Alkylation

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C-Alkylation of Ketones and Related Compounds by Alcohols: Transition-Metal-Catalyzed Dehydrogenation

*Fei Huang, Zhuqing Liu, and Zhengkun Yu**

alcohols · alkylation · borrowing hydrogen · green chemistry · transition metals

Transition-metal-catalyzed C-alkylation of ketones and secondary alcohols, with alcohols, avoids use of organometallic or environmentally unfriendly alkylating agents by means of borrowing hydrogen (BH) or hydrogen autotransfer (HA) activation of the alcohol substrates. Water is formed as the only by-product, thus making the BH process atom-economical and environmentally benign. Diverse homogeneous and heterogeneous transition-metal catalysts, ketones, and alcohols can be used for this transformation, thus rendering the BH process promising for replacing those procedures that use traditional alkylating agents. This Minireview summarizes the advances during the last five years in transition-metal-catalyzed BH α-alkylation of ketones, and β-alkylation of secondary alcohols with alcohols. A discussion on the application of the BH strategy for C–C bond formation is included.

1. Introduction

The construction of C–C bonds is among one of the most important tasks in organic synthesis. Diverse types of reactions can be utilized to form such chemical bonds. Transition-metal-catalyzed cross-coupling reactions have recently made great progress in C–C bond formation. However, traditional cross-coupling alkylation usually requires environmentally unfriendly organic or organometallic coupling partners, and in some cases, dangerous chemical materials.[1] Although various alkylating compounds have been successfully explored, there is still a need to develop readily available alkylating agents, as well as the corresponding effective catalytic systems, for the C-alkylation of ketones, secondary alcohols, and related compounds.

Alcohols are readily available and are considered potential alkylating agents. However, they are usually unreactive as alkylating agents because the OH group in an alcohol molecule cannot be easily replaced by a nucleophilic reagent. Thus, alcohols have to be used in reactions in the forms of halides, tosylates, triflates, and sulfonates, etc., that is, after converting the OH group into a better leaving functionality. In this situation, poor efficiency and the production of undesired waste are often encountered.[2] As far as modern synthetic chemistry is concerned, green processes are sought after in both academic laboratories and industry.

Since the groups of Grigg and Watanabe reported transition-metal-catalyzed N-alkylation of amines by means of alcohols as the alkylating agents,[3,4] continuous efforts have been made towards both N-alkylation of amines and C-alkylation of ketones and related compounds with alcohols as the alkylating agents, through a borrowing-hydrogen (BH)[5–12] or hydrogen-autotransfer (HA)[2,13,14] strategy. A typical BH or HA process is demonstrated in Scheme 1. In such a process, an alcohol transfers hydrogen to a transition-metal catalyst and forms the corresponding aldehyde or ketone intermediate. This intermediate is then transformed into either an imine by condensation with an amine or an olefin by condensation with the α-C–H unit of a ketone. Subsequent addition of hydrogen to either the imine or olefin intermediate, from the transition-metal hydride species, gives the product with a newly formed C–N (Scheme 1a) or C–C (Scheme 1b) bond, respectively, thus forming water as the only by-product. To simplify the description, the concepts of BH and HA will herein be presented as borrowing hydrogen (BH).

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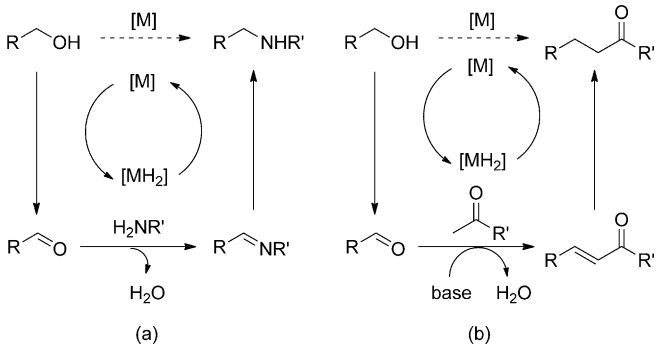
Transition-metal-catalyzed BH activation of alcohols has recently attracted much attention. Various transition-metal catalysts, challenging substrates, and processes have been documented.[15–19] It is notable that an alternative strategy for alcohol activation by temporary oxidation to an aldehyde has been developed by Krische et al., wherein dehydrogenation of the primary alcohol in the presence of a π-unsaturated reactant provides an aldehyde/organometal pair which combines to form the product of carbonyl addition in the absence of a stoichiometric amount of organometallic reagent.[20]

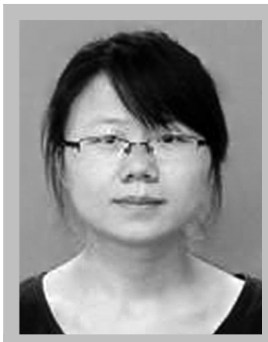


Scheme 1. BH or HA strategy for alcohol activation.

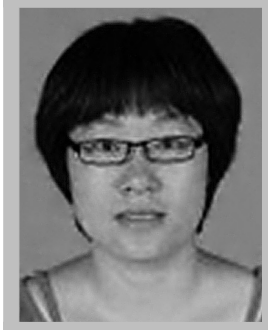
However, this review is focused on the progress made since 2009 in the C-alkylation of ketones and related compounds, with alcohols, by using a BH strategy.

2. Transition-Metal-Catalyzed C-Alkylation of Ketones and Secondary Alcohols with Primary Alcohols

Carbon–carbon bond formation by means of efficient, selective, and environmentally benign processes has been a challenging task in synthetic chemistry. α-Alkylation of the enolates of ketones with electrophilic alkylating agents was documented to construct a C–C bond,[7,21,22] but this protocol suffers from the production of stoichiometric amounts of undesirable salts as waste. In 2001, Shim, Cho, and co-workers reported ruthenium-catalyzed transfer hydrogenation of ketones with primary alcohols accompanied by C–C bond formation.[23] Later, Cho documented the ruthenium-catalyzed β-alkylation of secondary alcohols with primary alcohols.[24] Crabtree et al. reported ruthenium- and iridium-catalyzed cross-coupling reactions between secondary benzylic alcohols and primary alcohols.[25] These results have demonstrated that alcohols can be used as promising green alkylating agents for the α-alkylation of ketones and β-alkylation of secondary alcohols. Recently, transition-metal-catalyzed α-alkylation of ketones through a BH pathway has aroused considerable attention as an efficient and atom-economical method for constructing a C–C bond, and it allows convenient introduction of an alkyl group to the α-position of ketones with water formed as the only by-product.



Fei Huang studied pharmaceutical engineering at Liaoning University, Shenyang, China and received her BSc degree in July 2011. In September 2011, she joined Prof. Zhengkun Yu's group at Dalian Institute of Chemical Physics, Chinese Academy of Sciences, to pursue a PhD degree. Her current research is focused on copper-mediated cyclizations and related homogeneous catalysis.

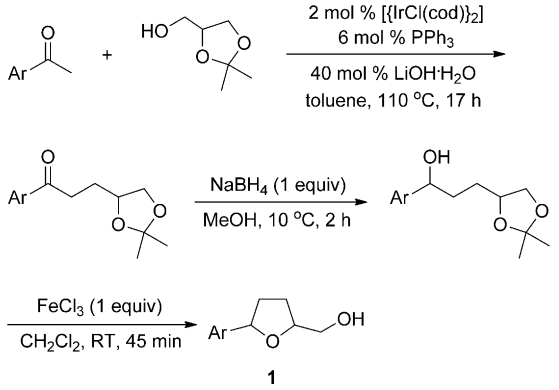


Zhuqing Liu studied chemistry at Qingdao University, Qingdao, China and received her BSc degree in July 2012. In September 2013, she joined Prof. Zhengkun Yu's group at Dalian Institute of Chemical Physics to pursue a PhD degree. Her current research is centered on transition-metal catalysis and synthetic methodologies.

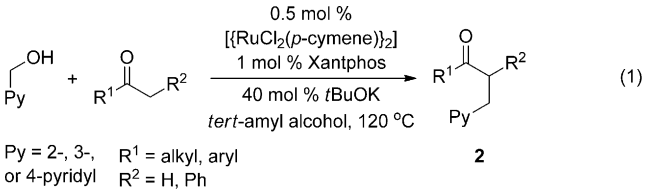
Zhengkun Yu obtained his PhD degree at Dalian Institute of Chemical Physics in 1995. Between 1995 and 2003 he worked as a post-doctoral associate in the laboratories of Prof. Rudolf Aumann (University of Münster), Prof. John G. Verkade (Iowa State University), and Prof. Chuck Winter (Wayne State University), and at Waseda University/Japan Corporation of Science and Technology. He returned to Dalian Institute in 2003. His research interests are focused on novel organometallic catalysts and activation of inert C–X bonds.

2.1. α-Alkylation of Ketones

α-Alkylation of ketones with alcohols through a BH process can be easily manipulated to furnish various products, such as alkylated ketones, α,β-unsaturated ketones, N-heterocycles, or alcohol derivatives, by choosing the appropriate starting ketones or functionalized alcohols.[26,27] The BH methodology was applied in the synthesis of 2,5-disubstituted tetrahydrofurans (**1**) from glycerol by the catalytic alkylation of ketones (Scheme 2).[28] [{IrCl(cod)}$_2$]-catalyzed α-alkylation of substituted acetophenones with solketal and subsequent reduction and iron-mediated cyclization provided **1**. By using the readily available [{RuCl$_2$(*p*-cymene)}$_2$]/Xantphos/*t*BuOK catalyst system, α-alkylation of ketones with pyridyl methanol was achieved, thus demonstrating a simple complement to the previously reported α-alkylation of ketones [Eq. (1); Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene].[29] Rhodium(III)-catalyzed methylation of ketones was also accomplished with methanol as the alkylating agent [Eqs. (2) and (3)].[30] Such a protocol features a relatively low reaction temperature and the ability to produce α-branched ketone products of the types **3** and **4**. Double alkylation of methyl ketones by two different alcohols (R^1CH_2OH and MeOH) supplied ketones (**5**) through



Scheme 2. Synthesis of 2,5-disubstituted tetrahydrofurans.[28] cod = 1,5-cyclooctadiene.



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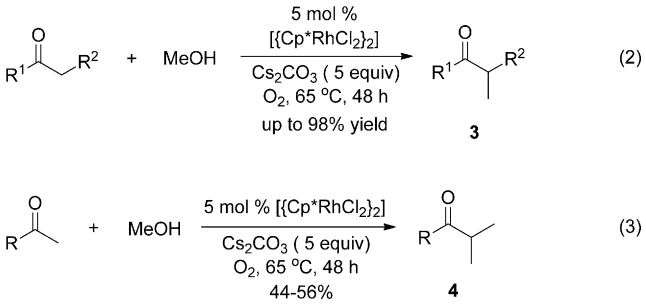
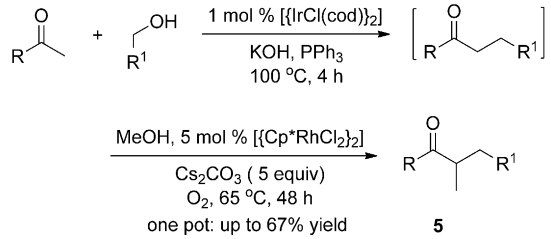


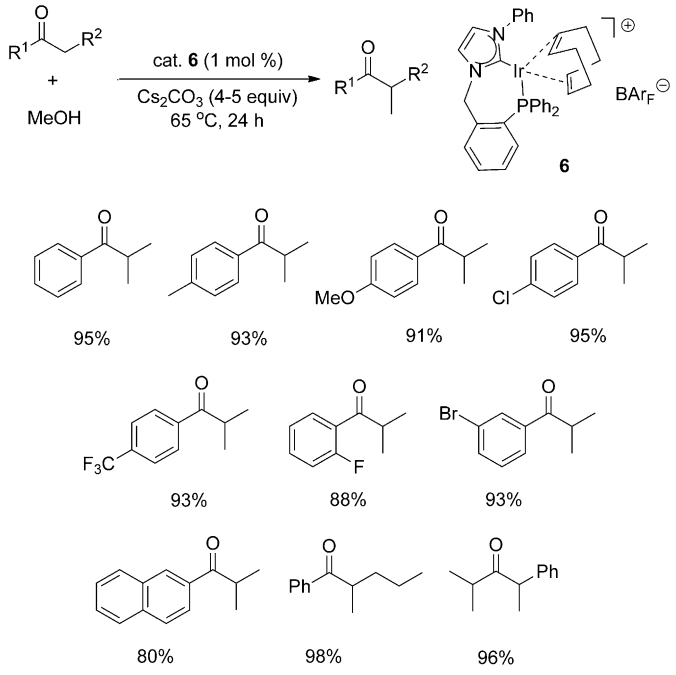
(2)

(3)

a sequential one-pot iridium- and rhodium-catalyzed process (Scheme 3).[30] With 5 mol% [{Cp*IrCl$_2$}$_2$]/50 mol% KOH as the catalyst system, α-methylation of ketones smoothly proceeded at 120 °C, and in a similar fashion, methylation of phenyl acetonitriles with methanol occurred.[31] With an N-heterocyclic carbene (NHC)/phosphine iridium complex (iridium/CNP complex **6**) as the precatalyst in the presence of Cs_2CO_3, C–C coupling of ketones with methanol was conducted, thus affording a number of branched ketones in good to excellent yields (Scheme 4).[32] For the reaction mechanism the authors propose dehydrogenation of methanol to form formaldehyde, followed by aldol condensation



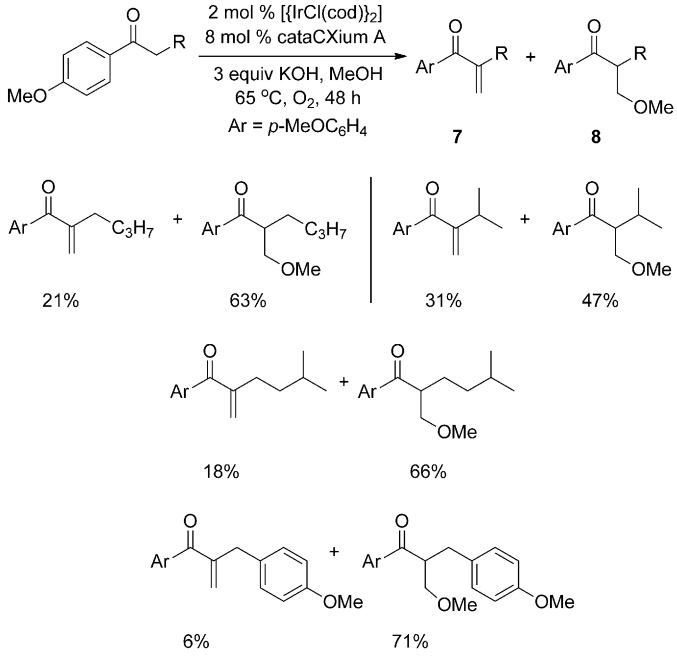
Scheme 3. Double alkylation of ketones.[30] Cp* = C_5Me_5.



Scheme 4. Efficient methylation of ketones with methanol.[32]

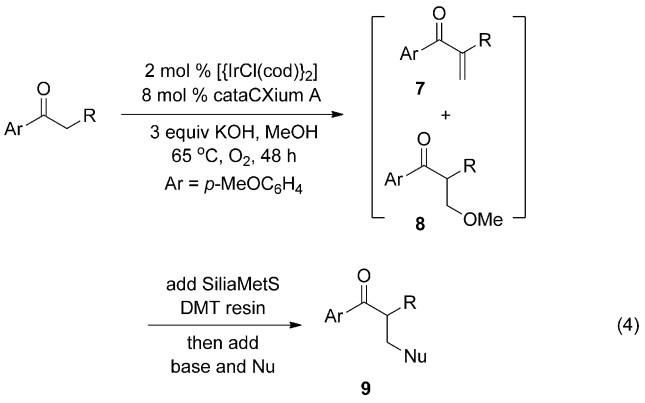
with the ketone substrate to generate a conjugated ketone, and final reduction to give the target product. Iridium/CNP complexes[33,34] and tris(acetylacetonato)rhodium[35] were also used to catalyze the α-alkylation of acetophenones with primary alcohols.

Interestingly, the interrupted-hydrogen-borrowing reaction of a ketone with methanol was achieved in the presence of a bulky monodentate phosphine ligand (cataCXium A;[36] Scheme 5), and subsequent addition of a pronucleophile to



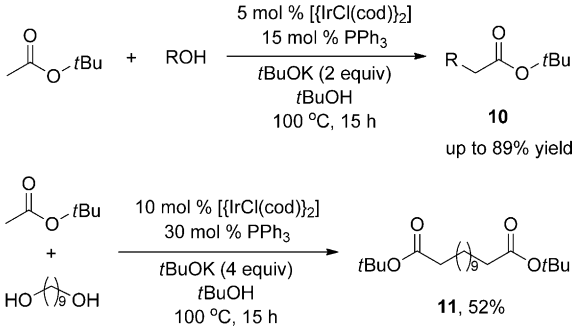
Scheme 5. Methylation of ketones by using a bulky phosphine ligand.[37]

the reaction mixture allowed a one-pot methylation/conjugate addition protocol to be established [Eq. (4)].[37] In this iridium-catalyzed interrupted process both the enone **7** and

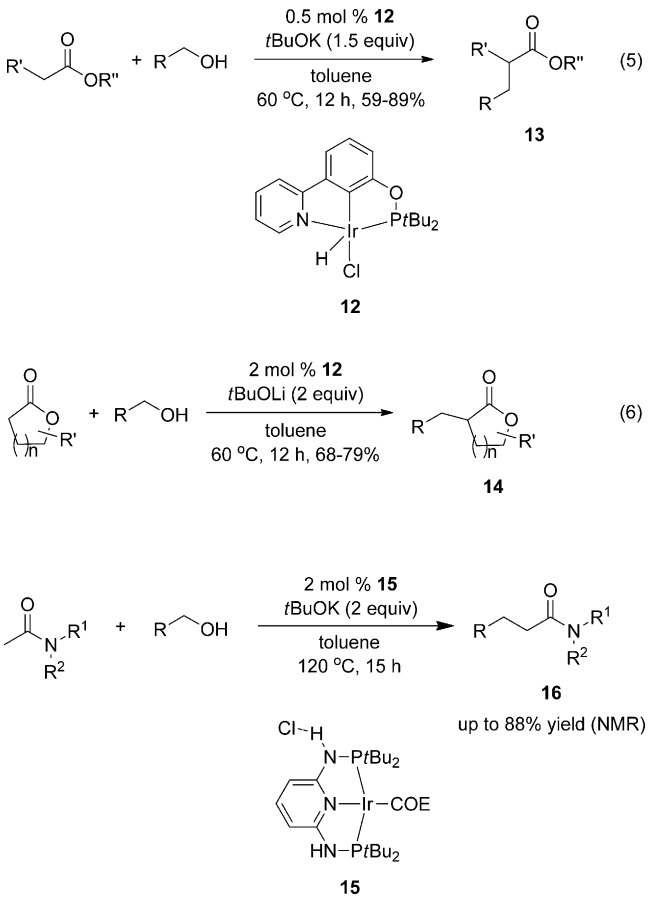


methoxy adduct **8** were not isolated but reacted in situ with an external nucleophile and extra base. It was found that treatment of the reaction mixture with the metal-scavenging resin (SiliaMetS DMT)[38] was beneficial to the subsequent reaction to produce the products **9**. $AgSbF_6$ was reported to catalyze the direct α-alkylation of unactivated ketones by benzylic alcohols.[39]

With $[\{IrCl(cod)\}_2]/PPh_3$ as the catalyst in the presence of *t*BuOK, primary alcohols reacted with *tert*-butyl acetate in *t*BuOH at 100 °C to form the α-alkylated esters **10** in up to 89 % yield (Scheme 6).[40] With 1,9-nonanediol as the alkylating agent the reaction gave di-*tert*-butyl tridecanoate (**11**), which can be applied in the synthesis of a fragrant compound, ethylene brassylate (Musk T). Mild catalytic α-alkylation of unactivated esters using alcohols was achieved by means of an iridium hydride complex (**12**) as the catalyst [Eq. (5)], and *t*BuOLi was an effective base for the α-alkylation of lactones, using the same catalyst [Eq. (6)].[41] The iridium pincer complex **15** exhibited a good catalytic activity for the α-alkylation of unactivated acetamides with alcohols (Scheme 7).[42] α-Alkylation of acetamides with primary alcohols was also efficiently conducted to give the amide products with $[RuHCl(CO)(PPh_3)_3]$/2,6-bispyrazolylpyridine as the catalyst.[43]



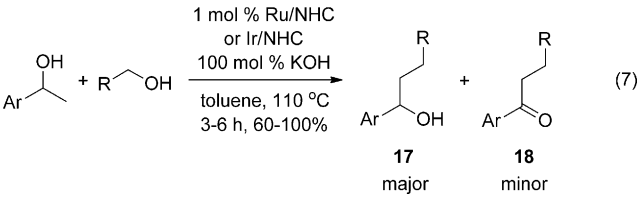
Scheme 6. α-Alkylation of acetates with primary alcohols or diols.[40]

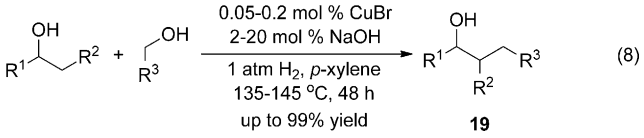


Scheme 7. α-Alkylation of acetamides with primary alcohols.[42] COE = cyclooctene.

2.2. β-Alkylation of Secondary Alcohols

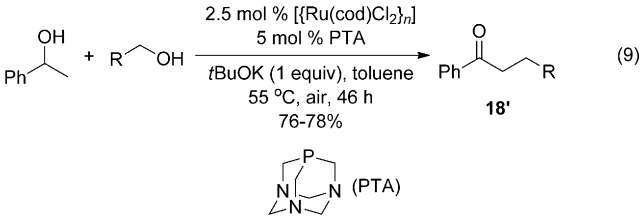
Direct C–C cross-coupling of secondary and primary alcohols can be catalyzed by various transition-metal catalysts among which the most generally used are ruthenium and iridium complexes.[25,44,45] The β-alkylation of secondary alcohols with primary alcohols in the presence of KOH and either a ruthenium(II)- or iridium(III)/NHC complex catalyst is highly selective in forming the alcohol products **17** [Eq. (7)].[45] The ruthenium complex $[RuCl_2(PPh_3)_2$(2-amino-methylpyridine)] effectively catalyzes the β-alkylation of both aryl- and alkyl-substituted secondary alcohols with benzylic and alkyl alcohols.[46] In the presence of external dihydrogen, the minor alkylated ketone species can be reduced to the corresponding alkylated alcohol [Eq. (8)].[47] Tris-(acetylacetonato)rhodium(III) was shown to be a versatile





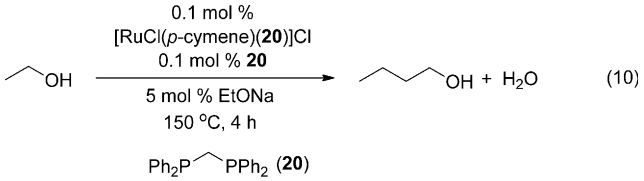
(8)

catalyst in the presence of DABCO (1,4-diazabicyclo-[2.2.2]octane) for the alkylation of aromatic amines, and α-alkylation of ketones, and it also effected β-alkylation of secondary alcohols to afford the alcohol products.[35] An iridium/NHC/KOH catalyst system behaved efficiently for the same reactions.[48] Under an air atmosphere, $Cu(OAc)_2$-catalyzed β-alkylation of secondary alcohols with primary alcohols could be accelerated as compared with that performed under a nitrogen atmosphere, and elevating the reaction temperature enhanced the reaction efficiency further.[49] However, the $[\{Ru(cod)Cl_2\}_n]$/PTA/*t*BuOK combination (PTA = 1,3,5-triaza-7-phosphaadamantane) promoted the reaction of 1-phenylethanol and primary alcohols to yield the ketone products **18′** [Eq. (9)].[50]



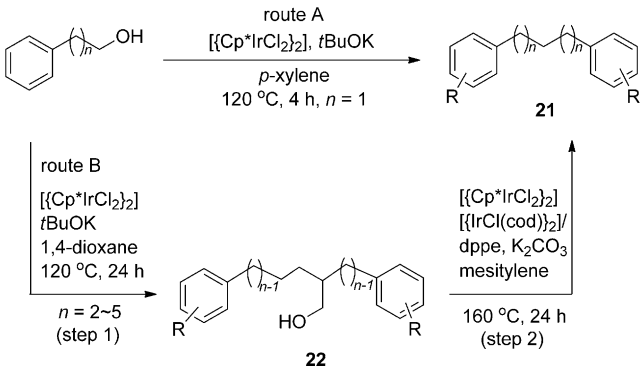
(9)

Self-coupling of alcohols can be applied for the production of versatile alcohol materials.[10] One example is the preparation of *n*-butanol, an advanced biofuel, from ethanol with 94% selectivity at over 20% conversion [Eq. (10)].[51]

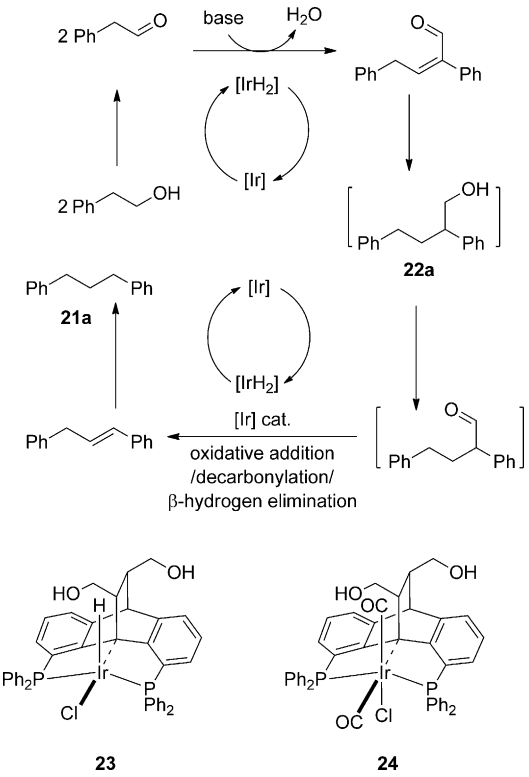


(10)

However, iridium-catalyzed reactions of readily accessible ω-arylalkanols afforded α,ω-diarylalkanes (**21**; Scheme 8).[52] The reaction was achieved by either a direct one-step method (route A) or a sequential two-step method via the intermediate **22** [route B: dehydrogenation/β-alkylation (step 1); dehydrogenation/decarbonylation (step 2)], depending on the alkyl chain length of the ω-arylalkanol used. The possible mechanism can be exemplified by the conversion of 2-phenylethanol into 1,3-diphenylpropane (**21a**; Scheme 9). Dehydrogenation of the starting alcohol results in the aldehyde intermediate which undergoes self-condensation to form an α,β-unsaturated aldehyde. Reduction by the in situ generated iridium hydride species leads to **22a**. A subsequent dehydrogenation reaction occurs to form another aldehyde which is further transformed into the olefin intermediate by a sequential reaction including oxidative addition, decarbonylation, and hydrogen elimination. Interaction of this olefin intermediate with the in situ formed iridium hydride species produces the target product **21a**. Self- or cross-coupling of alcohols was also realized with the ruthenium- and iridium-based catalysts **23** and **24** (Scheme 9), respectively.[53] It is noteworthy that the development of new highly efficient transition-metal catalysts is still the major task in this area.



Scheme 8. Preparation of α,ω-diarylalkanes from ω-arylalkanols.[52]

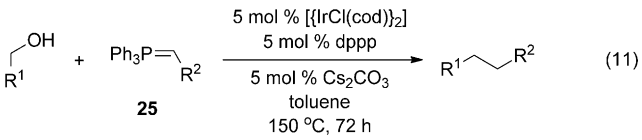


Scheme 9. A plausible reaction pathway for the formation of α,ω-diarylalkanes[52] and two other catalysts for the self- or cross-coupling of alcohols.[53]

2.3. Indirect Wittig Reactions to Form C–C bonds

In a fashion similar to the synthesis of amines through indirect Wittig reactions,[54] C–C bond formation can be achieved by the reaction of an alcohol with the Wittig ylide **25**

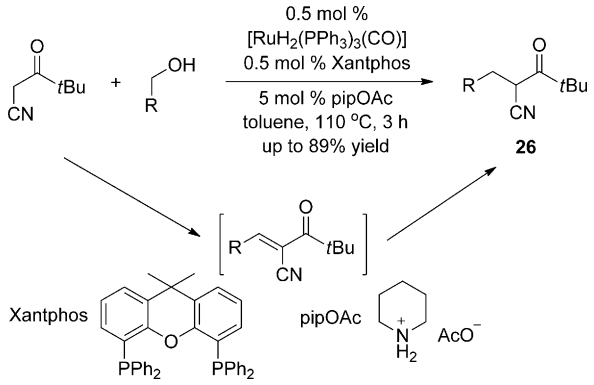
[Eq. (11); dppp = 1,3-bis(diphenylphosphanyl)propane].[55] [{IrCl(cod)}$_2$]/dppp acted as the effective catalyst, thus rendering the one-pot conversion of alcohols into alkanes. In the case of using a secondary alcohol, the product yield was dramatically decreased.



(11)

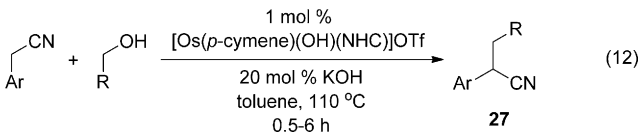
2.4. α-Alkylation of Nitriles

By using the BH strategy, the alkylation of ketonitriles with alcohols has been used for C–C bond formations. A combination of [RuH$_2$(PPh$_3$)$_3$(CO)] with Xantphos was catalytically active for the alkylation of *t*BuC(O)CH$_2$CN with primary alcohols in a model oxidation/Knoevenagel/reduction process (Scheme 10).[56] Piperidinium acetate was found



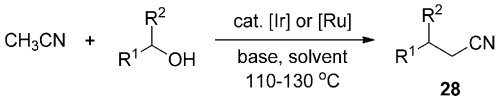
Scheme 10. Catalytic alkylation of ketonitriles with primary alcohols.[56]

to be an efficient additive to promote the reaction. An olefin intermediate was proposed to be formed during the reaction, and then reduced to the corresponding alkane product **26** by the ruthenium hydride species. A Ru/NHC complex catalyst was also successfully employed for the same reactions.[57] α-Alkylation of arylacetonitriles with primary alcohols occurred in the presence of an osmium(II) complex catalyst, thus efficiently affording the target products **27** [Eq. (12); Tf = trifluoromethanesulfonyl].[58]



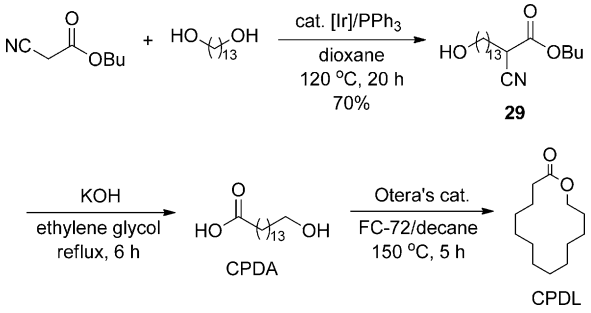
(12)

Direct coupling of arylacetonitriles with primary alcohols by [{Rh(cod)Cl}$_2$]/PPh$_3$/KOH was performed under microwave conditions, thus leading to α-alkylated arylacetamides in 74–92% yields.[59] Mechanistic studies revealed that arylacetonitriles are first α-alkylated with primary alcohols to produce α-alkylated arylacetonitriles, which are further hydrated with water, formed from the α-alkylation step, to give the target products. In the case of using acetonitrile, both [{Ir(OH)(cod)}$_2$]/PPh$_3$[60] and [RuHCl(PPh$_3$)$_3$(CO)][61] could effect its reaction with primary or secondary alcohols in the presence of a base [Eq. (13)]. This method provides a very clean and atom-economical direct route to substituted nitriles **28**, which are very important raw materials in organic and industrial chemistry.



(13)

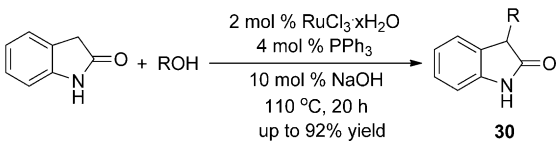
Iridium-catalyzed α-alkylation of butyl cyanoacetate with substituted benzyl and heteroaryl alcohols under solvent-free conditions afforded the corresponding monoalkylated products in moderate to high yields.[62] Alkylation of the same nitrile with 1,13-tridecanediol in the presence of [{IrCl(cod)}$_2$] or [{IrCl(coe)}$_2$] provided butyl 2-cyano-15-hydroxypentadecanoate (**29**) in 70% yield. This compound could be converted into 15-hydroxypentadecanoic acid (CPDA), an important precursor to the most widely produced macrocyclic synthetic musk lactone cyclopentadecanolide (CPDL). CPDA could then be easily converted into CPDL by using Otera's catalyst ([(*n*Bu$_2$SnCl)$_2$O]$_2$; Scheme 11).[63]



Scheme 11. α-Alkylation of butyl cyanoacetate with a diol.[63]

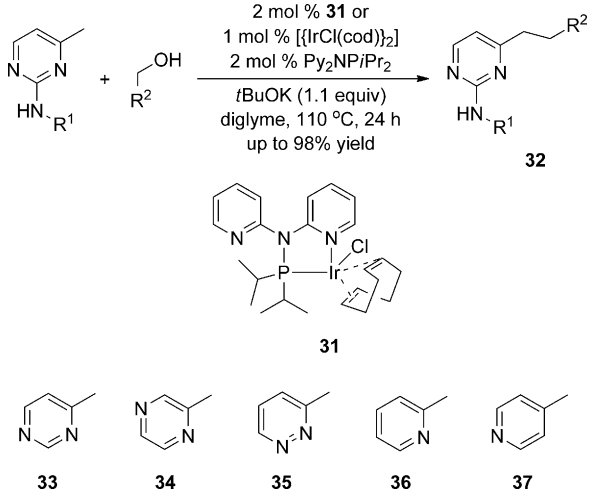
2.5. Alkylation of N-Heterocycles

Alcohols were successfully used for the alkylation of N-heterocycles themselves, as well as their functional groups, in the presence of a transition-metal catalyst. Under solvent-free conditions, 3-monoalkylation of oxindole proceeded with primary and secondary alcohols with the catalyst generated in situ from RuCl$_3$·*x*H$_2$O, PPh$_3$, and NaOH [Eq. (14)]).[64] The



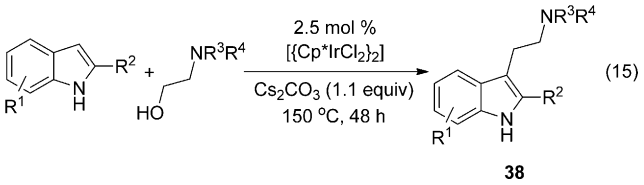
(14)

reactions occurred to give **30** in good to excellent yields with a wide range of aromatic, heteroaromatic, and aliphatic alcohols. [{Cp*IrCl$_2$}$_2$] acted as the catalyst for 3-alkylation of oxindole and *N*-methyl oxindole with various substituted benzyl and heteroaryl alcohols.[65] Catalytic alkylation of methyl-substituted N-heteroarenes with alcohols was performed in the presence of the P,N-ligand-stabilized iridium complex **31**, which was prepared or formed in situ from the reaction of [{IrCl(cod)}$_2$] and Py$_2$N*i*Pr$_2$ (Scheme 12).[66] These



Scheme 12. Alkylation of methyl-substituted N-heteroarenes with alcohols.[66]

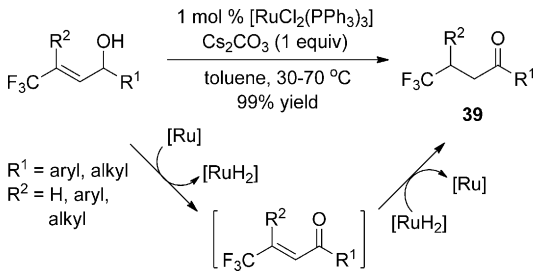
reactions had to be carried out under basic conditions to produce the target products **32**, and the N-heteroarenes **33**–**37** were also used as the substrates. In the presence of a Co^{III} complex catalyst, *N*-pyrimidin-2-yl-protected indoles underwent C2 allylation with allylic alcohols.[67] With [{Ir(OH)(cod)}$_2$]/PPh$_3$ as the precatalyst, alkylation of methylquinolines at the methyl substituent was realized with alcohols,[68] thus offering an atom-economical and convenient route to alkylquinolines from readily accessible methylquinolines. Selective 3-alkylation of indoles with N-protected ethanolamines was conducted to access the tryptamine derivatives **38** [Eq. (15)].[69]



(15)

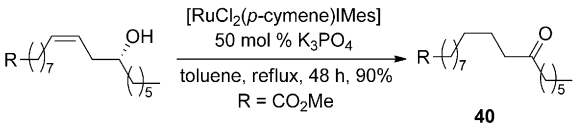
2.6. Versatile BH Sequences Involving Alcohols

Intramolecular BH transformations of trifluoromethylated allylic alcohols under ruthenium catalysis, led to the redox isomerization products **39** (Scheme 13).[70] The presence of the CF$_3$ substituent at γ-position of the substrates is crucial for



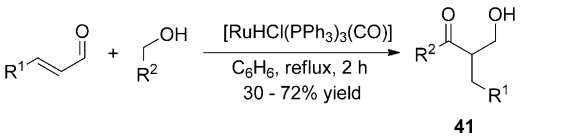
Scheme 13. An intramolecular BH process.[70]

the reaction to occur efficiently, and an α,β-unsaturated ketone is considered to be the intermediate species. In a similar fashion, the Ru^{II}/NHC complex [RuCl$_2$(*p*-cymene)IMes][71] catalyzed the in situ dehydrogenation/hydrogenation of methyl ricinoleate, a hydroxy-containing fatty acid methyl ester (FAME) which is usually used for the production of polyamide monomers.[72] Thus, it was converted into methyl 12-oxooctadecanoate [**40**; Eq. (16); R = CO$_2$Me].[73] This protocol provides a promising method to access FAME derivatives for the polymer-additive industry.



(16)

Ruthenium hydride complex [RuHCl(PPh$_3$)$_3$(CO)] catalyzed the cross-coupling reactions of α,β-unsaturated aldehydes with primary alcohols to afford 2-hydroxy ketones **41** [Eq. (17)].[74] The reaction is likely to proceed via the

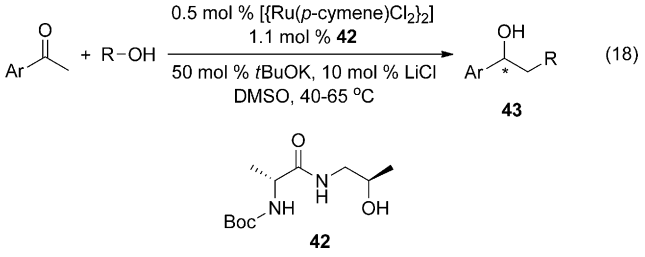


(17)

hydroruthenation of the α,β-unsaturated aldehyde followed by an aldol reaction of the resultant enolate with the in situ generated aldehyde from the alcohol to give an α-formylated keteone, which undergoes transfer hydrogenation with the primary alcohol, thus leading to **41**.

2.7. Enantioselective Functionalization with Alcohols

A tandem α-alkylation/asymmetric transfer hydrogenation of acetophenone with primary alcohols was established by means of [{Ru(*p*-cymene)Cl$_2$}$_2$] and the amino acid hydroxyamide **42**, thus giving the chiral secondary alcohol products **43** in up to 43% yield and 89% *ee* [Eq. (18); Boc = *tert*-butoxycarbonyl].[75] Asymmetric coupling of *meso*-diols with aldehydes was also realized by using the chiral iridium complex **44** [Eq. (19); Ts = 4-toluenesulfonyl].[76] In the



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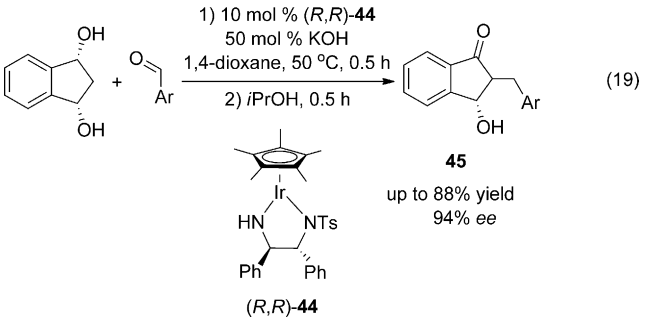

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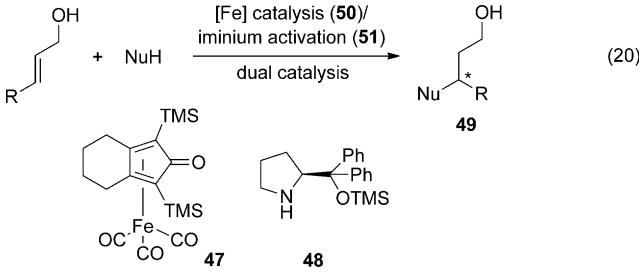
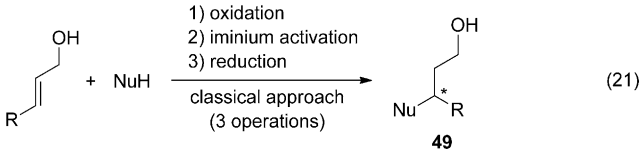


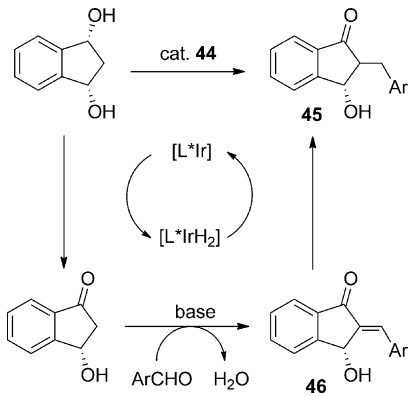
(20)

fashion. It is noted that three operations are required to get the same products by a classical approach [Eq. (21)].



(21)

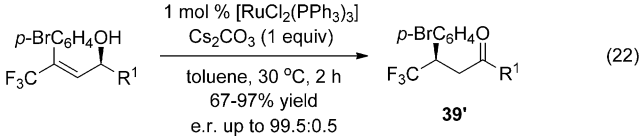
presence of an additional hydrogen donor, 2-propanol, the α-aryl-β-hydroxyindan-1-ones (**45**) were obtained with a one-pot method in up to 88% yield and 94% *ee*. In the absence of an additional hydrogen donor, the desired ketone **45** was obtained in 92% *ee* (for Ar = Ph), together with chiral enone **46** as the side-product. The reaction sequence consists of oxidative desymmetrization of the diol, aldol condensation with the aldehyde, and reduction of the enone intermediate by the in situ formed iridium hydride (Scheme 14).



Scheme 14. Asymmetric BH process to form C–C bonds.[76]

An iron/amine-catalyzed tandem process was successfully used for the enantioselective functionalization of allylic alcohols [Eq. (20); TMS = trimethylsilyl].[77] Combining the two orthogonal catalytic cycles (BH catalysis by the iron complex **47** and iminium activation by the chiral amine **48**) remarkably enhanced the hydrogen-transfer activity of the iron complex. This one-pot method features dual catalysis, thus enabling conversion of allylic alcohols into β-chiral alcohols under mild reaction conditions in an enantioselective

Under the reaction conditions shown in Scheme 13, the β-CF_3-substituted secondary (*R*)-allylic alcohol bearing a bromophenyl moiety (97% *ee*) was fully converted into the saturated (*R*)-ketone [94% *ee*; Eq. (22)].[70] The synthetic protocol provides an alternative route to the asymmetric synthesis of the CF_3 analogues of citronellol.

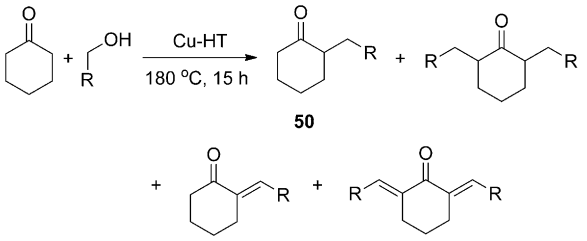


(22)

3. Heterogeneous Transition-Metal-Catalyzed C-Alkylation of Ketones and Secondary Alcohols with Alcohols

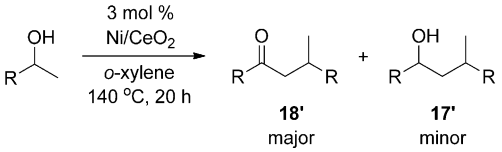
Most of the known catalyst systems for C-alkylation of ketones and secondary alcohols, with alcohols as the alkylating agents, are homogeneous transition-metal-based catalyst systems, which are not applicable for scale-up production because of the problem of reusability and/or the indispensable use of large amounts of additives or cocatalysts. Heterogeneous transition-metal catalysts can overcome some of the drawbacks of the homogeneous catalysts, but they usually suffer from harsh reaction conditions, low turnover numbers, limited substrate scope, and/or use of excessive amounts of alcohol to obtain satisfactory yields. Thus, exploration of efficient heterogeneous transition-metal catalyst systems has recently aroused much attention for BH processes.[19]

Using a Mg/Al-hydrotalcite-supported copper catalyst (Cu-HT, Mg/Al molar ratio = 2:1), the reaction of cyclohexanone with a primary alcohol at 180 °C gave a mixture of the α-alkylated ketone **50** and enone intermediates under solvent-free conditions [Eq. (23)].[78] Supported nickel cata-



(23)

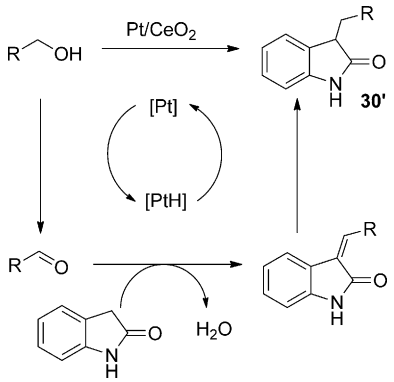
lysts effected the liquid-phase C–C self-coupling of aliphatic secondary alcohols under additive-free conditions [Eq. (24)].[79] Among the screened nickel catalysts, 1 and



(24)

3 wt% Ni/CeO_2 catalysts, pre-reduced in H_2, exhibited the highest yield (94%) of a dimer product (a higher-order ketone of type **18′**) for the self-coupling of 1-octanol at 130 °C, and the catalyst was reused. The catalysts were also effective for self-coupling of other secondary alcohols, thus offering the first heterogeneous catalytic system for the self-coupling of secondary alcohols under mild reaction conditions.[10] It was found that both CeO_2 and metallic nickel are indispensable for the reaction. The alcohols **17′** were formed as the side-products.

With a Pt/CeO_2 catalyst C3 alkylation of oxindole by primary alcohols produced the 3-alkylated oxindole products in up to 95% yields (Scheme 15).[80] Structure–activity

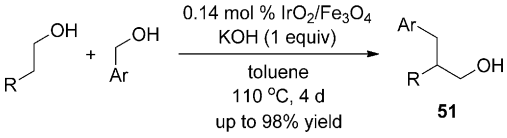


Scheme 15. Pt/CeO_2-catalyzed C3 alkylation of oxindole with alcohols.[80]

relationship studies have shown that the presence of both the surface Pt^0 species on the Pt metal clusters and the basic support are indispensable. In a fashion similar to the C_{sp^3}–H alkylation of methyl-substituted N-heteroarenes by $[\{Ir(OH)(cod)\}_2]/PPh_3$,[68] Pt/Al_2O_3 catalyzed the alkylation of 2-methylquinoline with alcohols at 170 °C under additive-free conditions, thus affording alkylquinolines in moderate to good yields.[81] β-Alkylation of secondary alcohols with primary alcohols was accomplished by means of a γ-alumina-supported silver sub-nanocluster catalyst because of the ability of $Ag/\gamma\text{-}Al_2O_3$ to facilitate alcohol dehydrogenation.[82] In the presence of the weak base Cs_2CO_3, the ketone products were selectively obtained [Eq. (25)].[83] The hybrid material $Ag_6Mo_{10}O_{33}$ was employed for the same purpose.[84]

(25)

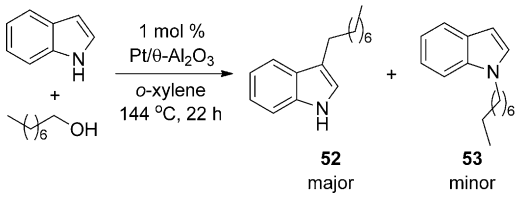
Cross-alkylation between two primary alcohols was performed by using a recyclable impregnated iridium-on-magnetite catalyst, that is, IrO_2/Fe_3O_4 [Eq. (26)].[85] The



(26)

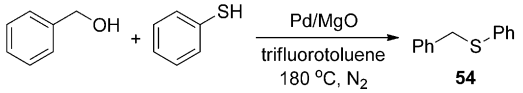
catalyst was easily removed from the reaction medium by magnetic sequestering. A silica-supported palladium/NiXantphos complex was found to be an efficient and high-turnover heterogeneous catalyst for the α-alkylation of ketones with readily available alcohols at 120–140 °C under neat conditions.[86] The catalyst could easily be separated with negligible palladium leaching. A SBA-15-supported Ir/NHC complex was also reported as the catalyst for β-alkylation of secondary alcohols with primary alcohols.[87]

A $Pt/\theta\text{-}Al_2O_3$ catalyst efficiently promoted the 3-alkylation of indoles [Eq. (27)].[88] It is notable that a base is not necessary for this conversion because of the support effect of $\theta\text{-}Al_2O_3$, which facilitates the aldol condensation of indole with the in situ generated aldehyde intermediate.



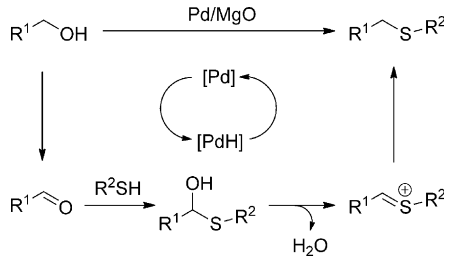
(27)

A palladium-catalyzed BH process was employed for the synthesis of thioethers, in which palladium on magnesium oxide was used as the catalyst to allow the reaction of thiol and alcohol to occur in a one-pot manner [Eq. (28)].[89]



(28)

Palladium hydride and aldehyde were considered as the intermediates, and the in situ generated aldehyde probably reacts with the thiol to form a thionium ion, which is then reduced by the in situ formed palladium hydride to afford the thioether product (Scheme 16).



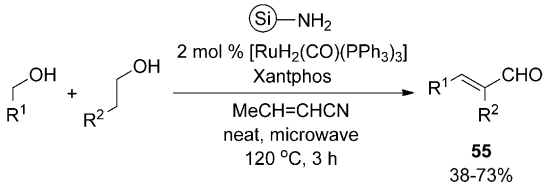
Scheme 16. Alkylation of a thiol with a primary alcohol.[89]

4. Relevant Reactions Involving Dehydrogenation of Alcohols

If the hydrogen generated in the dehydrogenation of an alcohol is returned to the desired product, a BH sequence is established. In contrast, if an external hydrogen acceptor is required to consume the generated hydrogen, a semi-BH sequence is effected.[18,19] If this type of reaction proceeds under acceptorless conditions and the in situ generated intermediate cannot consume the produced hydrogen, then hydrogen gas is liberated. Acceptorless dehydrogenation (AD) reactions usually result in simple release of hydrogen gas, which can be applied as an environmentally benign method for alcohol oxidation.[90]

4.1. Semi-BH Reactions

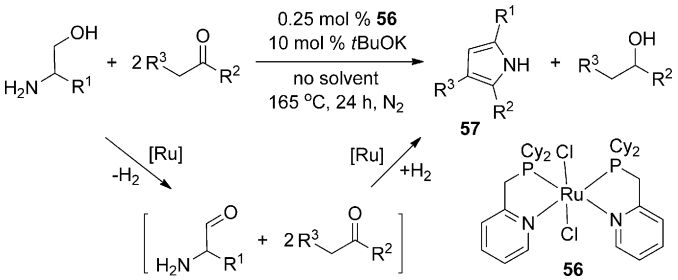
An efficient one-pot ruthenium-catalyzed hydrogen-transfer strategy was utilized for the direct synthesis of α,β-unsaturated aldehydes.[91] The employment of enolates prepared in situ from alcohols avoids handling of unstable aldehydes as the substrates, and provides a promising route to 2-substituted cinnamaldehydes [Eq. (29)]. A silica-grafted amine was used to enhance the reaction selectivity, and excessive amounts of the nitrile MeCH=CHCN were used as the external hydrogen acceptor.



(29)

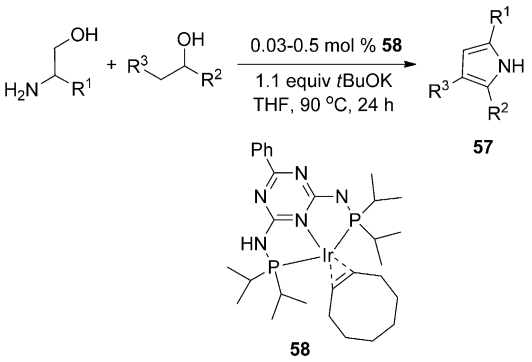
4.2. Synthesis of N-Heterocycles

N-Unsubstituted pyrroles (**57**) were synthesized through a ruthenium-promoted reaction of fully unmasked α-amino alcohols with ketones (Scheme 17). First, the α-amino alcohol was converted into the corresponding aldehyde, with subsequent cyclization of this aldehyde with the ketone substrate.[92] One additional equivalent of the ketone acted as the hydrogen acceptor during the reaction, and the overall reaction was salt-free and externally acceptorless, thus corresponding to a semi-BH reaction.



Scheme 17. Salt-free synthesis of pyrroles.[92]

By using the iridium complex **58** as the catalyst in the presence of *t*BuOK, a catalytic pyrrole synthesis was also achieved from secondary alcohols and α-amino alcohols [Eq. (30); THF = tetrahyrofuran].[93] Milstein's [RuH] complex[94] and iridium nanoparticles[95] were documented as catalysts for the same purpose. It should be noted that in these catalytic systems, dihydrogen and water were liberated in the course of the reaction, thus featuring an acceptorless dehydrogenative condensation of secondary alcohols and α-amino alcohols. A ruthenium(II)-catalyzed three-component reaction of a ketone, amine, and vicinal diol was also applied to the synthesis of pyrroles [Eq. (31)].[96] The catalyst system [{Ru(*p*-cymene)Cl_2}$_2$]/*t*BuOK is readily available, and the protocol features a wide substrate scope including aryl and



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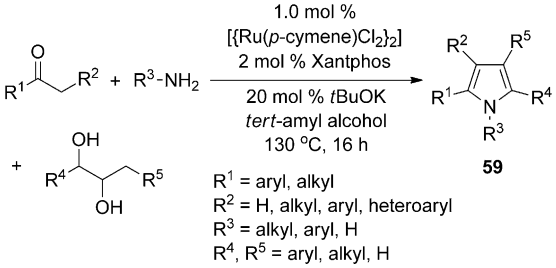
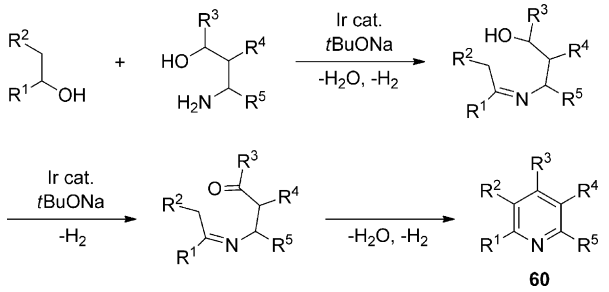


(31)

alkyl ketones, amines, and vicinal diols, thus affording multi-substituted pyrroles (**59**). Because stoichiometric amounts of additives or bases are not necessary, this synthetic method has the potential to be used frequently. With 1 mol% $[Ru_3(CO)_{12}]$ as the precatalyst in the presence of 20 mol% K_2CO_3, similar results were obtained.[97]

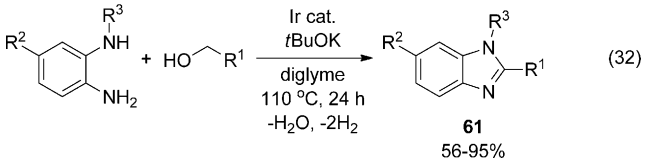
By means of an iridium(I) complex, which is structurally similar to **58**, as the precatalyst, either a primary or a secondary alcohol could react with a 1,3-amino alcohol, a C_2 building block, to form the pyridine derivatives **60** (Scheme 18).[98] Mechanistic studies indicate that oxidation of



Scheme 18. Synthesis of pyridines.[98]

the amino alcohol is very slow and thus enables the selective formation of the first imine intermediate. Subsequently, the remaining hydroxyalkyl group is dehydrogenated and the olefin intermediate (not shown) forms by intramolecular ring closure and elimination of water. Finally, aromatization with dihydrogen liberation affords the target pyridine products.

A ruthenium(II) hydride complex catalyzed the acceptorless dehydrogenative coupling of secondary alcohols and 1,3-amino alcohols to produce substituted pyridines and quinolines.[99] In a similar fashion, a combination of [{Ir(cod)(OMe)}$_2$] and a P,N-ligand effected the synthesis of quinolines from the reaction of 2-aminobenzyl alcohol with primary as well as secondary alcohols.[100] An iridium complex catalyst of type **58** promoted the synthesis of benzimidazoles (**61**) and quinoxalines (**62**) from aromatic diamines and alcohols through an acceptorless dehydrogenative alkylation [Eqs. (32) and (33)].[101]



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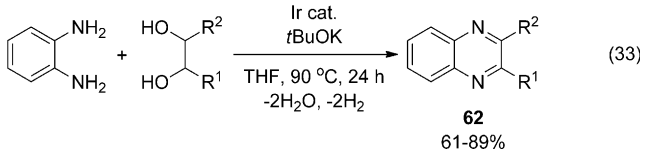
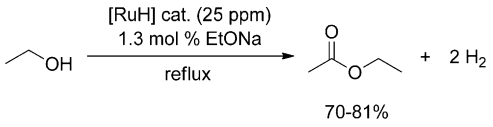


(33)

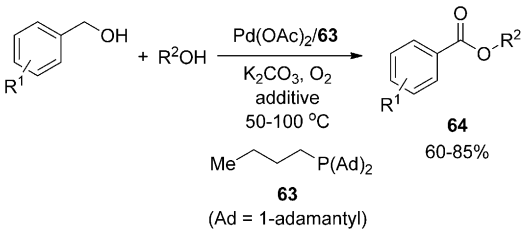
4.3. Synthesis of Esters and Acids

Direct synthesis of esters from alcohols seems to be a promising environmentally benign and atom-economical strategy, although elaborate catalytic systems have to be utilized.[102–104] Processes proceeding by dehydrogenation of alcohols have been achieved for the direct synthesis of esters. Refluxing an ethanol solution, containing 25 ppm of a [RuH] catalyst, led to direct synthesis of ethyl acetate through the efficient acceptorless dehydrogenation of ethanol [Eq. (34)].[105] An additive such as Mg_3N_2 may switch the



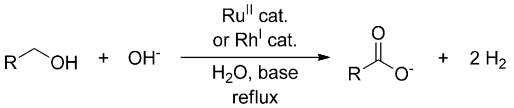
(34)

reaction pathway.[106] Under palladium[107] or cobalt[108] catalysis under oxygen, oxidative cross-esterification of benzyl alcohols was realized [Eq. (35)].[107] The reactions proceeded



(35)

with 2–5 mol% $Pd(OAc)_2$ as the catalyst under mild reaction conditions, thus giving the desired ester products in moderate to good yields, with water formed as the only by-product. The homocoupling (self-esterification) of different benzyl and heterobenzyl alcohols was also realized to give the corresponding benzoate esters in 60–85% yields. With water as the oxygen source, either ruthenium(II)-[109] or rhodium(I)-catalyzed[110] selective oxidation of alcohols in the presence of a base afforded the carboxylic acid salts [Eq. (36)]. Aqueous-phase methanol dehydrogenation has recently been established to produce hydrogen and carbon dioxide, thus offering a promising method to produce hydrogen from a renewable source at low temperature [Eq. (37)].[111,112]



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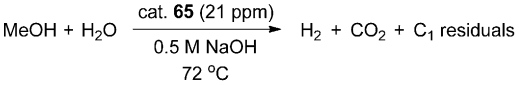

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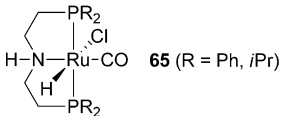
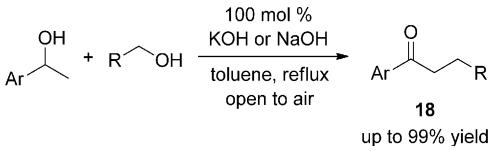


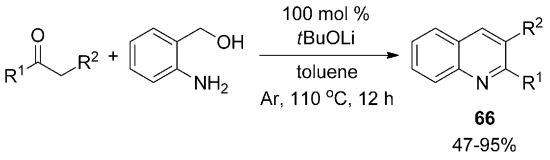
4.4. Transition-Metal-Free Reactions

The relevant transition-metal-free alkylation reactions of ketones and alcohols have been sparse throughout the literature. Crabtree et al. reported β-alkylation of benzylic secondary alcohols with primary alcohols mediated by either KOH or NaOH, thus eliminating the need for toxic and expensive transition-metal catalysts [Eq. (38)].[113] With



(38)

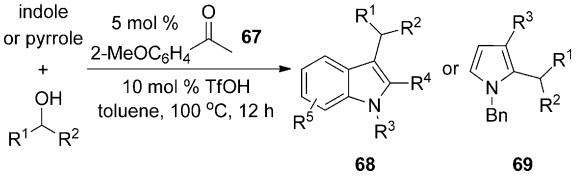
*t*BuOLi as the promoter, a similar reaction with ketones was efficiently performed. For example, when using (*o*-aminophenyl)methanol as the primary alcohol substituted quinolines (**66**) were obtained [Eq. (39)].[114] These reactions



(39)

also proceeded either under neat conditions at 130 °C in the presence of 100 mol % NaOH and a nitrogen atmosphere, or in refluxing toluene by means of 100 mol % KOH under an air atmosphere.[115] With an aldehyde as the catalyst dehydrative C-alkylation of methyl carbinols with alcohols was realized.[116]

By applying the concept of the redox chain reaction, indoles and pyrroles were alkylated with unactivated secondary alcohols [Eq. (40) and Scheme 19].[117] In this case, TfOH

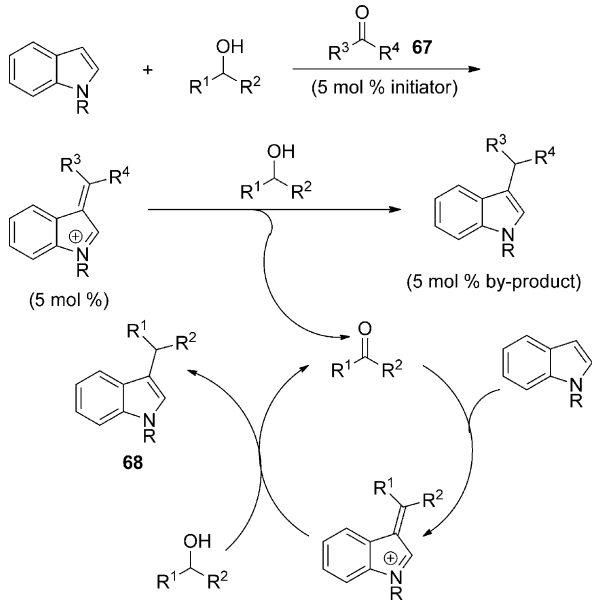


(40)

was the catalyst and 5 mol % 2′-methoxyacetophenone (**67**) was the initiator, thus rendering efficient reactions in toluene at 100 °C. With KOH as the promoter, 3-alkylation of indoles with benzylic and cyclic secondary alcohols occurred at 150 °C.[118]

5. Summary and Outlook

The advances made since 2009 in transition-metal-catalyzed BH C-alkylation of ketones, and related compounds, with alcohols has been summarized. Diverse homogeneous organometallic and heterogeneous transition-metal catalyst systems are presented. The aim of this Minireview is to provide chemists with new principles for activating substrates and establishing promising green processes to replace the relevant traditional synthetic methods for C–C bond formations.



Scheme 19. Brønsted acid catalyzed redox chain reaction.[117]

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