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3d-Metal Catalyzed C–C Bond Formation Through α-Alkylation of Ketones

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Contents

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Abstract The formation of C–C bonds is at the very heart of synthetic chemistry for building the carbon skeleton of molecules. This chapter gives an overview of the catalytic systems developed in recent years based on 3d metals for the α-alkylation of ketones with primary and secondary alcohols by hydrogen auto-transfer.

Keywords 3d metals · Alcohol · Alpha-alkylation · C–C bond formation · Ketone

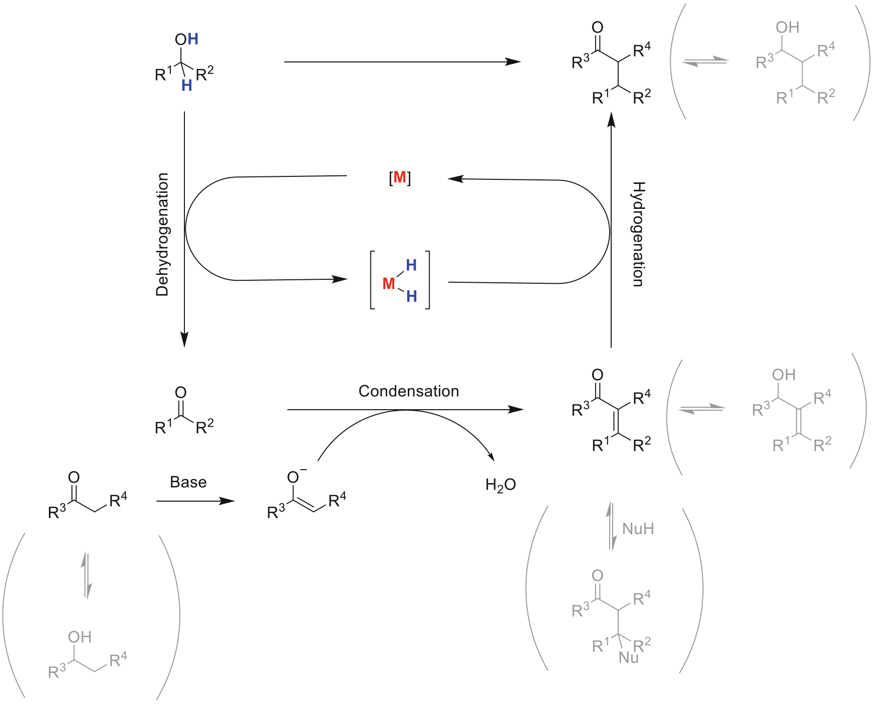
1 Introduction

The formation of C–C bonds is at the very heart of synthetic chemistry for building the carbon skeleton of molecules. Among the range of methods developed, alkylation of enolates with electrophiles, mainly alkyl (pseudo) halides, is a method of choice [1]. However, this route relies on potentially toxic, carcinogenic electrophiles such as iodomethane, and produces a stoichiometric amount of waste. The generation of enolate from ketones also requires a stoichiometric quantity of base. These aspects are not in line with the development of a more sustainable chemistry that is at the heart of current concerns. On the other hand, the aldolization reaction, using aldehydes as electrophiles, is also a convenient method for forming C–C bonds. Aldolization reaction combined with a crotonization step leading to the corresponding enone, followed by a reduction step of the conjugated C=C double bond, leads to the same type of product as those obtained by alkylation with halogenated electrophiles. The major disadvantage lies in the fact that the aldehydes are not quite stable and the reduction step requires either a reducing agent in a stoichiometric quantity or hydrogen pressure.

Since the pioneer contributions of Grigg et al. [2, 3], hydrogen borrowing reactions, based on dehydrogenation/hydrogenation shuttle processes, have emerged as a powerful method for coupling alcohols with many nucleophiles through oxidation of alcohols to carbonyl compounds [4]. It is a gentle method that meets the criteria of green chemistry. Alcohols are stable compounds, readily available and generally of low toxicity. The only side product is one molecule of water, and no excess hydrogen pressure is generated.

Alkylation of ketones with alcohols, by hydrogen auto-transfer, is an ideal solution to all the limitations mentioned below. The key steps of the α-alkylation of ketones with alcohols are (i) the dehydrogenation of the alcohol to the corresponding aldehydes, (ii) the aldol condensation followed by the crotonization and finally, (iii) the chemo-selective reduction of the α-β-unsaturated enones to the final alkylated ketones (Scheme 1).

The overall reaction seems quite straightforward, but several issues need to be overcome in order to develop an efficient process. First, as the catalysts used need to be efficient in both dehydrogenation of alcohols and hydrogenation of enones, often, undesired transfer hydrogenation of the substrate does occur leading to a mixture of alcohols. The selective reduction of the enone can also be an issue leading to allylic



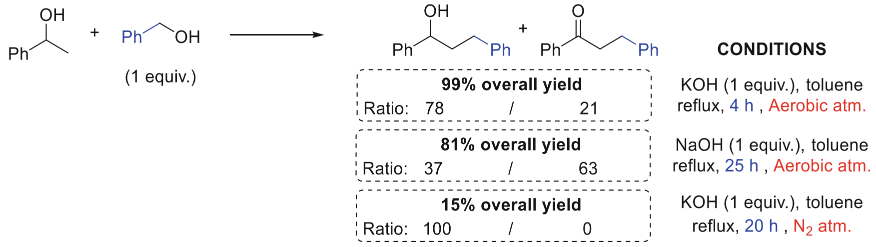
Scheme 1 General mechanism of α-alkylation of ketones with alcohols via hydrogen auto-transfer reaction

alcohol. Then the transient α,β, unsaturated enone is also a Michael acceptor, with which the enolate, or other nucleophiles, can react, affording in the former case 1,5-diketones. Therefore, the role of the catalyst, as well as the experimental conditions, is crucial in directing the successive reactions towards the selective formation of the desired product.

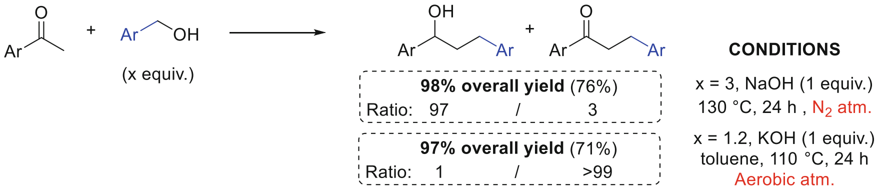
The α-alkylation of ketones was initially developed with precious transition metals, mainly ruthenium and iridium [5, 6]. One of the challenges at the beginning of the twenty-first century is to replace those rare and expensive transition metals by more abundant 3d metals [7]. Great progress has been accomplished in the last decade [8–14]. In this chapter, the development of α-alkylation of ketones with iron, manganese, cobalt, nickel, and copper is discussed in details.

2 α-C-Alkylation of Ketones Catalyzed by Bases

Before going any further in the chapter, we thought important to mention known reactions catalyzed only by bases in the absence of metal complexes, as a non-negligible amount of base is often used in ketone alkylation reactions [15]. In



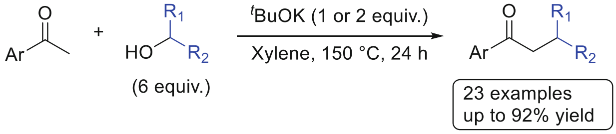
Scheme 2 β-Alkylation of secondary alcohols with primary alcohols catalyzed by bases



Scheme 3 α-Alkylation of ketones with primary alcohols catalyzed by bases

2010, Crabtree et al. described the β-alkylation of secondary alcohols with benzyl alcohols in the presence of alkali metal bases (Scheme 2) [16]. More specifically, in the presence of a stoichiometric amount of potash (KOH), sodium hydroxide (NaOH) or potassium tertbutylate (^{t}BuOK), in toluene, at reflux under an air atmosphere, one equivalent of 1-phenylethanol reacts with one equivalent of benzyl alcohol to form the corresponding β-alkylated product in yields of over 70%, with a marked preference for the alcohol at short times (from 78:21 to 99:1), then for ketones at longer times, probably due to aerobic oxidation of the product. Under a nitrogen atmosphere, conversion and yield dropped significantly (18% and 15%, respectively) with the formation of alcohol exclusively. The authors propose a mechanism based on an Oppenauer oxidation and a Merwein-Pondorff-Verley type reduction promoted by alkali metal bases [17, 18]. It is important to note that weak bases such as Cs_2CO_3, K_2CO_3, and K_3PO_4 did not promote such reaction. The same reaction was recently reinvestigated by Johnson et al. who found that performing the alkylation of secondary alcohols with benzylic alcohols in a sealed pressure tube under air allowed to decreased the amount of KOH to 25 mol% (toluene, 120°C, 18 h) while keeping high conversions and yields [19].

In the same vein, Xu et al. described the α-alkylation of ketones with primary alcohols in the presence of bases (Scheme 3) [20]. Under an inert atmosphere at 130° C over 24 h, in the presence of one equivalent of sodium hydroxide (NaOH) and an excess of primary alcohol (3 equivalents), reduced alkylation products were obtained with good selectivity. The absence of O_2 prevents the oxidation of alcohols and the excess of reactants favored the reduction of the alkylated product via MPV reaction. The alkylated ketones, on the other side, were obtained in the presence of one equivalent of KOH, at 110°C in toluene under aerobic conditions over 24 h. It is



Scheme 4 α-Alkylation of ketones with secondary alcohols catalyzed by bases

interesting to note that this "metal-free" reaction, as the one of Crabtree, is limited to benzyl alcohols, as with hexan-1-ol, only 40% yields were obtained after 3 days at 160°C in the presence of one equivalent of KOH.

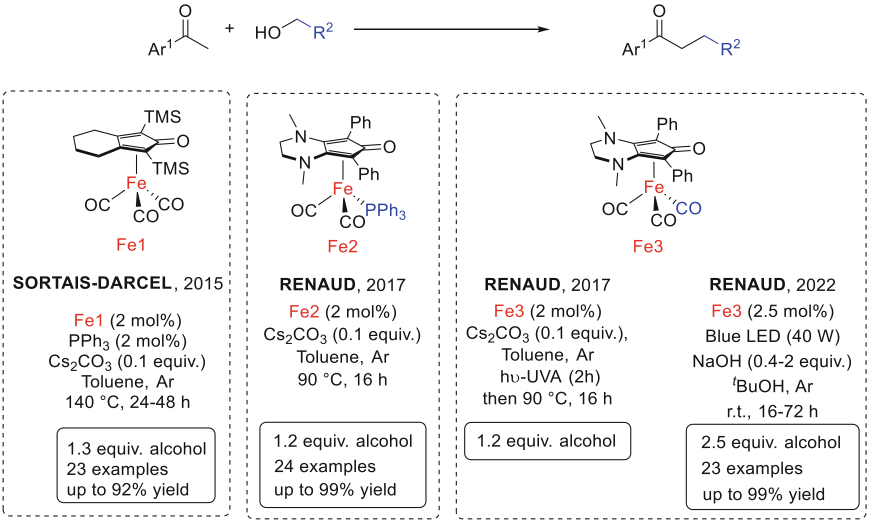
The alkylation of ketones with secondary alcohols was also described under metal-free conditions by Morrill et al. (Scheme 4) [21]. 1-(2,3,4,5,6-pentamethylphenyl) ethenone, as model substrate, was alkylated in good yield by a variety of secondary alcohols (6 equiv.) at 150°C in xylene in the presence of ^{t}BuOK (1 or 2 equiv.). Under these conditions, ^{t}BuONa and ^{t}AmONa bases also promoted the reaction, while KOH and K_2CO_3 were found to be inactive.

3 α-C-Alkylation of Ketones Catalyzed by Iron

3.1 Activation of Primary Alcohols

The first example of α-C-alkylation of ketones with 3d transition metals catalysts was accomplished with iron-based catalysts, namely Knölker-type complexes [22]. Knölker-hydride complex was first described in 1999 by Knölker et al. as an intermediate in the demetalation of tricarbonyl(cyclopentadienone) iron for the synthesis of five membered ring by [2 + 2 + 1] cycloaddition of two alkynes and one CO [23]. In 2007, a breakthrough was accomplished, when Casey et al. demonstrated that Knölker-hydride complex, the iron structural analogue of the ruthenium Shvo complex, was an efficient catalyst for hydrogenation and transfer hydrogenation of carbonyl derivatives [24, 25]. Soon after, cyclopentadienone iron tricarbonyl analogues were used as air stable precatalysts and Oppenauer oxidation were developed, opening the way to its use in hydrogen borrowing [26, 27]. Quintard et al. developed a cooperative iron-catalyzed borrowing-hydrogen/iminium-activation strategy for the transformation of allylic alcohols into β-chiral-alcohols [28]. Barta et al. pioneered the first direct N-alkylation of amines with alcohols [29]. A year later, Sortais et al. applied Knölker-type iron complexes for α-C-alkylation of ketones [30].

Using tricarbonyl cyclopentadienone iron complex **Fe1** (2 mol%) in combination with PPh_3 (2 mol%), in the presence of Cs_2CO_3 (10 mol%) in toluene, at 140°C, the alkylation of a variety of ketones was achieved in moderate to good yield with both benzylic and aliphatic alcohols (Scheme 5). A slight excess of alcohols (1.3 equiv.) was used to improve the overall yield, but in all the cases, a small amount of alcohols

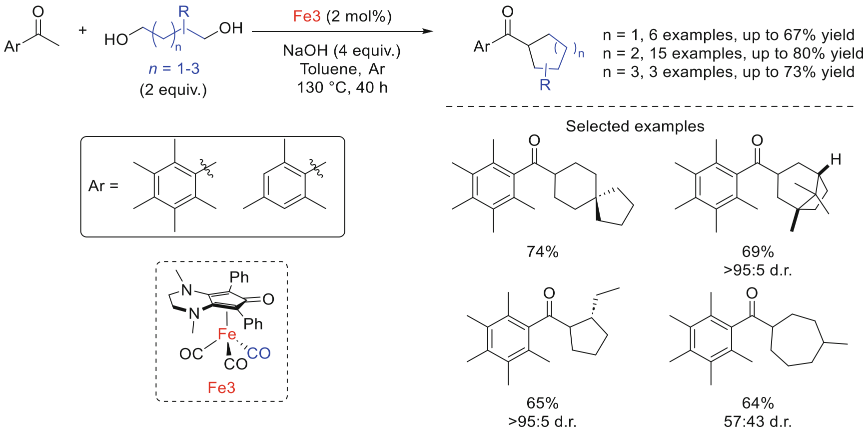


Scheme 5 Knölker type iron complexes for α-alkylation of ketones

arising from the reduction of the keto-group of both starting materials or products was detected. The same catalytic system was also proven to be efficient in Friedländer annulation to yield quinolines.

The overall efficiency of the α-alkylation of ketones was remarkably improved by Renaud et al. with modified Knölker complexes (Scheme 5). Considering the ambiphilic character of the active 16 electrons complex, namely dicarbonyl cyclopentadienone iron complex, that can be regarded as a "transition metal frustrated Lewis pair," Renaud et al. prepared an electron enriched N,N′-dimethyl 3,4-ethylenediamino-substituted cyclopentadienone as ligand [31–33]. Combining a thorough theoretical and experimental study, Renaud et al. showed that both iron complexes **Fe2** and **Fe3** bearing electron rich ligand were highly active in the α-alkylation of ketones [34]. The typical conditions were 90°C for 16 h in toluene in the presence of Cs_2CO_3 (10 mol%), **Fe2** (2 mol%), one equivalent of ketones and 1.3 equivalent of alcohol. With complex **Fe2** bearing a thermally labile PPh_3, thermal activation was sufficient whereas for **Fe3** with three carbonyl ligands, a preactivation step, i.e., irradiation by UV-A light, in order to decoordinate one CO was necessary. The main advantage over previous system, in addition to the lower temperature, was that no overreduction was detected, even in the presence of excess of alcohols.

Lately, the activity of diaminocyclopentadienone iron tricarbonyl complex was reinvestigated by the same authors under blue-light irradiation in order to develop a photoinduced process based on a single catalyst able to harvest the visible light and promote the chemical reaction [35]. Complex **Fe3** was able to play both role by promoting the α-alkylation of a variety of aromatic and aliphatic ketones with



Scheme 6 Synthesis of cycloalkanes via hydrogen borrowing reaction promoted by iron

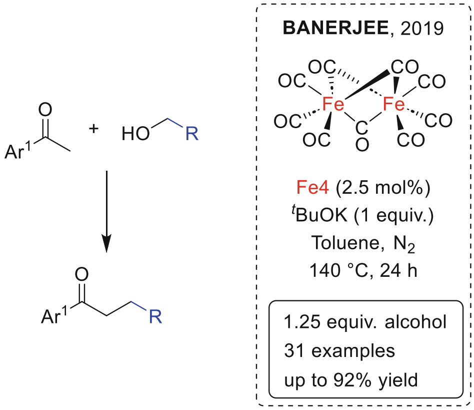
aliphatic or benzylic alcohols in ^{t}BuOH (or toluene) at room temperature in 16–72 h. The key of this success was the irradiation with 40 W Kessil blue LED lamp, lower power led to lower conversion. It should also be noticed that, unlike the thermal conditions described above, at least 40 mol% of NaOH were requested and that 2.5 equivalents of primary alcohols were used. Nonetheless, the process is quite efficient as even 1-butanol, a model aliphatic alcohol, can be used as electrophile, although it requires a stoichiometric amount of base (1 equivalent of NaOH, 72 h, 45% yield).

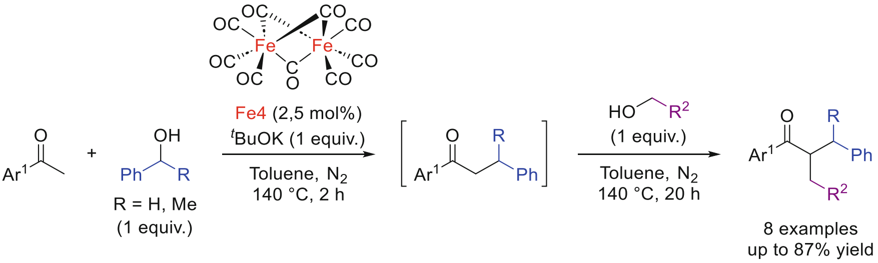
Preliminary insights were collected on the mechanism. It was shown that the visible light irradiation induced both the chemoselective reduction of enone to ketones and the dehydrogenation step at r.t, but did not promote the decoordination of one CO. The catalytic activity was rationalized by an initial Hieber-type activation in the presence of NaOH, followed by the release of H_2 by reaction with ^{t}BuOH to generate the active di-carbonyl 16 electrons iron species.

Double α, α-alkylation of ketones with 1,n-diols is more challenging than mono-α-alkylation of substituted methylketones as the 1,n-diols under hydrogen borrowing conditions can undergo various type of self-condensation, oligomerization, or polymerization. Inspired by the seminal contribution of Donohoe et al. with iridium catalysts [36], Renaud et al. succeeded in synthesizing cycloalkanes from terminal diols and 1-mesitylethan-1-one via hydrogen borrowing strategy [37]. The key parameters were: diaminocyclopentadienone iron tricarbonyl complex **Fe3** (2 mol%), a temperature of 130°C, NaOH (4 equivalents) as the base, an excess of diol (2 equivalents) and a concentrated reaction mixture (5 M) in toluene for 40 h (Scheme 6). Under such conditions, 5, 6, and, 7 membered cycloalkanes were constructed, including substituted diols.

Apart from catalytic systems based on Knölker-type complexes, few examples have been described in the literature. Banerjee et al. reported the alkylation of substituted methylketones with primary alcohols (1.25 equiv. excess) in toluene, at 140°C under N_2 atmosphere in the presence of $Fe_2(CO)_9$ (2.5 mol%) as catalyst and

Scheme 7 Non-Knölker type iron complex for α-alkylation of ketones





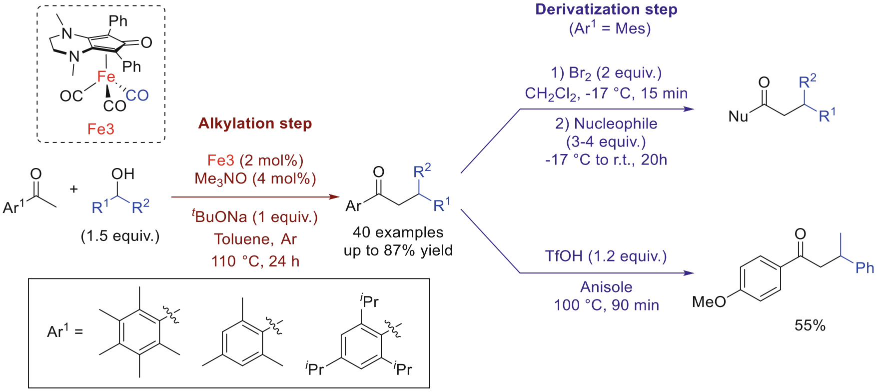
Scheme 8 Synthesis of dissymmetric α,α-disubstituted ketones from methylketones promoted by iron catalyst

^{t}BuOK (1 equiv.) (Scheme 7) [38]. A selectivity of 18:1 towards the α-substituted ketone vs the corresponding alcohol was recorded for the α-alkylation of propiophenone with benzyl alcohol. Blank experiments carried out in the absence of iron catalyst revealed the formation the product in low yield (24% in ketone, but 40% hydrogenated product). This transformation is not limited to benzylic alcohol as cyclopropyl methanol, cyclohexyl methanol or 1-butanol were amenable for this transformation.

The scope of the transformation was extended first to the cross-coupling reaction of secondary alcohols with primary alcohols and then to a one-pot sequential double alkylation of acetophenone derivatives with two different alcohols affording dissymmetric α,α-disubstituted ketones from methylketones (Scheme 8).

Yang et al. used FeCl$_2$ (1 mol%) in toluene at 150°C in the presence of ^{t}BuOK (10–50 mol%) under an argon atmosphere to achieve the alkylation of acetophenones derivatives with aliphatic and benzylic alcohols in moderate to good yield (60–90% in most cases) [39].

It also worth mentioning that an example of a heterogeneous system was reported by Namitharan et al. based on iron oxide nano-Fe$_2$O$_3$ (30 mol% catalyst, 30 mol% ^{t}BuOK, 135°C, toluene, argon, 24 h) [40].

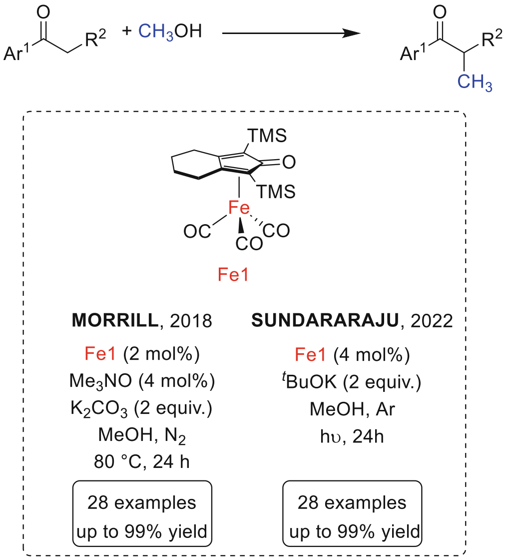


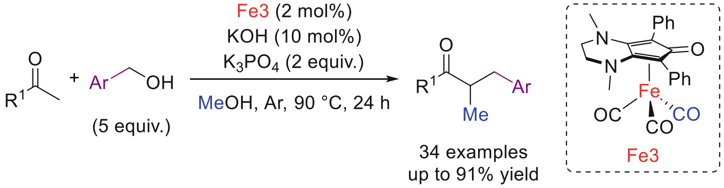
Scheme 9 Iron catalyzed α-alkylation of ketones with secondary alcohols

3.2 Activation of Secondary Alcohols

The alkylation of ketones with secondary alcohols is more complex than with primary alcohols. In addition to the difficulty of dehydrogenating secondary alcohols and reducing enones with triple-substituted C=C double bonds, the starting ketones and those generated by oxidation can self-condense, giving rise to a multitude of secondary products. Inspired by the pioneering work of Donohoe et al. [41], using aryl ketones bearing a 2,3,4,5,6-pentamethylphenyl (Ph*) group, Renaud et al., with the aid of the **Fe3** (diamino) complex, extended the alkylation of ketones to secondary alcohols (Scheme 9) [42]. The use of di-ortho-substituted ketones is a key element in obtaining products from cross-alkylations. In addition to 1-mesitylethan-1-one, 2,3,4,5,6-pentamethylphenyl ethan-1-one and 2,4,6-triisopropylphenyl ethan-1-one were also successfully submitted to the alkylation reaction. In toluene at reflux, in the presence of Me_3NO as decarbonylating agent (4 mol%), **Fe3** (2 mol%) and one equivalent of NaO^tBu as base, the hindered di-orthosubstituted aryl ketones were alkylated with a series of benzyl secondary alcohols as well as cyclic or acyclic aliphatic alcohols affording β-disubstituted carbonyl compounds (yields ranging from 60 to 80% in most cases). The synthetic utility of the Ph* group is that it can be substituted by various nucleophiles, via a retro-Friedel-Crafts acylation reaction with dibromine followed by a nucleophilic addition on the acyl bromide intermediate [43]. Renaud et al. demonstrated that the same strategy could be applied to trimethylarylketones leading to the formation of esters, amides and even a ketone, by performing a retro-Friedel Craft/Friedel Craft sequence promoted by triflic acid in anisole.

Scheme 10 Catalysts used to promote α-methylation of ketones





Scheme 11 Tandem three-component alkylation reaction yielding α-methyl-α-alkyl ketones

3.3 Activation of Methanol

Methanol is the simplest aliphatic alcohol from a structural point of view, but also the most difficult to activate by hydrogen auto-transfer, as the energy barrier of the dehydrogenation step is the highest among all the alcohols. Although methylation reactions are the subject of a specific chapter in this book, this chapter would not be complete without at least mentioning the systems that have been able to activate methanol.

Morrill et al. used Knölker type catalyst to promote the α-methylation of a large variety of ketones, under mild conditions (80°C in MeOH, 2 equiv. of K_2CO_3, **Fe1** 2 mol% and Me_3NO (4 mol%)) (Scheme 10) [44]. Sundararaju et al. succeeded in decreasing the temperature to 40°C, performing the reaction under continuous irradiation with LED bulbs (4 x 7 W) in the presence of catalyst **Fe1** (4 mol%) and ^{t}BuOK as a base (2 equiv.) (Scheme 10) [45].

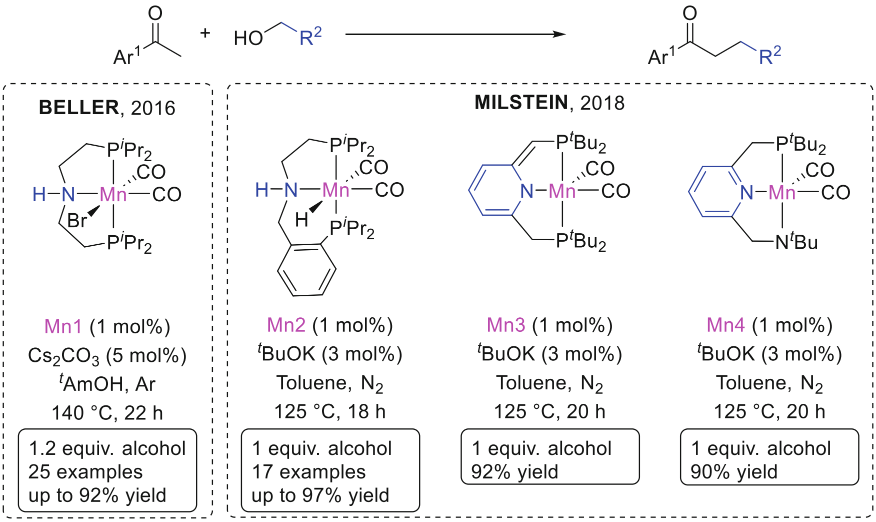
Finally, Renaud et al. has developed a tandem three-component alkylation reaction combining the α-alkylation of methylketones followed by the α-methylation of the resulting ketones yielding α-methyl-α-alkyl ketones (Scheme 11) [46]. (Hetero)-aromatic and alkyl ketones proved amenable to this reaction.

4 α-C-Alkylation of Ketones Catalyzed by Manganese

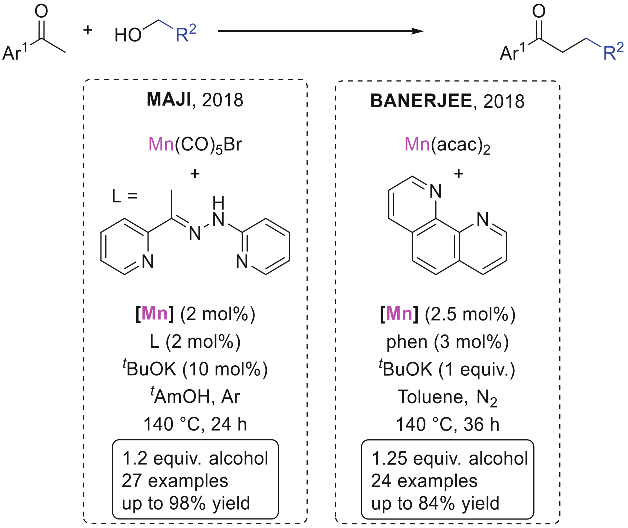
4.1 *Activation of Primary Alcohols*

After iron and titanium, manganese is the third most abundant transition metal in the earth's crust, making it an excellent candidate for developing sustainable chemistry. It is an affordable metal and it exists in many oxidation states in complexes, offering numerous possibilities in catalysis. Its use in hydrogenation reactions and hydrogen transfer for the reduction of polar unsaturated derivatives is relatively recent, as are the first examples in hydrogen borrowing [47].

In 2016, just after highlighting the potential of manganese (I) carbonyl complexes in the hydrogenation of ketones, nitriles and aldehydes [48] and N-alkylation of amines [49], Beller et al. described the first example of the alkylation of ketones with alcohols using [(PN(H)P)Mn(CO)$_3$Br] complex [50]. In the presence of only 2 mol% of complex **Mn1** stabilized by the ^{i}Pr$_2$P(CH$_2$)$_2$N(H)(CH$_2$)$_2$P^{i}Pr$_2$ ligand (also known as the MACHO-$^{\mathrm{IPr}}$ ligand), 5 mol% of Cs$_2$CO$_3$ and *tert*-amyl alcohol at 140°C, a variety of acetophenone derivatives were alkylated with benzyl and aliphatic alcohols (Scheme 12). It should be noted that no by-products were detected under these conditions. The robustness of the system was demonstrated by applying it to the late-stage functionalization of hormones such as estrone and testosterone.



Scheme 12 Well-defined manganese catalysts for the α-alkylation of ketones

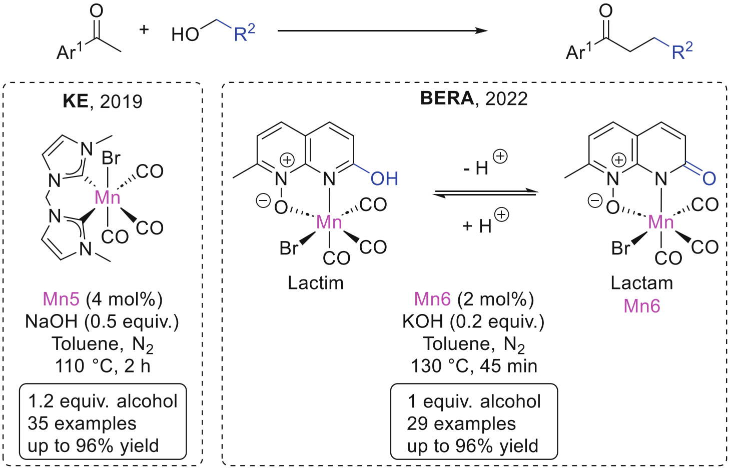


Scheme 13 In situ phosphorus-free manganese based catalytic system for α-alkylation of ketones

For their part, Milstein et al., after carrying out the first manganocatalyzed dehydrogenative coupling of amines and alcohols [51], used an asymmetric PN (H)P complex **Mn2** to couple ketones, as well as non-activated amides and esters, with alcohols [52]. It should be noted that the dearomatized Mn-PNP^{t}Bu **Mn3** and deprotonated Mn-PNN **Mn4** complexes were also active for this transformation (acetophenone (1 equiv.), benzyl alcohol (1 equiv.), 97%, 92%, and 90% yield, respectively, in 20 h at 125°C and toluene, ^{t}BuOK (3 mol%), [Mn] (1 mol%)) (Scheme 12).

With the aim of developing a simple, effective, and globally affordable catalytic system, Maji et al. have developed an in-situ system based on non-phosphorus ligands that are stable in air (Scheme 13) [53]. The combination of the precursor Mn(CO)$_5$Br (2 mol%) and the hydrazone-type pincer ligand derived from 2-hydrazinyl pyridine (2 mol%), ^{t}BuOK (10 mol%) in *tert*-amyl alcohol at 140°C led to the alkylation of a variety of aryl and alkyl ketones with aliphatic and benzylic primary alcohols in good yields.

Another practical phosphorus-free system generated in-situ was proposed by Banerjee et al. (Scheme 13) [54]. It is based on a manganese (II) precursor, Mn (acac)$_2$ (2.5 mol%) in the presence of 1,10-phenanthroline (3 mol%) (as for the nickel catalytic system [55, 56], vide infra). The use of manganese (II) precursor is unusual and original. However, a stoichiometric quantity of ^{t}BuOK is required to obtain the branched ketones in good yields at 140°C in toluene. This system allowed to perform a sequential one pot double alkylation using the same catalyst, by adding a second alcohol to the reaction mixture once the first alkylation was finished. More recently, the same group developed a heterogeneous catalyst, by immobilization of homogeneous [Mn(phen)Cl$_2$] into MOF pores [57].



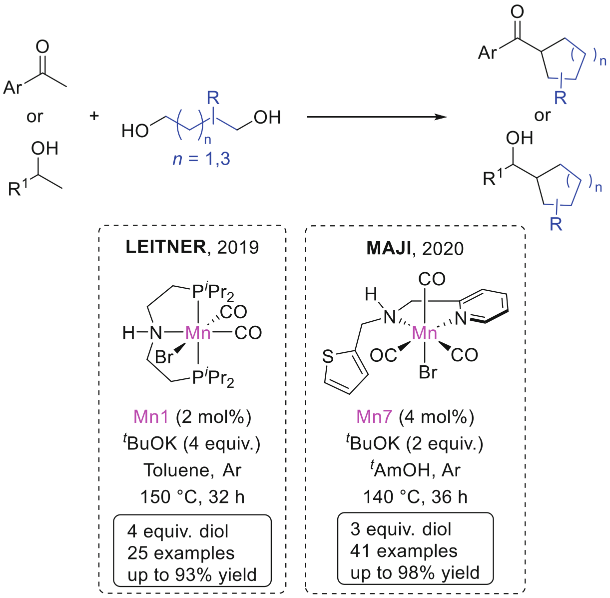
Scheme 14 Manganese catalysts with bidendate ligands

An original system based not only on a bidentate ligand, instead of the tridentate ligands that are largely dominant with manganese, but also on a non-bifunctional ligand, was proposed by the group of Liu and Ke (Scheme 14) [58]. Several manganese complexes incorporating bidentate ligands (pyridine-NHC, bipyridine, NHC-NHC) were tested and the complex bearing a di-carbon bis-NHC^{Me} ligand **Mn5** [59, 60] was found to be the most active. The reaction was carried out rapidly (2 h) at 110°C in toluene with 0.5 equivalent of sodium hydroxide. The theoretical mechanistic study concluded that the catalytic system proceeds according to an outer-sphere mechanism without decoordination of any of the three CO ligands.

Following a different strategy, Bera et al. prepared a manganese (I) complex displaying a 1,8-naphthyridine-N-oxide backbone ligand, bearing a proton responsive hydroxy unit capable of promoting the alkylation of ketones in 45 min (**Mn6** (2 mol%), KOH (20 mol%), toluene, 130°C) (Scheme 14) [61]. The equilibrium between the protonated lactim and deprotonated lactam forms, was established by NMR and UV spectroscopy and favors proton/hydride transfers during the catalytic cycle. This catalytic system was applied to the derivatization of pregnenolone and progesterone.

The synthesis of substituted cycloalkanes (C_5, C_6, and C_7) through the coupling of ketones, or secondary alcohols, with α-ω diols, was achieved by Leitner et al. under the catalysis of Mn-MACHO-^{iPr}. In the presence of 4 equivalents of diols and ^{t}BuOK, **Mn1** (2 mol%) at 150°C for 32 h in toluene, 1-(methylpolysubstituted-phenyl)-ethanones were alkylated without over reduction. The seven membered ring derivatives were produced in higher yields compared to six and five ones (Scheme 15) [62].

Maji et al. carried out the same reaction with an air-stable catalyst **Mn7** based on a tridendate phosphine-free NNS ligand, an aminomethylpyridine with a thiophene arm (Scheme 15) [63]. This system can be used not only to alkylate ketones with a



Scheme 15 Synthesis of cycloalkanes promoted by manganese catalysts

high degree of steric hindrance on the phenyl group, but also slightly hindered acetophenone derivatives. In the latter case, the corresponding alcohols were obtained. In addition to the bifunctional character of the picolylamine moiety, the role of the sulphur sidearm is essential in obtaining high yields, compared with its furan analogue. The hemilabile nature of the thiophenyl fragment has been demonstrated by theoretical studies, particularly in the key step of dehydrogenation by β-H elimination of the manganese-coordinated alkoxides to form the aldehydes.

Finally, three heterogeneous catalyst-based systems were also described for this transformation, based on Mn-N-graphene [64], Mn-MgO/Al_2O_3 [65], and δ-MnO_2 nanoparticles [66], respectively.

4.2 *Activation of Secondary Alcohols*

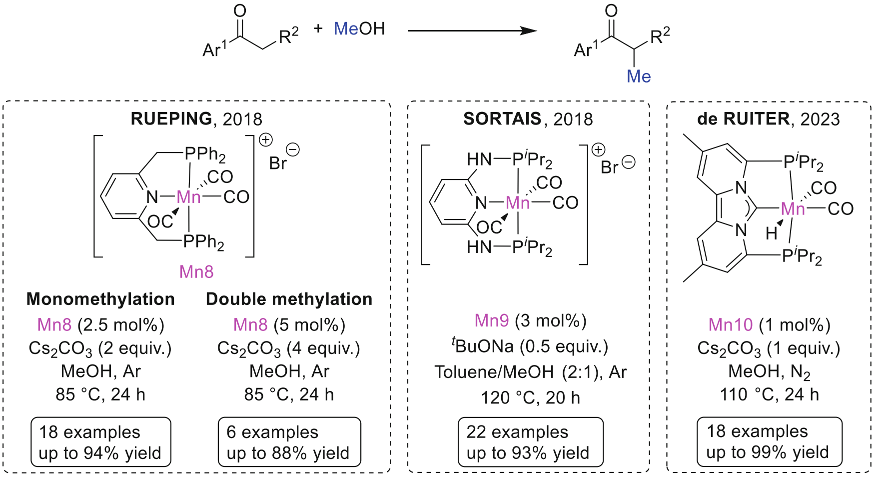
Following on from his study on the synthesis of substituted cycloalkanes, Maji et al. developed the only known manganese system for the synthesis of β-branched carbonyl compounds via the α-alkylation of ketones with secondary alcohols [67]. Using the same catalyst **Mn7** (Scheme 15) with the thiophene arm and the picolylamine moiety (2 mol%), hindered ketones, such as 2,3,4,5,6-pentamethyl acetophenone for example, were alkylated with a wide variety of secondary alcohols (various cyclic, acyclic, symmetrical, and unsymmetrical alcohols) at 140°C over 24 h in the presence of one equivalent of ${}^tBuOK$.

4.3 Activation of Methanol

The α-alkylation of ketones was reported in 2019 with two different PNP-manganese catalysts. El-Sepelgy et al. found that cationic diphenylphosphine-based complex featuring a pyridine core **Mn8** promoted efficiently the methylation of propiophenone, while aliphatic MACHO analogue led to moderate yield (Scheme 16) [68]. In the presence of 2 equivalent of Cs_2CO_3, at 85°C, with a catalytic charge of 2.5 mol%, propiophenone derivatives as well as heteroaryl, cyclic and alkyl ketones were mono-methylated and acetophenone derivatives were di–αmethylated in good yields. Particular attention was paid to the trideuteromethylation of ketones with deuterated methanol for the biological properties conferred by the CD_3 fragment [69]. A non-classical carbonylic carbon-centered mechanism was proposed by Schaefer for this transformation [70].

A similar cationic tricarbonyl PN^{3}P Mn catalyst **Mn9** (Scheme 16) [71], also active for the selective mono-N-methylation of anilines [72], was used by Sortais et al. for the methylation of a series of aromatic ketones (Mn catalyst 3 mol%; NaO^{t}Bu 50 mol%, MeOH/toluene, 0.08 M, 120°C) [73]. This system was particularly suitable for dihydrochalcone derivatives. It should be noted that CD_3OD was also amenable to this catalytic system. Interestingly, when the reaction was carried out in a more concentrated solution (0.1 M) with one equivalent of NaO^{t}Bu, the selectivity towards 1,5-diketones was reversed. In addition, the range of applications was extended to the α-methylation of carboxylic acid esters.

Recently, in 2023, a manganese hydride complex based on an original $PC_{NHC}P$ platform **Mn10**, with a central carbene as the coordination site, was described by de Ruiter et al. (Scheme 16) [74]. Unlike previous systems, this catalyst has no acidic NH or aromatic heterocyclic ring that could participate in cooperative methanol



Scheme 16 Manganese catalysts for the α-methylation of ketones

activation, but efficiently promotes methylation of ketones in the presence of Cs_2CO_3 (1 equiv.) at 110°C in methanol.

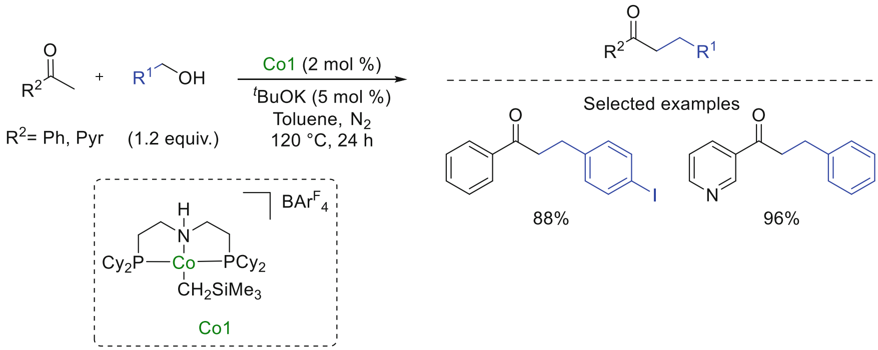
5 α-C-Alkylation of Ketones Catalyzed by Cobalt

5.1 Activation of Primary Alcohols

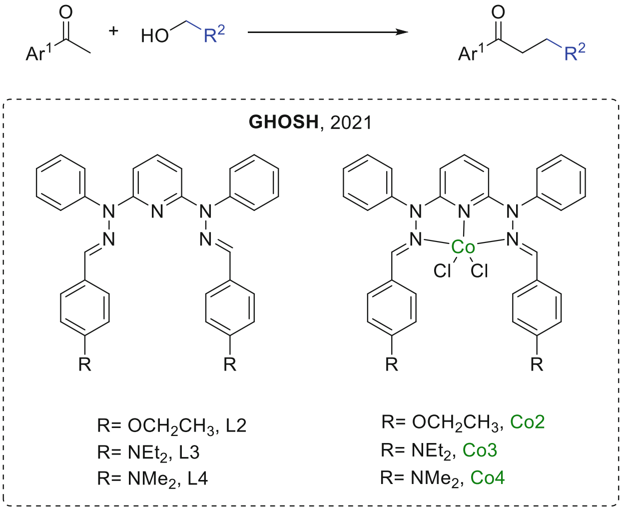
The formation of C–C bond with cobalt catalysts was initiated by Kempe et al. with the alkylation of unactivated amides and esters with PN_5P-pincer type ligands (see the corresponding chapter for more details) [75]. Regarding reactions with ketones, Zhang et al. reported the first example of α-alkylation with primary alcohols (Scheme 17) [76]. The catalytic system which relies on an ionic cobalt(II)-PNP complex $[(PNHPCy)Co(CH_2SiMe_3)][BAr^F_4]$ **Co1**, was a highly active catalyst initially developed by Hanson for the hydrogenation of alkenes and carbonyl derivatives [77] and reversible (de)hydrogenation of N-heterocycles [78]. Following his work on the N-alkylation of amines with alcohols [79] and amines [80], Zhang et al. studied the α-alkylation of ketones with the same catalyst. With a catalyst loading of 2 mol%; ^{t}BuOK (5 mol%), in toluene at 120°C for 24 h, acetophenone derivatives, including ketones with pyridine ring, were alkylated with both benzylic and aliphatic alcohols in moderate to good yields (26 examples). The system was tolerant toward halogens, even 4-iodobenzylic alcohol was successfully coupled.

Pincer ligands with phosphorus-based chelating groups, such as the Macho-type ligands in the previous example, are very commonly found in hydrogen auto-transfer systems. By contrast, non-phosphorus tridentate ligands are much rarer. Thus, Ghosh et al. prepared a series of three NNN-type ligands, with a central pyridine and two lateral imines as the coordination site, and the corresponding series of cobalt dichloride complexes (**Co2-Co4,** Scheme 18) [81].

All three complexes showed similar activity for the alkylation of ketones with a stoichiometric amount of alcohols at 110°C in toluene in the presence of ^{t}BuOK



Scheme 17 α-Alkylation of ketones with primary alcohols promoted by PNP-Cobalt catalyst

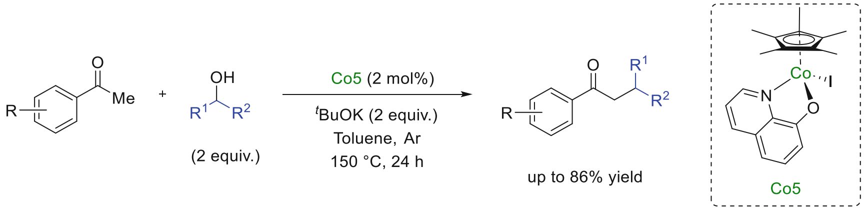


Scheme 18 Phosphine-free tridentate ligands suitable for the α-alkylation of ketones with cobalt

(50 mol%) and 2 mol% of catalyst. With benzyl alcohols, the yields are good (over 80% in most cases, 44 examples). Under these conditions, the mono-methylation and monoethylation of acetophenone could be carried out in good yields (69–78%).

An original approach was highlighted by Wang et al. to develop reusable catalysts [82]. Cobalt coordination polymer material (Co-CIA) and porous oval polymer material (Co-NCIA) have been prepared with an indole-based diacid moiety ligand. The alkylation of ketones with benzylic alcohols was achieved in water. Unlike previous systems, no strong alcoholic base was required, but instead one equivalent of both $AgNTf_2$ and KF, as well as TBAB as phase transfer catalyst (20 mol%) were found necessary to reach high conversion and yield. Both materials Co-CIA and Co-Co-NCIA are active, the former exhibiting slightly better performance than the latter. Interestingly, the catalyst can be recycled and reused, as the yield dropped only from 93% to 87% after five runs.

As an alternative to molecular defined organometallic complexes, Hara et al. developed a heterogeneous MgO-co-deposited Co on TiO_2 (Co-MgO/TiO_2) catalyst able to promote the C–C bond formation in toluene, under argon at 110°C without any base or any additive [83]. A series of control experiments demonstrated that both metal oxide support and co-deposited MgO, and direct contact between each component, are necessary for the reaction sequence to proceed well.



Scheme 19 α-Alkylation of ketones with secondary alcohols promoted by Co(III) catalyst

5.2 Activation of Secondary Alcohols

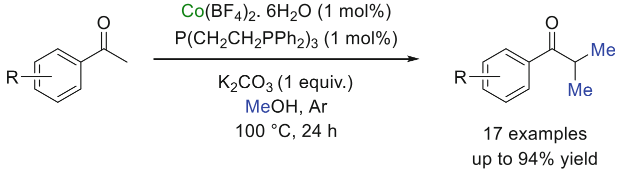
The first α-alkylation of ketones with secondary alcohols was indeed achieved with cobalt (III) based catalysts. Sundararaju et al., shortly after developing a new half-sandwich complex of cobalt (III) with an 8-hydroxyquinone (NO) ligand [Cp*Co (NO)I], which is stable in air and effective for the oxidation of secondary alcohols in acetone [84], investigated the usefulness of this complex for self-hydrogen transfer reactions, focusing on the coupling of ketones with secondary alcohols (Scheme 19) [85]. For unsubstituted aryl-methyl ketones, yields were low due to self-condensation processes. Using Donohoe's trick [41], i.e., by hindering the aromatic ring of the substrate, the desired β-branched C-alkylated products were obtained in moderate yields by working at 150°C, in toluene, with two equivalents of ^{t}BuOK and **Co5** (2 mol%).

In collaboration with the group of Poli and Manoury, the mechanism of the transformation was elucidated via a combined computational and experimental investigations, revealing that the dehydrogenation of the bound alkoxide in [Cp*Co(Oquin)(OR')] proceeded via a transfer of proton to the hydroxyquinoline ligand instead of a classical β-H elimination [86]. In the final rehydrogenation step, the proton from the coordinated ligand HOquin is transferred back to the product leading to the formation of the enolate product, evolving to the final ketone.

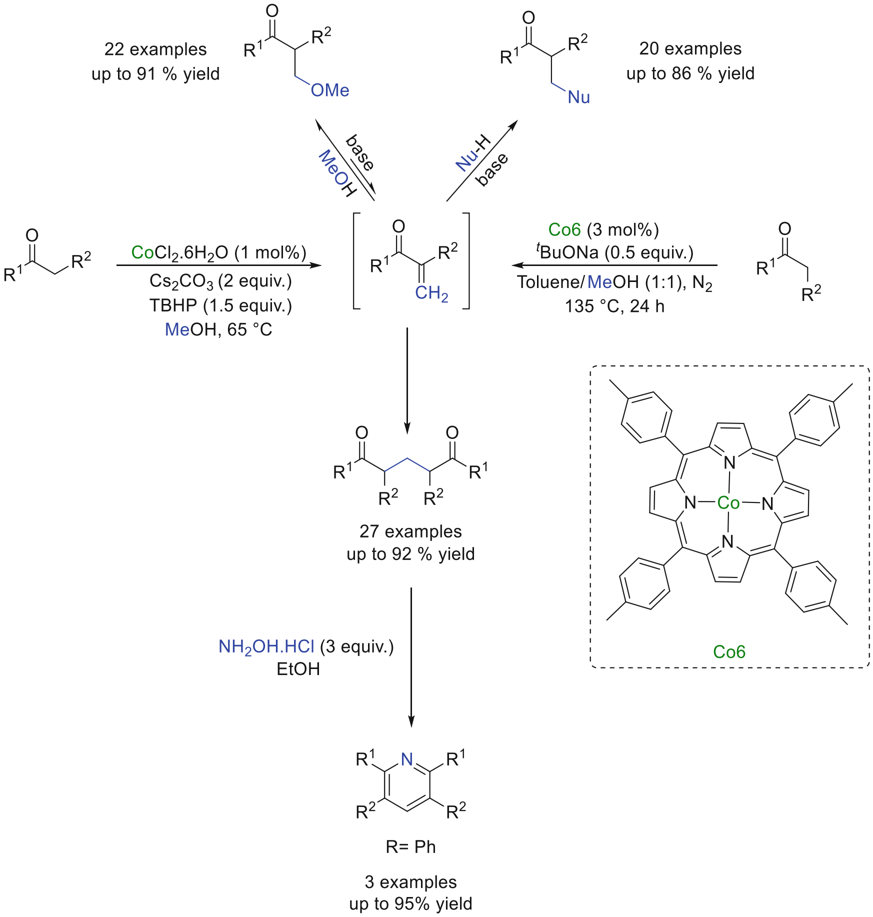
5.3 Activation of Methanol

To conclude this paragraph on cobalt catalyzed reactions, three contributions involving methanol as C1 source should be mentioned. The first one is the α,-α-dimethylation of methylketones reported by Liu et al., involving a very convenient catalytic system composed of commercially available tetradentate P $(CH_2CH_2PPh_2)_3$ ligand (1 mol%), $Co(BF_4)_2.6H_2O$ (1 mol%), K_2CO_3 (1 equiv.) in methanol as solvent at 100°C for 24 h (Scheme 20) [87].

The last two contributions are both based on the reactivity of the enone intermediate resulting from the addition of the ketone to the methanal formed in-situ and not reduced by the catalyst (Scheme 21). Xiao et al. developed α-methoxymethylation and α-aminomethylation reactions using $CoCl_2.6H_2O$ and tert-butyl hydroperoxide



Scheme 20 α,α-Dimethylation of methylketones promoted by cobalt catalyst



Scheme 21 α-Methoxymethylation, α-aminomethylation reactions and synthesis of 1,5-diketones

(TBHP) as the oxidant, resulting from the addition of methanol or amine to the enone intermediate (Scheme 21, top) [88]. Chandrasekhar and Venkatasubbaiah selectively obtained 1,5-diketones by addition of the enolate to the same intermediate (Scheme

21; bottom) [89]. Interestingly, cyclization of these diketones with $NH_2OH.HCl$ led to the formation of tetrasubstituted 2,3,5,6-pyridines in good yields.

6 α-C-Alkylation of Ketones Catalyzed by Nickel

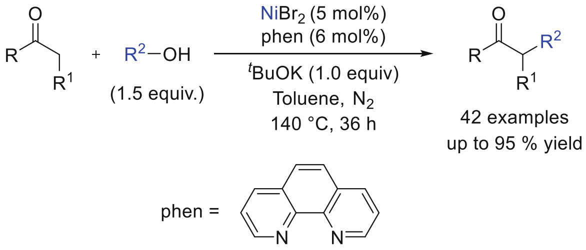
6.1 Activation of Primary Alcohols

The formation of ketones by α-alkylation with alcohols was mentioned in a patent by Sugitani et al. in 2002, in a reactor at 180°C with supported nickel complexes, but with unspecified structures [90]. In 2007, the work of Yus et al. was the starting point for the use of nickel in this area of chemistry [91, 92]. The use of nickel nanoparticles, obtained from anhydrous nickel(II) chloride, lithium powder and a catalytic quantity of 4,4′-di-tert-butylphenyl, enabled primary alcohols, in particular ethanol and n-propanol, to be activated and coupled with acetophenones. The nanoparticles are used in stoichiometric quantities but without any additional additives, i.e., hydrogen acceptor, ligand, or base.

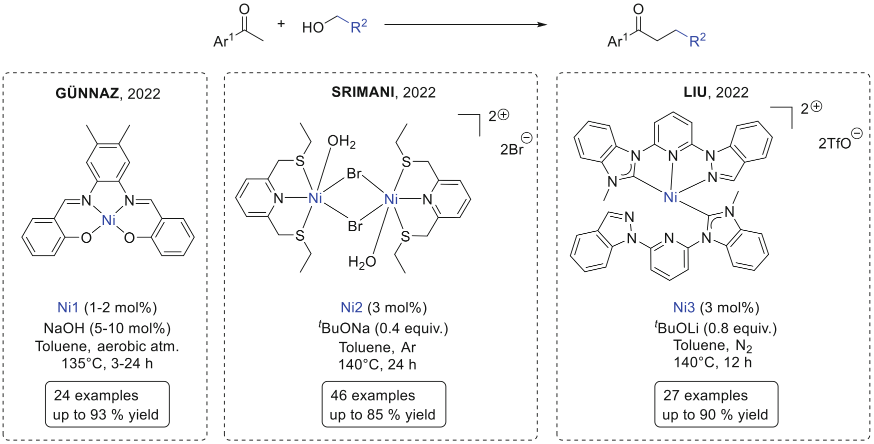
Although Yus et al. reported that the heterogeneous Ni Raney and Ni/Al_2O_3 catalysts did not catalyze the reaction under the conditions used with the nanoparticles (THF, 76°C, 24 h) [92], Métay et al. succeeded in developing a solvent-free system based on heterogeneous catalysts [93]. Using Ni/SiO_2-Al_2O_3 (20 mol%), a weak base (K_3PO_4, 10 mol%), at 175°C, a slight excess of ketones (1.2 equiv.), the alkylation of acetophenone with benzyl alcohol proceeded with total conversion and a yield of 86%. The difference between yields and conversions is due to the formation of by-products specific to the reactivity of nickel, generally not observed with other metals, namely toluene and benzene. Toluene is formed by hydrogenolysis of benzyl alcohol and benzene by decarbonylation of benzaldehyde. In addition, under their conditions, the formation of 1,5-diketones, resulting from the addition of acetophenone to the intermediate chalcone, is reversible, as the by-product is observed at short reaction times but then disappears on full conversion. In terms of scope, the main limitations are chlorine derivatives, which lead to dehalogenation, and aliphatic derivatives, which provide moderate yields. Interestingly, the catalytic cycle could be recycled five times without loss of activity.

Recyclable magnetic nanocatalysts Fe_3O_4@CS-Ni, based on Fe_3O_4 nanoparticles coated with chitosan and decorated with nickel nanoparticles, have been developed by Eshghi et al. [94]. Under the optimal conditions (toluene, 110°C, K_3PO_4 (1 equiv.), Ni 4 mol%, sealed tube, 7 h), a series of dihydrochalcones were obtained from substituted acetophenones and benzyl alcohols. Using an external magnet to remove the nanoparticles, the catalyst was reused up to six runs.

With in-situ generated molecular catalysts, Banerjee initially focused on the synthesis of gem-bis(alkyl) branched ketones (α,α-disubstituted ketones) [55]. Using a relatively simple catalyst system, $NiBr_2$ (5 mol%), 1,10-phenanthroline (6 mol%), a slight excess of alcohol (1.5 equivalents) and one equivalent of ^{t}BuOK at 140°C under N_2 in toluene, a series of propiophenones were alkylated with benzyl



Scheme 22 Nickel catalyzed synthesis of α,α-disubstituted ketones



Scheme 23 Well-defined nickel catalysts for α-alkylation of ketones

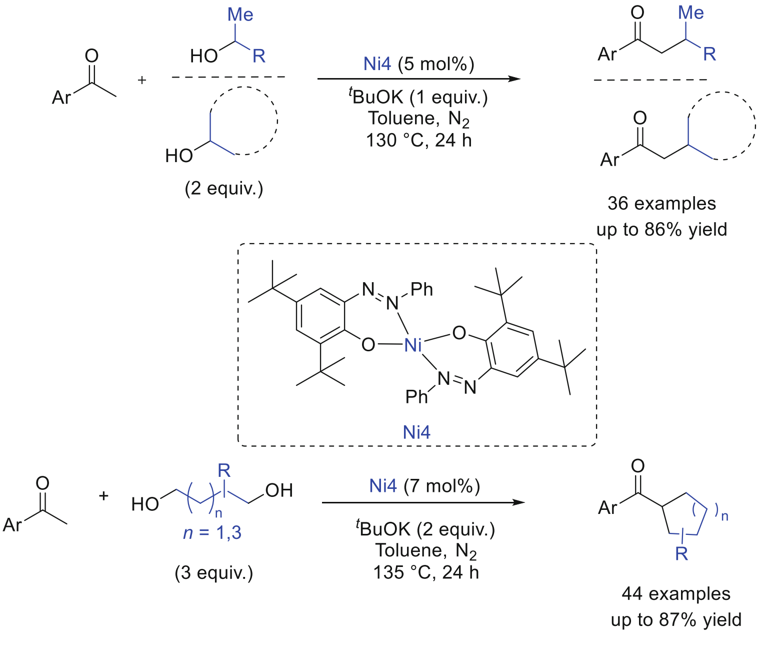
alcohols in moderate to good yields (Scheme 22). Switching to aliphatic ketones or aliphatic alcohols, including methanol, led to more modest yields. Nevertheless, this system is tolerant towards double and triple substituted double bonds such as those present in oleic alcohol and citronellol.

The same group reoptimized the catalytic system to obtain the mono-α-alkylation products of methyl-ketones selectively [56]. The use of a weaker base Cs_2CO_3, in catalytic quantity (10 mol%) in 1,4-dioxane with more catalyst (10% $NiBr_2$) or less strong base (^{t}BuOK, 20 mol%) was the key to not observing over-alkylation of acetophenones.

For their part, the groups of Günnaz [95], Srimani [96], and Liu [97] have used well-defined nickel complexes to promote this transformation (Scheme 23). Günnaz's system is based on tetradentate salen ligands, ONNO, Srimani's on tridentate SNS ligands with a pyridine core and two thioether arms and Wu's on tridentate CNN, benzimidazole/pyridine/pyrrole ligands. All three systems were operated in toluene at 135–140°C in the presence of a catalytic amount of base (NaOH, 5 mol%, NaO^{t}Bu 40 mol% and LiO^{t}Bu, 80 mol%, respectively).

6.2 Activation of Secondary Alcohols

The sole example of nickel catalytic system for the difficult alkylation of ketones with secondary alcohols was reported by Adhikari et al. in 2022 [98]. Simple nickel salts in combination with bidentate ligands did not promote the coupling with secondary alcohols. Therefore, the authors turned their attention towards well-defined and air-stable azo-phenolate ligand-coordinated nickel catalyst, originally developed for N-alkylation of amines (Scheme 24) [99–101]. With a catalyst charge of 5 mol%; 1 equivalent of ^{t}BuOK and 2 equivalents of alcohols, sterically hindered aryl methyl ketones were alkylated with cyclic, acyclic secondary alcohols, including pure aliphatic ones such as isopropanol. The efficiency of the protocol was demonstrated with cholesterol as coupling partner. The homogeneous character of the catalytic system was proven with the mercury test. The mechanistic studies demonstrated that the reaction proceeds through a radical pathway involving as a first step the one electron reduction of the azo functionality of the ligand by ^{t}BuOK, followed by hydrogen atom transfer [100, 102]. It is worth noting that the same catalysts were also applied for the synthesis of cycloalkanes from (1,n)-diols with methyl-ketones [103] (Scheme 24, bottom) and for the dehydrogenative cross-coupling of primary and secondary alcohols to α-alkylated ketones [102].

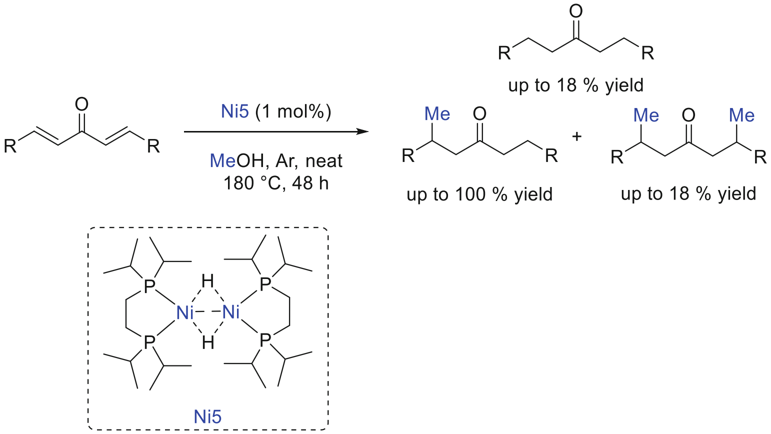


Scheme 24 Nickel catalyzed α-alkylation of ketones with secondary alcohols

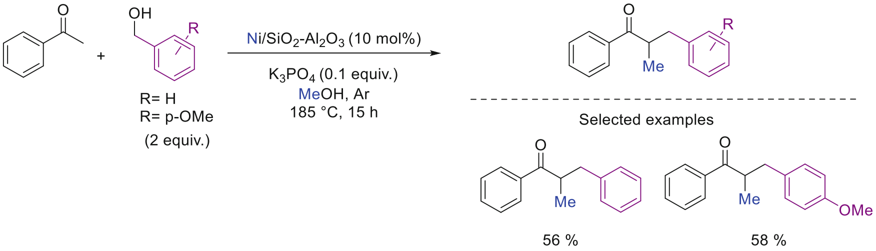
6.3 Activation of Methanol

Examples of nickel catalyzed α-methylation of ketones are rare. During the reduction of dibenzylidene acetone with $[(dippe)Ni(\mu\text{-}H)]_2$ by transfer hydrogenation with methanol as hydrogen donor, Garcia et al. observed the formation of the β-monomethylated ketone, resulting from the alkylation of the α,β-unsatured ketones (Scheme 25) [104]. The catalytic system is likely composed of both homogeneous Ni(0) complexes and nickel nanoparticles.

For so far, only Métay and Duguet's heterogeneous Ni/SiO_2-Al is capable of satisfactorily activating methanol [105]. The conditions had to be made more severe than for aliphatic alcohols (185°C, neat, 21 equivalents of methanol) but good yields of di-methylation of acetophenones and mono-methylation of tetralones have been obtained. Methylation of aliphatic ketones was more tedious, leading to mixtures of mono, di and tri-methylation. The efficiency of the system was also demonstrated by carrying out a three-component cross-benzylation-methylation reaction of acetophenones (Scheme 26).



Scheme 25 Nickel promoted formation of β-methylated ketones from dibenzylidene acetone



Scheme 26 Three-component cross-benzylation-methylation reaction of acetophenones promoted by nickel

7 α-C-Alkylation of Ketones Catalyzed by Copper

7.1 *Activation of Primary Alcohols*

Copper has very rarely been used in ketone alkylation reactions. In 2012, Xu et al. developed a very simple system based on $Cu(OAc)_2.H_2O$ (1 mol%), NaOH (90 mol %), in air, at 120°C in 12 h to couple acetophenones and alcohols (3 equiv.) to the corresponding β-alkylated alcohols, without any solvent [106]. The first stage of the reaction is based on copper-promoted aerobic oxidation of the alcohol to aldehyde, followed by aldolization/crotonization and finally a hydrogen transfer step. In 2013, Mishra et al. used a copper catalyst supported over Mg-Al hydrotalcite to promote the formation of C–C bonds at 180°C in 15 h [107]. Lately, Bala et al. used Cu (I) complexes based on triazolium ligands in the presence of 2 equivalents of KOH in refluxing THF for the coupling of benzyl alcohols and acetophenones [108]. Finally, Sang et al. immobilized $[(Binap)CuI]_2$ complexes on hydrotalcite, forming a heterogeneous system that can be recycled several times, for the formation of monoalkylated ketones with benzyl alcohols [109].

8 Conclusion

This chapter gives an overview of the catalytic systems developed in recent years based on 3d metals for the α-alkylation of ketones with primary and secondary alcohols by hydrogen auto-transfer. Well-defined complexes of iron, manganese, cobalt, and nickel have demonstrated their ability to effectively promote this reaction under homogeneous conditions, whereas in the case of copper mainly heterogeneous systems have been applied. The structural diversity of the ligands efficiently applied in the field, whether bidentate, tridentate, phosphine-containing or not, as well as displaying or not cooperative properties, leave a vast field for the optimization of the future catalytic systems.

The excellent selectivities and reactivities of the catalytic systems reported in the literature make this catalytic reaction a useful tool to enhance the chemist's toolbox while meeting the criteria of green chemistry and current societal challenges by using inexpensive and abundant metals that are relatively less toxic than the noble metals historically used in this chemistry. However, certain parameters need to be improved before this catalytic process can be applied on an industrial scale. The reaction temperatures are still generally high (around 130–150°C with a few exceptions), the quantities of catalysts are generally of the order of a percent and would need to be reduced by a factor of 10–100, and the quantities of additives and in particular of base are also still too high. In our opinion, this last aspect can be explained by the generation of water in stoichiometric quantities, which neutralizes part of the base. It should also be noted that to date no catalytic system based on titanium, vanadium, or chromium has been reported for the α-alkylation of ketones.

We can therefore still expect significant advances in this area of chemistry in the coming years, leading to interesting spin-offs in the field of synthesis and potential applications.

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