

Efficiency in chemistry: from hydrogen autotransfer to multicomponent catalysis

Francisco Alonso · Francisco Foubelo ·
José C. González-Gómez · Ricardo Martínez ·
Diego J. Ramón · Paola Riente · Miguel Yus

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Abstract A hydrogen autotransfer reaction has been applied to the α -alkylation of ketones, with primary alcohols as the electrophilic component, either under homogeneous (using a Ru complex as catalyst) or under heterogeneous (using Ni nanoparticles) conditions. This process is both very efficient (concerning atom economy) and ecologically friendly (water as the only by-product generated). On the other hand, three multicomponent reactions, namely, the Strecker reaction (without any catalyst), the aza-Sakurai process (catalyzed by ferrite), and the addition of in situ generated Zn enolates to chiral sulfinylamines (catalyzed by Cu), have proven to be very efficient in the generation of a diversity of polyfunctionalized molecules.

Keywords Hydrogen autotransfer · Alcohols as electrophiles · Atom efficiency processes · Multicomponent catalysis

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F. Alonso · F. Foubelo · J. C. González-Gómez · R. Martínez ·
D. J. Ramón · P. Riente · M. Yus (✉)
Instituto de Síntesis Orgánica and Departamento de Química Orgánica,
Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080
Alicante, Spain
e-mail: yus@ua.es
URL: <http://iso.ua.es/>; <http://dqorg.ua.es>

F. Alonso
e-mail: falonso@ua.es

F. Foubelo
e-mail: foubelo@ua.es

D. J. Ramón
e-mail: djramon@ua.es

Introduction

Since the famous report *Opportunities in Chemistry* by Prof. George C. Pimentel [1] at the last Seventh Framework Program of the EU [2], the corresponding committees have conclude that, independent of the different priority areas of each program, it is necessary to improve the efficiency of chemical processes. The main task for organic chemists is still to form C–C and C–X bonds using only a few types of general reactions, including substitutions, additions, and cycloadditions, and involving classical reagents, such as nucleophiles, electrophiles, or radicals.

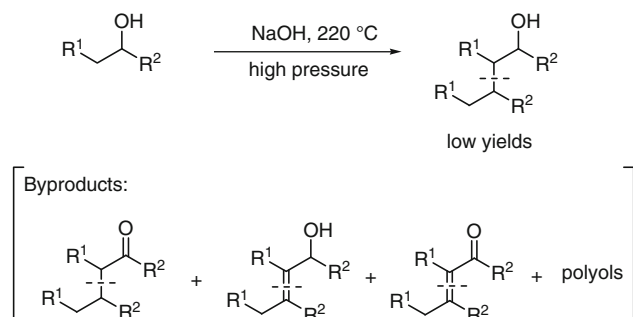
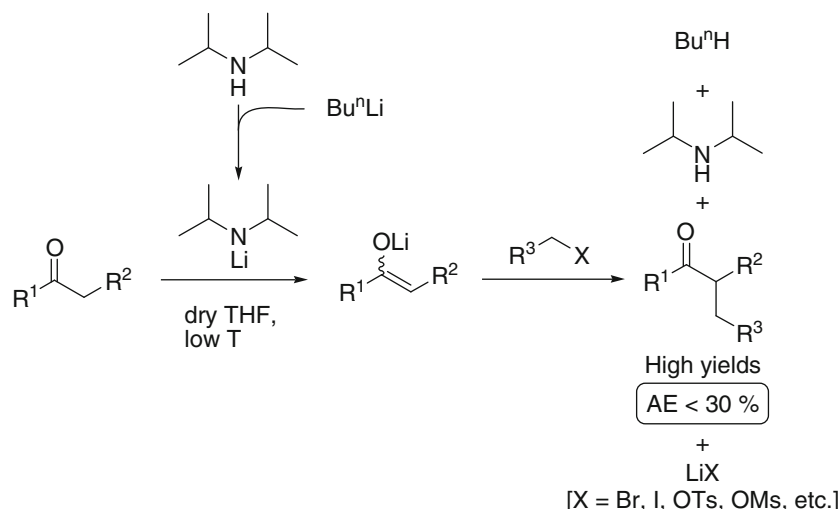
The efficiency in chemistry can be assessed in many ways [3], with the atom efficiency (AE) being very simple to calculate according to Eq. (a). These values give an idea of the benefit on the incorporation of reagents to the final product and, therefore, also provide information about waste, which is related to the sustainability of the process (“green chemistry”).

Atom Efficiency (% AE)

$$\begin{aligned} &= \text{Yield}(\%) \\ &\times \frac{\text{Mw of final product}}{\sum_{i=\text{reagents}} (\text{Equiv.} \times \text{Mw})_i + \sum_{j=\text{catalysts and additives}} (\text{Equiv.} \times \text{Mw})_j} \end{aligned} \quad (\text{a})$$

A paradigmatic case of atom efficiency is the well-known α -alkylation of carbonyl compounds, which falls into the type of electrophilic substitution reactions (Scheme 1). This reaction is a well-established protocol in which, although yields are generally very high, the corresponding atom efficiency never exceeds 30% due to the high weight of molecular waste. For instance, the standard benzylation of cyclohexanone gave 86% yield but only 30% AE [4]. By using other bases with lower molecular weights, such as KH, 98% yield and 26% AE

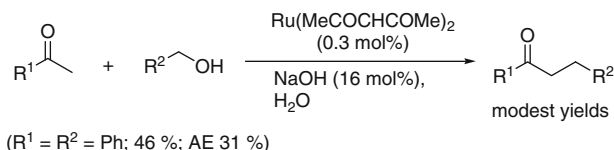
Scheme 1 Standard electrophilic alkylation of a ketone



Scheme 2 The Guerbet reaction

were obtained in the methylation of acetophenone [5]. Similar results were obtained for the enamine formation strategy applied to the allylation of cyclohexanone (66% yield and 22% AE) [6]. In addition, other more sophisticated strategies, such as those involving aldehydes as alkylating agents [7], rendered good yields but very modest atom efficiency. For instance, the benzylation of acetophenone gives 80% yield and 28% AE.

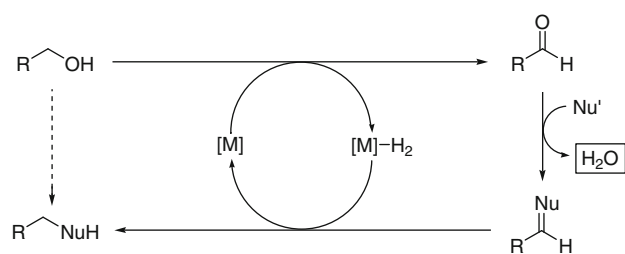
A simple look at the reaction schemes shows that both the base and the leaving group of the electrophile decrease the atom efficiency. Therefore, a decrease in molecular weight of the leaving group will directly increase atom efficiency. The use of alcohols as electrophiles could be an ideal case with the hydroxy moiety being the leaving group. However, this group has a very poor leaving group capacity which is even lower under the classical basic conditions of the alkylation processes. Notwithstanding, at the beginning of the last century, this strategy was assayed by Guerbet [8] in the reaction of different alcohols with sodium hydroxide at very high temperatures. High pressure was required in some cases to afford the new alcohols (Scheme 2) with low yields due to the presence of many different by-products.



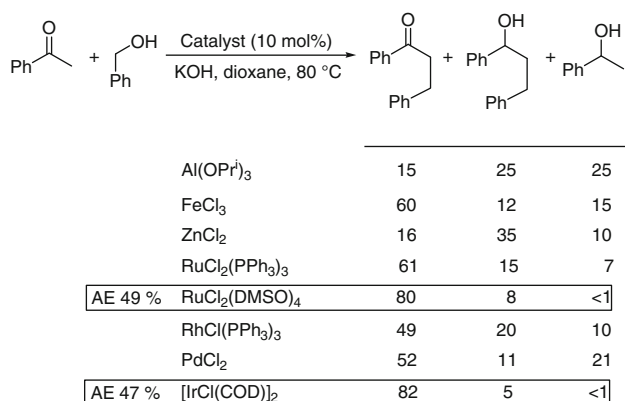
Scheme 3 Alkylation of ketones with alcohols catalyzed by ruthenium species

The Guerbet reaction protocol proved that it was possible to use alcohols (with a low molecular weight leaving group) as electrophiles in the alkylation process, although the low yields and the large amounts of by-products diminished its impact in synthetic chemistry. However, this strategy was revisited nearly 70 years later [9]: The Rhône-Poulenc Company patented a new protocol for the alkylation of methyl ketones, using simple alcohols as electrophiles, in the presence of different ruthenium salts (Scheme 3). Although the yields were generally modest, it should be pointed out that the atom efficiency was as high as those obtained by other strategies.

As it was shown in the aforementioned reactions, the use of primary alcohols as electrophiles is possible due to the change in the oxidation state of the starting reagents. The oxidation of the nucleophilic alcohols by a metal catalyst gives the corresponding metal hydride and aldehydes, which have a high electrophilic character. Then, the condensation with the nucleophile renders an unsaturated intermediate. The final hydrogenation of this double bond by the former metal hydride gives the reaction product, with the whole process resembling an alkylation reaction (Scheme 4). Since the reaction started by dehydrogenation and finished with the return of the hydrogen atoms to the product, it can be considered as a hydrogen autotransfer process [10].



Scheme 4 General scheme for a hydrogen autotransfer process by activation of intermediate



Scheme 5 Catalyst optimization in the alkylation of acetophenone with benzyl alcohol

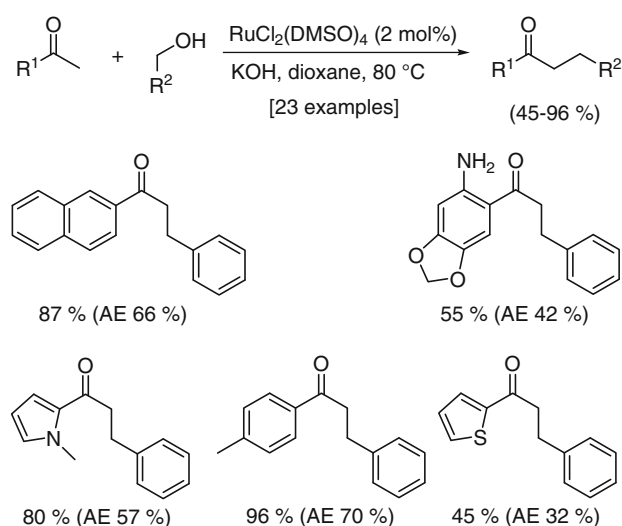
Discussion

Hydrogen autotransfer under homogeneous conditions

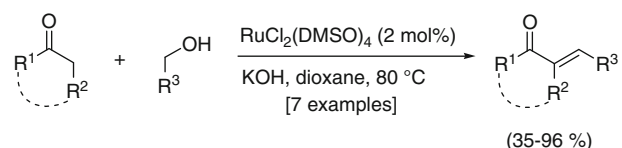
The initial standard reaction depicted in Scheme 5 was chosen to test the activity of different simple catalysts. The ratio of the reaction products was shown to strongly depend on the metal used. For instance, the expected alkylated ketone was the minor product using a typical Meerwein–Ponndorf–Verley catalyst, such as Al(OPrⁱ)₃, while the secondary alcohol obtained by the direct hydrogen transfer was the main product. Among all the tested catalysts [11], the complexes RuCl₂(DMSO)₄ and [IrCl(COD)]₂ gave the best yields, with the former increasing slightly the atom efficiency.

Once the catalyst was optimized, the scope of the reaction was studied. It was found that the reaction gave good results for aryl and heteroaryl methyl ketones with benzyl alcohol derivatives, independent of the nature of the substituents or their position on the aromatic ring. In all cases, the atom efficiency was higher than 30%, indicating that the synthetic approach is very convenient from a sustainability point of view. However, the results were modest in the case of using aliphatic ketones or aliphatic alcohols [11, 12] (Scheme 6).

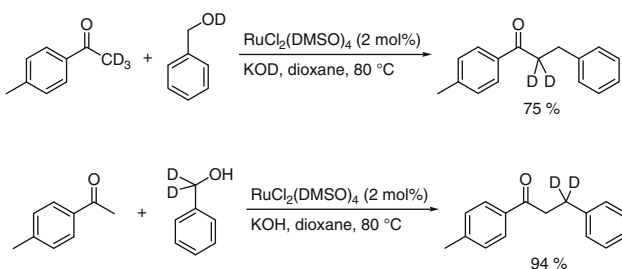
Surprisingly, the hydrogen autotransfer process stopped at the condensation step when the same protocol was applied



Scheme 6 Ruthenium-catalyzed α -alkylation of methyl ketones with alcohols



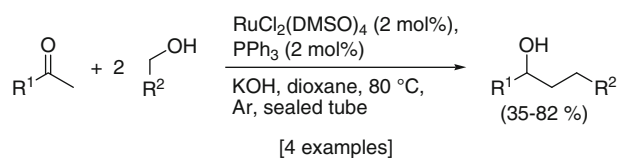
Scheme 7 Ruthenium-catalyzed α -alkylation of cyclic ketones with alcohols



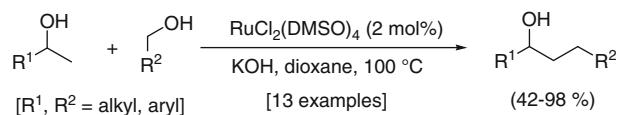
Scheme 8 Labeling studies (% of deuterium incorporation)

to cyclic ketones (Scheme 7) giving the corresponding α , β -unsaturated ketones in good yields. The reason for this behavior is not clear; however, we can hypothesize that this is related to the high stability of the resulting trisubstituted olefin, as well as to the possible steric hindrance [11].

Different labeling experiments were conducted to understand the possible reaction mechanism (Scheme 8). When the reaction was performed using one deuterium labeled reagent, such as the starting ketone at the α -position, the *O*-deuterated benzyl alcohol, or the base, the expected ketone, mono-labeled at the α -position with low deuterium incorporation was the only product obtained. When the same reaction was performed using the three labeled reagents, the incorporation of deuterium was good (75%), but still at the α -position. Only when the labeled reagent was benzyl alcohol deuterated at



Scheme 9 Hydrogen autotransfer and Meerwein–Ponndorf–Verley reduction tandem process



Scheme 10 Ruthenium-catalyzed alkylation of secondary alcohols

the α , α -position, the final product was doubly labeled at the β -position of the ketone with 94% of deuterium incorporation. This behavior (no deuterium scrambling) was rationalized on the basis of the formation of a ruthenium hydride species by dehydrogenation of the starting alcohol but not from an acid–base process. Then, the formed ruthenium hydride would react with the intermediate α , β -unsaturated ketone in a Michael-type addition, but not in a typical hydrogenation mode [11].

The aforementioned protocol could be coupled with a typical Meerwein–Ponndorf–Verley reduction (i.e., alkylation and reduction of the starting ketone) in a one tandem process only by increasing the amount of the primary alcohol and performing the reaction under an argon atmosphere in a sealed tube (Scheme 9). As in the previous cases, yields were good for aryl ketones and benzylic alcohols and modest for aliphatic reagents. The reaction occurs through the alkylation of the ketone to give the corresponding alkylated ketone (see above), which undergoes reduction in the presence of an extra-equivalent of primary alcohol to give the final secondary alcohol [11, 12].

The above-mentioned protocol could be a little more complicated with secondary alcohols as the source of the nucleophile, and primary alcohols as the source of the electrophile. Under these new conditions, the β -alkylation of secondary alcohols by primary ones could be performed selectively (Scheme 10). It should be pointed out that, in spite of the fact that four possible products (two arising from the auto-alkylation processes and two more from the cross-alkylation) can be obtained, only one product was detected (the cross-alkylated product). Moreover, in the case of using aliphatic secondary alcohols, the reaction took place regioselectively at the methyl group, although with a modest yields, as in previous cases, when using aliphatic reagents [13]. The mechanism seems to involve the dehydrogenation of alcohols to ketones and aldehydes, followed by cross-aldol condensation to give the corresponding α , β -unsaturated ketone intermediate. The latter undergoes a Michael-type addition of the

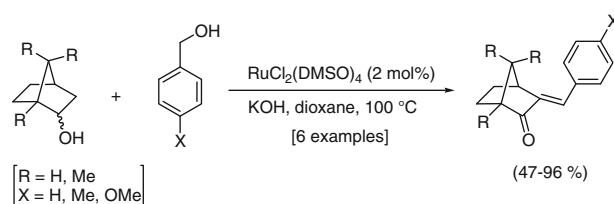
ruthenium hydride followed by hydrolysis of the resulting enolate to give the alkylated ketone, which is finally reduced to the alkylated secondary alcohol.

When the reaction was performed using cyclic secondary alcohols, and as in the previous case of using starting ketones, the reaction stopped at the formation of the corresponding α , β -unsaturated ketone (Scheme 11) with the possible explanation being the same as for the aforementioned case.

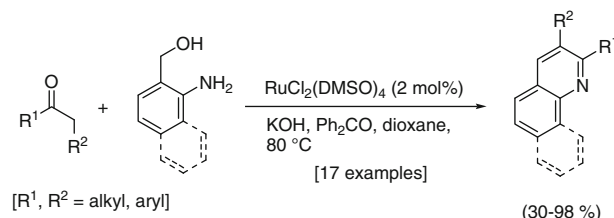
Quinolines, depicted in Scheme 12, were obtained generally with excellent yields when the aforementioned protocol of alkylation of ketones was applied to 2-aminophenylmethanol derivatives [11, 12]. The best results were obtained when a hydrogen scavenger was present in the reaction medium, with benzophenone showing the best results. This methodology represents a new indirect entry to the Friedländer synthesis of quinolines.

The indirect Friedländer synthesis of quinolines could also be performed using secondary alcohols and 2-aminophenylcarbaldehydes or ketones by changing the reaction conditions (Scheme 13). Thus, the reaction in the absence of solvent gave the expected quinolines generally with excellent results. In these cases, the use of aliphatic secondary alcohols was not a handicap, selectively giving only one quinoline in high yields [14].

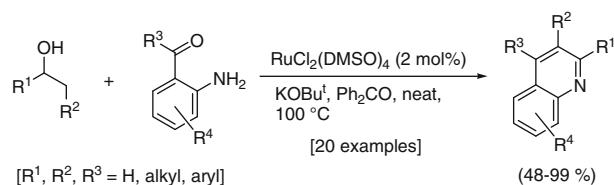
The indirect Friedländer synthesis of quinolines could even be performed using only alcohols as starting reagents, maintaining the high yields obtained previously. The protocol permitted to carry out the reaction with aryl or alkyl 2-aminophenylmethanol derivatives. This result was unexpected since the direct reaction using the corresponding 2-aminophenyl ketone failed under basic conditions, and the reaction had to be performed under harsh acid conditions. In any case,



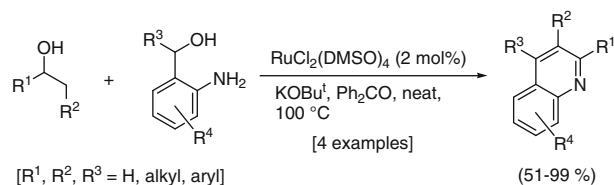
Scheme 11 Ruthenium-catalyzed alkylation of cyclic secondary alcohols



Scheme 12 Ruthenium-catalyzed indirect Friedländer reaction using 2-aminobenzyl alcohol derivatives



Scheme 13 Ruthenium-catalyzed indirect Friedländer reaction using alcohols



Scheme 14 Ruthenium-catalyzed indirect Friedländer reaction using two alcohol derivatives

catalytic amounts of $\text{RuCl}_2(\text{DMSO})_4$ afforded the expected quinolines with an excellent performance. The reaction gave also good yields for aliphatic alcohols, even for primary ones, providing in all cases only one quinoline isomer, which arose from the cross-aldol condensation through the less-hindered kinetic enolate.

Finally, it should be pointed out that we recently found out that the above indirect Friedländer synthesis of quinolines could be performed in absence of any transition-metal catalysis with similar results to those presented in Schemes 12–14 [15]. This synthetic strategy has been applied to the synthesis of chiral camphorsulfonamide-based quinoline derivatives, which in turn have been used in the enantioselective addition of organozinc reagents to aldehydes [16].

Hydrogen autotransfer under heterogeneous conditions

Once we found the hydrogen autotransfer process catalyzed by $\text{RuCl}_2(\text{DMSO})_4$ as an excellent synthetic approach to increase the molecular diversity with good yields and atom efficiencies, we focused on the recyclability of the catalyst. For that purpose, we prepared a ruthenium species supported on magnetite [17] by impregnation of commercially available magnetite (Fe_3O_4) with an aqueous solution of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, the pH of which was increased by a slow addition of an aqueous solution of NaOH. A new catalyst with 2.2% incorporation of ruthenium and a BET area of $11.86 \text{ m}^2/\text{g}$ (adsorption of N_2) was obtained. The new catalyst $[\text{Ru}(\text{OH})_n\text{-Fe}_3\text{O}_4]$ showed the typical magnetic properties of magnetite, with its energy dispersive X-ray spectra showing the presence of ruthenium species. Small clusters of ruthenium species on the structure of the magnetite could be observed in the TEM images (Fig. 1).

When the above ruthenium-supported magnetite catalyst was used in the standard hydrogen autotransfer reaction

depicted in Scheme 5, the yields were modest (40%) and the catalyst lost its activity after one use, independent of the reaction conditions assayed [18].

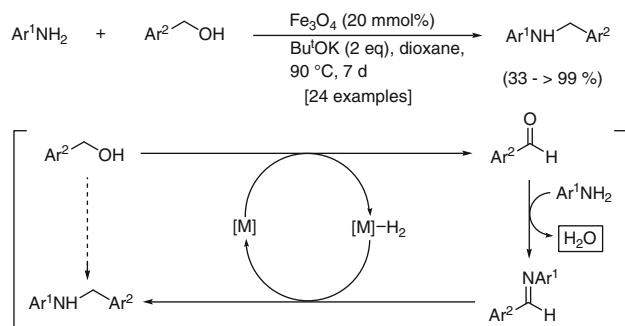
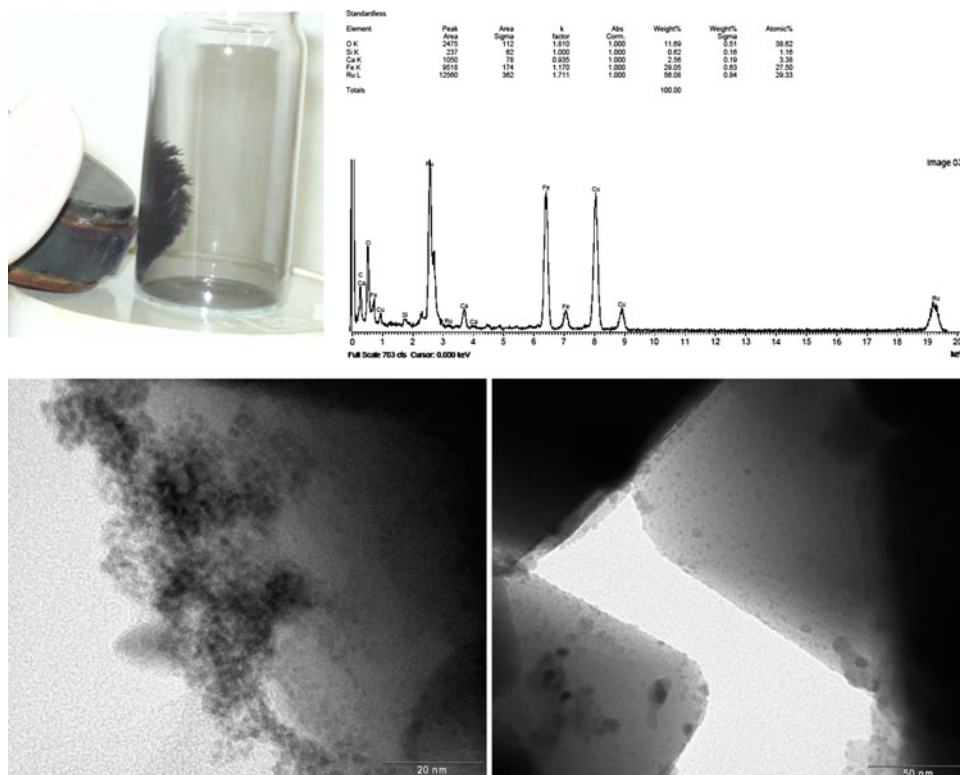
Notwithstanding of this initial disappointing result, we learned that magnetite alone could be an excellent catalyst for the alkylation of aromatic amines (Scheme 15). Thus, the reaction of different arylmethanol derivatives with aryl amines gave selectively the corresponding secondary amines. The reaction worked excellently for electron-poor aromatic amines, such as pyridyl and pyrimidyl amines, and 4-chloroaniline, with practically quantitative yields independent of the arylmethanol partner used. However, yields for electron-rich aromatic amines were much lower. The reaction seemed to be very selective, since in competitive experiments between aromatic and aliphatic amines or alcohols the only detected product was always that one arising from the reaction between both aromatic partners [19].

On the other hand, due to our continuing interest in active metals [20–22], few years ago we reported a fast and mild synthesis of nickel(0) nanoparticles (Ni Nps), from different nickel(II) chloride-containing systems by reduction with lithium powder and a catalytic amount of an arene (e.g., 4,4'-di-*tert*-butylbiphenyl, DTBB) in THF at room temperature (Scheme 16 and Fig. 2) [23,24]. The high reactivity and versatility of these nanoparticles were demonstrated in different functional group transformations [20–22], as well as in the highly selective semihydrogenation of alkynes and dienes [25,26] and conjugate reduction of α , β -unsaturated carbonyl compounds [27].

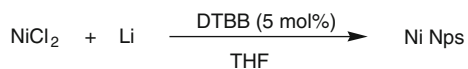
More recently, we reported for the first time the application of catalytic nickel(0) nanoparticles to the transfer hydrogenation with isopropanol of a variety of carbonyl compounds in the absence of any added base at 76°C (Scheme 17) [28,29]. Modest-to-high yields of the corresponding alcohols were obtained, depending on the functional groups and/or the structure of the substrate. The reducing system showed to be diastereoselective for most of the cyclic ketones studied and superior to other forms of nickel under the same reaction conditions. Moreover, it could be reutilized several times in a very simple reaction medium composed of the nickel nanoparticles, isopropanol, and the substrate. According to deuteration experiments, the reaction seems to proceed through a dihydride-type mechanism in which the two hydrogen atoms of the donor become equivalent after being transferred to the metal to give the dihydride (Scheme 18).

Based on the hydrogen transfer of Ni Nps from alcohols, we also described for the first time the use of nickel for the activation of primary alcohols in the α -alkylation of ketones [30,31]. The Ni Nps were shown to be a potential alternative in this reaction to noble-metal catalysts such as those derived from palladium, ruthenium, or iridium. A variety of acetophenones was successfully alkylated with aliphatic and benzylic alcohols to give the corresponding products in moderate-

Fig. 1 Ru(OH)_n-Fe₃O₄ catalyst, EDX and TEM images



Scheme 15 Magnetite-catalyzed selective *N*-monoalkylation of (hetero)arylamines



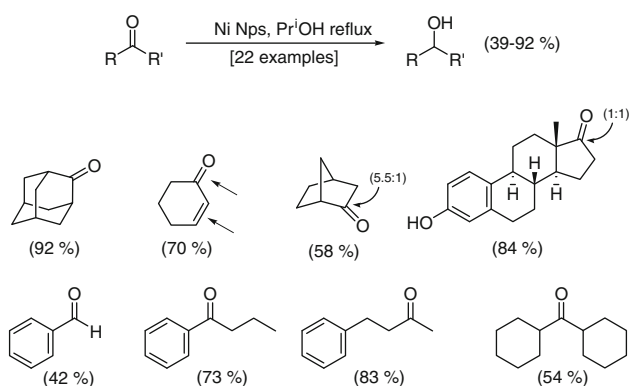
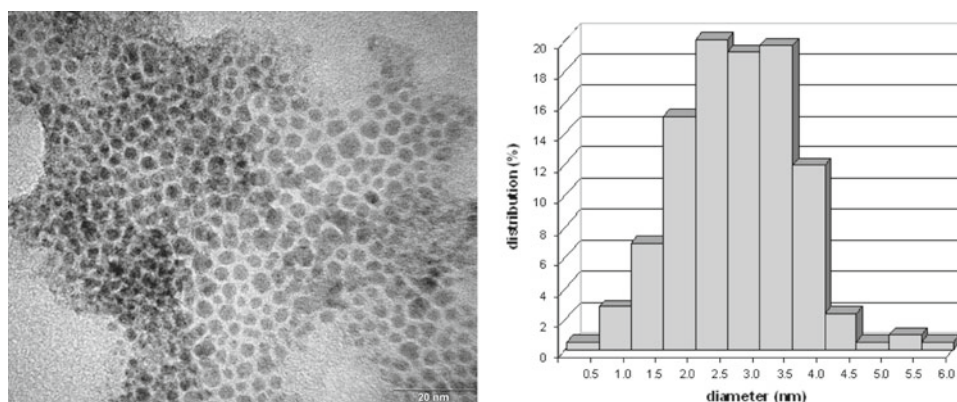
Scheme 16 Generation of nickel(0) nanoparticles

to-high yields (Scheme 19). It is noteworthy that ethanol and *n*-propanol were used for the first time as alkylating agents in this reaction. The alkylation of alkyl methyl ketones was, in general, less efficient and could only be applied to benzylic alcohols. Deuterium labeling experiments brought evidence about a dihydride-type reaction mechanism operating in this reaction and consistent with the results obtained in the hydrogen-transfer reduction of carbonyl compounds (Scheme 19). According to this mechanism, the dehydroge-

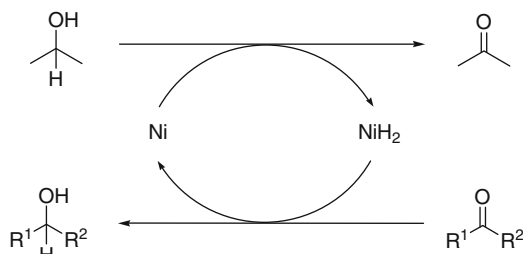
nation of the alcohol would give the corresponding aldehyde and nickel dihydride species. Aldol condensation followed by dehydration would lead to the α , β -unsaturated ketone, which would undergo reduction by hydrogen transfer from nickel (Scheme 20).

Following a similar type of chemistry, we also studied the reactivity of the Ni Nps in the indirect aza-Wittig reaction. In the classical aza-Wittig reaction [32], phosphazenes (iminophosphoranes) react with carbonyl compounds in an analogous manner to phosphorus ylides in the Wittig reaction, to give carbon–nitrogen double bonds. To the best of our knowledge, the conversion of alcohols into *N*-alkyl anilines, through an indirect aza-Wittig reaction, has been only carried out under iridium catalysis [33]. The Ni Nps also found application in the indirect aza-Wittig reaction of alcohols with (triphenylphosphoranyliden)aniline, leading to *N*-alkylated anilines in moderate yields but with wider substrate scope, milder reaction conditions, and simpler reaction system than under iridium catalysis (Scheme 21) [31]. Based on the above mechanistic proposal, a similar reaction pathway was invoked for the indirect aza-Wittig reaction (Scheme 22). In this case, the in situ generated aldehyde would undergo an aza-Wittig reaction with *N*-(triphenylphosphoranyliden)aniline to give the corresponding imine. Reduction of the imine by hydrogen transfer from the alcohol mediated by the Ni Nps would provide the expected *N*-alkylated aniline. It is noteworthy

Fig. 2 TEM micrograph and size distribution of nickel nanoparticles. The sizes were determined for 220 nanoparticles selected at random



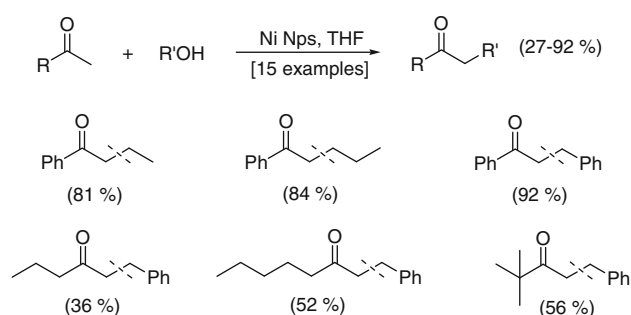
Scheme 17 Hydrogen-transfer reduction of carbonyl compounds catalysed by Ni Nps



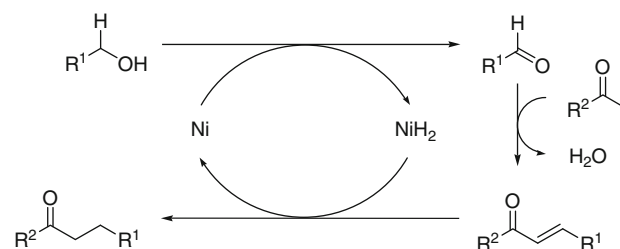
Scheme 18 The dihydride-type mechanism for the Ni Nps-catalyzed transfer hydrogenation of carbonyl compounds with isopropanol

that the Ni Nps were shown to be superior to other common nickel catalysts in both the α -alkylation of ketones and indirect aza-Wittig reaction, proceeding in the absence of any hydrogen acceptor, ligand, or added base.

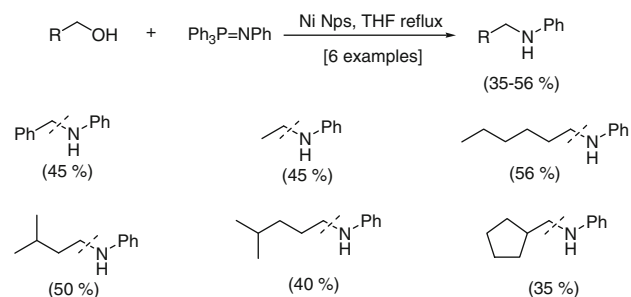
A variety of procedures for the in situ oxidation-Wittig olefination of primary alcohols has been developed involving different oxidizing systems [34]. Most of these procedures involve stabilized ylides and, though all are carried out in one pot, some of them are sequential. Therefore, the course of the alcohol oxidation needs monitoring before the ylide addition. Recently, we have demonstrated that the Ni Nps can promote the Wittig-type reaction of benzyl alcohols and phosphorus ylides to give the corresponding olefins in



Scheme 19 α -Alkylation of ketones with primary alcohols promoted by Ni Nps

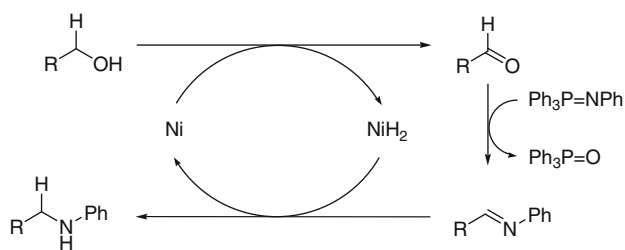


Scheme 20 General reaction pathway for the α -alkylation of ketones with alcohols promoted by Ni Nps

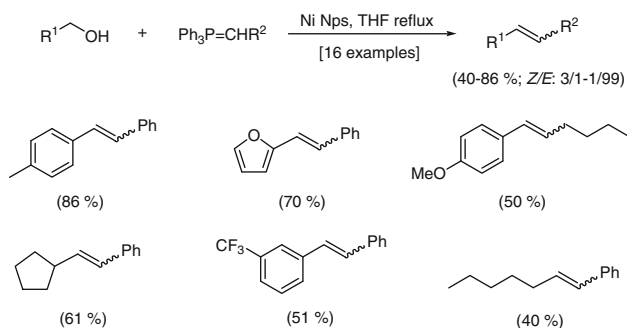


Scheme 21 Indirect aza-Wittig reaction of alcohols with *N*-(triphenylphosphoranylidene)aniline promoted by Ni Nps

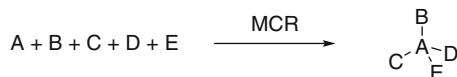
modest-to-high isolated yields (Scheme 23) [35]. In the case of stilbene products, the *Z/E* mixtures can be separated by column chromatography or quantitatively transformed into



Scheme 22 General reaction pathway for the indirect aza-Wittig reaction of alcohols with *N*-(triphenylphosphoranylidene)aniline promoted by Ni Nps



Scheme 23 Wittig-type olefination of benzyl alcohols and phosphorus ylides promoted by Ni Nps



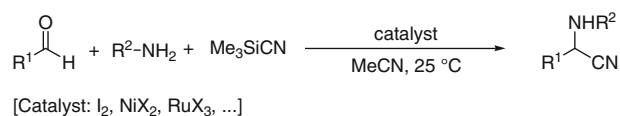
Scheme 24 General scheme for a multicomponent reaction

the *E* stereoisomers by iodine-catalyzed isomerization. To the best of our knowledge, this is the first metal-mediated chemoselective Wittig-type olefination reaction with alcohols, in which there is no standard redox step. Moreover, the reaction also proceeds in the absence of any additive as a hydrogen acceptor.

Multicomponent reactions

Efficiency in chemistry is not only a matter of environment or economics but also to the creation of bonds to give complex structures. Without any doubt, multicomponent reactions (MCR) are a new way of facing the preparation of molecules with high levels of molecular diversity. Multicomponent reactions are those reactions which involve the simultaneous combination of three or more reactants leading to a new product bearing substantial parts of each reactant (Scheme 24) [36]. This approach has been widely applied in organic synthesis, even in asymmetric synthesis [37], as well as in organocatalyzed protocols [38].

In our continuous effort to develop new and simple catalysts for efficient chemistry, we faced the problem of using some of the aforementioned catalysts in multicompo-



Scheme 25 General scheme for a catalyzed multicomponent Strecker reaction

nent reactions. We thought that an ideal case would be the multicomponent Strecker reaction [39,40], since there is a plethora of Lewis acid catalysts which have catalyzed this reaction including iodine, nickel (II) chloride, and ruthenium (III) chloride (Scheme 25).

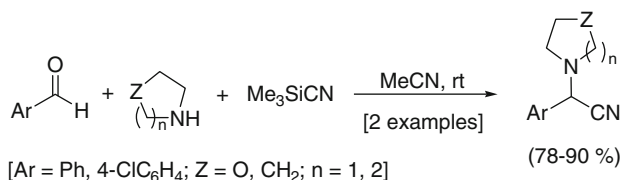
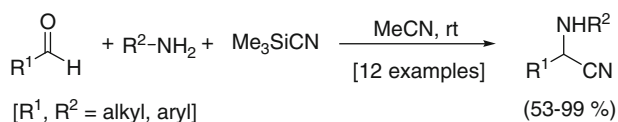
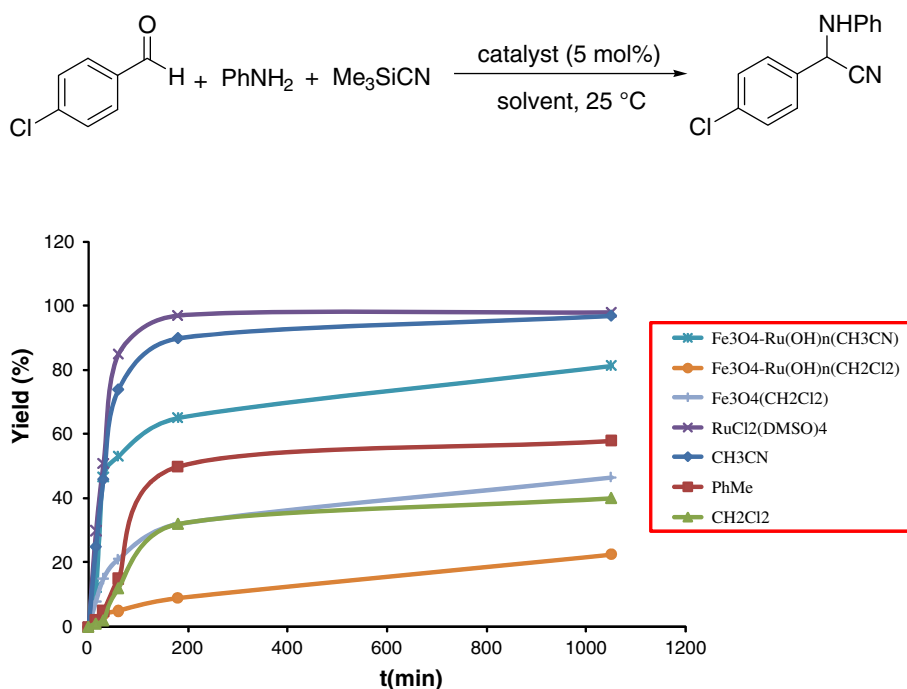
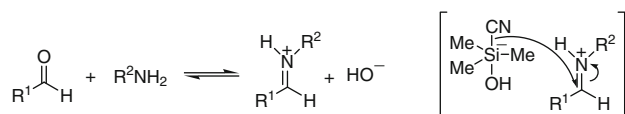
The reaction chosen (Scheme 26) was performed in different solvents and in the presence of different catalysts, with the best catalyst being RuCl₂(DMSO)₄. Surprisingly, the reaction kinetics was similar with and without catalyst when the solvent was acetonitrile [41]. This unexpected result revealed that the role of previous reported catalyst was nearly superfluous, since the same results were obtained in absence of the Lewis acid catalyst. The reaction profiles for other catalysts, such as iodine, nickel chloride, and ruthenium chloride, were similar to that of the uncatalyzed protocol.

This new protocol for the multicomponent Strecker reaction was applied to a broad variety of aldehydes (aliphatic and aromatic) as well as to primary and secondary amines (Scheme 27). In general, the results were excellent and independent of the nature of reagent used [41].

The competitive experiments performed in the absence of some of reagents showed interesting characteristics. For instance, the reaction of highly electrophilic aldehydes and trimethylsilyl cyanide failed in absence of the amine. The reaction of the previously formed imine with trimethylsilyl cyanide also failed [18], even in the presence of water. These facts seemed to indicate that the real nucleophile is not the starting reagent, and that the electrophile could not be the expected imine. Therefore, we hypothesized that the reaction goes through the formation of an iminium hydroxide, and this anion reacts with the starting silyl derivative to form a highly nucleophilic penta-coordinated derivative (Scheme 28). Now, there are two highly reactive species, which could direct the reaction to give the expected amino nitrile.

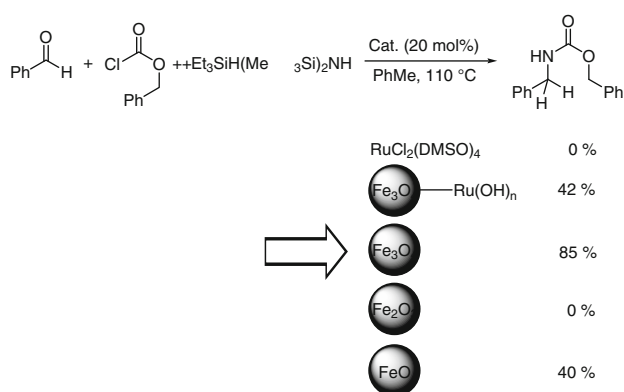
After the above surprising results, we tested our above-mentioned catalysts in the four-component version of the aza-Sakurai reaction (Scheme 29). In this case, the reaction failed in the presence of RuCl₂(DMSO)₄, but the magnetite-supported Ru(OH)_n-Fe₃O₄ catalyst gave a promising 42% yield. However, the reaction with nano-powder magnetite gave the best result. The reaction with other iron oxides showed that the real catalyst center was the iron(II), the presence of iron(III) enhancing its reactivity [42].

The reaction showed a very broad scope, including aromatic and aliphatic acyl chlorides, aldehydes, and ketones,

Scheme 26 Kinetics of the multicomponent Strecker reaction**Scheme 27** Uncatalyzed multicomponent Strecker reaction**Scheme 28** Possible pathway for the uncatalyzed multicomponent Strecker reaction

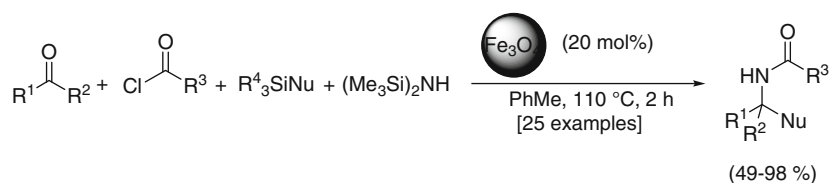
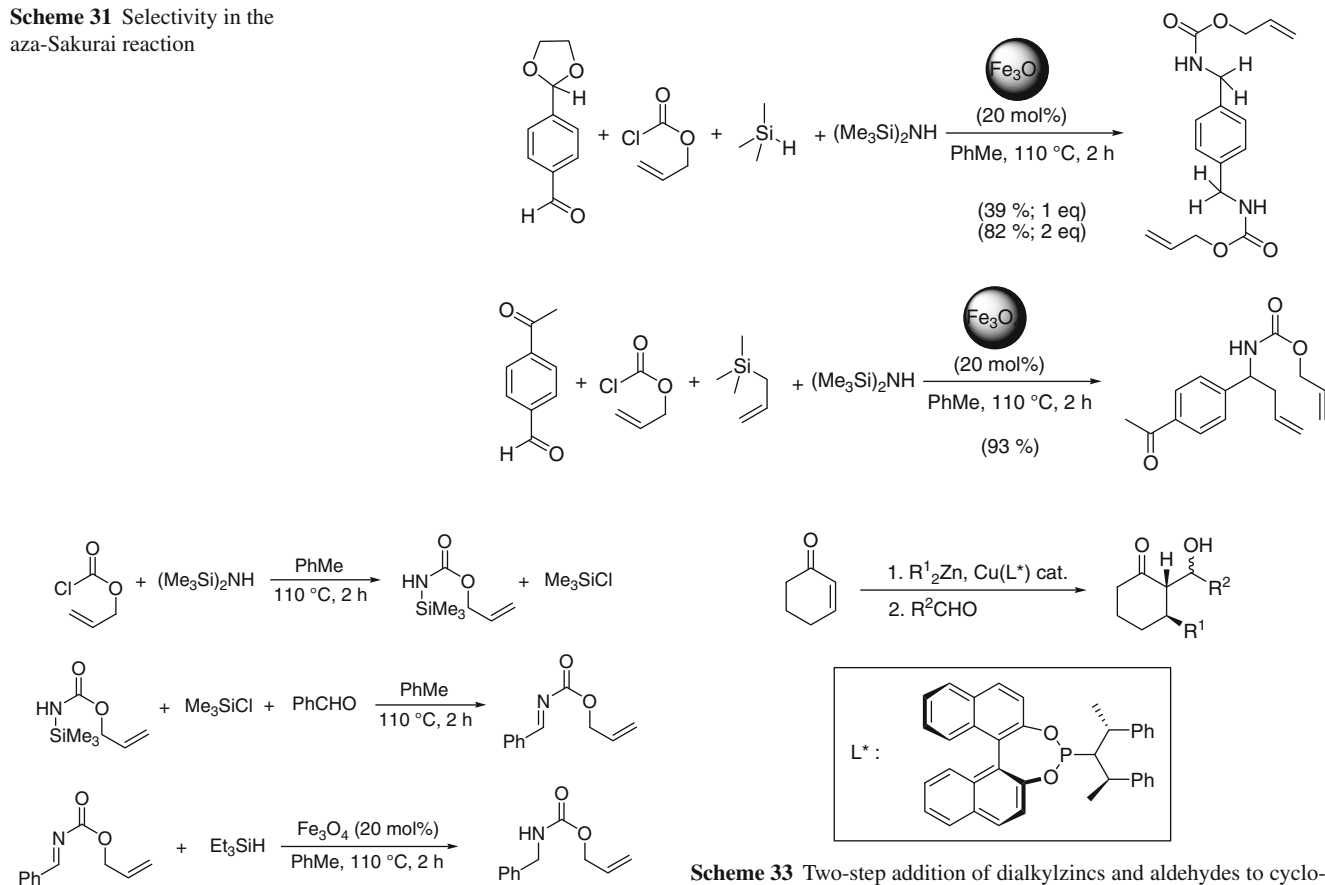
as well as allyl silane derivatives (Scheme 30). The results were quite uniform and, only in the case of using ketones, the reaction time should be increased to keep the previous good results; the catalyst could be reused up to 15 times without any loss of activity. Moreover, the TEM images, the BET areas before and after the reaction cycles, as well as FAAS experiments of reaction solutions, showed a non-degradation of the starting magnetite [42].

The aforementioned difference in reactivity prompted us to study the possible selectivity of the reaction (Scheme 31),

**Scheme 29** Optimization of catalyst for the multicomponent aza-Sakurai reaction

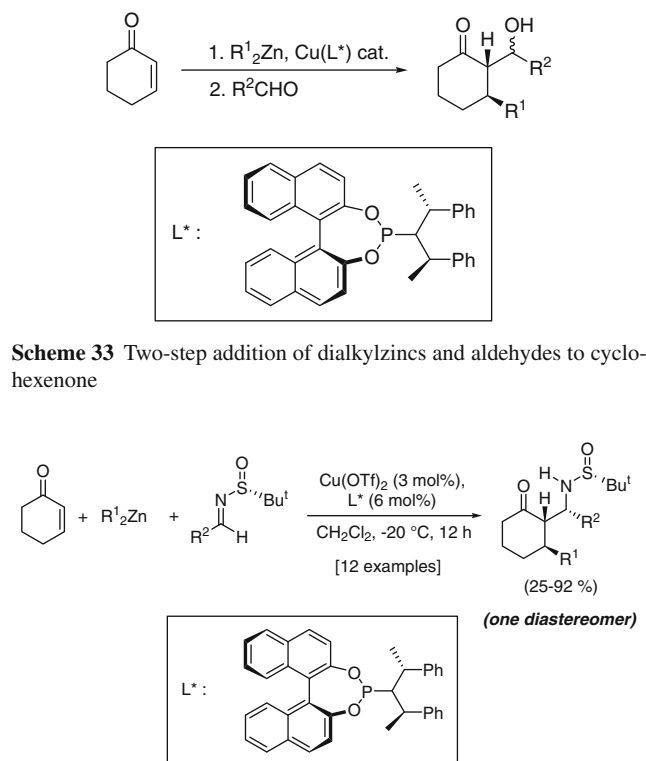
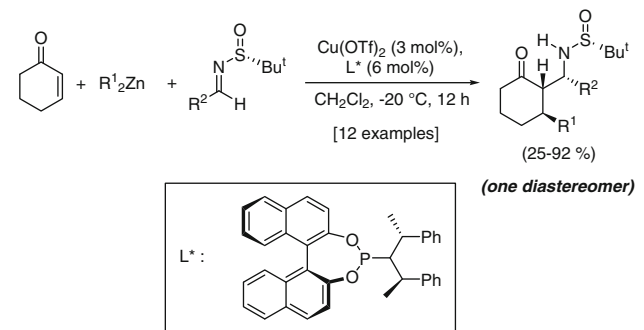
finding that aldehydes and the related ketals reacted in a similar way, thus being indistinguishable. However, when the reaction was performed using a keto-aldehyde derivative the addition was chemoselective reacting only at the most electrophilic aldehyde functionality.

In order to understand the possible pathway of the reaction and the catalyst effect, different experiments were carried out (Scheme 32). For instance, the reaction of a chloroformate with a silylamino derivative gave the corresponding carbamate, independent of the presence or absence of the catalyst, with the yields being practically the same in both cases. The same behavior was observed for the reaction of the former carbamic derivative with benzaldehyde in the presence of trimethylsilyl chloride (by-product formed in the first reaction). Finally, we studied

Scheme 30 Tetracomponent aza-Sakurai reaction**Scheme 31** Selectivity in the aza-Sakurai reaction**Scheme 32** Possible mechanistic pathway for the multicomponent aza-Sakurai reaction

the reaction of the corresponding imine carbamate with triethylsilane to give the expected product, the results of which depended on the presence of different catalysts. Thus, the uncatalyzed reaction failed, even in the presence of trimethylsilyl chloride. The reaction in the presence of magnetite gave a poor result (<10%), and only when the reaction was performed in the presence of both substoichiometric amounts of magnetite and stoichiometric amounts of trimethylsilyl chloride, the yield was 90%, similar to that obtained in the multicomponent version [42].

Chiral enolates are readily accessible in high yields and stereoselectivities (ee > 98%) through the copper-catalyzed addition of dialkylzinc reagents to cyclic enones in the presence of phosphoramidite ligand **L*** [43,44]. These chiral enolates react with different electrophiles to give predominantly

**Scheme 33** Two-step addition of dialkylzincs and aldehydes to cyclohexenone**Scheme 34** Addition of dialkylzincs and chiral aldimines to cyclohexen-2-one

trans substitution. However, when pro-stereogenic aldehydes are used as electrophiles, the newly generated stereogenic center β to the carbonyl group is usually formed in a stereo-random manner (Scheme 33) [44,45].

The multicomponent assembly of dialkylzinc reagents, cyclohex-2-enone, and chiral *N-tert*-butanesulfinyl aldimines led to chiral β -amino ketones in a highly stereoselective manner and good yields. These chiral aldimines are of interest due to the ready availability of both antipodes and the high stereinduction of the *tert*-butyl group. After optimization of the reaction conditions, it was found that 3 mol% of copper, 4 equiv of R_2Zn , and 3 equiv of cyclohex-2-enone were required for a good conversion of the aldimine (Scheme 34) [46,47].

This tandem enantioselective conjugate addition–Mannich reaction provided a selective route to four diastereomeric β -amino ketones by choosing the appropriate configurations of the phosphoramidite ligand and the chiral aldimine. The combination of phosphoramidite L^* and (*R*)-sulfinimine derived from benzaldehyde with Et_2Zn gave the expected β -amino ketone in good yield as a single diastereoisomer (Scheme 35). Similar results were obtained when Et_2Zn was added either before or after the sulfinimine, indicating that enolate formation is possible in the presence of the electrophile, this process being therefore a truly multicomponent reaction. When the pairs L^* -(*S*)-sulfinimine or *ent*-

L^* -(*R*)-sulfinimine were used, the expected β -amino ketones were obtained although with a slightly worse stereoselectivity (about 9:1 dr). This possible mismatch effect could be overcome by using a larger excess of Et_2Zn [46,47].

The substrate scope was found to be broad for aromatic and aliphatic sulfinimines, when Et_2Zn and cyclohex-2-enone were used (Chart 1). It is noteworthy that aliphatic unbranched imines were more reactive than aromatic substrates and that an α, β -unsaturated sulfinimines were compatible with this protocol. Similar levels of chemical efficiency and asymmetric induction were observed when *n*- Bu_2Zn and *i*- Pr_2Zn were used and even with the poorly reactive Me_2Zn . However, a lower yield was obtained in the case of Ph_2Zn (49%) and for α -branched sulfinimines (25% for the aldimine derived from isobutyraldehyde). In general, under the previously optimized conditions, only one of the four possible diastereomers was observed for all sulfinimines used [46,47].

Cyclopent-2-enone is a special case due to: (a) its flatness, which makes it less sensitive to the steric requirements of the chiral ligand, and (b) the resulting enolate is reactive enough to undergo Michael addition to the remaining enone. Conjugate addition to cyclopentenone takes place generally

Scheme 35 Addition of dialkylzincs and chiral aldimines to cyclohexenone: Stereochemistry

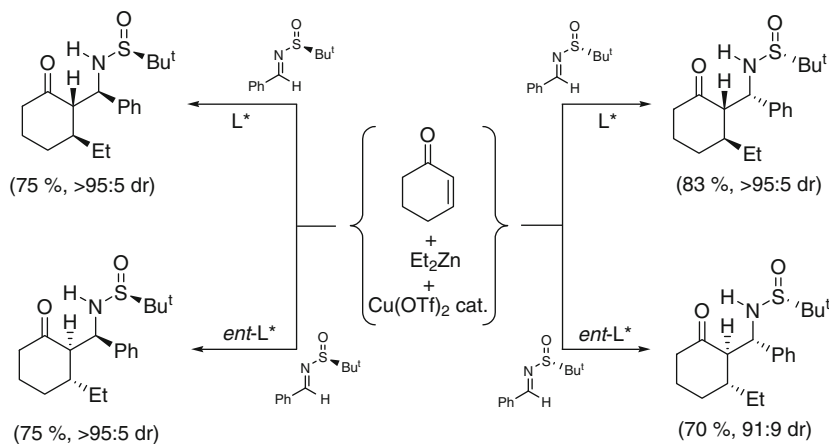
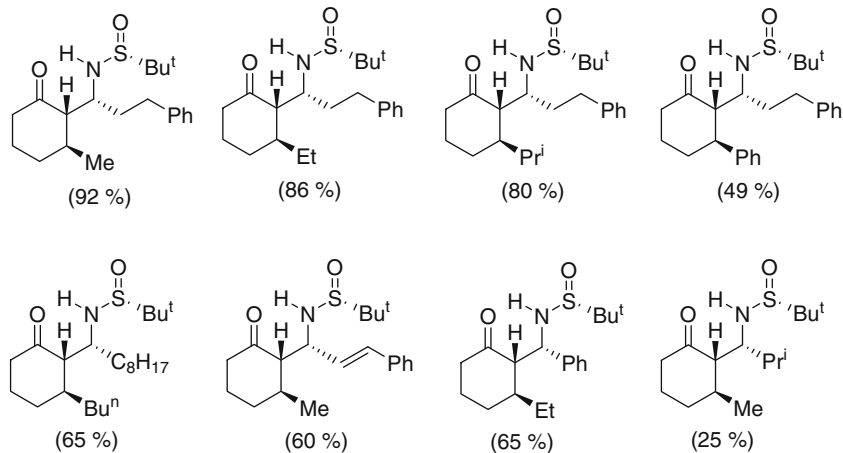
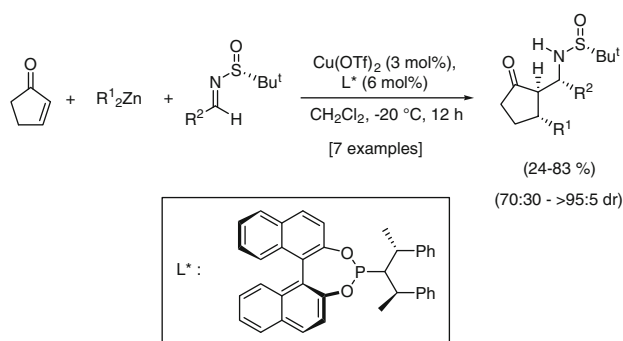


Chart 1 Addition of dialkylzincs and chiral aldimines to cyclohexen-2-one: Scope





Scheme 36 Addition of dialkylzincs and chiral aldimines to cyclopent-2-enone

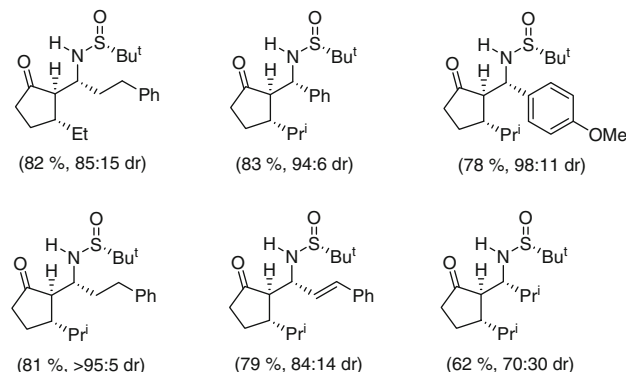


Chart 2 Addition of dialkylzincs and chiral aldimines to cyclopent-2-enone: Scope

with lower ee values than for cyclohexenone and products are isolated in lower yields. Surprisingly, a good diastereoselection was observed when the multicomponent protocol was used with **L***. This excellent diastereoselection is in marked contrast with the very poor enantioselection reported for the conjugate addition of R_2Zn to cyclopentenone using ligand **L*** [46]. Ligand **L*** induces the opposite absolute configuration on the enolate, compared with cyclohexenone. In

this case, a matched combination was observed for ligand **L***-(*R*)-sulfonimine (Scheme 36) [48].

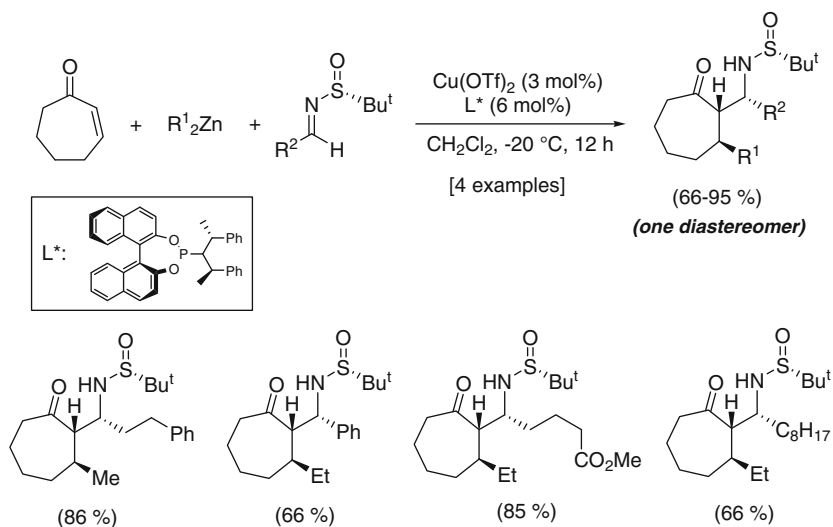
Unfortunately, the diastereoselection was very dependent on the *N*-sulfonimine moiety when examining the scope of the reaction using *i*-Pr $_2$ Zn, and the products of these reactions ranged from a single isomer to 70:30 dr. Very good diastereoselection was achieved when unbranched aliphatic and neutral aromatic sulfonimines were used. Modest diastereoselectivity was observed for the *p*-methoxyphenylsulfonimine, as well as for an α , β -unsaturated sulfonimine. The lowest diastereoselectivity was observed again for the sulfonimine derived from isobutyraldehyde (Chart 2). As expected, excellent diastereocontrol is exerted by the *N*-*tert*-butylsulfonyl group at the Mannich stereocenter, and the minor stereoisomer arises due to poor enantioselection in the conjugate addition to the cyclopent-2-enone [48].

Finally, the use of cycloheptenone was also explored in this reaction, observing a performance similar to cyclohexenone. The mild conditions used were also compatible with the ester group, therefore, providing access to a highly functionalized compound in high yield (85%) (Scheme 37) [48].

Moreover, excellent regioselectivities and isolated yields were obtained for the Baeyer–Villiger oxidation of some five- and six-membered ring β -amino ketones obtained by the present methodology [48]. In addition, reduction of the amino ketones with NaBH $_4$ or LiBHET $_3$ allows access to a wide range of enantiomerically pure *N*-*tert*-butylsulfonyl-1,3-aminoalcohols with five stereogenic centers [49].

As a general conclusion, we have proven that both the hydrogen autotransfer reaction [either under homogeneous using a commercially available ruthenium catalyst or under heterogeneous conditions (a ruthenium-supported catalyst, magnetite, or nickel nanoparticles)] and the multicomponent process (non-catalyzed Strecker reaction, the magnetite-cat-

Scheme 37 Addition of dialkylzincs and chiral aldimines to cyclohept-2-enone: Scope



alyzed aza-Sakurai process, and the copper-catalyzed addition of zinc enolates to chiral sulfinylimines) are useful and versatile methodologies to synthesize a variety of polyfunctionalized molecules in a very efficient and diverse manner.

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