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REVIEW

C-Alkylation by Hydrogen Autotransfer Reactions

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Abstract The development of practical, efficient, and atom-economical methods for the formation of carbon–carbon bonds remains a topic of considerable interest in current synthetic organic chemistry. In this review, we have summarized selected topics from the recent literature with particular emphasis on *C*-alkylation processes involving hydrogen transfer using alcohols as alkylation reagents. This review includes selected highlights concerning recent progress towards the modification of catalytic systems for the α-alkylation of ketones, nitriles, and esters. Furthermore, we have devoted a significant portion of this review to the methylation of ketones, alcohols, and indoles using methanol. Lastly, we have also documented recent advances in β-alkylation methods involving the dimerization of alcohols (Guerbet reaction), as well as new developments in *C*-alkylation methods based on sp^3 C–H activation.

Keywords Hydrogen transfer · Alkylation · Alcohol · Metal halide · Methanol · Guerbet reaction

1 Introduction

The construction of carbon–carbon bonds is one of the most important transformations in organic synthesis, and considerable research efforts have been directed towards the development of new methods in this area. Importantly, transformations of this type provide access to a wide variety of organic compounds that can be used as synthetic building blocks in the fine chemical and pharmaceutical industries, as well as key intermediates in the preparation of drugs and functional materials.

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The classical methodology for the formation of carbon–carbon bonds involves cation–anion-based nucleophilic substitution reactions between organometallic reagents and organohalides. However, there are several disadvantages associated with methods of this type, including the handling of reactive reagents (such as air- and moisture-sensitive organometallic agents) and the production of stoichiometric amounts of salt-based waste products during the course of the reaction [1–7].

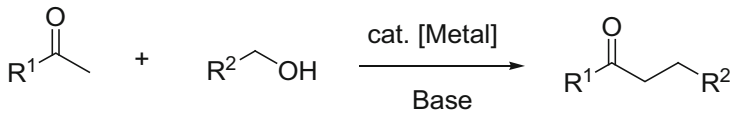
Recent progress in this area has culminated in the development of transition-metal-catalyzed cross-coupling reactions, which have provided several useful *C*-alkylation methods for introducing various aryl, vinyl, and alkyl groups [8]. Furthermore, significant research efforts have recently been focused on the development of "direct coupling" methods involving the oxidative activation of C–H bonds. Notably, these reactions do not require organometallic and/or organohalide substrates, and are therefore much more atom-economical and environmentally friendly than their predecessors [9–19].

As a promising alternative to the *C*-alkylation methods described above, hydrogen transfer using alcohols represents a useful and environmentally benign process, which uses alcohols as alkylation agents with water being generated as the only major by-product. Considerable research interest has recently been focused on the development of highly atom-efficient processes capable of minimizing the amount of waste generated in the form of by-products during organic transformations. In this regard, *C*-alkylation reactions involving a transfer hydrogenation step (or hydrogen borrowing/hydrogen autotransfer methodologies) represent one of the ultimate goals of modern synthetic chemistry for the formation of C–C bonds [20–22].

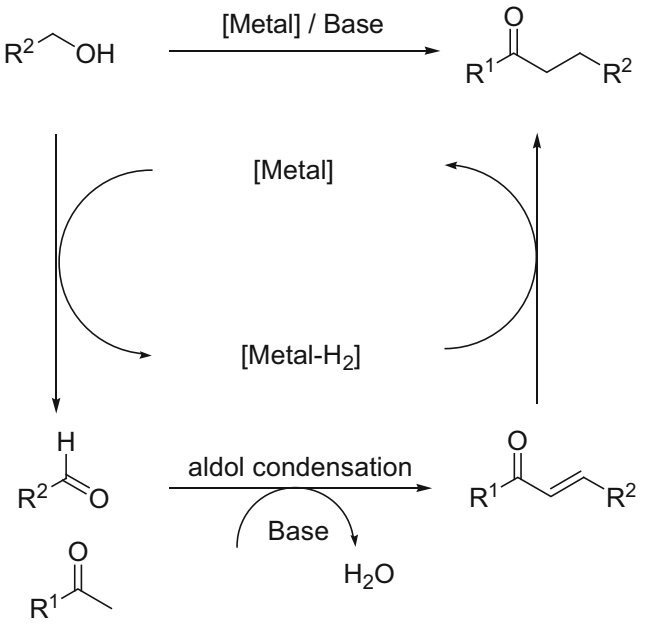
This field presents many opportunities; therefore, there has been a significant increase in the number of research groups working towards the development of new *C*-alkylation processes involving transfer hydrogenation. Consequently, many interesting review articles have been reported to date regarding all aspects of this emerging methodology [23–45].

Some of the most commonly reported *C*-alkylation methods involving the transition-metal-catalyzed transfer hydrogenation of alcohols can be described as follows: (1) the α-alkylation of ketones and carbonyl compounds; (2) alcohol–alcohol coupling reactions to afford ketones; and (3) β-alkylation by alcohol dimerization, which is also referred to as a Guerbet reaction.

The first of these reactions, the α-alkylation of ketones and carbonyl compounds, involves the following process (as shown in Schemes 1, 2) [46–57]: (1) the initial oxidation of the alcohol substrate, through a hydrogen transfer process to give the corresponding aldehyde and metal-hydride intermediate; (2) the aldol condensation of the enol (generated by the tautomerization of the ketone substrate) with the



Scheme 1 Metal-catalyzed α-alkylation of ketones



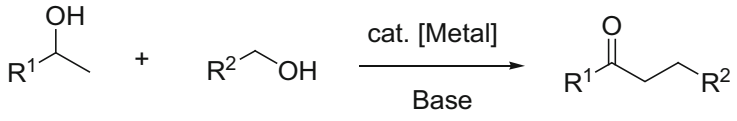
Scheme 2 Representative reaction pathway for the α-alkylation of ketones

aldehyde generated in the previous step to give the corresponding α,β-unsaturated ketone; and (3) the hydrogenation of the α,β-unsaturated ketone with the metal hydride generated in step (1) of this process to give the α-alkylated ketone product.

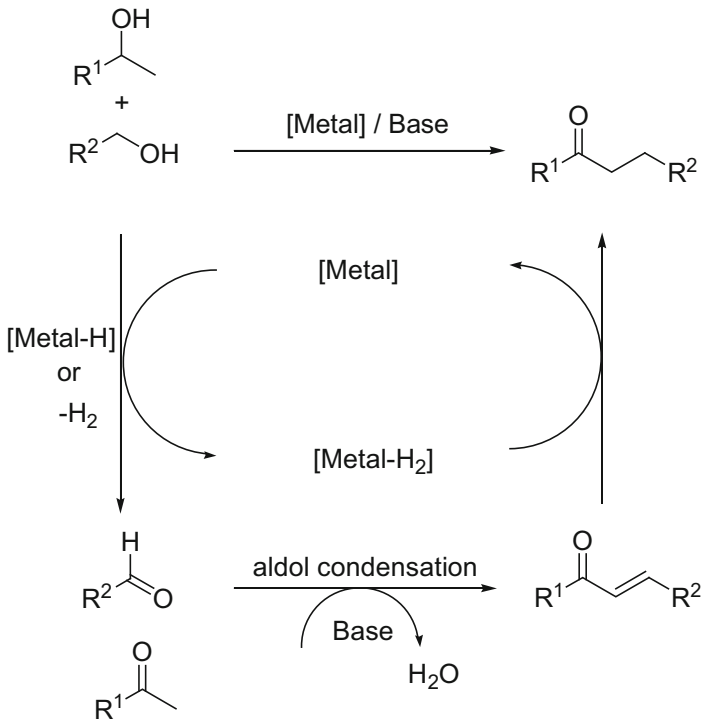
The second of the three reactions described above (i.e., alcohol–alcohol coupling reactions to afford ketones) provides another route for the construction of *C*-alkylated ketones via the formation of two distinct aldehydes from the different alcohols [58–68].

The alcohol–alcohol coupling reaction involves the following steps (Schemes 3, 4): (1) the initial simultaneous transition-metal-catalyzed dehydrogenation of the two different alcohols to afford the corresponding carbonyl compounds and metal halide; and (2) the aldol condensation of the carbonyl compounds and the subsequent hydrogenation of the resulting unsaturated carbonyl compounds in a similar manner to that described above for the ketone α-alkylation reaction (Schemes 3, 4) to give the *C*-alkylated ketone product.

The third of the reactions described above (i.e., the Guerbet reaction of primary alcohols) allows for the self-condensation/dimerization of alcohols to give the



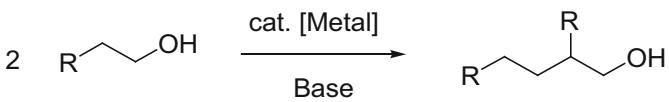
Scheme 3 Metal-catalyzed *C*-alkylation of ketones from primary and secondary alcohols



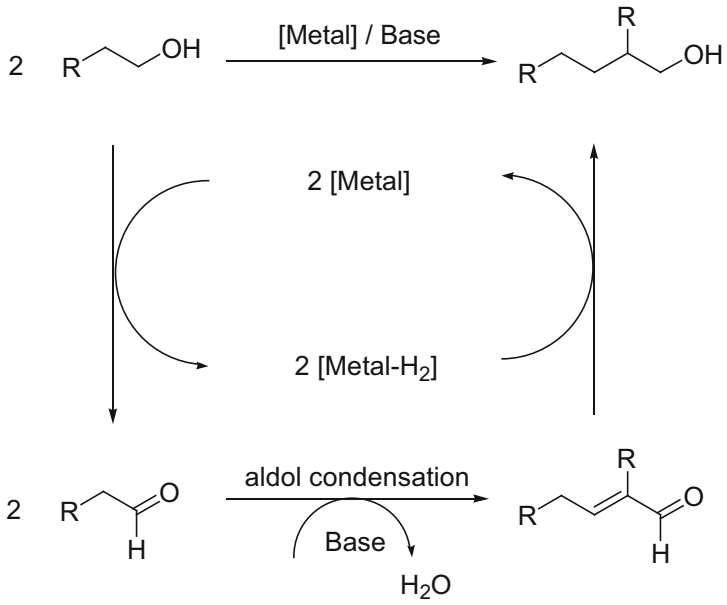
Scheme 4 Representative reaction pathway for the *C*-alkylation of primary and secondary alcohol to afford ketones

corresponding β-alkylation products (Schemes 5, 6) [69–90]. This process involves the following steps: (1) the initial metal-catalyzed dehydrogenation of the primary alcohol substrate to afford two molecules of the corresponding aldehyde and a metal-hydride intermediate; (2) the aldol condensation of these aldehydes to afford the corresponding α,β-unsaturated aldehyde; and (3) the hydrogenation of this system to afford the desired β-alkylated product (Scheme 6).

In this review, we have focused primarily on developments towards *C*-alkylation methods involving the use of alcohols as alkylating agents through hydrogen transfer during the last 3 years.



Scheme 5 Metal-catalyzed β-alkylation by alcohol dimerization (Guerbet reaction)



Scheme 6 Representative reaction pathway for the β-alkylation of alcohols

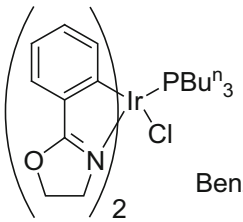
2 *C*-Alkylation Based on Ligand Modifications to the Transition-Metal Catalyst

2.1 *C*-Alkylation Based on Ligand Modifications Involving an Ir Catalyst

Research towards increasing the catalytic activity of transition-metal catalysts (e.g., iridium and ruthenium) with the aim of transferring hydrogenation through the modification of the ligands involved in their metal–ligand complexes has been a topic of recent interest [91–106]. To date, several research groups have reported the development of effective *C*-alkylation catalysts by the ligand modification of the transition-metal complex.

With regard to most interesting examples reported during the last 3 years, Ding and co-workers reported an Ir complex bearing a benzoxazolyl ligand, which exhibited high catalytic activity towards the *C*-alkylation of numerous ketones and

Scheme 7 Benzoxazolyl–iridium complex



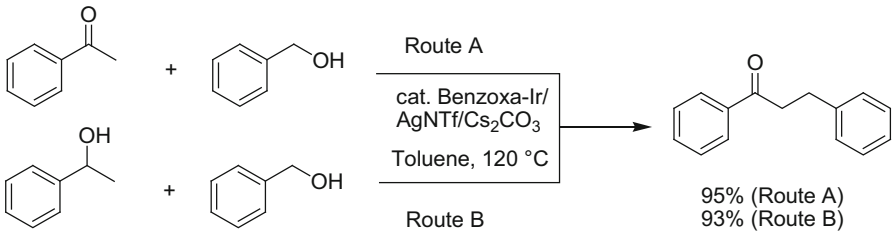
alcohols with alcohol through a transfer hydrogen reaction. For example, the reaction of acetophenone (1.0 mmol) with benzyl alcohol (1.1 mmol) in the presence of a benzoxazolyl iridium(III) complex (as shown in Scheme 7) (2 mol%, 0.02 mmol) combined with AgNTf (0.02 mmol) and cesium carbonate (1.0 mmol) in toluene at 120 °C gave the corresponding α-alkylation product 1,3-diphenyl-1-propanone in 95 % yield (Scheme 8, route A).

Furthermore, the same catalytic system was successfully applied to the alkylation reaction of secondary and primary alcohols. For example, the reaction of 1-phenylethanol (1.0 mmol) with benzyl alcohol (1.1 mmol) under the conditions described above gave 1,3-diphenyl-1-propanone in 93 % yield (Scheme 8, route B).

This catalytic system also performed effectively under solvent-free conditions, where it afforded the desired *C*-alkylated products in high yields. Moreover, the same authors reported that the analogous benzothienyl–iridium complexes afforded high levels of catalytic activity in the *C*-alkylation reactions of primary and secondary alcohols, as well as the reaction of ketones and primary alcohols through transfer hydrogen processes [107–109].

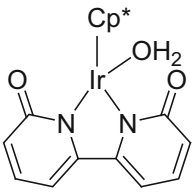
The ligand modification of Cp*Ir complexes has also been investigated as a strategy for the development of active *C*-alkylation catalysts. In a recent example of this approach, Li and co-workers reported the development of a Cp*Ir complex bearing a bipyridonate ligand (as shown in Scheme 9), which performed as an effective catalyst for the α-alkylation of ketones [110]. In a typical example, the reaction of acetophenone (1.0 mmol) with benzyl alcohol (1.1 mmol) was carried out in the presence of a catalytic amount of the Cp*Ir-bipyridonate complex (see Scheme 9; 1.0 mol%) and Cs_2CO_3 (0.1 mol) in *t*-amyl alcohol at 110 °C under air to give 1,3-diphenyl-1-propanone in 92 % yield. Notably, several other conventional Ir complexes such as $[Cp^*IrCl_2]_2$ and $[Ir(cod)Cl]_2$ exhibited low catalytic activity towards this reaction under the same conditions.

It has been proposed that the carbonyl group of the bipyridonate ligand could activate the alcohol substrate (as a reactant) by accepting a proton from this species, which would serve as an important step in the transfer hydrogenation reaction. The Cp*Ir-bipyridonate complex described above also showed high catalytic activity towards the α-methylation of ketones with methanol. The details of this reaction will be described in greater detail later in this article.



Scheme 8 Benzoxazolyl–iridium complex-catalyzed *C*-alkylation reactions

Scheme 9 Bipyridonate iridium Cp* complex



Bipyridonate-Ir

2.2 Ruthenium-Catalyzed *C*-Alkylation Reactions

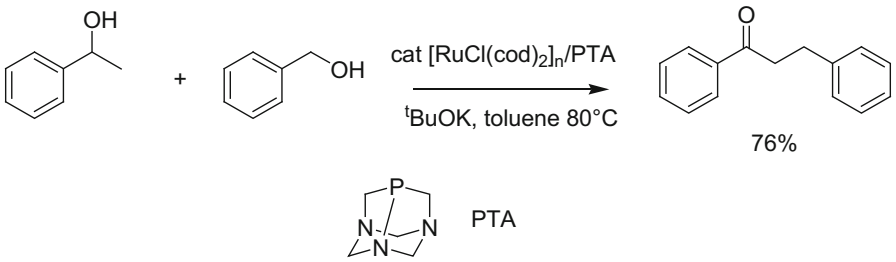
Several ruthenium-based catalysts have also been developed as effective *C*-alkylation catalysts. In a recent example of work in this area, Taddei and co-workers reported that $[Ru(cod)Cl_2]_n$/PTA (PTA = 1,3,5-triaza-7-phosphaadamantane: shown in Scheme 10) showed high catalytic activity in the coupling of secondary and primary alcohols to afford the corresponding ketone products [111].

In a representative example of this work, the reaction of 1-phenylethanol (1.0 mmol) with benzyl alcohol (1.1 mmol) in the presence of $[Ru(cod)Cl_2]_n$ (2.5 mol%) combined with PTA (5 mol%) and *t*-BuOK (1.0 mmol) in toluene led to the formation of 1,3-diphenyl-1-propanone in 76 % yield, together with negligible amounts of the homo-coupled products. Using this $[Ru(cod)Cl_2]_n$/PTA catalyst system, the *C*-alkylation reactions of the secondary and primary alcohols proceeded smoothly at the relatively low temperature of 55 °C.

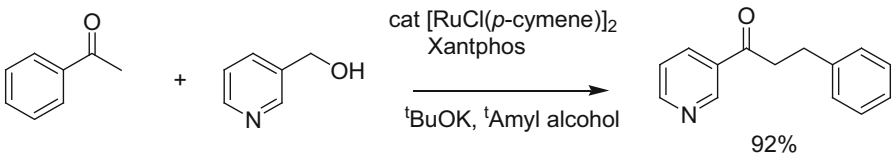
Zhang and co-workers reported the use of this Ru-catalyzed α-alkylation methodology to synthesize a series α-pyridyl methylated ketones using pyridyl methanol derivatives (Scheme 11) [112].

In a typical example of this process, acetophenone (1.2 mmol) was reacted with 3-(hydroxymethylpyridine) (1.0 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (1 mol%) combined with xantphos (1 mol%; the structure is shown in Scheme 12) and *t*-BuOK (0.4 mmol) in *t*-amyl alcohol at 120 °C to give 3-(3-pyridinyl)-1-phenylpropan-1-one in 92 % yield.

It was considered that the reaction initiated by dehydrogenation of pyridyl methanol through base-assisted deprotonation of the OH group/Ru-catalyzed β-hydride elimination led to the corresponding aldehyde. Aldol condensation of the

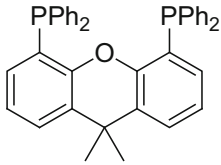


Scheme 10 Ru/PTA (PTA = 1,3,5-triaza-7-phosphaadamantane)-catalyzed α-alkylation reaction



Scheme 11 Ru/xantphos-catalyzed α-alkylation of 3-pyridinyl alcohol

Scheme 12 Xantphos ligand



resulting aldehyde with ketone led the enone followed by hydrogenation to give the α-alkylation product.

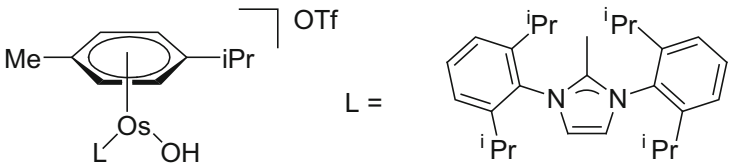
2.3 Osmium-Catalyzed α-Alkylation Reactions

In addition to recent advances in iridium- and ruthenium-based catalysts for the *C*-alkylation reactions, osmium has also been identified as an efficient catalyst for this process.

In a recent example of the use of osmium in this regard, Esteruelas and co-workers reported the development of an osmium catalyst bearing an *N*-heterocyclic carbene complex (NHC) (Scheme 13), which exhibited efficient catalytic activity towards the α-alkylation of methyl ketones as well as arylacetonitriles [113].

In a representative example of the α-alkylation of methyl ketones using this system, acetophenone (3.0 mmol) was reacted with benzyl alcohol in the presence of an Os–NHC complex (as shown in Scheme 13) (1 mol%) combined with KOH (20 mol%) in toluene (0.3 M) at 110 °C for 1.5 h to give 1,3-diphenyl-1-propanone in 99 % yield. This reaction proceeded at a fast rate and the turnover frequency at 50 % conversion was calculated to be 194 h^{-1}.

This osmium catalyst system was also found to be effective for the α-alkylation of aryl acetonitrile, where it exhibited a high turnover frequency of up to 675 h^{-1}.



Scheme 13 Osmium–NHC complex used as a catalyst for α-alkylation reactions

3 *C*-Alkylation of Methanol in Hydrogen Transfer Reactions

3.1 Methylation Reactions Using Methanol Involving Hydrogen Transfer Reaction

Because methylation plays a vital role in the functionalization of biologically active compounds, the development of synthetic methods for the methylation of various substrates continues to attract considerable interest [114, 115].

The methylation of ketones is traditionally achieved using diazomethane or iodomethane, which are both highly toxic materials that pose significant handling issues. Furthermore, the former of these two agents is highly explosive. For this reason, the application of diazomethane and iodomethane on an industrial scale has been limited and there is an urgent need for safer alternatives [116, 117].

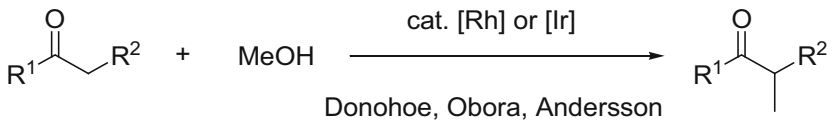
The use of a hydrogen transfer method involving methanol provides an efficient alternative to iodomethane or diazomethane that can be applied to the methylation of various substrates through the activation of methanol. Methanol is the simplest of all of the alcohols and represents an abundant bio-based resource and fundamental renewable C1 source [118, 119].

Methanol has been utilized as a practical C1 source in bulk-scale methanol-to-gasoline and methanol-to-olefin processes [120–123], as well as processes for the production of acetic acid, such as the Monsanto and Cativa processes [124–128].

However, the use of methanol in methylation processes is considered to be inefficient because of the high level of dehydrogenation energy required by these transformation compared with those of higher alcohols [129, 130].

Several methanol dehydrogenation processes have recently been developed using transition-metal catalysts to afford formaldehyde, hydrogen, and carbon dioxide [131–137].

As part of their pioneering work towards the development of novel methanol-based C–C coupling methodologies, Krische and co-workers reported the C–C coupling of methanol with allenes using an *o*-cyclometalated iridium complex, which provided access to the corresponding homoallylic alcohol products [138]. Li et al. [139, 140] subsequently reported an iridium-catalyzed method for the preparation of 3,3′-bisindolylmethanes using methanol and indoles. Several other interesting reactions have also been reported involving the use of methanol, including the N-formylation and methylation reactions of amines, as well as the formation of dialkyl ketones via the C–H bond activation of *N*-methylamine [141–143].



Scheme 14 Transition-metal-catalyzed α-methylation of ketones using methanol

With regard to the α-methylation of ketones using methanol as an alkylating agent through a hydrogen transfer process, several iridium and rhodium catalysts have recently been developed to achieve this transformation (Scheme 14).

Donohoe and co-workers reported the development of a rhodium-catalyzed reaction for the methylation of ketones (Scheme 15). In a typical example of this reaction, phenyl butyl ketone (0.3 mmol) was reacted with methanol (1.5 mL) in the presence of $[Cp^*RhCl_2]_2$ (5 mol%) combined with Cs_2CO_3 (5 equiv) to give the corresponding methylated product in 98 % yield (Scheme 15) [144].

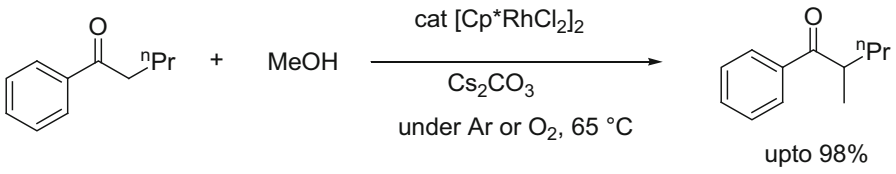
Obora and co-workers reported the development of an iridium-catalyzed process for the methylation of ketones using methanol. In a representative example of this method, acetophenone (1.0 mmol) was reacted with methanol (1.5 mL) in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$ (5 mol%) combined with KOH (50 mol%) at 120 °C to give the corresponding α,α-dimethylated product in 83 % yield with high selectivity (Scheme 16) [145].

In the methylation reaction, the choice of the base efficiently controlled the mono- and dimethylation selectivity. Thus, the $[Cp^*IrCl_2]_2$-catalyzed reaction of benzyl ethyl ketone (1.0 mmol) with methanol (1.5 mL) carried out under these conditions by using a strong base like KOH gave the dimethylated product, while the use of Na_2CO_3 gave monoalkylation product exclusively (Scheme 17).

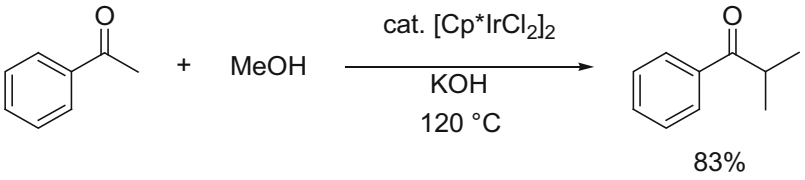
In another example of the Ir-catalyzed α-methylation of ketones, Donohoe and co-workers reported the α-methylation of an arylalkylketone with methanol using $[Ir(cod)Cl_2]_2$ (1 mol%) as a catalyst with PPh_3 (4 mol%) and KOH (2 equiv) under an oxygen atmosphere, which gave the α-methylated product in 94 % yield. Notably, the choice of ligand and base was discovered to be critical to controlling the selectivity of this reaction (Scheme 18) [146].

The reaction is considered to proceed by an Ir-catalyzed hydrogen transfer (or hydrogen borrowing) process by using ketone and methanol. Furthermore, the use of methanol in transfer hydrogenation is difficult. Here, the use of dioxygen (O_2) is effective to enhance the reactivity of methylation and methylenation. In addition, the choice of hindered phosphine in the presence of oxygen is also effective to interrupt the enone hydrogenation step.

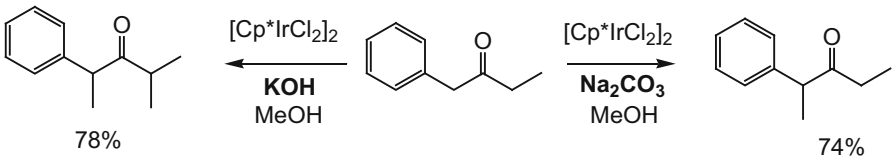
With regard to the methylation of ketones using methanol as a methyl source, Andersson and co-workers reported the use of an Ir-NHC complex as an efficient catalyst for these reactions [147]. In a typical example of this process, phenylpropyl ketone (0.1 mmol) was reacted with methanol (0.5 mL) in the presence of a catalytic amount of the Ir-NHC catalyst (as shown in Scheme 19) (1.0 mol%)



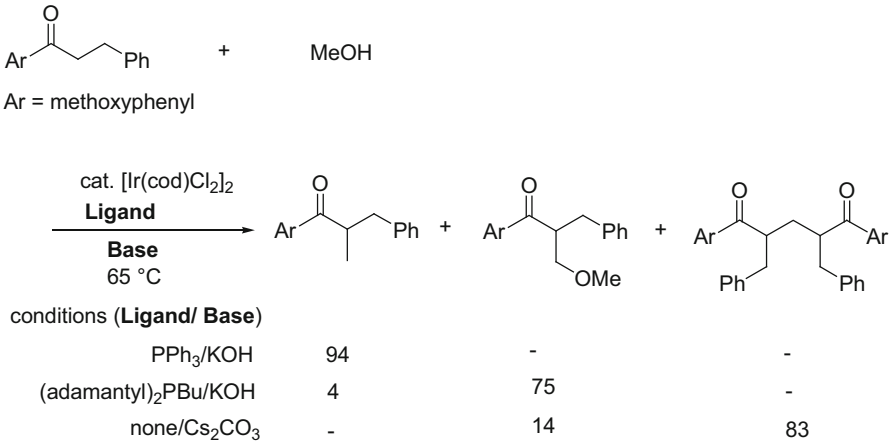
Scheme 15 Donohoe's Rh-catalyzed α-methylation of ketones using methanol



Scheme 16 Obora's Ir-catalyzed α-methylation of ketones using methanol



Scheme 17 Mono- and dimethylation reactions of ketones

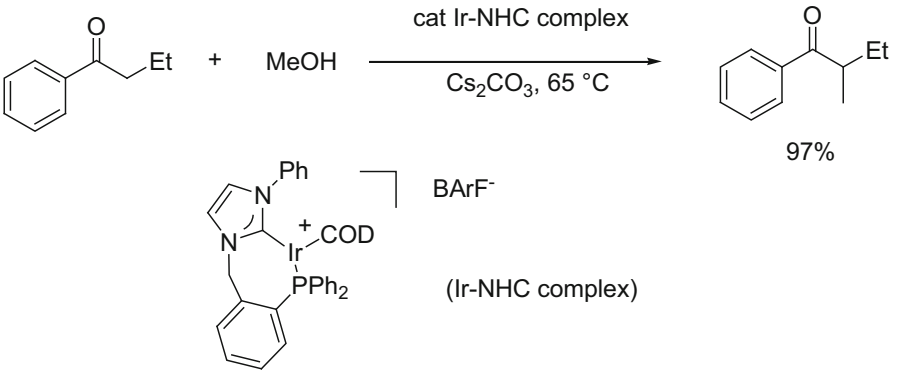


Scheme 18 Selectivity of the Ir-catalyzed α-methylation of ketones with methanol reported by Donohoe

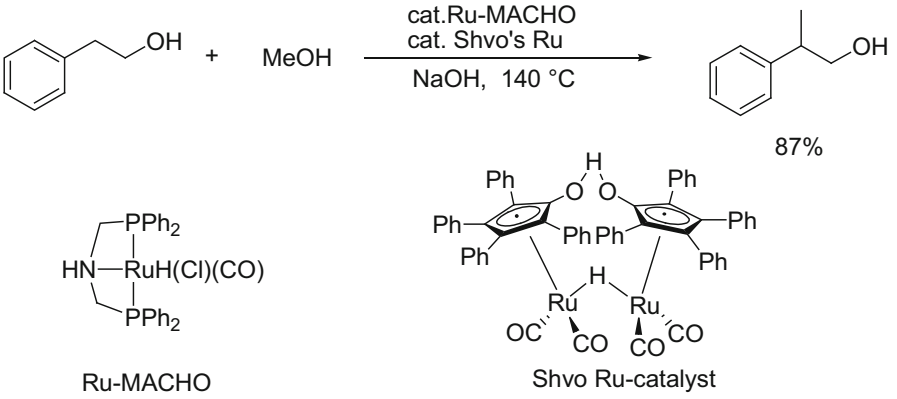
combined with Cs_2CO_3 (5 equiv) at 65 °C to give the corresponding α-methylated product in 97 % yield (Scheme 19).

3.2 Methylation of Alcohols Using Methanol as an Alkylating Agent

With regard to using methanol as a methyl source in methylation reactions, Beller and co-workers reported a ruthenium-catalyzed reaction for the methylation of 2-arylethanols with methanol [148]. In a typical example of this transformation, 2-phenylethanol (2.5 mmol) was reacted with methanol (2 mL) in the presence of a mixture of Ru-MACHO (0.1 %), Shvo's Ru complex (0.05 %) and NaOMe (10 %) at 140 °C to give the methylated product in 87 % yield (Scheme 20). In this

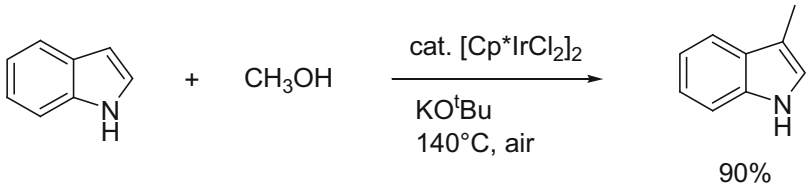


Scheme 19 Andersson's Ir-catalyzed α-methylation of ketones using methanol



Scheme 20 Beller's Ir-catalyzed methylation of alcohols using methanol

reaction, the use of a combination of two different ruthenium complexes (i.e., Ru-MACHO and Shvo's Ru complex) and the release of any pressure formed in the reactor during the reaction were essential to achieve a high yield of the desired product.



Scheme 21 Cai's Ir-catalyzed methylation of indole using methanol

3.3 Methylation of Indoles and Pyrroles Using Methanol as an Alkylating Agent

Cai and co-workers reported the Ir-catalyzed methylation of indoles using methanol. According to this report, the reaction of indole (0.3 mmol) with methanol in the presence of $[Cp^*IrCl_2]_2$ (1 mol%) combined with *t*-BuOK (1 equiv) at 140 °C under an air atmosphere gave the corresponding methylated product in 90 % yield (Scheme 21) [149].

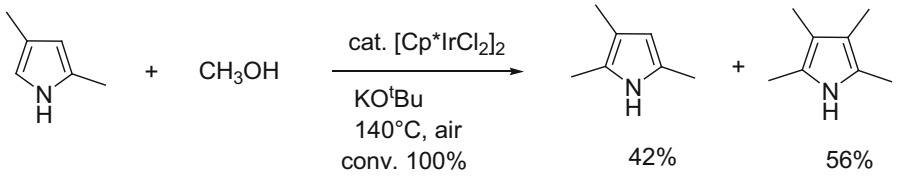
Notably, this reaction can also be applied to the methylation of pyrroles under the same conditions, with the use of 3,5-dimethylpyrrole as a substrate leading to the formation of a mixture of 2,3,5-tri- and 2,3,4,5-tetramethylpyrrole in high yield (Scheme 22).

4 α-Alkylation of Nitriles, Acetonitrile, Acetoamide, and Esters

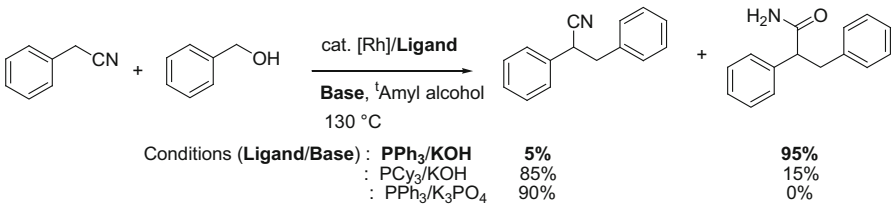
4.1 α-Alkylation of Nitriles

Following on from the pioneering works of Grigg, Watanabe, and Tsuji, there has been an intense period of research focused on the α-methylation of arylnitriles using methanol with a transfer hydrogenation method [150–162].

In contrast to the previously reported α-alkylation reactions of arylnitriles using alcohols in the presence of a Ru, Pd, Ir, or Os complex catalyst (which gave the corresponding α-alkylated arylacetonitriles), Li and co-workers reported the reaction of arylacetonitriles with primary alcohols to give the corresponding α-alkylated arylacetamides using a Rh complex catalyst. In this reaction, the resulting α-alkylated arylacetonitriles were hydration by H_2O, which was generated as a by-product during the reaction, to achieve "complete atom economy". In a typical example of this reaction, phenylacetonitrile (1.0 mmol) was reacted with benzyl alcohol (1.1 mmol) in the presence of a catalytic amount of $[Rh(cod)Cl_2]_2$ (1 mol%) combined with PPh_3 (10 mol%) and KOH (0.4 mmol) in *t*-amyl alcohol at 130 °C to give 2,3-diphenylpropanamide in 95 % yield. The selectivity towards the α-alkylated arylacetonitrile and α-alkylated arylacetamide products could be controlled by varying the nature of the phosphine ligand and base used in the reaction; conducting the reaction in the presence of PCy_3/KOH (ligand/base) or PPh_3/K_3PO_4 mainly led to the selective formation of the α-alkylated arylacetonitrile products (Scheme 23).



Scheme 22 Ir-catalyzed methylation of 3,5-dimethylpyrrole using methanol



Scheme 23 Rh-catalyzed formation of arylacetamide by the reaction of arylacetonitriles with primary alcohols

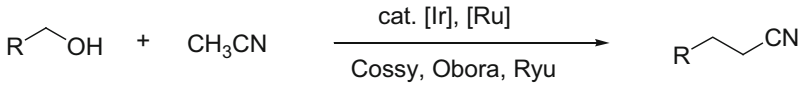
4.2 α-Alkylation Reactions of Acetonitrile and Acetamides

Acetonitrile is produced as a by-product of the industrial Sohio process during the synthesis of acrylonitrile [163]. The *C*-alkylation of acetonitrile by transfer hydrogenation using methanol as an alkylating agent therefore represents an efficient route for the synthesis of functionalized nitrile compounds.

Several recently reported examples of the α-alkylation of acetonitrile include (1) Cossy and co-workers' study, which reported that the reaction of acetonitrile with benzyl alcohol in the presence of $[IrCl(cod)]_2$ as a catalyst combined with Cs_2CO_3 at 180 °C afforded the corresponding α-alkylated nitriles; (2) Obora and co-worker's study, which reported that the reaction of acetonitrile with *n*-hexanol in the presence of $[Ir(OH)(cod)]_2$ as a catalyst combined with PPh_3 and *t*-BuOK at 130 °C gave the corresponding α-alkylation products; and (3) Ryu and co-workers' study, which reported that the use of a mixture of $[RuHCl(CO)(PPh_3)_3]$ and K_3PO_4 as a catalyst for the reaction of acetonitrile with benzyl alcohol afforded the alkylated product in good yield (Scheme 24) [164–166].

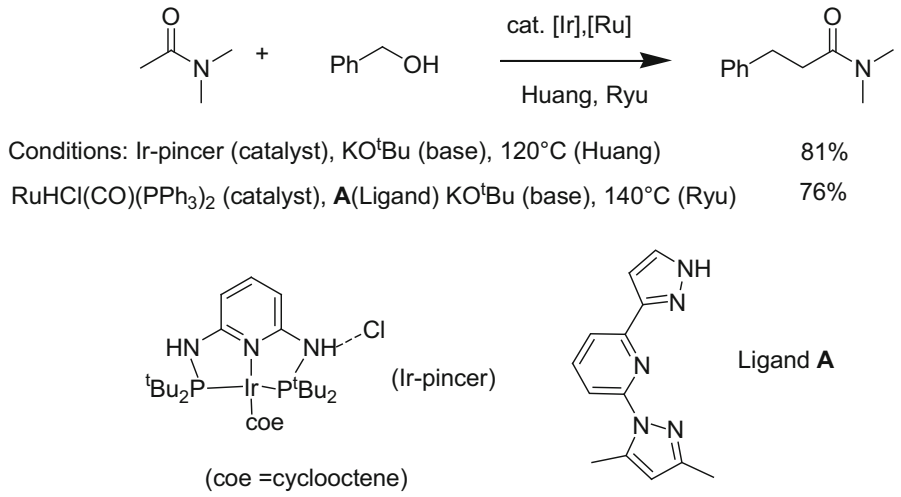
α-Alkylation of poorly activated acetamides represents another challenging target for this area of research. In a recent example of research in this area, Huang and co-workers reported the use of an Ir-pincer complex as an effective catalyst for the α-alkylation of acetamides (Scheme 25). In a typical example of this process, benzyl alcohol was reacted with 2 equivalents of *N*,*N*-dimethylacetamide using 2 mol% of an Ir-pincer-type complex combined with 2 equivalents of *t*-BuOK at 120 °C to give the corresponding alkylated product in 81 % yield (Scheme 25) [167].

In another study pertaining to the α-alkylation of acetamide reported by Ryu and co-workers, the reaction of *N*,*N*-dimethylacetamide with benzyl alcohol was carried



Conditions: $[Ir(cod)Cl]_2$ (catalyst), Cs_2CO_3 (base), 180 °C (Cossy)
$[Ir(OH)(cod)]_2$ (catalyst), PPh_3 (Ligand), tBuOK (base), 130 °C (Obora)
$[RuHCl(CO)(PPh_3)]$ (catalyst), K_3PO_4 (base), 110 °C (Ryu)

Scheme 24 α-Alkylation reactions of acetonitriles



Scheme 25 α-Alkylation of acetamide

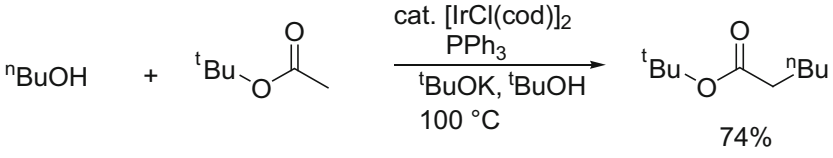
out in the presence of 3 mol% [RuHCl(CO)(PPh$_3$)$_3$] combined with *N*,*N*,*N*-tridentate ligand **A** (as shown in Scheme 25) and *t*-BuOK to give the desired alkylation product in 76 % yield (Scheme 25) [168].

4.3 α-Alkylation of Esters

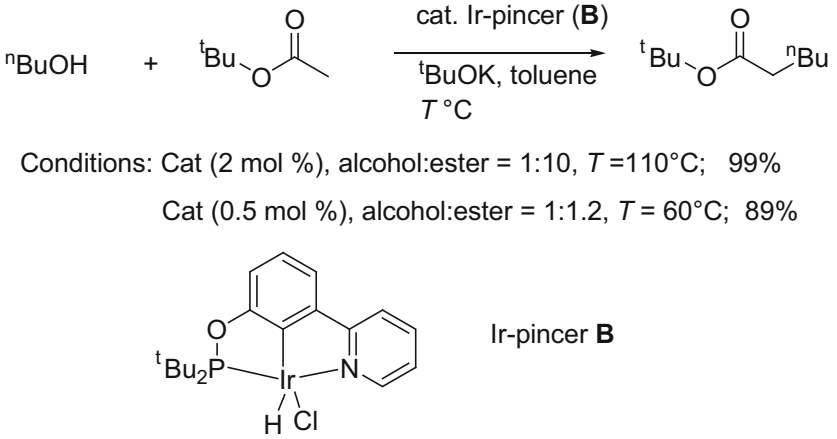
The α-alkylation of esters is an important process in organic chemistry and the transition-metal-catalyzed α-alkylation of esters with alcohols using a transfer hydrogenation method represents an attractive alternative to conventional processes involving the reaction of metal-based enols with alkylhalides [169–171].

Ishii and co-workers reported the α-alkylation of *t*-butyl esters using an iridium catalyst [172]. In a typical example of this process, *t*-butyl acetate (10 mmol) was reacted with *n*-butanol (1.0 mmol) in the presence of a catalytic amount of [IrCl(cod)]$_2$ (5.0 mol) combined with PPh$_3$ (15 mol%) and *t*-BuOK (2 equiv) in *t*-BuOH at 100 °C to give the desired α-alkylated product in 74 % yield (Scheme 26).

Huang and co-workers subsequently reported the use of an Ir-pincer complex as an effective catalyst for the α-alkylation of esters (Scheme 27) [173]. For the reaction of *t*-butyl acetate, the optimized reaction conditions were reported to be as follows: mix 10 equivalents of *t*-butyl acetate with benzyl alcohol in the presence of



Scheme 26 α-Alkylation of *t*-butyl acetate



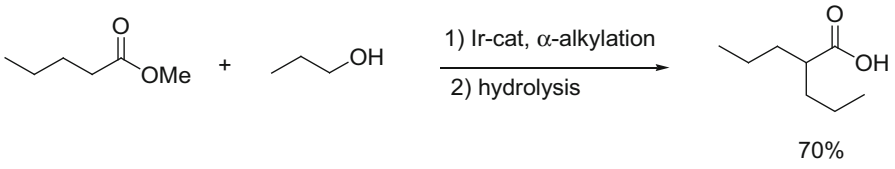
Scheme 27 Huang's α-alkylation of *t*-butyl acetate

2 mol% of Ir-pincer complex **B** (as shown in Scheme 27) combined with 2 equivalents of *t*-BuOK in toluene at 110 °C to give the corresponding α-alkylated ester in 99 % yield (Scheme 27). Notably, the reaction of *t*-butyl acetate with benzyl alcohol was successfully conducted with a molar ratio of 1.2:1 using a smaller amount of the Ir-pincer catalyst (0.5 mol%) and a lower reaction temperature (60 °C). Under these conditions, the desired alkylated product was formed in high yield (89 %) (Scheme 27).

This ester alkylation system was also successfully applied to the synthesis of valproic acid. According to the reported procedure, a mixture of methyl valerianate (10 mmol) was reacted with *n*-propanol (8 mL) under the Ir-catalyzed conditions described above to give the corresponding valproic ester, which was hydrolyzed to give valproic acid in 70 % overall yield (Scheme 28).

5 α-Alkylation of Methyl-*N*-Heteroaromatic Compounds

Transition-metal-catalyzed *C*-alkylation methods have been successfully applied to the alkylation of several methyl-*N*-heteroaromatic compounds, including methyl pyrimidines and methyl quinolones.



Scheme 28 Synthesis of valproic acid via the α-alkylation of an ester

The *C*-alkylation of methyl piperidine was achieved by Kempe and co-workers using an Ir complex containing a pyridyl-bearing phosphine ligand. In a typical example of this procedure, *N*-benzylated 4-methylpyrimidin-2-ylamine (1.0 mmol) was reacted with benzyl alcohol (1.1 mmol) in the presence of $[IrCl(cod)]_2$ (1 mol%) combined with $(iPr)_2PNPy_2$ (Pr = propyl, Py = pyridinyl) (2 mol%) (as a ligand) and *t*-BuOK (1.1 mmol) in diglyme at 110 °C to give the *C*-alkylated product in 98 % yield (Scheme 29) [174].

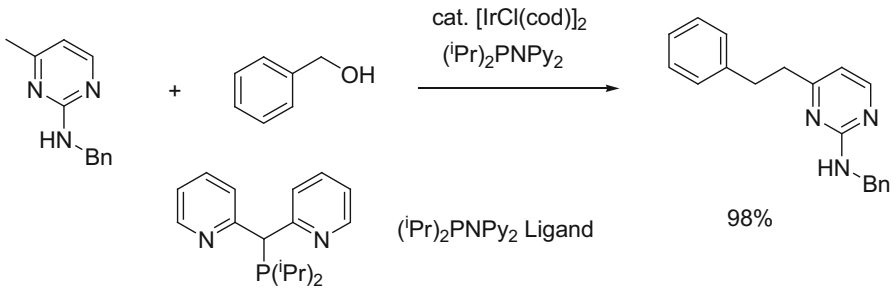
With regard to the alkylation of methyl quinolones, Obora and co-workers reported that the reaction of 2-methylquinoline (3.0 mmol) with benzyl alcohol (1.0 mmol) in the presence of $[Ir(OH)(cod)]_2$ (5 mol%) combined with PPh_3 (20 mol%) and *t*-BuOK (50 mol%) in 1,4-dioxane at 130 °C gave the desired *C*-alkylated product in 92 % isolated yield (Scheme 30) [175].

Furthermore, Shimizu and co-workers achieved the additive-free *C*-alkylation of methylquinoline using an alcohol as the alkylating agent with a heterogeneous Pt/γ-Al_2O_3 catalyst [176].

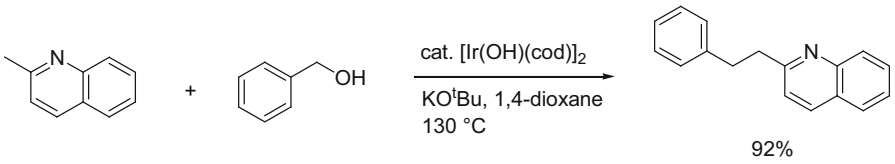
6 Ruthenium-Catalyzed Synthesis of 1,2,3,4-Tetrahydronaphthyridines via the Transfer Hydrogenation of a Pyridyl Ring with Alcohol

The hydrogen transfer method has been successfully applied to the synthesis of several heterocyclic compounds using a transition-metal-catalyzed annulation reaction [177].

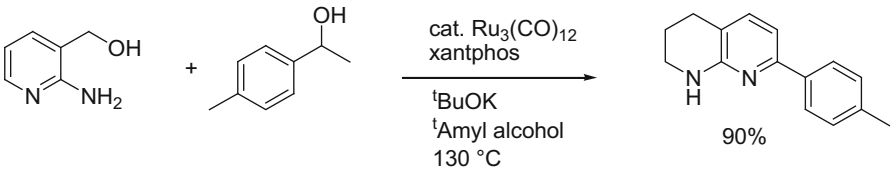
Zhang and co-workers recently reported the ruthenium-catalyzed synthesis of 1,2,3,4-tetrahydronaphthyridines from (2-amino-pyridin-3-yl)methanol and a suitable alcohol. In a typical example of this reaction, (2-aminopyridin-3-yl)methanol (0.5 mmol) was reacted with 1-(*p*-tolyl)ethanol (0.5 mmol) in the presence of $Ru_3(CO)_{12}$ (1 mol%) combined with xantphos (3 mol%) and *t*-BuOK (50 mol%) in *t*-amyl alcohol at 130 °C to give 7-(*p*-tolyl)-1,2,3,4-tetrahydro-1,8-naphthyridine in 90 % yield with high selectivity (Schemes 31, 32) [178].



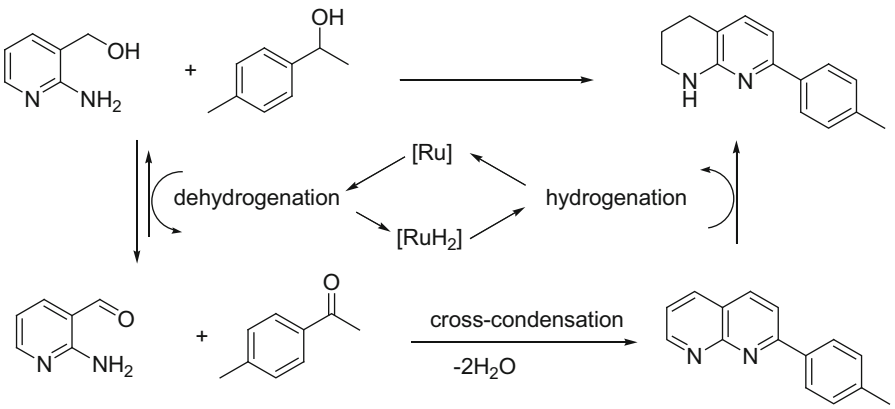
Scheme 29 *C*-Alkylation of methyl pyrimidine



Scheme 30 *C*-Alkylation of methylquinoline



Scheme 31 Ru-catalyzed synthesis of tetrahydronaphthyridines



Scheme 32 A possible reaction pathway

7 β-Alkylation of Alcohols Using Hydrogen Autotransfer Reactions

Alcohol–alcohol coupling reactions leading to the formation of β-alkylated products are known as the Guerbet reaction, and numerous examples of this reaction have been reported in the literature [179–182]. The Guerbet reaction has been used extensively to afford long-chain higher alcohols from readily accessible short-chain alcohols.

In the recent literature, Ramón and co-workers reported the successful Guerbet cross-alkylation reaction of two different alcohols using an iridium/magnetite catalyst [183]. In a typical example of this reaction, a mixture of 2-phenylethanol (1.0 mmol) and benzyl alcohol (2.0 mmol) was reacted with a catalytic amount of iridium/magnetite nanoparticles of IrO_2–Fe_3O_4 (0.14 mol%) combined with KOH

in toluene at 110 °C to give the corresponding Guerbet reaction product in 96 % yield (Scheme 33). Notably, the iridium/magnetite (IrO_2–Fe_3O_4) catalyst used in this case was reused more than 10 times without any discernible decrease in its catalytic activity by simply washing the catalyst with toluene.

Furthermore, Jia and co-worker recently reported the Ru-catalyzed Guerbet-type β-alkylation of primary and secondary alcohols [184]. In a representative example of this reaction, 1-phenyl ethanol (1.0 mmol) was reacted with benzyl alcohol (2.0 mmol) in the presence of $RuCl_2(PPh_3)_2(2\text{-}NH_2CH_2Py)$ (2-NH_2CH_2Py = 2-aminomethyl pyridine) (1 mol%) combined with *t*-BuOK in toluene at 105 °C to give the corresponding β-alkylated product in quantitative yield (Scheme 34).

Considerable research interest has recently been directed towards the use of ethanol as a bioresource substrate to provide access to *n*-butanol and higher alcohols using the Guerbet process.

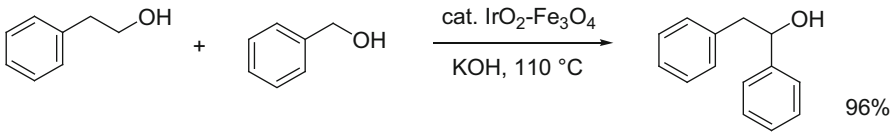
For example, Wass and co-workers recently reported that *trans*-$[RuCl_2(DPPM)_2]$ (DPPM = bis(diphenylphosphino)methane) showed good catalytic activity for the selective conversion of ethanol to *n*-butanol and that the selectivity towards butanol was 94.1 % at conversions greater than 20 % [185].

Tian and co-workers reported the hydrothermal synthesis of *n*-butanol from ethanol [186]. This process used commercially available cobalt powder as a catalyst combined with $NaHCO_3$ (0.01 mol) as a base under hydrothermal conditions using 0.15 mol of ethanol and water (11.24 mL) at 200 °C for 3 days to give *n*-butanol with 69 % selectivity.

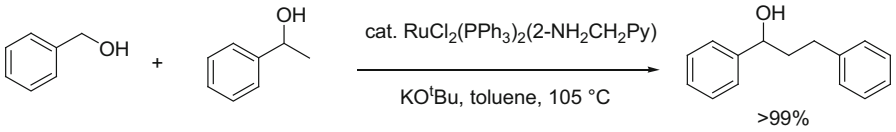
8 Iridium-Catalyzed Guerbet/Decarbonylation Reaction of Arylalkanols

In an extension of the Guerbet reaction, Obora and co-workers reported the development of an Ir-catalyzed reaction for the conversion of arylalkanols to α,ω-diarylalkanes [187], which have been widely used as chromophores and functional fluorescent materials [188–191].

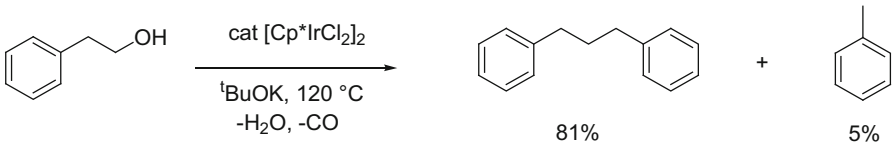
In a typical example of this transformation, 2-phenylethanol (2.0 mmol) was treated with *t*-BuOK (40 mol%) in *p*-xylene in the presence of $[Cp^*IrCl_2]_2$ (1 mol%) at 120 °C to give 1,3-diphenylpropane in 81 % yield with a small amount of toluene (5 %) as a by-product (Scheme 35). This reaction proceeded via the formation of the dimerized β-alkylation alcohol (Guerbet reaction product) as an intermediate. The resulting alcohol was subsequently dehydrogenated by the iridium complex to afford an aldehyde, followed by sequential decarbonylation and



Scheme 33 Ir-catalyzed Guerbet reaction involving the cross-alkylation of two alcohols



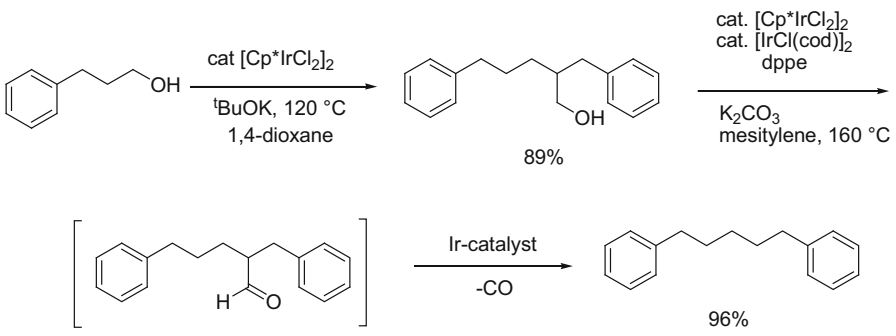
Scheme 34 Ru-catalyzed Guerbet reaction involving the cross-alkylation of two alcohols



Scheme 35 Ir-catalyzed formation of 1,3-diphenylpropane from 2-phenylethanol

hydrogenation reactions to give the α,ω-diarylalkane product. Notably, the use of 2-arylethanol as a substrate in this reaction led to the "direct" formation of α,ω-diarylalkane, as shown in Scheme 35.

In contrast, the use of arylalkanols with longer alkyl chains as substrates, such as 3-phenylpropanol, required the use of a two-step reaction to attain the desired α,ω-diarylalkane products. This process is shown in Scheme 36. Briefly, the reaction of 3-phenylpropanol (2.0 mmol) with $[Cp^*IrCl_2]_2$ (1 mol%) and *t*-BuOK (40 mol%) in 1,4-dioxane at 120 °C in a pressure tube led to the formation of β-(phenylmethyl)benzenepentanol as the Guerbet reaction product in 89 % yield. The subsequent reaction of this product with $[Cp^*IrCl_2]_2$ (2 mol%), [IrCl(cod)]2 (4 mol%), dppe (dppe = 1,2-bid(diphenylphosphino)ethane) (8 mol%), and K_2CO_3 (20 mol%) in mesitylene at 160 °C gave 1,5-diphenylpentane in 96 % yield (Scheme 36).



Scheme 36 Ir-catalyzed formation of 1,5-diphenylpentane by the two-step reaction of 3-phenylpropanol

9 Dehydrogenative Cross-Coupling by Transfer Hydrogenation

9.1 Dehydrogenative Cross-Coupling of Alcohols Involving Transfer Hydrogenation

Madsen and co-worker reported that a ruthenium–NHC complex (shown in Scheme 37) showed good catalytic activity towards the dehydrogenative Guerbet reaction of secondary alcohols to give the corresponding dimeric ketones with the concomitant release of hydrogen and water as by-products. In this reaction, the alcohol substrate underwent a β-alkylation/self-coupling reaction in a similar manner to the Guerbet reaction to afford the β-alkylated alcohol through an aldol reaction. The subsequent dehydrogenation took place under this catalyst system (Scheme 38) [192].

In a typical example of this process, 2-hydroxyhexane (5.0 mmol) was reacted with a catalytic amount of [$RuCl_2$(IiPr)(*p*-cymene)] (2 mol%) in the presence of $PCy_3 \cdot HBF_4$ (20 mol%) and KOH (5 mmol) in toluene at 110 °C to give the corresponding dehydrogenative self-coupling product in 95 % yield (Scheme 38).

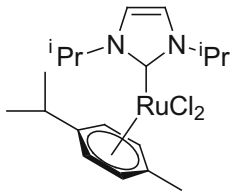
9.2 Dehydrogenative Alcohol–Alcohol Cross-Coupling Reactions

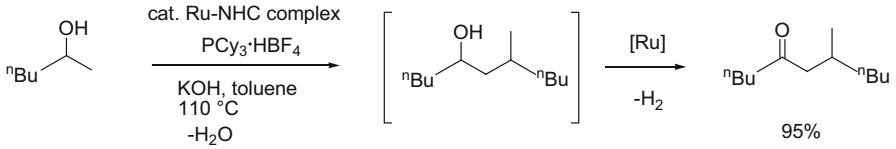
The dehydrogenative cross-coupling of primary alcohols in the presence of an amine has been further extended to the synthesis of α,β-unsaturated aldehydes via the formation of imine intermediates.

For example, Porcheddu and co-workers recently reported the synthesis of a series of α,β-unsaturated aldehydes by the dehydrogenative cross-coupling of primary alcohols, which reacted with an amine to form the corresponding imine, followed by a Mannich-type condensation reaction (Scheme 39) [193].

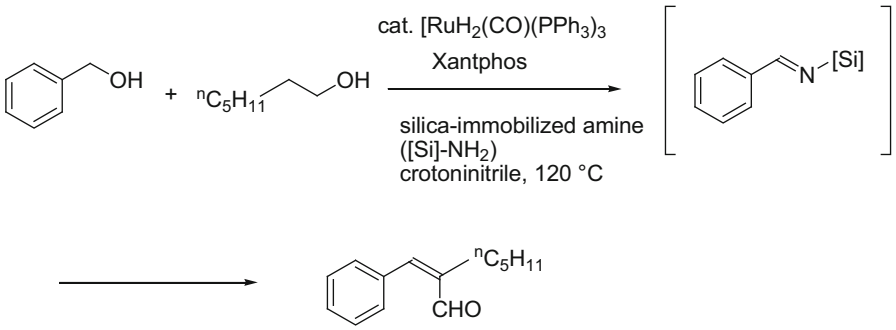
In a typical example of this process, benzyl alcohol (3.0 mmol) was reacted with heptanol (1.0 mmol) in the presence of $RuH_2(CO)(PPh_3)_3$ (4 mol%) combined with xantphos (4 mol%), silica-immobilized amine (0.9 mmol), and crotononitrile (5.0 mmol) as a hydrogen acceptor at 120 °C under microwave irradiation for 3 h to give the corresponding cross-coupled α,β-unsaturated aldehydes in 75 % yield (Scheme 39). In this reaction, the silica-immobilized amine was recycled (by simple filtration) at least five times without considerable loss in its catalytic activity.

Scheme 37 Ruthenium–NHC complex





Scheme 38 Ruthenium–NHC complex-catalyzed dehydrogenative Guerbet reaction



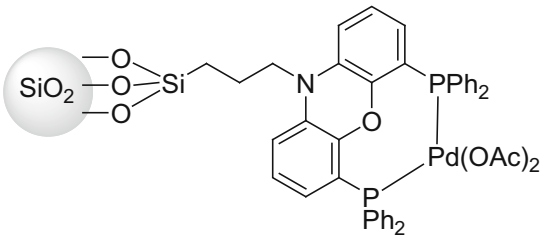
Scheme 39 Ruthenium–NHC complex-catalyzed dehydrogenative Guerbet reaction

10 Heterogeneous Catalysts for *C*-Alkylation Reactions

Heterogeneous catalysts can efficiently catalyze hydrogen transfer reactions and show good recyclability characteristics, as well as achieving high turnover numbers (TONs). To date, various heterogeneous metal/metal nanoparticle catalysts immobilized on metal oxide supports (e.g., TIO_2, MgO, mesoporous silica) have been used as catalysts for transfer hydrogenation reactions involving alcohols [194–223].

In a recent example of this type of reaction, Seayad and co-workers reported the use of an effective silica-supported palladium catalyst, which showed high catalytic activity towards the α-alkylation of ketones. In a representative example of this transformation, acetophenone (2.0 mmol) was reacted with benzyl alcohol (6.0 mmol) in the presence of the silica-supported heterogenized palladium catalyst (as shown in Scheme 40) combined with LiOH (20 mol%) at 140 °C to give the corresponding α-alkylated product, 1,3-diphenylpropan-1-one, in 83 % yield. Using this heterogenized Pd catalyst system, it is possible to recycle the catalyst by a

Scheme 40 Silica-supported heterogenized palladium catalyst for the α-alkylation of ketones



simple filtration step and still achieve a high turnover number (up to 4000) for the α-alkylation (Scheme 40) [224].

11 Activation of sp^3 C–H bonds Involving Hydrogen Transfer Reactions

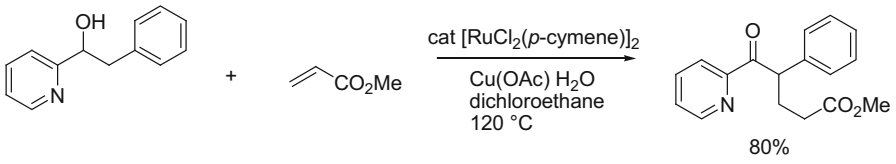
The functionalization of sp^3 C–H bonds by the arylation of the α-carbon of a ketone through a direct oxidative coupling has recently been developed as a viable strategy for the formation of C–C bonds [225–233].

Alternatively, Dixneuf and co-workers reported the Ru-catalyzed alkylation of the sp^3 C–H bonds of alcohols using an alkene via the dehydrogenation of the alcohol substrate (Scheme 41) [234]. In a representative example of this transformation, benzyl 2-pyridyl alcohol (0.25 mmol) was reacted with methyl acrylate (1.0 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) combined with $Cu(OAc)\cdot H_2O$ (0.8 equiv) in dichloroethane to give the corresponding α-alkylated product in 80 % yield (Scheme 41).

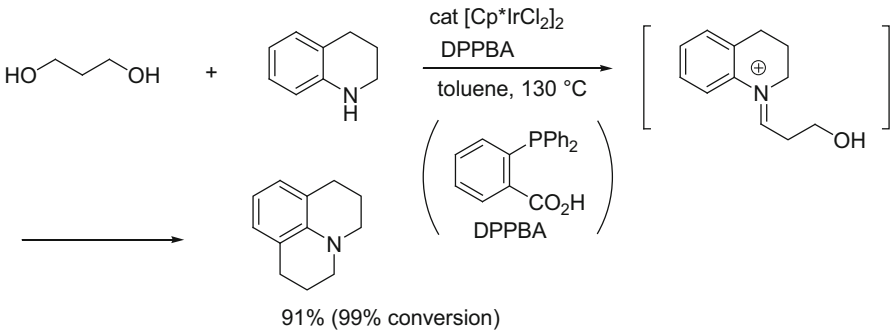
Achard and co-workers reported the development of an Ir-catalyzed reaction for the formation of julolidines via a cyclization step involving a hydrogen transfer reaction with 1,3-propanediol and tetrahydroquinoline. In a representative example, 1,3-propanol (1 equiv) was reacted with 1,2,3,4-tetrahydroquinoline (2 equiv) in the presence of $[Cp^*IrCl_2]_2$ (1 mol%) combined with diphenylphosphinobenzoic acid (DPPBA) (2 mol%) in toluene at 130 °C to give julolidine in 91 % yield (Scheme 42) [235]. This reaction proceeded via the formation of an enaminoiminium intermediate.

12 Transition-Metal-Free *C*-Alkylation

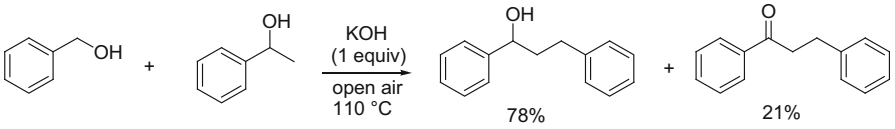
In 2010, Crabtree and co-workers reported β-alkylation reaction of 1-phenylethanol (2 mmol) with benzyl alcohol was achieved by using simple alkali base KOH (2 mmol) under transition-metal free aerobic conditions, giving the corresponding ketones and alcohols in 78 and 21 %, respectively (Scheme 43) [236]. The reaction proceeded by an Oppenauer oxidation of these alcohols to give the ketone and aldehyde. Subsequently, base-assisted aldol reaction followed by Meerwein–Ponndorf–Verley (MPV) reduction and isomerization gave the β-alkylated products.



Scheme 41 Ru-catalyzed alkylation of the sp^3 C–H bond of an alcohol



Scheme 42 Ir-catalyzed synthesis of julolidine by transfer hydrogenation



Scheme 43 Transition-metal-free β-alkylation with alcohols

In addition, transition-metal-free dehydrogenative α-alkylation of ketones with primary alcohols involving the Meerwein–Ponndorf–Verley–Oppenauer redox cycle has recently been developed by using LiO*t*Bu or NaOH as base [237, 238].

13 Conclusion and Future Outlook

This review has focused on recent advances in *C*-alkylation methods involving transfer hydrogenation with an alcohol as the alkylating agent. This area of research has continued to grow and provide environmentally benign and practical organic synthetic methodologies.

Although transition-metal-free *C*-alkylation reactions have only recently been developed [236–238], existing transition-metal-catalyzed *C*-alkylation methods involving the transfer hydrogenation of an alcohol have been enhanced considerably though ligand modification, reaction rate acceleration, and the development of reactions that run under base-free conditions. Furthermore, these methods may be used for the activation of unactivated compounds, such as methanol, acetonitrile, acetamide, and esters, which are all important chemical feedstock in organic synthesis.

C-Alkylation methods involving the transfer hydrogenation of alcohols represent atom-economical and green chemical transformations. With this in mind, we hope that this review will act as an informative reference and provide support to researchers interested in the utilization of hydrogen transfer as a *C*-alkylation method. We also hope that this review will inspire researchers to develop new innovative transformations in the field of *C*-alkylation involving transfer hydrogenation.

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