymmetrical ones.^[304,306] Chemical modification of cinchonidinium salts consists of their O-allylation in a 50% aqueous sodium hydroxide–dichloromethane system.^[318] 2-Ethoxyphenol, an important intermediate in perfumery, is synthesized by alkylation of ethanol with 2-chlorophenol, using phase-transfer catalysis under microwave irradiation.^[319] *gem*-Dichlorocyclopropanes substituted with electron-withdrawing groups undergo reaction with the anions generated from phenols^[44,320] or alcohols,^[320] affording the respective cyclopropanone acetals.

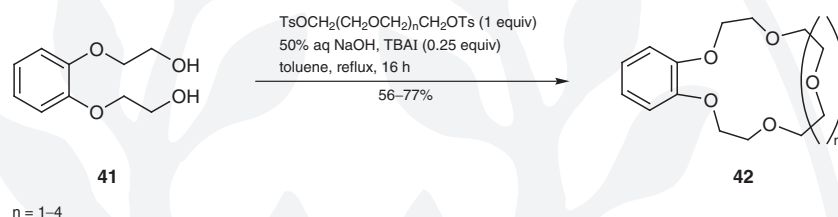
Phenols undergo facile alkylation^[321–323] or nitroarylation^[322] under phase-transfer catalysis conditions with a variety of alkylating agents; even 2,6-disubstituted, sterically crowded phenols undergo efficient methylation (Scheme 34).^[321] The ambident 2-naphthol anion is exclusively O-alkylated.^[321] The reaction of 1-bromo-3-chloropropane with phenols under phase-transfer catalysis conditions affords 3-chloro- and small amounts of 3-bromopropyl aryl ethers via halogen exchange.^[324]

Scheme 34 Phase-Transfer-Catalyzed Synthesis of Alkyl Aryl Ethers^[321–323]



2-Aminophenols^[325] and 2-aminopyridin-3-ols^[326] undergo regioselective O-alkylation. Phase-transfer-catalyzed reaction of *ortho*-dihydroxybenzenes with dibromomethane^[327] or dihaloalkanes under solvent-free conditions^[323] allows the synthesis of cyclic products. Methyltriocetylammmonium chloride is the most efficient of the catalysts tested.^[323] Reaction of bis(*o*-phenylene) glycol (**41**) with oligo(ethylene glycol) di-4-toluenesulfonates (carried out by phase-transfer catalysis),^[328] or catechol with bis(2-chloroethyl) ether (in the presence of solid sodium hydroxide in butanol),^[329] affords benzocrown ethers **42** (yields up to 77%) or dibenzo-18-crown-6 (yields 39–48%), respectively (Scheme 35). Other phase-transfer-catalyzed synthetic approaches to benzocrown ethers are known.^[328]

Scheme 35 Phase-Transfer-Catalyzed Synthesis of Benzocrown Ethers^[328]



Oxime anions, generated under phase-transfer catalysis conditions, furnish the O-substituted products in reactions with alkyl halides,^[330,331] but the attempted butylation of *anti*-benzaloxime gives the corresponding nitron preferentially.^[330] Reactions of oximes with dichloromethane give methylene dioximes in high yield.^[330,332] *N,N*-Diethylhydroxylamine undergoes O-alkylation, and it was observed that electron-transfer processes occur when 4-nitrobenzyl halides are used.^[333] Alcohols undergo acetylation using acetic anhydride in the presence of a catalytic amount of sodium hydroxide under microwave irradiation, with yields exceeding 90%.^[334] Benzophenone imines of methyl esters of amino acids and peptides undergo saponification and O-alkylation under phase-transfer catalysis conditions.^[335] Aromatic and heterocyclic nitro compounds undergo hydroxylation with *tert*-butyl or cumyl hydroperoxide anions, generated with sodium hydroxide in liquid ammonia,^[336] according to the vicarious nucleophilic substitution pathway.^[154–157]

3-Methoxy-1-phenylprop-1-ene (40, R¹ = CH₂CH=CHPh; R² = Me); Typical Procedure:^[305]

CAUTION: Dimethyl sulfate is corrosive and irritating to the skin, eyes, and respiratory system and is a probable human carcinogen.

A mixture of 3-phenylprop-2-en-1-ol (67.1 g, 0.5 mol), TBAI (1 g), petroleum ether (bp 50–70 °C, 200 mL), and 50% aq NaOH (69 mL) was vigorously stirred for 15–30 min (a slight exothermic effect was observed). With cooling, dimethyl sulfate (75.7 g, 0.6 mol) was added dropwise during 1 h, maintaining the temperature below 45 °C. The reaction mixture was stirred for 2–3 h, concd aq NH₃ (10 mL) was added, and stirring was continued for 30 min at rt. The mixture was diluted with H₂O, the phases were separated, the organic phase was washed with H₂O, dried (Na₂SO₄), and evaporated to dryness. The residue was purified by distillation; yield: 66.7 g (90%); bp 115 °C/12 Torr.

Benzo-18-crown-6 (42, n = 2); Typical Procedure:^[328]

To a stirred soln of glycol **41** (9.91 g, 50 mmol) and TBAI (4.62 g, 12.5 mmol) in toluene (300 mL) was added 50% aq NaOH (100 mL) at 50–60 °C. The mixture was stirred at this temperature for 0.5 h, whereupon a soln of triethylene glycol di-4-toluenesulfonate (22.93 g, 50 mmol) in toluene (300 mL) was added. The resulting mixture was refluxed for 16 h. The organic layer was separated, washed with H₂O (3 × 200 mL) and then brine

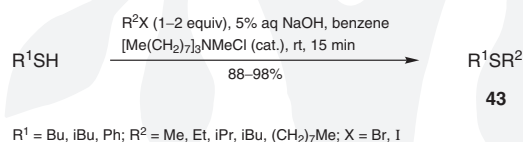
for references see p 1117

(100 mL), dried (MgSO_4), and concentrated to dryness under reduced pressure. The residue was extracted with boiling hexane (3×150 mL). After cooling, the pure product was obtained as colorless crystals; yield: 15.62 g (69%).

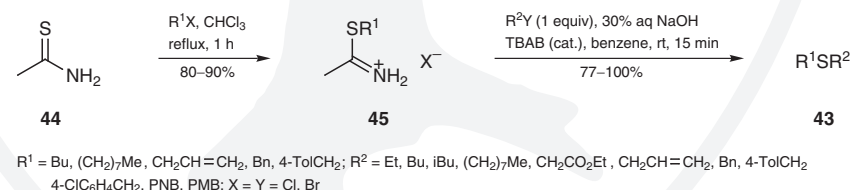
8.2.4.1.2.2 Variation 2: Reactions of S-Anions

Alkylation of benzenethiol with 1-bromooctane in a two-phase system involving aqueous sodium hydroxide can be catalyzed by quaternary ammonium or phosphonium salts,^[337] or by more complex polypode ligands.^[338] Unsymmetrical sulfides are prepared rapidly under phase-transfer catalysis conditions from sodium thiolates and primary alkyl halides (secondary alkyl halides undergo reaction more slowly) in nearly quantitative yields (Scheme 36).^[339,340] Even neopentyl bromide undergoes reaction with sodium benzenethiolate to give neopentyl phenyl sulfide in 78–85% yield.^[341] Alkyl aryl sulfides are prepared by a phase-transfer-catalyzed reaction of diaryl disulfides with alkyl halides or aryl bromomethyl selenides.^[342] Unsymmetrical sulfides **43** are also obtained via an efficient reaction of 1-(alkylsulfanyl)ethaniminium halides **45** [prepared from thioacetamide (**44**) and alkyl halides] with alkyl halides under phase-transfer catalysis conditions (Scheme 37).^[343] The synthesis of formaldehyde dithioacetals from the reaction of alkane- or benzenethiols with dichloromethane^[340] or the cyclization of benzene-1,2-dithiol with deuterated dichloromethane^[344] occurs in high yield. The latter product is used for the preparation of aldehydes deuterated at the carbonyl carbon.^[344] 1,3-Benzoxathioles are prepared by phase-transfer-catalyzed reactions of 2-hydroxybenzenethiols with dibromomethane, in yields ranging from 70 to 81%.^[345] Ethane-1,2-dithiol and cyclic thiourea derivatives give heterocyclic compounds when treated with dibromoalkanes under phase-transfer catalysis conditions.^[346]

Scheme 36 Phase-Transfer-Catalyzed Synthesis of Unsymmetrical Sulfides from Thiols^[340]



Scheme 37 Phase-Transfer-Catalyzed Synthesis of Unsymmetrical Sulfides from Thioacetamide^[343]



Symmetrical disulfides are prepared by reaction of alkyl halides with elemental sulfur, either in the presence of solid sodium hydroxide in dimethyl sulfoxide,^[195] or by using the solid base and PEG-400 as the catalyst in dimethylformamide under microwave irradiation.^[347] The latter method affords the products in higher yields.

S-Anions, generated in situ from the corresponding 3-(acetoxysulfanyl)alkanals under phase-transfer catalysis conditions, enter into reactions with α,β -unsaturated aldehydes which lead to the formation of 5-thiacyclohex-1-enecarbaldehydes. 2-Sulfanyl aldehydes or ketones undergo reaction with α -chloroacrylonitrile, giving epoxy nitriles. Both

types of compound are formed via multistep processes.^[348] *gem*-Dichlorocyclopropanes substituted with electron-withdrawing groups undergo reaction with benzenethiol under phase-transfer catalysis conditions, affording the corresponding cyclopropanone dithioacetals.^[44,320]

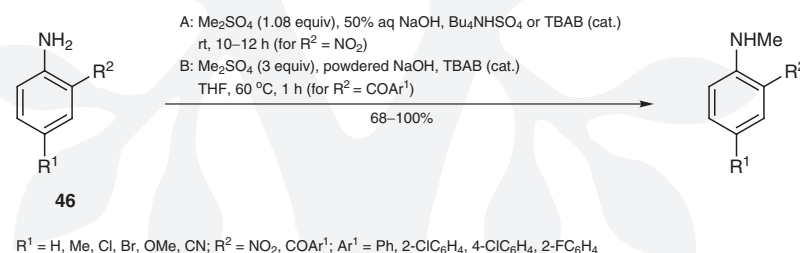
Ethyl Phenyl Sulfide (43, R¹ = Ph; R² = Et); Typical Procedure:^[340]

A mixture of PhSH (5.0 g, 0.46 mmol), EtBr (5.0 g, 0.046 mol), NaOH (3.0 g, 75 mmol), H₂O (50 mL), and methyltriethylammonium chloride (ca. 0.1 g) was vigorously stirred at rt for 15 min. The organic phase was separated, washed with H₂O, dried (MgSO₄), and concentrated to give a colorless oil. The residue was distilled under reduced pressure; yield: 5.94 g (93%); bp 110 °C/20 Torr.

**8.2.4.1.2.3 Variation 3:
Reactions of N-Anions**

The catalytic effect of Q⁺X[−] on the alkylation of aromatic amines in the presence of an aqueous solution or solid sodium hydroxide is observed, in spite of their low acidity, which precludes the generation of amide anions with sodium hydroxide.^[1,349] The N-anions are possibly involved during the selective and efficient N-monomethylation of 2-nitroanilines with dimethyl sulfate^[350] or the N-monoalkylation of 2-aminobenzophenones **46** (Scheme 38).^[351]

Scheme 38 Phase-Transfer-Catalyzed N-Methylation of Anilines which are *ortho* Substituted with Electron-Withdrawing Groups^[350,351]

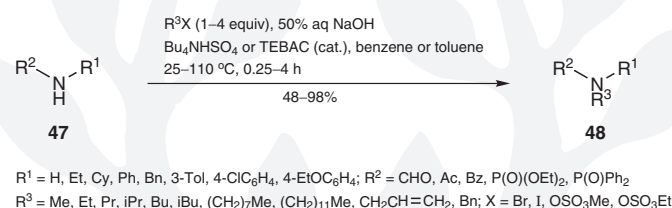


When an electron-withdrawing group (cyano,^[352,353] formyl,^[354] acyl,^[355–360] sulfonyl,^[358,361] diethoxyphosphoryl,^[362] or diphenylphosphoryl^[363]) is connected to nitrogen, the resulting compounds **47** can be smoothly alkylated under conditions of phase-transfer catalysis, e.g. to give **48** (Scheme 39). Thus cyanamide leads only to dialkylation,^[352] giving *N,N'*-dicyano[3,3]azacyclophanes from reactions with bis- or tris(bromomethyl) aromatic compounds.^[353] Cyano group(s) are easily cleaved from the products, affording secondary amines.^[352,353] A liquid–liquid phase-transfer catalysis system is suitable for the alkylation of *N*-acyl,^[355,357] and *N*-formylanilines,^[357] as well as benzamide^[358] and sulfonamides.^[358,361] In spite of the fact that sulfonamides are stronger NH acids than amides, the latter are often *N,N*-dialkylated in a solid–liquid system.^[358] Alkylation of sulfonamides using long-chain dihaloalkanes leads to the formation of macrocyclic products.^[361] Aza crown ethers or cryptands are synthesized by phase-transfer-catalyzed reactions of bis-sulfonamides with ethylene glycol dibromides or bis-tosylates.^[364] *N*-Alkylation of *N*-substituted formamides,^[354] amides,^[356] and propanamide or *N,N*-dialkylation of benzamide^[358] requires the use of a mixture of solid sodium hydroxide with potassium carbonate and tetrabutylammonium hydrogen sulfate as the catalyst. *N*-Aryl amides, *ortho* substituted with electron-withdrawing groups,^[359] and 2-nitrotrifluoroacetanilides^[360] undergo one-pot methylation^[359,360] or alkylation^[360] followed by hydrolysis to give *N*-methyl or *N*-alkyl *ortho*-substituted anilines. Sterically hindered *N*-substituted α -aminocarboxamides are prepared

for references see p 1117

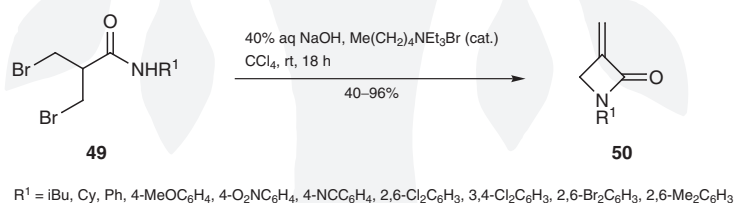
from α -bromocarboxamides and primary or secondary amines under phase-transfer catalysis conditions. Zwitterions from amides are possibly involved in this process.^[365] Aliphatic isocyanates are prepared by tetrabutylammonium hydrogen sulfate catalyzed reaction of amides with aqueous sodium hydroxide and bromine (Hofmann reaction^[366]); poorer yields are observed in reactions with chlorine.^[367] Phase-transfer-catalyzed alkylation of diethyl phosphoramidates,^[362] diphenylphosphinic amide,^[363] or diphenylphosphinic hydrazide^[14] is employed in the efficient preparation of primary and secondary amines or monoalkylhydrazines, respectively. *N*-(Diethoxyphosphoryl)aziridine, a reagent for two-carbon homologation of Grignard reagents, is prepared by cyclization of *N*-(2-chloroethyl)phosphoramidate under conditions of solid-liquid phase-transfer catalysis.^[368]

Scheme 39 Phase-Transfer-Catalyzed Alkylation of NH Acids Substituted with Electron-Withdrawing Groups^[357,358,362,363]



Cyclization of 3-bromo-2-(bromomethyl)propanamides **49**^[369] and a one-pot reaction of β -haloacyl chlorides with α -amino acids^[370] in liquid-liquid phase-transfer catalysis systems provide effective syntheses of substituted α -methylene- β -lactams **50** or β -lactams, respectively (Scheme 40). β -Lactams are also obtained by cyclization of *N*-substituted α,β -dihalo- α -methylpropanamides in the presence of 50% aqueous sodium hydroxide and various α -amino acids as catalysts.^[370]

Scheme 40 Phase-Transfer-Catalyzed Synthesis of α -Methylene- β -lactams^[369]

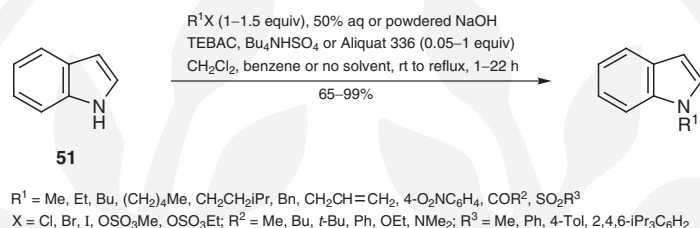


Phenylhydrazones,^[371] 1,3-diaryltriazenes,^[372] or tosylhydrazones^[373] undergo *N*-alkylation under phase-transfer catalysis conditions; in the latter case, iodomethane is used most often and the process is carried out in the presence of 15% aqueous sodium hydroxide. Aminocarbene complexes of chromium and tungsten undergo methylation and cycloalkylation in the presence of aqueous sodium hydroxide and tetrabutylammonium bromide. A large excess of iodomethane is required in order to obtain dimethyl derivatives in good yield.^[374]

Nitrogen heterocycles constitute another class of compound which are alkylated under phase-transfer catalysis.^[375] Worthy of mention are the alkylation of aziridine and derivatives, sometimes occurring in quantitative yield,^[376] the *N*-alkylation of indole (**51**)^[377-379] (carried out in the presence of Q^+X^- ^[377-379] or in aprotic dipolar solvents^[377]), and the alkylation of substituted indoles (Scheme 41).^[380-382] The use of reactive alkylating agents (allyl, propargyl, or benzyl halides) leads invariably to some 3- and/or 1,3-disubstitution.^[377,379,382] Indole undergoes smoothly *N*-acylation^[383] and sulfonylation^[384] under phase-transfer catalysis conditions. The phase-transfer-catalyzed reaction of azoles with

2-chloroethylamine affords *N*-(aminoethyl)azoles.^[385] 1,4-Dihydropyridine-3,5-dicarbonitriles are *N*-alkylated using benzyldodecyldimethylammonium bromide as the catalyst.^[386] Ambident 2- or 4-hydroxypyridine anions undergo both *N*- and *O*-alkylation, but the former prevails irrespective of the alkylating agents;^[387] on the other hand, lactams undergo exclusive *N*-alkylation under phase-transfer catalysis conditions.^[388]

Scheme 41 Phase-Transfer-Catalyzed Alkylation, Acylation, and Sulfonation of Indole^[377–379,383,384]



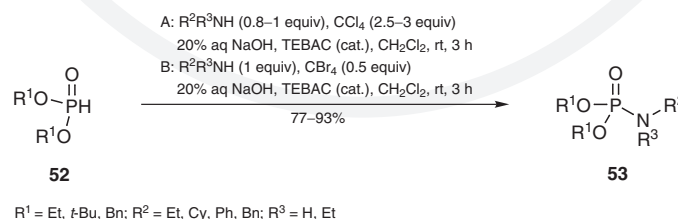
***N*-Propylbenzamide (48, $\text{R}^1 = \text{H; R}^2 = \text{Bz; R}^3 = \text{Pr}$); Typical Procedure:**^[358]

A soln of PrBr (7.38 g, 0.06 mol) in benzene (10 mL) (**CAUTION: carcinogen**) was added dropwise with efficient stirring to a refluxing mixture of benzamide (6.05 g, 0.05 mol), 50% aq NaOH (50 mL), Bu_4NHSO_4 (1.7 g, 0.005 mol), and benzene (50 mL). After the addition was complete (1.5 h), stirring was continued for 2.5 h at reflux temperature. The mixture was cooled and diluted with H_2O (30 mL), the organic phase was separated, washed with H_2O (3×20 mL) until neutral, dried (MgSO_4), and concentrated to dryness to give the crude product as a crystalline solid, which was recrystallized; yield: 6.53 g (80%); mp 83–84 °C (Et_2O).

8.2.4.1.2.4 Variation 4: Reactions of P-Anions

Phase-transfer-catalyzed alkylation of dialkyl hydrogen phosphonates with alkyl chloroacetates^[389] or chloroacetamides^[390] produces dialkyl alkylphosphonates (Michaelis–Becker reaction^[391]). The process is carried out at temperatures not exceeding 30 °C, in the presence of 50% aqueous sodium hydroxide, in dichloromethane.^[390] Similarly, dialkylphosphine oxides undergo reaction with alkylating agents to give the corresponding trialkylphosphine oxides.^[390,392] This reaction is applied to soluble and cross-linked chloromethylated polystyrenes to give polymers with phosphine oxide groups.^[392] Phase-transfer catalysis has been applied to the phosphorylation of amines (e.g., to give **53**),^[393] sulfonamides,^[394] alcohols, and phenol^[395] by means of halophosphates, generated in situ from dialkyl phosphites **52** and carbon tetrahalides (Atherton–Todd method) (Scheme 42). Di-*tert*-butyl halophosphates are synthesized by this method in high yields (ca. 90%).^[396] Phosphorylation of *N*-arylformamides or chloroacetamides gives unstable *N*-phosphorylated amides which, when treated with water, afford phosphorylated anilines.^[397]

Scheme 42 Synthesis of Phosphorylated Amines by the Atherton–Todd Method^[393]



for references see p 1117

Diethyl Cyclohexylamidophosphate (53, R¹ = Et; R² = Cy; R³ = H); Typical Procedure:^[393]

A soln of diethyl phosphite (17.3 g, 0.125 mol) and CyNH₂ (9.9 g, 0.1 mol) in CH₂Cl₂ (30 mL) was added dropwise to a stirred two-phase system consisting of CH₂Cl₂ (30 mL), CCl₄ (30 mL) (**CAUTION: toxic**), 20% aq NaOH (40 mL), and TEBAC (1.0 g). The temperature of the strongly exothermic reaction was kept at 0–5 °C (ice/salt bath). The stirring was continued for 1 h at 0–5 °C and then for 1 h at rt. The mixture was diluted with CH₂Cl₂ (25 mL), the phases were separated, the organic phase was washed with 5% aq HCl (50 mL) and then H₂O (2 × 50 mL) and dried (MgSO₄), and evaporated to dryness. The product was purified by recrystallization; yield: 20.9 g (89%); mp 75–76 °C [hexane/benzene (**CAUTION: carcinogen**) 1:1].

8.2.4.1.3

**Method 3:
Reactions of Sodium Hydroxide as a Nucleophile**

Except for a few special cases,^[398,399] phase-transfer-catalyzed reactions of alkyl halides with sodium hydroxide lead to the formation of ethers rather than alcohols, since the latter are readily deprotonated and alkylated to give ethers (see Section 8.2.4.1.2.1). The rate of hydrolysis of (trichloromethyl)benzene with aqueous sodium hydroxide is accelerated by different catalysts, evidencing micellar catalysis rather than typical phase-transfer catalysis.^[400] Acyl chlorides do not form the corresponding carboxylic acids when treated with molar equivalents of sodium hydroxide under phase-transfer catalysis conditions, and symmetrical carboxylic anhydrides are produced instead.^[401] On the other hand, hydrolysis of long-chain alkanesulfonyl chlorides by aqueous base may be accelerated by a Q⁺X[−] catalyst.^[294] Thiocarbonyl groups in thioketones, thioamides, dithioesters, and thioureas are converted into carbonyl groups by the simple treatment with dilute sodium hydroxide and tetrabutylammonium hydrogen sulfate.^[402]

The hydroxide anion (50% aqueous sodium hydroxide, tetrabutylammonium hydrogen sulfate) enters into a nucleophilic aromatic substitution reaction with fluorobenzenes to give single fluorophenols undergoing reaction even when there is more than one fluorine atom on the ring, e.g. hexafluorobenzene affords pentafluorophenol in 71% yield.^[403]

8.2.4.1.4

**Method 4:
Generation and Reactions of Ylides**

Deprotonation of sulfonium,^[404,405] sulfoxonium,^[404–406] ammonium,^[404,405,407] or phosphonium^[408–410] salts with sodium hydroxide, or other bases, generates the corresponding ylides which participate in many synthetically important processes. When a two-phase system with sodium hydroxide is used, these reactions can often be carried out without the catalyst (Q⁺X[−]), since the starting onium salts themselves can play this role. Furthermore, the ylides are neutral molecules and thus, when generated at the phase boundary of a two-phase system, can freely diffuse into the organic phase and enter into chemical reactions.^[411]

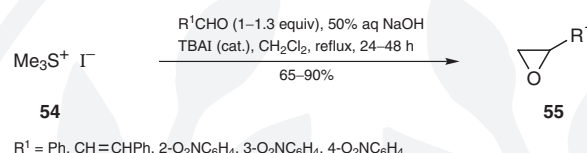
8.2.4.1.4.1

**Variation 1:
Reactions of Sulfur Ylides**

The reaction of the ylide generated from trimethylsulfonium iodide (**54**) (using 50% aqueous sodium hydroxide and the catalyst tetrabutylammonium iodide in dichloromethane) with aldehydes (benzaldehyde, cinnamaldehyde,^[412] nitrobenzaldehydes,^[413] polynuclear aromatic aldehydes^[414]) constitutes a highly efficient synthesis of substituted oxiranes **55** (Scheme 43). The use of a concentrated aqueous base is critical for obtaining high yields of the oxiranes. When the reactions are carried out in benzene, sulfonium chlorides having one long chain appear to be the best precursors of the ylide.^[415] Trialkyl-, allyl-, and ben-

zyldimethylsulfonium chlorides,^[416] benzylsulfonium salts,^[417] and trimethyl- or triethylsulfonium alkylsulfates^[418] undergo reaction with aldehydes^[416–418] and ketones^[418] in the presence of aqueous sodium hydroxide without a catalyst to give the corresponding oxiranes. The synthesis of these products is also carried out under conditions of triphase catalysis with sulfonium salts bonded to insoluble polymers.^[419]

Scheme 43 Phase-Transfer-Catalyzed Synthesis of Oxiranes from Trimethylsulfonium Iodide and Aldehydes^[412,413]

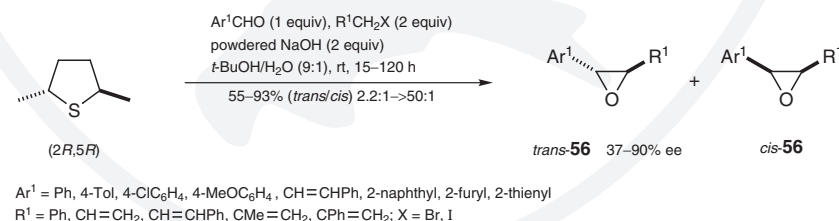


The reaction of benzylsulfonium salts with aromatic aldehydes leads predominantly to *trans*-epoxides, while aliphatic aldehydes give mixtures of *cis*- and *trans*-epoxides.^[416,417] The anionic tetrakis[3,5-bis(trifluoromethyl)phenyl]borate catalyst (used as the sodium salt) promotes oxirane formation from carbonyl compounds and trimethylsulfonium chloride in a two-phase system.^[420] S-Methylated formaldehyde dithioacetals, when treated with 50% aqueous sodium hydroxide in dimethylformamide, form ylides which subsequently undergo reaction with aromatic aldehydes to form 2-(alkylsulfanyl)-3-aryl-oxiranes. Depending upon the substituents on the aromatic ring, the latter either undergo further rearrangement or are isolated.^[421]

The reaction of chiral benzyl-^[422–425] or [(*N,N*-dialkylcarbamoyl)methyl]sulfonium salts^[426] (derived from *C*₂-symmetric thiolanes,^[422] thianiumbicyclo[3.2.1]octane,^[423] Eliel's oxathiane,^[424] pinene,^[425] or camphor^[426]) with carbonyl compounds (usually aromatic aldehydes) carried out in the presence of sodium hydroxide (often with Q⁺X[–] as the catalyst^[422–425]) leads to the formation of chiral oxiranes in up to 100% ee.^[424]

A simple catalytic process for oxirane synthesis consists of a one-pot reaction of a sulfide with an alkyl halide, a carbonyl compound, and a base.^[427] Thus, the combination of ferrocenyl sulfides, benzyl bromide, and aldehydes or ketones give, in the presence of sodium hydroxide in *tert*-butyl alcohol–water, the corresponding oxiranes in good yields.^[428] The reaction of aldehydes, chiral sulfides, and alkylating agents [(2*R*,5*R*)-2,5-dialkylthiolanes and benzyl bromide^[429,430] or allyl halides,^[431] *C*₂-symmetrical sulfides and benzyl bromide^[432]] in the presence of sodium hydroxide (with addition of tetrabutylammonium iodide^[430]) leads to the formation of chiral oxiranes **56** in up to 96% ee^[429] and with high diastereomeric excess (Scheme 44).^[429–432]

Scheme 44 Phase-Transfer-Catalyzed Asymmetric Synthesis of Oxiranes from In Situ Generated Sulfonium Salts and Aldehydes^[429–431]

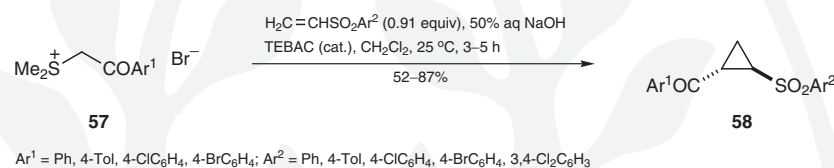


[(*N,N*-Dialkylcarbamoyl)methyl]dimethylsulfonium salts undergo reaction in dichloromethane with aqueous sodium hydroxide and D-glyceraldehyde^[433] or carbohydrate derivatives^[433–435] to afford substituted 2,3-epoxy amides, some of which are useful acyclic chiral templates.^[434]

for references see p 1117

Trimethylsulfoxonium methylide, generated from the corresponding iodide by phase-transfer catalysis, is usually a poor reagent for the epoxidation of aldehydes.^[412] However, it undergoes smooth reaction with α,β -unsaturated carbonyl compounds, with formation of the corresponding substituted cyclopropanes.^[412,436–438] If the trimethylsulfoxonium salt is substituted with a cyano^[439] or an aroyl group (e.g., **57**^[440–444]), the corresponding ylides generated using sodium hydroxide, either without the Q^+X^- catalyst^[439,440] or in its presence,^[441–444] undergo reaction with benzylidenemalonate or benzylidenemalononitrile,^[439] as well as with α,β -unsaturated carbonyl compounds^[440–443] or aryl vinyl sulfones,^[444] to give cyclopropanes (e.g., **58**) substituted with the corresponding electron-withdrawing groups (Scheme 45).

Scheme 45 Phase-Transfer-Catalyzed Synthesis of Cyclopropanes from Aryl Vinyl Sulfones and Sulfonium Salts^[444]



Aldehyde imines or arylhydrazones undergo reaction with trimethylsulfoxonium iodide under phase-transfer catalysis conditions, giving substituted aziridines in high yields.^[445]

Suitably substituted sulfonium salts treated with sodium hydroxide afford the corresponding ylides which subsequently enter into sigmatropic rearrangements.^[446–449]

2-(4-Nitrophenyl)oxirane (**55**, $\text{R}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$); Typical Procedure:^[413]

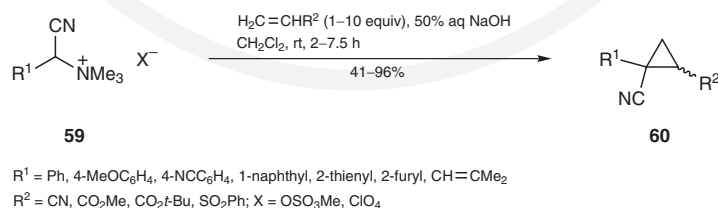
To a vigorously stirred soln of 4-nitrobenzaldehyde (7.4 g, 0.049 mol), TBAI (0.1 g), and finely powdered $\text{Me}_3\text{S}^+\text{I}^-$ (**54**; 10.2 g, 0.06 mol) in CH_2Cl_2 (200 mL), 50% aq NaOH (50 mL) was added. The mixture was refluxed for 24 h, cooled and poured into ice-cold H_2O (200 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3×50 mL), the combined organic extracts were washed with H_2O ($3 \times$), sodium metabisulfite, and H_2O again; the extracts were then dried and concentrated to dryness. The residue was purified by column chromatography (silica gel, CH_2Cl_2) and/or crystallization; yield: 6.07 g (75%); mp $85\text{--}86^\circ\text{C}$.

8.2.4.1.4.2

Variation 2: Reactions of Nitrogen Ylides

Ammonium ylides generated from ammonium salts **59** using 50% aqueous sodium hydroxide in dichloromethane undergo reaction with alkylating agents, carbonyl compounds, or electrophilic alkenes to give substituted cyanoalkenes, -oxiranes, or -cyclopropanes **60**, respectively, usually in high yield (Scheme 46).^[275] Tetramethylammonium salts substituted with electron-withdrawing groups^[170] participate in vicarious nucleophilic substitution reactions (see Section 8.2.4.1.1.2).^[154–157]

Scheme 46 Synthesis of Cyclopropanes from Ammonium Salts and Electrophilic Alkenes^[275]



Suitably substituted aliphatic^[450,451] or alicyclic^[448,450,452] ammonium salts, on treatment with sodium hydroxide, afford ylides which enter into 1,2- (Stevens) and/or 2,3- (Sommelet–Hauser) sigmatropic rearrangements.^[404,405,407,453]

Methyl 2-Cyano-2-phenylcyclopropanecarboxylate (60, R¹ = Ph; R² = CO₂Me);

Typical Procedure:^[275]

To a vigorously stirred soln of salt **59** (R¹ = Ph; X = OSO₃Me; 0.86 g, 3 mmol) and methyl acrylate (2.58 g, 30 mmol) in CH₂Cl₂ (45 mL), 50% aq NaOH (7.5 mL) was added and the stirring was continued at rt for 2 h. The mixture was diluted with H₂O (100 mL), the phases were separated, the aqueous phase was extracted with CH₂Cl₂ (3 × 25 mL), and the combined organic extracts were washed with H₂O (3 × 40 mL), dried (MgSO₄), and concentrated to dryness. The residue was purified by Kugelrohr distillation and column chromatography (silica gel, hexane/EtOAc gradient) to give an oil; yield: 549 mg (91%); bp 135–145 °C/0.07 Torr.

8.2.4.1.4.3

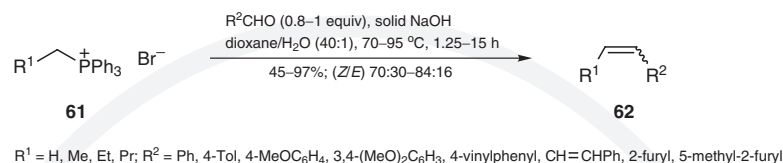
Variation 3:

Phosphorus Ylides; Alkenation by the Wittig Reaction

The Wittig reaction^[408–410] of phosphorus ylides generated from phosphonium (usually substituted triphenylphosphonium) salts with aqueous or solid sodium hydroxide in various solvents is practically insensitive to the presence of a phase-transfer catalyst.^[454–457] The ylide generated at the interphase of two-phase systems can freely migrate into the organic phase and enter into Wittig reactions. However, some alkenation reactions are carried out with Q⁺X[−] as the catalyst.^[458] Heterogeneous Wittig reactions of suitably P-substituted triphenylphosphonium salts with aldehydes are successfully applied to the preparation of various mono- and disubstituted ethenes^[454,455,459,460] (including 1-phenylalkenes^[454] or styrenes by reaction of methylphosphonium salts with benzaldehyde^[459] or benzylphosphonium salts with aqueous formaldehyde^[455,460]), conjugated dienes and trienes,^[454,459,461] stilbenes,^[457,462] 6-styryl- or 6-phenylbutadienyl heptalenes,^[463] racemic or chiral vinyl sulfoxides,^[458] and vinyl selenides.^[464] The Wittig reaction of benzyl(triphenyl)- or alkyl(triphenyl)phosphonium salts **61** with aromatic or aliphatic aldehydes carried out in the presence of solid sodium hydroxide and a minute amount of water in 1,4-dioxane affords mainly *Z*-alkenes **62** in good yield.^[465,466] Phase-transfer-catalyzed alkenation may also be carried out with polymer-supported phosphonium salts.^[467] Phosphonium ylides may be generated from triphenylphosphine and chloroform or alkyl (or phenyl) dichloromethyl sulfide in the presence of concentrated aqueous sodium hydroxide, with benzyltriethylammonium chloride catalyst, and applied in situ to the alkenation of aldehydes.^[468] Mixtures of stabilized triphenylphosphonium salts and benzylic alcohols enter into tandem deprotonation–oxidation–Wittig reaction in a sodium hydroxide–manganese(IV) oxide–dichloromethane system.^[469]

The stereochemistry of two-phase alkenation depends on the substrate structure and the reaction conditions. Stilbenes are usually formed as mixtures of *Z*- and *E*-isomers in a ca. 1:1 ratio,^[454,459,466] except when substituents are present in both phenyl rings,^[457] particularly in *ortho* and/or *ortho'* positions. In the latter case the *Z/E* ratio varies from 95:5 to 1:99.^[462] The use of a slightly hydrated base increases the *Z* selectivity in the case of 1,2-disubstituted ethenes (Scheme 47).^[465,466] β -Aryl-substituted electrophilic alkenes, produced from the in situ generated aldehydes, are formed mainly as *Z*-isomers (*Z/E* from 80:20 to 100:0).^[469] (Methoxycarbonylmethylene)tributylphosphorane, generated from the corresponding bromide by means of aqueous sodium hydroxide, undergoes reaction, in a separate step, with α -alkoxy aldehydes and sugar lactols to give the corresponding *E*- α,β -unsaturated esters with high selectivity and yield.^[470]

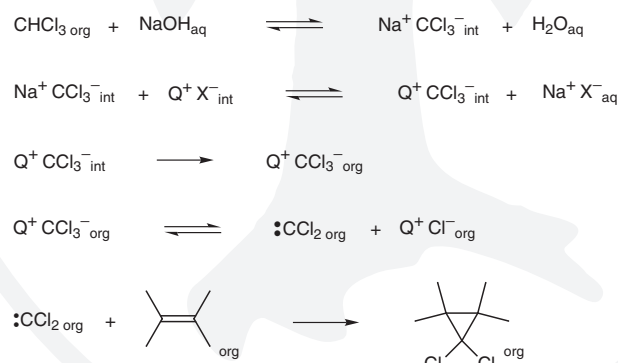
for references see p 1117

Scheme 47 Synthesis of Alkenes by a Two-Phase Wittig Reaction^[465,466]**1-Phenylbut-1-ene (62, R¹ = Et; R² = Ph); Typical Procedure:**^[465]

A mixture of phosphonium bromide **61** (R¹ = Et; 7.71 g, 0.02 mol), NaOH (3 g, 0.075 mol), 1,4-dioxane (20 mL), H₂O (0.5 mL), and benzaldehyde (2.12 g, 0.02 mol) was shaken at 70 °C for 6 h. The mixture was filtered, the filtrate was concentrated, and the residue was purified by column chromatography on a short and broad column (silica gel, hexane) to give the product as a mixture of isomers (Z/E 83:17); yield: 2.25 g (85%).

**8.2.4.1.5 Method 5:
Elimination Reactions**
**8.2.4.1.5.1 Variation 1:
α-Elimination (Generation and Reactions of Carbenes, Nitrenes,
and Their Precursors)**

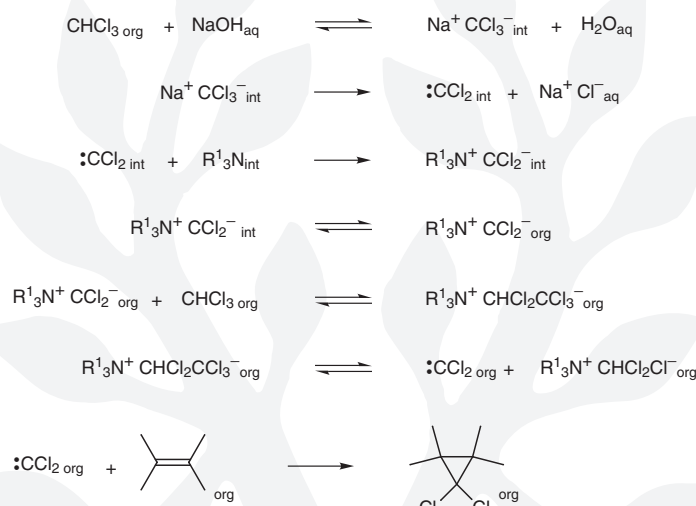
Reaction of trihalomethanes with sodium hydroxide, a phase-transfer catalyst (usually Q⁺X[−]), and alkenes is the simplest and often the most efficient method for synthesis of *gem*-dihalocyclopropanes (Scheme 48).^[3,6,7] The reaction occurs by deprotonation of the trihalomethane by the hydroxide anion at the interphase, resulting in the generation of trihalomethyl anion–sodium cation pairs, which form lipophilic ions via exchange with Q⁺X[−]. The latter penetrates into the organic phase and undergoes dissociation into dihalocarbenes and halide anions; the carbene then undergoes stereospecific addition to the alkene, with formation of the *gem*-dihalocyclopropane.^[3,6,7,13,471–473]

Scheme 48 Generation of Dichlorocarbene by Phase-Transfer Catalysis: Catalysis by Q⁺X[−]^[3,6,7,13,471–473]

A significant feature of phase-transfer catalysis is the high efficiency of the dihalocarbene cycloaddition reaction.^[13] The carbenes are generated inside the organic phase, free of hydroxy anions and water (the former promotes hydrolysis of dihalocarbene at a very high rate). While the addition of a carbene to an alkene is a relatively slow process, the reversible generation of the carbene allows it to be “stored” as the Q⁺CX₃[−] species. Since dihalocarbenes are quickly hydrolyzed, their generation is carried out in the presence of either a

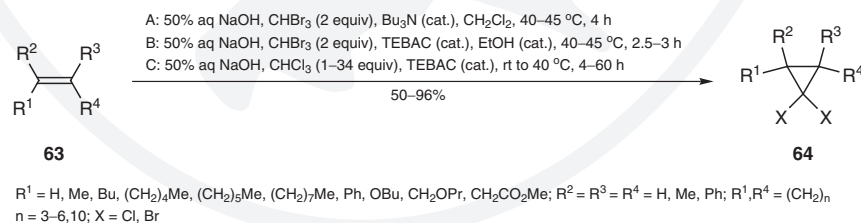
concentrated aqueous solution of, or solid, sodium hydroxide. Generation of dihalocarbenes from trihalomethanes and sodium hydroxide is also catalyzed by tertiary amines (Scheme 49).^[474,475] In this case, the dihalocarbene, generated from trihalomethane anion–sodium cation pairs at the interphase, is trapped with the amine, giving an ammonium ylide which is easily soluble in the organic phase. The ylide acts as the base, deprotonating the trihalomethane and generating the dihalocarbene, which in the organic phase adds to the alkene.^[475]

Scheme 49 Generation of Dihalocarbenes by Phase-Transfer Catalysis: Catalysis by Tertiary Amines^[474,475]



Dihalocarbenes are electrophilic species; under phase-transfer catalysis conditions the free carbenes are the reactive intermediates, not the carbenoids. Dibromocarbene is more reactive than dichlorocarbene, but the latter undergoes faster reaction than difluorocarbene. Using the simple phase-transfer catalysis methodology with sodium hydroxide, all *gem*-dihalocyclopropanes (e.g., dichloro^[476–478] or dibromo^[479–481] **64** from **63**) can be prepared from the corresponding trihalomethanes and various alkenes (Scheme 50); the results of these investigations have been reviewed.^[3,6,7,15,471–473] The reactions of chlorodifluoromethane constitute an exception and give *gem*-difluorocyclopropanes in very low yields.^[482] The yields of *gem*-dibromocyclopropanes are improved by the addition of a small amount of ethanol^[480] or pinacol^[302] to the reaction mixture or by using a tertiary amine as the catalyst.^[481]

Scheme 50 Phase-Transfer-Catalyzed Synthesis of *gem*-Dihalocyclopropanes^[476–478,480,481]

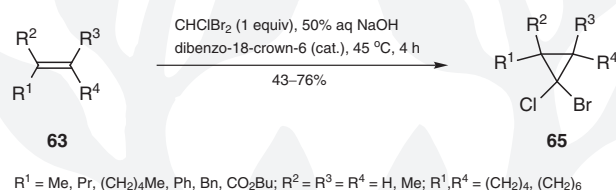


The reactions of dibromochloro^[484] or bromodichloromethane,^[483,484] as well as dibromoiodo- or bromodiiodomethane,^[485] with alkenes in the presence of 50% aqueous sodium hydroxide and benzyltriethylammonium chloride catalyst afford mixtures of all possible

for references see p 1117

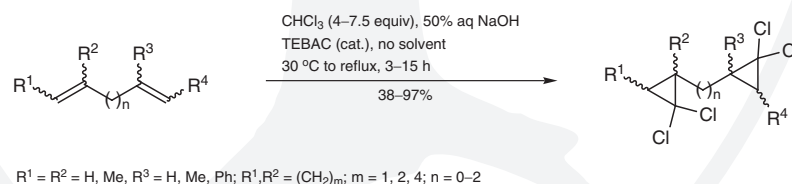
gem-dihalocyclopropanes. This result is due to dihalocarbene–halide anion equilibria, which produce different trihalomethyl anions, and hence different carbenes and cyclopropanes.^[483–485] Under suitable conditions, the phase-transfer-catalyzed reaction of chloroform with sodium iodide, bromoform with sodium chloride,^[486] or chloroform with bromoform^[487] serve for the preparation of chlorodiiodomethane, dibromochloromethane,^[486] or the latter and bromodichloromethane, respectively.^[487] However, when dibenzo-18-crown-6,^[488] or other crown ethers, or very hydrophilic tetramethylammonium chloride^[486] are used as the catalysts, *gem*-bromochlorocyclopropanes **65** are obtained from the reactions of dibromochloromethane with alkenes **63** with high selectivity (Scheme 51). Compared with other phase-transfer catalysts, the rate of cyclopropanation with tetramethylammonium salts is very low.^[486]

Scheme 51 Phase-Transfer-Catalyzed Synthesis of *gem*-Bromochlorocyclopropanes^[488]



The addition reaction of 2 equivalents of dichlorocarbene to conjugated dienes^[477,489–492] is carried out with an excess of trichloromethane and assisted by sonication,^[491] or by a two-step procedure,^[492] because the double bond in the monoadduct is deactivated (Scheme 52). In cases involving a nonconjugated chain,^[490,491,493] or cyclic^[490,493] di- and polyenes, all of the double bonds are readily involved in cyclopropanation, unless tetramethylammonium chloride,^[493] or a multisite quaternary ammonium salt,^[494] is used as the catalyst. In such cases, monoaddition is favored. Adducts of dichlorocarbene to 1,2-diphenylcyclobutene,^[495] norbornadiene and hexamethyldewarbenzene,^[489] substituted cyclopentadienes,^[496] or bexadiene^[497] undergo rearrangement and, often, undergo further reactions. On the other hand, adducts of cyclopentene,^[478,498] higher cycloalkenes,^[478] or bis-adduct of cyclopentadiene^[489,490] are easily isolated. As a rule, allenes form unstable adducts with dihalocarbenes, e.g. the products originating from 1,1-diaryl-substituted allenes undergo trimethylenemethane rearrangement.^[499]

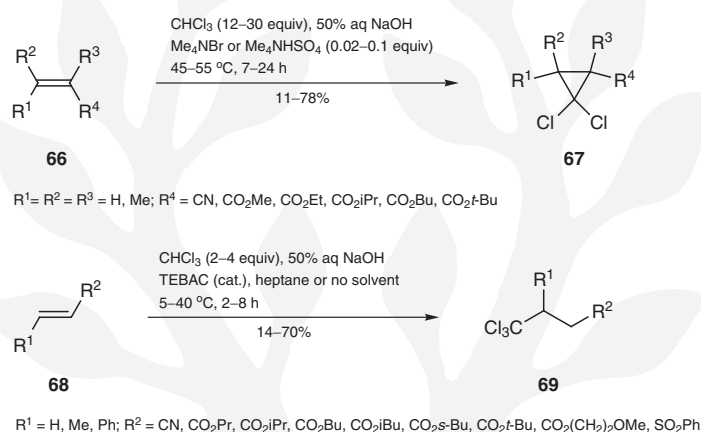
Scheme 52 Addition of Dihalocarbenes to Dienes^[490]



The results of reactions of alkenes **66** and **68**, substituted with electron-withdrawing groups, (cyano,^[500–503] alkoxycarbonyl,^[44,500–502,504–509] carbonyl,^[501,505,506,510,511] sulfonyl^[500,512]) with haloforms (usually chloroform) reveal that Michael adducts **69** of the trihalomethyl anion can seriously compete with products **67** of dihalocarbene cycloaddition, as occurs in the case of nitriles^[500,501] and esters (Scheme 53).^[500,501,506,508,509] The structure of the electrophilic alkene, the nature of the solvent,^[508] and, again, the structure of the catalyst,^[44,502,506,508] play important roles in these processes. In the case of alkyl acrylates, further transformations of the cycloadducts occur.^[501,504,506] Aldehyde enol esters, when treated with chloroform in the presence of benzyltriethylammonium chloride

catalyst, afford the products of formal addition of the trichloromethyl anion to C1 of the ester group^[209] (see Section 8.2.4.1.1.4), while using tetramethylammonium hydrogen sulfate, dichlorocyclopropanation decidedly prevails.^[513] Even with benzyltriethylammonium chloride catalyst, the latter process takes place in the case of ketone-derived enol esters^[513] and 5-alkyl-3*H*-furan-2-ones.^[514] Dihalocarbenes, generated by phase-transfer catalysis, usually undergo facile addition to vinyl ethers, sulfides,^[512] silanes, enamines, α -fluorostyrenes^[515] (but not fluoroalkenes,^[515] or di-, tri-, or tetrachloroethenes), as well as those with a remote functionality.^[472,473]

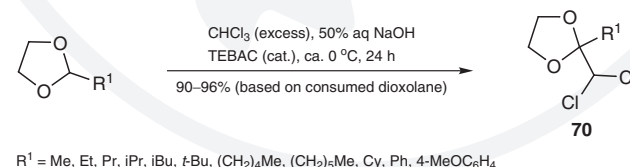
Scheme 53 Products of Phase-Transfer-Catalyzed Reactions of Chloroform with Electrophilic Alkenes^[500,502,508]



The catalyst structure affects the outcome of the reaction of tribromomethane with allylic bromides:^[516,517] the ratio of dibromocarbene cycloaddition to tribromomethyl anion substitution varies from 92:1 to 1:91.^[517]

C–H bonds that are allylic, benzylic, secondary, tertiary, or next to oxygen can undergo insertion reactions with phase-transfer catalysis generated dihalocarbenes.^[518–523] Double insertion of dichlorocarbene is observed with 2,5-dimethyltetrahydrofuran.^[522] The yield of dichloro- and dibromocarbene insertion products is usually mediocre (although a high yield in the case of 2,4,5-trisubstituted 1,3-dioxolanes is observed^[523]), but pure products are usually easily isolated by distillation. 2-(Dichloromethyl)dioxolanes **70** are used for the preparation of pure dichloromethyl ketones (Scheme 54).^[521] For some alkenes, insertion of dichlorocarbene may compete with cycloaddition.^[524] Stereospecific insertion of dichlorocarbene into methyl- or *tert*-butyldimethylsilyl-protected chiral secondary alcohols and acetonide-protected chiral diols is known.^[524]

Scheme 54 Phase-Transfer-Catalyzed Insertion of Dichlorocarbene into 1,3-Dioxolanes^[521]

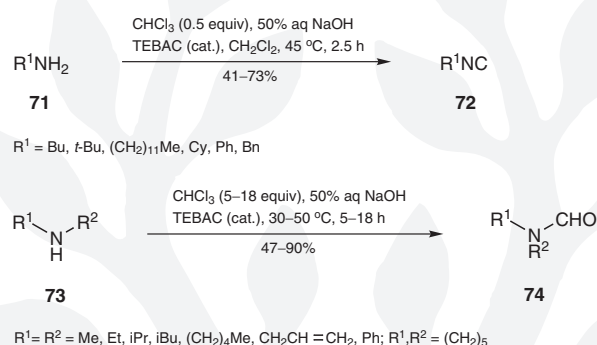


When the substrate contains oxygen, sulfur, or nitrogen, its reaction with the dihalocarbene leads to the formation of the corresponding ylide, which then undergoes further transformations. Thus, alcohols (ethanol, 2,2,2-trifluoroethanol) give orthoformates in

for references see p 1117

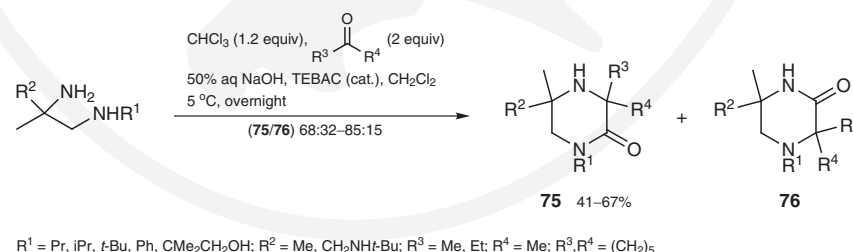
yields of ca. 35% with trichloromethane under phase-transfer-catalyzed conditions,^[525] but the overall process is rather complicated.^[525,526] Phase-transfer-catalyzed reactions of chloroform with primary amines **71** lead to the formation of isocyanides **72**,^[527,528] while with secondary amines **73** the N,N-disubstituted formamides **74** are obtained (Scheme 55).^[529,530] Even the double bond in diallylamine is not attacked by dichlorocarbene, and diallylformamide results.^[529] Dichlorocarbene is possibly involved in the dehydration of amides,^[531,532] thioamides, aldioximes, and ureas.^[531] Sulfur ylides resulting from the reactions of allyl sulfides with dichlorocarbene give products of a 2,3-sigmatropic rearrangement, which undergo hydrolysis upon chromatography to give allylic sulfenate esters.^[533]

Scheme 55 Phase-Transfer-Catalyzed Reactions of Amines with Chloroform^[528,529]



Low-temperature phase-transfer-catalyzed reactions of chloroform with carbonyl compounds lead to 2,2,2-trichloroethanols (via addition of the trichloromethyl anion to the carbonyl carbon), which can be O-methylated with dimethyl sulfate.^[534] In the case of pyridinecarbaldehydes, the solid-liquid system gives better results than the liquid-liquid one.^[535] Low stereoselectivity is observed when the process is carried out in the presence of *N*-benzyl *Cinchona* alkaloids.^[535,536] In a narrow range of temperatures ($56 \pm 2^\circ\text{C}$), chloroform affords α -hydroxyalkyl carboxylic acids^[534] or mandelic acids^[537] in yields of 75–83%, in reactions with ketones^[534] or aromatic aldehydes.^[537] Ferrocenecarbaldehyde or tricarbonyl(η^5 -cyclopentadienyl)manganese (cymantrene) gives the respective hydroxy carboxylic acids in yields of 35–49%.^[538] The phase-transfer-catalyzed reaction of chloroform with cyclohexanone at 20°C gives 2-chlorocyclohexanecarboxylic acid, while at 50 – 55°C , a mixture also containing the corresponding α -hydroxy acid is produced.^[539,540] Dichlorooxiranes are possibly involved in this process.^[534,537,539,541] Intra- or intermolecular reaction of dichlorooxiranes in the presence of a nucleophile leads to the formation of hindered α -amino amides,^[542] nitrogen heterocycles,^[543–547] (e.g., **75** and **76**) (Scheme 56),^[544] or imines.^[548]

Scheme 56 Phase-Transfer-Catalyzed Synthesis of Substituted Piperazinones^[544]

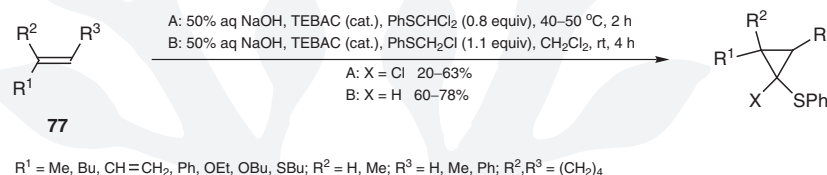


The electrophilic properties of dichlorocarbene are also evident in its reactions with phenolates, leading to the formation of 2- and 4-hydroxybenzaldehydes (Reimer-Tiemann re-

action^[549,550]). Reactions of chloroform with phenols are usually realized in the presence of sodium hydroxide without a catalyst, but catalysis by tertiary amines greatly improves the yield of product in the reaction involving salicylaldehyde.^[551] 2,4,6-Trisubstituted phenols undergo reaction with haloforms, under phase-transfer catalysis conditions, to give the expected dihalomethyl-substituted derivatives;^[552,553] the best results are observed in the combination of phase-transfer catalysis with ultrasonication.^[553] Complexes of phenols with α - or β -cyclodextrin lead to the formation of *para*-formyl isomers only, because the *ortho* positions of the complexed phenols are not available for the reaction with carbene.^[554]

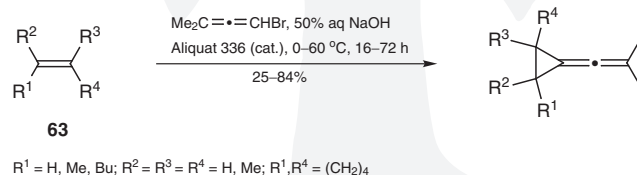
Chloro(phenylsulfanyl)-,^[555] chloro(methylsulfanyl)-,^[556] and (phenylsulfanyl)carbenes,^[557] generated by the phase-transfer catalysis techniques (50% aqueous sodium hydroxide and benzyltriethylammonium chloride as the catalyst) from dichloromethyl phenyl, dichloromethyl methyl, and chloromethyl phenyl sulfides, respectively, undergo addition to alkenes **77** (Scheme 57). Similarly, dichloromethyl phenyl ether gives the nucleophilic chloro(phenoxy)carbene which undergoes addition to styrenes, providing cyclopropanes in low yields (6–11%).^[558]

Scheme 57 Phase-Transfer-Catalyzed Synthesis of Sulfur-Substituted Cyclopropanes^[555,557]



Generation and cycloaddition of alkylidene^[559–561] (from *N*-nitrosooxazolidinones or chain *N*-nitroso amides) and alkenylidenecarbenes^[562,563] to alkenes **63** is realized under conditions of phase-transfer catalysis (Scheme 58). For generation of the latter species, both propargyl and allenyl halides are used.

Scheme 58 Phase-Transfer-Catalyzed Synthesis of (Dimethylvinylidene)cyclopropanes^[562]



The reactions of carbenes, including those generated by phase-transfer catalysis, with heterocyclic compounds have been reviewed.^[564] Depending upon the type of carbene and the structure of the heterocycle, various products result, e.g. in the case of five-membered heterocycles (indoles, imidazoles, dihydrofuran) or dihydropyran, cycloaddition and then ring expansion and/or insertion of dihalocarbenes is observed.^[565]

Ethoxycarbonylnitrene, generated from the reaction of *N*-(tosyloxy)urethane using aqueous sodium hydroxide in the presence of cetyltrimethylammonium bromide, gives *N*-(ethoxycarbonyl)azepine (13%), three isomeric methyl-*N*-(ethoxycarbonyl)azepines (total 18%), or cyclohexylurethane (12%) in reactions with benzene, toluene, or cyclohexane, respectively.^[566] Owing to the high acidity of nitrene precursors, ethoxycarbonylnitrene is usually generated by phase-transfer catalysis using weak bases (e.g., sodium bicarbonate).

for references see p 1117

***trans*-1,1-Dichloro-2,3-diphenylcyclopropane** (64, $R^1 = R^4 = \text{Ph}$; $R^2 = R^3 = \text{H}$; $X = \text{Cl}$);

Typical Procedure:^[477]

To a soln of (*E*)-stilbene (1.6 g, 8.9 mmol) in CHCl_3 (30.0 g, 0.25 mol) was added TEBAC (200 mg) and a cold soln of 50% aq NaOH (13.3 mL). The mixture was stirred for 48 h, at first with cooling, then at rt, poured into H_2O , the phases were separated, the aqueous phase was extracted with CHCl_3 , and the combined organic extracts were dried and evaporated. The residue was purified by Kugelrohr distillation; yield: 2.25 g (96%); bp $100^\circ\text{C}/0.001\text{ Torr}$; mp 39°C .

Butyl 4,4,4-Trichlorobutanoate (69, $R^1 = \text{H}$; $R^2 = \text{CO}_2\text{Bu}$); **Typical Procedure:**^[508]

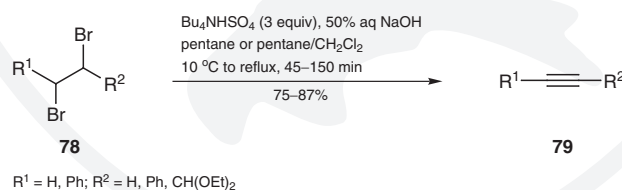
To a vigorously stirred mixture of butyl acrylate (12.8 g, 0.1 mol), CHCl_3 (60.0 g, 0.5 mol), TEBAC (0.46 g, 2 mmol), and heptane (40 mL), 50% aq NaOH (40 mL, 0.75 mol) was added dropwise at 40°C . The reaction was stirred at 40°C for 3 h, cooled, diluted with H_2O (100 mL) and CHCl_3 (50 mL), and the whole was filtered through a pad of Celite. The phases were separated, the aqueous phase was extracted with CHCl_3 ($2 \times 30\text{ mL}$), the combined organic extracts were washed with 2% aq HCl (40 mL) and then H_2O (100 mL). The extracts were dried (MgSO_4), and concentrated to dryness. The residue was distilled under reduced pressure; yield: 15.8 g (64%); bp $70\text{--}72^\circ\text{C}/0.12\text{ Torr}$.

8.2.4.1.5.2

Variation 2: β -Elimination

β -Elimination often accompanies nucleophilic aliphatic substitution in reactions carried out under phase-transfer catalysis conditions.^[304] Effective phase-transfer-catalyzed elimination of hydrogen halides from organic compounds requires extraction of the basic hydroxy or fluoride anion into the organic phase. Yet the concentration of these highly hydrophilic anions in the organic phase is negligible, particularly when more lipophilic anions, such as bromide or iodide, are generated during the elimination reaction (see Section 8.2.4.1). To overcome this unfavorable situation, β -elimination reactions can be effected using more than 1 molar equivalent (per eliminated hydrogen halide) of the rather expensive tetrabutylammonium hydrogen sulfate (Scheme 59).^[567,568] In the case of (1-haloethyl)- or (2-haloethyl)benzenes, the catalyst promotes elimination by forming the $\text{QX}\cdot\text{HX}$ adduct which undergoes decomposition at the interphase by sodium hydroxide.^[569] Conversion of (2-bromoethyl)benzene to styrene is accelerated when a three-liquid-phase system is used, comprising of concentrated sodium hydroxide, toluene, and tetrabutylammonium bromide (the latter in a large but still substoichiometric amount).^[570] Chloro-^[571] and dichloroacetylene^[288,289] may be synthesized from 1,1-dichloro- and trichloroethene, respectively, by phase-transfer catalysis.

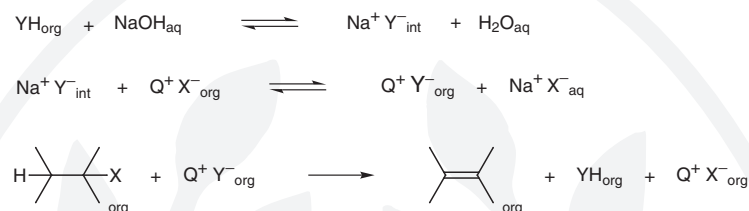
Scheme 59 Synthesis of Alkynes by Phase-Transfer-Catalyzed β -Elimination^[567]



Efficient β -elimination occurs when a small amount of a cocatalyst (YH) is added to the two-phase system, generating lipophilic, strongly basic, but moderately nucleophilic anions (Scheme 60).^[572,573] These anions are produced continuously at the interphase and

enter into the organic phase, in the form of ion pairs with Q^+ , where they promote elimination. The cocatalyst and the catalyst are regenerated simultaneously; hence the cycle is repeated.

Scheme 60 Cocatalysis in Phase-Transfer-Catalyzed β -Elimination Reactions^[572,573]

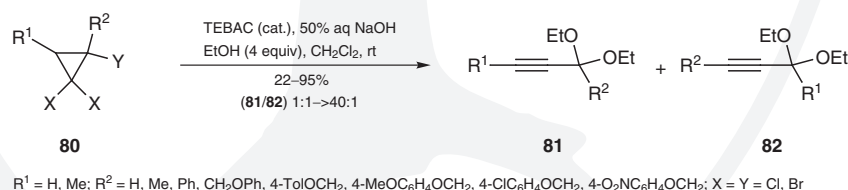


Compounds such as 2,2,2-trifluoroethanol, 2-methylindole, and some alcohols can act as cocatalysts.^[572] Also, the product formed by β -elimination can play this role, e.g. phenylacetylene produced from (*E*)- β -bromostyrene.^[573] Competitive decomposition of tetraalkylammonium salts (usually by Hofmann elimination^[574]) affects the outcome of these reactions.^[569,573]

Ammonium cyanomethylides, generated from the quaternary ammonium salts by means of concentrated aqueous sodium hydroxide, undergo reaction in situ with active alkylating agents leading to the formation of cyanoalkenes, conjugated cyanodienes, or trienes, via an alkylation–elimination pathway.^[275] An elimination reaction is also encountered during phase-transfer-catalyzed reactions of halo sulfones^[124] and in the alkylation of *gem*-dihalocyclopropanes.^[45,320] Methine isocyanides, alkylated under phase-transfer catalysis conditions with benzyl or nitrobenzyl halides, undergo elimination of the isocyanide group to afford the corresponding alkenes.^[67,68]

In addition to the elimination reactions described above, phase-transfer catalysis induces more complex processes. Alkynyl acetals and ketals **81** and **82** are formed in variable ratios when 1,1,2-trihalocyclopropanes **80** in dichloromethane are treated with 50% aqueous sodium hydroxide, ethanol, in the presence of benzyltriethylammonium chloride as the catalyst (Scheme 61). Cyclopropene derivatives are involved in this ring-opening process.^[575–578]

Scheme 61 Phase-Transfer-Catalyzed Synthesis of Alkynyl Acetals and Ketals by Ring Opening of 1,1,2-Trihalocyclopropanes^[576,578]



1,2-Diphenylacetylene (79, $R^1 = R^2 = \text{Ph}$); Typical Procedure:^[567]

To a vigorously stirred mixture of dibromide **78** ($R^1 = R^2 = \text{Ph}$; 3.4 g, 0.01 mol) and Bu_4NHSO_4 (10.2 g, 0.03 mol) in pentane (20 mL) and CH_2Cl_2 (5 mL), 50% aq NaOH (7 mL) was added dropwise. The reaction mixture was refluxed for 15 min (exothermic reaction). The stirring was continued for 30 min at rt (by this time, the phases had separated), the organic phase was decanted, the residue was washed with pentane, and the combined organic extracts were washed with H_2O and dried, and concentrated to dryness. The product was purified by crystallization (EtOH); yield: 1.35 g (75%).

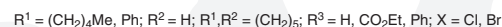
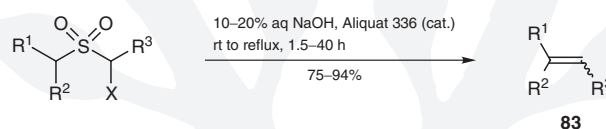
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8.2.4.1.6

**Method 6:
Ramberg–Bäcklund Reaction**

The reaction of α -halo sulfones possessing α' -hydrogen(s) with a base, often sodium hydroxide, to give alkenes (via thiirane dioxides which extrude sulfur dioxide) is named the Ramberg–Bäcklund reaction.^[579–583] When this process is applied to chloromethyl cyclohexyl sulfone, it affords methylenecyclohexane in 80% yield.^[584] When the starting sulfones contain more halogens, the reaction often gives mixtures containing haloalkenes, alkynes, and α,β -unsaturated sulfonic acids.^[585–588] The Ramberg–Bäcklund reaction may be carried out under phase-transfer catalysis conditions, in the presence of dilute sodium hydroxide, affording alkenes **83** in 75–94% yield (Scheme 62).^[183,589] Sulfones substituted with the trifluoromethyl group potentially appear to be very useful substrates, and they require equimolar amounts of tetrabutylammonium hydrogen sulfate for successful Ramberg–Bäcklund reaction.^[589] Among other synthetic applications, this approach is used in the preparation of the *Artemisia* ketone from a trifluoromethyl-substituted oxo sulfone.^[589] A one-pot phase-transfer-catalyzed reaction of dibenzyl sulfone with carbon tetrachloride leads directly to (*E*)-stilbene in yields of 94–100%.^[177,183]

Scheme 62 Alkenes Prepared by the Phase-Transfer-Catalyzed Ramberg–Bäcklund Reaction^[183]



8.2.4.1.7

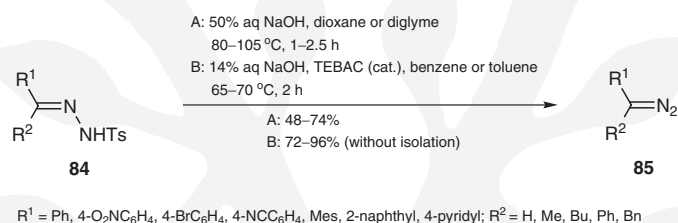
**Method 7:
Cannizzaro Reaction**

The base-mediated (usually aqueous sodium or potassium hydroxide) disproportionation of aldehydes into alcohols and carboxylic acids is named the Cannizzaro reaction. A useful modification, consisting of the reaction of an aldehyde with formaldehyde, leads to the formation of the alcohol and the alkali salt formate (crossed Cannizzaro reaction).^[590] A single-electron-transfer process is possibly involved in the formation of Cannizzaro products.^[591] The starting aldehydes should not possess hydrogen atoms on the α -carbon, otherwise aldol products are formed which in turn may enter into the Cannizzaro process. Benzyltriethylammonium chloride^[219] or tetrakis[3,5-bis(trifluoromethyl)phenyl]borate salts^[420] suppress the Cannizzaro reaction of benzaldehyde when carried out in the presence of concentrated sodium hydroxide,^[219] but in the case of the crossed process, both selectivity and rate are improved by hydrotropes [poly(ethylene glycols)];^[592] the rate is also dramatically enhanced by microwave irradiation.^[593] The rate of Cannizzaro product formation is significantly increased when the reaction is carried out in a solvent-free system in the presence of a sodium hydroxide–basic alumina mixture and aided by microwave irradiation.^[594] Pyridine-4-carbaldehyde undergoes the Cannizzaro reaction when stirred in chloroform under phase-transfer catalysis conditions, while the isomeric 2- and 3-substituted aldehydes give the corresponding (trichloromethyl)pyridylmethanols. Such reactivity of the former aldehyde is ascribed to the facile formation of a tetrahedral intermediate, e.g. hydration of the formyl group.^[535] The Cannizzaro reaction is sometimes observed to accompany other processes, e.g. the Wittig reaction of alkyltriphenylphosphonium salts with benzaldehyde carried out in the presence of slightly hydrated solid sodium hydroxide in dioxane.^[466]

8.2.4.1.8

**Method 8:
Bamford–Stevens Reaction**

The base-mediated decomposition of sulfonylhydrazones (usually tosylhydrazones) to diazo compounds is named the Bamford–Stevens reaction.^[595] Sodium hydroxide, often as an aqueous solution, is applied to execute this transformation. Under suitable conditions, diazo compounds give alkenes^[596] or undergo reaction with an added compound, e.g. a dipolarophile. Monotosylhydrazones of cyclic α -dicarbonyl compounds^[597,598] and isatin and its ring-substituted derivatives^[599] undergo the aqueous sodium hydroxide mediated Bamford–Stevens reaction to give the corresponding α -diazo carbonyl compounds in yields exceeding 90%. The decomposition of tosylhydrazones **84** of aromatic aldehydes^[600–602] or ketones^[600,601] by 50%^[600,601] or 14% aqueous sodium hydroxide and benzyltriethylammonium chloride catalyst^[602] leads to the formation of the corresponding diazo compounds **85** in good yields (Scheme 63). Unstable diazocycloheptane undergoes further reaction, giving cycloheptene.^[600] Aqueous sodium hydroxide mediated decomposition of tosylhydrazones carried out in the presence of alkenecarbonitriles,^[603] terminal alkynes, or *N*-vinylimidazole^[604] affords cyclopropanecarbonitriles^[603] or substituted pyrazoles.^[604]

Scheme 63 Synthesis of Diazo Compounds in an Aqueous Two-Phase System^[601,602]

8.2.4.1.9

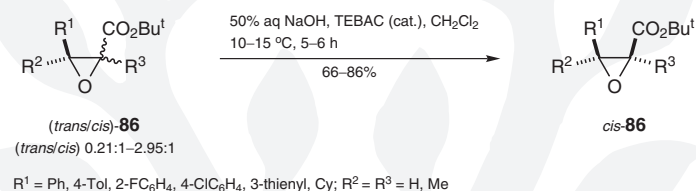
**Method 9:
Hydrolysis Reactions**

The hydrolysis of esters is usually carried out with an aqueous or alcoholic–aqueous solution of sodium hydroxide at elevated temperatures.^[605] Particularly susceptible to these conditions are the esters of primary and secondary alcohols. The hydrolysis of alkyl formates is a fast, exothermic process and is utilized as the second step in a useful phase-transfer-catalyzed synthesis of alcohols from alkyl halides and sodium formate.^[606] Two-phase hydrolysis of dimethyl adipate is catalyzed by Q^+X^- , but in the case of an ester of a long-chain carboxylic acid, namely methyl tetradecanoate, the process is slow and incomplete.^[294] Esters are very efficiently hydrolyzed by 50% aqueous sodium hydroxide in the presence of anionic and neutral surfactants. Because carboxylate anions are more lipophilic than the hydroxide anion, surface, micellar (with a suitable Q^+X^-), and typical phase-transfer catalysis seems to merge in these processes.^[607] Hydrolysis of alkyl acrylates carried out by 50% aqueous sodium hydroxide and, in the presence of benzyltriethylammonium chloride catalyst depends on the substituents on the double bond and ester alkyl group.^[505] Powdered sodium hydroxide with tetrabutylammonium hydrogen sulfate (0.5 equiv) as the catalyst in tetrahydrofuran or dichloromethane are efficient media for the hydrolysis of acetates, benzoates, or pivalates as well as acetates of sterically crowded phenols.^[608] Alkyl benzoates and mesitoates undergo hydrolysis using sodium or potassium hydroxide under conventional heating or microwave irradiation, with or without a phase-transfer catalyst; the use of microwaves usually affords the corresponding acids in higher yield. In the phase-transfer-catalyzed hydrolysis of mesitoates, the microwave effect is more pronounced when sodium hydroxide is used.^[609] Microwave irradiation of aliphatic, aromatic, or heterocyclic nitriles with moistened solid sodium hydroxide and PEG-

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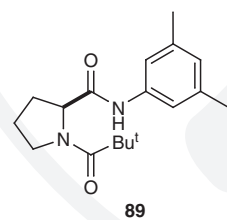
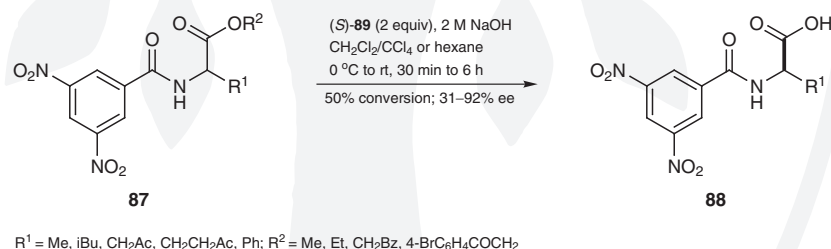
400,^[610] or without any catalyst,^[49] leads to the formation of amides^[49,610] or acids.^[49] Concerning the esters of cyclic carboxylic acids, ethyl *trans*-2-phenylcyclopropanecarboxylate undergoes hydrolysis more rapidly than the *cis*-isomer. When a mixture of both isomeric esters is used, this process leads to the *cis*-ester, from which pure *cis*-2-phenylcyclopropanecarboxylic acid is obtained.^[611] Similarly, when a mixture of *tert*-butyl *trans*- and *cis*-3-aryl- or -3-alkyl-substituted oxiranes **86** is stirred with concentrated sodium hydroxide and benzyltriethylammonium chloride catalyst under mild conditions, pure *cis*-isomers result (Scheme 64).^[237] The yields of 66–86% are based on the amount of *cis*-**86** in a *cis/trans* mixture. Depending upon the conditions, sodium hydroxide mediated reaction of fluorinated enol 4-toluenesulfonates leads to the formation of α -fluoro- β,β -dialkoxy^[612] or α -fluoromethyl ketones.^[613] Benzyl and 4-methoxybenzyl ethers are deprotected by a one-pot, stepwise reaction using chlorosulfonyl isocyanate–sodium carbonate, followed by sodium hydroxide.^[614]

Scheme 64 Phase-Transfer-Catalyzed Synthesis of *tert*-Butyl *cis*-3-Substituted Glycidates^[237]



Hydrolytic kinetic resolution of esters **87** derived from N-acylated α -amino acids in a basic two-phase system in the presence of proline derivative **89** as the chiral selector affords the corresponding N-acylated α -amino acids **88** in up to 92% ee (Scheme 65). One-pot tandem hydrolysis–esterification gives the esters of the acylated amino acid in 100% ee.^[615]

Scheme 65 Enantioselective Hydrolysis of N-Acylated α -Amino Esters^[615]



***cis*-tert-Butyl 3-Phenyloxirane-2-carboxylate (*cis*-86, R¹ = Ph; R² = R³ = H);**

Typical Procedure:^[237]

A mixture of (*trans/cis*)-*tert*-butyl 3-phenylglycidate (*trans/cis* ca. 0.25:1; 1.15 g, 5.2 mmol), 50% aq NaOH (4 mL), TEBAC (0.05 g, 0.22 mmol), and CH₂Cl₂ (4 mL) were vigorously stirred at 10–15 °C for 6 h. The mixture was diluted with H₂O, the phases were separated, the aqueous phase was extracted with CH₂Cl₂ (2 × 10 mL), and the combined organic extracts

were washed with H₂O and dried (MgSO₄), and the solvents were removed under reduced pressure. The residue was distilled in a Kugelrohr apparatus; yield: 0.75 g (84%, based on the amount of *cis*-isomer in the substrate); purity $\geq 97\%$ (GC); bp 120 °C/0.6 Torr (bath temperature).

8.2.4.2 Sodium Methoxide

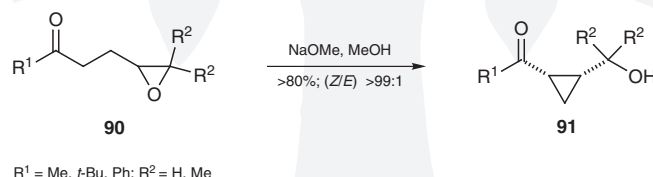
Sodium methoxide is a colorless, crystalline solid, which is soluble in methanol but is decomposed by moisture. Solutions in methanol are prepared by dissolving metallic sodium.^[616] Evaporation of the solvent gives the solid alkoxide, which can be suspended in different solvents. It is applied in the deprotonation of acidic compounds and in the introduction of methoxy groups via nucleophilic substitution. This base is commercially available but usually gives better results when freshly prepared.

8.2.4.2.1 Method 1: Generation and Reactions of Carbanions

8.2.4.2.1.1 Variation 1: Reactions of Carbanions with Alkylating Agents

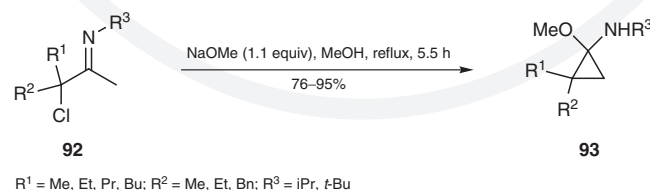
The alkylation reactions of esters^[617] and nitriles^[16,617] have been reviewed. When methoxide is used as the base, methyl esters should be used since transesterification can lead to formation of additional products. Dimethyl malonate^[618] and fluoromalonate^[619] undergo alkylation with allyl bromide^[618] or alkyl halides.^[619] With the former ester, 1,1-dichloro-3,4-epoxy-4-methylpent-1-ene gives the corresponding substituted γ -butyrolactone.^[620] Carbanions generated from β,γ -epoxy sulfones enter into intramolecular ring opening; the products thus formed undergo reaction further to give acetals of α,β -unsaturated aldehydes.^[621] Intramolecular reactions of enolates generated from γ,δ -epoxyalkyl phenyl or alkyl ketones **90** lead to the formation of *cis*-1-acyl-2-(hydroxymethyl)cyclopropanes **91** with complete diastereocontrol (Scheme 66).^[622]

Scheme 66 *cis*-1-Acyl-2-(hydroxymethyl)cyclopropanes from γ,δ -Epoxy Ketones^[622]



N,2,2-Trialkyl-1-methoxycyclopropanamines **93**, useful precursors of cyclopropylamines, are obtained by cyclization of α -chloroimines **92** into cyclopropylideneamines, which then undergo addition of methoxide (Scheme 67).^[623–625]

Scheme 67 2,2-Disubstituted *N*-Alkyl-1-methoxycyclopropanamines from α -Chloroimines^[623–625]



for references see p 1117

A rather strong CH acid, methyl nitroacetate, undergoes alkylation with methyl bromoacetate in a methanol–dimethylacetamide mixture, but the expected dimethyl nitrosuccinate is obtained only in 23–27% yield; the main byproduct is the doubly alkylated ester.^[626] Derivatives of benzyl bromide^[627] and 6-(bromomethyl)pyrimidinediones^[628] afford the formylated products from reactions with the 2-nitropropane salt (from the nitro compound and sodium methoxide). When an excess of this base is used, deformylation occurs.^[628] Arylation of dimethyl malonate with 2-halobenzoic acids is carried out by means of sodium methoxide and aided by copper(I) bromide.^[629] Monomethylation of fluorene at C9 is realized via a high-temperature reaction with methanol–sodium methoxide, carried out in a steel bomb. This procedure is used for the preparation of other monoalkylated fluorenes.^[630]

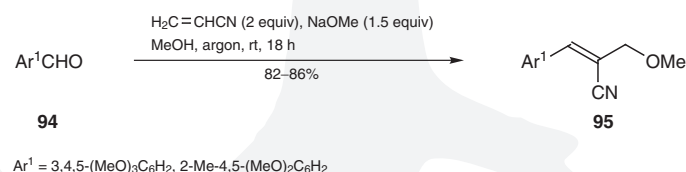
8.2.4.2.1.2

Variation 2:**Reactions of Carbanions with Carbonyl Compounds and Imines**

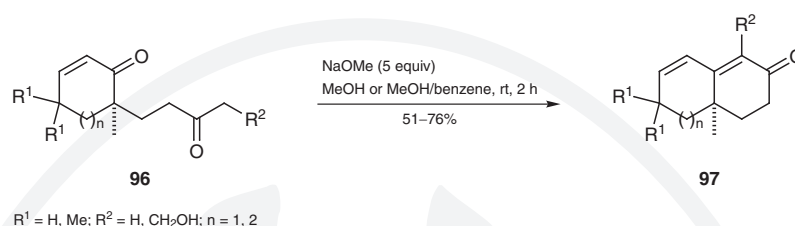
The reaction of a carbanion to a carbonyl group which bears a good leaving group (e.g., halide, alkoxy, acyloxy) leads to the generation of a tetrahedral intermediate from which the carbonyl group is regenerated by departure of the leaving group. Typically, enolate anions undergo reaction with esters, acyl halides, and anhydrides, to give 1,3-dicarbonyl compounds (Claisen and related condensations^[631–633]). These processes are usually carried out with sodium ethoxide,^[631,632] but in the case of the Claisen condensation of methyl esters, methoxide is used as well.^[634] The base is applied in formylation reactions of 2-methylcyclohexanone with ethyl formate^[635] and 3-methoxypropanenitrile with methyl formate.^[636] In the latter case, the reaction is carried out under carbon monoxide pressure and the sodium salt of the crude product undergoes methylation, giving mainly the *O*-methyl derivative.^[636]

The oxyanion generated by the addition of the enolate anion to an aldehyde or ketone yields, after protonation, the β -hydroxy carbonyl compound, or undergoes further reaction by elimination of water, affording the α,β -unsaturated product (aldol-type condensations^[200,201]). The reaction of 3-methoxypropanenitrile (also formed in situ by addition of methoxide to acrylonitrile^[636]) with aromatic aldehydes **94** leads to the formation of unsaturated nitriles **95**, which are useful for the preparation of 5-substituted pyrimidine-2,4-diamines (Scheme 68).^[636,637]

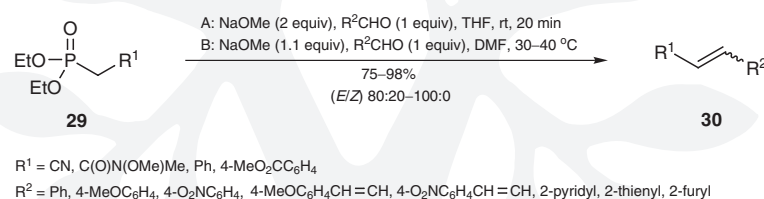
Scheme 68 Condensation of Aromatic Aldehydes with In Situ Generated 3-Methoxypropanenitrile Anion^[636]



γ -Butyrolactone undergoes condensation in the presence of sodium methoxide to provide the unsaturated dimeric product (by an aldol-type process) used in the synthesis of dicyclopropyl ketones.^[638] Intramolecular condensation of cyclic ketones **96** substituted at C2 with a 2-acylethyl group is used for the preparation of fused, doubly unsaturated bicyclic ketones **97** (Scheme 69).^[639]

Scheme 69 Bicyclic Dienones by a Robinson Annulation Reaction^[639]

When phosphorus ylides, or phosphorus- or silicon-stabilized anions, are allowed to react with carbonyl compounds, the intermediate oxyanions undergo elimination, leading to the formation of substituted alkenes **30** (Wittig,^[408–410] Horner–Wadsworth–Emmons,^[244,245] or Peterson^[640] reactions). Sodium methoxide in dimethylformamide or tetrahydrofuran efficiently catalyzes reactions used in the synthesis of carotenoids and polyenes,^[408] including vitamin A and its derivatives. Thus Wittig condensation^[641] and, separately, Horner–Wadsworth–Emmons reaction of diethyl methylphosphonates **29** containing electron-withdrawing groups with 4-nitro- or 4-methoxybenzaldehydes or cinnamaldehydes^[253] and diethyl benzylphosphonate with benzaldehyde or heteroaromatic aldehydes is accomplished (Scheme 70).^[642]

Scheme 70 Alkenes from Phosphonates by the Horner–Wadsworth–Emmons Reaction^[253,642]

The methoxide base promotes cleavage of the C–Si bond in bis- and tetra(trimethylsilyl)-methanes or in bis(trimethylsilyl)(phenyl)methane, generating the corresponding carbanions, which undergo reaction with benzophenone or *tert*-butyl phenyl ketone (2,2-dimethyl-1-phenylpropan-1-one) to afford substituted alkenes^[643] (Peterson reaction^[640]).

Yet another possibility exists when the CH acid is α -substituted with a halogen atom. Reaction of such a derived carbanion with a carbonyl compound generates the corresponding halohydrin anion, which undergoes cyclization into an oxirane derivative (Darzens condensation^[227]). This process is exemplified by the sodium methoxide mediated synthesis of methyl 3-(4-methoxyphenyl)glycidate from anisaldehyde and methyl chloroacetate.^[644]

Carbanions undergo addition to imines with the formation of stable amine derivatives. Thus, sodium methoxide induced addition of methyl cyanoacetate^[645] or phenylsulfonylacetonitrile^[646] to activated imines (alkyl *N*-cyanoimides) gives adducts which are transformed into 2,4-dioxo-^[645] or 2-oxopyrimidines.^[646] Reaction of malononitrile with cyanoimides leads directly to pyrimidine derivatives.^[645]

3-(4,5-Dimethoxy-2-methylphenyl)-2-(methoxymethyl)acrylonitrile [95, Ar¹ = 2-Me-4,5-(MeO)₂C₆H₂]; Typical Procedure:^[636]

A soln of 4,5-dimethoxy-2-methylbenzaldehyde (90.0 g, 0.5 mol) and acrylonitrile (53.1 g, 1.0 mol) in MeOH (135 mL) was added during 1 h to a stirred, cooled (ca. 10 °C) soln of freshly prepared NaOMe (81.0 g, 1.5 mol) in MeOH (200 mL). The mixture was stirred under argon at rt for 18 h, cooled to –15 °C, and the resulting solid was collected by filtration.

for references see p 1117

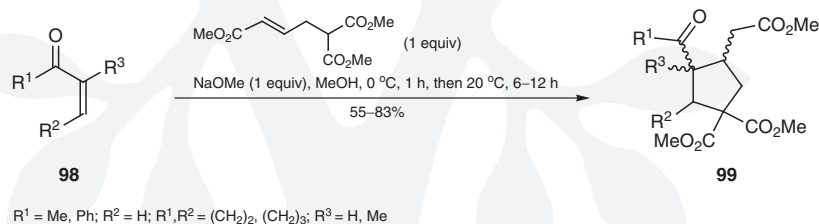
It was washed with cold H₂O (3 × 200 mL) and cold (−15 °C) 75% aq MeOH (2 × 100 mL) to give the product; yield: 105.8 g (86%); mp 70–71 °C.

8.2.4.2.1.3

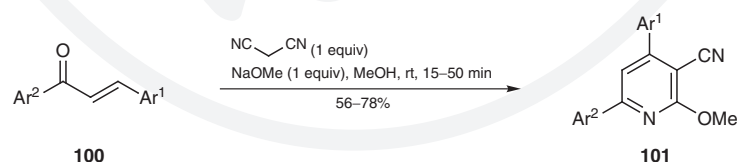
Variation 3:**Reactions of Carbanions with Electrophilic Alkenes**

Addition of carbanions to alkenes bearing electron-withdrawing groups (the Michael reaction) is often followed by other reactions such as aldol-type condensations, eliminations, among others, leading to the formation of cyclic products. Processes of such type are encountered when the starting CH acid or the Michael acceptor possess more than one electron-withdrawing group, or when a good leaving group is present in either of the substrates. The subjects of cyanoethylation,^[256] the Michael reaction,^[257,647] the intramolecular Michael reaction,^[258] and addition reactions of nitrile-stabilized carbanions^[16] have been reviewed.

Sodium methoxide induced Michael addition of ketones to methyl vinyl ketone (but-3-en-2-one) (under solvent-free conditions), followed by an aldol-type condensation, leads to cyclohexenones (Robinson annulation reaction).^[648] α,β -Unsaturated cyclic ketones undergo reaction with ethyl acetoacetate, affording bicyclo[3.3.1]nonane or bicyclo[4.3.1]decane derivatives.^[649] Tandem Michael reactions of methyl (*E*)-5-(methoxycarbonyl)hex-2-enedioate with acyclic or cyclic unsaturated ketones **98** give 4,4-bis(methoxycarbonyl)-2-[(methoxycarbonyl)methyl]cyclopentyl ketones **99** and the corresponding functionalized bicyclic structures (Scheme 71).^[650]

Scheme 71 Substituted Cyclic Ketones by Tandem Michael Additions^[650]

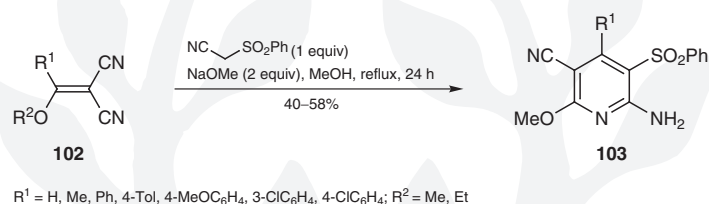
2-Arylidene-1-tetralones,^[651] chalcones (1,3-diphenylprop-2-en-1-ones) **100**,^[652] and 3-cinnamoyltropolones^[653] give 2-methoxypyridine-3-carbonitrile derivatives **101** when allowed to react with malononitrile in the presence of sodium methoxide (Scheme 72). The products are formed via a multistep process, which starts with Michael addition of the nitrile anion to the unsaturated ketone. Under similar conditions, *N*-(cyanoacetyl)piperidine gives Michael adducts with chalcones, while (cyanoacetyl)urea gives highly substituted cyclohexanol derivatives with this Michael acceptor. In the latter case, 1 equivalent of the donor undergoes reaction with 2 equivalents of the chalcone.^[654]

Scheme 72 4,6-Diaryl-2-methoxypyridine-3-carbonitriles from Substituted Chalcones and Malononitrile^[652]

$\text{Ar}^1 = \text{Ph, 4-Tol, 4-MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2,4-(\text{MeO})_2\text{C}_6\text{H}_3, 3,4-\text{Cl}_2\text{C}_6\text{H}_3$
 $\text{Ar}^2 = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2,4-(\text{MeO})_2\text{C}_6\text{H}_3, 2\text{-naphthyl}$

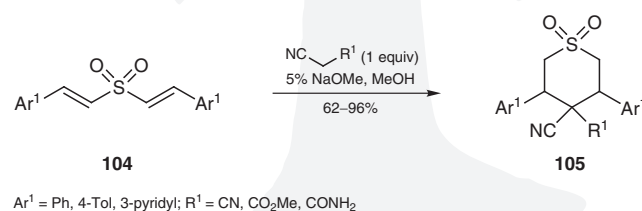
π -Electrons of the aromatic ring are engaged when the cyanobenzyl carbanion, generated from 2-(cyanomethyl)-2',4'-dimethoxybenzophenone and sodium methoxide in dimethyl sulfoxide, undergoes intramolecular reaction to give 10-hydroxy-2-methoxyanthracene-9-carbonitrile quantitatively.^[655] 5-Chloro-2-methoxy- and 2,5-dichlorotropone undergo reaction with dimethyl malonate to give normal or *cine*-substitution products, the ratio of which depends on the starting tropone and the solvent used.^[656] 3-Ethoxy-^[657] or 3-methoxy-2-cyanopropenenitriles **102**, substituted at C3 with a methyl or aryl group,^[658] undergo reaction with benzenesulfonylacetonitrile in the presence of methoxide to give derivatives **103** of 6-methoxypyridin-2-amine (Scheme 73).

Scheme 73 4-Substituted 6-Amino-2-methoxy-5-(phenylsulfonyl)pyridine-3-carbonitriles^[657,658]



Ring closure to dihydropyridin-2-one derivatives results when 2-substituted methyl acrylates are treated with malononitriles and sodium methoxide.^[659] Sodium methoxide and other bases induce tandem Michael addition–retro-Dieckmann reaction of 3-substituted 2-(methoxycarbonyl)cyclopentanones with α,β -unsaturated nitriles, esters, and ketones. The process offers a one-pot approach to polyfunctionalized acyclic compounds.^[660] Depending upon the structure of the nitroalkenes, their reactions with cyclohexane-1,3-dione and dimedone (5,5-dimethylcyclohexane-1,3-dione) give either Michael adducts, hexahydro-1,2-benzoxazine, or benzofuranone derivatives.^[661] Both double bonds of distyryl sulfones **104** are engaged in its reaction with methyl cyanoacetate, malononitrile, and cyanoacetamide, providing derivatives of 2*H*-thiopyran-4-carbonitrile 1,1-dioxides **105** (Scheme 74).^[662]

Scheme 74 Double Michael Addition of Active Methylene Compounds to Distyryl Sulfones^[662]



2-Methoxy-4-(4-methoxyphenyl)-6-phenylpyridine-3-carbonitrile (101, Ar¹ = 4-MeOC₆H₄; Ar² = Ph); Typical Procedure:^[652]

To freshly prepared soln of NaOMe generated from Na (0.39 g, 0.017 mol) and dry MeOH (150 mL), malononitrile (1.12 g, 0.017 mol) was added with stirring. 3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (4.05 g, 0.017 mol) was added and the mixture was stirred at rt for 45 min. The solid product was collected by suction filtration, washed with cold MeOH, and crystallized; yield: 3.87 g (72%); mp 182–183 °C (EtOH).

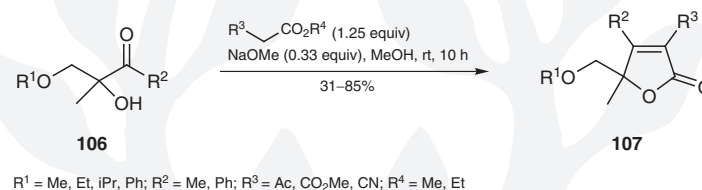
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8.2.4.2.2 Method 2: Generation and Reactions of Heteroanions

8.2.4.2.2.1 Variation 1: Reactions of O-Anions

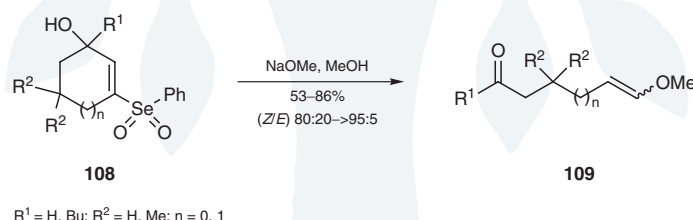
Transesterification of dimethyl malonate, ethyl cyanoacetate, and ethyl acetoacetate with α -hydroxy ketones **106**, carried out in the presence of sodium methoxide, constitutes the first step in the preparation of 5-(alkoxymethyl)- or 5-(phenoxymethyl)furan-2(5H)-ones **107** (Scheme 75).^[663]

Scheme 75 3,4-Disubstituted 5-(Alkoxymethyl)- or 5-(Phenoxymethyl)furan-2(5H)-ones^[663]

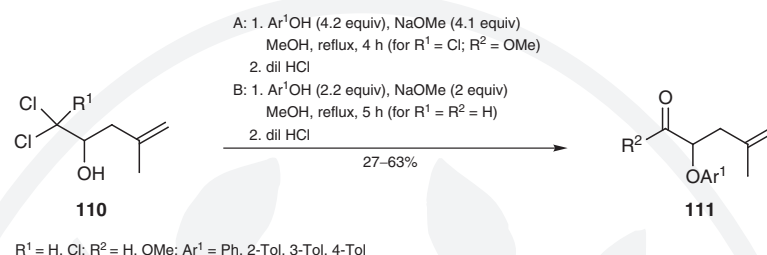


N-(2-Hydroxyethyl)oxazolidin-2-one, an intermediate for the preparation of commercially important *N*-vinylloxazolidin-2-one, is synthesized in quantitative yield by the reaction of diethanolamine, diethyl carbonate, and alkoxide.^[664] Cyclic selenones **108** undergo reaction with sodium methoxide by 1,4-fragmentation, giving alkenyl **109** (Scheme 76) or alkynyl ketones.^[665]

Scheme 76 Fragmentation of Hydroxyvinyl Selenones in the Presence of Sodium Methoxide^[665]



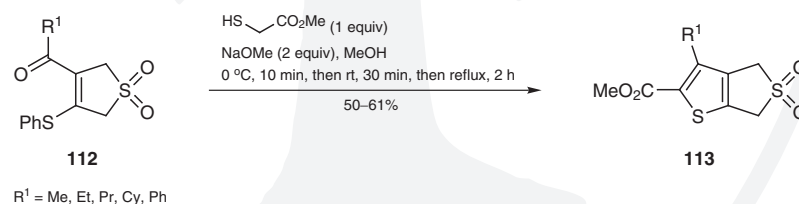
The formation of an oxirane derivative by a methoxide-mediated cyclization of a substituted 2-tosyloxy alcohol is a key step in the preparation of (\pm)-metoprolol.^[666] Methyl 2-aryloxy-4-methylpent-4-enoates or 2-aryloxy-4-methylpent-4-enals **111** may be prepared by reaction of sodium phenolates with 1,1,1-trichloro-4-methylpent-4-en-2-ol or 1,1-dichloro-4-methylpent-4-en-2-ols **110**, respectively (Scheme 77). Similarly, the synthesis of 2-methoxy-substituted esters and aldehydes may be carried out. The corresponding 1,1-dichloro and monochloro epoxides are possibly involved in these processes.^[667] Phenolates, derived from the reaction of 2',6'-dihalo-2-hydroxybenzophenones with sodium methoxide, undergo cyclization to give xanthenes, with simultaneous replacement of chlorine at C6 by methoxide.^[668]

Scheme 77 Synthesis of 2-Aryloxy-4-methylpent-4-enals and Methyl 3-Aryloxy-4-methylpent-4-enoates^[667]**Methyl 5-(Methoxymethyl)-4,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (107, R¹ = R² = Me; R³ = CO₂Me); Typical Procedure:**^[663]

To a soln of NaOMe, prepared from Na (0.23 g, 10 mmol) in dry MeOH (10 mL), was added, in one portion, 3-hydroxy-4-methoxy-3-methylbutan-2-one (3.96 g, 30 mmol) and dimethyl malonate (5.3 g, 40 mmol). The mixture was kept at rt for 10 h and acidified with 10% AcOH (6 mL). MeOH was removed under reduced pressure, the product was extracted with CH₂Cl₂ and the extract was dried (Na₂SO₄), and the solvent was removed under reduced pressure. The product was crystallized; yield: 4.6 g (72%); mp 87 °C (hexane/iPrOH).

**8.2.4.2.2.2 Variation 2:
Reactions of S-Anions**

The reaction of 4-acyl-3-(phenylsulfanyl)-3-sulfolenes (2,5-dihydrothiophene 1,1-dioxides) **112** with methyl thioglycolate and sodium methoxide gives 3-substituted 2-(methoxycarbonyl)-4,6-dihydrothieno[3,4-*b*]thiophene 5,5-dioxides **113** (Scheme 78). At 200 °C, these products undergo fragmentation to yield 2,3-dimethylenethiophene intermediates, which are trapped with *N*-phenylmaleimide in [4 + 2]-cycloaddition reactions.^[669] Sodium thiolates and benzenethiolate effect cleavage of methylenedioxy rings in aromatic compounds bearing electron-withdrawing groups.^[670]

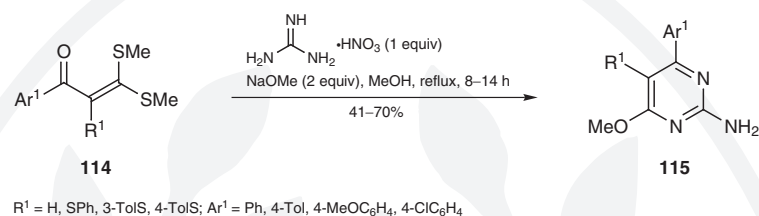
Scheme 78 Reaction of 4-Acyl-3-(phenylsulfanyl)-2,5-dihydrothiophene 1,1-Dioxides with Methyl Thioglycolate^[669]**8.2.4.2.2.3 Variation 3:
Reactions of N-Anions**

Sodium methoxide promoted condensation of urea with diethyl oxalate affords parabanic acid.^[671] Condensation of urea or thiourea with phthalaldehyde leads to the formation of complex derivatives of *s*-indacenone or *s*-indacenethione.^[672] Sodium methoxide is used in the preparation of derivatives of pyrimidine and pyrimidinones. Thus, pyrimidine derivatives, e.g. **115** and **116**, result from the condensation of guanidine nitrate with α -oxo-^[673] or α -aryl- α -oxothioketene dithiocetals **114**^[674] or of cyanamide with 3-alkoxy-, 3-alkoxy-3-aryl- or 3-alkoxy-3-alkyl-2-cyanopropenenitriles **102**,^[675] respectively (Schemes 79 and 80). These heterocycles are also prepared by reaction of thiourea with ethyl aceto-

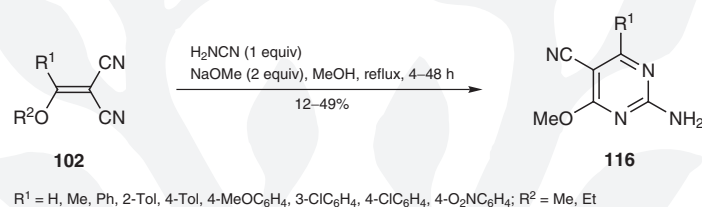
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acetate^[676] and acetamidine or benzamidine hydrochlorides with β -alkoxyvinyl trifluoromethyl ketones.^[677] In the latter process, depending on conditions, derivatives of 3,4,5,6-tetrahydropyrimidine are also formed.^[677]

Scheme 79 Synthesis of 4-Aryl-6-methoxypyrimidin-2-amines^[673,674]

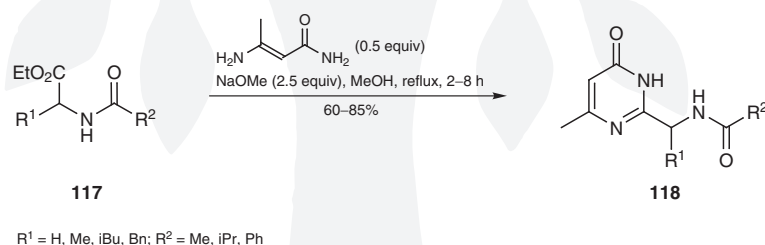


Scheme 80 Synthesis of 2-Amino-6-methoxypyrimidine-5-carbonitriles^[675]

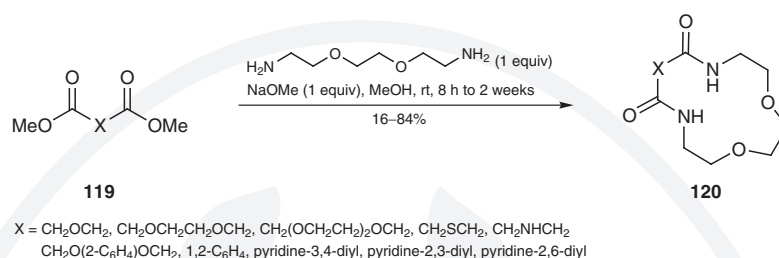


Substituted pyrimidin-4(3*H*)-ones, e.g. **118**, result from the reactions of cyanamide with methyl 3-aryl-2-cyano-3-methoxypropenoates^[678] or β -aminocrotonamide with esters of *N*-acylated amino acids **117** (Scheme 81).^[679]

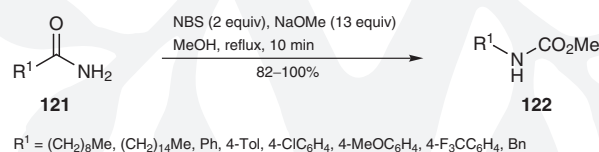
Scheme 81 Reaction of β -Aminocrotonamide with Esters of *N*-Acylated Amino Acids^[679]



Sodium methoxide promoted condensation of diethyl oxalate with enantiopure *N'*-benzyl-*N*-sulfinyldiamino alcohols gives piperazine-2,3-diones, which, after reduction with diborane, give enantiopure 2,3-disubstituted 1-benzylpiperazines. A similar condensation with 3-amino-2-(benzylamino)-2,4-dimethylpentanol leads to the formation of substituted (hydroxymethyl)dihydroimidazoles, which may be further elaborated.^[680] Macrocyclic diamides **120** are prepared from methoxide-catalyzed reaction of diamines with diesters **119** (Scheme 82). Compared to other methods, the reaction is carried out under mild conditions.^[681]

Scheme 82 Synthesis of Macrocyclic Diamides^[681]

Derivatives of 2,3,4,5-tetrahydro-1*H*-2-benzazepine are synthesized by methoxide-induced cyclization of ring-substituted methyl 2-(3-aminopropyl)benzoates.^[682] Desilylation of trimethylsilylamines by sodium methoxide yields sodium amides, which give the corresponding secondary amines when treated with alkyl halides.^[683] The *N*-ylide, generated from the reaction of 1,1,1-trimethylhydrazinium iodide with methoxide, enters into a vicarious nucleophilic substitution reaction^[154–157] with 1-methyl-4-nitroimidazole to afford the corresponding 5-amino derivative. Electron-transfer processes are involved in this reaction.^[684] Amides of aliphatic,^[685,686] cyclic,^[685] or aromatic^[686] carboxylic acids **121** are converted in high yields into the corresponding methyl carbamates **122** when allowed to react with sodium methoxide, bromine,^[685] or *N*-bromosuccinimide^[686] (Hofmann rearrangement^[366]) (Scheme 83). The process is even applicable to compounds which are highly susceptible to electrophilic addition reactions.^[685]

Scheme 83 Hofmann Rearrangement of Amides with *N*-Bromosuccinimide and Sodium Methoxide^[686]

Sodium salts of tosylhydrazones of carbonyl compounds (prepared with sodium methoxide) are thermally converted into diazo compounds (e.g., phenyldiazomethane^[687]) or directly into alkenes (Bamford–Stevens reaction^[595,596]). The reaction of tosylhydrazones of conjugated carbonyl compounds with sodium methoxide in boiling methanol gives allyl methyl ethers, usually without allylic rearrangement.^[688] *N*-Alkylchlorobenzamidines undergo rearrangement by means of sodium methoxide in refluxing methanol into *N*-alkyl-*N'*-phenyl-*O*-methylisoureas, often accompanied by methyl benzoate.^[689]

2-Amino-4-(4-chlorophenyl)-6-methoxypyrimidine-5-carbonitrile (**116**, $\text{R}^1 = 4\text{-ClC}_6\text{H}_4$);

Typical Procedure:^[675]

A soln of NaOMe (1.08 g, 20 mmol), cyanamide (0.42 g, 10 mmol), and dinitrile **102** ($\text{R}^1 = 4\text{-ClC}_6\text{H}_4$; $\text{R}^2 = \text{Me}$; 2.19 g, 10 mmol) in dry MeOH (50 mL) was refluxed for 4–48 h (time according to TLC analysis) and the reaction mixture was cooled and poured into H_2O . The precipitate thus formed was collected and crystallized; yield: 1.2 g (46%); mp 202–203 °C (EtOH).

Methyl (4-Methoxyphenyl)carbamate (**122**, $\text{R}^1 = 4\text{-MeOC}_6\text{H}_4$); Typical Procedure:^[686]

To a soln of NaOMe, prepared from Na (0.1 g, 1.85 mmol) and MeOH (5 mL), was added 4-methoxybenzamide (50 mg, 0.33 mmol) and NBS (60 mg, 0.34 mmol), and the soln was refluxed. After time intervals of 3 and 6 min, additional portions of NBS (30 mg, 0.17 mmol) were added. After heating for a total of 10 min, MeOH was removed under re-

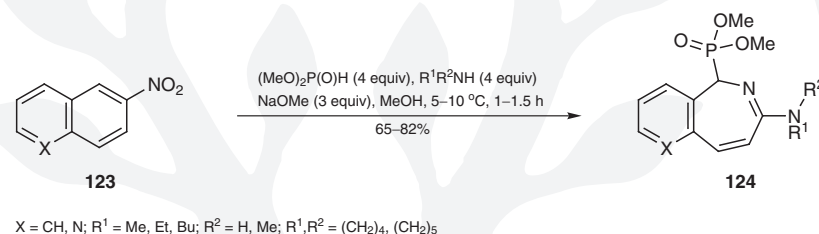
for references see p 1117

duced pressure. The resulting mixture was diluted with EtOAc (100 mL), and the whole was washed with H₂O and dried (MgSO₄), and the solvent was removed. The residue (yellow solid) was purified by flash column chromatography (silica gel, CH₂Cl₂ then CH₂Cl₂/EtOAc 3:1) to give the product as a colorless solid; yield: 49 mg (82%); mp 88–89 °C.

8.2.4.2.2.4 Variation 4: Reactions of P-Anions

The anion of dimethyl phosphite (from dimethyl phosphite and sodium methoxide) undergoes reaction with 4-methoxy- or 4-amino-1-nitronaphthalene to give diphosphorylated dihydronaphthalenes or naphthalene derivatives.^[690] When this reaction is carried out with nitronaphthalenes or nitroquinolines and primary or secondary amines, the corresponding 1*H*-, 3*H*-, or 5*H*-2-benzazepine or pyridazepine derivatives are obtained, e.g. **124** from **123** (Scheme 84).^[691] Nitrene species (generated from the nitro group) participate in these processes.^[690,691]

Scheme 84 Reaction of Aromatic Nitro Compounds with Dimethyl Phosphite^[691]



8.2.4.2.3 Method 3: Reactions of Sodium Methoxide as a Nucleophile

8.2.4.2.3.1 Variation 1: Aliphatic Nucleophilic Substitution

Displacement of a nucleofugal group in aliphatic derivatives by methoxide leads to the formation of methyl ethers (Williamson synthesis^[692]). Successful preparation of ω -haloalkyl methyl ethers depends on the structure of the substrates. Thus, 3-chlorobutyl methyl ether is prepared from the reaction of 3-chlorobutyl benzenesulfonate with sodium methoxide in 35% yield, while the yield of the 3-bromo analogue from the reaction of 1,3-dibromobutane with methoxide is only 4%. Similarly, 4-chloropentyl methyl ether results from the reaction of 1-bromo-4-chloropentane with this nucleophile, while the analogous reaction of dibromopentane gives poorly reproducible results.^[693] Substitution of allylic halogens occurs easily, giving the substituted allyl methyl ethers.^[694] 3-Tosylated allylic bromides are generated from the corresponding 2,3-dibromoalkyl sulfones and undergo reaction in situ with methoxide, affording predominantly allylic methyl ethers.^[695] A mixture of *tert*-propargyl and allenyl chlorides gives, when treated with sodium methoxide, mixtures of propargyl and allenyl methyl ethers, 3-en-1-yne, and unreacted chlorides.^[696] *N*-(1-Halo-2-alkylidene)amines (α -halomethylketenimines)^[697] or *N*-2-(1,1-dichloroalkylidene)cyclohexanamines^[698] undergo methoxylation and then hydrolysis with aqueous acid to give α -methoxy- or α,α -dimethoxymethyl ketones, respectively. In the case of *N*-aryl- α,α -dichloroarylketenimines, the nucleophilic substitution is accompanied by elimination, nitrogen atom migration, among other processes, leading to the formation of product mixtures.^[699]

Benzylic halides (often prepared by halogenation of toluenes) are smoothly converted into benzyl methyl ethers.^[700,701] Highly selective replacement of only one bromine in

1,3-bis(bromomethyl)benzene is possible.^[627] Indazole derivatives, 3-substituted with an α,α -dichloroalkyl group, undergo substitution of both chlorine atoms by methoxide and the acetals thus formed, undergo hydrolysis to give the corresponding carbonyl derivative.^[702] Methyl α -bromo(aryloxy)acetates^[703] and optically active α -bromopropananilide^[704] both undergo bromine displacement by methoxide, with considerable racemization in the latter case. Methyl α,α -dimethoxy(aryl)acetates are synthesized via reaction of arylacetic acids with thionyl chloride–pyridine followed by treatment with sodium methoxide in methanol.^[705] 2-Chloro-1-(4-hydroxyphenyl)ethanone derivatives form the corresponding methoxy derivatives in 90% yield.^[666] [2 + 2] Cycloadducts of haloketenes with alkenes (except cyclopentadiene) undergo replacement of halogen at the α -carbon, giving α -methoxy-substituted cyclobutanones (*cine* substitution).^[706] Methoxide also undergoes reaction with α -chloro- α' -(acyloxy)cyclobutanones, either by replacement of the acyloxy group (via the oxyallyl cation) or the acyl group. In the latter case, the O-anion undergoes fragmentation with concomitant ring opening. The type of product formed depends on the stereochemistry of the cyclobutanone and on the structure of the acyloxy group.^[707,708] Reaction of 2,4-dichlorobicyclo[3.2.1]oct-6-en-3-one and its derivatives with methoxide gives rise to bicyclic α -oxo acetals by an enolization–ionization pathway.^[709] Chloro- or bromomethyl 4-tolyl sulfoxides^[710] (also in optically active form^[711]) afford methoxymethyl derivatives from reactions with methoxide. Examples of these substitution reactions in aliphatic compounds **125** to give methoxy-substituted derivatives **126** are given in Scheme 85.

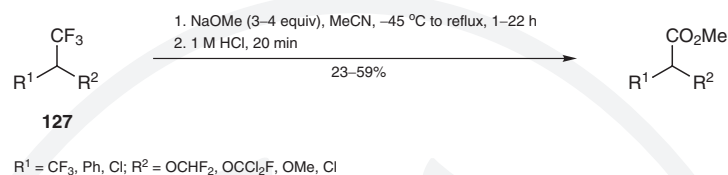
Scheme 85 Displacement of Halogen by Methoxide in Aliphatic Compounds^[627,666,693,694,697,701,703,704,710]

$\begin{array}{c} \text{X} \\ \\ \text{R}^1 - \text{C} - \text{R}^2 \\ \text{125} \end{array} \xrightarrow{\text{NaOMe}} \begin{array}{c} \text{OMe} \\ \\ \text{R}^1 - \text{C} - \text{R}^2 \\ \text{126} \end{array}$						
R ¹	R ²	X	NaOMe (equiv)	Conditions	Yield (%)	Ref
3-(BrCH ₂)C ₆ H ₄	H	Br	0.8	MeOH, benzene, 0 °C, 3 h	53	[627]
4-HOC ₆ H ₄ CO	H	Cl	2.2	MeOH, rt, 24 h	90	[666]
(CH ₂) ₄ Cl	H	Br	1.0	MeOH, reflux, 1 h	76	[693]
CH=CHCH(OMe) ₂	H	Br	2.5	MeOH, reflux, 4 h	73	[694]
C(<i>t</i> -Bu)=N(<i>i</i> Pr)	H	Br	3.0	MeOH, reflux, 0.5 h	75	[697]
2,5-(MeO) ₂ -4-MeC ₆ H ₂	H	Br	5.0	MeOH, rt, 2 h	96	[701]
CO ₂ Me	OPh	Br	1.0	THF, 60 °C, 6 h	46	[703]
CONHPh	Me	Br	n.r. ^a	MeOH, rt, 15 h	71	[704]
S(O)-4-Tol	H	Cl	3.0	MeOH, reflux, 75 h	80	[710]

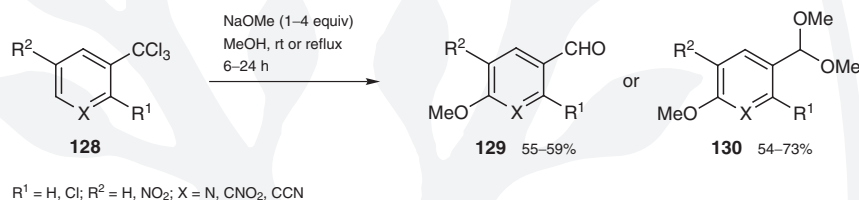
^a n.r. = not reported.

Dibromo ketones, prepared by addition of bromine to arylideneacetophenones, undergo reaction with an excess of sodium methoxide to give β -methoxy unsaturated products. The latter are used in the preparation of dibenzoylmethane^[712] or 2,4-diarylfurans.^[713] Based on a similar approach, 3,4-dibromotetrahydrothiophene 1,1-dioxide is converted into 3,3-dimethoxytetrahydrothiophene 1,1-dioxide by a multistep process.^[714] Trifluoromethyl groups in aliphatic (e.g., **127**) or aromatic compounds are converted into methoxycarbonyl groups by reaction with sodium methoxide followed by aqueous acidic workup (Scheme 86).^[715]

for references see p 1117

Scheme 86 Transformation of a Trifluoromethyl Group into a Methoxycarbonyl Group^[715]

The reaction of 3-(trichloromethyl)pyridines,^[716] 1-nitro-3- or 1,3-dinitro-5-(trichloromethyl)benzenes, and 3-(trichloromethyl)benzonitriles **128**^[717] with methoxide takes place by chloride replacement or *tele* nucleophilic aromatic substitution and, depending upon conditions and on the workup of the reaction mixture, results in the formation of methyl carboxylates or methoxy-substituted aromatic or heteroaromatic aldehydes **129** and dimethyl acetals **130** (Scheme 87).

Scheme 87 Transformation of Trichloromethyl Aromatic Compounds into Methoxy-Substituted Aldehydes or Dimethyl Acetals^[716,717]

Reaction of 1-(bromoethyl)cyclopropane with methoxide leads to the formation of 1-(methoxyethyl)cyclopropane and 1-methoxypent-3-ene via a homoallylic ring opening; higher 1-(bromoalkyl)cyclopropanes undergo reaction without rearrangement.^[718] Methoxymethyl ethers are formed from the reaction of 2-[(triphenylphosphonio)methyl]-substituted imidazoles^[719] with indol-3-ylmethyl-*S*-acetic acid or -*S*-propanoic acid^[720] and sodium methoxide via an elimination-addition pathway.

(*E*)-1,1,4-Trimethoxybut-2-ene [126, $\text{R}^1 = \text{CH}=\text{CHCH}(\text{OMe})_2$; $\text{R}^2 = \text{H}$]; **Typical Procedure:**^[694]

Under an atmosphere of argon, a suspension of NaOMe (4.38 g, 81.1 mmol) in MeOH (30 mL) was added to a soln of *E*-bromo acetal **125** [$\text{R}^1 = \text{CH}=\text{CHCH}(\text{OMe})_2$; $\text{R}^2 = \text{H}$; $\text{X} = \text{Br}$; 6.32 g, 32.4 mmol] in MeOH (20 mL), and the mixture was refluxed for 4 h and then cooled to rt. H_2O and Et_2O (20 mL) were added, the organic phase was separated, the aqueous layer was extracted with Et_2O (2 ×), and the combined organic extracts were dried (MgSO_4) and evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether/ Et_2O 9:1) to give the product as a pale yellow oil; yield: 3.45 g (73%).

8.2.4.2.3.2

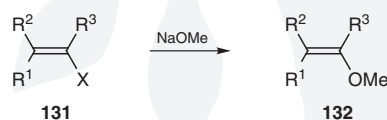
Variation 2:**Vinylic Nucleophilic Substitution and Related Processes**

Nucleophilic substitution of a nucleofugal group at the vinylic carbon in activated alkenes usually takes place by an addition-elimination pathway, involving a stabilized carbanion intermediate.^[721] Use of an excess of nucleophile often leads to the formation of a saturated derivative. Thus, 3-chloro-^[722] or 3,3-dichloroprop-2-enenitrile, and its 2-substituted derivatives,^[723] in a stepwise reaction with sodium methoxide give 3-methoxyprop-2-enenitrile and 3,3-dimethoxypropanenitrile^[722] or 3-chloro-3-methoxy-, 3,3-dimethoxyprop-2-enenitrile, and 3,3,3-trimethoxypropanenitriles,^[723] respectively. Replacement of chloride in methyl (*E*)-3-chloro-2-methylbut-2-enoate by methoxide occurs

with complete retention of configuration.^[724] The benzotriazolyl group, when present in dimethyl maleate derivatives, is easily replaced by this nucleophile.^[725] Arylsulfanyl, alkylsulfanyl, and alkylsulfinyl groups at C2 in unsaturated ketones also act as nucleofugal groups in reactions with methoxide; the reaction with the latter requires milder conditions, giving methoxyvinyl ketones in higher yield.^[726] Derivatives of 3-oxodihydrofuran or γ -butyrolactone substituted with a dihalomethylene group at C2 or C3, respectively, undergo reaction with sodium methoxide to give ortho esters which undergo hydrolysis to give methyl esters of the corresponding carboxylic acids.^[727]

β -Bromo- and β,β -dibromofluorovinyl phenyl sulfones undergo replacement of either the bromide or the phenylsulfonyl group when treated with sodium methoxide;^[728] in the case of haloenynesulfones, substitution of halogen occurs. Examples of the conversion of alkenes **131** into methyl vinyl ethers **132** are given in Scheme 88.^[729] The reaction of β -styryl sulfones with 1 equivalent of sodium methoxide in dimethyl sulfoxide leads to the formation of β -methoxystyrenes, while β -hydroxy sulfones, with an excess of this nucleophile, afford the corresponding dimethyl acetals.^[730] 2-Chloro- or 2,2-dichloro- and 1,2,2-trichloronitroethene, in reaction with methoxide anion, give 2,2-dimethoxy- or 2,2,2-trimethoxynitroethane, respectively, via an elimination–addition pathway.^[731] Substitution at C2 in fused quinazolinones and pyrimidinones by methoxide under aeration occurs with ring cleavage, followed by intramolecular oxidative trapping.^[732] Sodium methoxide in dioxane effects replacement of the chloride at C4, but in methanol at C5, in N-alkylated 4,5-dichloropyridazin-3(2H)-ones.^[733] Vinyl selenoxides undergo reaction with sodium methoxide to give the corresponding vinylic substitution products with complete retention of configuration via a selective reaction at the α -carbon. On the other hand, vinyl selones undergo reaction at either the α - or β -carbon to give the isomeric methoxyvinyl ethers, and extensive isomerization of phenyl (Z)- β -styryl selone to the E-isomer is observed.^[734]

Scheme 88 Methyl Vinyl Ethers from Vinyl Halides, Sulfides, Sulfoxides, and Selenoxides^[722,724,726,729,733–736]



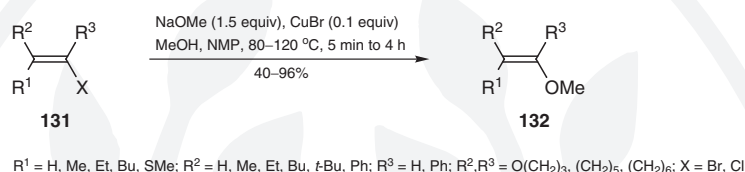
R ¹	R ²	R ³	X	Equiv of NaOMe	Conditions	Yield (%)	Ref
CN	H	H	Cl	0.91	MeOH, 20 °C	85	[722]
Me	CO ₂ Me	Me	Cl	1.0	MeOH, reflux, 2 h	46	[724]
Bz, H ^a		Me	SEt	1.2–2.0	MeOH, rt, 16 h	78	[726]
H	C(O)CH ₂ CMe ₂ CH ₂		S(O)Et	1.2–2.0	MeOH, benzene, rt, 6 h	84	[726]
C≡Ct-Bu	H	SO ₂ Ph	Cl	2.0	MeOH	72	[729]
Cl	CH=NN(Bn)C(O)		Cl	1.0	dioxane, rt, 1 h	74	[733]
Cl	C(O)N(Bn)N=CH		Cl	1.0	MeOH, rt, 1 h	85	[733]
H	Ph	H	Se(O)Ph	4.0	DMF, rt, 4 h	80	[734]
Br	Br	F	Br	1.0	MeOH, 30–40 °C, stir overnight	68	[735]
F	CF ₃	Cy	F	2.0	MeOH, reflux, argon	72	[736]

^a Stereochemistry not determined.

for references see p 1117

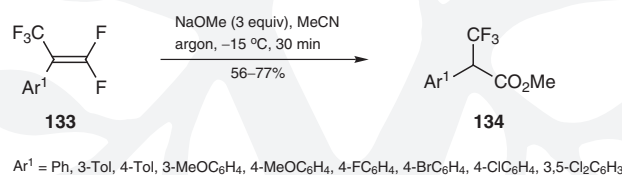
Photolysis of triaryl bromoethenes with sodium methoxide in methanol leads to the formation of both *ipso* and vinylic substitution products.^[737] Nonactivated aliphatic and cyclic vinylic halides **131** undergo reaction with methoxide in a copper(I) bromide catalyzed reaction in *N*-methylpyrrolidin-2-one, to give methyl vinylic ethers **132** in good yield (Scheme 89). The configuration of the substrates is completely retained in the products.^[738]

Scheme 89 Copper(I) Bromide Catalyzed Synthesis of Methyl Vinyl Ethers from Unactivated Vinyl Halides and Sodium Methoxide^[738]



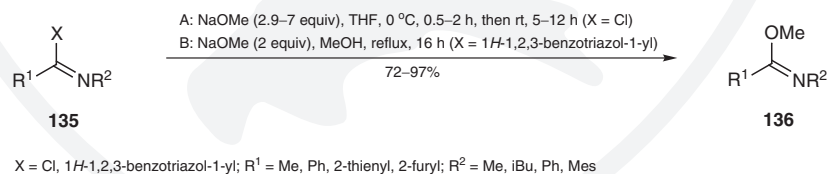
Fluoro substituents and/or the trifluoromethyl group activate double bonds sufficiently for nucleophilic vinylic substitution to proceed.^[736,739] Thus, reaction of (*Z*)-2-cyclohexyl-1,2-difluoro-1-(trifluoromethyl)ethene with sodium methoxide gives 2-methoxy-substituted ethenes (*Z/E* 31:1).^[736] 1-Aryl-2,2-difluoro-1-(trifluoromethyl)ethenes **133** are useful substrates for the synthesis of methyl α -trifluoromethyl-substituted arylacetates **134** (Scheme 90).^[739]

Scheme 90 Synthesis of Methyl α -(Trifluoromethyl)arylacetaes^[739]



Complex product mixtures, the composition of which depends markedly upon the conditions, result from the reactions of bromofluoroethenes with sodium methoxide.^[735] Imines substituted at carbon with nucleofuges (one^[740] or two^[741] chloro groups, benzotriazolyl groups^[742]) resemble activated alkenes in their reactivity with methoxide ion. Thus, imidoyl chlorides^[740] and imidoylbenzotriazoles **135**^[742] yield imidates **136**, but in the case of doubly chlorinated imidoyl chlorides, displacement of only one chloro group takes place (Scheme 91).^[741]

Scheme 91 Synthesis of Methyl Imidates from Imino Chlorides and Benzotriazolyl Derivatives^[740,742]



(*E*)-1-Methoxy-2-phenylbut-1-ene (132, $\text{R}^1 = \text{Et}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{H}$); Typical Procedure:^[738]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

To a stirred suspension of NaOMe (4.1 g, 75 mmol) in NMP (12 mL) and MeOH (3 mL), *E*-bromoalkene **131** ($\text{R}^1 = \text{Et}; \text{R}^2 = \text{Ph}; \text{R}^3 = \text{H}; \text{X} = \text{Br}$; 10.6 g, 50 mmol) and CuBr (0.72 g, 5 mmol) were added. The mixture was stirred at 110 °C for 1 h (GLC monitoring), cooled, 5% aq

NaCN (75 mL) was added, the mixture was extracted with Et₂O (5 × 25 mL), and the combined organic layers were dried (MgSO₄) and evaporated. The product was purified by distillation; yield: 6.9 g (85%); bp 60 °C/0.5 Torr.

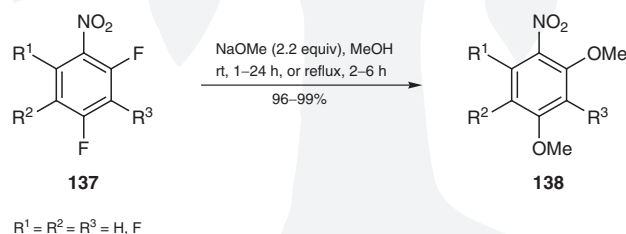
Methyl 3,3,3-Trifluoro-2-phenylpropanoate (134, Ar¹ = Ph); Typical Procedure:^[739]

To a dry soln of MeOH (0.1 g, 3.0 mmol) in MeCN (10 mL) was added NaH (120 mg, 3.0 mmol) (60% dispersed in oil) at rt, and the mixture was stirred for 30 min under an argon atmosphere. Fluoropropene **133** (Ar¹ = Ph; 0.208 g, 1.0 mmol) was added dropwise at –15 °C and the mixture was stirred at –15 °C for 30 min, followed by warming to rt. The mixture was then poured on ice water, the whole was extracted with Et₂O, and the combined organic phases were dried and concentrated to dryness. The residue was purified by column chromatography (silica gel, hexane/EtOAc 9:1) to give the product as an oil; yield: 0.168 g (77%).

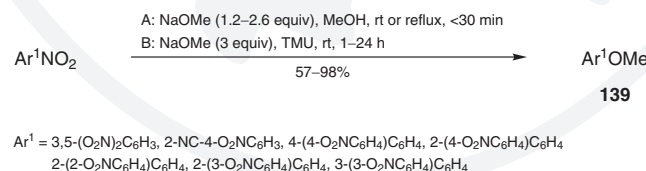
**8.2.4.2.3.3 Variation 3:
Aromatic Nucleophilic Substitution**

Sodium methoxide is commonly applied for the introduction of the methoxy group in aromatic and heteroaromatic compounds by a nucleophilic substitution reaction. Depending upon the kind of substituents and their location in the aromatic ring, this process takes place according to an addition–elimination pathway (S_NAr),^[743] or via an arylene intermediate,^[744] and can be aided by copper salts.^[745] The reaction occurs easily when the nucleofuge occupies a *para* and/or *ortho* position to an electron-withdrawing group, but is also possible when these substituents are *meta* arranged. Thus, both fluoro groups are replaced in substituted 2,4-difluoronitrobenzenes **137** to give 2,4-dimethoxynitrobenzenes **138** in yields exceeding 96% (Scheme 92).^[746] Methoxide replaces the nitro group in *sym*-trinitrobenzene^[747] and 2,5-dinitrobenzonitrile,^[748] while in 1,3-dinitrobenzene, and in biphenyl substituted with nitro groups in both rings, using tetramethylurea (TMU) as solvent to give **139** (Scheme 93).^[749]

Scheme 92 Nucleophilic Aromatic Substitution by Methoxide in 2,4-Difluoronitrobenzenes^[746]



Scheme 93 Nucleophilic Substitution of Aromatic Nitro Groups by Methoxy Groups^[747–749]

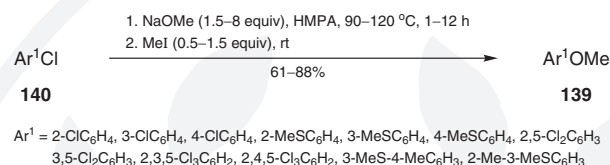


In the case of unactivated aryl chlorides **140**, the reactions with methoxide is carried out in hexamethylphosphoric triamide at temperatures of 90–120 °C (Scheme 94). When di- and polychlorinated aromatics are used, only one chloro group is replaced by methox-

for references see p 1117

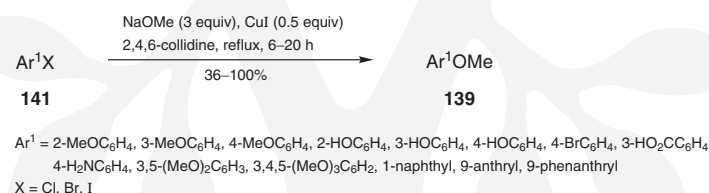
ide.^[750–752] The chloroanisoles thus formed often enter into side reactions with sodium methoxide, giving chlorophenols which are converted into methyl ethers by addition of iodomethane.^[752]

Scheme 94 Synthesis of Aryl Methyl Ethers from Unactivated Aryl Chlorides in Hexamethylphosphoric Triamide^[751,752]



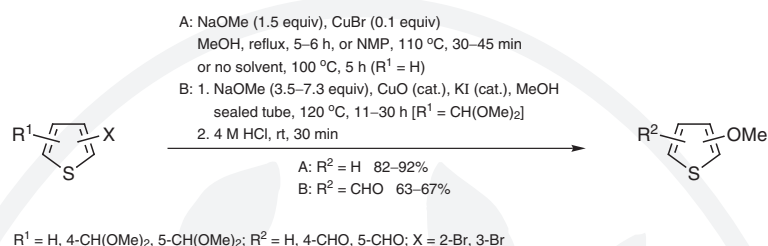
For nonactivated haloaromatic compounds **141**, copper(I) salts catalyze the nucleophilic aromatic substitution with sodium methoxide.^[745] By this approach, aryl methyl ethers **139** are synthesized from halobenzenes,^[753–756] or from 1- or 2-bromonaphthalene, or from halo polyaromatic compounds,^[753] often in high yields (Scheme 95). The process has been thoroughly optimized,^[755,756] particularly in the case of the reaction of sodium methoxide with bromobenzene.^[755] Reduction (dehalogenation) often competes with the nucleophilic substitution.^[753,754,756] The rate of the copper(I)-catalyzed aryl bromide displacement by methoxide is significantly enhanced in the presence of esters. Soluble complexes of copper(I) with esters are probably responsible for this effect.^[757]

Scheme 95 Copper(I) Iodide Catalyzed Transformation of Aryl Halides into Aryl Methyl Ethers^[753,754]



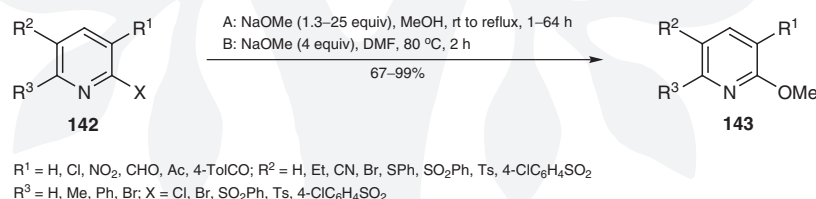
An efficient and selective catalyst for methoxylation of nonactivated bromo aromatic compounds comprises a copper(II)–carbon dioxide combination in methanol, but the process has to be carried out in an autoclave at 125 °C.^[758]

The bromo substituent in 2-acyl-5-bromofurans,^[759] the chloro function in 2-acetyl-5-chloro-4-nitrothiophene,^[760] and the nitro group in nitropyrroles^[748] are all replaced by the methoxy group. Thus copper(I) halide catalyzed substitution of bromo in bromothiophenes,^[756,761] -furan, -pyrrole, or -pyridine^[756] leads to the formation of the corresponding methoxy derivatives, often in high yields (Scheme 96). Replacement of bromo by methoxide in the acetal of 4-bromothiophene-2-carbaldehyde or 5-bromothiophene-3-carbaldehyde and of iodo in 2-iodothiophene is catalyzed by copper(II) oxide, while both iodo substituents in 2,5-diiodothiophene are replaced in a reaction catalyzed by copper(I) oxide. The halo replacement in bromothiophene also requires potassium iodide and the process is often carried out in a sealed tube at 120 °C.^[762] Reactions of isomeric bromiodothiophenes with sodium methoxide in various solvents give mixtures of 3-bromo-, bromo-iodo-, bromodiiodo-, and bromotriiodothiophenes (halogen dance). In the presence of copper(I) oxide in methanol, 4-bromo-2-methoxythiophene is obtained from 2,4-dibromothiophene in low yield.^[763]

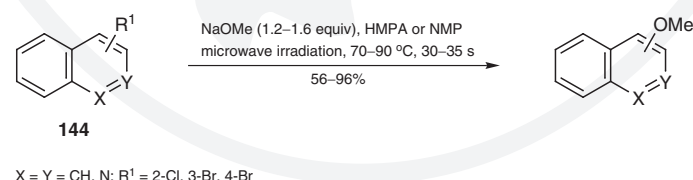
Scheme 96 Methoxythiophenes from Bromothiophenes and Sodium Methoxide under Copper Catalysis Synthesis^[756,761,762]

Either 6-^[764] or 5-bromoindole,^[765] and their derivatives, afford the corresponding methoxy-substituted products; evidently the 5-bromo derivative undergoes reaction more sluggishly, requiring elevated temperatures and catalysis by copper(I) iodide. 4-Iodoindole-3-carbaldehyde also gives the corresponding methoxy derivative;^[766] the entire transformation can be carried out in one pot starting from indole-3-carbaldehyde, which is treated with thallium(III) trifluoroacetate in trifluoroacetic acid, then with iodine and copper(I) iodide in dimethylformamide, and finally with sodium methoxide.^[766]

Nucleofuges (chlorine,^[767–774] bromine,^[768,775,776] arylsulfonyl group^[769]) at C2 in **142** and/or C4 of a pyridine ring are easily replaced by methoxide, e.g. to give **143** (Scheme 97), but, in the case of C3-substituted derivatives, slightly forced conditions are required.^[775,776] Equally prone to substitution is the chloro group or the nitro group in pyridine *N*-oxides,^[777] the bromo at C3 in furopyridine,^[776] and the chlorino groups in 3,5-dichlorothieno[3,2-*b*]pyridine.^[778]

Scheme 97 2-Methoxypyridines from 2-Halo- and 2-Arylsulfonylpyridines^[769–771,773,775]

2,4-Dihaloquinolines undergo replacement of chloro or bromo substituents at C2 by the methoxy group in a heterogeneous sodium methoxide–toluene medium, the regioselectivity being due to a surface reaction.^[779] The rate of nucleophilic substitution of halogen in 2-chloro- and 3-bromoquinoline or 4-bromoisoquinoline **144** by methoxide may be significantly improved by focused microwave irradiation (Scheme 98).^[780]

Scheme 98 Methoxyquinolines or Methoxyisoquinolines from Halo Derivatives under Microwave Irradiation^[780]

for references see p 1117

Methoxy-induced cleavage of the C–S bond in thioquinanthrene ([1,4]dithiino[2,3-c:5,6-c']-diquinoline) by methoxide affords the corresponding thiolate anion intermediate, which is subsequently methylated.^[781] *ipso* Substitution of the 2-methylsulfinyl- and 2-methylsulfonyl groups in 2-substituted 1*H*-imidazoles leads to the formation of the corresponding methoxy derivatives.^[782]

Methoxy-substituted pyrimidines are synthesized by displacement of the chloro group at C2^[783,784] or C4.^[785] A similar reaction occurs in the case of dihydrothiopyrano-,^[786] dihydropyrido-,^[787] and imidazopyrimidines.^[788] The methoxy group is introduced by nucleophilic substitution of the chloro group in substituted pyrazines or pyrazine *N*-oxides,^[789] triazolopyridazines,^[790] and 3,4,5-trichloropyridazine.^[791] In the latter case, a step-wise process allows replacement of all three chloro substituents.^[791] Isomeric nitro(phenyl)furoxanes give the corresponding methoxy derivatives via an exchange of the nitro group.^[792] Derivatives of chloro *as*-^[793,794] or *s*-triazine, (methylsulfonyl)benzotriazine, and bromotetrazine^[794] lose these nucleofugal groups with the formation of methoxylated products. *as*-Triazines substituted at C6 with dichloromethyl and at C5 with chloro or trichloromethyl groups undergo reaction with methoxide to give 5-methoxy-6-(dimethoxymethyl)triazines by aromatic and aliphatic nucleophilic substitution, respectively.^[795] Nucleophilic substitution of the chloro group in purines,^[796] benzo-,^[797] and benzofuro-naphthyridine,^[798] and the trifluoromethanesulfonate group in pteridines^[799] lead to the formation of the corresponding methoxylated products.

2-Fluoro-1,3-dimethoxy-4-nitrobenzene (138, R¹ = R² = H; R³ = F); Typical Procedure:^[746]

A 25% MeOH soln of NaOMe (3.73 g, 69 mmol) was added dropwise to a soln of 1,2,3-trifluoro-4-nitrobenzene (5.53 g, 31.2 mmol) in MeOH (78–104 mL) under N₂ at 4 °C. The resulting mixture was stirred at rt for 1–24 h (reaction progress was monitored by TLC). The mixture was quenched with 1 M citric acid (0.6 g, 3.12 mmol) and the MeOH was removed under reduced pressure. The residue was taken up in Et₂O, and the resulting soln was washed with 1 M citric acid (2 ×) and brine, and dried (Na₂SO₄), and the solvent was removed. The residue was purified by flash column chromatography (EtOAc/hexane) to give a pale yellow crystalline solid; yield: 6.20 g (99%); mp 59–61 °C (petroleum ether/CH₂Cl₂).

5-Bromo-2-methoxypyridine (143, R¹ = R³ = H; R² = Br); Typical Procedure:^[775]

To a stirred soln of 2,5-dibromopyridine (R¹ = R³ = H; R² = X = Br; 10.94 g, 46 mmol) in anhyd MeOH (25 mL) was added a 25% soln of NaOMe (210 mmol) in MeOH (50 mL). The mixture was refluxed for 7 h and then poured into cold, stirred 5% aq NaHCO₃ (75 mL). The mixture was extracted with Et₂O (4 × 30 mL), the combined organic extracts were washed with brine (3 × 30 mL), dried (MgSO₄), and concentrated. The residue was purified by Kugelrohr distillation to give the product as a clear liquid; yield: 7.96 g (92%); bp 65–70 °C/3.5 Torr.

8.2.4.2.3.4

Variation 4:

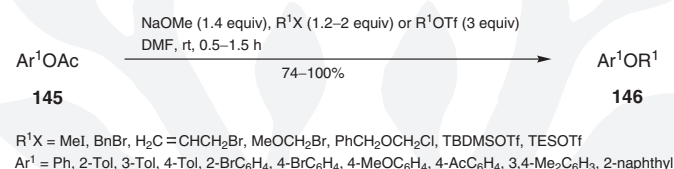
Reactions with Esters and Carbonyl, Thiocarbonyl, and Related Compounds

Addition of methoxide to a carbonyl group generates a tetrahedral intermediate which is transformed into the corresponding methyl ester by expulsion of the nucleofuge. In the case of esters, lactones, and related derivatives, the C–O bond is cleaved, while the C–C bond is broken with carbonyl compounds α -substituted with an electron-withdrawing group. When the carbonyl group is part of a ring, this process leads to ring cleavage. The anions formed via either reaction (usually oxyanions) may undergo reaction with electrophiles in an inter- or intramolecular manner.

In the simplest case, reaction of sodium methoxide with acid chlorides^[800,801] or fluorides^[802] leads to the formation of the corresponding methyl carboxylates. A similar pro-

cess occurs with 3-substituted *N*-pivaloyl-*S*-(3-sulfanylpropyl)pyrrolidine-2-carbothioates^[803] and trichloromethyl ketones^[804,805] (haloform reaction). Substitution of a chiral oxazolidinone group by methoxide [a step in the preparation of (+)-macbecin I] occurs in high yield.^[806] When an alkyl trihaloacetate is treated with methoxide in the presence of an alkene, the generated trihalomethyl anion undergoes fragmentation into dihalocarbene (and halide anion) which undergoes addition to the alkene to form a *gem*-dihalo-cyclopropane.^[473,807] The synthesis of dibromonorcarane by reaction of methoxide, ethyl dibromomalonate, and cyclohexene takes place via a more complex pathway.^[808] Benzoate esters of carbohydrates, formed by oxidation of the corresponding benzyl ethers with tetrabutylammonium peroxydisulfate are, without isolation, cleaved into the deprotected carbohydrates in 85–90% overall yield.^[809] Phenolates generated from aryl acetates **145** and sodium methoxide enter into an in situ reaction with active alkylating agents,^[810,811] or silyl trifluoromethanesulfonates,^[811] giving the corresponding aryl ethers **146** in high yields (Scheme 99). The process is chemoselective in that the aryl acetates undergo reaction at much higher rates than alkyl acetates do.^[810,811]

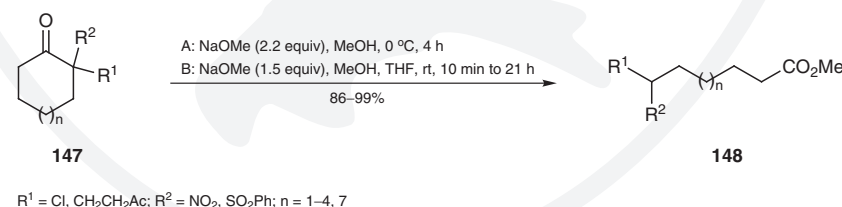
Scheme 99 Conversion of Aryl Acetates into Alkyl Aryl or Aryl Silyl Ethers^[810,811]



Reaction of α -cyanovinyl acetates with sodium methoxide affords the corresponding methyl carboxylates.^[812] β -*N*-Alkyl- or β -*N*-aryl- α,α -dichloroiminocarbonyl compounds undergo regiospecific fragmentation into α,α -dichloroketenimines and dimethyl carbonate.^[813]

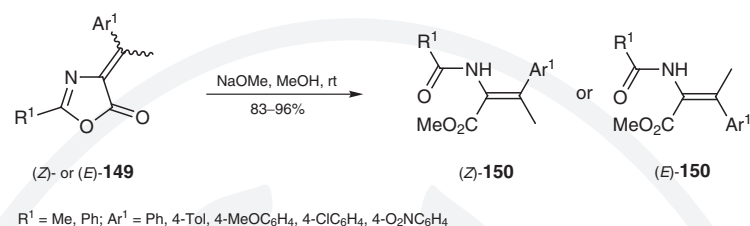
Sodium methoxide effects transformation of the anhydride of pyridinedicarboxylic acid into the monomethyl ester^[814] and 4-isopropyl-3-methyleneoxetan-2-one into methyl 3-hydroxy-4-methyl-2-methylenepentanoate,^[815] while derivatives of Meldrum's acid are converted into the corresponding monomethyl esters of cyclopropane-1,1-dicarboxylic acid.^[816] Depending on the substituents on the benzene ring of benzocyclobutanones, reactions with methoxide give either methyl benzoates, methyl phenylacetates, or their mixtures.^[817] Addition of methoxide followed by ring cleavage occurs in the case of spirotriones,^[818] 2-(2-acetyylethyl)-2-nitro^[819] and 2-chloro-2-(phenylsulfonyl)cycloalkanones **147**, e.g. to give **148** (Scheme 100).^[820]

Scheme 100 Ring Opening of Cycloalkanones α -Substituted with Electron-Withdrawing Groups^[819,820]

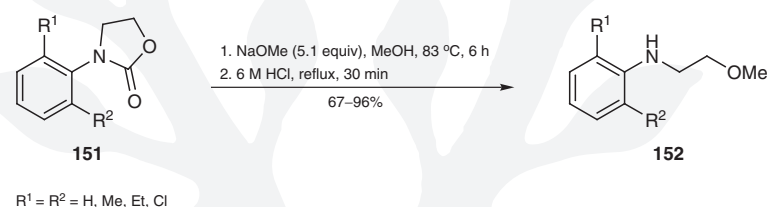


Methyl (*Z*)- and (*E*)-2-(acylamino)-3-arylbut-2-enoates **150** are obtained by a stereoselective ring opening reaction of suitably substituted (*Z*)- and (*E*)- α -(arylethylidene)oxazol-5(4*H*)-ones **149** with sodium methoxide (Scheme 101).^[821]

for references see p 1117

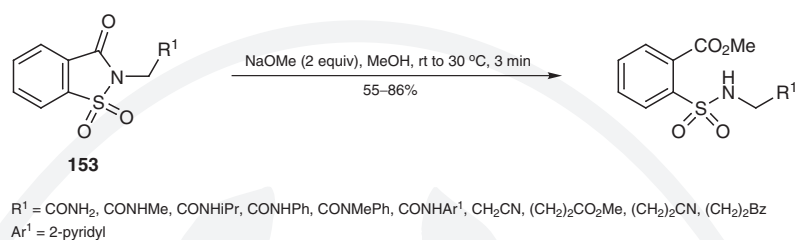
Scheme 101 Synthesis of Methyl 2-(Acylamino)-3-arylbut-2-enoates^[821]

A similar process affords methyl 2-[(alkoxycarbonothioyl)amino]-3-(*N*-hetaryl-*N*-methyl)-propenoates from 2-alkoxy-4-[(hetaryl amino)methylene]thiazol-5(4*H*)-ones^[822] and α -(methoxycarbonyl)amino ketones or aldehydes from oxazolidin-2-ones and oxazol-2(3*H*)-ones.^[823] An unexpected ring opening of *N*-aryloxazolidin-2-ones **151** with sodium methoxide, followed by decarboxylation of the intermediate carbamic acids, leads to the formation of *N*-(2-methoxyethyl)anilines **152** in ca. 90% yield (Scheme 102).^[824]

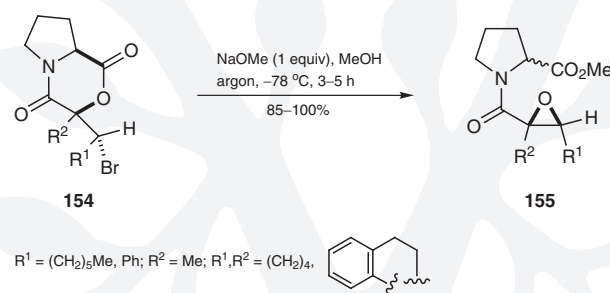
Scheme 102 Substituted *N*-(2-Methoxyethyl)anilines from *N*-Aryloxazolidin-2-ones^[824]

When the heterocyclic substrate possesses a carbonyl and a thiocarbonyl group, the latter may be attacked by the methoxide with concomitant ring opening, e.g. conversion of dithiotriuret into thiocarbamates.^[825] Deprotection of indole derivatives which are *N*-substituted with the *tert*-butoxycarbonyl group is carried out by methoxide; simultaneously the present dithiocarbamate substituent is converted into monothiocarbamate.^[826]

The transient alkoxy anion resulting from addition of methoxide to C=O, followed by fragmentation of the tetrahedral intermediate, can enter into subsequent intra- or intermolecular reactions. Thus, esters of 2,4-dibromo-1,2,3,4-tetrahydronaphthalen-1-ol treated with methoxide afford the corresponding naphthalene 1,2-oxides by generation of the O-anion followed by its cyclization and concomitant dehydrobromination. This is a general method of synthesis of non-*K*-region arene oxides.^[827] Tandem ester cleavage–Michael addition of methyl (*E*)-6-acetoxy-3-methylhex-2-enoate induced by methoxide leads to the formation of 2-[(methoxycarbonyl)methyl]-2-methyltetrahydrofuran in 90% yield.^[828] When treated with methoxide, 2-(methoxycarbonyl)-2-methylcyclopentanone gives the 2-(methoxycarbonyl)-5-methyl ketone, by a ring opening–ring closure reaction. The product thus formed enters into Michael addition with methyl acrylate, followed by ring opening.^[829] Ring opening is observed in the case of saccharin-2-acetic acid derivatives **153** (Scheme 103). These processes usually start by addition of methoxide to the carbonyl carbon.^[830–834]

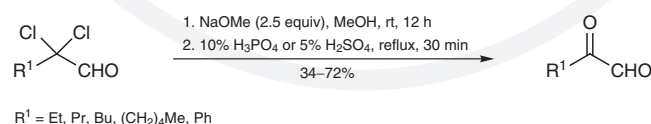
Scheme 103 Ring-Opening Reactions of N-Substituted Saccharins^[831,833]

The combination of sodium methoxide with alkyl iodides in dimethylformamide effects transformation of activated thiohydantoin into hydantoin.^[835] The preparation of optically active α,β -epoxy aldehydes from α,β -unsaturated carboxylic acids involves ring cleavage of proline bromolactones **154** with methoxide and trapping of the resulting oxyanion by bromide displacement, resulting in the formation of methyl N-epoxyprolinates **155** but not without concomitant racemization (Scheme 104).^[836]

Scheme 104 Epoxides from Bromolactones by Ring Opening–Ring Closure^[836]

The tosyloxy group in butyrolactone derivatives also serves to trap the oxyanion, for example in the synthesis of (R)-(-)- γ -(hydroxymethyl)- γ -butyrolactone^[837] or methyl (2S,3R)-2,3-epoxy-4-hydroxybutyrate from the chiral β -hydroxy- α -(tosyloxy)butyrolactone and methoxide.^[838] A multistep, one-pot synthesis of methyl 1-alkyl-2-methylpyrrole-3-carboxylates is initiated by the ring opening of 2-acetimidoyl-2-chlorobutyrolactones with sodium methoxide.^[839] Oxyanions, generated by addition of methoxide to the carbonyl group in 3,7-dihalobicyclo[3.3.1]nonane-2,6-diones, are intramolecularly intercepted by chloro displacement to give 4-halo-3-methoxy-2-oxatricyclo[4.3.1.0^{3,8}]decan-10-ones.^[840]

Typically, α -chloro,^[841] α -bromo,^[842] and α,α -dichloro aldehydes^[843] or α -bromo^[844–846] and α,α -dihalo ketones,^[847,848] lacking α' -hydrogen atoms, undergo reaction with methoxide by addition–ring closure to give methoxyoxiranes,^[841,842,844,846] while opening of the oxirane ring occurs by using excess of this nucleophile (Scheme 105).^[841,843,845–847] The structure of the final products depends upon the site of methoxide attack on the methoxyoxirane.

Scheme 105 α -Oxo Aldehydes from α,α -Dichloro Aldehydes and Sodium Methoxide^[843]

for references see p 1117

Bromomethyl 2-chloroalkyl ketones afford, with excess of sodium methoxide, 3,3-dimethoxytetrahydrofurans by a ring closure–ring opening–intramolecular O-alkylation sequence. These products are cleaved by aqueous acid into 4,4-dialkyltetrahydrofuran-3-ones.^[849] α,α' -Dihaloalkane-1,2-diones give, by reaction with excess of sodium methoxide, 2,3:4,5-diepoxy-3,4-dimethoxyalkanes, useful precursors of 4-hydroxyfuran-3(2H)-ones.^[850] Addition of methoxide to an aldehyde and subsequent intramolecular capture of the oxyanion thus formed with an α,β -unsaturated carbonyl moiety constitutes a stereocontrolled lactone annulation.^[851] O-Alkyl arenecarbothioates undergo reaction with sodium methoxide to give S-anions which, without isolation, undergo reaction with alkyl iodides to yield monothioortho esters.^[852]

Methyl 6-Chloro-6-(phenylsulfonyl)hexanoate (148, $R^1 = \text{Cl}$; $R^2 = \text{SO}_2\text{Ph}$; $n = 1$);

Typical Procedure:^[820]

To a soln of 2-chloro-2-(phenylsulfonyl)cyclohexanone (68 mg, 0.25 mmol) in THF (1 mL) and MeOH (3 mL), a soln of NaOMe (0.38 mmol, prepared from NaH and MeOH) in MeOH (1 mL) was added. The mixture was stirred at rt for 10 min, then quenched with sat. aq NH_4Cl and the solvent was evaporated. The residue was extracted with Et_2O /benzene (**CAUTION: carcinogen**), the extract was concentrated to dryness, and the product was purified by column chromatography (silica gel) to give a colorless low-melting solid; yield: 76 mg (99%).

Methyl 1-([(2R,3S)-2-Methyl-3-phenyloxiran-2-yl]carbonyl)prolinate (155, $R^1 = \text{Ph}$; $R^2 = \text{Me}$);

Typical Procedure:^[836]

A soln of NaOMe (935 mg, 17.3 mmol) in MeOH (52 mL) was added over 5 min to a stirred soln of crude bromolactone **154** ($R^1 = \text{Ph}$; $R^2 = \text{Me}$; 5.84 g, 17.3 mmol) in MeOH (52 mL) at -78°C under argon. After stirring at -78°C for 4 h, the soln was concentrated under reduced pressure below 0°C . The oily residue was dissolved in Et_2O , dried, filtered, and the filtrate was concentrated to give the crude product as a pale yellow oil; yield: 4.51 g (90%).

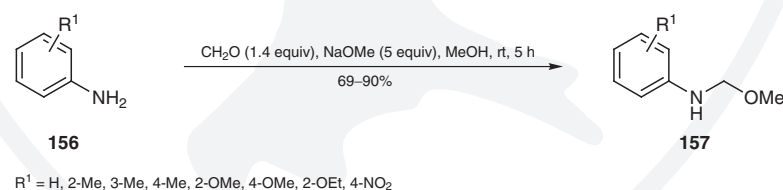
8.2.4.2.3.5

Variation 5:

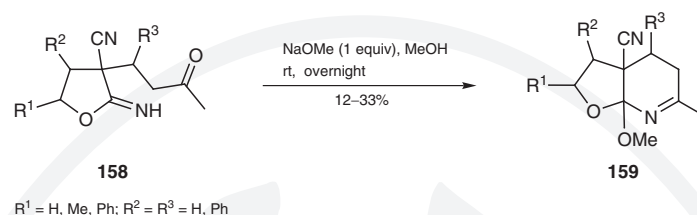
Reactions with Imines, Isothiocyanates, and Carbodiimides

Addition of methoxide to a $\text{C}=\text{N}$ bond generates the corresponding N-anion, which can undergo an inter- or intramolecular reaction. Thus, reaction of aromatic amines **156** with paraformaldehyde and sodium methoxide leads to the formation of N-aryl-N-(methoxymethyl)amines **157**, the equivalent of methyleneamines (Scheme 106).^[853]

Scheme 106 Synthesis of N-Aryl-N-(methoxymethyl)amines^[853]

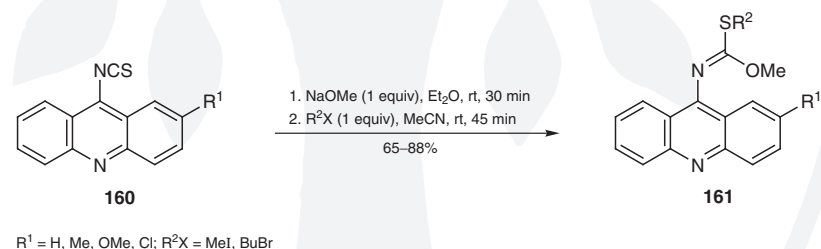


N-Anions formed by addition of methoxide to δ -chloro imines enter into intramolecular alkylation reactions, giving substituted N-alkyl-2-methoxypiperidines.^[854] Derivatives of 2-imino-3-(3-oxobutyl)tetrahydrofuran-3-carbonitrile **158**, upon treatment with this nucleophile, give hexahydrofuro[2,3-*b*]pyridines **159** via an addition–cyclization–dehydration route (Scheme 107).^[855]

Scheme 107 Cyclization of 5-Imino Ketones Using Sodium Methoxide^[855]

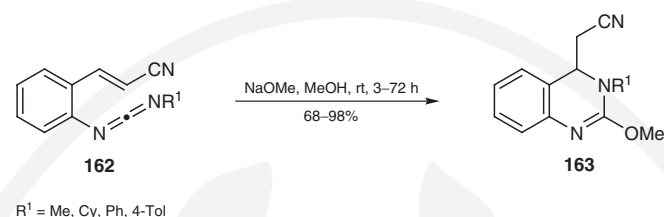
The reactions of the tautomeric forms of α -(aroylamino)- β,β -dichloroacrylic acid^[856] or *tert*-butyl 2-(*N*-acetyl-*N*-bromo)aminoalk-2-enoates^[857] give substituted 2-aryl-4-methoxy-oxazoles or *tert*-butyl 4-methoxydihydrooxazole-4-carboxylates, respectively. 2-(Chloroalkyl)benzothiazoles undergo reaction with sodium methoxide either by addition to imines and subsequent rearrangement and/or nucleophilic substitution.^[858] *N*7-Alkoxy-substituted adeninium salt species undergo reaction with methoxide to afford 8-methoxy derivatives via an addition–elimination pathway.^[859] Photolysis of azidopyridines^[860] or -quinolines^[861] in the presence of methoxide results in a ring expansion to give diazepines or benzodiazepines via the reaction of the transient azirine derivatives with this nucleophile.

9-Isothiocyanatoacridines **160** undergo addition of sodium methoxide with the generation of the highly nucleophilic *N*-acridin-9-yl-*O*-methyliminothiocarbonate anion, which undergoes reaction with iodomethane or bromobutane to form the corresponding *N*-acridin-9-yl-*S*-alkyl-*O*-methyliminothiocarbonate **161** (Scheme 108),^[862] while with alkyl bromoacetates, the spiro[dihydroacridine-9(10*H*)-4'-thiazolines] are obtained.^[863] Aryl isothiocyanates undergo reaction with an excess of sodium methoxide and alkyl bromoacetates to give *N*-aryl-*S*-[(methoxycarbonyl)methyl]-*O*-methyliminothiocarbonates.^[863]

Scheme 108 Synthesis of *N*-Acridin-9-yl-*S*-alkyl-*O*-methyliminothiocarbonates^[862]

Intramolecular interception of the *S*-anion formed from 3-aryl-2-chloro-1-isothiocyanatopropanes and sodium methoxide anion leads to the formation of 5-substituted 2-methoxy-2*H*-2,3-dihydrothiazoles.^[864] Dihydroquinazolines **163** result from treating 1-substituted 3-[2-(β -cyanovinyl)phenyl]carbodiimides **162** with sodium methoxide using the nucleophilic addition–heterocyclization sequence strategy (Scheme 109).^[865]

for references see p 1117

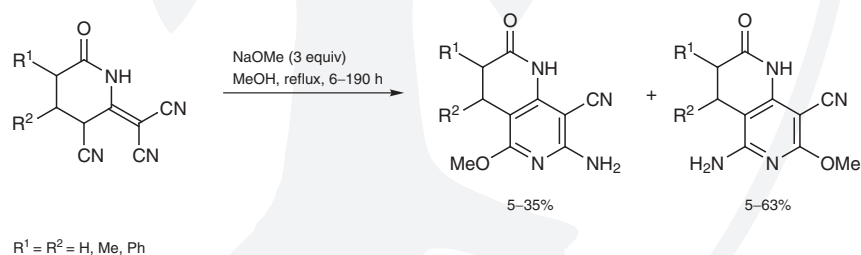
Scheme 109 Synthesis of Dihydroquinazolines by Tandem Methoxide Addition–Intramolecular Michael Reaction^[865]**N-(Methoxymethyl)aniline (157, R¹ = H); Typical Procedure:**^[853]

Na (2.3 g, 100 mmol) was slowly added to MeOH (30 mL). Once the evolution of H₂ had ceased, PhNH₂ (1.86 g, 20 mmol) was added and the resulting hot soln was poured onto a suspension of paraformaldehyde (0.84 g, 28 mmol) in MeOH (20 mL). The resulting mixture was stirred at rt for 5 h, treated with ice-cold H₂O, and the whole was extracted with Et₂O. The combined organic extracts were dried (Na₂SO₄) and carefully evaporated (below 25 °C) to give the product as an oil; yield: 2.33 g (85%); it should be stored at –18 °C.

8.2.4.2.3.6

**Variation 6:
Reactions with Nitriles**

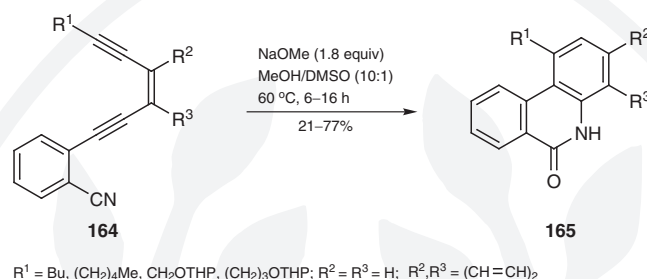
Addition of methoxide to nitriles yields imino ethers which, under hydrolytic conditions, readily afford methyl esters.^[866] Reaction of sodium methoxide with cyanogen bromide and methanol (or with other alcohols) affords the dimethyl (or the methyl alkyl) ester of iminocarbonic acid.^[867] 3-(Cyanomethyl)pyridine-2- and -4-carbonitriles undergo cyclization to amino(methoxy)naphthyridines when treated with sodium methoxide.^[868] Similarly, cyclization of substrates which contain the 1,1,3-tricyanopropenyl moiety into derivatives of 2,4-diamino-6-methoxy- and 4,6-diamino-2-methoxypyridine-3-carbonitriles is induced by methoxide (Scheme 110).^[869,870]

Scheme 110 Synthesis of 2,4-Diamino-6-methoxy- and 4,6-Diamino-2-methoxypyridine-3-carbonitrile Derivatives^[869]

Intramolecular interception of N-anions, derived from addition of methoxide to the cyano group, by the ethoxycarbonyl substituent in derivatives of 2-(ethoxycarbonyl)-3-(2,2-dicyanoethyl)indole lead to the formation of azepino[3,4-*b*]indoles.^[871] Depending on the substituent in 2-(2-substituted ethynyl)benzonitriles, the reaction with methoxide leads to the formation of 3-substituted isoquinolones, accompanied sometimes by 1-methoxyisoquinolines (for alkyl derivatives) or arylideneisoindolones (for aryl derivatives). In one case, addition of 1 equivalent of methoxide to the ethynyl bond in diarylacetylenes is observed.^[872] Anionic cycloaromatization initiated by methoxide addition to the cyano group of 6-substituted 2-[(*Z*)-hex-3-ene-1,5-diynyl]benzonitriles and 2-[2-(2-alkynylphenyl)ethynyl]benzonitriles **164** affords phenanthridinones **165** (21–77%) and benzo[*c*]phen-

anthridinones **165** [$R^2, R^3 = (CH=CH)_2$] (31–57%); the formation of biaryls is also observed in some cases (Scheme 111).^[873]

Scheme 111 Phenanthridinones and Benzo[c]phenanthridinones from Addition of Methoxide to Enediynylbenzonitriles^[873]



11-Butylbenzo[c]phenanthridin-6(5H)-one [**165**, $R^1 = \text{Bu}$; $R^2, R^3 = (CH=CH)_2$];

Typical Procedure:^[873]

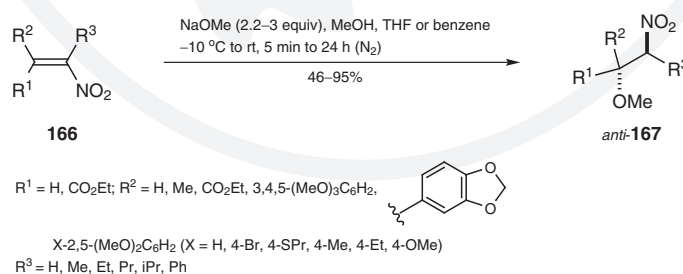
To a soln of enediynylbenzonitrile **164** [$R^1 = \text{Bu}$; $R^2, R^3 = (CH=CH)_2$] (312 mg, 1.1 mmol) in MeOH (20 mL) and DMSO (2 mL) was added freshly cut Na (46 mg, 2 mmol). The resulting soln was heated to 60 °C and stirred at this temperature for 6 h. After cooling to rt, MeOH was removed under reduced pressure, H_2O was added to the residue, which was then extracted with EtOAc. The combined organic extracts were dried (MgSO_4) and concentrated to dryness. The residue was purified by flash chromatography (silica gel) to give a colorless solid; yield: 190 mg (57%); mp 230 °C.

8.2.4.2.3.7

Variation 7: Reactions with Alkenes

Electrophilic alkenes undergo smooth addition of methoxide, generating an anion which can be protonated or intercepted with electrophiles through an intra- or intermolecular reaction.^[874] Thus, α -(arylmethyl)-3-methoxyprop-2-enenitriles undergo addition of methoxide to form 3,3-dimethoxy derivatives.^[875] At low temperatures, methyl acrylate β -substituted with a chiral group undergoes reaction with sodium methoxide with good *threo* selectivity.^[876] Aliphatic^[877] (including β -methoxy^[878]) and cyclic^[879] α, β -unsaturated ketones lead to the formation of β -methoxylated products. β -Chloro-substituted conjugated dienones give rise to products possessing up to three methoxy groups by an addition–vinyllic substitution sequence.^[880] 5-(Dichloromethylene)- or 5-(trichloromethyl)oxazolidin-4-ones undergo addition of methoxide to give 5-methoxy derivatives. Trichloromethyl derivatives undergo initial elimination of hydrogen chloride, affording dichloromethylene derivatives.^[881] Nitroalkenes **166** are strong electrophiles, easily undergoing reaction with this nucleophile, e.g. to give predominantly *anti*-**167** (Scheme 112).^[882–884]

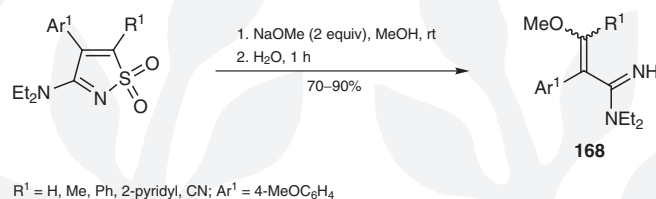
Scheme 112 Addition of Sodium Methoxide to Nitroalkenes^[882–884]



for references see p 1117

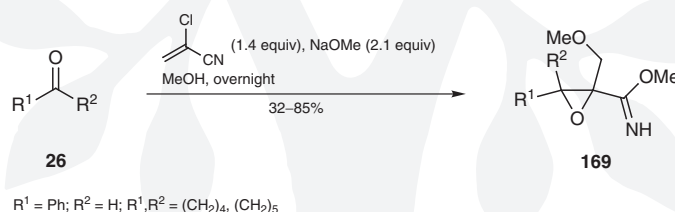
From the point of view of electron-withdrawing character, the ethoxycarbonyl group does not compete with the nitro group and β -substituted ethyl β -nitroacrylates produce ethyl α -methoxy- β -nitroalkanoates.^[884] Vinyl selones undergo reaction with methoxide to give stable conjugate addition products in excellent yields.^[885] The C=C bond in 4-(4-methoxyphenyl)isothiazole 1,1-dioxides is prone to methoxide addition, but the adducts subsequently undergo ring opening with concomitant loss of sulfur dioxide to give 3-methoxy- **168** or 3,3-dimethoxy-2-(4-methoxyphenyl)propenamidines (Scheme 113).^[886]

Scheme 113 Propenamidines by Ring Opening of Isothiazole 1,1-Dioxides^[886]



Treatment of the trifluoromethanesulfonate of *N*-benzyl dihydropyridine with methoxide leads to the formation of the 4-methoxytetrahydro derivative.^[887] Transient anions generated by addition of methoxide to α -chloroacrylonitrile or alkyl α -haloacrylates are intercepted by carbonyl compounds **26**, affording the substituted 2-(methoxymethyl)-2-glycidoimino methyl esters **169** (a Darzens-like process) and the corresponding methyl esters or derivatives of cyclopropanecarboxylic acid (Scheme 114).^[888,889]

Scheme 114 Derivatives of Oxirane-2-carboximidates from α -Chloroacrylonitrile, Carbonyl Compounds, and Sodium Methoxide^[888,889]



Dimethyl (2-bromo-2-methylpropylidene)malonate^[890,891] or (1-aryl-2-bromoalkylidene)malononitriles,^[892,893] upon treatment with sodium methoxide, afford the corresponding cyclopropane derivatives via an addition–cyclization pathway. Use of an excess of this nucleophile results in cyclopropane ring opening.^[891] In the case of a malononitrile derivative substituted with the 2-bromomethyl group on the benzene ring, the *N*-anion generated by addition of the methoxide to the cyano group undergoes cyclization to give a benzazepine derivative.^[893] The transient anion from the addition of methoxide to α -chloroacrylonitrile is trapped by 1,3-dinitrobenzene, giving the product of a vicarious nucleophilic substitution reaction,^[154–157] or, with excess sodium methoxide, an α -cyanostyrene derivative.^[894] Iodoperfluoroalkanes undergo reaction with alkyl vinyl ethers and sodium methoxide to give alkyl (2-perfluoroalkyl-1-methoxy)ethyl acetals via radical intermediates.^[895]

1,4-Dimethoxy-2-(1-methoxy-2-nitroethyl)benzene [167, $\text{R}^1 = \text{R}^3 = \text{H; R}^2 = 2,5\text{-(MeO)}_2\text{C}_6\text{H}_3$];

Typical Procedure:^[883]

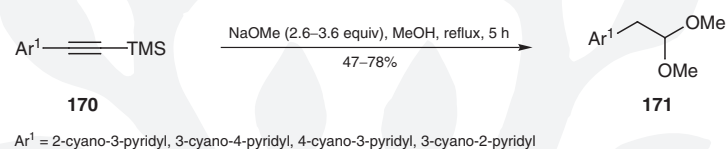
To a stirred, cooled (0–5 °C) soln of 1,4-dimethoxy-2-[(*E*)-2-nitrovinyl]benzene (8.8 g, 42 mmol) in dry benzene (80 mL) (**CAUTION: carcinogen**) under N_2 was added a soln of 3.3 M NaOMe [prepared from Na (4.5 g) in MeOH (60 mL)] in MeOH (18.0 mL). After 5 min, the mixture was acidified with glacial AcOH (15 mL), the whole was stirred for 5 min, and H_2O (ca. 100 mL) was added. The organic layer was separated, washed with H_2O , the aque-

ous layer was extracted with CH_2Cl_2 , and the combined organic extracts were dried (CaCl_2) and concentrated to dryness. The product was purified by flash chromatography (silica gel, CHCl_3); yield: 9.4 g (93%); mp 58–61 °C.

8.2.4.2.3.8 Variation 8: Reactions with Alkynes

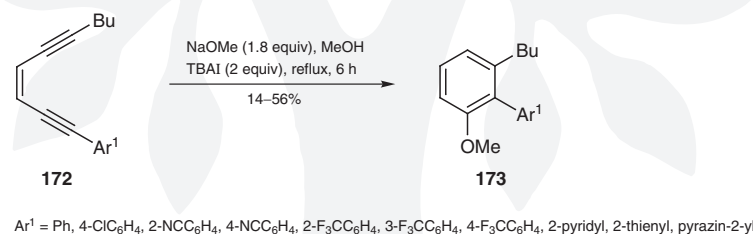
Alkynes, even those lacking strongly electron-withdrawing groups, relatively easily undergo addition of nucleophiles, including methoxide.^[896] As examples, four isomeric pyridinecarbonitriles **170** with neighboring, trimethylsilyl-substituted ethynyl groups undergo desilylation and then addition of 2 equivalents of methoxide, resulting in the formation of 2,2-(dimethoxyethyl)-substituted pyridinecarbonitriles **171** (Scheme 115).^[897] A similar process occurs with aromatic and isoquinoline derivatives; in the former case, the simple desilylated compound is a byproduct.^[898]

Scheme 115 Methyl Acetals from Trimethylsilylalkynes and Sodium Methoxide^[897]



The reaction of (*Z*)-1-aryldec-3-ene-1,5-diynes **172** with sodium methoxide and 2 equivalents of tetrabutylammonium iodide gives biaryls **173** in 14–56% yield (Scheme 116). A similar approach is applied to the preparation of oligobenzene derivatives.^[873]

Scheme 116 Substituted Biphenyls from 1-Aryldec-3-ene-1,5-diynes^[873]



Sodium methoxide initiates a Michael-type addition–lactonization of 1-[(2-ethoxycarbonyl)ethynyl]-1-(hydroxy)cycloalkanes into tetronates.^[899] Addition of the methoxide anion to β -(2-aminophenyl)- α,β -ynones promotes an annulation reaction, leading to the formation of 2,4-disubstituted quinolines.^[900] Depending on the workup conditions, the product of methoxide anion addition to *tert*-butyl (*R*)-5-hydroxyundec-2-ynoate either undergoes cyclization to (*R*)-dihydropyran-2-one or elimination of water to give the methoxy-substituted dienonic acid.^[901]

2-Butyl-6-methoxy-4'-(trifluoromethyl)biphenyl (**173**, $\text{Ar}^1 = 4\text{-F}_3\text{CC}_6\text{H}_4$);

Typical Procedure:^[873]

To a soln of alkyne **172** ($\text{Ar}^1 = 4\text{-F}_3\text{CC}_6\text{H}_4$; 359 mg, 1.1 mmol) in MeOH (20 mL) containing TBAI (813 mg, 2.2 mmol) was added freshly cut Na (46 mg, 2 mmol). The resulting soln was heated to 60 °C and stirred at this temperature for 16 h. After cooling to rt, MeOH was removed under reduced pressure, H_2O was added to the residue, and the whole was extracted with EtOAc . The combined organic extracts were dried (MgSO_4) and the solvent was removed. The residue was purified by flash chromatography (silica gel) to give an oil; yield: 146 mg (43%).

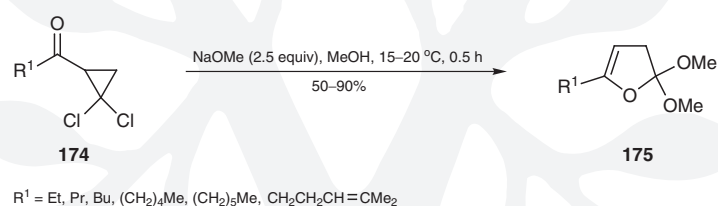
for references see p 1117

8.2.4.2.4 Method 4: Cleavage of Cyclic Compounds

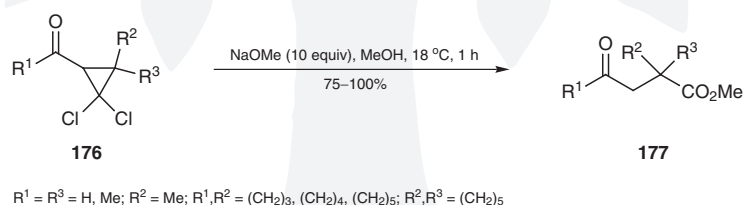
8.2.4.2.4.1 Variation 1: Cleavage of Cyclopropanes

Depending on the substituent on the cyclopropane ring, and the reagent, *gem*-dichlorocyclopropanes either enter into a nucleophilic substitution (see Section 8.2.4.2.3.1) or a ring cleavage reaction. Except for a few cases, the methoxide anion usually undergoes reaction according to the latter pathway.^[473,902] Thus, 2-alkyl-3,3-dichlorospiro[cyclopropane-1,9'-fluorenes], in reactions with sodium methoxide in dimethyl sulfoxide, give either enyne, butadiene, or butatriene derivatives. The process is initiated by formation of a cyclopropane carbanion.^[903] 1,2-Dichloro-3,3-difluorocyclopropene undergoes ring opening on treatment with excess of methoxide, affording a mixture of three products, but, under strictly anhydrous conditions, 3-chloro-2-fluoro-1,1,1-trimethoxyprop-2-ene is preferentially produced.^[904] In the case of *gem*-dichlorocyclopropanes substituted with a phenyl,^[905] benzoyl,^[906] or acyl group,^[907,908] ring cleavage is preceded by an elimination reaction^[905–907] and, in the case of **174**^[908] or **176**,^[907] leads to the formation of 5-substituted 2,2-dimethoxy-2,3-dihydrofurans **175**^[906,908] or β -(methoxycarbonyl) aldehydes and ketones **177**, respectively (Schemes 117 and 118).^[907]

Scheme 117 Synthesis of 2,2-Dimethoxy-2,3-dihydrofurans^[908]



Scheme 118 Ring Cleavage of Dichlorocyclopropyl Ketones by Sodium Methoxide^[907]



Prolonged heating of 1,1-dichloro-2-(phenylsulfonyl)cyclopropane, or its derivatives substituted at C3 with one or two methyl groups, with sodium methoxide in methanol, gives the corresponding ortho esters.^[909] Reaction of nitrocyclopropanes, *gem*-substituted with a methoxycarbonyl group, with methoxide affords the corresponding methyl β -alkyl- or β -aryl- α -methoxyvinylmalonates.^[910]

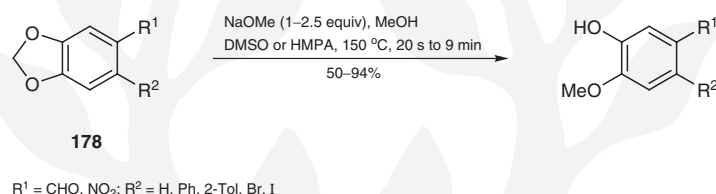
5-Pentyl-2,2-dimethoxy-2,3-dihydrofuran [**175**, $\text{R}^1 = (\text{CH}_2)_5\text{Me}$]; Typical Procedure:^[908]

To a stirred soln of NaOMe, prepared from Na (5.75 g, 0.25 mol) in MeOH, ketone **174** [$\text{R}^1 = (\text{CH}_2)_5\text{Me}$; 20.91 g, 0.1 mol] dissolved in MeOH (50 mL) was added with stirring at 15–20 °C. The mixture was stirred for 0.5 h, diluted with H₂O (200 mL), and the whole was extracted with hexane (3 \times 50 mL). The combined organic extracts were dried (MgSO₄) and evaporated to dryness, and the residue was distilled under reduced pressure to give the product; yield: 14.42 g (72%); bp 79–80 °C/2 Torr.

8.2.4.2.4.2 Variation 2: Cleavage of Methylenedioxy Derivatives

The methylenedioxy ring fused to aromatic compounds undergoes cleavage by reaction with sodium methoxide in dimethyl sulfoxide^[911–914] or hexamethylphosphoric triamide,^[914] giving phenolic products. High regioselectivity is observed for compounds **178** substituted with formyl and nitro groups (Scheme 119), and for 2,2-dimethyl-substituted dihydrobenzopyran-4-one derivatives.^[915] The process is carried out by heating the reactants at ca. 150 °C for a few minutes.^[911–914] The ring cleavage takes place either by attack of the methoxide in an *ipso* manner or on the carbon atom in the methylenedioxy ring. Interestingly, no nucleophilic substitution of halo groups is observed.

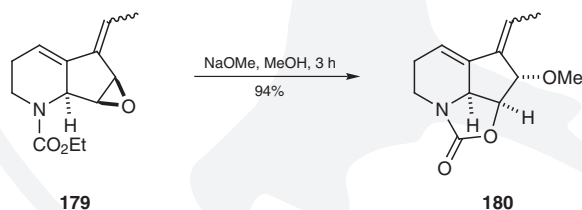
Scheme 119 Regioselective Cleavage of the Methylenedioxy Ring^[911,912,914]



8.2.4.2.4.3 Variation 3: Cleavage of Three-Membered Heterocycles

Oxiranes undergo reaction with sodium methoxide to give β -methoxy alcohols.^[916] Well-known examples involve cyclohexene oxide^[917] or stilbene oxide; in the latter case, the *cis*-oxide undergoes reaction faster than the *trans*-isomer.^[918] Monosubstituted ethene and cyclohexene oxides undergo attack mainly at the less sterically crowded carbon, with very high regioselectivity in the case of alkyl-substituted derivatives; all products are obtained in yields of ca. 95%.^[919] Both the oxirane carbons in 2,3-anhydro-4,6-dideoxy- α -D-ribohexopyranoside undergo attack by methoxide.^[920] Both the naphthalene *anti*- and *syn*-1,2:3,4-dioxides undergo reaction with sodium methoxide at C1 and C4, usually in the *anti* mode.^[921] The oxyanion resulting from the ring opening of epoxide **179** by methoxide undergoes reaction with the proximate ethoxycarbonyl group, leading to the formation of the lactone **180** (Scheme 120).^[922]

Scheme 120 Synthesis of a Lactone by a Ring Opening–Ring Closure Reaction^[922]



Similarly, bicyclic^[923] or steroidal^[924] α,β -epoxy ketones undergo reaction with sodium methoxide to give α -methoxy- α,β -unsaturated ketones via a ring opening–elimination process. Formation of transient alkynyl, allenyl, or methylene epoxides is suggested to occur during the reaction of some chlorooxiranes with sodium methoxide.^[925]

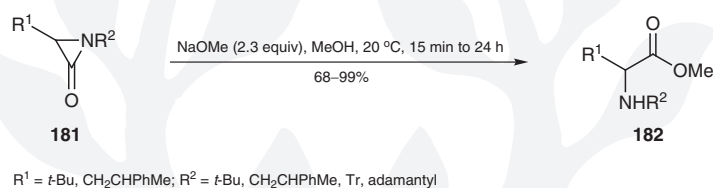
The reaction of alkoxides with thiiranes produces polymeric products, due to the high nucleophilicity of the S-anion. When the reaction of thiirane and alkoxides (or aryl-oxides), including sodium methoxide, is carried out with reactive electrophiles, namely

for references see p 1117

allyl or benzyl chloride, the corresponding 2-alkoxy- or 2-(aryloxy)ethyl allyl (or benzyl) sulfides are obtained in yields of 50–75%.^[926]

Unlike stilbene oxide, *trans*-2,3-diphenyl-1-(phenylsulfonyl)aziridine undergoes reaction with sodium methoxide to give ring-opened products at a higher rate than the *cis*-isomer.^[918] *cis*-2-Benzyl-3-phenyl-1-(phenylsulfonyl)aziridine undergoes ring opening with alkoxy anions in three ways: by attack at C2, at C3, or at the benzylic carbon; the particular pathway depends upon the basicity and size of the alkoxide as well as on the reaction conditions. Methoxide anion attacks the C2 and C3 positions; the latter attack prevails to give the substituted *threo*-2-(methoxyethyl)-*N*-sulfonylamine.^[927] α -Lactams **181** (aziridinones) with bulky groups on nitrogen and carbon undergo reaction with sodium methoxide to form methyl esters of α -amino acids **182**, in high yield (Scheme 121).^[928–930]

Scheme 121 Ring Opening of Substituted Aziridinones by Sodium Methoxide^[928]

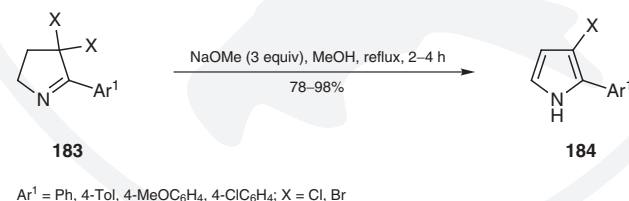


8.2.4.2.5

Method 5: Elimination Reactions

Sodium methoxide is a sufficiently strong base to initiate various kinds of eliminations.^[931] Depending on the amount of this base used and the structure of the products formed, further reactions are possible. Thus, 5,6-epoxy-5,6-dihydro- and 7,8-epoxy-7,8-dihydroisoquinolines are prepared by elimination of hydrogen bromide from the corresponding bromo(epoxy)tetrahydroquinolines.^[932] 2-Ethoxy-2*H*-pyran-6-carbonitrile derivatives, formed from 3-bromodihydropyrans by elimination, undergo electrocyclic valence tautomerizations which lead to methyl dienates; methoxide addition to the cyano group competes with the elimination.^[933] Formation of 5-methoxy- or 5,5-dimethoxy-4-methyl-1,5-dihydro-2*H*-pyrrol-2-ones, from *N*-substituted 4-methylpyrrolidin-2-ones carrying at least two chloro substituents at C3 and C6, is initiated by elimination of hydrogen chloride.^[934] 2-Aryl-3-chloro- or -3-bromopyrroles **184** are synthesized from 5-aryl-4,4-dihalo-3,4-dihydro-2*H*-pyrroles **183** using an excess of sodium methoxide in refluxing methanol (Scheme 122).^[935]

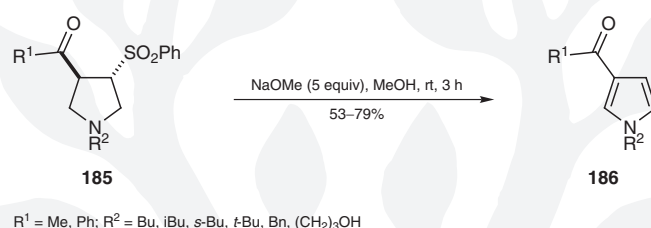
Scheme 122 2-Aryl-3-halopyrroles by Dehydrohalogenation of 5-Aryl-4,4-dihalo-3,4-dihydro-2*H*-pyrroles^[935]



Chlorination of 5-methyl- or 5-alkyl-3,4-dihydro-2*H*-pyrroles with a large excess of *N*-chlorosuccinimide leads to the formation of 4,4-dichloro-5-(trichloromethyl)- or 4,4-dichloro-5-(1,1-dichloroalkyl)-3,4-dihydro-2*H*-pyrroles, respectively. These penta- and tetrachlorinated pyrroles are easily transformed into 3-chloro-2-(trimethoxymethyl)- or 3-chloro-2-

(1,1-dimethoxyalkyl)pyrroles by an elimination–addition pathway when allowed to react with sodium methoxide. Their further treatment with aqueous hydrochloric acid gives 3-chloro-2-(methoxycarbonyl)- or 3-chloro-2-acylpyrroles; all steps of this procedure occur in high yield.^[936] Methoxide mediated dehydrohalogenation of α,γ,γ -trichloro- β -imino esters leads to the formation of methyl 3-chloroanthranilates.^[937] Benzotriazolyl enol trifluoromethanesulfonates, treated first with sodium methoxide and then with concentrated alcoholic hydrochloric acid, undergo an elimination–addition–hydrolysis reaction, giving methyl alkanoates via ethynyl- and (1-methoxyvinyl)benzotriazoles. In a separate synthesis, the latter compounds were isolated, often in high yield.^[938] Dehydrosulfonylation with concomitant oxidation by air is involved in the transformation of 1-substituted *trans*-3-acyl-4-(phenylsulfonyl)pyrrolidines **185** into 3-acyl-1-alkylpyrroles **186** (Scheme 123).^[939]

Scheme 123 3-Acyl-1-alkylpyrroles by Dehydrosulfonylation–Oxidation of Trisubstituted Pyrrolidines^[939]



Desilicohalogenation of the addition products of chlorine or bromine to (*Z*)- or (*E*)-1-(trimethylsilyl)hex-1-enes occurs with high stereoselectivity, affording (*E*)- or (*Z*)-1-halo-hexenes, respectively.^[940]

Sodium methoxide behaves both as a base and a nucleophile in a reaction with 2-methyl-3,4-dihydro-1*H*-2-benzoseleninium salts, giving a mixture of 2-[(methylselanyl)-methyl]-2-vinylbenzene (main product) and 2-(methoxymethyl)phenylethyl methyl selenide.^[941]

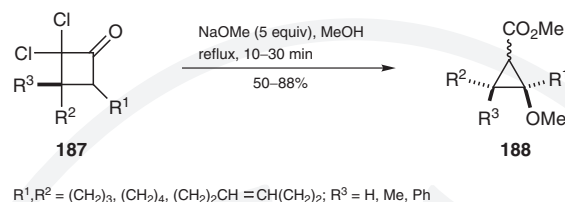
8.2.4.2.6 Method 6: Rearrangements

8.2.4.2.6.1 Variation 1: Favorskii and Related Rearrangements

The reaction of α -halogenated ketones possessing at least one hydrogen at an α' -carbon with a base leads to the formation of salts, esters, or amides of the rearranged carboxylic acids (Favorskii rearrangement^[942–944]). A similar process occurs with α,β -epoxy ketones. Application of sodium methoxide results in the formation of the corresponding methyl esters. At least two mechanistic pathways are possible, involving the formation of either a cyclopropanone or a dipolar intermediate. Nucleophilic substitution and addition to the carbonyl group of the basic/nucleophilic reagent may seriously compete with the Favorskii rearrangement.

In the case of cyclic halo ketones, the Favorskii reaction occurs with ring contraction, e.g. the synthesis of methyl cyclopentanecarboxylate from 2-chlorocyclohexanone and sodium methoxide.^[945] Similarly, adducts of halo ketenes with cyclopentadiene enter into Favorskii-type rearrangements to give methylbicyclo[3.1.0]hex-2-ene-6-carboxylates.^[706] In the case of 2,2-dichlorocyclobutanones **187** (adducts of dichloroketene with cycloalkenes), a simultaneous ring contraction and chlorine displacement take place, giving methyl 2-methoxycyclopropanecarboxylates **188** in 50–88% yield (Scheme 124).^[946,947]

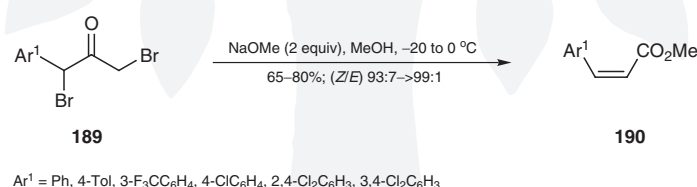
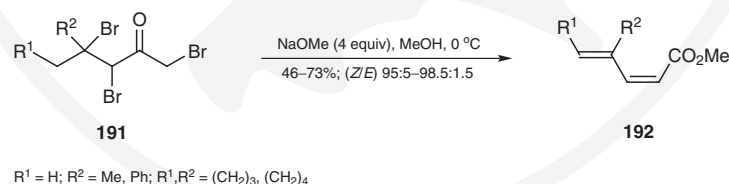
for references see p 1117

Scheme 124 Rearrangement of α,α -Dichlorocyclobutanones^[946]

The chlorohydrin derivative of (+)-carvone undergoes a stereoselective Favorskii process; the product is used for the preparation of (+)-dihydronepetalactone and (+)-iridomyrmecin.^[948] A vinylogous cyclic halo ketone, 4-chloroisophorone, gives Favorskii products but an S_N2' process with methoxide significantly competes and only the latter reaction is observed in the case of the analogous bromo ketone.^[949] 2,3-Epoxy cyclohexanones undergo nonstereoselective rearrangement, giving mixtures of the methyl esters of *cis*- and *trans*- γ -hydroxy acids as the main products.^[950]

Reaction of aliphatic α -bromo ketones takes place via the substituted cyclopropanones which, depending on the conditions, form one or two isomeric methyl esters by attack of methoxide on either one of the cyclopropanone carbons.^[951,952] A stereoselective rearrangement of 2-substituted *cis*-1-acetyl-1-chlorocyclohexanes takes place in 1,2-dimethoxyethane,^[953,954] but the reaction is nonstereoselective in methanol.^[953]

Favorskii rearrangement of α,α' -dibromo ketones mediated by methoxide anion leads to the formation of methyl esters of α,β -unsaturated carboxylic acids, e.g. methyl cycloundecene-1-carboxylate is obtained from 2,12-dibromocyclododecanone,^[955] and methyl (*Z*)-cinnamates **190** are synthesized from 1-aryl-1,3-dibromoacetones **189** (Scheme 125).^[956] 1,3,4-Tribromoalkanes **191** afford the corresponding methyl penta-2,4-dienoates **192** with high *Z* selectivity, accompanied by 4-methoxypentenoates as byproducts (Scheme 126).^[957]

Scheme 125 Stereoselective Synthesis of Methyl (*Z*)-Cinnamates by the Favorskii Rearrangement^[956]**Scheme 126** Stereoselective Synthesis of (*Z,Z*)-Penta-2,4-dienoates by the Favorskii Rearrangement^[957]

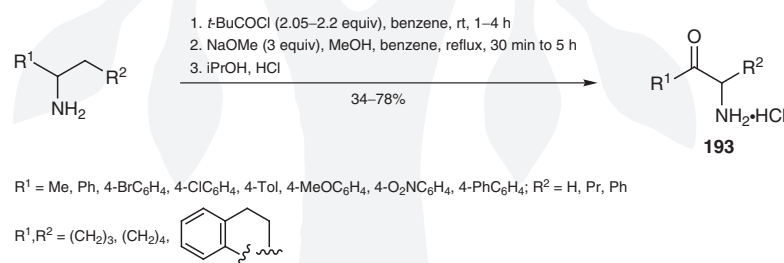
The sodium methoxide–methanol system induces a clean Favorskii transformation of primary dichloromethyl ketones into the corresponding esters;^[958] similar results are observed with secondary dichloromethyl ketones,^[958,959] but in this case, variable amounts of other products are also formed.^[958]

α -Halo (usually chloro) imines give, with sodium methoxide, the products of Favorskii rearrangement, but, depending upon the conditions and the structure of substrates, they are accompanied by products of side reactions, including nucleophilic substitution, dehydrochlorination, self-condensation, among others.^[942–944] Thus, *N*-alkyl- α -chloro- α -phenylketenimines with an excess of sodium methoxide in tetrahydrofuran afford the rearranged carboxylic imidates, in nearly quantitative yields.^[960] The *N*-isopropyl imine of *sym*-tetrachloroacetone gives rise to methyl *N*-isopropyl-3,3,3-trimethoxypropanimidate, by a rearrangement–elimination–Michael addition sequence. α -Bromoketenimines undergo predominantly dehydrobromination.^[960] Primary *N*-2-(1,1-dichloroalkylidene)anilines produce methyl *cis*-*N*-aryl- α,β -unsaturated imidates (by stereoselective rearrangement) and/or *N*-2-(1,1-dimethoxyalkylidene)anilines (by nucleophilic substitution), while the corresponding secondary anilines give mixtures of *cis*- and *trans*-imidates (by nonstereoselective rearrangement), dimethoxy derivatives, and/or *N*-2-(1,3-dimethoxyalkylidene)anilines (by solvolysis).^[961]

8.2.4.2.6.2

**Variation 2:
Neber Rearrangement**

Reaction of *N,N*-dichloroamines (synthesized by chlorination of primary amines with *tert*-butyl or sodium hypochlorite) with sodium methoxide, followed by treatment with hydrochloric acid, gives α -amino ketone hydrochlorides and is named the Neber rearrangement.^[962] The reaction is usually carried out by addition of sodium methoxide (solid or methanolic solution) to a solution of the dichloroamine in refluxing alcohol or benzene. The process is exemplified by the preparation of phenacylamine hydrochloride from α -phenethylamine^[963,964] and, similarly, of other α -amino ketone salts **193** (Scheme 127).^[963,964]

Scheme 127 α -Amino Ketone Hydrochlorides by Neber Rearrangement^[963,964]

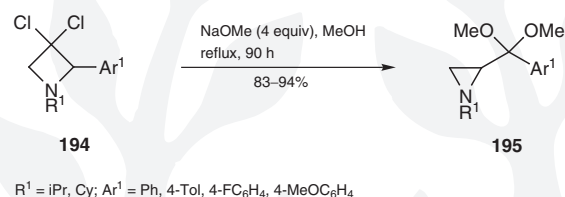
The Neber rearrangement occurs by initial generation of a transient azirine, which then gives the corresponding methoxyaziridine which subsequently undergoes rearrangement into the amino ketone hydrochloride upon treatment with hydrochloric acid.^[964] The intermediate methyl ketal of the α -amino ketone may be isolated in the reaction of 3-aminopentane with sodium hypochlorite followed by methoxide.^[965] Amidoximesulfonates treated with sodium methoxide give 1*H*-azirin-2-amines, which are isolated in high yields. Arylamino carbonyl-substituted azirines undergo rearrangement into 2-aminoimidazol-5-ones when treated with methoxide.^[966] Dimethylhydrazone quaternary salts may be used in the Neber rearrangement, but the reaction of 2-phenylcyclohexanone trimethylhydrazone iodide, carried out at low temperature, does not give the expected product.^[967]

for references see p 1117

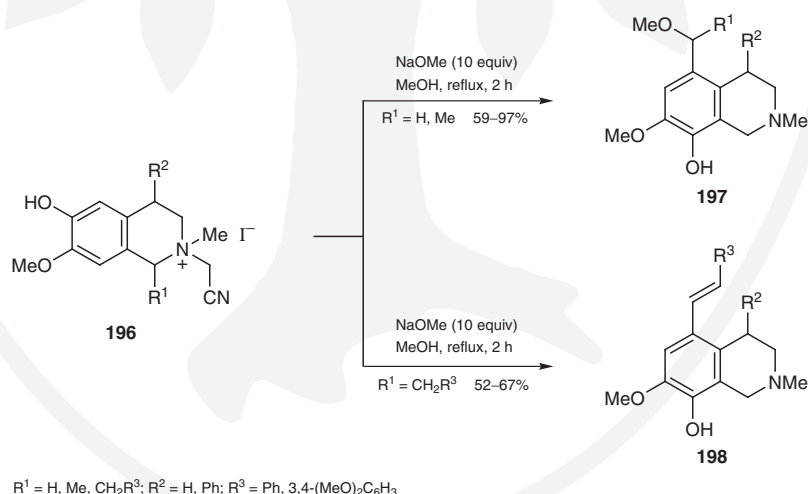
8.2.4.2.6.3

Variation 3:
Other Rearrangements

1-Alkyl-2-aryl-3,3-dichloroazetidines **194** undergo reaction with sodium methoxide with ring contraction to give 1-alkyl-2-[(α,α -dimethoxy)benzyl]aziridines **195** (Duhamel ring contraction of heterocyclic enamines^[968]). This process is initiated by the formation of 1,2-dihydroazetes, followed by addition of methoxide and subsequent generation of the bicyclic aziridinium intermediate, which gives the product by ring opening (Scheme 128).^[969]

Scheme 128 Rearrangement of 2-Aryl-3,3-dichloroazetidines^[969]

The reaction of optically active (*R*)-3-*tert*-butylcyclobutane-1,2-dione with sodium methoxide gives methyl (1*R*,2*R*)-2-*tert*-butyl-1-hydroxycyclopropanecarboxylate (yield 91%, 95% de).^[970] α -(Methylsulfanyl)- or α -(phenylsulfanyl)chloromethyl ketones treated with sodium methoxide in methanol give α -methoxy- α -(methylsulfanyl) or α -methoxy- α -(phenylsulfanyl) aldehydes in yields of 80–95%.^[971] Deprotonation of the 6-hydroxy group in 1,2,3,4-tetrahydroisoquinolinium salts **196** leads to C1–N bond scission which is followed by recyclization, via formation of an intermediate imminium ion, to give 8-hydroxy-5-(methoxymethyl) derivatives **197** or **198** (Scheme 129). This approach is used in the synthesis of the alkaloid litebamine.^[972]

Scheme 129 Rearrangement of 2-(Cyanomethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodides^[972]**2-[Dimethoxy(phenyl)methyl]-1-isopropylaziridine (195, $Ar^1 = Ph$; $R^1 = iPr$);****Typical Procedure:**^[969]

To 3,3-dichloro-1-isopropyl-2-phenylazetidine (1.0 g, 4.1 mmol) was added a 2 M soln of NaOMe (16.4 mmol) in MeOH (8.2 mL). The reaction was heated at reflux for 90 h, cooled,

and the solvent was removed. The residue was taken up in H₂O and extracted with CH₂Cl₂ (3 ×). The combined organic extracts were dried (MgSO₄) and evaporated to give the crude product (<2% of impurities according to NMR data); yield: 0.89 g (92%). If necessary, the crude product was further purified by flash chromatography (CH₂Cl₂/MeOH 19:1).

8.2.4.2.7

**Methods 7:
Other Methods**

Butyl- and phenylmagnesium methoxide are prepared by the reaction of the corresponding bromomagnesium compounds with sodium methoxide in tetrahydrofuran.^[973] Sodium borohydride in the presence of sodium methoxide effects reduction of 1-substituted 4-nitroimidazoles to imidazolidin-4-one oximes, and nitropyrazoles and nitropyridines into their respective azoxy compounds.^[974] The reaction of pteridine derivatives with α -chloromethyl sulfones or haloforms carried out in the presence of sodium methoxide in liquid ammonia^[975] affords products of vicarious nucleophilic substitution.^[154–157] The reactions of 1-aryl^[976] or 1,2,3-triarylbenzo[*b*]thiophenium salts^[977] with methoxide occur by fission of the S⁺–C2 bond of the thiophenium ring, resulting in the formation of 2-methoxy-1-(2-phenylsulfanyl)phenylethenes,^[976,977] -allenes, or -alkynes.^[976] In the case of the latter salts, the reaction takes place with complete retention of configuration, giving *Z*-ethenes.^[977] Hydroboration of alkenes in conjunction with iodination^[978] or bromination^[979] in the presence of sodium methoxide provides a convenient method for the preparation of iodo- or bromoalkenes, respectively. These processes take place contrary to the Markovnikov rule, and sodium methoxide appears to be a superior base compared to sodium hydroxide in terms of improved yields.^[978,979]

8.2.4.3

Sodium Ethoxide

Sodium ethoxide is a hygroscopic solid, prepared by dissolving metallic sodium in anhydrous ethanol.^[616,980] The solid base and its ethanolic solutions are commercially available; for the preparation and reactions of alumina-impregnated sodium ethoxide, see Section 8.2.4.3.1.1. It is commonly applied for the generation of carbanions as well as heteroanions and for the introduction of the ethoxy group into organic compounds. The reactions of sodium ethoxide resemble those of sodium methoxide.

8.2.4.3.1

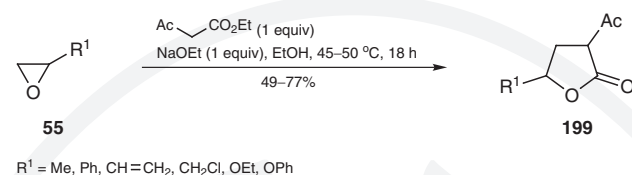
**Method 1:
Generation and Reactions of Carbanions**

8.2.4.3.1.1

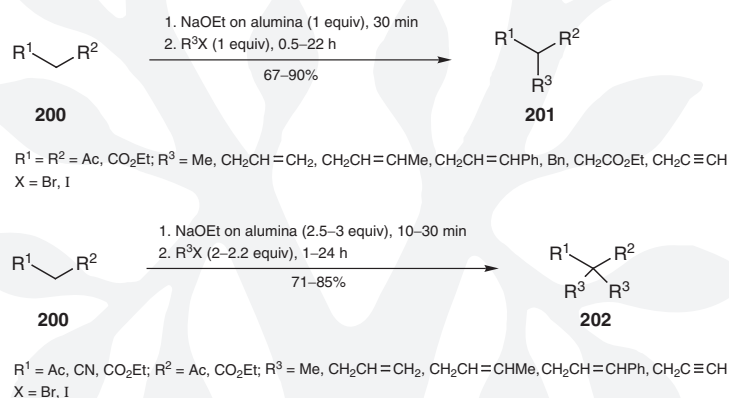
**Variation 1:
Reactions of Carbanions with Alkylating Agents**

Sodium ethoxide is a suitable base to carry out the alkylation of the ethyl esters of β -oxo or β -cyano acids and 1,3-dicarbonyl compounds.^[617] Ethyl malonate undergoes successful monoalkylation with bromomethane,^[981] benzyl chloride,^[982] 3-chlorocyclopentene^[983] butyl bromide,^[984] and *sec*-butyl bromide;^[985] the process is more sluggish with ethyl fluoromalonate.^[619] A significant feature of these processes is their selectivity in terms of monoalkylation. Similarly, ethyl acetoacetate undergoes alkylation with butyl bromide,^[986] while its reaction with monosubstituted oxiranes **55** leads to the formation of 5-substituted 3-acetyldihydrofuran-2(3*H*)-ones **199** (Scheme 130).^[987]

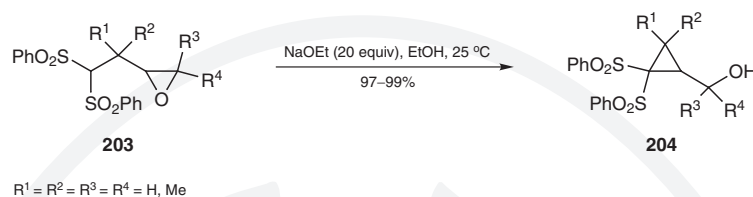
for references see p 1117

Scheme 130 5-Substituted 3-Acetyldihydrofuran-2(3*H*)-ones from Epoxides and Ethyl Acetoacetate^[987]

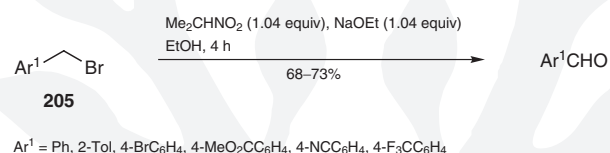
Attempted alkylation of 2-(ethoxycarbonyl)cycloalkanones using sodium ethoxide as the base results in total or partial ring cleavage in the case of five-^[988] or six-membered^[988,989] derivatives. Only a seven-membered ketone undergoes alkylation without cleavage.^[988] A highly efficient methodology for mono- or dialkylation of aliphatic and alicyclic 1,3-dicarbonyl compounds **200** with reactive alkylating agents to give **201** or **202** consists of the use of alumina impregnated with sodium ethoxide (Scheme 131).^[990,991]

Scheme 131 Solvent-Free Mono- or Dialkylation of Methylene CH Acids with Alumina Impregnated with Sodium Ethoxide^[990,991]

Diethyl cyclobutane-1,1-dicarboxylate is prepared by alkylation of diethyl malonate either with 1,3-dibromo-^[992] or 1-bromo-3-chloropropane^[993] and is isolated in the latter case in moderate yields of 53–55%. Cyclization of diethyl 2,3-dibromopropylmalonate gives the corresponding bromomethyl-substituted cyclopropane in 44% yield.^[994] Ethyl (1-ethylpropylidene)cynoacetate affords ethyl (1-ethylpropenyl)methylcyanoacetate by α -methylation.^[995] Bis-monobenylation of diethyl adipate takes place by a repeated cyclization–alkylation–ring opening process.^[996] Sodium ethoxide is too weak a base to be useful in the direct alkylation of the esters of monocarboxylic acids, but an intramolecular reaction leading to substituted ethyl cyclopropanecarboxylates is possible.^[620] Depending upon the length of the alkyl chain, intramolecular reactions of carbanions from epoxy-alkyl 1,1-bis(sulfones) result in the formation of 2-(hydroxymethyl)-1,1-bis(sulfonyl)cycloalkanes and/or 2,2-bis(sulfonyl)cycloalkanols.^[997] On the other hand, γ,δ -epoxy bis(sulfones) **203** afford the corresponding (hydroxymethyl)bis(sulfonyl)cyclopropanes **204** in nearly quantitative yields (Scheme 132).^[998]

Scheme 132 *gem*-(Phenylsulfonyl)cyclopropanes from γ,δ -Epoxy Sulfones^[998]

Cyclization of bis(sulfonyl)-stabilized carbanions by intramolecular displacement of the halide anion^[999] or aryl(ethyl)sulfonium ion^[1000] leads to the formation of bis(sulfonyl)cycloalkanes in high yield. A general and interesting method for the synthesis of aromatic aldehydes consists of the reaction of the 2-nitropropane anion with benzyl halides **205**,^[1001,1002] e.g. 2-methylbenzaldehyde is prepared from the reaction of *o*-xylyl bromide and 2-nitropropane in the presence of sodium ethoxide in yields of 68–73% (Scheme 133).^[1003]

Scheme 133 Aromatic Aldehydes from Benzyl Bromides and 2-Nitropropane^[1002,1003]

O-Tosylhydroximates react with an excess of this base, affording α -amino ortho esters by cyclization to azirines, addition of ethoxide, and ring opening.^[1004] The preparation of 9-ethylfluorene is carried out by heating fluorene and sodium ethoxide to a temperature above 200 °C in a steel bomb (84% yield).^[630]

Ethyl 2,2-Bis(but-2-enyl)-3-oxobutanoate (202, $R^1 = \text{Ac}$; $R^2 = \text{CO}_2\text{Et}$; $R^3 = \text{CH}_2\text{CH}=\text{CHMe}$);

Typical Procedure:^[991]

To a soln of NaOEt (1.02 g, 15 mmol) in dry EtOH, neutral alumina (9.75 g) (activated by heating at 180 °C under reduced pressure for 2 h followed by cooling and storage under argon) was added with stirring. Evaporation of the solvent under reduced pressure gave an easy flowing powder. Ethyl acetoacetate (0.65 g, 5 mmol) was added dropwise to the NaOEt on alumina under N_2 , with vigorous stirring. Stirring was continued for 10 min at rt; then the mixture was cooled in ice and 1-bromobut-2-ene (1.49 g, 11 mmol) was added dropwise, with stirring. The mixture was then allowed to attain rt and left at rt with intermittent stirring (to ensure complete mixing) until completion of the reaction (monitored with TLC). The product was extracted from the solid mass by filtration chromatography (neutral alumina, CH_2Cl_2). The residue, after evaporation, was purified by column chromatography (neutral alumina, EtOAc/petroleum ether 3:97) to give the product as a colorless oil; yield: 0.97 g (81%).

8.2.4.3.1.2

Variation 2:

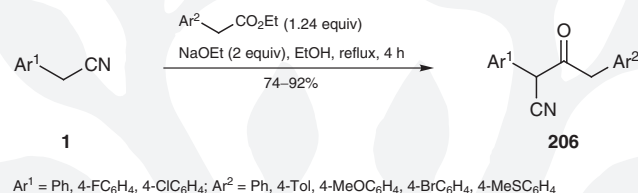
Reactions of Carbanions with Carbonyl Compounds

Depending upon the structure of the CH acid and the carbonyl compound, their reactions carried out in the presence of sodium ethoxide afford a variety of important compounds.^[631–633] The reactions of esters or ketones with ethyl formate give the rather labile hydroxymethylene (formyl) derivatives,^[632] which are used directly for the preparation of carbocyclic^[1005] or heterocyclic^[1006] products. The condensation of esters^[1007–1011] or ace-

for references see p 1117

tone^[1012] with ethyl oxalate leads to the formation of ethoxalyl derivatives which undergo facile loss of carbon monoxide when heated under reduced pressure.^[1009,1010] This simple methodology allows the preparation of diethyl phenyl^[1009] or alkylmalonate.^[1010] Acylation of ketones with esters affords 1,3-dicarbonyl compounds,^[632,633] e.g. the synthesis of diacetyl^[1013] or dibenzoylmethane^[1014] from the reaction of acetone with ethyl acetate or acetophenone with ethyl benzoate, respectively, and sodium ethoxide. Autocondensation of esters leads to β -oxo esters (Claisen condensation).^[631] The reaction of methylene (e.g., phenylacetonitrile^[1015]) or methyl CH acids (e.g., ethyl acetate^[1016]) with aromatic aldehydes gives α,β -unsaturated products, usually in high yield.^[200,201] Diethyl carbonate is a suitable reagent for introduction of the ethoxycarbonyl group, e.g. conversion of phenylacetonitrile into ethyl phenylcyanoacetate.^[1017] Similarly, acylation of arylacetonitriles **1** with ethyl arylacetates affords 1,3-diaryl-1-cyanoacetones **206** (Scheme 134),^[1018] which are further transformed into 1,3-diarylacetones.^[1019]

Scheme 134 Acylation of Arylacetonitriles with Ethyl Arylacetates^[1018]



Replacement of the acetyl group with the benzoyl group occurs when ethyl acetoacetate undergoes reaction with ethyl benzoate and sodium ethoxide.^[1020] The self-condensation of diethyl succinate gives 2,5-bis(ethoxycarbonyl)cyclohexane-1,4-dione, which is then thermally converted into cyclohexane-1,4-dione.^[1021]

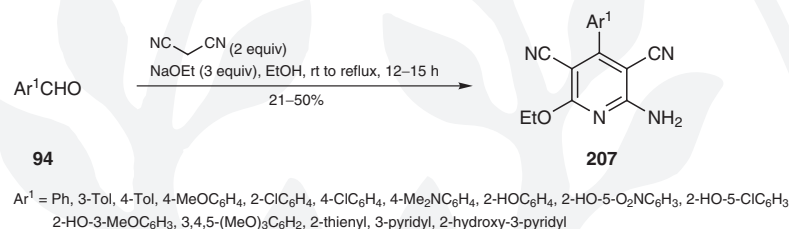
The reaction of diethyl succinate with aldehydes or ketones leading to monosodium salts of ethyl alkylidenesuccinates (substituted itakonic acids), often promoted by sodium ethoxide, is named the Stobbe condensation. The products of the Stobbe condensation are useful for the preparation of γ -lactones, naphthols, cyclic ketones, among other compounds.^[1022] These processes are exemplified by the reaction of 2-acetylnaphthalene with diethyl succinate and sodium ethoxide and the further transformation of the initial Stobbe product into γ -methyl- γ -(2-naphthyl)butyrolactone.^[1023]

When ethyl esters of α -chlorocarboxylic acids are allowed to react with carbonyl compounds and sodium ethoxide, the intermediate halohydrin anions undergo cyclization to give substituted ethyl glycidates (Darzens condensation).^[227] Thus, reaction of 2-[(dimethylamino)methyl]cyclohexanone with ethyl chloroacetate carried out with this base affords 4-[(dimethylamino)methyl]-2-(ethoxycarbonyl)-1-oxaspiro[2.5]octane in yields of 43–57%.^[1024]

The intramolecular reaction of anions from esters with the carbonyl carbon of another ester group leads to the formation of cyclic ketones that are α -substituted with the alkoxycarbonyl group (Dieckmann condensation^[633,1025]). This process is carried out in the presence of sodium ethoxide, usually in an aprotic solvent, and allows the synthesis of 5-(ethoxycarbonyl)-2-methylcyclopentanone,^[1026] as well as of cyclic sulfur^[786] and nitrogen^[1027] oxo esters. 2-Alkyl-5-(ethoxycarbonyl)cyclopentanones are also obtained from 2,2-disubstituted ketones and sodium ethoxide by a tandem ring opening–Dieckmann cyclization.^[1026] A similar ring-closure reaction is used to prepare ethyl 4-hydroxy-2H-1,2-benzoxazine-3-carboxylate 1,1-dioxide,^[830] the corresponding 3-carboxamides,^[831] and 4-hydroxy-3-(2-methoxyphenyl)-1,5- and -1,8-naphthyridin-2(1H)-ones.^[798] Condensation of the anion from a β -oxo ester with the carbonyl group located in the same molecule leads to the formation of ethyl 5,5-dimethyl-2-oxo-2,3,3a,4,5,6-hexahydropentalene-1-carboxylate in 84% yield.^[851]

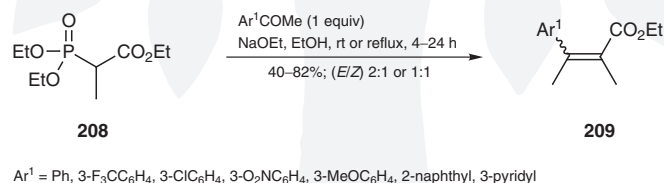
The addition product from the reaction of nitromethane and cyclohexanone, 1-(nitromethyl)cyclohexanol, is sufficiently stable to be isolated, but it is used directly for the preparation of cycloheptanone.^[1028] Stepwise or one-pot reactions of ethyl cyanoacetate with α -hydroxy ketones and aromatic aldehydes, carried out under focused microwave irradiation, give 5,5-dialkyl-4-(2-arylvinyl)-2-oxo-2,5-dihydrofuran-3-carbonitriles.^[1029] A multistep reaction of malononitrile with aldehydes **94**, mediated by sodium ethoxide, is used for the preparation of 4-substituted 2-amino-6-ethoxypyridine-3,5-dicarbonitriles **207** (Scheme 135).^[1030,1031] Aromatic aldehydes afford these products in 30–50% yield,^[1030,1031] while aliphatic aldehydes give lower yields.^[1030]

Scheme 135 Synthesis of 4-Substituted 2-Amino-6-ethoxypyridine-3,5-dicarbonitriles^[1030,1031]



The preparation of alkenes by the reaction of carbonyl compounds with phosphonium salts (Wittig reaction^[408–410]) or diethyl alkylphosphonates (Horner–Wadsworth–Emmons reaction^[244,245]) is conveniently carried out by means of sodium ethoxide. 2-(2-Arylviny)-1-methylimidazoles,^[1032] stilbenes and cinnamic acid derivatives,^[1033] 1-phenylcyclopentene^[1034] (by an intramolecular reaction), and *para,para'*-disubstituted α,ω -diphenylpolyenes^[1035] are prepared by the Wittig reaction. The Horner–Wadsworth–Emmons reaction of ethyl 2-(diethoxyphosphoryl)propanoate **208** with aryl methyl ketones is utilized for synthesis of trisubstituted ethyl acrylates **209** (Scheme 136).^[1036]

Scheme 136 Synthesis of Trisubstituted Acrylates by the Horner–Wadsworth–Emmons Reaction^[1036]



2-Amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**207**, Ar¹ = Ph);

Typical Procedure:^[1030]

To a soln of NaOEt (4.08 g, 0.06 mol) in abs EtOH (50 mL) was added a soln of malonitrile (2.64 g, 0.04 mol) in EtOH (20 mL), and then PhCHO (2.12 g, 2.0 mL, 0.02 mol) was added at once. The mixture was refluxed for 3 h and then allowed to stand for 12 h at rt. The mixture was poured into cool H₂O (300 mL). The crude product was separated by filtration and recrystallized; yield: 2.64 g (50%); mp 238–239 °C (CHCl₃).

8.2.4.3.1.3

Variation 3:

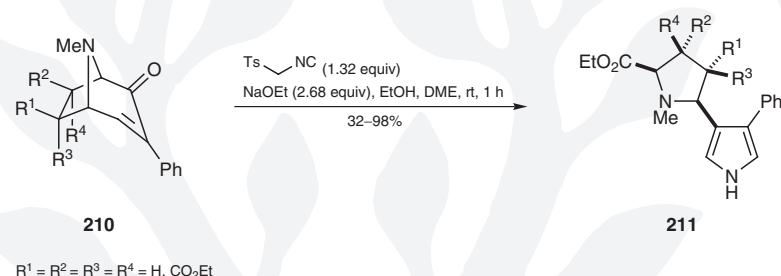
Reactions of Carbanions with Electrophilic Alkenes

Electrophilic alkenes easily undergo addition of carbanions, but, depending upon the structure of the substrates, this step is often followed by further reactions.^[16,256–258,647] Thus, sodium ethoxide promotes simple addition of nitroethane to 4-methylpent-3-en-2-one,^[1037] but reactions using an excess of aryl methyl ketones with (*E*)-dibenzoyl-

for references see p 1117

ethene,^[1038] or ethyl acetoacetate with cyclohexenone^[649] or cycloheptenone,^[1039] lead to the formation of 4-aryl-2,3,5-tribenzoyl-1-phenylcyclohexanols or ethyl 5-hydroxy-3-oxobicyclo[3.3.1]nonane-2-carboxylate and ethyl 1-ethoxy-8-oxobicyclo[4.3.1]decane-7-carboxylate, respectively. The reaction of cyclohexanone enolate with (*E*)- or (*Z*)-methyl styryl sulfone results in the formation of a mixture of derivatives of octahydro-1*H*-2-benzothiopyran 2,2-dioxide and 3,4,5,6,7,8-hexahydro-1*H*-2-benzothiopyran 2,2-dioxide.^[1040] On the other hand, the α -cyano carbanions from 2-amino-4,5-dihydrofuran-3-carbonitrile derivatives give easily isolable adducts from the reactions of α,β -unsaturated aldehydes with ketones.^[855] A multistep reaction of the tosylmethyl isocyanide anion with 3-phenyltrop-3-en-2-ones **210** affords 3-phenyl-4-pyrrolidin-2-ylpyrroles **211** in 32–98% yield (Scheme 137).^[1041]

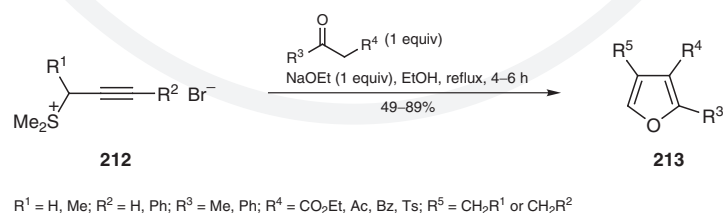
Scheme 137 3-Phenyl-4-pyrrolidin-2-ylpyrroles from Tosylmethyl Isocyanide and 3-Phenyltrop-3-en-2-ones^[1041]



The reaction of diethyl malonate with mesityl oxide and sodium ethoxide gives the enolate of cyclohexane-1,3-dione, which, when treated with potassium hydroxide, affords (after acidification) 5,5-dimethylcyclohexane-1,3-dione (dimedone) in good yield.^[1042] The first step of a useful synthesis of substituted 3-cyano-2-ethoxypyridines consists of the Michael addition of the malononitrile anion to chalcones,^[652] 3-cinnamoyltropolones,^[653] 2-arylidene-1-tetralones,^[651] or 2,5-diarylidene-cyclopentanones.^[1043]

2-Methylhepta-2,5-dien-4-one undergoes addition of 1 equivalent of diethyl malonate to the less-substituted double bond, but the adduct does not undergo cyclization under a variety of conditions. Other CH acids, in reactions with divinyl ketones, give the corresponding derivatives of cyclohexanone by a one- or two-step process.^[1044] Double Michael reaction of indane-1,3-dione and cyclohexane-1,3-dione with 1,5-disubstituted pentadien-3-ones, carried out with sodium ethoxide, gives *cis*- and/or *trans*-spiranes.^[1045] 1-(Arylalkylidene)cyanoacetates undergo addition of cyanoacetamide anion to form β -alkyl- β -aryl- α,α' -dicyanoglutarimides in high yield.^[1046,1047] Dimethyl(propargyl)sulfonium salts **212** undergo reaction with 1,3-dicarbonyl compounds or β -oxo sulfones in the presence of sodium ethoxide to give 2,3,4-trisubstituted furans **213** (Scheme 138).^[1048,1049] The process starts with the addition of the enolate anion to the β -carbon of an allenyl bond resulting from an alkyne–allene rearrangement.^[1048]

Scheme 138 2,3,4-Trisubstituted Furans from Sulfonium Salts and Methylene CH Acids^[1048,1049]



The intermediate anion resulting from the addition of diethyl methylmalonate enolate to 2-chloroacrylonitrile gives, in reaction with 1,3-dinitrobenzene, the product of a vicarious nucleophilic substitution^[154–157] in low yield (20%), together with a piperidinedione derivative (30%).^[894]

3-Acetyl-2,4-dimethylfuran (213, R³ = R⁵ = Me; R⁴ = Ac); Typical Procedure:^[1048]

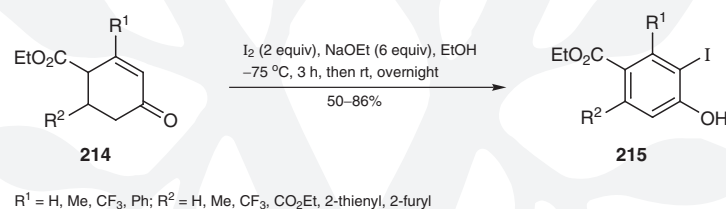
A soln of dimethyl(prop-2-ynyl)sulfonium bromide (1.67 g, 10 mmol) in EtOH (110 mL) was treated with a soln of pentane-2,4-dione (1.0 g, 10 mmol) and NaOEt (0.68 g, 10 mmol) in EtOH (100 mL). The mixture was refluxed for 4 h, EtOH was distilled off, the residue was treated with Et₂O, the suspension was filtered, the solvent was removed by distillation, and the residue was distilled under reduced pressure to give the product: yield: 1.25 g (89%); bp 82–85 °C/11 Torr.

8.2.4.3.1.4

**Variation 4:
Reactions of Carbanions with Other Electrophiles**

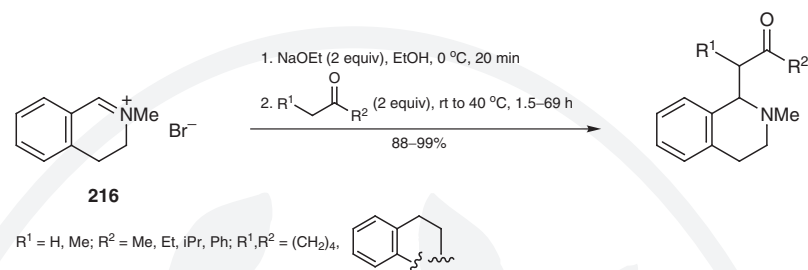
Both 3- and 5-substituted 4-(ethoxycarbonyl)cyclohex-2-enones **214** give 2-iodophenols **215** when treated with an excess of sodium ethoxide and 2 equivalents of iodine (Scheme 139).^[1050]

Scheme 139 2-Iodophenols from 4-(Ethoxycarbonyl)cyclohexen-2-ones^[1050]



α -Ethoxylation of ethyl arylacetates is realized by their reaction with sodium ethoxide and (diacetoxyiodo)benzene. Intermediates in this process are esters α -substituted with an iodine(III) derivative.^[1051] Sodium ethoxide induces the Thorpe reaction,^[633,1025,1052] i.e. cyclization or dimerization of nitriles (e.g., 2-cyanobenzyl cyanide^[1053]) or of rarely encountered *N*-alkylcyanoacetamides.^[1054] The reaction of adiponitrile with sodium ethoxide and ethyl carbonate affords 2-[(ethoxycarbonyl)amino]cyclopentenecarbonitrile.^[1055] Intramolecular addition of the carbanions derived from 2-phenyl-1,3-dicarbonyl compounds to the imine functional group located at the *ortho* position affords substituted dihydroindoles.^[1056] An adduct of the ethyl cyanoacetate anion with carbonyl sulfide undergoes S-alkylation, then O-methylation (with diazomethane), yielding ethyl β -(alkylsulfanyl)- β -(methoxyethylidene)cyanoacetates.^[1057] Anions from (arylsulfonyl)acetonitriles undergo reaction with aryl isothiocyanates to form substituted cyanothioacetamides; the latter give ethyl 3,5-diamino-4-(arylsulfonyl)thiophene-2-carboxylates by reaction with chloroacetic acid.^[1058] 2-Methyl-3,4-dihydroisoquinolinium bromide (**216**) undergoes addition to enolate anions in yields of 88–99% (Scheme 140).^[1059]

for references see p 1117

Scheme 140 Reactions of Dihydroisoquinolinium Bromide with Carbonyl Compounds^[1059]

Ethyl 4-Hydroxy-5-iodo-2-(trifluoromethyl)benzoate (215, $\text{R}^1 = \text{H}; \text{R}^2 = \text{CF}_3$);

Typical Procedure:^[1050]

To a soln of NaOEt (10.21 g, 0.15 mol) in EtOH (80 mL) at -78°C was added ester **214** ($\text{R}^1 = \text{H}; \text{R}^2 = \text{CF}_3$; 6.0 g, 0.025 mol). After 15 min, I_2 (12.7 g, 0.05 mol) was added in small portions and the mixture was stirred at -78°C for 3 h and at rt overnight; it was then acidified with 5% aq HCl, the solvent was evaporated, and the residue was dissolved in $\text{H}_2\text{O}/\text{EtOAc}$ (1:1). The organic layer was separated, washed with sat. $\text{Na}_2\text{S}_2\text{O}_3$, dried (MgSO_4), and evaporated. The crude product was purified by preparative LC (EtOAc/hexanes 1:4) to give a colorless solid; yield: 7.75 g (86%); mp $136\text{--}138^\circ\text{C}$.

8.2.4.3.2

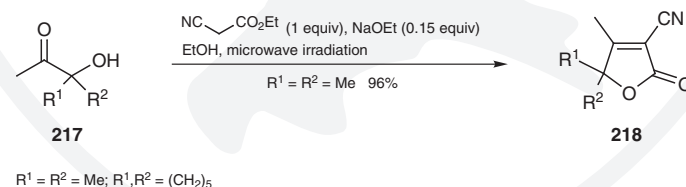
Method 2:
Generation and Reactions of Heteroanions

8.2.4.3.2.1

Variation 1:
Reactions of O-Anions

The majority of alcohols are less acidic than ethanol;^[1060] therefore their equilibration with sodium ethoxide does not lead to the formation of alkoxides in significant concentration. In spite of this, sodium ethoxide is used for the generation of alkoxides, which undergo further reactions. The equilibrium reaction of sodium ethoxide with phenols is shifted to the right, producing phenolates in high concentration.^[1060] Despite such a favorable situation, phenols are usually alkylated in the presence of alkali metal hydroxides or carbonates and not sodium ethoxide.

Sodium ethoxide mediated transesterification of ethyl cyanoacetate with α -hydroxy ketones **217** comprises the first step in the synthesis of 2-oxo-2,5-dihydrofuran-3-carbonitriles **218**, carried out under focused microwave irradiation (Scheme 141).^[1029]

Scheme 141 2-Oxo-2,5-dihydrofuran-3-carbonitriles from Ethyl Cyanoacetate and α -Hydroxy Ketones^[1029]

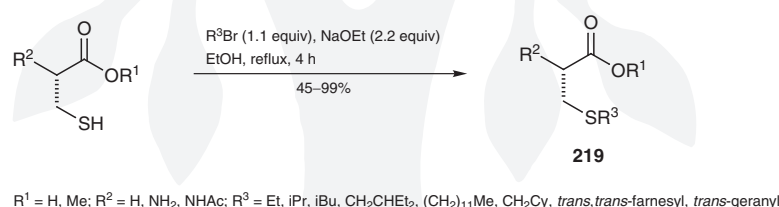
The O-anion from 1-butyl-3-(phenylselenonyl)cyclohex-2-en-1-ol undergoes fragmentation with the formation of 1-ethoxydec-1-en-6-one (*E/Z* 40:60) in 84% yield.^[665] 2',6'-Dihalo-2-hydroxybenzophenones undergo ring closure with replacement of the halogen, to give 1-ethoxyxanthenes. These products are sometimes accompanied by 1-haloxanthenes.^[668] O-Alkylation of acetone oxime with ethyl 2-bromopropionate leads to the formation of ethyl 2-(isopropylideneaminoxy)propanoate in 55–59% yield.^[1061]

4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-carbonitrile (218, R¹ = R² = Me);**Typical Procedure:**^[1029]

3-Hydroxy-3-methylbutan-2-one (0.31 g, 3 mmol) and ethyl cyanoacetate (0.34 g, 3 mmol) were added simultaneously to a soln of NaOEt (31 mg, 0.45 mmol) in EtOH (0.25 mL). The mixture was then irradiated by a focused microwave in a Pyrex tube (internal diameter 10 mm) at 20 W for 10 min. The solvent was removed under reduced pressure, and the residue was acidified by 18% aq HCl (0.6 mL) and the whole was extracted with Et₂O (3 × 7.5 mL). The organic phases were washed with brine, dried (MgSO₄), and the solvent was removed under reduced pressure to give an oil, which was crystallized (EtOH) to give the product; yield: 0.44 g (96%).

**8.2.4.3.2.2 Variation 2:
Reactions of S-Anions**

Generally, SH acids undergo quantitative deprotonation with sodium ethoxide, giving the highly nucleophilic S-anions, which may be readily alkylated, usually in high yield. Thus, using ethoxide as the base, benzenethiol undergoes alkylation with excess 1,2-dibromoethane, affording 2-bromoethyl phenyl sulfide which, without isolation, is converted into phenyl vinyl sulfide.^[1062,1063] The same reaction carried out with 4-methylbenzenethiol does not give the corresponding vinyl sulfide, but instead 2-ethoxyethyl 4-tolyl sulfide is produced quantitatively.^[1063] To overcome this difficulty, 2-chloroethanol is used as the alkylating agent, resulting in successful alkylation of 4-methylbenzenethiol; the crude product serves for the preparation of 4-tolyl vinyl sulfide.^[1063] The reaction of ethane-1,2-dithiol with 1,2-dibromoethane and sodium ethoxide affords 1,4-dithiane in 55–60% yield.^[1064] The same base is used for S-alkylation of *N*-acetyl-L-cysteine, cysteine methyl ester, or 3-sulfanylpropanoic acids with alkyl bromides (Scheme 142).^[1065]

Scheme 142 S-Alkylation of Cysteine Derivatives^[1065]***N*-Acetyl-S-isobutyl-L-cysteine (219, R¹ = H; R² = NHAc; R³ = *i*Bu); Typical Procedure:**^[1065]

Freshly cut Na (0.51 g, 22 mmol) was dissolved in anhyd EtOH (50 mL) under an atmosphere of N₂. To the soln was added *N*-acetyl-L-cysteine (1.63 g, 10 mmol) followed by 1-bromo-2-methylpropane (1.51 g, 11 mmol) and the mixture was heated at reflux for 4 h, during which time a colorless precipitate was formed. After cooling, the reaction was quenched with a small amount of H₂O, the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The soln was washed with 1 M HCl, then brine, dried (MgSO₄), and the solvent was removed under reduced pressure to give the product as a colorless solid; yield: 1.62 g (74%).

**8.2.4.3.2.3 Variation 3:
Reactions of N-Anions**

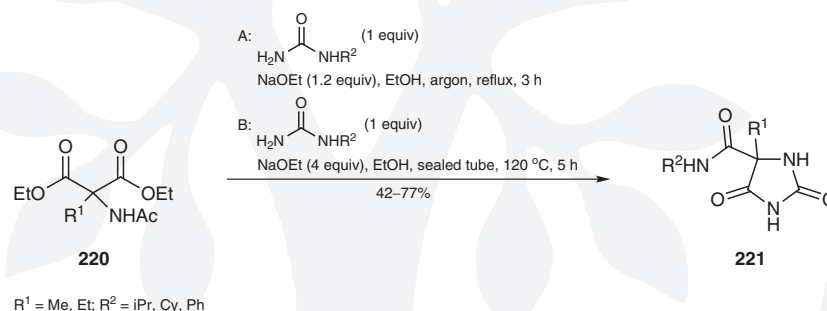
Compounds possessing the amine moiety connected to an electron-withdrawing group (cyano, acyl, sulfonyl, etc.) form N-anions upon treatment with sodium ethoxide; however, simple aliphatic or aromatic amines are too weak NH acids to generate the corresponding amide anions with this base. Despite this, it is observed that the reproducibility and

for references see p 1117

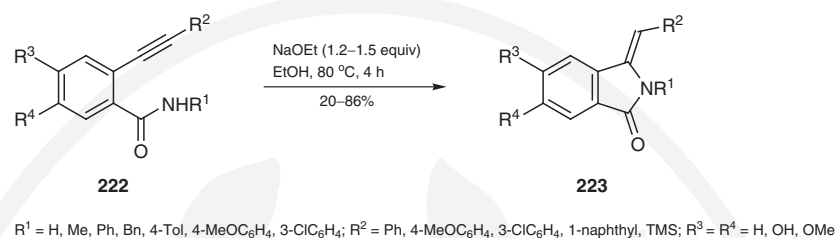
yields of the N-alkylation of a ribofuranosylamine salt with a derivative of chloropyrimidinone are improved when the process is carried out with sodium ethoxide in ethanol.^[1066] The reaction of cyanamide and sodium ethoxide with (ethoxymethylene)-malononitrile leads to the formation of the 2-cyano-3-(cyanoamino)propenenitrile sodium salt (95% yield), which is used for preparation of 4-amino-2-halopyrimidine-5-carbonitriles.^[784] A wide range of nitrogen heterocycles is synthesized from suitable substrates and this base via transient N-anions. Thus, substituted pyrimidines result from the condensation of thiourea or guanidine nitrate with α -aroylketene S,S-diacetals,^[673] cyanamide with 3-aryl-2-cyano-3-methoxypropenenitriles,^[675] urea with ethyl cyanoacetate,^[1067] thiourea with (ethoxymethylene)cyanoacetate,^[1068] acetamidine or benzamidine hydrochlorides with β -alkoxyvinyl trifluoromethyl ketones (in this case, tetrahydropyrimidines are formed as well),^[677] α -methyl- α -phenylguanidine with β -oxo esters,^[783] and heterocyclic α -ethoxycarbonyl-substituted ketones with urea or guanidine.^[786] The reaction of 2-amino-4-methoxy-6-phenylpyrimidine-5-carbonitrile with guanidinium sulfate affords 2,5,7-triamino-4-phenylpyrimido[4,5-*d*]pyrimidine in 92% yield.^[675]

The condensation of cyanamide with methyl 2-cyano-3-methoxy-3-(4-methoxyphenyl)propenoate leads to the formation of 2-ethoxy-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile.^[678] 5,5-Disubstituted hydantoins **221** are prepared by the reaction of diethyl 2-(acylamino)-2-alkylmalonates **220** with substituted ureas and sodium ethoxide (Scheme 143).^[1069]

Scheme 143 5,5-Disubstituted Hydantoins from 2-Substituted 2-(Acylamino)malonates and Ureas^[1069]



A precursor to an 18-membered aza-crown ether may be synthesized by alkylation of the disodium salt of a tosylated diamine with a suitable dimethanesulfonate.^[1070] Intramolecular N-alkylation of 4-[alkyl(bromoacetyl)amino]-3-(phenylcarbamoyl)isosenazoles (or isothiazoles) gives 4,5,7,8-tetrahydro-6*H*-isosenazolo- or -isothiazolo[4,3-*e*][1,4]diazepines in yields of 56–83%.^[1071] The reaction of phthalaldehyde with urea or thiourea leads to the formation of structures with five fused rings.^[672] Generated by means of sodium ethoxide, N-anions from pyridine-2-, -3-, or -4-carboxamides^[897] or -benzamides **222**^[1072] which possess an *ortho*-ethynyl or substituted-ethynyl group, undergo cyclization to form naphthyridinones^[897] or dihydroisoindolones **223** and/or isoquinolinones,^[1072] respectively (Scheme 144).

Scheme 144 3-Substituted Dihydroisindol-1-ones by Cyclization of 2-Alkynylbenzamides^[1072]

Ethoxide anion catalyzes the synthesis of pyridines by condensation of compounds possessing neighboring amino and cyano groups (2-aminopyrrole-3-carbonitriles,^[801] 1-amino-2-cyanocycloalkenes, etc.^[1073]) with α,β -unsaturated carbonyl compounds. 1-Substituted isoquinoline derivatives are obtained from the reaction of 1-substituted 1-(acetyl-imino)- or 1-(acetilamino)-3-methyl-1*H*-benzo[*c*]pyran-4-carbonitriles with sodium ethoxide.^[1074] A slight excess of sodium ethoxide promotes the rearrangement of tosylhydrazones of *cis*-*N*-alkyl-3-phenylaziridin-2-yl phenyl ketones into the corresponding 1,6-dihydro-1,2,3-triazine derivatives. With a large excess of ethoxide, a suitably substituted tosylhydrazone gives 1-(isopropylamino)-3,5-diphenylpyrazole. Triazine can be transformed into pyrazole using ethoxide.^[1075] *N*-Alkyl-*N'*-chloroamidines undergo rearrangement when treated with sodium ethoxide, giving *O*-ethylisoureas and ethyl carboxylates.^[689]

5-Methyl-5-(phenylcarbamoyl)hydantoin (221, R¹ = Me; R² = Ph); Typical Procedure:^[1069]

Ester **220** (R¹ = Me; 1.16 g, 5 mmol) and phenylurea (0.68 g, 5 mmol) were added to a soln of Na (138 mg, 6 mmol) in anhyd EtOH (25 mL). The mixture was heated at reflux for 3 h under an argon atmosphere, cooled, and concentrated to dryness under reduced pressure. The residue was dissolved in H₂O and insoluble material was removed by filtration. The filtrate was acidified with 1 M HCl to pH 2–3. The precipitate was filtered, washed with H₂O, and dried. If necessary, the crude product was purified by crystallization; yield: 0.9 g (77%); mp 154–156 °C (EtOH).

8.2.4.3.3 Method 3:
Reactions of Sodium Ethoxide as a Nucleophile

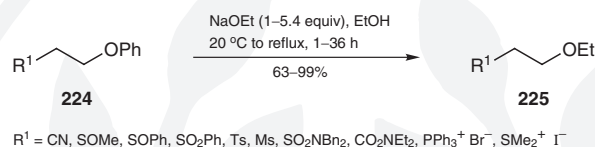
8.2.4.3.3.1 Variation 1:
Aliphatic Nucleophilic Substitution

Sodium ethoxide is commonly used for introduction of the ethoxy group by nucleophilic substitution, e.g. preparation of benzyl ethyl ether from benzyl bromide and ethoxide catalyzed by tetrabutylammonium iodide.^[1076] The reaction of chloro-^[1077] or dichloroacetic acid^[1078] with excess sodium ethoxide leads to the formation of ethyl ethoxy- or diethoxyacetate, respectively, which are further transformed into the corresponding ethyl esters. In each case, 1 equivalent of alkoxide is consumed in the formation of the sodium salts of the acids. Displacement of bromide by ethoxide in α -bromo acid derivatives, namely in ethyl bromo(phenyl)acetate^[1040] and in L(-)-2-bromo-*N*-phenylpropanamide,^[704] is known. In the latter case, inversion of configuration is accompanied by considerable racemization.^[704] Trichloronitromethane undergoes reaction with four equivalents of sodium ethoxide to form ethyl orthocarbonate (46–49% yield).^[1079] Benzylic fluoro groups in 2-nonafluorobutylaniline are smoothly replaced with ethoxide, giving the *gem*-diethoxy derivative (98% yield), which is, with difficulty, transformed into 2-aminophenyl heptafluoropropyl ketone, or, by reaction with ketones under acidic conditions, cyclized to give sub-

for references see p 1117

stituted 4-(heptafluoropropyl)quinolines (70–98% yield).^[1080] When the β -carbon (relative to the leaving group) is substituted with an electron-withdrawing group, the replacement takes place according to an elimination–addition pathway. A series of 2-ethoxyethanes **225** substituted at C1 with phosphonium, sulfonium, sulfonyl, cyano, and other electrophilic groups is prepared in such a way from the reaction of the corresponding 2-phenoxyethyl derivatives **224** with sodium ethoxide (Scheme 145).^[1081]

Scheme 145 Ethyl Ethers from Phenoxyethyl Derivatives^[1081]



The reaction of ethoxide with 5-ethoxy-4-[(4-tosyl)methyl]-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one proceeds with two consecutive S_N2' displacements.^[1082] Ethoxymethyl ethers are formed from the reaction of indol-3-yl-1-methyl-*S*-acetic or -*S*-propanoic acid with sodium ethoxide via an elimination–addition pathway.^[720]

8.2.4.3.3.2

Variation 2:

Vinyl and Related Nucleophilic Substitutions

Electrophilic alkenes **131**, which are β -substituted with a nucleofugal group, usually undergo reaction with replacement of the nucleofuge by the ethoxy group according to an addition–elimination mechanism. Sodium ethoxide used in excess often undergo addition to the products, with the formation of β,β -diethoxy-substituted compounds.^[721] Thus, 3-chloroprop-2-enenitrile^[722] and β -chloro- α -cyano-2-nitrocinnamionitrile^[1083] undergo replacement of chloride by the ethoxy group in high yield (Scheme 146). When an excess of ethoxide is used, 3,3-diethoxypropanenitrile is produced.^[722] Similarly, the substitution of the vinylic chloride in ethyl (*Z*)- and (*E*)-3-chlorobut-2-enoate or (*E*)-3-chloro-2-methylbut-2-enoate may be realized.^[1084] Stereoselective replacement of the chloro substituent in α -chloroenyne sulfone,^[729] and of either of the halogens and/or the sulfonyl group in fluorobromovinyl sulfones,^[728] is also observed. The benzotriazolyl group at the β -carbon in α,β -unsaturated esters is another nucleofuge which undergoes a facile nucleophilic displacement.^[725] The fluorine atom at the β -vinylic carbon in α,β -unsaturated esters^[1085] or in trifluoromethylated ethenes^[736,739] is substituted with ethoxide; in the case of the former compounds, the addition of another equivalent of ethoxide takes place.^[1085] Under suitable conditions, 2,2-difluoro-1-phenyl-1-(trifluoromethyl)ethene is converted by means of sodium ethoxide into ethyl (α -trifluoromethyl)phenylacetate in 72% yield.^[739] Photolysis or solvolysis of triarylbromoethenes carried out in the presence of sodium ethoxide leads to the formation of vinylic products, in addition to significant amounts of the *ipso* substitution products. Ethenes α -substituted with bromine and possessing two *para*-substituted phenyl rings at the β -vinylic carbon undergo rearrangement of the β -aryl group; the products thus formed enter, in turn, into vinylic and *ipso* substitution reactions.^[737] Depending on the solvent used, 4,5-dichloro-2-phenylpyridazin-3(2*H*)-one undergoes replacement of either of the two chloro groups.^[1086]

Scheme 146 Synthesis of Ethyl Vinyl Ethers from Vinylic Halides^[722,736,1083,1084,1086]

R ¹	R ²	R ³	X	NaOMe (equiv)	Conditions	Yield (%)	Ref
CN	H	H	Cl	0.91	EtOH, 20 °C	90	[722]
H	CN	H	Cl	0.91	EtOH, 20 °C	91	[722]
CN	CN	2-O ₂ NC ₆ H ₄	Cl	1.0	EtOH, 40 °C, 2 h	82	[1083]
CO ₂ Et	H	H	Cl	1.2	EtOH, 0 °C, 24 h	88	[1084]
H	CO ₂ Et	H	Cl	1.1	EtOH, 0 °C, 24 h	87	[1084]
Me	CO ₂ Et	Me	Cl	1.0	EtOH, 78 °C, 2 h	82	[1084]
F	CF ₃	Cy	F	1.5	EtOH, 80 °C	58	[736]
Cl	C(O)NPhN=CH		Cl	1.0	EtOH, reflux, 30 min	95	[1086]
Cl	CH=NNPhC(O)		Cl	1.0	1,4-dioxane, rt, 30 min	75	[1086]

Fused quinazolinones and tetrahydro[1]benzothieno[2,3-*d*]pyrimidinones undergo reaction with excess sodium ethoxide under aeration by ring opening and subsequent intermolecular oxidative trapping of the intermediate S-anions.^[732] *O*-Ethyl *S*-methyl and bis-*S*-methyl *N*-cyanocarbonimidothioates^[1087] or imidoylbenzotriazoles^[742] undergo substitution of the *S*-methyl or benzotriazolyl group, respectively, by ethoxide.

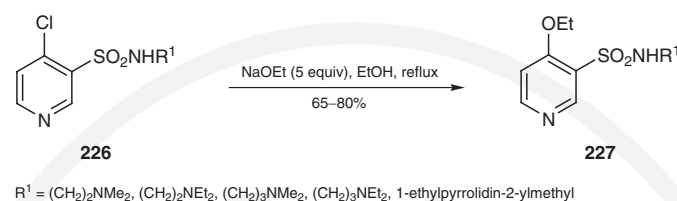
8.2.4.3.3.3 Variation 3: Aromatic Nucleophilic Substitution

Substitution of a nucleofuge in aromatic compounds by ethoxide is possible, and the process is especially facile when an electron-withdrawing group (particularly the nitro group) is present at the *ortho* and/or *para* positions to the leaving group.^[743] When the electron-withdrawing group(s) is absent, the reaction requires forced conditions unless it is carried out in the presence of a catalyst, e.g. a copper salt.^[745] Thus, chloro for ethoxy substitution occurs in aryl chlorides and chloroaryl alkyl sulfides when these compounds are heated at 120 °C with sodium ethoxide in hexamethylphosphoric triamide. This process is accompanied by *O*-dealkylation; addition of iodoethane to the reaction leads to transformation of the products of dealkylation (the corresponding phenols) into the ethoxy derivatives.^[751]

The reaction of various fluoroaromatic compounds in refluxing ethanol leads to a partial substitution of the aromatic halogens.^[1088] Copper facilitates the nucleophilic aromatic substitution by ethoxide,^[745] both in the case of aryl^[753,756] as well as hetaryl^[756] halides (halothiophenes and -pyridines).

Reduction of the aryl halogen is an often encountered side reaction.^[753,756] Pyridines substituted at C2 or C4 with halogen, usually chloro groups,^[767,772,774] or with a sulfinyl^[767] or sulfonyl group,^[767,1089] readily undergo replacement of these nucleofuges by ethoxide, e.g. transformation of **226** into **227** (Scheme 147).^[772] The reaction takes place equally well with 2-sulfonyl-^[1089] and 2-sulfinylpyridine *N*-oxides,^[1090] comprising a useful method for the preparation of various sulfinic acid derivatives. In 5-chloro-3-methoxy-2-nitropyridine *N*-oxide, the nitro group is preferentially replaced by ethoxide, but in low yield.^[777]

for references see p 1117

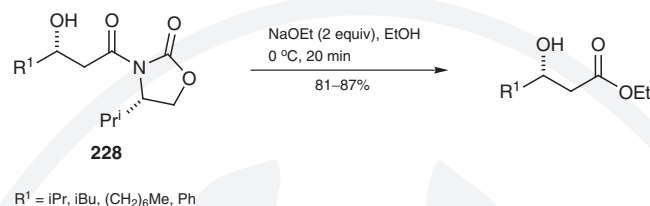
Scheme 147 4-Ethoxypyridine-3-sulfonamides from the 4-Chloro Derivatives^[772]

Treatment of 2,4-dihaloquinolines with ethoxide leads to the regioselective formation of 2-ethoxy-4-haloquinolines.^[779] Focused microwave irradiation of mixtures of 2-halopyrimidines, 2-chloropyrazine,^[1091] or 2-chloroquinoline^[780] with sodium ethoxide in dipolar aprotic solvents dramatically shortens the reaction time for the ethoxylation reaction. Reactions of chlorodiazines,^[1092] 2-bromothiazole, 2-chloroquinoline, and 1-chloroisoquinoline^[1093] in refluxing ethanol give ethoxylated products, usually in high yields. As expected, however, the replacement of chlorine in 3-chloroisoquinoline requires forced conditions (heating in a sealed tube at 150 °C for 15 h).^[1094] A one-pot synthesis of 4-ethoxyindole-3-carbaldehyde involves treating indole-3-carbaldehyde with thallium(III) trifluoroacetate in trifluoroacetic acid, then with iodine and copper(I) iodide in dimethylformamide, and finally with sodium ethoxide (overall yield ca. 50%).^[766] Derivatives of 2-sulfinyl- and 2-sulfonyl-1*H*-imidazole yield products of *ipso* ethoxide substitution.^[782] Replacement of one or two halogen atoms with the ethoxy group in 5,7-dichlorothieno[3,2-*b*]pyridine,^[778] 4-amino-2-bromopyrimidine-5-carbonitrile,^[784] 5-alkyl-2,4-dichlorouracils (pyrimidines),^[1094] 4-chlorobenzo[*c*][2,7]naphthyridine,^[797] 5-chloro-6-methyl-3-phenyl- or 5-chloro-3,6-diphenyl-*as*-triazines,^[793] and 2-amino-4-bromo- or -chloro-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones^[787] may be carried out. Reactions of sodium ethoxide with thioquinanthrene ([1,4]dithiino[2,3-*c*:5,6-*c'*]diquinoline) result in cleavage of the dithiane ring.^[781]

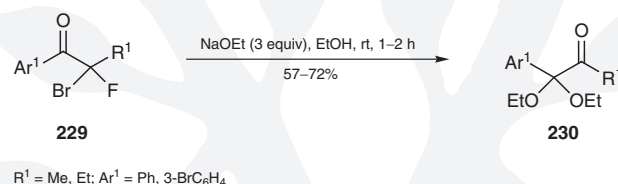
8.2.4.3.3.4

Variation 4:**Reactions with Esters and Carbonyl and Thiocarbonyl Compounds**

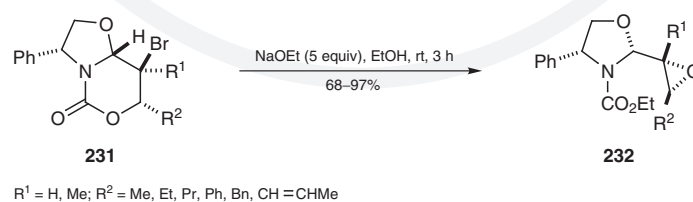
Addition of ethoxide to a carbonyl group generates an unstable oxyanion which can be stabilized in different ways. In the simplest case, departure of the nucleofuge (e.g., halogen, alkoxy, or trihalomethyl anion) from the tetrahedral intermediate affords ethyl esters. When the neighboring α -carbon carries a halogen, the oxyanion produces an oxirane, which often enters into further reaction. Thus, a derivative of 3-(trichloroacetyl)-1,4-dihydropyridine gives the 3-ethoxycarbonyl-substituted product with concomitant release of the trichloromethyl anion in 90% yield.^[804] The acyl fluoride of 8-(ethoxycarbonyl)-6-fluoro-6-methyloctanoic acid, generated by the electrochemical oxidation of 2-[2-(ethoxycarbonyl)ethyl]-2-methylcyclohexanone, produces the corresponding ethyl ester when treated with sodium ethoxide.^[802] Chiral, substituted 3-(3-hydroxypropanoyl)-1,3-oxazolidin-2-ones **228** undergo replacement of the oxazolidinyl moiety by the ethoxy group (Scheme 148); the reaction proceeds without loss of optical activity.^[1095]

Scheme 148 Conversion of Chiral β -Hydroxy Carboximides into the Chiral β -Hydroxy Esters^[1095]

1,3-Dicarbonyl compounds substituted at C2 undergo deacetylation with sodium ethoxide.^[1096] The reaction of *N*-alkyllactams with dimethyl sulfate and then with sodium ethoxide affords the corresponding lactam diethyl acetals.^[1097] Both chloro substituents in α,α -dichloroaldehydes^[843] may be replaced with ethoxy groups, while 1-bromo-1-fluoroalkyl aryl ketones **229**^[847] produce 1-aryl-1,1-diethoxyalkan-2-ones **230** via 2-ethoxy-1-fluorooxiranes in an overall carbonyl transposition process (Scheme 149). The intermediate (2-chloroethyl)ethoxyoxirane, obtained from 4-bromo-1-chloro-2,2-dimethylbutan-3-one, undergoes reaction with ethoxide to give 3,3-diethoxy-4,4-dimethyltetrahydrofuran.^[849]

Scheme 149 Synthesis of α -Oxo Acetals from α -Bromo- α -fluoro Ketones^[847]

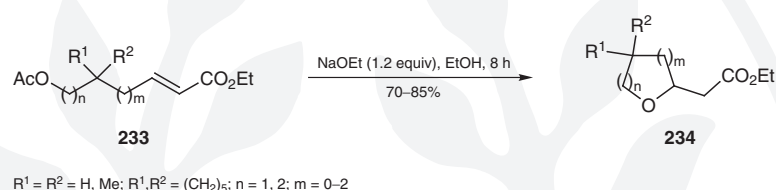
Attack of the ethoxide anion on a ring carbonyl can lead to ring opening, the reaction usually being driven by resulting carbanion stabilization. Such a process is observed for derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione),^[1098] 2-(acetyethyl)-2-nitrocycloalkanones,^[819] 2-chloro-2-(phenylsulfonyl)cycloalkanones,^[820] alkyl 1-[(alkyl-sulfanyl)carbonothioyl]-2-oxocyclopentanecarboxylates,^[1096] α -methylene- β -lactones,^[815] 2,2'-spirobiindane-1,1',3,3'-tetraones,^[818] dithiotriuret derivatives,^[825] and spiro-2,3-dihydro-1*H*-pyrazoles.^[1099] In the last case, starting with optically active material, both enantiomers of 3-(ethoxycarbonyl)-4-phenyl-2,3-dihydro-1*H*-pyrazoles can be prepared.^[1099] Ring opening in *N*-(2,6-dialkylphenyl)oxazolidin-2-ones, followed by decarboxylation of the intermediate carbamic acid, leads to the formation of 2,6-dialkyl-*N*-(2-ethoxyethyl)anilines.^[824] Cleavage of the oxazinone ring in chiral 8-bromo-3-phenyltetrahydrooxazolo-[3,2-*c*][1,3]oxazin-5-ones **231** generates oxyanions, which undergo reaction at a neighboring carbon bearing a nucleofuge, to produce the chiral ethyl 2-(oxiran-2-yl)-4-phenyloxazolidine-3-carboxylates **232** (Scheme 150).^[1100] Based on a similar approach, (3*R*,4*R*)-4-hydroxy-3-[(tosyl)oxy]dihydrofuran-2(3*H*)-one is transformed into (2*S*,3*R*)-ethyl 4-hydroxy-2,3-epoxybutyrate.^[838]

Scheme 150 Chiral Epoxyoxazolidines from Bromooxazinones^[1100]

for references see p 1117

A multistep ethoxide-mediated reaction of N-substituted 2-acetimido-2-chlorobutyrolactones gives rise to N-substituted 3-(ethoxycarbonyl)-2-methylpyrroles in low yield (18–29%).^[839] Oxyanions resulting from sodium ethoxide mediated cleavage of an acetoxy group, e.g. in **233**,^[828] or from addition to a carbonyl group,^[840] may also be intramolecularly trapped with electrophilic C=C bonds (Michael addition)^[828] or with a distant electrophilic carbon bearing a halogen atom,^[840] with the formation of α -(ethoxycarbonyl)methyl-substituted cyclic ethers **234** or 2-oxaprotoadamantane derivatives, respectively (Scheme 151).

Scheme 151 Oxygen Heterocycles from Acetoxyalkenoates^[828]



N-Substituted saccharin derivatives undergo reaction with sodium ethoxide by ring opening, forming N-substituted derivatives of ethyl 2-sulfamylbenzoates.^[830,831,833] Addition of ethoxide to the thiocarbonyl group of O-alkyl arenecarbothioates generates the corresponding S-anions, which are intercepted with alkyl iodides to give monothioortho esters.^[852]

Ethyl (2R,4R)-2-[(2R,3S)-2-Methyl-3-phenyloxiran-2-yl]-4-phenyl-1,3-oxazolidine-3-carboxylate (232, R¹ = Me; R² = Ph); Typical Procedure:^[1100]

Oxazinone **231** (R¹ = Me; R² = Ph; 374 mg, 1 mmol) was added to a soln of NaOEt (340 mg, 5 mmol) in abs EtOH (8 mL), and the mixture was stirred at rt for 3 h. Sat. aq NH₄Cl was then added and the resulting mixture was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Et₂O/petroleum ether 2:3) to give the product as a colorless solid; yield: 300 mg (85%); mp 65 °C.

8.2.4.3.3.5

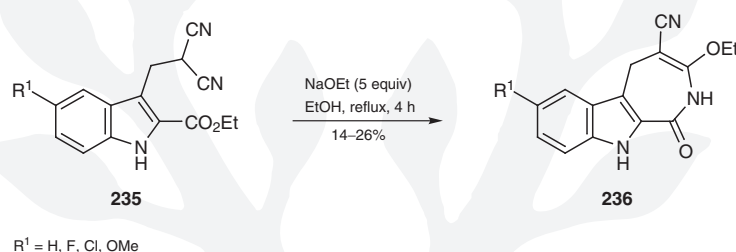
**Variation 5:
Reactions with Imines**

3-Alkyl derivatives of 2-(N-cyanoimino)thiazolidine undergo reaction with sodium ethoxide by ring opening, followed by O→S alkyl transfer, to give sodium salts of cyanourea. The latter can be N-benzylated or converted into 1,1-disubstituted biurets by heating with hydrochloric acid.^[1101] 2-(Chloroalkyl)benzothiazoles undergo ring expansion to 2-ethoxybenzothiazines upon treatment with ethoxide (10–63% yield). The yield of the thiazines depends upon the solvent used.^[858] 3-Substituted 2-imino-3-tetrahydrofuran-3-carbonitriles undergo reaction with sodium ethoxide via addition to the imino functional group, followed by cyclization, which leads to the formation of 7a-ethoxyhexahydrofuro[2,3-b]pyridine-3a-carbonitrile derivatives.^[855] α -(Arylamido)- β,β -dichloroacrylic acids^[856] or 2-(N-acetyl-N-bromo)aminoalk-2-enoates^[857] undergo reaction with ethoxide to afford 2-aryl-4-ethoxyoxazoles or 4-ethoxydihydrooxazole-4-carboxylates, respectively. In the latter case, the structure of one of the products was confirmed by an independent synthesis from 1-acetyl-3-alkyl-2-chloro-2-(ethoxycarbonyl)aziridine by the reaction with sodium ethoxide.^[857] The strongly electrophilic properties of 2-methyl-3,4-dihydroisoquinolinium bromide are evidenced by the formation of the addition product in 90% yield upon treatment with ethoxide.^[1059]

8.2.4.3.3.6 Variation 6: Reactions with Nitriles

Addition of alkoxides to the cyano group produces imino ethers.^[866] Thus, a convenient conversion of glycidinitriles into ethyl glycidates involves their reaction with sodium ethoxide in ethanol followed by acidic hydrolysis of the intermediate glycidoimino ethers.^[1102] When nitrile compounds possess other functional groups (carbonyl, alkoxy-carbonyl, cyano, among others), further reactions are possible, often leading to the formation of cyclic products. Thus, 3-(cyanomethyl)pyridine-2- and -4-carbonitriles give the corresponding amino(ethoxy)naphthyridines when treated with sodium ethoxide.^[868] A similar process with 2-cyanobenzyl cyanide leads only to the formation of dimers.^[1053] The cyclization of ethyl 3-(2,2-dicyanoethyl)indole-2-carboxylates **235** to the azepino-[3,4-*b*]indoles **236**, occurs upon treatment with ethoxide (Scheme 152).^[871]

Scheme 152 Azepino[3,4-*b*]indoles by Cyclization of Ethyl 3-(2,2-Dicyanoethyl)-indole-2-carboxylates^[871]



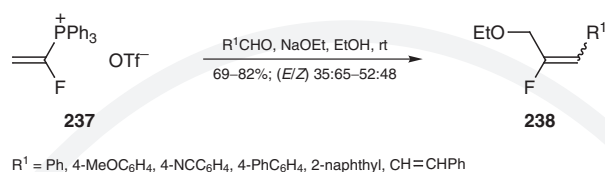
Symmetrical and unsymmetrical esters of iminocarboxylic acid are prepared from the reaction of cyanogen bromide, sodium ethoxide, and alcohols in yields of 75–84%.^[867]

8.2.4.3.3.7 Variation 7: Reactions with Alkenes

Ethoxide easily undergoes addition to electrophilic alkenes, forming β -ethoxy-substituted products.^[874] When the alkene possesses a nucleofuge, the intermediate carbanion may be intercepted to give cyclic products; intermolecular interception of the anion is also possible.

The diastereomeric ratio of products resulting from the addition of ethoxide to chiral α,β -unsaturated esters depends upon the reaction time and temperature; *threo* selectivity as high as 86:14 (*threo/erythro*) has been observed.^[876] α,β -Unsaturated heterocyclic ketones,^[879] vinyl sulfoxides,^[1103] and phenyl styryl sulfones^[1040] undergo smooth addition of ethoxide. (2-Bromo-2-methyl-1-phenylpropylidene)malononitrile undergoes reaction with sodium ethoxide, affording 2-ethoxy-3,3-dimethyl-2-phenylcyclopropane-1,1-dicarbonitrile by an addition–cyclization pathway, while the reaction with other (bromo-alkylidene)malononitriles leads to the formation of glassy products.^[892] Ethyl 4-bromo-2-(ethoxycarbonyl)pent-2-enoate undergoes reaction by addition–cyclization–ring opening, giving diethyl [(2,2-diethoxy-1-methyl)ethyl]malonate (yield: 73%).^[1104] Reaction of the anion derived from the addition of ethoxide to 2-chloroprop-2-enenitrile, with 1,3-dinitrobenzene, gives rise to the product of a vicarious nucleophilic substitution^[154–157] reaction.^[894] α -(Fluorovinyl)phosphonium salt **237** undergoes addition of ethoxide, and the ylide thus generated may be trapped with aromatic aldehydes (Wittig reaction^[408,410]) to give 1-aryl-3-ethoxy-2-fluoropropenes **238** in 69–82% yield, with the *Z*-isomers usually being produced in slight excess (Scheme 153).^[1105]

for references see p 1117

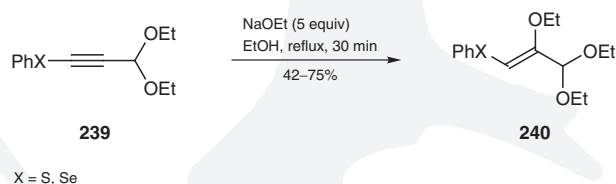
Scheme 153 Synthesis of Alkenes from α -(Fluorovinyl)phosponium Salts^[1105]

3-(Diethylamino)-4-(4-methoxyphenyl)isothiazole 1,1-dioxide without a substituent at C5, or C5-bromo-substituted, undergo reaction with 2 equivalents of ethoxide by addition or vinylic substitution; the subsequent ring fission–sulfur dioxide extrusion affords 3-ethoxy- (mixture of *E*- and *Z*-isomers) or 3,3-diethoxy-substituted propenamides.^[886] Addition of sodium ethoxide to 5-(dichloromethylene)oxazolidinones gives rise to 5-(dichloromethyl)-5-ethoxyoxazolidin-4-ones.^[881] Chlorotrifluoroethene^[1106] or hexafluoropropene^[619] easily undergo addition of ethoxide to the carbon substituted with two fluorine atoms. Further chemical transformations of the adduct allow preparation of ethyl fluoromalonate.^[619]

8.2.4.3.3.8

Variation 8:
Reactions with Alkynes

Alkynyl compounds exhibit electrophilic properties and hence a variety of nucleophiles, including the ethoxide anion, easily undergo addition to the triple bond.^[896] Thus, the reaction of crude 2-[(trimethylsilyl)ethynyl]nitrobenzene with a large excess of sodium ethoxide in ethanol produces 2-(2,2-diethoxyethyl)nitrobenzene, which can be transformed into indole. In a similar synthesis of 4-methyl- or 4-(ethoxycarbonyl)indole, 3-methyl- or 3-(ethoxycarbonyl)-2-[(trimethylsilyl)ethynyl]nitrobenzenes, respectively, are used as the starting materials. The same approach is used in the preparation of various pyrrolopyridines.^[1107] Desilylation of the (trimethylsilyl)ethynyl group in 4,5-dimethoxy-2-[(trimethylsilyl)ethynyl]benzonitrile, followed by the addition of 1 equivalent of ethoxide to the triple bond and hydration of the cyano group, leads to the formation of 2-(2-ethoxyvinyl)-4,5-dimethoxybenzamide, which can be transformed into 6,7-dimethoxyisoquinol-1(2*H*)-one.^[898] Ethoxide undergoes addition to C2 of 3,3-diethoxy-1-(phenylselanyl)- or 3,3-diethoxy-1-(phenylsulfanyl)propyne **239**, giving the corresponding *Z*-adducts **240** (Scheme 154).^[1108]

Scheme 154 *Z*-Prop-2-enal Acetals from Alkynes and Sodium Ethoxide^[1108]

(*Z*)-2-Ethoxy-3-(phenylselanyl)prop-2-enal Diethyl Acetal (240, X = Se);

Typical Procedure:^[1108]

A soln of acetal **239** (X = Se; 1.85 g, 6.53 mmol) in EtOH (5.0 mL) was added dropwise to a soln of NaOEt, prepared from Na (0.75 g, 32.7 mmol) in EtOH (20 mL). The mixture was refluxed for 30 min and cooled. The solvent was removed under reduced pressure, the mixture was poured into H₂O (100 mL), and the organic layer was separated; the aqueous layer was extracted with Et₂O, and the combined organic layers were dried (MgSO₄) and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/hexane 1:10) to give the product as a yellow oil; yield: 1.6 g (75%).

**8.2.4.3.4 Method 4:
Cleavage of Ring Compounds****8.2.4.3.4.1 Variation 1:
Cleavage of Cyclopropanes**

Ring cleavage of cyclopropanes by a base and/or nucleophile takes place when they are substituted by a leaving group (e.g., a halogen atom) and/or an electron-withdrawing group.^[473,902] Thus, 2-alkyl-3,3-dichlorospiro[cyclopropane-1,9'-fluorene] derivatives, when treated with sodium ethoxide in ethanol, give ethoxybuta-1,3-dienes in low yields.^[903] Depending upon the substituents at C3 in 1,1-dichloro-2-(phenylsulfonyl)cyclopropanes, they undergo reaction with ethoxide by nucleophilic substitution or ring opening. Thus, the 3,3-dimethyl derivative affords, in boiling ethanol, a mixture of 1,1-diethoxycyclopropane and 1,1,1-triethoxy-2,2-dimethyl-3-(phenylsulfonyl)propane (combined yield 45%), while at room temperature the former product is obtained in 92% yield. Depending on the temperature, 1,1-dichloro-2-(phenylsulfonyl)cyclopropane gives 1,1,1-triethoxy-3-(phenylsulfonyl)propane in yields of 65–85%.^[909] The reaction of 1,1-dichloro-2-phenylcyclopropane with sodium ethoxide in ethanol or dimethylformamide leads to the formation of 2-ethoxy-2-phenylcyclopropene, 1,1-diethoxy-2-phenylcyclopropane, or 2-phenylpropenal diethyl acetal, depending on the conditions.^[905] *gem*-Dichlorocyclopropyl ethers, in alcohol solvents, undergo ring opening in the presence of the base with formation of the acetals of α -chloro- α,β -unsaturated aldehydes. The process is independent of the base; sodium ethoxide serves only to neutralize the acid formed.^[1109] 2-Alkyl-1,1,2-trihalocyclopropanes afford 3-alkyl-3,3-diethoxyprop-1-ynes upon treatment with sodium ethoxide in tetrahydrofuran.^[575,577]

**8.2.4.3.4.2 Variation 2:
Cleavage of Three-Membered Heterocycles**

Symmetrically substituted oxiranes, upon treatment with sodium ethoxide, easily undergo formation of the corresponding 2-ethoxy-substituted ethanols,^[916] e.g. *trans*-2-ethoxycyclohexanol from cyclohexene oxide in a yield of 77%.^[917] Furthermore, oxirane ring opening is often encountered during reactions of halocarbonyl compounds with ethoxide (see Section 8.2.4.3.3.4). 1-(Benzylsulfonyl)pentan-3-one is obtained by the reaction of thiirane with sodium ethoxide carried out in the presence of benzyl chloride.^[926] Both *cis*- and *trans*-2,3-diphenyl-1-(phenylsulfonyl)aziridine give cleanly the *threo*- and *erythro*-*N*-(2-ethoxy-1,2-diphenylethyl)benzenesulfonamides in yields of 59 and 97%, respectively, with a faster conversion for the *trans*-isomer.^[918] Reaction of *cis*-2-benzyl-3-phenyl-1-(phenylsulfonyl)aziridine with ethoxide leads to the formation of product mixtures by attack on both aziridine ring carbons as well as by a nucleophilic eliminative ring opening initiated by deprotonation at the benzylic site.^[927]

**8.2.4.3.5 Method 5:
Elimination Reactions**

Sodium ethoxide is used as a base for the elimination of hydrogen halides, water, and other molecules.^[931] Thus, 3-chloro-1,1,1-triphenylpropane is converted by this base in dimethyl sulfoxide into 3,3,3-triphenylpropene in 90% yield.^[1110] Dehydrochlorination of α,γ,γ -trichloro- β -imino esters leads to the formation of ethyl 3-chloroanthranilates.^[937] Ethyl fluoromalonate is obtained from tetrafluoropropanenitrile by elimination–addition and then acidic hydrolysis.^[619] Six equivalents of sodium ethoxide effect the transformation of 3,3-dichloro-2-(trichloromethyl)-3,4-dihydro-2*H*-pyrrole into 3-chloro-2-(triethoxymethyl)pyrrole by an elimination–nucleophilic substitution sequence in 79% yield.^[936]

for references see p 1117

Treatment of 3-bromo-6-cyano-2-ethoxy-4-(ethoxycarbonyl)-3,4-dihydro-2*H*-pyran with ethoxide gives diethyl 2-(2-ethoxyvinyl)but-2-enedioate by a multistep process which comprises hydrogen bromide elimination, electrocyclic ring opening of the resulting 2*H*-pyran, and replacement of the cyano group.^[933] Elimination of water from the intermediate bicyclic α -hydroxyamine initiates a series of transformations which, after acidic workup, affords 1-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one.^[1111] (Z)-3,4-Diethoxy-1-phenyl-5-(phenylselanyl)pentan-1-one undergoes elimination of ethanol when treated with sodium ethoxide, and results in the formation of 4-ethoxy-1-phenyl-5-(phenylselanyl)penta-2,4-dien-1-one in a yield of 71% (2*E*/2*Z* 90:10). The same reaction carried out with lithium diisopropylamide gives the product in 45% yield (2*E*/2*Z* 81:19).^[1108]

8.2.4.3.6 Method 6: Rearrangements

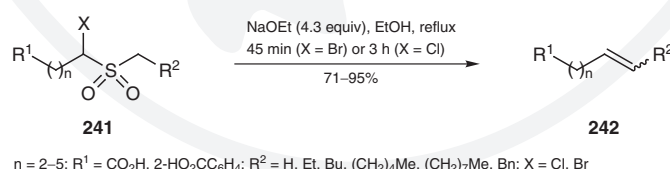
8.2.4.3.6.1 Variation 1: Favorskii and Related Rearrangements

Reaction of sodium ethoxide with α -halo ketones possessing an α' -hydrogen leads to the formation of ethyl esters (Favorskii rearrangement^[942–944]). However, this base is not as often used for this reaction as sodium methoxide. 2-Bromo-2-methylpentan-3-one undergoes reaction with sodium ethoxide to give two isomeric rearranged esters, ethyl 2,2-dimethylbutanoate (the main product) and ethyl 2,3-dimethylbutanoate.^[952] The reaction of 1,3,4-tribromo-4-methylpentan-2-one with ethoxide leads to the formation of ethyl (*E*)-4-methylpenta-2,4-dienoate in 57% yield.^[1112] α -Chloro- α -phenyl-*N*-isopropylketenimine gives rise, upon treatment with sodium ethoxide, to the Favorskii product, ethyl *N*-isopropyl-3-phenylpropanimidate (98% yield).^[960]

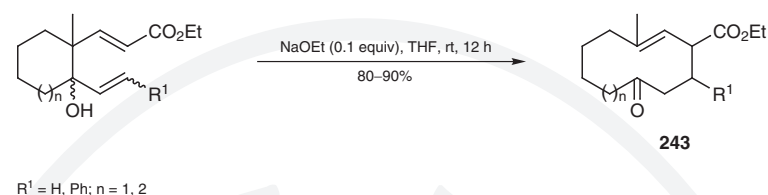
8.2.4.3.6.2 Variation 2: Other Rearrangements

Suitably substituted oxiranes or cyclopropanes undergo a nucleophilic eliminative ring fission under the influence of sodium ethoxide.^[1113] Thus, [(ethylsulfonyl)methyl]oxirane, upon treatment with the ethanolic base and immediately acidified, affords ethyl 3-hydroxyprop-1-enyl sulfone. When the reaction is carried out for 16 h, the formation of ethyl 2-ethoxy-3-hydroxypropyl sulfone results instead.^[1114] In the case of [(phenylsulfonyl)methyl]cyclopropanes substituted at C2 with phenylsulfonyl-, cyano-, or ethoxycarbonyl group(s), this reaction offers little practical value because of the formation of unstable dienoic products.^[994] α -Halo sulfones **241**, substituted with a remote carboxylic group, undergo extrusion of sulfur dioxide upon treatment with ethoxide, forming the corresponding unsaturated carboxylic acids **242**^[1115] (Ramberg–Bäcklund reaction^[579–581]) (Scheme 155).

Scheme 155 Unsaturated Acids from α -Halo Sulfones: Ramberg–Bäcklund Reaction^[1115]



Catalytic sodium ethoxide is used for the syntheses of functionalized medium-size rings **243**^[1116] (Scheme 156) and bicyclic [4.3.0] or [4.4.0] compounds^[1117] by the oxy-Cope rearrangement.^[1118]

Scheme 156 Synthesis of Cyclic Ketones by Oxy-Cope Rearrangement^[1116]

2-Ethoxy-2*H*-pyran-6-carbonitriles undergo reaction with sodium ethoxide to give the corresponding ring-opened valence isomers, the 4-ethoxy-1-(cyanocarbonyl)-1,3-dienes, which, under the conditions of the reaction, undergo replacement of the cyano group by the ethoxy group.^[933] 2-(Cyanomethyl)-6-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium iodide, when treated with ethoxide, undergoes rearrangement with the formation of 5-(ethoxymethyl)-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline in 91% yield.^[972]

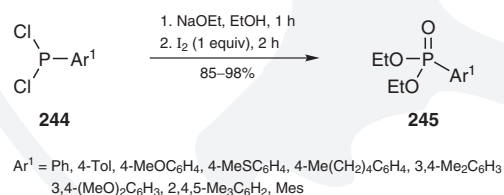
Oct-5-enoic Acid (242, $R^1 = CO_2H$; $R^2 = Et$; $n = 3$); Typical Procedure:^[1115]

A soln of NaOEt, prepared from Na (200 mg, 8.7 mmol) in EtOH (10 mL), was mixed with a soln of acid **241** ($R^1 = CO_2H$; $R^2 = Et$; $n = 3$; 485 mg, 2 mmol) in EtOH (10 mL). The mixture was heated at reflux for 3 h, cooled, poured into H_2O , and acidified, and the whole was extracted with Et_2O (3 ×). The organic phase was washed with brine, dried, and evaporated. The residue was distilled under reduced pressure to give the product; yield: 237 mg (76%); bp 85 °C/0.1 Torr.

8.2.4.3.7

**Methods 7:
Other Methods**

O-Alkylation of *N,N*-disubstituted amides in the presence of sodium ethoxide gives 1-ethoxy-*N,N*-dimethylvinylamines.^[1119] γ -Sultones undergo ring opening resulting in the formation of the sodium salts of 2-(ethoxymethyl)-1-sulfonic acids.^[1120] Sodium ethoxide in refluxing ethanol effects cleavage of the methylenedioxy ring in 2,2-dimethyl-6,7-(methylenedioxy)dihydrobenzopyran-4-one giving 7-ethoxy-6-hydroxy-2,2-dimethyldihydrobenzopyran-4-one in 60% yield.^[915] Diethyl arylphosphonates **245** are synthesized from arylchlorophosphines **244** by treatment with sodium ethoxide and iodine in yields of 85–98% (Scheme 157).^[1121]

Scheme 157 Diethyl Arylphosphonates from Aryldichlorophosphines^[1121]

The reaction of phenyl- or butylmagnesium bromide with sodium ethoxide gives the corresponding magnesium ethoxides.^[973]

for references see p 1117

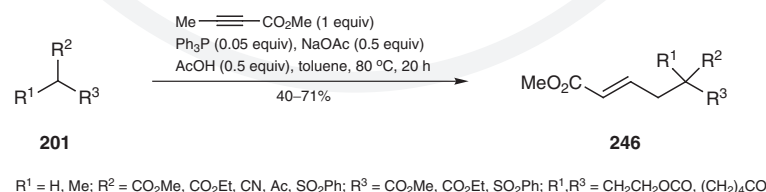
8.2.4.4 Sodium Acetate

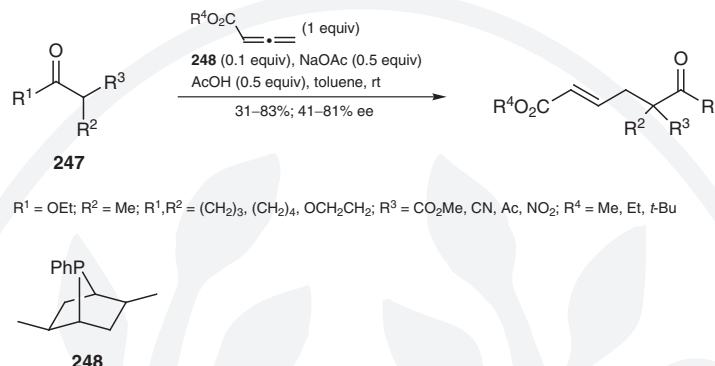
Sodium acetate is a colorless, crystalline compound, commercially available in anhydrous form or as the trihydrate. It is applied as a weak base for maintaining pH, particularly together with acetic acid, as well as for introduction of the acetoxy group into organic compounds. It is often used together with organometallic catalysts, especially those containing palladium.^[1122]

8.2.4.4.1 Method 1:
Generation and Reactions of Carbanions

Usually, sodium acetate is not a sufficiently strong base for effective deprotonation of CH acids. However, condensation of aromatic aldehydes with carboxylic anhydrides in the presence of an alkali metal salt of a carboxylic acid corresponding to the anhydride leads to α,β -unsaturated carboxylic acids (Perkin reaction).^[1123] Reactions with acetic anhydride are carried out in the presence of sodium or potassium acetate (e.g., the preparation of 3-nitrocinnamic acid from 3-nitrobenzaldehyde, acetic anhydride, and sodium acetate in yields of 74–77%^[1124]), but the effect of either salt depends upon the aldehyde structure.^[1125] A related process, the reaction of aromatic aldehydes with *N*-acylglycine derivatives, in a mixture of acetic anhydride and sodium acetate, gives 1,3-oxazol-5(4*H*)-ones (Erlenmeyer reaction),^[1123] e.g. the 1,3-oxazol-5(4*H*)-one from α -(benzoylamino)- β -(3,4-dimethoxyphenyl)acrylic acid (69–73% yield).^[1126] Condensation of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde with 1,3-dicarbonyl compounds carried out in acetic anhydride in the presence of sodium acetate affords the corresponding α,β -unsaturated 1,3-dicarbonyl compounds.^[1127] *N*-Bromoacetamide undergoes addition to α -nitroalkenes and also to carbohydrate derivatives. When the nitro group is situated in a terminal position, the adducts undergo bromination with the formation of β -(acylamino)- α,α -dibromo- α -nitroalkanes. The process is performed with a catalytic amount of sodium acetate (without which it fails), and is likely of ionic character.^[1128] 2,4,6-Triphenylpyrylium perchlorate undergoes condensation with ethyl pyruvate, in the presence of 2 equivalents of acetate, forming ethyl 2-benzoyl-3,5-diphenylbenzoate, or with 1 equivalent of this salt to give ethyl 3,5-diphenylbenzoate. In the latter case, other condensing reagents give better results.^[1129] The reactions of but-2-ynoic acid derivatives,^[1130,1131] or alkyl buta-2,3-dienoates,^[1131] with 1,3-dicarbonyl compounds, disulfonylmethane, cyanomethyl phenyl sulfones, 2-nitrocyclohexanone, or ethyl 2-cyanopropanoate, e.g. **201** and **247**, a catalytic amount of phosphine, and sodium acetate in acetic acid afford products, e.g. **246**, with the formation of a new C–C bond at C4 of the alkynyl or the allenic ester and simultaneous conversion of the intermediate alkynyl (or allenic) moiety into a vinylic group, in good yield (Schemes 158 and 159). When the process is performed with a chiral phosphine, e.g. **248**, the products are obtained in up to 81% ee.^[1131] The postulated mechanistic pathway^[1130,1131] assumes deprotonation of the CH acid by the intermediate betaine, but deprotonation by sodium acetate cannot be excluded. In fact, without this salt, the reaction in acetic acid does not take place; however, it proceeds in good yield with sodium acetate itself.^[1131]

Scheme 158 Reaction of CH Acids with Methyl But-2-ynoate in the Presence of Phosphines and Sodium Acetate^[1130]



Scheme 159 Reaction of CH Acids with Alkyl Butadienoates in the Presence of Chiral Phosphine and Sodium Acetate^[1131]

Trimethyl (3E)-But-3-ene-1,1,4-tricarboxylate (246, $\text{R}^1 = \text{H}; \text{R}^2 = \text{R}^3 = \text{CO}_2\text{Me}$);

Typical Procedure:^[1130]

A mixture of methyl but-2-ynoate (98 mg, 1.0 mmol), dimethyl malonate (132 mg, 1 mmol), Ph_3P (13 mg, 0.05 mmol), AcOH (30 mg, 0.5 mmol), and NaOAc (42 mg, 0.5 mmol) in toluene (2 mL) was heated at 80 °C for 20 h under N_2 . Upon cooling, the mixture was filtered and the collected solid was washed with Et_2O . The combined organic filtrates were concentrated and the residue was purified by column chromatography (silica gel, hexane/ EtOAc 5:1) to give the product; yield: 145 mg (63%).

8.2.4.4.2

Method 2:

Reactions of Sodium Acetate as a Nucleophile

8.2.4.4.2.1


Variation 1:

Nucleophilic Substitution

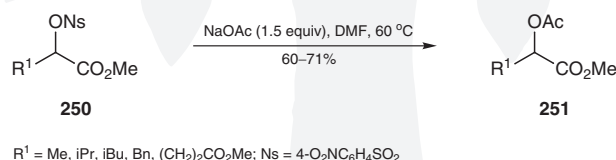
The reaction of sodium acetate with alkyl halides leads to the formation of esters of acetic acid and can be conveniently carried out under solid–liquid phase-transfer catalysis conditions, in the presence of a crown ether or a quaternary ammonium salt as the catalyst,^[15] e.g. the synthesis of benzyl or butyl acetate **249** (Scheme 160).^[1132] Pentyl acetate results from the reaction of chloropentane with solid sodium acetate and traces of water, carried out in the presence of tetrabutylammonium bromide as well as acetyltrimethylammonium bromide; in the latter case, the transfer of the acetate anions to the organic phase occurs via inverted micelles.^[1133] In solid–liquid systems, sodium acetate effects the acetoxy for chloro displacement in (chloromethyl)trimethylsilane (82%)^[1134] or in epichlorohydrin [2-(chloromethyl)oxirane] (92%);^[1135] in a liquid–liquid system, both bromo substituents in 3,5-dibromocyclopent-1-ene are replaced.^[1136] In the latter case, a higher yield may be obtained using lithium acetate or potassium acetate in the presence of trialkylphosphines or -amines.^[1136] Small, but definite, amounts of water play an important role in the heterogeneous reaction of solid alkali acetates with bromooctane performed in the presence of alumina.^[1137] A transient dipolar species, generated by the base-promoted cyclization of 2-vinylbenzohydrazonyl chlorides under liquid–liquid phase-transfer catalysis conditions, was intercepted with acetate and hydroxy anions, to give mixtures of 5-acetoxy- and 5-hydroxy-4,5-dihydro-1H-1,2-benzodiazepines which can be converted into 1H-1,2-benzodiazepines.^[1138] High yields of alkyl acetates are obtained in the reaction of solid sodium acetate with gaseous alkyl halides promoted by tetraalkylphosphonium salts and carried out under continuous-flow conditions (so-called gas–liquid phase-transfer catalysis, GLPTC).^[1139]

for references see p 1117

Scheme 160 Acetates from Alkyl Halides by Reaction with Sodium Acetate^[1132–1135,1139]

$R^1X \xrightarrow{NaOAc} R^1OAc$		249		
R^1	X	Conditions	Yield (%)	Ref
Bn	Cl	NaOAc, Aliquat 336 (0.1 equiv), MeCN/CH ₂ Cl ₂ , 4.5–5 h	100	[1132]
(CH ₂) ₄ Me	Cl	NaOAc (2.5 equiv), TBAB (cat.), H ₂ O (cat.)	57	[1133]
CH ₂ TMS	Cl	NaOAc (1.1 equiv), TBAB (cat.), CCl ₄ , reflux, 4 d	82	[1134]
	Cl	NaOAc (0.5 equiv), 15-crown-5 (cat.), MeCN, time according to TLC	92	[1135]
(CH ₂) ₅ Me	Br	NaOAc (1.5 equiv), Bu ₄ P ⁺ Br [–] (cat.), flow rate 40 mL·h ^{–1} , 150 °C	84	[1139]

A technique alternative to phase-transfer catalysis involves the use of dipolar aprotic solvents. Alkyl, allyl, and benzyl chlorides, bromides, and iodides undergo reaction with sodium acetate in hexamethylphosphoric triamide to give esters in yields exceeding 90%.^[1140] The replacement of the chloro group in 1-(1-chlorobutyl)- or 1-(1-chlorobenzyl)-benzotriazole is carried out in a dimethyl sulfoxide/tetrahydrofuran mixture or in acetic acid,^[1141] while the chloro groups of 1,3-dichloroacetone are replaced by acetoxy and then by phenylsulfanyl groups in one-pot reactions in dimethylformamide.^[1142] Bromination of the benzophenone imine of glycine ethyl ester in the presence of sodium acetate results in the formation of an α -acetoxy derivative, which may also be displaced by other nucleophiles.^[1143] Treatment of 2-nosyloxy [2-(4-nitrobenzenesulfonyloxy)] carboxylates **250** with sodium acetate in dimethylformamide leads to the formation of 2-acetoxy esters **251** in good yield (Scheme 161).^[1144]

Scheme 161 Methyl 2-Acetoxy-carboxylates from 4-Nitrobenzenesulfonates and Sodium Acetate^[1144]

Butyl acetate is obtained in high yield by heating sodium acetate with tributyl phosphate.^[1145] Pyrolysis of *N*-alkyl- or *N*-(arylmethyl)-substituted 2,4,6-triphenylpyridinium tetrafluoroborate with sodium acetate gives alkyl acetates in yields of 60–79%.^[1146] Replacing the chloro substituent in β -oxosulfonyl chloride gives an acetoxy sulfonyl derivative.^[1147] 5-Bromo-1,3,6-trimethyluracil undergoes reaction with sodium acetate by nucleophilic substitution with concomitant acetoxy migration to the allylic position, forming the 6-acetoxymethyl derivative.^[1148] The reaction of acetate with difluorocarbene affords difluoromethyl acetate in 52% yield.^[1149] *N*-(4-Nitrophenyl)alkanehydrazonoyl bromides undergo replacement of bromide by the acetoxy group, but the product undergoes rearrangement by O→N acetyl migration, giving *N*-acyl-*N'*-acetyl-*N'*-(4-nitrophenyl)hydrazines.^[1150] Chlorobis(triphenylphosphine)palladium(II) catalyzes the formation of 3-oxo-1,3-dihydroisobenzofuran-1-yl acetate from the reaction of 2-bromobenzaldehyde, carbon monoxide, and sodium acetate.^[1151]

Oxiran-2-ylmethyl Acetate (249, R¹ = Oxiran-2-ylmethyl); Typical Procedure:^[1135]

15-Crown-5 (25 μ L) was dissolved in dry MeCN and NaOAc (4.1 g, 0.05 mol) was added. The soln was stirred for 30 min, then 2-(chloromethyl)oxirane (9.25 g, 0.1 mol) was added and the mixture was stirred for 13 h (the reaction progress was monitored by TLC). The solvent was removed under reduced pressure and the residue dissolved in Et₂O. After standard workup, the organic extract was washed with H₂O, then with aq NaHCO₃, dried (MgSO₄), and evaporated to dryness. The product was purified by column chromatography (petroleum ether/EtOAc 7:3); yield: 10.7 g (92%).

Methyl 2-Acetoxypropanoate (251, R¹ = Me); Typical Procedure:^[1144]

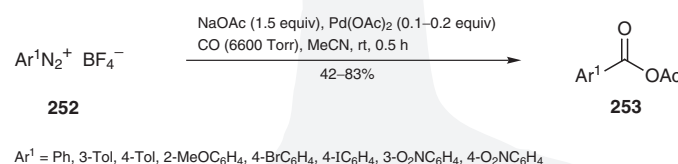
Nosylate ester **250** (R¹ = Me; 0.52 g, 1.8 mmol) and NaOAc (0.22 g, 2.7 mmol) were dissolved in DMF (5.4 mL) and the resulting mixture was heated at 60 °C until the starting material was consumed, as determined by periodic analysis of the reaction by TLC (hexane/EtOAc 1:1) (ca. 5 h). The mixture was diluted with cold H₂O (30 mL) and the whole was extracted with Et₂O (3 \times 30 mL); the combined Et₂O extracts were washed with H₂O (2 \times 40 mL) and brine (2 \times 40 mL), and dried (MgSO₄). The solvent was removed to give a yellow oil which was purified by bulb-to-bulb distillation to provide the product as a clear oil; yield: 0.17 g (65%).

8.2.4.4.2.2

Variation 2:**Reactions with Carbonyl Compounds and Diazonium and Ammonium Salts**

The reaction of sodium carboxylates with acyl chlorides leads in the presence of sodium acetate to the formation of carboxylic anhydrides.^[1152] Thus, the reaction of 2-(benzoylsulfanyl)-1-methylpyridinium chloride [prepared in situ from benzoyl chloride and 1-methylpyridine-2(1*H*)-thione] with sodium acetate in a water/chloroform two-phase system gives rise to acetic benzoic anhydride.^[1153] The reaction of phenylmalonyl dichloride with sodium acetate gives 6-acetoxy-3,5,7-triphenylfuro[3,2-*b*]pyran-2-one.^[1154] Mixed acetic aromatic acid anhydrides **253** result from the reaction of arenediazonium tetrafluoroborates **252**, carbon monoxide, and sodium acetate under palladium(0) catalysis (Scheme 162).^[1155] Acetate undergoes addition to dialkyl(methylene)ammonium halides to give acetates of (dialkylamino)methanol.^[1156]

Scheme 162 Mixed Anhydrides from Arenediazonium Salts by Palladium-Catalyzed Carbonylation in the Presence of Sodium Acetate^[1155]

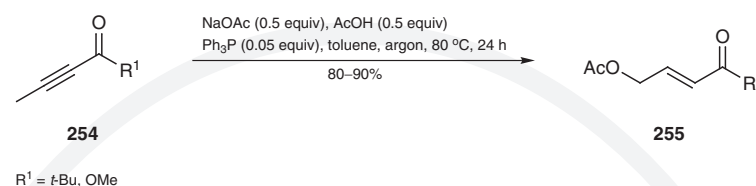


8.2.4.4.2.3

Variation 3:**Reactions with Alkenes**

The reactions of methyl but-2-ynoate and *tert*-butyl prop-1-ynyl ketone **254** with sodium acetate–acetic acid and triphenylphosphine as the catalyst give the corresponding allylic acetates **255** in 60–90% yields (Scheme 163). The key step of this process is the addition of acetate to the transient vinylphosphonium salt (Trost's reaction^[1130,1131]).^[1157]

for references see p 1117

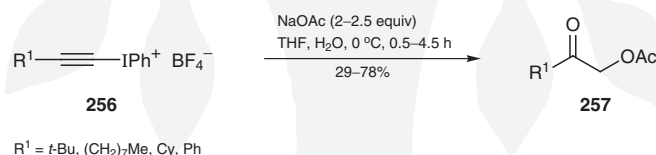
Scheme 163 Allylic Acetates from Alkynyl Esters or Ketones and Sodium Acetate^[1157]**Methyl 4-Acetoxybut-2-enoate (255, R¹ = OMe); Typical Procedure:**^[1157]

A mixture of the methyl but-2-ynoate (196 mg, 2.0 mmol), Ph₃P (26 mg, 0.1 mmol), NaOAc (82 mg, 1.0 mmol), and AcOH (60 mg, 1.0 mmol) in toluene (5 mL) was heated at 80 °C for 24 h under argon. Upon cooling, the mixture was filtered and the solid was washed with Et₂O. The combined organic filtrates were concentrated and the product was purified by chromatography (silica gel, hexane/EtOAc 9:1); yield: 285 mg (90%).

8.2.4.4.2.4

**Variation 4:
Reactions with Alkynes**

The reaction of sodium acetate with alkynyl(phenyl)iodonium tetrafluoroborates **256** leads to the formation of α -acetoxy ketones **257** (Scheme 164). The reaction occurs by *trans* addition of acetate to the triple bond, followed by the hydrolysis of the acetoxy group and acetate displacement of the diphenyliodonium group.^[1158] Catalyzed by palladium(II) acetate, regio- and stereospecific hydroacetoxylation of alk-2-ynoic acid derivatives by acetate leads to the formation of (*Z*)-3-acetoxyalk-2-enoic acid derivatives in good yield.^[1159]

Scheme 164 Acetoxy Ketones from the Reaction of Alkynyliodonium Salts with Sodium Acetate^[1158]**2-Cyclohexyl-2-oxoethyl Acetate (257, R¹ = Cy); Typical Procedure:**^[1158]

A soln of tetrafluoroborate **256** (R¹ = Cy; 40 mg, 0.1 mmol) in freshly distilled THF (1 mL) was added dropwise to a stirred soln of NaOAc (205 mg, 2.5 mmol) in H₂O (0.5 mL) at 0 °C under N₂. The mixture was stirred at rt for 0.5 h, then poured into H₂O and the whole was extracted with Et₂O; the organic layer was dried (MgSO₄) and the solvent was removed. The crude product was purified by preparative TLC to provide colorless prisms; yield: 11 mg (58%); mp 40 °C (Et₂O/hexane).

8.2.4.4.3

**Method 3:
Cleavage of Ring Compounds**

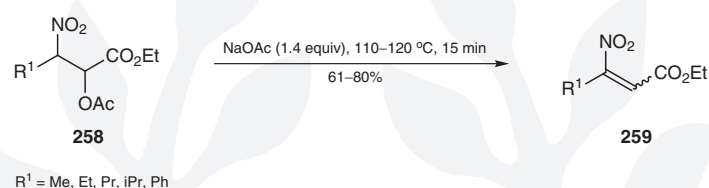
Ring opening via a 1,4-*syn* mechanism of cyclopentadiene oxide by sodium acetate in the presence of copper(I) chloride gives (*Z*)-1-acetoxy-4-hydroxycyclopent-2-ene in 70% yield.^[1160] The reaction of acetate with [1-(ethoxycarbonyl)cyclopropyl]triphenylphosphonium tetrafluoroborate leads to the ring-opened product, [3-acetoxy-(1-ethoxycarbonyl)propylidene]triphenylphosphorane, which, in a separate step, is converted into ethyl 5-methyl-2,3-dihydrofuran-4-carboxylate.^[1161]

8.2.4.4.4

**Method 4:
Elimination Reactions**

The weakly basic properties of sodium acetate suffice for carrying out some eliminations, particularly when the leaving group is located at a β -carbon relative to a strongly electron-withdrawing group. Thus, ethyl 2-acetoxy-3-nitroalkanoates **258** afford α,β -unsaturated ethyl β -nitrocarboxylates **259** when heated with sodium acetate (Scheme 165).^[1162]

Scheme 165 Nitroalkenoates from 2-Acetoxy-3-nitroalkanoates by Elimination Reactions^[1162]



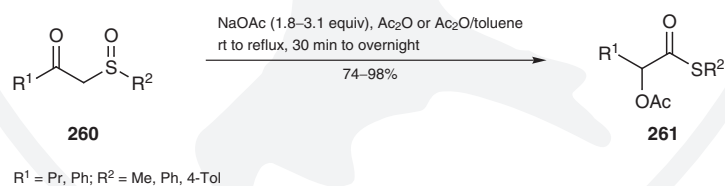
Both *erythro*- and *threo*-1-bromo- or -1-chloro-1,2-diphenyl-2-tosylethanes undergo *anti* elimination upon treatment with sodium acetate, giving (*Z*)- and (*E*)- α -(4-tolylsulfonyl)-stilbene, respectively.^[1163] 2-Nosyloxy esters enter into nucleophilic substitution reactions with sodium acetate (see Section 8.2.4.4.2.1), while methyl 2-(nosyloxy)succinate undergoes elimination exclusively, with the formation of dimethyl fumarate.^[1144] Sodium acetate in acetic acid causes *syn* elimination in β -hydroxysilanes,^[1164] the final step of the Peterson alkenation reaction.^[640]

8.2.4.4.5

**Method 5:
Rearrangements**

The products obtained from the reactions of sodium acetate with six-membered cyclic bromo or dibromo 1,3-diketones depend upon their structure and the kind of the solvent used. These processes afford mixtures which contain products of ring contraction, nucleophilic substitution, and/or halogen reduction.^[1165] β -Oxo sulfoxides **260** give α -acetoxy acid thioesters **261** in high yields upon treatment with acetic anhydride and sodium acetate (Pummerer-type rearrangement^[1166]), which are useful precursors for various types of derivatives of α -hydroxy acids (Scheme 166).^[1167]

Scheme 166 Acetoxy Acid Thioesters by Rearrangement of Oxo Sulfoxides^[1167]



Sodium acetate is a sufficiently strong base to generate an azasulfonium ylide from azasulfonium salts; the ylide readily enters into a [2,3]-sigmatropic (Sommelet–Hauser) rearrangement. The reaction comprises a useful *ortho* functionalization method for aromatic amines.^[1168]

for references see p 1117

2-(4-Tolylsulfanyl)-2-oxo-1-phenylethyl Acetate (261, R¹ = Ph; R² = 4-Tol);**Typical Procedure:**^[1167]

A stirred mixture of sulfoxide **260** (R¹ = Ph; R² = 4-Tol; 0.48 g, 1.86 mmol), NaOAc (0.48 g, 5.85 mmol), and Ac₂O (5 mL) in toluene (10 mL) was heated at 115 °C overnight. The mixture was concentrated to give a residue which was suspended in benzene/hexane (3:7) and subjected to chromatography [silica gel, benzene (**CAUTION: carcinogen**)/hexane 1:1] to give the product; yield: 413 mg (74%).

8.2.4.4.6**Methods 6:****Other Methods**

A high-yielding synthesis of azines from the reaction of aldehydes or ketones with hydrazine sulfate using sodium acetate–calcium chloride may be greatly accelerated by microwave irradiation under solvent-free conditions.^[1169] Benzyl acetates are obtained by acetoxylation of toluenes by means of peroxydisulfate in acetic acid in the presence of copper(II) acetate and sodium acetate. This reaction involves the acetoxylation of benzyl radicals.^[1170] Sodium acetate is an often encountered component of organometallic catalysts, especially those containing palladium.^[1122]

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8.4.3 Product Subclass 3: Rubidium and Cesium Carbonates

R. M. Kellogg

General Introduction

There has been much more interest in cesium carbonate than in rubidium carbonate. Both of these carbonates are dry, colorless powders and neither is unusually hygroscopic nor appreciably soluble in the dipolar aprotic solvents usually used. Dimethylformamide is often employed as solvent, although acetonitrile, tetrahydrofuran, and even the protic solvent ethanol have been used (see Section 8.4.3.2.3 for the use of toluene or benzene together with crown ethers as reaction media). Finely divided suspensions of cesium carbonate are formed in dimethylformamide and these are very effective at deprotonating acidic compounds, almost always the first step in the reactions mediated by this reagent. There is sometimes an advantage in using preformed cesium salts, which are best prepared in a protic solvent such as methanol and then rendered solvent-free, followed by suspension/dissolution in dimethylformamide.

The original idea to enhance the nucleophilicity of a carboxylate by conversion into the cesium salt appears to have been motivated by the problem of attaching protected amino acids to Merrifield resins via the carboxylate groups.^[1] This requires a nucleophilic substitution by the carboxylate group on a benzylic chloride on the resin. These S_N2 reactions are in practice often difficult to bring to completion. According to Gisin:^[1] “A cesium salt, containing a cation larger than lithium, sodium, or potassium might be expected to be more lipophilic and therefore more compatible with the resin. In addition, in a polar solvent, such as dimethylformamide, the salt of a carboxylic acid should be dissociated to a greater extent if the cation is large than if it small.” The assumption was clearly that a “naked” carboxylate would be more reactive in a nucleophilic substitution than one that is ion-paired.

Excellent results were realized when *tert*-butoxycarbonyl-protected valine was coupled to Merrifield resin when the amino acid was deprotonated with cesium carbonate in dimethylformamide. Carboxylates derived from other alkali metal carbonates were, as predicted, significantly less reactive. Today we would expect that the chief reason for the success is that cesium carboxylates are essentially solvent-separated ion pairs in solvents such as dimethylformamide. Other advantages are that cesium carbonate is clearly sufficiently basic to deprotonate the acids completely, that no water is generated on deprotonation, and that the cesium carboxylates are in general reasonably soluble in dipolar aprotic solvents.

Interest in cesium carbonate dramatically increased when it was reported that macrocyclic lactones could be prepared in remarkably high yields by cyclization of the cesium salts of long-chain carboxylic acids provided with appropriate leaving groups at the end of the chain (see Section 8.4.3.1.1).^[2] Various methods have been developed to optimize these reactions further, and some of these techniques are discussed in the following sections.

Cesium-promoted ring closures proceed best with relatively apolar materials. Crown thioethers (thiocrown ethers), macrocyclic lactones, and, in general, macrocycles bearing large apolar segments are the typical classes of compounds readily prepared by this technique. For the synthesis of crown ethers composed (chiefly) of polyethylene glycol or ethylene diamine segments, “templating” methods based on the coordinative powers of sodium or potassium cations are generally better. Moreover, such ring closures for oxa-

for references see p 1514

crown ethers usually require the alkoxide to act as the nucleophile. Cesium carbonate is not basic enough to deprotonate alcohols readily.

There is no particular reason to think that the cesium cation acts as a template that folds chains up and brings the ends together, analogously to the manner in which sodium or potassium cations act in templating the synthesis of, for example, 18-crown-6. At one point, the idea that templating might be involved was attractive. On the basis of data available in 1981,^[2] it appeared that cesium and carboxylate ions might still be associated in solvents such as dimethyl sulfoxide and dimethylformamide, and that the cesium ion could act as a polarizable surface to promote the S_N2 substitution leading to ring closure. It has been shown, however, that cesium carboxylates, and presumably other cesium salts, are not significantly associated in these solvents and that the cesium cation itself is well-solvated.^[3]

Why then do these macrocyclizations in which cesium salts are used work so well? Mandolini and co-workers have pointed out that for the formation of macrocyclic lactones by ring closure through nucleophilic substitution by the carboxylate, at concentrations equal to the effective molarity for ring closure (usually around 10^{-2} M for most macrocyclic rings), one would, on the basis of kinetic considerations, anticipate at least a 50% yield of cyclized product.^[4,5] In other words, if the concentration in homogeneous solution is 10^{-2} M or less, one automatically expects at least 50% cyclization. "Templating", if it exists, would then allow one to work at concentrations somewhat above the effective molarity with maintenance of the good yields, providing the materials are soluble at these concentrations. Mandolini has convincingly shown that the cesium ion, compared to other alkali metal cations, has no rate-accelerating effect on the macrocyclization.

In our experience, and judging from other reports in the literature, the concentrations used for macrocyclizations, if the reagents are added all at once, generally to range between 10^{-2} and 10^{-1} M. Often slow-addition ("high-dilution") techniques are used to lower the effective concentrations in solution. Experience has shown, however, that the use of the same techniques, but with other alkali metal ion carboxylates will often lead to poorer experimental yields.

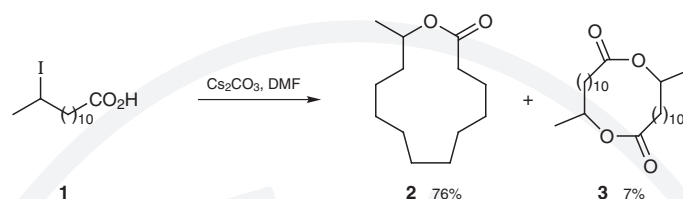
Other factors that cannot readily be examined separately are also likely to play a positive role. Solvent-separated ion pairs, relatively high solubility, and fairly high yields of cyclized products, whereby workup becomes easier, are all contributing factors. Whatever their relative roles, it is obvious that this method has been a major boon to the synthesis of many macrocyclic systems.

Applications of Product Subclass 3 in Organic Synthesis

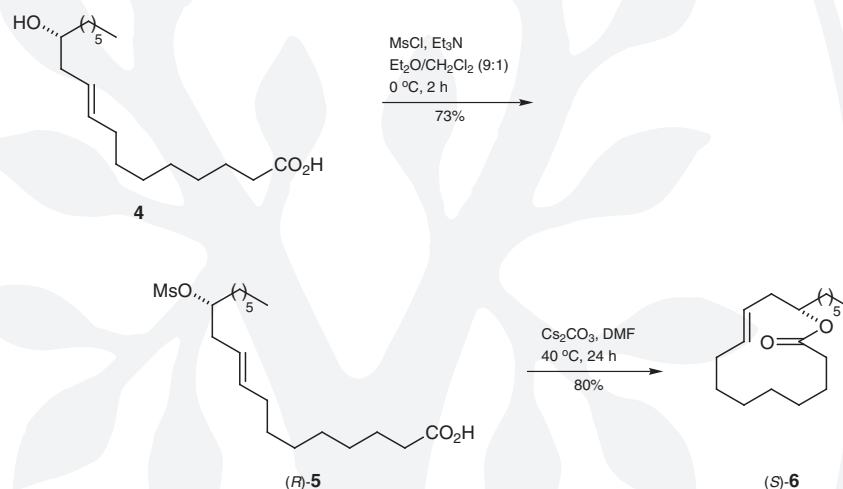
8.4.3.1 Method 1: Synthesis of Macrocycles

8.4.3.1.1 Variation 1: Macrocyclic Lactones

On treatment with cesium carbonate (10^{-2} M in DMF), the (racemic) iodo-substituted carboxylic acid **1** affords lactone **2** in 76% yield and lactone dimer **3** in 7% yield (Scheme 1).^[2] In the synthesis of an analogous 16-membered-ring lactone, the following different alkali metal carbonates have been compared (the yield of the monomeric lactone is given in parentheses): cesium carbonate (80%), rubidium carbonate (68%), potassium carbonate (67%), sodium carbonate (54%), and lithium carbonate (0%, no conversion). Conversions were highest and most rapid when cesium carbonate was used.

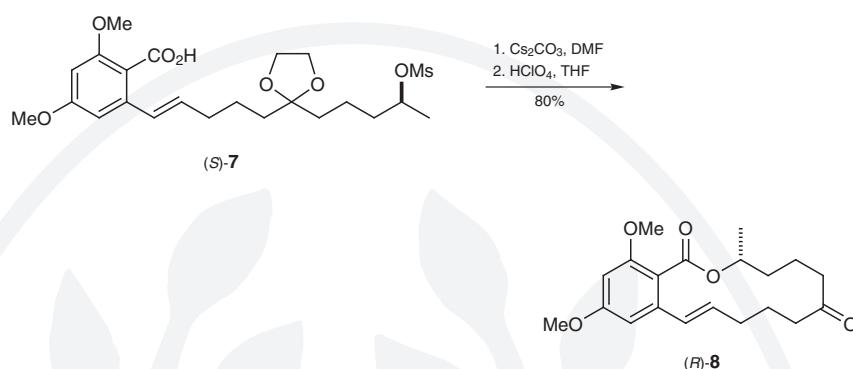
Scheme 1 Synthesis of a Macrocyclic Lactone in the Presence of Cesium Carbonate^[2]

The cesium carbonate effect is general for a large range of macrocyclic lactones. The synthesis of (*S*)-lactone **6** from the methanesulfonate **5** of (*R*)-ricinelaidic acid (**4**) is cleanly carried out in 80% yield by this methodology (Scheme 2);^[2] by comparison of the optical rotation of the product lactone (*S*)-**6** with that of known material of the opposite configuration, it was demonstrated that ring closure occurred with inversion, as expected.

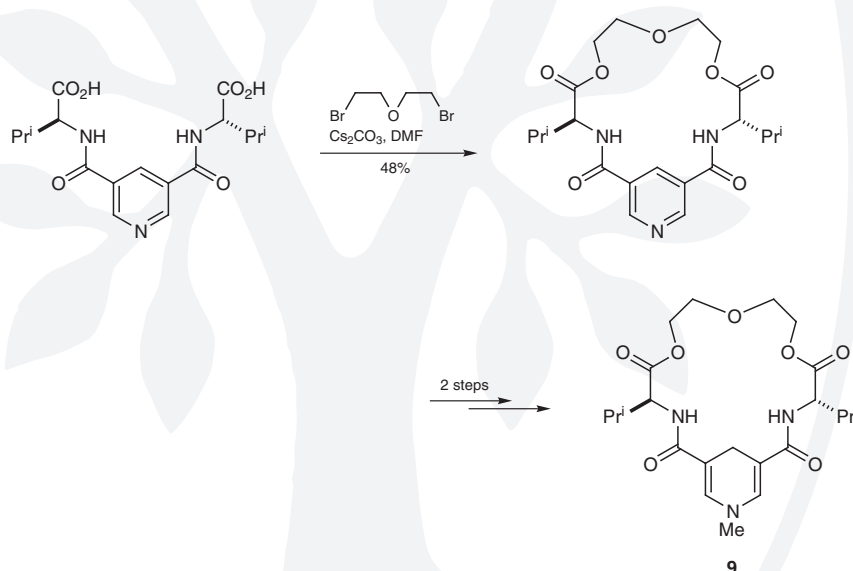
Scheme 2 Synthesis of the (*S*)-Lactone of (*R*)-Ricinelaidic Acid^[2]

The synthesis of the benzolactone intermediate (*R*)-**8** of the natural product (*R*)-zearalenone from methanesulfonate **7** is illustrative of the potential of this methodology (Scheme 3);^[2] substitution at the secondary carbon atom proceeds with inversion of configuration, although the reaction is complicated by subsequent racemization, which takes place by a mechanism peculiar to this particular compound. Other syntheses of simple macrocyclic lactones have also been described.^[6]

for references see p 1514

Scheme 3 Synthesis of an (*R*)-Zearalenone Intermediate^[2]

The NADH mimic **9**, one of many prepared, may be synthesized by the cesium carbonate method (Scheme 4).^[7,8] Furans and thiophenes may be incorporated in macrocycles in an analogous manner.^[9]

Scheme 4 Synthesis of a Macrocyclic NADH Model^[6]

(+)-(10*E*,13*S*)-13-Hexyloxacyclotridec-10-en-2-one [(*S*)-6]:^[2]

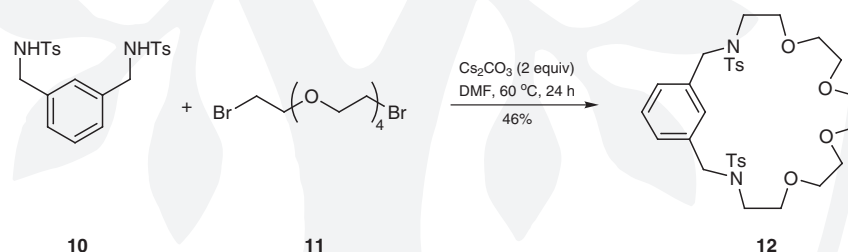
For this reaction, the pure *E*-isomer of hydroxyalkenoic acid **4** {ricinelaidic acid; mp 51–51.5 °C; $[\alpha]_{\text{D}}^{20} +6.6$ (*c* 1, EtOH)} was used. To a sample of hydroxyalkenoic acid **4** (1 g, 3.3 mmol) and Et_3N (1 g, 10 mmol) in an $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ mixture (9:1, 25 mL), well-stirred at 0 °C, was added MsCl (0.85 g, 7.5 mmol). After 2 h, the mixture was filtered, and the filtrate was washed with H_2O (2×25 mL). The organic layer was dried (MgSO_4) and then concentrated to dryness. The residue (base-insoluble, IR $\tilde{\nu}$: 1810 cm^{-1}) was taken up in sat. aq Na_2CO_3 (20 mL), and the soln was kept at 20 °C for 3 h, after which it was acidified with dil HCl and extracted with Et_2O (3×25 mL). Concentration to dryness gave crude methanesulfonate (*R*)-**5**; yield: 0.90 g (73%). A portion of **5** (300 mg, 0.8 mmol) was dissolved in dry DMF (80 mL) to which dry Cs_2CO_3 (0.39 g, 1.2 mmol) was added. The mixture was stirred at 40 °C for 24 h, after which the DMF was removed under reduced pressure. Brine soln was added, and extraction was carried out with Et_2O (25-mL portions). The organic extract was dried

(MgSO₄), the solvent was removed under reduced pressure, and lactone (*S*)-**6** was obtained after the crude product had been subjected to Kugelrohr distillation (120 °C/0.01 Torr). This material gave a single spot on TLC (pentane/Et₂O); yield: 0.18 g (80%); [α]_D²⁰ -43 (c 1, CHCl₃) {cf. [α]_D²⁰ +42 (c 1, CHCl₃) for optically pure lactone (*R*)-**6**}.^[10]

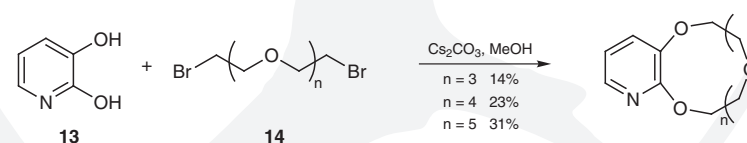
8.4.3.1.2 Variation 2: Macrocyclic Amines

Macrocyclization of amines promoted by cesium carbonate has proven to be widely applicable. Ring closure in the presence of cesium amides is also possible. Illustrative cases are given in Schemes 5 and 6. The example in which bis(sulfonamide) **10** is used as the nucleophile, reacting with dibromide **11** to give macrocycle **12** (Scheme 5), is illustrative of the scope and limitations of this method.^[11] There are many examples of similar applications.^[12] Cesium carbonate readily effects deprotonation of carboxylic acids, phenols, thiophenols, and aliphatic thiols, with release of carbon dioxide. In other words, the reaction does not stop at the intermediate stage of cesium hydrogen carbonate, which is less basic than cesium carbonate, and thus each equivalent of cesium carbonate is equivalent to 2 equivalents of base. On the other hand, amines, aromatic or aliphatic, are not readily deprotonated by cesium carbonate. The same is true of alcohols (for an exception, see Section 8.4.3.5). Procedures to accomplish this, in which the more strongly basic cesium hydroxide is used, have been developed.^[13] The amine can be made more acidic by tosylation, e.g. bis(sulfonamide) **10** (Scheme 5). However, in this case each cesium carbonate neutralizes only one proton, because cesium hydrogen carbonate is not sufficiently basic to effect deprotonation of a sulfonamide group.

Scheme 5 Macrocyclization of a Bis(sulfonamide)^[11]

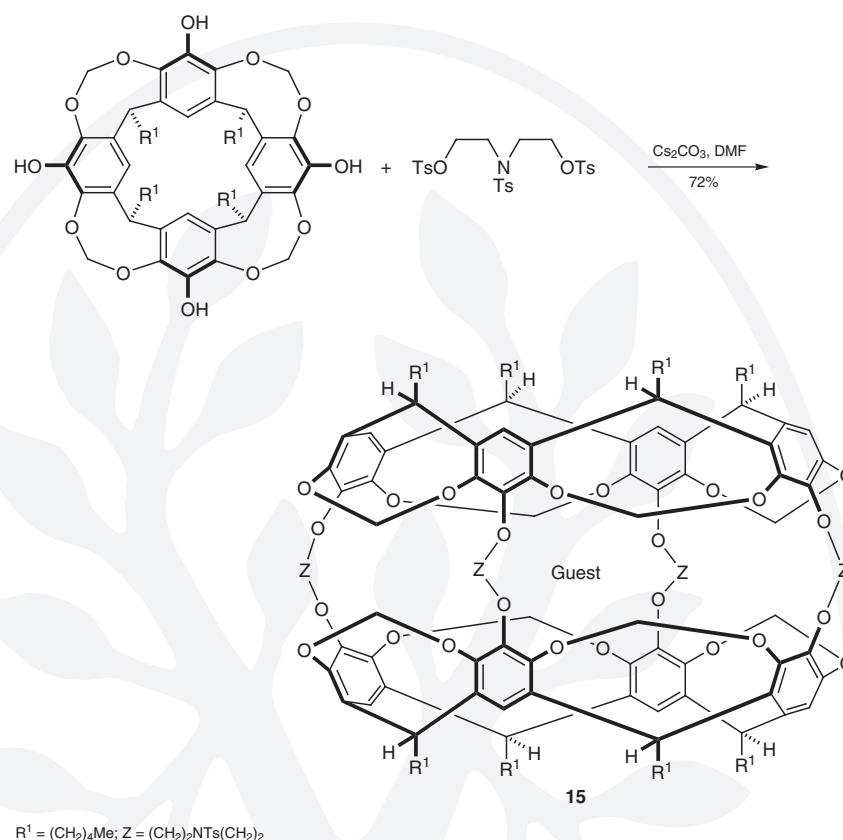


Scheme 6 Macrocyclization of Pyridine-2,3-diol^[14]



The macrocyclization of pyridine-2,3-diol (**13**) with α,ω -dibromo ethers **14**, promoted by cesium carbonate (Scheme 6), is typical of the possibilities for the application of this method to a broad range of 1,2- (and in some cases 1,3-) dihydroxy aromatics.^[14,15] Particularly elegant use of this method has been made in the cyclization of phenanthroline phenols.^[16–18] Organic host molecules containing pyridines and bipyridines have been prepared with the use of cesium carbonate in dimethylformamide for cyclization.^[19] Cavitand **15** is an example of the structural complexity that can be achieved; it has been prepared in a series of one-pot macrocyclizations, with the use of cesium carbonate and dimethylacetamide as template (Scheme 7).^[20]

for references see p 1514

Scheme 7 Synthesis of a Cavitand in the Presence of Cesium Carbonate^[20]

A rather unusual example of macrocyclization wherein carbon dioxide is captured by (nonactivated) amine has been reported.^[21]

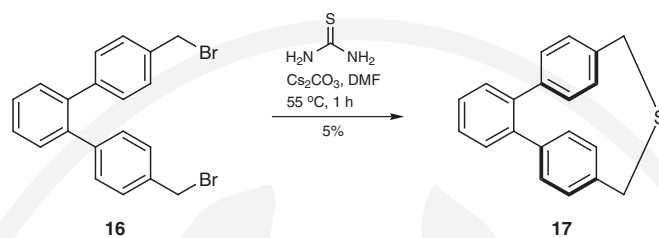
2,17-Ditosyl-5,8,11,14-tetraoxa-2,17-diazabicyclo[16.3.1]docosa-1(22),18,20-triene (12):^[11]

A 250-mL, round-bottomed flask was filled with freshly distilled DMF (100 mL) to which was added bis(sulfonamide) **10** (440 mg, 1 mmol) and dry, powdered Cs_2CO_3 (685 mg, 2.1 mmol). α,ω -Dibromo ether **11** (364 mg, 1 mmol) dissolved in DMF (40 mL) was added over 2–3 h to the magnetically stirred soln, which was then heated at 60 °C for 24 h. About half of the DMF was removed by distillation, H_2O was added, and the resulting crude precipitate was filtered. Recrystallization (EtOH) afforded analytically pure macrocycle **12**; yield: 300 mg (46%); mp 105 °C.

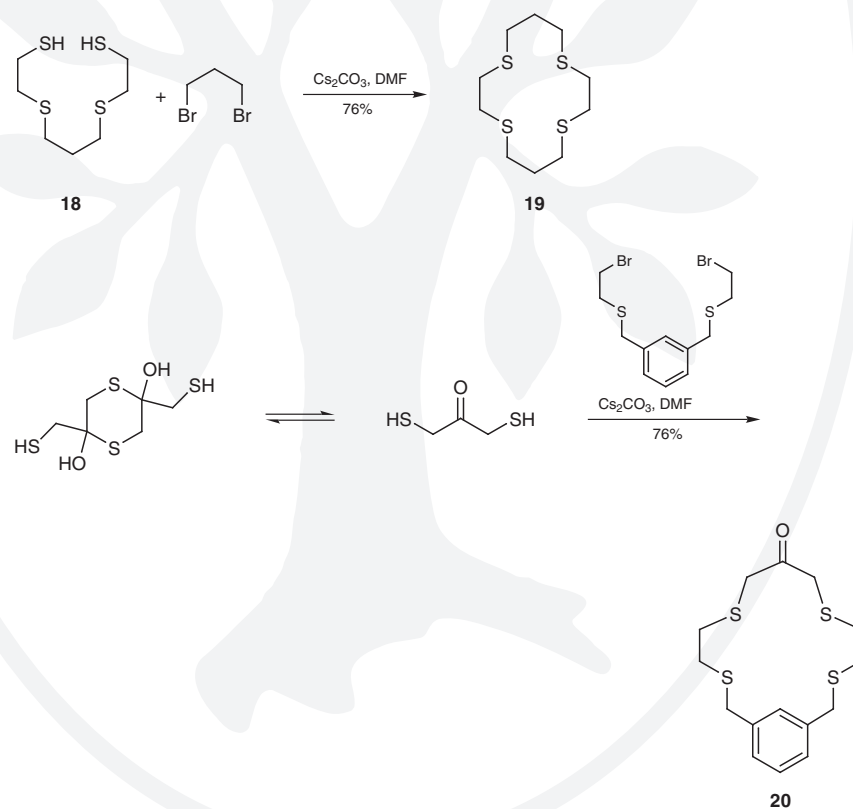
8.4.3.1.3

**Variation 3:
Crown Thioethers**

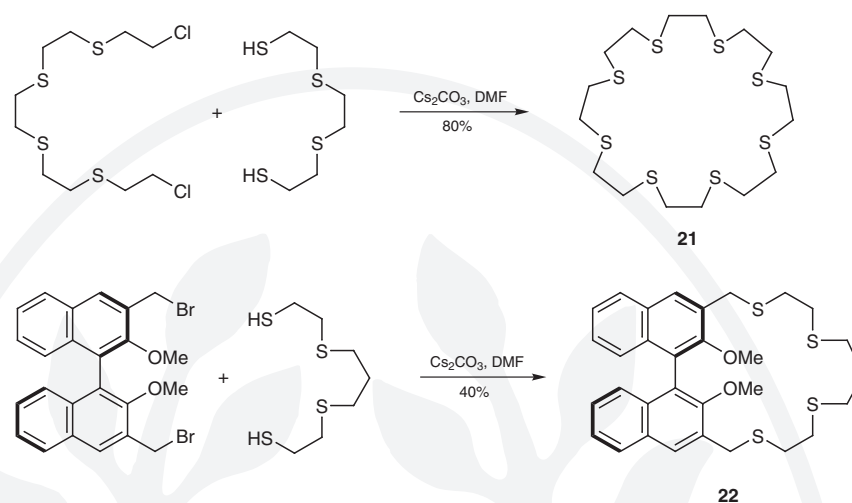
In pioneering work on the cesium-aided synthesis of strained thia-bridged cyclophanes,^[22–25] the preparation of highly strained prototype compound sulfur-bridged terphenyl **17** has been accomplished, albeit in low yield, from dibromoterphenyl **16** (Scheme 8). This product does not form at all when other bases are attempted for the cyclization. Slow addition of the reactants to cesium carbonate suspended in dimethylformamide is used to maintain a low concentration and to promote intramolecular cyclization.

Scheme 8 Synthesis of a Highly Strained Sulfur-Bridged Terphenyl^[24]

This approach has been readily extended to the synthesis of crown thioethers (thiocrown ethers), e.g. **19–22** (Scheme 9).^[26–33] Sulfides are much more hydrocarbon-like than their oxygen or aza counterparts. Cesium thiolates are in general obtained readily by deprotonation in situ of the corresponding thiols, e.g. **18**, in dimethylformamide, although, in some cases, stoichiometric preparation in a protic solvent such as methanol, followed by drying and transfer to dimethylformamide may be preferred. Macrocyclization is then readily accomplished.

Scheme 9 Synthesis of Crown Thioethers from α,ω -Dihalides and Cesium Thiolates, Mediated by Cesium Carbonate^[26,28,30]

for references see p 1514

**5,7-Dihydro-1,4:8,11-dietheno-6-benzothiacyclotridecine (17):**^[24]

A soln of terphenyl **16** (420 mg, 1 mmol) in DMF (50 mL) and a soln of thiourea (75 mg, 1 mmol) in DMF (volume not specified, but probably 50 mL) were simultaneously added dropwise from two precision addition funnels over 5 h to a well-stirred suspension of Cs₂CO₃ in DMF (250 mL) at 55 °C under N₂. After the addition was completed, the mixture was stirred for 1 h at 55 °C, after which the DMF was removed under reduced pressure. The residue was washed with H₂O (2 × 100 mL) and dried (Na₂SO₄). The crude product was purified by chromatography [silica gel, CCl₄ (**CAUTION: toxic**)] followed by recrystallization (iPrOH); yield: 5%; mp 197–201 °C.

1,4,8,11-Tetrathiacyclotetradecane (19):^[26]

This procedure was developed to restrict the quantities of DMF required. Cs₂CO₃ (3.6 g, 11 mmol) was suspended in well-stirred DMF (1.7 L) at 45–50 °C under N₂. A soln of dithiol **18** (2.28 g, 10 mmol) and 1,3-dibromopropane (2.0 g, 10 mmol) in DMF (200 mL) (dithiol **18** and 1,3-dibromopropane do not react spontaneously under these conditions) was added from a slow-dropping funnel over 12–15 h. After this, more Cs₂CO₃ (11 mmol) was added at once, followed by slow addition of another charge of dithiol **18** (10 mmol) and 1,3-dibromopropane (10 mmol), added over 12–15 h. The DMF was removed under reduced pressure, and the residue was taken up in CH₂Cl₂, and the organic extract was washed with H₂O and dried (MgSO₄). The crude substance was recrystallized from EtOH to give 1,4,8,11-tetrathiacyclotetradecane (**19**) as colorless crystals; yield: 76%; mp 116–118 °C.

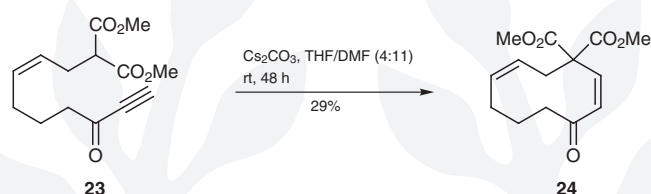
8.4.3.1.4

**Variation 4:
Carbocycles**

The formation of a C–C bond as a ring-closure step seems intrinsically more demanding from a steric standpoint, as carbon, in general, bears more substituents than, say, carboxylate or thiolate. The stereochemical aspects of such ring closures have been examined in detail, and the methodology has been developed into an effective tool for the synthesis of a wide range of medium-sized-ring carbocycles. One of these techniques, which is extensively used, is the addition of a malonate nucleophile to an α,β -unsaturated carbonyl compound (Michael addition).^[34–38] Both enones and ynones undergo reaction; an example is the conversion of ynone **23** into carbocycle **24** (Scheme 10). Intermediates in the addition to an ynone that are conceivable on the basis of classical concepts of hybridization are either an enone anion (vinyl carbanion) or an allenic enolate (negative charge located on

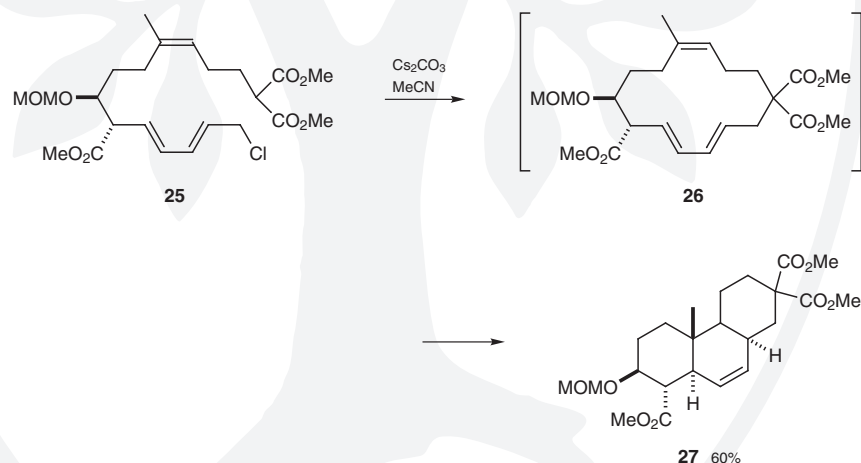
oxygen) or an equilibrium between the two intermediates (not resonance structures). The latter is predicted to be somewhat more stable.^[39,40] The ease with which these intermediates are formed in a macrocyclization is noteworthy. The required *endo-dig* approach^[41,42] of the nucleophile to the acetylenic segment of ynone **23** is relatively easy to visualize; this is less readily done for the synthesis of five- and six-membered rings by analogous intramolecular additions to ynones, even though these proceed readily in the presence of cesium carbonate.^[34–38]

Scheme 10 Synthesis of a Medium-Sized-Ring Carbocycle by Cyclization of an Ynone in the Presence of Cesium Carbonate^[34]



Examples of cyclizations achieved by S_N2 substitutions on allylic halides have also been developed.^[43–46] A particularly instructive example is the ring closure of triene **25** (Scheme 11) to provide (presumably) cyclic triene **26**, which immediately undergoes an intramolecular Diels–Alder reaction that leads to tricycle **27**, an intermediate in a total synthesis of (\pm)-Momilactone A.^[43]

Scheme 11 Synthesis Aided by Cesium Carbonate of a Carbocycle from a Triene, Followed by an Intramolecular Diels–Alder Reaction To Provide a Tricyclic Intermediate in the Total Synthesis of (\pm)-Momilactone A^[43]



Dimethyl (2Z,8Z)-4-Oxocyclodeca-2,8-diene-1,1-dicarboxylate (24**):**^[34]

Dry, powdered Cs_2CO_3 (amount unspecified) was added to (oxoalkenynyl)malonate **23** (21 mg, 0.079 mmol) dissolved in a mixture of THF (4 mL) and DMF (11 mL). The soln was stirred for 48 h at rt, after which it was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by chromatography on a small column (silica gel, hexane/EtOAc 3:1); yield: 6 mg (29%).

for references see p 1514

8.4.3.2

Method 2:**Use of Cesium Carbonate To Generate Nucleophiles**

Cesium carbonate has found widespread use as a base with which to deprotonate, irreversibly and completely, carboxylic acids, thiols, and related acidic compounds. Compared to other salts, the nucleophiles derived on deprotonation are in general reasonably soluble, particularly in dimethylformamide and related dipolar aprotic solvents. In most cases the cesium ion will be well-solvated and the nucleophile will not be strongly associated with the cation. This combination of factors allows for high initial rates of reactions; the appreciable solubility makes it possible to use relatively large quantities of material in limited amounts of solvents. The solubilities of lithium, sodium, potassium, and cesium carbonates (that of rubidium carbonate is not reported) in dipolar aprotic solvents are given in Table 1.^[47] For comparison purposes, the solubilities of some alkali metal propanoates are given in Table 2.^[3]

Table 1 Solubilities of Alkali Metal Carbonates in Dipolar Aprotic Solvents^[47]

Solvent	Solubility (mol·L ⁻¹)				Ref
	Li ₂ CO ₃	Na ₂ CO ₃	K ₂ CO ₃	Cs ₂ CO ₃	
DMF	0.004	0.24	0.054	0.367	[47]
DMSO	0.019	0.135	0.34	1.11	[47]
DMA	0.005	0.020	0.033	0.15	[47]
sulfolane	0.028	0.029	0.12	1.21	[47]
NMP	0.019	0.196	0.711	2.22	[47]

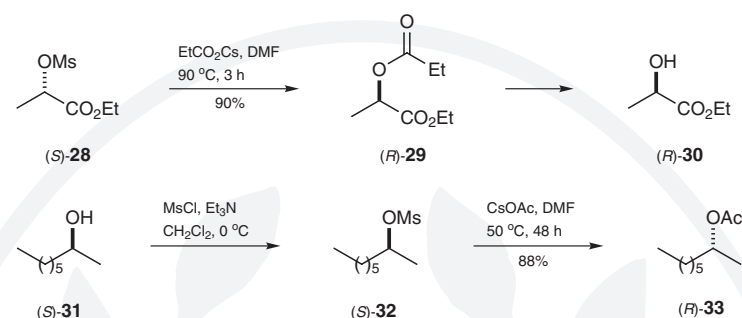
Table 2 Solubilities of Alkali Metal Propanoates^[3]

Solvent	Solubility (10 ⁻² mol·L ⁻¹)				Ref
	EtCO ₂ Cs	EtCO ₂ Rb	EtCO ₂ K	EtCO ₂ Na	
MEK	1.02	0.42	0.06	0.03	[3]
DMF	12.4	3.55	0.46	0.25	[3]
DMSO	>100	22.6	3.87	3.24	[3]

8.4.3.2.1

Variation 1:**Nucleophilic Substitution with Cesium Carboxylates**

The greatest advantage of cesium carboxylates doubtlessly has been the possibility to carry out nucleophilic substitutions with little or no racemization on sensitive compounds. For example, the reaction of enantiomerically pure ethyl (*R*)-lactate [(*R*)-**30**] from the enantiomerically pure methanesulfonate (*S*)-**28** of ethyl (*S*)-lactate [(*S*)-**30**] [alternatively, the ethyl ester of 2-chloropropanoate, obtained from diazotization of (*S*)-alanine can also be used] occurs with S_N2 inversion and lack of racemization to provide ethyl (*R*)-2-(propanoyloxy)propanoate [(*R*)-**29**],^[48] whose propanoyl group may be removed by transacylation (Scheme 12).^[49]

Scheme 12 Nucleophilic Substitution of Mesyloxy Groups by Cesium Carboxylates^[48–50]

That the yield of the substitution product is often higher with cesium than with other alkali metal propanoates arises at least in part from the relatively high solubility of the former in dimethylformamide. The overall rates of nucleophilic substitution owing to this concentration effect are probably highest in this solvent. Moreover, bimolecular substitution also has the best chance of proceeding to completion with a relatively high concentration of nucleophile. Several effects probably contribute to ensure that little or no racemization occurs with cesium propanoate, whereas this is a problem with nucleophiles bearing other alkali metal cations. Firstly, the nucleophilicity of cesium propanoate seems simply to be greater than that of other propanoates, allowing substitution to compete more effectively with the racemization of the starting material (in principle, both second-order processes are equally affected by relative concentrations). Secondly, racemization of the product may occur; if the reaction is completed quickly, the concentration of nucleophile/base also diminishes rapidly and the product is better protected from racemization conditions. This is likely the more important factor.

Cesium acetate may also be used instead of the corresponding propanoate. For example, methanesulfonate (S)-**32** [from alcohol (S)-**31**] undergoes substitution with cesium acetate to give (R)-**33** (Scheme 12).^[50] This has the advantage of providing substitution products with simpler NMR spectra; the acetate (R)-**33** is, however, somewhat more hygroscopic.^[50]

Even compounds more sensitive to racemization such as the methanesulfonate of the dimethylamide of mandelic acid undergo substitution with little or no racemization, although less basic cesium benzoate must be used, as the propanoate substitution product in the presence of cesium propanoate undergoes easy racemization.^[48] Problems of racemization are greater if other alkali metal carboxylates are used, as are synthetic problems such as incomplete substitution, formation of gels during reaction, and more difficult workup of mixtures.

Ethyl (R)-2-(Propanoyloxy)propanoate [(R)-**29**]:^[48]

EtCO₂Cs was prepared by treatment of Cs₂CO₃ (1.6 g, 5 mmol) in dry MeOH (40 mL) with EtCO₂H (1.1 mL, 15 mmol) dissolved in dry MeOH (10 mL). An excess of EtCO₂H was used to effect a complete reaction. After the mixture was stirred for 30 min, the MeOH was removed under reduced pressure, and the remaining colorless powder was washed thoroughly on a filter with dry Et₂O. This material was used in the following reaction. A soln of 2-(mesyloxy)propanoate (S)-**28** (prepared by treatment of optically pure ethyl lactate with 0.1 M MsCl/Et₃N in DMF) and EtCO₂Cs in DMF was stirred under N₂ at 90 °C for 3 h. The DMF was removed under reduced pressure, the residue was taken up in Et₂O, and the Et₂O extract was dried (MgSO₄) and evaporated to dryness; yield: 90%; [α]_D²⁰ +41.9 (c 5, CHCl₃) {cf. ethyl (S)-2-(propanoyloxy)propanoate [(S)-**29**] prepared by acylation of the starting ethyl lactate (S)-**30** with EtCOCl; [α]_D²⁰ –41.8 (c 5, CHCl₃)}.

for references see p 1514

(R)-1-Methylheptyl Acetate [(R)-33]:^[50]

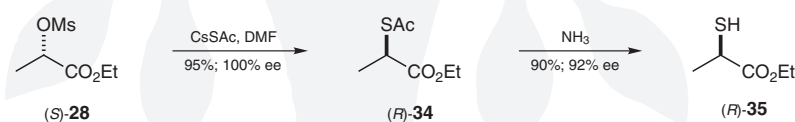
Methanesulfonate (S)-**32** was prepared by the reaction of (S)-octan-2-ol [(S)-**31**] in CH₂Cl₂ with MsCl (1.1 equiv) and Et₃N (1.5 equiv) at 0 °C under N₂. After standard workup, the crude material was used without further purification. CsOAc was prepared by addition of glacial AcOH (2 equiv) to Cs₂CO₃ (1 equiv) in dry MeOH (to make up a 0.1 M CsOAc soln). The soln was stirred at rt for 1 h, after which the MeOH was removed under reduced pressure. Unchanged AcOH was removed by azeotropic distillation with dry toluene, and the residual colorless powder was dried under reduced pressure for 4–5 h. The substitution reaction was carried out in the same flask in which CsOAc was prepared. DMF was added to the CsOAc to make up a 0.1 M soln. To this was added a 1 M soln of methanesulfonate (S)-**32** in dry DMF. The mixture was heated under a N₂ atmosphere at 50 °C for 48 h, then cooled, diluted with H₂O, and extracted with CH₂Cl₂/Et₂O (1:3). The organic extracts were washed with 5% aq HCl, H₂O, and brine, and dried, and the solvent was removed under reduced pressure. Acetate (R)-**33** was purified by flash chromatography; yield: 88%. Hydrolysis afforded (R)-octan-2-ol [(R)-**31**]; [α]_D²⁷ –10.2 (c 0.295, CHCl₃) {cf. literature^[48] value: [α]_D²⁰ –8.9 (c 10, CHCl₃)}.

8.4.3.2.2

Variation 2:**Substitutions Using Cesium Thiocarboxylates**

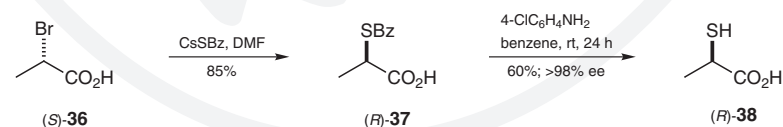
A compound enormously prone to base-catalyzed racemization is the ester of thiolactic acid.^[51] It has been shown, however, that its nearly enantiomerically pure ethyl ester (R)-**35** may be formed from the methanesulfonate (S)-**28** of ethyl (S)-lactate by substitution with cesium thioacetate in dimethylformamide, followed by deacylation of thioacetate (R)-**34** with ammonia (Scheme 13).^[52] A small amount of racemization occurs on deacylation.^[52]

Scheme 13 Nucleophilic Substitution of the Mesyloxy Group of the Methanesulfonate Derivative of Ethyl (S)-Lactate by Cesium Thioacetate^[52]



Virtually enantiomerically pure (R)-thiolactic acid [(R)-**38**] itself may be prepared by substitution of the bromo group of (S)-2-bromopropanoic acid [(S)-**36**] [obtained by diazotization of (S)-alanine in the presence of a bromide] by cesium thiobenzoate, followed by deacylation of the intermediate, (R)-2-(benzoylsulfanyl)propanoic acid [(R)-**37**], with 4-chloroaniline (Scheme 14).^[52] Note that (R)-2-(benzoylsulfanyl)propanoic acid [(R)-**37**] was recrystallized, and that it is possible that a small amount of racemic material was lost at that stage.^[52]

Scheme 14 Synthesis of (R)-Thiolactic Acid by Nucleophilic Substitution of (S)-2-Bromopropanoic Acid^[52]



The more sensitive thiomandelic acid derivatives may be obtained in high (but not perfect) enantiomeric excess by substitution of the methanesulfonate of the *N,N*-dimethylamide with cesium thioacetate in ethanol, a solvent in which less racemization occurs

than in dimethylformamide.^[52] This example illustrates well the subtlety of the competition between substitution and racemization.

(R)-2-Sulfanylpropanoic Acid [(R)-Thiolactic Acid; (R)-38]:^[52]

(S)-2-Bromopropanoic acid {(S)-**36**; $[\alpha]_D^{20}$ -26.1 (neat); 9.0 g, 59 mmol} [obtained by diazotization of (S)-alanine in the presence of NaBr] was treated with a soln of CsSBz (16.7 g, 62 mmol) in DMF (125 mL). After removal of the DMF, treatment of the residue with brine, extraction of the mixture with Et₂O, and drying (MgSO₄) of the organic phase, a thick oil was obtained, which slowly crystallized. Recrystallization (cyclohexane) afforded (R)-2-(benzoylsulfanyl)propanoic acid [(R)-**37**] as colorless needles; yield: 10.5 g (85%); mp 62.5–63 °C. (R)-2-(Benzoylsulfanyl)propanoic acid [(R)-**37**; 5.25 g, 25 mmol] was treated with 4-chloroaniline (3.51 g, 27.5 mmol) at rt in benzene (25 mL) (**CAUTION: carcinogen**) for 24 h. After the reaction, the soln was set aside at 10 °C for 3 h, and the resulting precipitate was removed by filtration. After concentration of the filtrate, the residue was subjected to short-column chromatography (silica gel, CH₂Cl₂) to remove excess 4-chloroaniline (*R_f* 0.9). Evaporation to dryness and distillation (100 °C/4 Torr) of the (oxidation-sensitive) (R)-2-sulfanylpropanoic acid [(R)-**38**] provided a clear oil in >98% ee (by ³¹P NMR^[53]); yield: 1.59 g (60%); $[\alpha]_D^{23}$ +56.3 (c 4, EtOAc).

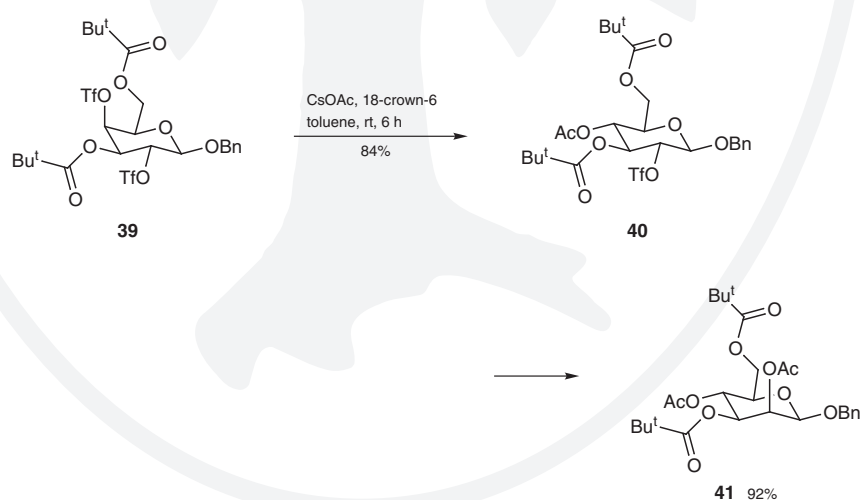
8.4.3.2.3

Variation 3:

Substitution Using Cesium Carboxylates Activated by Crown Ethers

Dimethylformamide, which has been used in reactions described in the preceding sections, is rather high-boiling, and this can provide experimental problems, especially with temperature-sensitive products. Alternative procedures have been developed in which benzene or toluene is used as solvent, and 18-crown-6 is used to solubilize and activate the cesium (and, in some cases, potassium) carboxylates.^[54] This methodology may be applied in the conversion of the protected and activated β-D-galactopyranoside **39** into the protected β-D-mannopyranoside **41** via **40** (Scheme 15).^[55] Other, related conversions are known.^[56–58]

Scheme 15 Conversion of a Galactose into a Mannose Derivative Using Cesium Acetate^[55]

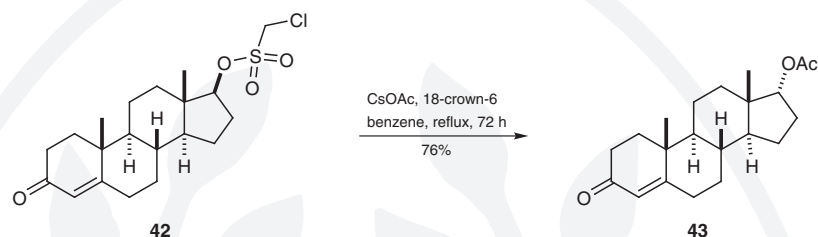


The use of (chloromethyl)sulfonyloxy as a leaving group in sensitive substrates for reactions with cesium acetate, activated with 18-crown-6, as nucleophile is known.^[59] The inversion of severely hindered testosterone derivative **42** (Scheme 16) is a testing example.

for references see p 1514

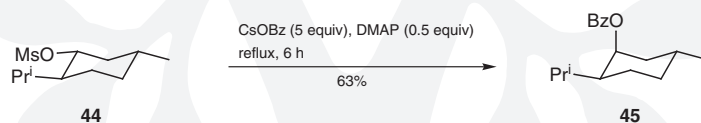
The analogous methanesulfonate derivative is reported to be totally inert, whereas the chloromethanesulfonate **42** gives 17- α -testosterone acetate (**43**) in 76% yield together with a 10% yield of unidentified alkenes.^[59]

Scheme 16 Synthesis of 17- α -Testosterone Acetate Using Cesium Acetate^[59]



Another interesting variation involves activation of cesium acetate with less than stoichiometric amounts of 4-(dimethylamino)pyridine in toluene as solvent. The formation of an undefined complex between cesium and 4-(dimethylamino)pyridine with the generation of a “free” and highly reactive acetate as nucleophile has been postulated. A practical application is the conversion of the hindered (–)-menthyl methanesulfonate (**44**) into isomenthyl benzoate (**45**) (Scheme 17).^[60] Using cesium acetate and 4-(dimethylamino)pyridine, 80% of the product is an alkene formed by elimination; when cesium benzoate is used, mainly S_N2 substitution occurs.

Scheme 17 Conversion of the Methanesulfonate of Menthol into the Benzoate of Isomenthol by Use of Cesium Benzoate and 4-(Dimethylamino)pyridine^[60]



Benzyl 2,4-Di-O-acetyl-3,6-di-O-pivaloyl- β -D-mannopyranoside (41**):**^[55]

A mixture of β -D-galactopyranoside **39** (2.09 g, 2.97 mmol), CsOAc (0.86 g, 4.2 mmol), and 18-crown-6 (1.18 g, 4.5 mmol) in dry toluene (50 mL) was stirred for 6 h at rt, after which no starting material could be detected by TLC (hexane/EtOAc 3:1). The mixture was poured into sat. aq NaHCO₃, and the phases were separated. The aqueous layer was extracted with EtOAc (3 \times), and the combined organic layers were washed with brine and H₂O, and then dried (MgSO₄). Evaporation to dryness under reduced pressure and purification of the crude product by column chromatography (silica gel, hexane/EtOAc 4:1) gave β -D-glucopyranoside **40**; yield: 84%. If the mixture was refluxed and/or subjected to ultrasonication for 1 h, followed by workup as described above, β -D-mannopyranoside **41** was obtained; yield: 92%; mp 138–139°C.

(17 α)-3-Oxoandrost-4-en-17-yl Acetate (17 α -Testosterone Acetate; **43):**^[59]

Testosterone was converted into the chloromethanesulfonate derivative **42** by treatment with ClCH₂SO₂Cl in pyridine. A soln of the crude chloromethanesulfonate **42** (quantity and concentration not reported), CsOAc (3.0 equiv), and 18-crown-6 (0.5 equiv) in benzene (**CAUTION: carcinogen**) was refluxed for 72 h. Workup afforded 17 α -testosterone acetate (**43**) together with unidentified alkene(s) (10%); yield: 76%. [17 α -Testosterone acetate (**43**) was identified by hydrolysis to 17 α -testosterone, which was compared with an authentic sample.]

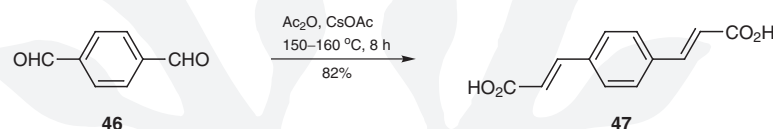
(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl Benzoate (Isomenthyl Benzoate; 45).^[60]

A 0.3 M soln of (–)-menthyl methanesulfonate (**44**; 1 equiv), CsOBz (5 equiv), and DMAP (0.5 equiv) in dry toluene was refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc. This soln was washed with H₂O, 1 M HCl, and brine and dried (Na₂SO₄). Removal of the solvent gave the crude product, which was purified by flash chromatography (silica gel, hexane/EtOAc 10:1 to 6:1). The alkenes eluted first, followed by benzoate **45** (identified by comparison with an authentic sample), and, thereafter, unchanged methanesulfonate **44** (20%); yield: 63%.

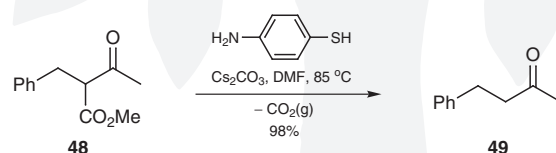
8.4.3.3

Method 3:**Further Synthetic Uses of Cesium Nucleophiles**

As a first step in a synthesis of various 3-acyltetrahydrothiophenes, methanesulfonates of α -hydroxy ketones are substituted by cesium phenylmethanethiolate.^[61] In addition to their use as nucleophiles, cesium carboxylates are effective as bases. For example, cesium acetate has been reported to be more effective than sodium acetate in the Perkin synthesis of bis(acrylic acid) **47** from benzene-1,4-dicarbaldehyde (**46**) (Scheme 18).^[62]

Scheme 18 Perkin Reaction of Benzene-1,4-dicarbaldehyde Using Cesium Acetate^[62]

Cesium thiolates have been used to induce decarboxylation of methyl esters of β -oxo esters, e.g. **48**, to give ketones, e.g. **49** (Scheme 19).^[63] Cesium 4-aminobenzenethiolate, formed in solution, doubtlessly attacks the methyl group in an S_N2 reaction, followed by decarboxylation; in accord with this hypothesis, ethyl esters are barely reactive.^[63]

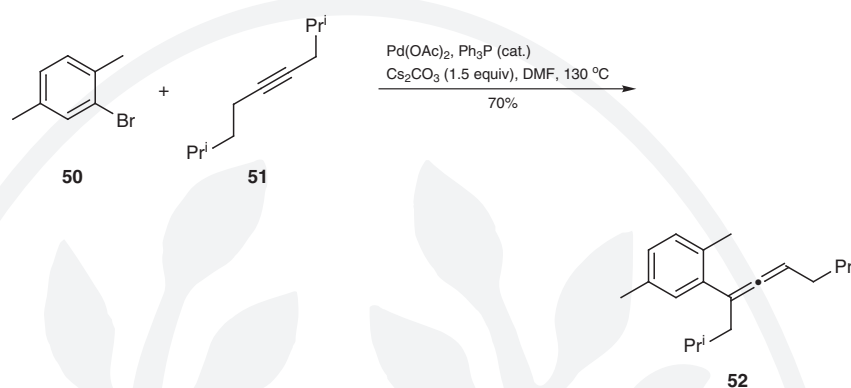
Scheme 19 Cesium Thiolate Induced Decarboxylation of a β -Oxo Ester^[63]

8.4.3.4

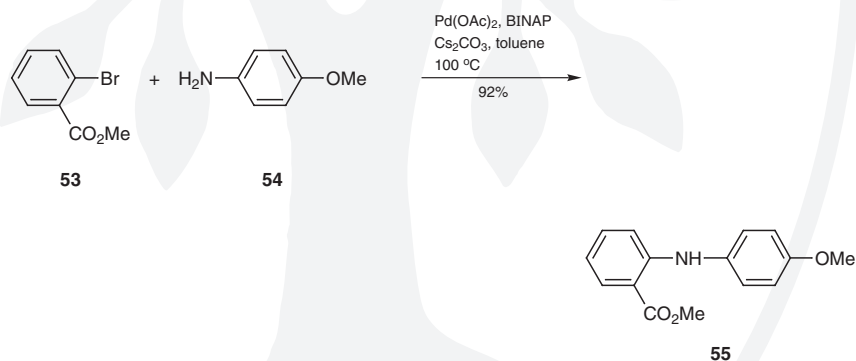
Method 4:**Use of Cesium Carbonate in Cross-Coupling Reactions**

Cesium carbonate has been used as an effective base in various cross-coupling reactions, for example, the preparation of allene **52** from bromobenzene **50** and alkyne **51** (Scheme 20).^[64,65]

for references see p 1514

Scheme 20 Preparation of an Allene in a Cross-Coupling Reaction Mediated by Cesium Carbonate as a Base^[64]

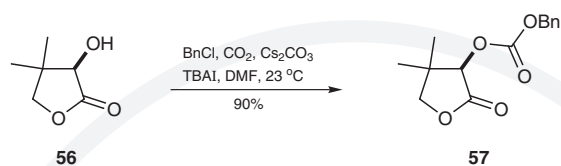
Palladium-catalyzed cross-coupling reactions of bromoarenes with amines are appreciably improved in the presence of cesium carbonate as base rather than, for example, potassium *tert*-butoxide, as illustrated in the synthesis of diphenylamine **55** from bromobenzene **53** and aniline **54** (Scheme 21).^[66–68] Cross-coupling reactions between haloarenes and ureas have also been reported.^[69] Although not a catalyzed cross coupling, phosphoryl-stabilized carbanions derived by deprotonation with cesium carbonate effect substitution on π -complexes of chloro- and bromoarenes.^[70] Cesium carbonate (and other cesium salts) is a generally effective base for C–C cross-coupling reactions by the Suzuki–Miyaura protocol.^[71]

Scheme 21 Palladium-Catalyzed Amination of a Bromobenzene Using Cesium Carbonate as a Base^[66]

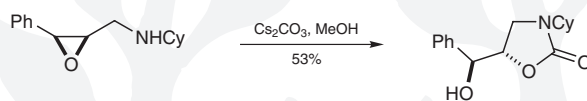
8.4.3.5

**Method 5:
Carboxylation Mediated by Cesium Carbonate**

Cesium carbonate can be used as a promoter, as illustrated by the reaction of (*R*)-pantolactone (**56**) with benzyl chloride and carbon dioxide, to give carbonate **57** (Scheme 22).^[72] A positive pressure of carbon dioxide is maintained during the reaction, and tetrabutylammonium iodide is added as promoter. Thiocarbonates and thiocarbamates can be made by similar procedures.^[73,74] Mixed carbonates can also be prepared.^[75]

Scheme 22 Carboxylation of Pantolactone Induced by Cesium Carbonate^[72]

Amines also undergo carboxylation using cesium carbonate, and the resulting carboxylate may participate in an intramolecular ring opening (Scheme 23).^[76] The carboxylation of amines^[77] and alcohols in the presence of cesium carbonate and tetrabutylammonium iodide appears to be a fairly general process.

Scheme 23 Ring Opening and Carboxylation Mediated by Cesium Carbonate^[76]

for references see p 1514

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