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Recent Advances in α-Alkylation Reactions using Alcohols with Hydrogen Borrowing Methodologies

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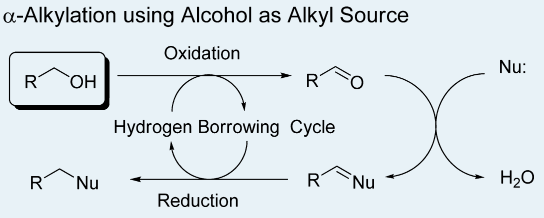
ABSTRACT: This paper summarizes recent advances in α-alkylation reactions based on hydrogen borrowing methodologies using alcohol as an alkylating agent. This review provides a summary of recent progress toward the α-alkylation of carbonyl substrates, as well as relatively unactivated substrates bearing fewer acidic α-hydrogens, such as acetonitriles, acetamides, esters, methylpyrimidines, and methylquinolines. A summary of recent improvements in α-methylation strategies based on hydrogen borrowing methodologies has also been provided. Particular emphasis has been placed on highly practical and green chemistry approaches involving modified catalytic systems, including metal-supported heterogeneous catalysts and nanoparticle-based catalysts, as well as reactions conducted in the absence of a transition-metal catalyst. A review of recent achievements in methylation strategies using methanol as a methyl source, and their application to the α-methylation of ketones using transition-metal catalyzed hydrogen borrowing methodology, has also been documented.



KEYWORDS: *α-alkykation, hydrogen borrowing, alcohol, ketone, methanol*

INTRODUCTION

Carbon−carbon bond formation reactions are fundamentally important transformations in organic synthesis. The formation of C−C bonds by the electrophilic alkylation of an alkyl halide/pseudohalide with a nucleophile results in the production of a stoichiometric amount of salt as well as the desired alkylation product.[1] In particular, the α-alkylation of carbonyl compounds such as ketones occurs via the reaction of the corresponding ketone enolate species with an alkyl halide, and it represents one of the most widely used methods for the preparation of α-alkylated ketones.[2]

The development of a practical, green, and atom-economical alkylation process for the formation of C−C bonds is therefore strongly desired. To be successful in this regard, any new process should avoid the formation of significant amounts of byproduct and involve the use of inexpensive and readily available chemical starting materials. Given the importance of C−C-bond-forming reactions to organic synthesis, there has been considerable research interest in the development of new reactions in this area.

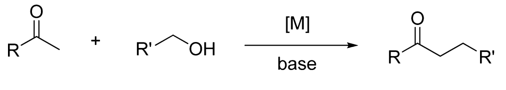
Hydrogen autotransfer (or hydrogen borrowing) represents a promising alternative approach for the formation of C−C bonds via the alkylation of carbonyl compounds using alcohols as the alkylating agent. To date, a wide variety of transition metals have been used to facilitate the hydrogen borrowing/autotransfer hydrogenation of alcohols to aldehydes and ketones.[3]

The success of this methodology has a significant impact on organic synthesis because it has allowed chemists to affect the formation of C−C bonds via a C-alkylation reaction using alcohols as the alkylating agent. Following on from the pioneering work conducted by Grigg and co-workers,[4] hydrogen borrowing has been investigated extensively by numerous research groups, and several reviews have been published pertaining to alkylation reactions involving autotransfer hydrogenation using alcohols.[3,5]

A variety of transition-metal catalysts, including $RuCl_2(PPh_3)_3$, $RuCl_2(DMSO)_4$, $[Ir(cod)Cl_2]_2/PPh_3$, Pd/C, and $RuHCl(CO)(PPh_3)_3$, have been developed for the α-alkylation of carbonyl compounds using alcohols, and these reaction are generally conducted in the presence of a base and/or hydrogen acceptor system.[6] More recent reports have identified cyclometalated Ir(III)[7] and Ir-thioether-dithiolate[8] complexes as efficient catalysts for the α-alkylation of carbonyl compounds using alcohols.

GENERAL REACTION MECHANISM OF THE α-ALKYLATION

Hydrogen borrowing for the α-alkylation of carbonyl compounds using alcohols generally occurs via the process depicted below (eq 1 and Scheme 1). Briefly, initial hydrogen autotransfer from alcohol **A** to a metal would lead to the formation of aldehyde **B** and the metal-hydride intermediate **C**. Subsequent base-mediated aldol condensation of an enol



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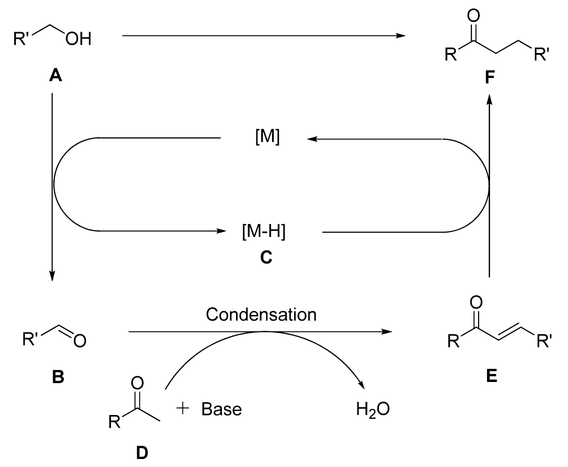
Scheme 1. α-Alkylation of Carbonyl Compounds with Alcohols



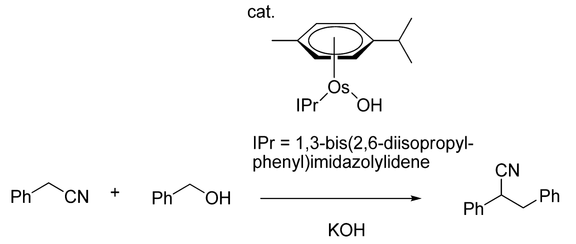
derived from a carbonyl compound with **D** would gives the α,β-unsaturated ketone **E**, which would undergo a hydrogenation reaction in the presence of metal-hydride **C** to give the α-alkylated carbonyl compound **F**.

This review has been focused primarily on recent progress toward alkylation reactions based on hydrogen borrowing. The most notable advances during this time involve the development of new and improved catalytic systems, including improved systems for the α-alkylation of unactivated substrates bearing weakly acidic methyl carbons, greener α-alkylation approaches, and α-methylation reactions using methanol.

1. Recent Achievements in the Transition-Metal-Catalyzed α-Alkylation of Nitriles, Acetonitriles, Esters, and Acetamides Involving the Autotransfer Hydrogenation of Alcohols. The development of synthetic strategies for the functionalization of nitriles is important in organic chemistry because nitrile-containing compounds can be readily synthesized and used as intermediates for the construction of complex systems in fine chemistry.[9] Linear nitriles show good biodegradability, making them environmentally friendly raw materials for use in industrial processes.[10] Furthermore, nitriles can be readily converted to a variety of different functional groups, including amides, amines, and carboxylic acids.[11] One of the most common approaches for the synthesis of an alkylated nitrile is the nucleophilic substitution of an alkyl halide with a cyanide ion, which occurs with the concomitant formation of a stoichiometric amount of the corresponding halide salt.[12]

Following on from the pioneering work Grigg et al.[13] toward the Ru-catalyzed α-alkylation of aryl acetonitrile, many other groups reported the development of similar reactions involving hydrogen borrowing (or autotransfer hydrogenation) for the alkylation of α-functionalized activated nitriles using alcohols as the alkylating agents.[14]

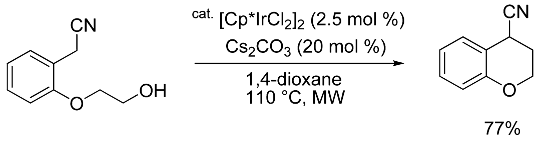
In terms of recent progress toward the alkylation of nitrile compounds, Esteruelas, Yus, and co-workers reported the osmium complex $[\mathrm{Os}(\eta^6\text{-p-cymene})(\mathrm{OH})(\mathrm{IPr})]\mathrm{OTf}$ as an efficient catalyst for the α-alkylation of arylacetonitriles and methyl ketones.[15] In one example, phenylacetonitrile was reacted with benzyl alcohol in the presence of the osmium catalyst (1 mol %) and 20 mol % KOH in toluene (0.3 M) at 110 °C for 30 min to give the alkylated product in 98% yield (eq 2).



(2)

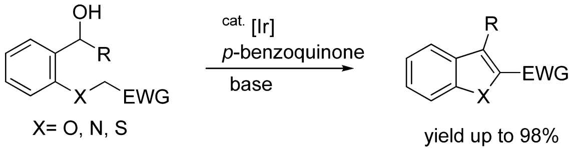
The osmium catalyst used in this particular case gave the alkylated product in a very short reaction time with a turnover frequency value of 514 h^{-1} at 50% conversion. Notably, this value was much faster than that reported for the iridium dimer $[\mathrm{Cp^*IrCl_2}]_2$ system, even under microwave irradiation conditions (100 h^{-1}).[14a] This osmium catalyst also exhibited good catalytic activity toward the α-alkylation of methyl ketones.

Cossy et al. reported the intramolecular alkylation of nitriles with a range of primary and secondary alcohols.[16] In a typical example of their work, 2[2-(2-hydroxyethoxy)phenyl]-acetonitrile (0.5 mmol) (**1**) was treated with Cs_2CO_3 (0.1 mmol) and a catalytic amount of $[\mathrm{Cp^*IrCl_2}]_2$ (2.5 mol %) in 1,4-dioxane (0.5 mL) under microwave irradiation at 110 °C for 15 h to give the cyclized nitrile in 77% isolated yield (eq 3). This reaction is particularly interesting because it could be used to provide access to biologically active compounds such as arylmethylamines.[17]



(3)

In an extension of this work, Cossy et al. reported the development of an intramolecular α-alkylation involving the reaction of nitriles bearing a heteroatom side chain with primary and secondary benzyl alcohol derivatives.[18] Treatment of these substrates with a mixture of $[\mathrm{Cp^*IrCl_2}]_2$ (2.5 mol %), base and *p*-benzoquinone (1.1 equiv), which was used as co-oxidant, at 110 °C resulted in a hydrogen autotransfer/cyclization reaction to give the corresponding 2,3-disubstituted benzofuran, benzothiophene, and indole derivatives in high yields (eq 4).

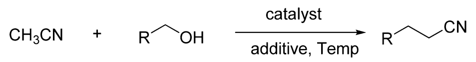


(4)

Acetonitrile is the simplest and most abundant of all of the cyano-containing compounds, and this material is produced as a byproduct during the industrial-scale preparation of acrylonitrile (i.e., the SOHIO process).[19] The development of a synthetic method for the construction of functionalized nitriles using acetonitrile as a nitrile source is highly desirable from both a commercial and atom-economical point of view. With this in mind, considerable research efforts have recently been focused on the development of practical methods for the α-alkylation of acetonitrile.

Cossy et al. reported the Ir-catalyzed monoalkylation of acetonitrile with a series of primary alcohols.[20] In a typical example, acetonitrile (10 equiv) was reacted with benzyl alcohol (1 equiv) in the presence of $[Cp^*IrCl_2]_2$ or $[IrCl(cod)]_2$ (2 mol %) and Cs_2CO_3 (0.2 equiv) at 180 °C for 20 min under microwave irradiation to give the corresponding α-alkylated nitriles in good yield (Scheme 2; Route A). It is noteworthy that this reaction proceeded smoothly with a broad range of alcohols, including substituted benzylic alcohols, heteroarylmethanols, and aliphatic alcohols, to give the corresponding nitriles in good yield.

Scheme 2. Strategies for the α-Alkylation of Acetonitrile



Route A (Cossy): (i) Cs_2CO_3 (0.2 equiv), 180 °C, MW
(ii) $[Ir(cod)Cl]_2$ (2 mol %), 180 °C, MW
Route B (Obora): $[Ir(OH)(cod)]_2$ (5 mol %),PPh_3 (15 mol %), ^{t}BuOK (10 mol %), 130 °C
Route C (Ryu): $[RuHCl(CO)(PPh_3)]$ (3 mol %), K_3PO_4 (1.1. equiv), 110 °C

Obora et al. reported the use of $[Ir(OH)(cod)]_2$/PPh_3-^{t}BuOK as an efficient catalytic system for the preparation of substituted nitriles by the α-alkylation of acetonitrile using primary and secondary alcohols and α,ω-dienes as alkylating agents (Scheme 2; Route B).[21] In a typical example, a mixture of acetonitrile (10 mmol) and *n*-hexanol (1 mmol) in 1,3-dioxane was heated at 130 °C in the presence of $[Ir(OH)(cod)]_2$ (5 mol %), PPh_3 (15 mol %) and ^{t}BuOK (5 mol %) to give the corresponding acetonitrile in an isolated yield of 66%.

Ryu et al. reported an alternative procedure for the α-alkylation of acetonitrile using a Ru catalyst.[22] Briefly, a mixture of acetonitrile (1.5 mL) and benzyl alcohol (1 mmol) was heated at 110 °C for 20 h in the presence of $[RuHCl(CO)(PPh_3)_3]$ (3 mol %) combined with K_3PO_4 (1.1 mmol) to give the alkylated product in an isolated yield of 67% (Scheme 2; Route C).

Development of new methodologies for the α-alkylation of amides represents another challenging area of research, and developments in this area could be used to allow for the facile modification of peptides.[23] Compared with conventional C−C-bond-forming approaches involving the electrophilic reaction of alkyl halides with amide enolates,[24] the development of an α-alkylation methodology involving the reaction of an amide enolate with an alcohol through hydrogen borrowing would be far more beneficial. However, because the α-hydrogens of amides are only weakly acidic compared with those of an ester, progress in this area has been limited to a few examples involving the α-alkylation of amide-like substrates, such as oxindoles and 4-hydroxyquinolones.[25]

Huang et al. reported the α-alkylation of a series of acetamides as unactivated amides using a pincer-type PN^{3}P iridium complex as a catalyst precursor (Figure 1).[26]

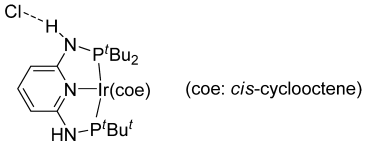
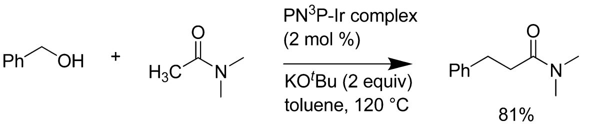


Figure 1. Pincer-type iridium complex used as a catalyst precursor for the α-alkylation of acetamides.

This pincer PN^{3}P-type iridium complex was prepared by the reaction of *N*,*N*-bis(di-*tert*-butylphosphino)-2,6-diaminopyridine with $[IrCl_2(coe)_2]_2$.

In a typical example of their work, Huang et al. reacted *N*,*N*-dimethylacetamide (2 mmol) with benzyl alcohol (1 mmol) in the presence of the Ir pincer complex (2 mol %) and KO^{t}Bu (2 equiv) in toluene at 120 °C to give *N*,*N*-dimethyl-3-phenylpropionamide in an isolated yield of 81% (eq 5).[26]



(5)

This methodology was compatible with various primary alcohols, including benzylic and aliphatic alcohols, which reacted primary, secondary, and tertiary amides to give the corresponding α-alkylated amides in high yields (53−83%).

Ryu et al. reported an alternative procedure for the α-alkylation of acetamides with primary alcohols to afford the corresponding alkylated amines.[27] In a typical procedure, *N*,*N*-dimethylacetamide (0.55 mmol) was reacted with benzyl alcohol (0.5 mmol) in the presence of $RuHCl(CO)(PPh_3)_3$ (3 mol %), with bipyridine (10 mol %) and KO^{t}Bu (1.3 equiv) to give the α-alkylated product in 68% yield. The isolated yield of the α-alkylated product was improved to 76% using the *N*,*N*,*N*-tridentate ligand (10 mol %) shown in Figure 2 (eq 6).

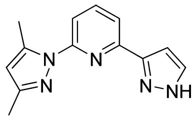
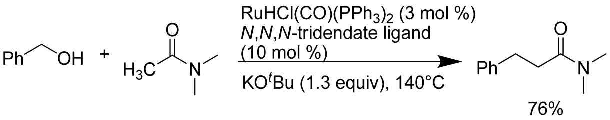


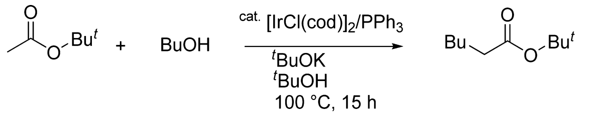
Figure 2. *N*,*N*,*N*-Tridentate ligand for the alkylation of acetamides.



(6)

α-Alkylation of methyl esters can be challenging because the α-hydrogen of esters are less acidic than those of the corresponding acetonitrile substrates. Given the ubiquitous nature of carboxylic acids and their esters in organic chemistry, and their widespread use in a broad range of industrial processes, the development of a robust α-alkylation protocol based on hydrogen borrowing is highly desired.[28] The alkylation of esters is one of the most important methods for the formation of α-functionalized carboxylic acids, and this process is generally achieved by the cross-coupling of an ester enolate with an electrophile species such as an alkyl halide or tosylate.[29]

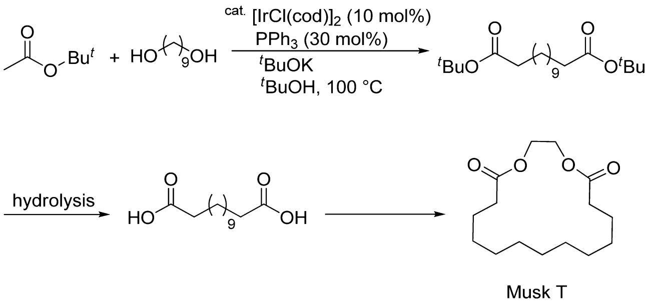
Ishii et al. reported the iridium-catalyzed α-alkylation of *tert*-butyl acetate with a range of primary alcohols and α,ω-diols.[30] In a typical example, a mixture of *tert*-butyl acetate (10 mmol) and *n*-butanol (1 mmol) in *tert*-butyl alcohol (1 mL) was heated at 100 °C for 15 h in the presence of $[IrCl(cod)]_2$ (0.05 mmol), PPh_3 (0.15 mmol), and KO*t*Bu (2 mmol) to give the corresponding alkylated ester in 74% yield (eq 7).



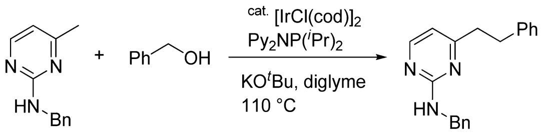
(7)

This particular method was applied to the synthesis of a di-*tert*-butyl ester, which was used an intermediate in the large-scale synthesis of the fragrant compound ethylene brassylate (Musk T).[30] In this particular case, the Ir-catalyzed *α*-alkylation of *tert*-butyl acetate with 1,9-nonanediol proceeded smoothly to give the dialkylated diester product di-*tert*-butyl tridecanoate. Subsequent hydrolysis of the diester gave the corresponding dicarboxylic acid, which was heated in ethylene glycol under acidic conditions[31] to give ethylene brassylate (Scheme 3).

Scheme 3. Preparation of Ethylene Brassylate (Musk T) through Ester Alkylation



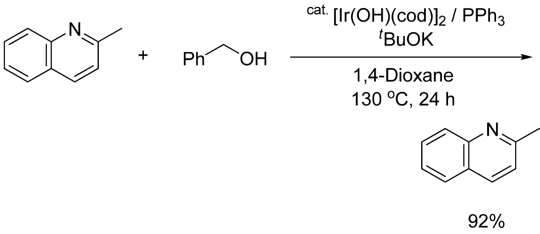
2. Transition-Metal Catalyzed *α*-Alkylation of Methyl-*N*-Heteroaromatics. Kempe et al. reported the *α*-alkylation of methyl-*N*-heteroaromatic compounds with alcohols in the presence of $[IrCl(cod)]_2$ and $Py_2NP(^iPr)_2$ under basic conditions.[32] In a typical procedure, a mixture of *N*-benzylated 4-methylpyrimidin-2-ylamine (1.0 mmol) and benzyl alcohol (1.1 mmol) in diglyme was heated at 110 °C in the presence of $[IrCl(cod)]_2$ (1 mol %), $Py_2NP(^iPr)_2$ (2 mol %), and KO*t*Bu (1.1 mmol) to give the alkylated product in 87% isolated yield (eq 8). The use of $Py_2NP(iPr)_2$ as a ligand led to a significant increase in the activity of the iridium catalyst compared with PPh_3, with the $Py_2NP(^iPr)_2$ and PPh_3 ligands giving turnover numbers of 243 and 137, respectively. A variety of different alcohols were well-tolerated by this reaction, including benzylic and aliphatic alcohols. This reaction also performed well on aromatic substrates bearing nitrogen atoms at the 2- and 4-positions of their ring, such as 2- and 4-methylpyrimidines. However, 3-picoline, toluene, and pentafluorotoluene did not react under these conditions.



(8)

Obora et al. also reported a new method for the selective alkylation of methylquinolines with alcohols using the $[Ir(OH)(cod)]_2$ complex with a phosphine ligand and a base.[33] In a typical example, a mixture of 2-methylquinoline (3 mmol) and benzyl alcohol (1 mmol) in 1,4-dioxane (1 mL) was heated at 130 °C in the presence of $[Ir(OH)(cod)]_2$ (5 mol %), PPh_3 (20 mol %), and KO*t*Bu (50 mol %) to give the alkylated compound in an isolated yield of 92% (eq 9).

The acidity of the methyl protons in methyl quinoline was discovered to be of critical importance to the success of the *α*-alkylation process. Indeed, 4-methylquinoline, 2-methylquinoxaline, and 2-methylbenzoxazole all reacted smoothly under the conditions described above to give the alkylation products. In contrast, 3- and 6-methylquinoline were totally inactive, presumably because the methyl groups were positioned *β* to the nitrogen and therefore less acidic than those positioned *α* or *γ* to the nitrogen atoms in the ring. Furthermore, the use of 2-methylpyridine gave the corresponding alkylated pyridine, albeit in a low yield (21%).[33]

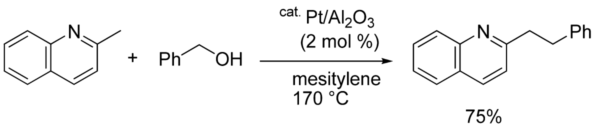


(9)

These results suggest that the acidity of the *α*-hydrogen had a significant influence on the reactivity of these systems toward the *α*-alkylation reaction, and that the *α*-protons in 2- and 4-methylquinoline were sufficiently acidic to allow for the deprotonation step and the addition of the base to the catalytic system [pK_a values in the parentheses: 2-methylquinoline (25), 4-methylquinoline (25), 3-methylquinoline (32), 2-methylpyridine (29.5)].[34]

3. Recent Examples of *α*-Alkylation Reactions on a Supported Transition-Metal (Heterogeneous) Catalyst. *α*-Alkylation involving autotransfer hydrogenation has been also achieved using heterogeneous catalysts, and several green *α*-alkylation methods have also been developed using supported catalysts with alcohol as the alkyl source. To date, several hydrogen-borrowing methods have been reported involving heterogeneous transition-metal systems and metal oxides as efficient catalysts for the formation of C−C bonds.[35]

In a recent report, Shimizu et al. used a Pt nanocluster-loaded *γ*-Al_2O_3 catalyst (Pt/Al_2O_3) for the alkylation of 2-methylquinoline with alcohols.[36] This particular catalyst was prepared using an impregnation method followed by a reduction step, which was conducted in H_2 at 500 °C. In a typical example of this alkylation reaction, a mixture of 2-methylquinoline (1 mmol) and benzyl alcohol (1.1 mmol) in mesitylene was heated at 170 °C for 36 h in the presence of Pt/Al_2O_3 (2 mol %) to give 2-(2-phenylethyl)quinoline in 75% yield (eq 10).



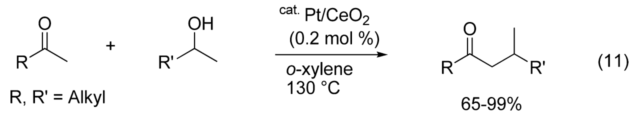
(10)

It is noteworthy that this reaction was conducted under additive-free conditions and that the catalyst could be reused at least five times without any discernible reduction in its catalytic activity. The total TON (turnover number) for these five cycles was reported to be 195 s^{-1}.

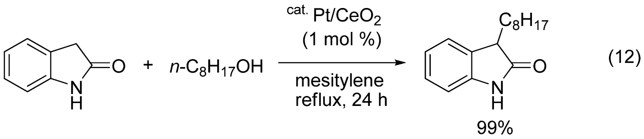
Shimizu et al. reported that CeO_2-supported platinum (Pt/CeO_2) (1 wt % Pt) showed good catalytic activity and reusability toward the *α*-alkylation of methyl ketones.[37]

PREPARATION OF PT/CEO$_2$CATALYST

The Pt/CeO_2 catalyst was prepared using an impregnation method, followed by calcination under a flow of H_2 at 300 °C.[37] Alkyl ketones (1 mmol) reacted smoothly with secondary alcohols (1 mmol) in the presence of the Pt/CeO_2 catalyst (0.2 mol %) at 130 °C over 48 h to afford the corresponding α-alkylation products in good to excellent yields (up to 99%) (eq 11).

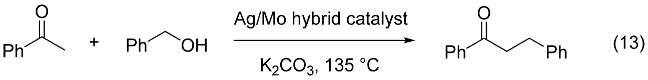


Shimizu et al. reported a process for the selective C-3 alkylation of indoles.[38] The precursor catalyst for this process, 1 wt % Pt/CeO_2, was prepared using an impregnation method with CeO_2 and $Pt(NH_3)_3(NO_3)_2$ in an aqueous HNO_3 solution, followed by a reduction step, which was conducted under H_2 at 500 °C. In a typical example of their alkylation reaction, a mixture of oxindole (1 mmol) and 1-octanol (1.1 mmol) in mesitylene (1.5 g) was heated at 170 °C for 24 h in the presence of Pt/CeO_2 (1 wt %) to give the corresponding C3-alkylated oxindole in quantitative yield (eq 12).



The X-ray absorption near edge structure and extended X-ray absorption fine structure spectra of Pt/CeO_2 indicated that metallic Pt^0 species were present of the Pt surface of the basic support and that these Pt^0 species exhibited a high level of catalytic activity toward the present reaction. The catalyst could be reused more than three times when it was reduced under H_2 at 500 °C for 0.5 h.

Shi et al. reported the preparation of Ag/Mo hybrid materials such as $Ag_6Mo_{10}O_{33}$ which showed a high level of catalytic activity toward the α-alkylation of ketones.[39] These catalysts were prepared by the reaction of $AgNO_3$ with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, followed by hydrothermal treatment at 140 °C, filtration, and calcination at 450 °C. Acetophenone (2 mmol) reacted with various benzyl alcohols (10 mmol) in the presence of the Ag/Mo hybrid catalyst (40 mg) and K_2CO_3 (20 mol %) to give the corresponding α-alkylated products in 87−92% yields (eq 13).



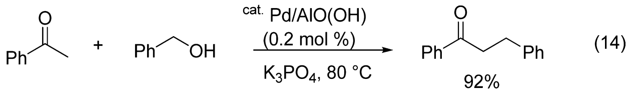
Mishra et al. reported the use of a hydrotalcite supported copper catalyst (Cu-HT) as an catalyst for the α-alkylation of ketones.[40]

PREPARATION OF Cu-HT CATALYST

The Cu-HT catalyst was prepared by the wet impregnation of hydrotalcite with a 0.025 M aqueous solution of copper acetate at room temperature followed by filtration, washing with water, and drying at 70 °C for 12 h. The resulting Cu-HT material was calcined at 520 °C for 4 h to form Cu-containing metal oxides of MgO and Al_2O_3 (Cu-AHT) as a catalyst. The Cu-HT and Cu-AHT catalysts, containing 3.0 and 3.5 wt % of copper, respectively, were evaluated as a catalyst for the reaction of acetophenone (10 mmol) with benzyl alcohol (10 mmol). The conversions of acetophenone were 80 and 30% for the Cu-HT and Cu-AHT catalysts, respectively. Furthermore, the Cu-HT catalyst was 60% selective for the saturated α-alkylation product, where the Cu-AHT catalyst was 95% selective toward the α,β-unsaturated alkylation product (Scheme 4).

4. α-Alkylation Reactions using Nickel and Palladium Nanoparticles. Nanoparticles have been identified as potentially interesting materials for exploring the activity of metal catalysts toward α-alkylation reactions based on hydrogen borrowing

In an early example of research in this area, Park et al. reported that Pd nanoparticles immobilized on aluminum hydroxide showed catalytic activity toward the α-alkylation of ketones.[41] The aluminum hydroxide supported Pd nanoparticle-catalyst Pd/AlO(OH), which contained 0.86 wt % Pd, was prepared by the reaction of $Pd(PPh_3)_4$ with tetra(ethylene glycol) and (*sec*-BuO)$_3$Al in butanol at 120 °C for 10 h. Subsequent treatment of the resulting suspension with water, followed by stirring at 120 °C, filtration, and drying at room temperature gave the desired catalytic material in good yield.[42] The activity of the Pd/AlO(OH) catalyst toward the α-alkylation of ketones was evaluated using the reaction of acetophenone (1 mmol) with benzyl alcohol (1.2 mmol) as a model reaction. When this reaction was performed in the presence of Pd/AlO(OH) (0.2 mol %) and K_3PO_4 (3 mmol) in toluene at 80 °C for 8 h under Ar, the corresponding α-alkylated product was obtained in 92% yield (eq 14).

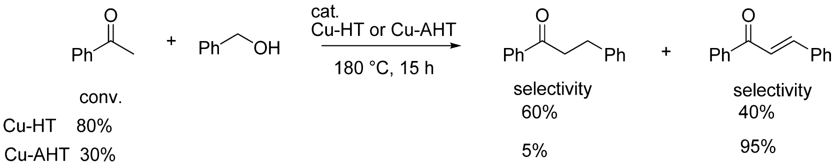


When the reaction was conducted under an atmosphere of oxygen (1 atm) instead of Ar, the oxygen acted as an efficient hydrogen acceptor, and chalcone was selectively obtained in 95% yield.

This catalyst could be recycled by simple filtration and the recovered catalyst retained a high level of catalytic activity without the need for any reactivation treatment. Furthermore, the catalyst could be recycled at least six times without any discernible decrease in its catalytic activity.

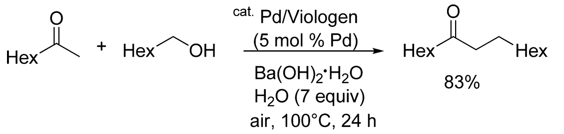
Another approach involving the use of a nano-Pd catalyst in an α-alkylation reaction was reported by Uozumi et al.[43] In this particular study, a solid-phase self-organized nano-Pd catalyst was prepared by the reaction of viologen polymer with an aqueous solution of $PdCl_2$ in NaCl at 25 °C, followed by reduction of the resulting material with $NaBH_4$ in EtOH at 25 °C. The nano-Pd product was obtained as an insoluble black

Scheme 4. α-Alkylation of Ketones using a Mg−Al Hydrotalcite Copper Catalyst



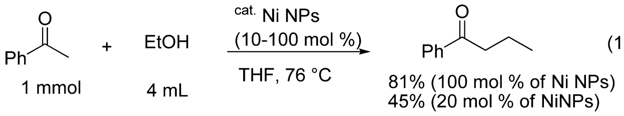
polymeric material. TEM analysis of this material showed that the Pd existed as nanosized (2 nm) particles in the polymeric complex.

With the nano-Pd/viologen catalyst in hand, Uozumi et al. investigated the α-alkylation of 2-octanone with 1-octanol (2 equiv) using 5 mol % of the catalyst combined with barium hydroxide octahydrate (1 equiv) and H_2O (7 equiv) at 100 °C for 24 h, which gave the desired α-alkylated product in 83% yield (eq 15).[43]



(15)

Yus et al. reported that Ni(0) nanoparticles (NiNPs) generated in situ from the reaction of $NiCl_2$ (1 mmol), Li (2 mmol) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (0.5 mmol) in THF promoted the α-alkylation of acetophenone with a variety of different alcohols, including ethanol (eq 16).[44]



(16)

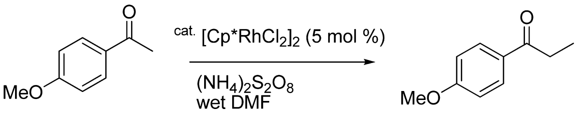
For the reaction between acetophenone (1 mmol) and ethanol (4 mL), the use of a stoichiometric amount of Ni nanoparticles was required to give the best yield of the α-alkylated product (81% yield). However, the use of a catalytic amount (20 mol %) of Ni nanoparticles gave the α-alkylated product in only moderate yield (45% yield).

This Ni-nanoparticle-based catalyst showed a high level of catalytic activity toward the α-alkylation reaction even in the absence of an external ligand, inorganic/polymer support, hydrogen acceptor, and base.

5. Methylation and Hydrohydroxymethylation using Methanol.

Methylation is a fundamentally important organic transformation, which plays a critical role in the functioning of numerous biologically active molecules.[45] Because of the importance of this transformation, various protocols have been developed as selective methylation strategies.[46] The α-alkylation of ketones is generally achieved using iodomethane or diazomethane as a methylation agent.[47]

In terms of recently developed methods for the transition-metal catalyzed α-methylation of ketones, Xue, Xiao, and colleagues reported the Rh-catalyzed methylation of a variety of different ketones using DMF as methyl carbon source.[48] In a typical example, a mixture of *p*-methoxyacetophenone, wet DMF (2 mL), $[Cp^*RhCl_2]_2$ (5 mol %) (as catalyst), and $(NH_4)_2S_2O_8$ (3.0 mmol) (as oxidant) was heated at 110 °C for 3 h to give *p*-methoxypropiophenone in 84% yield (eq 17).

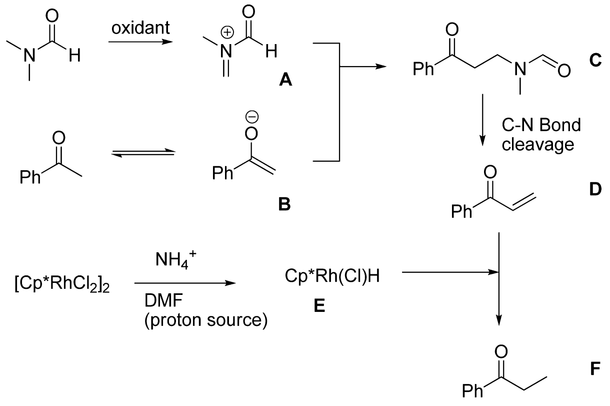


(17)

MECHANISM FOR DMF-MEDIATED METHYLATION

A mechanism was proposed for this reaction, which is shown in Scheme 5. Briefly, DMF would be oxidized by $(NH_4)_2S_2O_8$ to give iminium intermediate **A**, which would react with enolate **B** derived from acetophenone to form intermediate **C**. Subsequent C−N bond cleavage would give the unsaturated ketone **D**, which would undergo a hydrogenation reaction in the presence of Cp*Rh(Cl)H (derived from $[Cp^*RhCl_2]_2$, NH_4^+, and DMF) to give the methylated product **F**. It is noteworthy that DMF would serve as both a methylene source and hydrogen source to form the Rh−H intermediate.

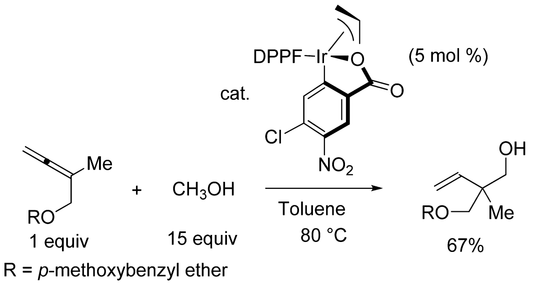
Scheme 5. Proposed Reaction Mechanism for the α- Methylation of Ketones with DMF



Methanol is an abundant, biobased, renewable C1 source. To date, several dehydrogenative homologation processes (i.e., oligomerization reactions) have been reported for methanol, including the methanol to gasoline (MTG) and methanol to olefin (MTO) processes.[49] Furthermore, Rh- and Ir-catalyzed methanol carbonylation reactions have been developed as important industrial processes for the production of acetic acid, including the Monsanto and Cativa processes.[50]

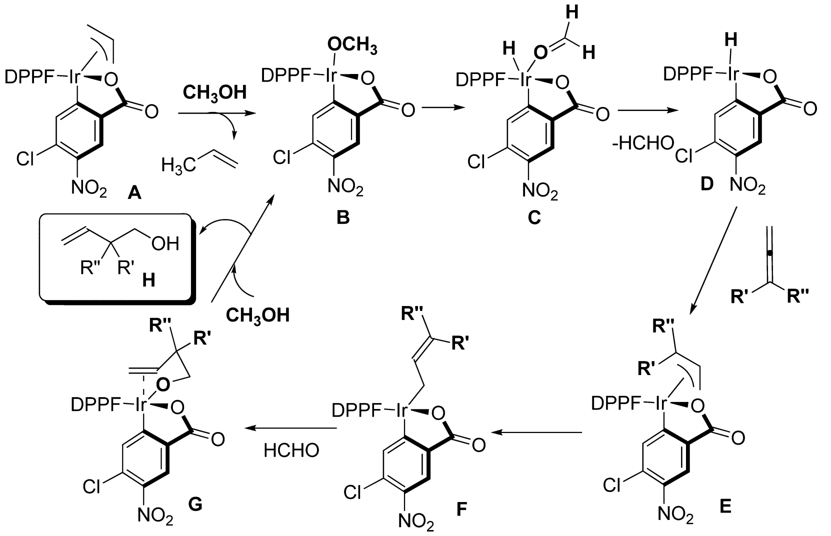
Because methanol is an important feedstock, it could potentially be used as a methylation source in α-alkylation reactions based on autotransfer hydrogenation methodology. Indeed, methanol has been investigated extensively as a substrate in a variety of different catalytic dehydrogenation reactions leading to the formation of hydrogen, carbon dioxide, and formamide (by the reaction of amines).[51]

Krische et al. reported that the *ortho*-cyclometalated π-allyl iridium *C*,*O*-benzoate complex prepared by the reaction of $[IrCl(cod)]_2$ with 4-chloro-3-nitrobenzoic acid, allyl acetate, and 2,2′-bis(diphenylphosphino)ferrocene (DPPF) served as an efficient catalyst for the formation of a C−C bond between allenes and methanol.[52] A typical reaction is shown in eq 18. Thus, the reaction of an allene with methanol (10 equiv) in the presence of the iridium catalyst (5 mol %) in toluene at 80 °C for 24 h led to a hydrohydroxymethylation reaction to give the homoallylic neopentyl alcohol product in 67% yield (eq 18).



(18)

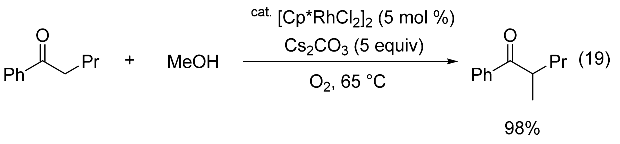
Scheme 6. Proposed Mechanism for the Ir-Catalyzed Reaction of Methanol with Allenes



REACTION MECHANISM OF HYDROHYDROXYMETHYLATION WITH METHANOL

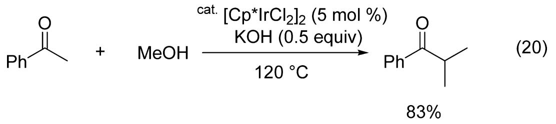
The authors proposed a mechanism for this hydrohydroxymethylation reaction, which is shown in Scheme 6. The reaction would begin with the methanolysis of the π-allyl moiety of the Ir complex **A**, which would result in the formation of the Ir-methoxy intermediate **B**. Subsequent β-H elimination from **B** would lead to the formation of formaldehyde and the Ir-hydride intermediate **D** via **C**. Hydrometalation of the allene with Ir-hydride **D** would give allyl Ir intermediate **E**, which would rearrange to give **G** through **F**. Subsequently, which would react with methanol to give the desired hydrohydroxymethylation product with the concomitant regeneration of the Ir(I) species **A**. Given that the dehydrogenation of methanol (oxidation) requires more energy compared with higher alcohols, the turn overlimiting step in this reaction would be the oxidation of methanol.

It terms of methanol being used as methyl source in α-alkylation reactions, Donohoe et al. recently reported the development of a rhodium-catalyzed process for the methylation of ketones using methanol.[53] In a typical example of their work, valerophenone (0.3 mmol) was reacted with methanol (1.5 mL) in the presence of $[Cp^*RhCl_2]_2$ and Cs_2CO_3 (5 equiv) to give the α-methylated product in 98% yield with high selectively (eq 19). This reaction performed especially well



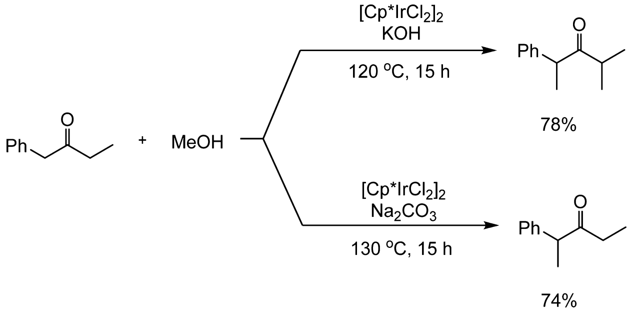
when it was carried out under oxygen (i.e., 98% yield), with a much lower yield being obtained when the reaction was conducted under Ar (57%). It is noteworthy that this reaction did not require anhydrous methanol, which shows that this reaction is more practical compared with conventional alkylation methods using a lithium enolate.

Obora et al. reported the development of an Ir-catalyzed method for the alkylation of ketones using methanol. In a typical procedure, acetophenone (1 mmol) was reacted with methanol (1.5 mL) in the presence of $[Cp^*IrCl_2]_2$ (5 mol %) and KOH (0.5 mmol) at 120 °C to give the α-methylated product in 83% yield with high selectivity.[54] This reaction proceeded in a highly chemoselective manner to afford the dimethylated ketone exclusively (eq 20).



Benzyl ethyl ketone also reacted under these conditions to give the dimethylated product selectively. Interestingly, the use of Na_2CO_3 in the reaction instead of KOH led to selective monomethylation at the benzylic position (Scheme 7). This selectivity was attributed to differences in the pK_a values of the α-protons at the benzylic and ethyl positions.

Scheme 7. Selective Monomethylation and Dimethylation Reactions of Ketones



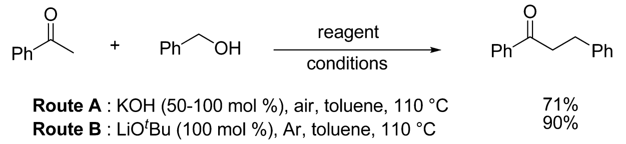
6. Transition-Metal-Free α-Alkylation Reactions. The development of transition-metal-catalyzed α-alkylation reactions based on hydrogen borrowing methods has inspired research efforts toward the development of transition-metal-free α-alkylation reactions.

In terms of the redox process between carbonyl compounds and the corresponding alcohols, it is well-known that alkali metals function as a base in the Oppenauer oxidation of alcohol to aldehydes and ketones, as well as the Meerwein–Ponndorf–Verley

(MPV) reduction of aldehydes and ketones to the corresponding alcohols.[55]

Xu et al. reported that the α-alkylation of ketones with alcohols could be achieved using KOH in the absence of a transition-metal catalyst.[56] In a typical example of their work, a mixture of acetophenone (2 mmol), benzyl alcohol (2.4 mmol), and KOH (2 mmol) in toluene (4 mL) was heated at 100 °C in a sealed tube under air to give the α-methylated product in 71% yield with high selectivity. Furthermore, this reaction led to the formation of the α-alkylated product in high yield when it was conducted in the presence of only 50 mol % of KOH (Scheme 8; Route A).

Scheme 8. Transition-Metal-Free α-Alkylation



In another example of a transition-metal-free reaction, Xu reported the LiO*t*Bu-mediated α-alkylation of ketones with high selectivity.[57] In this particular case, a mixture of acetophenone (0.5 mmol) and benzyl alcohol (0.75 mmol) in toluene (2 mL) was heated at 110 °C for 12 h in the presence of LiO*t*Bu (1 mmol) to give the α-methylated product in 90% yield (Scheme 8; Route B).

7. Outlook. The direct α-alkylation of carbonyl compounds though hydrogen borrowing (or hydrogen autotransfer) represents a powerful technique for the formation of C−C bonds, which could be used to synthesize a variety of important organic compounds. The α-alkylation reactions reported in this review are practical and green chemical processes because they use less toxic and readily available alcohols as the alkylation agent, and produce H_2O as a sole byproduct. Remarkable achievements have been made in the field of the α-alkylation during the past 10 years, and these achievements have been summarized in this review. The most notable of these achievements include the development of more active catalysts, recyclable heterogeneous catalysts, and the use of methanol as a methyl source in α-alkylation reactions.

The methodology discussed in this review will hopefully continue to develop toward the identification of increasingly practical methods for the α-alkylation of carbonyl compounds. Hopefully this review will act as a useful reference to scientists currently working in this area and that it will inspire further research of this protocol toward the development of waste-free and environmentally benign processes for the production of chemicals.

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Notes

The authors declare no competing financial interest.

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