Top Curr Chem (Z) (2016) 374:27
DOI 10.1007/s41061-016-0027-1

REVIEW

N-Alkylation by Hydrogen Autotransfer Reactions

Xiantao Ma[1,2] · Chenliang Su[2] · Qing Xu[1]

Received: 4 January 2016 / Accepted: 13 April 2016 / Published online: 29 April 2016

Abstract Owing to the importance of amine/amide derivatives in all fields of chemistry, and also the green and environmentally benign features of using alcohols as alkylating reagents, the relatively high atom economic dehydrative *N*-alkylation reactions of amines/amides with alcohols through hydrogen autotransfer processes have received much attention and have developed rapidly in recent decades. Various efficient homogeneous and heterogeneous transition metal catalysts, nano materials, electrochemical methods, biomimetic methods, asymmetric *N*-alkylation reactions, aerobic oxidative methods, and even certain transition metal-free, catalyst-free, or autocatalyzed methods, have also been developed in recent years. With a brief introduction to the background and developments in this area of research, this chapter focuses mainly on recent progress and technical and conceptual advances contributing to the development of this research in the last decade. In addition to mainstream research on homogeneous and heterogeneous transition metal-catalyzed reactions, possible mechanistic routes for hydrogen transfer and alcohol activation, which are key processes in *N*-alkylation reactions but seldom discussed in the past, the recent reports on computational mechanistic studies of the *N*-alkylation reactions, and the newly emerged *N*-alkylation methods based on novel alcohol activation protocols such as air-promoted reactions and transition metal-free methods,

This article is part of the Topical Collection "Hydrogen Transfer Reactions"; edited by Gabriela Guillena, Diego J. Ramón.

✉ Qing Xu
qing-xu@wzu.edu.cn

[1] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang 325035, China

[2] SZU-NUS Collaborative Innovation Center for Optoelectronic Science and Technology, Key Laboratory of Optoelectronic Devices and Systems of Ministry of Education and Guangdong Province, College of Optoelectronic Engineering, Shenzhen University, Shenzhen 518060, China

are also reviewed in this chapter. Problems and bottlenecks that remained to be solved in the field, and promising new research that deserves greater future attention and effort, are also reviewed and discussed.

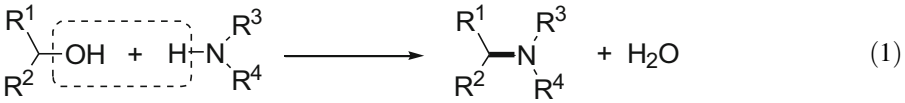
Keywords Alcohols · Alcohol activation · Alcohol oxidation · Amines · Amine oxidation · Amides · *N*-Alkylation · Asymmetric *N*-alkylation · Reductive *N*-alkylation · Dehydration · Hydrogen autotransfer · Borrowing hydrogen · Relay race · Transfer hydrogenation · Anaerobic dehydrogenation · Aerobic oxidative dehydrogenation · Homogeneous catalysis · Heterogeneous catalysis · Transition metal catalysts · Transition metal-free · Catalyst-free · Autocatalysis

1 Introduction and Background

Nitrogen is one of the most important essential elements for life. It has been chosen by nature to build essential molecules such as amino acids and nucleotides in the construction of life. Consequently nitrogen-containing compounds play important roles in all fields of chemistry, and in all aspects of life in living organisms. For example, nitrogen functionalities and organonitrogen blocks are abundant in numerous natural products, biologically active molecules, agrochemicals, synthetically and pharmaceutically significant compounds. Commonly used pharmaceuticals usually contain at least one nitrogen atom.

Amines and amine derivatives are the most fundamental and significant organonitrogen compounds because they can be used as starting materials for the preparation of other organonitrogen blocks. The reaction of ammonia/amines with organohalides to produce alkylated amines [1], namely the Hofmann *N*-alkylation reaction discovered by A. W. Hofmann in 1850 [2], is included in all text books as a basic method of amine derivative synthesis [3]. However, this method uses active and toxic organohalides as reactants, and is low in selectivity and atom efficiency, producing a mixture of different amines and inevitable ammonium salts as byproducts, which leads to serious problems with product separation and purification. Since then, various more selective, efficient, and atom economic methods have been developed for the synthesis of different amines and amine derivatives to meet specific synthetic needs, which include mainly the Gabriel method, reduction of nitro compounds, Ullmann/Buchwald–Hartwig type transition metal (TM)-mediated/catalyzed couplings of N–H compounds with aryl halides and pseudohalides, reductive alkylation of amines with carbonyl compounds, transition metal-catalyzed hydroamination/hydroaminomethylation of carbon–carbon unsaturated compounds, as well as dehydrative *N*-alkylation reactions of amines/amides with alcohols. The latter method, *N*-alkylation of amines/amides using alcohols as the alkylating reagents (Eq. 1), seemingly a direct dehydrative substitution of alcohol's hydroxyl group by the amines/amides, is a relatively environmentally benign alternative, not only because comparatively high atom efficiency can be achieved by generating water as the only byproduct, but also because alcohols are more available, more stable, lower in toxicity, more easily stored and handled, much lower in cost,

and are a class of greener chemicals than the corresponding organohalides or carbonyl compounds.

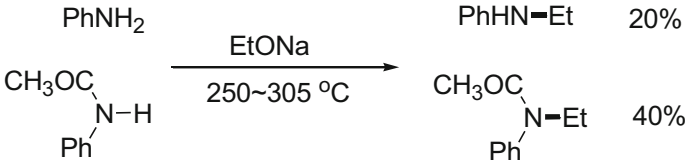


(1)

In fact, in the early twentieth century, just half a century after Hofmann's report, J. U. Nef [4] first discovered that *N*-alkylation of amines/amides could be achieved using alcohols at high temperatures under strong basic conditions, albeit the yields and selectivities were not high (Scheme 1). This is mostly due to the fact that alcohols are generally inactive in nature, and because hydroxyl is not a good leaving group and thus activation for further transformations is difficult.

Following Nef's report, other chemists also developed a number of methods for *N*-alkylation of amines with alcohols, by using main group metal (Na, K, Al, Mg, etc.) hydroxides or alkoxides [5–9], or heterogeneous transition metal (TM)-impregnated silica or alumina catalysts, or metal alloys, metal salts, mixed oxides of metals, or directly silica-alumina as the catalysts [10–12]. However, these methods still require forcing reaction conditions such as high temperatures (200–400 °C), high pressure, using large amounts of bases, and still suffer from the problems of long reaction time, low yields, and low selectivities.

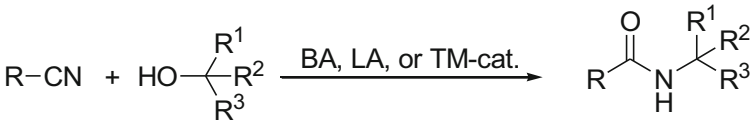
As more and more TM complexes were developed and applied in organic synthesis, TM-catalyzed synthetic methods progressed quickly. In 1981 and 1982, the groups of Grigg [13], Watanabe [14], and Murahashi [15] independently reported the earliest homogeneous TM-catalyzed *N*-alkylation reactions of amines with alcohols using [Ru], [Ir] or [Rh] complexes. A main difference of these reactions compared to the previous methods is that, by using the noble transition metal complexes, *N*-alkylation reactions could be achieved under milder conditions (<200 °C) and tolerate a broader scope of substrates. Realizing TM catalysts' higher activity in alcohol activation, and their potential in the dehydrative alkylation reactions, more and more chemists became interested in this research and the field has progressed rapidly in the past three decades, especially after the 1990s due to chemists' growing awareness of environmental concerns regarding chemical reactions, and the need to develop greener and more sustainable reactions to replace traditional methods. In addition, in 2005, the ACS Green Chemistry Institute (GCI) and global pharmaceutical companies founded an ACS GCI Pharmaceutical Roundtable to promote the development of green chemistry and green engineering



Scheme 1 Nef's initial findings on dehydrative *N*-alkylation [4]

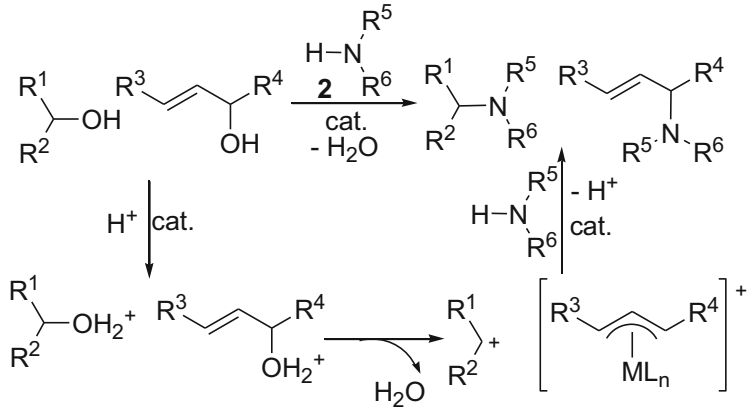
in pharmaceutical industry. The inclusion of direct transformations of alcohols into pharmaceutically useful chemicals as one of its key research areas by the ACS GCI Pharmaceutical Roundtable also promoted the progress of alcohol-based research in organic and pharmaceutical synthesis. Therefore, numerous homogeneous and heterogeneous TM-, Lewis acids-, Brönsted acids-, or co-catalysts-catalyzed methods for dehydrative *N*-alkylation of amines and amides with alcohols have been developed in recent years.

In general, these alcohol-based dehydrative *N*-alkylation reactions can be classified into two categories. One is the direct nucleophilic substitution of the hydroxy group by amines/amides mediated/catalyzed by Brönsted acids, Lewis acids, or TM complexes via formation of carbocation or coordinated cationic metal complexes under acidic conditions (Scheme 2) [16–20]. The famous Ritter reaction of nitriles and alcohols giving alkylated amides may be classified as one of these reactions, in which the nitriles serve as the *N*-nuleophile (Eq. 2) [21, 22].

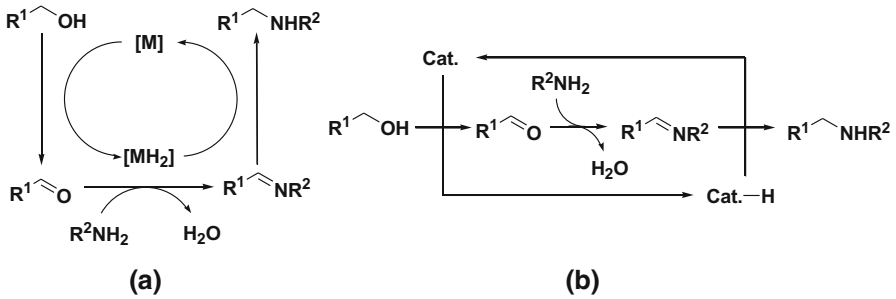


(2)

The other category, as termed by the leading chemists in the area, is the "borrowing hydrogen" [12, 23–32] or "hydrogen autotransfer" [9] methodology, or more simply "hydrogen transfer reactions" [33, 34] that involve characteristic hydrogen transfer processes in the reactions (Scheme 3). In these reactions, alcohols are generally believed to be dehydrogenatively activated under inert conditions by TM catalysts to form the more active aldehydes and the reducing hydridometal species [MH] or [MH_2], which then return the hydrogen atoms to the intermediate imines to give the final alkylated amine/amide products. The method is thus mainly suitable for primary amines and alcohols. According to this recapitulatory general



Scheme 2 General mechanism for direct nucleophilic substitution reactions of alcohols by amines/amides

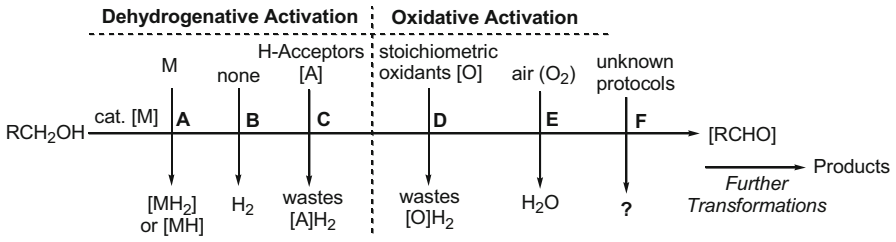


Scheme 3 General mechanism for alcohol-based borrowing hydrogen (**a**) or hydrogen autotransfer reactions (**b**)

mechanism (Scheme 3), hydrogen transfer from alcohols to TM catalysts and then from [MH]/[MH_2] to intermediate imines are the typical key processes of the methods. It should also be pointed out that inorganic bases were usually required in hydrogen autotransfer reactions for deprotonation of the alcohols to facilitate their coordination with TM catalysts. Since bases were usually used in large excess amounts in the early TM-free methods [4–10], they were used only as additives but not as catalysts in TM-catalyzed reactions [10–12, 23–34], even though in many cases they were also used in catalytic amounts.

The direct nucleophilic substitution reactions (Scheme 2) [16–22], restricted mainly to π-activated alcohols such as secondary arylmethanols, allylic and propargylic alcohols, and tertiary alcohols that can readily form stable carbocationic intermediates, are mechanistically different to hydrogen autotransfer reactions. Although these reactions are not the focus of this chapter, since they are also very relevant research areas, this brief introduction is anticipated to provide potentially helpful references to assist interested researchers in their studies, especially in boardline research where elucidation of reaction mechanisms is difficult.

In the case of *N*-alkylation reactions by hydrogen autotransfer processes, asymmetric reactions, nano materials, electrochemical methods, biomimetic methods, reactions using amines as the alkylating reagents, the more practical aerobic *N*-alkylation methods, and even some simple and efficient TM-free methods have also been reported in recent years. It was proposed that, in addition to anaerobic dehydrogenative for activation of the alcohols (Scheme 4, methods A–B), more alternative protocols should also be available, which may include the use of



Scheme 4 Known and potential protocols for alcohol activation

hydrogen acceptors, oxidants or organocatalysts, aerobic oxidative methods, etc. (methods C–F) [36]. Since TM-catalyzed aerobic oxidation of alcohols has been the standard method for aldehyde synthesis [36–41], oxidative dehydrogenation methods using various oxidants have been intensively employed in cross-dehydrogenative coupling (CDC) reactions for substrate activation [42, 43], and stoichiometric oxidants have also been employed for synthesis of alkylated amines from alcohols and amines by one-pot multi-step oxidation–reduction reactions [44, 45], these new protocols for alcohol activation should be good complements to the anaerobic dehydrogenation protocol.

Since there have been several important and excellent reviews on *N*-alkylation reactions of the hydrogen transfer type in recent years [10–12, 23–35], this chapter highlights mainly some typical examples of the main progress, technical and conceptual advances, and recent mechanistic achievements contributing to development of this research in the last decade. In addition to mainstream research on homogeneous and heterogeneous transition metal-catalyzed reactions, possible mechanistic routes for hydrogen transfer and alcohol activation that are the key processes in *N*-alkylation reactions but seldom discussed in the past, recent achievements on computational mechanistic studies of the *N*-alkylation reactions, and some newly emerged *N*-alkylation methods based on novel alcohol activation protocols such as air-promoted aerobic *N*-alkylation reactions and transition metal-free methods are also reviewed in this chapter. Problems and bottlenecks remain in the field, and promising new research that deserves greater future attention and effort, such as potential protocols for alcohol and amine activation, meaningful and attractive new methods or catalysts, and experimental and computational mechanistic studies that can provide deeper insight into the alcohol activation and hydrogen transfer processes and contribute to the design and development of new *N*-alkylation methods, are also reviewed and discussed.

2 Hydrogen Autotransfer *N*-Alkylation Reactions Using Alcohols as the Alkylating Reagents

2.1 Mechanistic Aspects of TM-Catalyzed *N*-Alkylation Reactions

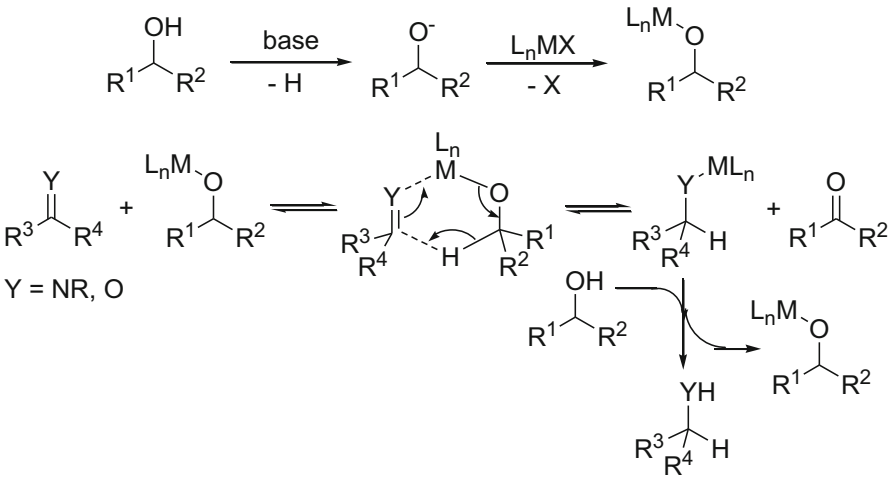
TM-catalyzed *N*-alkylation reactions of amines/amides with alcohols are usually held to proceed via the general borrowing hydrogen or hydrogen autotransfer mechanism (Scheme 3) [10–12, 23–34]. This is based mostly on the concept that TM catalysts can "borrow" and "return" hydrogen atoms from the alcohols and to the products with temporary hydrogen storage by formation of [MH]/[MH_2] species. Therefore, the key to judge whether an *N*-alkylation reaction is a true borrowing hydrogen or hydrogen autotransfer reaction would be the determination of the [MH]/[MH_2] species formed in situ in the reaction medium. However, this is not that easy. Alternatively, according to the proposed general mechanism (Scheme 3), whether the TM catalyst can directly produce aldehydes by alcohol dehydrogenation: (1) under anaerobic conditions, (2) without external oxidants or hydrogen acceptors, and (3) without aldehyde contamination in the substrate alcohols, which

could lead to misleading results and conclusions, are also acting standards to help making the judgement.

In fact, the borrowing hydrogen or hydrogen autotransfer concept, and generation of [MH]/[MH_2] species in alcohol-based *N*-alkylation reactions were, to a large extent, based on the well-documented transfer hydrogenation reactions of unsaturated compounds, especially the carbonyl compounds and imines with alcohols [46–51]. The last step of the borrowing hydrogen mechanism (Scheme 3), namely the reduction of imine intermediates by alcohols, is, in effect, a transfer hydrogenation reaction. The only difference is, in conventional transfer hydrogenation reactions, excess alcohols such as isopropanol are used only as a hydrogen source, and byproduct acetone is generated as a waste product [46–51]; while in *N*-alkylation reactions, the alcohols are both the hydrogen and alkyl source, and byproduct aldehydes are recovered in the catalytic cycle. Therefore, the mechanistic aspects of these two transformations have much in common.

2.1.1 Mechanistic Possibilities for Transfer of Hydrogens from Alcohols to Intermediate Imines

In spite of much work, the mechanism of a given *N*-alkylation reaction, especially the question of how hydrogens are transferred from alcohols to intermediate imines, remains to be elucidated specifically in each case. Several possibilities might exist, and the reaction mechanism may vary depending on the substrates, TMs and ligands used, and the specific reactions conditions employed [26]. On the other hand, the general mechanism (Scheme 3) gives little insight into how hydrogen atoms are transferred. Since little attention has been paid to this aspect in the past, and the hydrogen transfer process is closely related to the key alcohol activation step, this introductory discussion is designed to stimulate more focus on these mechanisms in future studies.

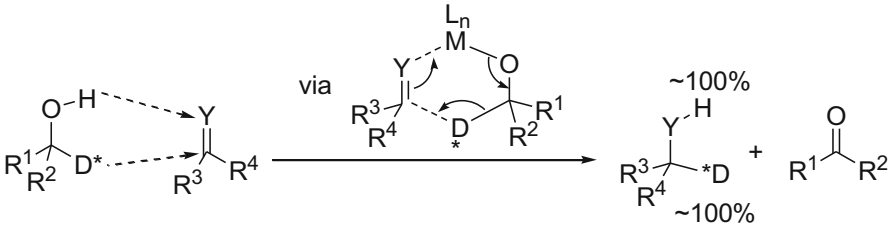


Scheme 5 Direct hydrogen transfer route

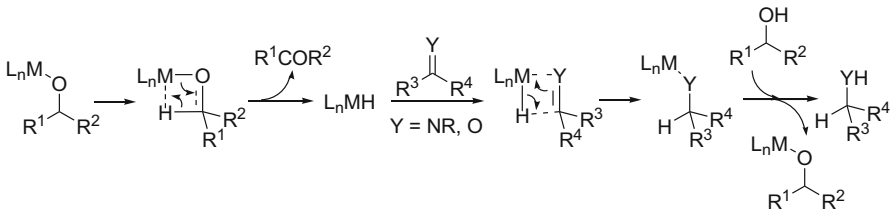
As summarized in review papers, there may be several possibilities for hydrogen transfer from alcohols to unsaturated bonds (C=O and C=N bonds in particular) under TM-catalyzed conditions [26, 46–51]. One is the direct hydrogen transfer route, involving a TM-templated concerted process with six-membered cyclic transition states [47, 48]. As shown in Scheme 5, the base first deprotonates the alcohol to facilitate its coordination with the TM pre-catalyst, which then coordinates with the C=Y compound, making both the alcohol and C=Y moieties bind to the metal center in close proximity. The metal acts as a template to provide correct orientation for a concerted hydride shift from the alcohol to the C=Y bond. As a result, both the β-C-H and O-H of the alcohol are transferred selectively to become the β-C-H and Y-H of the product, as can be inferred by using deuterium-labeled alcohols as the hydrogen source and measuring the deuterium content of Y-H and C-H in the product (Scheme 6). The direct hydrogen transfer route is similar to the Meerwein-Pondorf-Verley reduction and Oppenauer oxidation (MPV–O) route of the main group metals (Schemes 39, 40 vide infra) [52–54]. Although the MPV–O route is typical of the main group metals, it cannot be excluded completely in TM-catalyzed reactions [47, 48], especially for TM pre-catalysts, with which it is difficult to form hydridometal species, or under conditions not suitable for formation of hydridometals.

Other possible routes include hydride routes, especially for TM pre-catalysts, which can readily form [MH]/[MH_2] species [26, 46–51]. To form [MH]/[MH_2] species, coordination of TMs with strong electron-donating ligands, such as phosphines, seems to be indispensible. Nevertheless, most [MH]/[MH_2] are still known to be sensitive, short-lived, and prone to react with oxidants such as molecular oxygen. [MH]/[MH_2] species are thus usually obtained under anaerobic conditions (such as in a glove box), or prepared/characterized in situ in the presence of ligands. Hence, a borrowing hydrogen or hydrogen autotransfer *N*-alkylation reaction is typically performed under anaerobic conditions with inert atmosphere protection.

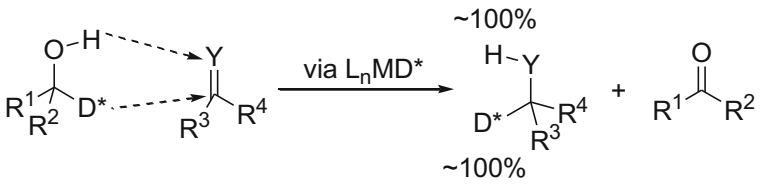
There are two routes for hydride transfer. One is the monohydride route (Scheme 7). It is commonly held that, after alcohol deprotonation by the base and coordination with the TM, the TM center abstracts only the β-C-H of the alcohol to give [MH] species via a four-membered cyclic transition state, which then reduces the C=Y bond via a similar but reverse hydride transfer route. Consequently, if a deuterium-labeled alcohol is used as the hydrogen source (Scheme 8), both the β-C-



Scheme 6 Deuterium labeling of direct hydrogen transfer route



Scheme 7 Monohydride route

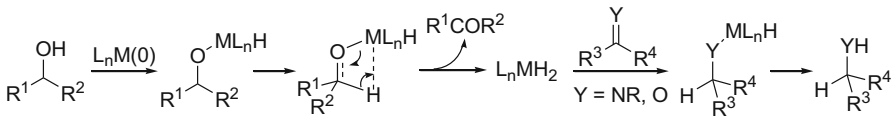


Scheme 8 Deuterium labeling of the monohydride route

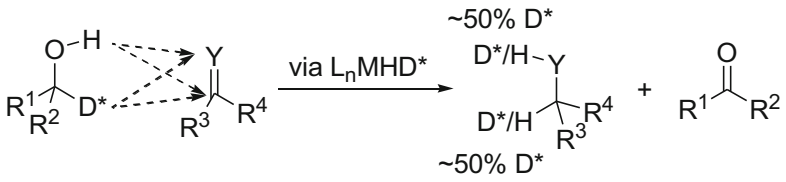
D* and O-H of the alcohol can be transferred selectively to become β-C-D* and Y-H in the product, respectively [49, 50]. Since this process is the same with the direct hydrogen transfer (Scheme 6) and TM-free MPV–O (Scheme 40, vide infra) routes, the deuterium labeling method cannot be used to distinguish them.

The other route is the dihydride route, involving sequential abstraction of both the O-H and β-C-H of the alcohol onto the TM center (Scheme 9) [26, 49–51]. It is commonly held that zero-valent TM first inserts into the O–H bond of the alcohol, followed by β-H elimination to give $[MH_2]$ species. $[MH_2]$ then reduces C=Y compounds via a similar but reverse route. As a result, this route is not selective regarding the hydride transfer processes. If a deuterium-labeled alcohol is used, the deuterium contents of Y–H and C–H in the product should both be around 50 % (Scheme 10) [50, 51].

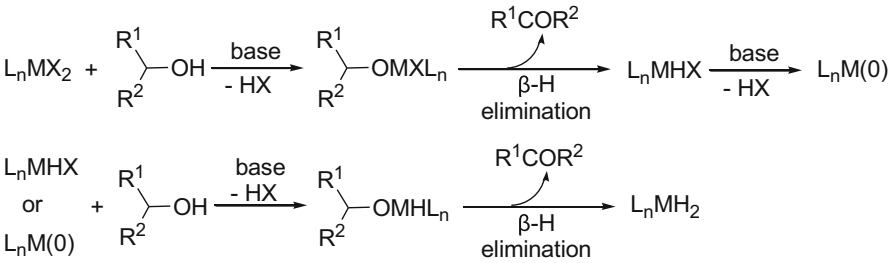
Mechanistically, reactions taking the dihydride route should not require bases. Indeed, several base-free *N*-alkylation reactions have been reported. Heterogeneous catalysts impregnated with zero-valent TMs may therefore also belong to this class. Besides, zero-valent TM catalyst $L_nM(0)$ and/or $[MH_2]$ may also be generated in situ from the corresponding TM pre-catalysts, such as the frequently used $RuCl_2L_3$ and PdX_2L_n, via reduction by alcohols [49–51]. In such cases, bases are also required to facilitate the generation of $L_nM(0)$ and $[MH_2]$ species. As shown in



Scheme 9 Dihydride route



Scheme 10 Deuterium labeling of the dihydride route

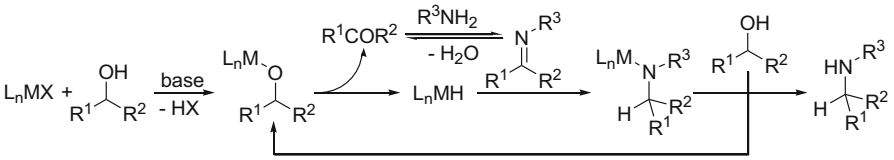


Scheme 11 In situ generation of $L_nM(0)$ and $[MH_2]$ species from transition metal (TM) pre-catalysts

Scheme 11, this transformation is accomplished by a stepwise reduction of the TM precatalyst by the alcohol via formation of monohydride.

2.1.2 *Mechanistic Aspects of Dehydrogenative Activation of Alcohols to Carbonyl Intermediates*

Since hydroxyl is not a good leaving group, alcohols usually need to be activated for further transformations. In TM-catalyzed *N*-alkylation reactions via the hydrogen autotransfer processes, alcohols are believed to be activated to carbonyl compounds by anaerobic dehydrogenation. However, alcohol dehydrogenation with formation of $[MH]/[MH_2]$ species or extrusion of H_2 is known as a thermodynamically unfavorable uphill process [55, 56], being in many cases the rate-limiting step of the whole reaction. Meanwhile, substrate and product amines as well as intermediate imines are all known to be good ligands that may complex with TMs, possibly poisoning, or even deactivating, the TM catalysts. Therefore, to accomplish dehydrogenative alcohol activation, the activity of TMs needs to be enhanced. Capricious ligands are hence adopted to improve TM activity and stabilize the $[MH]/[MH_2]$ species; exceptions to this are rare.



Scheme 12 Possible mechanism of *N*-alkylation reactions via the monohydride route

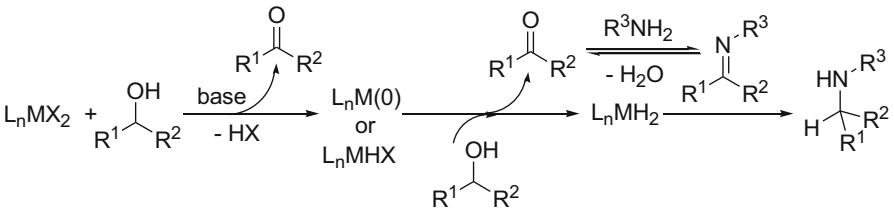
Based on the general mechanism (Scheme 3), borrowing hydrogen or hydrogen autotransfer catalysts should be able to dehydrogenate alcohols to carbonyl compounds and form [MH]/[MH_2] species under inert conditions. As shown in Scheme 12, with the monohydride route, carbonyl compounds and [MH] species are first generated by β–H elimination of the metal alcoholate complex. Imine intermediates formed by simultaneous condensation of the carbonyl intermediates with amines are then reduced by [MH] to give a metal–product complex, and finally the product via proton exchange. This may imply that, with monohydride mechanism, TM catalysts can activate the alcohols to carbonyl compounds followed by formation of imine intermediates, which then serve as the hydrogen acceptor to oxidize [MH] species. By analogy, the monohydride mechanism (Scheme 12) may be most consistent with the general borrowing hydrogen or hydrogen autotransfer mechanism (Scheme 3).

In the dihydride mechanism (Scheme 13), generation of the [MH_2] species requires an initial alcohol dehydrogenation process to reduce TM pre-catalysts to $L_nM(0)$ with formation of the first carbonyl intermediate, followed by $L_nM(0)$ activation of the alcohol to give [MH_2] and the second carbonyl intermediate. Consequently, with the dihydride mechanism, TM catalysts can readily activate the alcohols to carbonyl compounds without much difficulty.

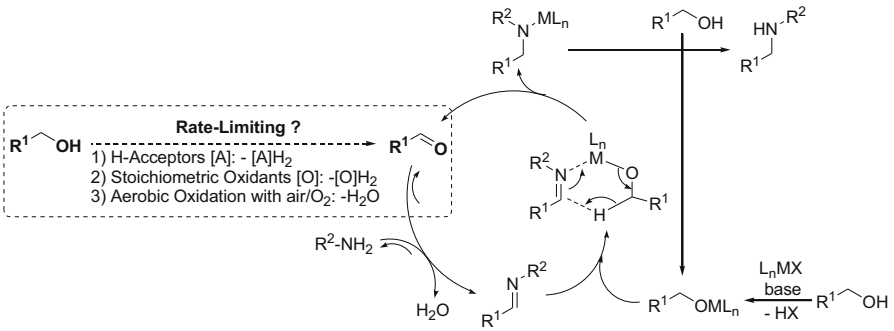
In contrast, in the direct hydrogen transfer route, no carbonyl compound is generated simultaneously with, or prior to, the hydrogen transfer step (Scheme 5). Thus, no imine intermediates can be employed as the hydrogen acceptor to accomplish hydrogen transfer from the alcohol. The initial step of alcohol activation to carbonyl compounds is thus an issue to be solved in the catalytic cycle, which may become the rate-limiting step in the whole reaction. Hence, alternative means of alcohol activation should be adopted (Scheme 14). According to recent developments, this may include aerobic *N*-alkylation reactions using air as the promoter of the reactions, or reactions involving metal oxidants- or hydrogen acceptors-initiated processes.

2.1.3 Computational Mechanistic Studies on TM-Catalyzed N-Alkylation Reactions

Mechanisms of TM-catalyzed *N*-alkylation reactions have also been investigated in recent years by employing computational methods such as density functional theory (DFT) calculations [57–63]. In 2008, Eisenstein and coworkers [57] performed a DFT calculation on the mechanism of the [$Cp^*IrCl_2]_2$/K_2CO_3-catalyzed



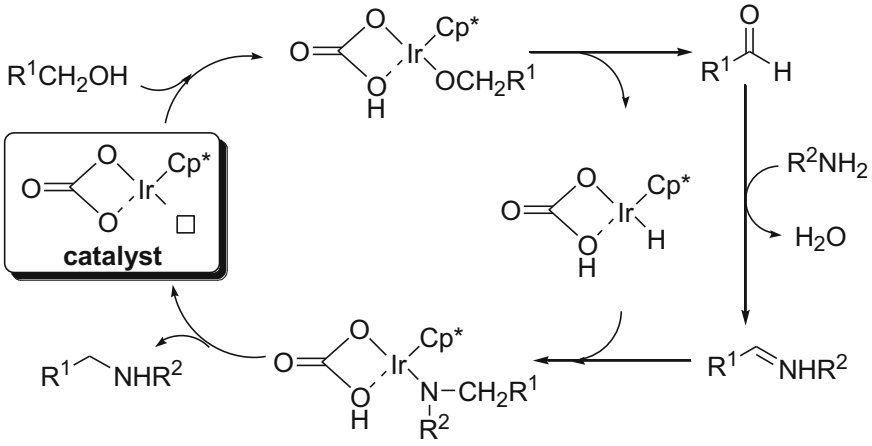
Scheme 13 Possible mechanism of *N*-alkylation reactions via the dihydride route



Scheme 14 Possible mechanism of *N*-alkylation reactions via the direct hydrogen transfer route

($Cp^* = \eta^5$-C_5Me_5) *N*-alkylation reaction of amines and alcohols. They found that the reaction favors the product-forming direction because the alcohol dehydrogenation step by β–H elimination has a lower barrier than dehydrogenation of the product amines. Besides, the two hydrogen atoms transferred from the alcohol to the imine intermediate are transferred as one hydride H^- and one proton H^+ (Scheme 15). The hydride goes from the alcohol to the metal, and then from the metal to the imine, which is consistent with the monohydride mechanism (Scheme 12); while the proton goes from the alcohol to the carbonate base and further to the product amine, which differs slightly from the monohydride mechanism (Scheme 12), because the ancillary carbonate ligand was found to coordinate with Ir and thus be involved in the hydrogen transfer step (Scheme 15).

In 2012, Fristrup and Madsen studied the mechanism of the same *N*-alkylation reaction as above by combining experimental and theoretical methods [58]. In contrast to Eisenstein's proposal [57], Fristrup and Madsen's results suggested that both aldehyde and hemiaminal intermediates stay coordinated to the iridium catalyst



Scheme 15 Proposed mechanism for $[Cp^*IrCl_2]_2/K_2CO_3$-catalyzed *N*-alkylation reaction supported by Eisenstein's density functional theory (DFT) calculation [57]

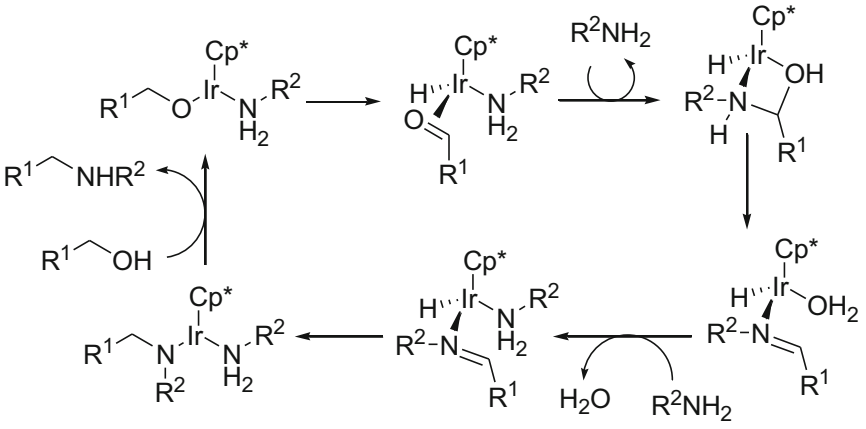
in the catalytic cycle. Further dehydration to imine and reduction to product amine also take place without breaking the coordination to the catalyst (Scheme 16).

In 2015, Liu and co-workers also re-investigated the DFT calculation of the above $[Cp^*IrCl_2]_2/K_2CO_3$-catalyzed *N*-alkylation reaction [59]. They found the initial alcohol dehydrogenation to aldehyde and the second aldehyde-amine condensation steps are thermodynamically endergonic; whereas the third imine reduction to product amine step is highly exergonic, being the driving force for the whole catalytic cycle. For the alcohol dehydrogenation and imine reduction steps, the most favorable pathways are the inner-sphere hydrogen transfer pathway under the catalysis of Cp*Ir(NHPh)Cl, and the inner-sphere hydrogen transfer pathway with $KHCO_3$ as the proton donor.

In addition to the above computational studies on the mechanism of Ir-catalyzed *N*-alkylation reactions, in 2015 Martín-Matute and co-workers [60] also investigated a bifunctional iridium complex-catalyzed *N*-alkylation reaction of amines and alcohols by a combination of experimental and computational methods. The mechanisms of Ru- [61], Cu- [62], and Pd-catalyzed [63] *N*-alkylation reactions have also been studied by DFT calculations.

2.2 Recent Advances in Homogeneous TM-Catalyzed *N*-Alkylation Reactions

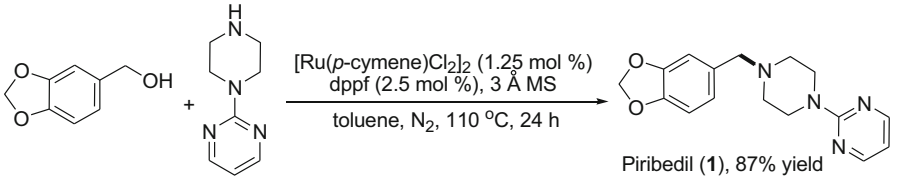
Homogeneous TM-catalyzed *N*-alkylation methods for synthesis of amine/amide derivatives are the mainstream of hydrogen autotransfer reactions. Since the seminal reports from the groups of Grigg, Watanabe and Murahashi in the early 1980s [13–15], more and more TM complexes, such as [Rh], [Pd], [Au], [Ag], [Pt], [Os] and [Re], and even the non-noble metals [Ni], [Cu], [Fe], and [Co], have been found to be active catalysts in the last decade [10, 23–34]. Recently, more environmentally benign methods such as reactions in aqueous media, at much lower temperatures, with very low catalyst loadings, or using biomass-derived alcohols, have gradually



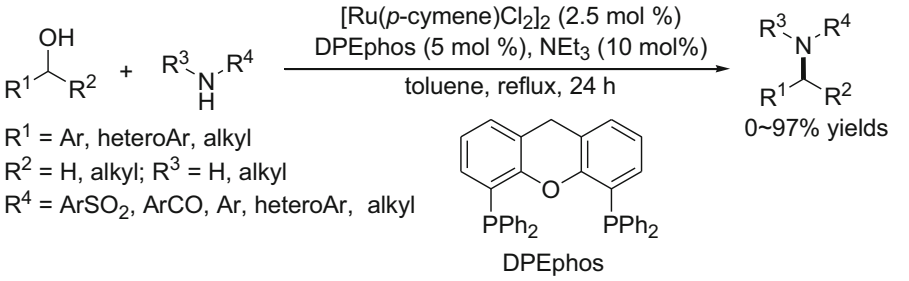
Scheme 16 Revised catalytic cycle for $[Cp^*IrCl_2]_2/K_2CO_3$-catalyzed *N*-alkylation reaction supported by Fristrup and Madsen's DFT calculation [58]

appeared in the field. Applications of *N*-alkylation reactions in the synthesis of bioactive and pharmaceutical molecules have also been reported.

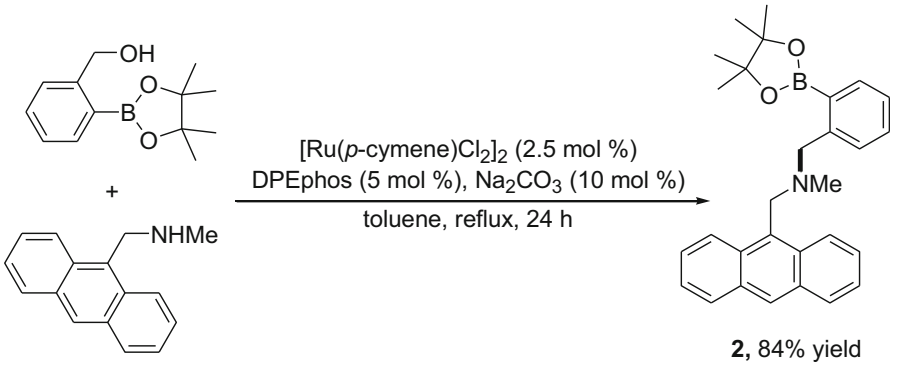
In 2007, Williams and co-workers [64] reported a [Ru(*p*-cymene)Cl_2]$_2$/dppf-catalyzed *N*-alkylation of secondary amines with alcohols. Piribedil (**1**), a piperazine dopamine agonist used in the treatment of Parkinson's disease, could be obtained in 87 % yield (Eq. 3). In 2009, by using DPEphos as the ligand instead of dppf, the same group achieved a general *N*-alkylation method for a wide range of amines such as primary and secondary amines, sulfonamides, and amides. *N*-Heterocycles could also be obtained by the reaction of diols and primary amines (Eq. 4) [65, 66]. In 2013, the Williams group extended the method to the synthesis of amines with a boronic ester group. Saccharide sensor **2** could be prepared in 84 % yield (Eq. 5) [67].



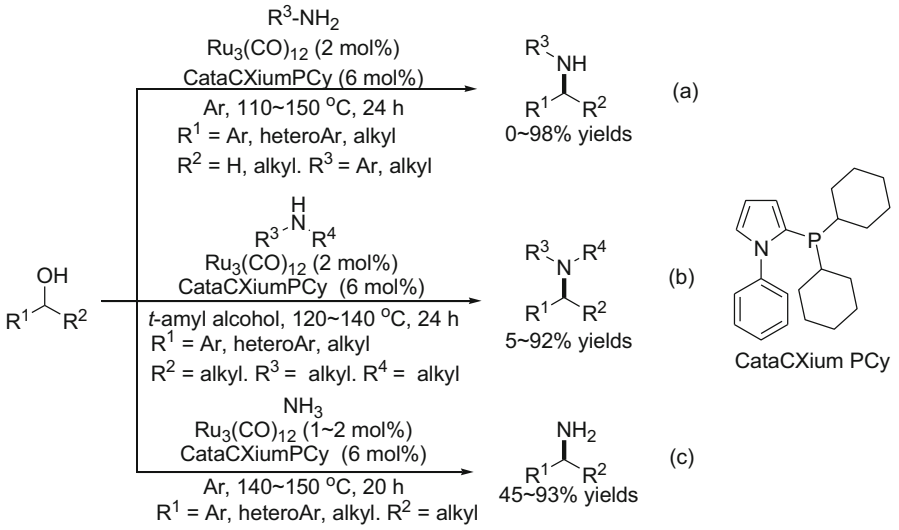
(3)



(4)

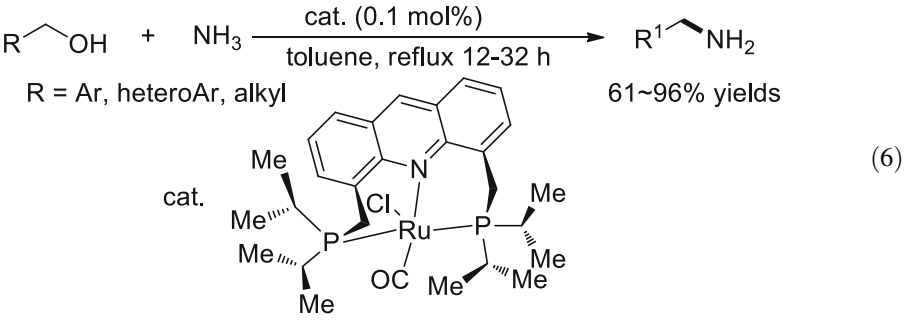


(5)



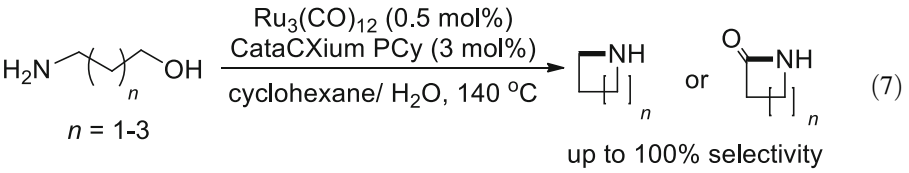
Scheme 17 $Ru_3(CO)_{12}$/CataCXiumPCy-ctalyzed *N*-alkylation of primary and secondary amines and ammonia with alcohols

In 2006, Beller and co-workers [68] reported a reaction of primary amines with primary and secondary alcohols using an $Ru_3(CO)_{12}$/tri(*o*-tolyl)-phosphine catalyst. In 2007, they developed an improved $Ru_3(CO)_{12}$/CataCXiumPCy catalyst, with which a variety of functionalized alcohols and amines could be converted into the corresponding secondary amines in high yields (Scheme 17a) [69]. In 2008, the Beller group extended the method to the reactions of alcohols and secondary amines (Scheme 17b) [70]. In 2010, the Beller group and the Vogt group simultaneously reported the amination of secondary alcohols with ammonia catalyzed by $Ru_3(CO)_{12}$/CataCXiumPCy complex (Scheme 17c) [71, 72], which represents further progress after Milstein's first report on the amination of primary alcohols with ammonia using an acridine-based pincer Ru complex (Eq. 6) [73]. In Milstein's method (Eq. 6), the precatalyst **3** might be first reduced by the alcohol to give [RuH] complex **4**, which rapidly converts to the active catalyst [RuH] complex **5** in the presence of ammonia (Scheme 18) [74].



(6)

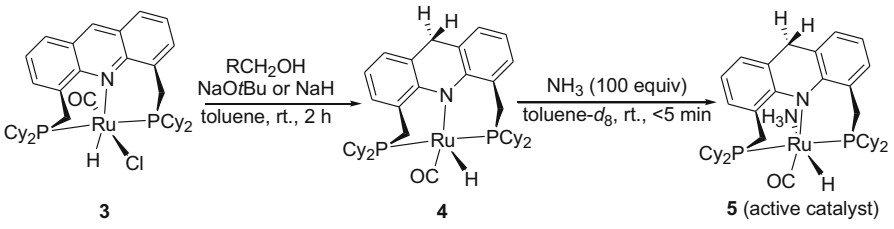
In 2014, Vogt and co-workers reported the selective synthesis of cyclic amides/amines from amino-alcohols catalyzed by $Ru_3(CO)_{12}$/CataCXiumPCy with catalyst loadings as low as 0.5 mol% (Eq. 7) [75]. Interestingly, upon addition of water, cyclic amines could be produced as the major product. The authors proposed that this may be attributed to water which possibly acts as a weak acid to facilitate the dehydration of the cyclic half-aminals by hydrogen bonding to give imine intermediates.



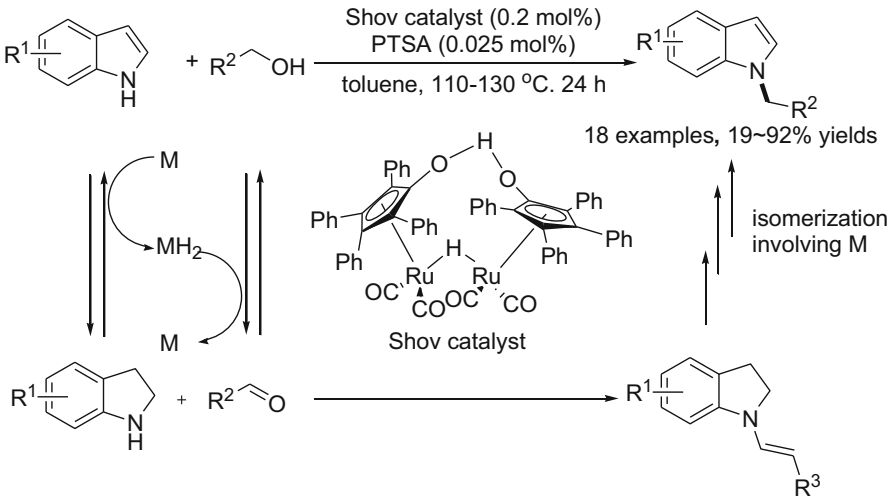
(7)

In 2010, Williams, Beller, and co-workers [76] achieved the first homogeneous *N*-alkylation of indoles with alcohols catalyzed by Shov catalyst with a low catalyst loading (0.2 mol%) (Scheme 19). Unlike Grigg and co-workers' C-3-alkylation of indoles in the presence of KOH (20 mol%) [77], in the former work, a catalytic amount of PTSA (0.025 mol%) was added, which may have led to a change in pH, and thus the selectivity of the reaction.

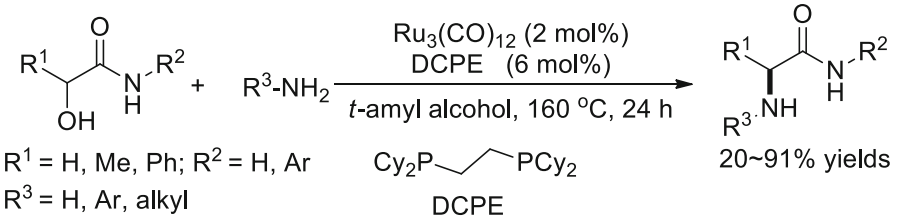
In 2011, Beller and co-workers reported the direct synthesis of α-amino acid derivatives from the reaction of α-hydroxy amides and esters with anilines, primary and secondary aliphatic amines, and ammonia (Eq. 8) [78]. After screening 17 different ligands, [$Ru_3(CO)_{12}$] and a bulky phosphine ligand, DCPE gave the best results. In the same year, the authors also reported that [$Ru(CO)ClH(PPh_3)_3$]/Xantphos is an excellent catalyst for the amination of challenging substrates such as the diamination of isosorbide with ammonia (Eq. 9) [79]. In 2013, Deutsch and co-workers reported a similar [$Ru(CO)ClH(DPEphos)(PPh_3)$]-catalyzed aminnation of alcohols with ammonia [80]. Primary and secondary alcohols, hydroxy esters, and diols are all suitable substrates. Mechanism of the ruthenium-catalyzed direct amination reaction was later investigated by Vogt in 2014, revealing that the initially formed inactive [RuH_2] species could be (re)activated by intermediate imine [81]. Later, the correlation of ligand fluxionality and catalytic performance of the catalyst were investigated by the same group [82].



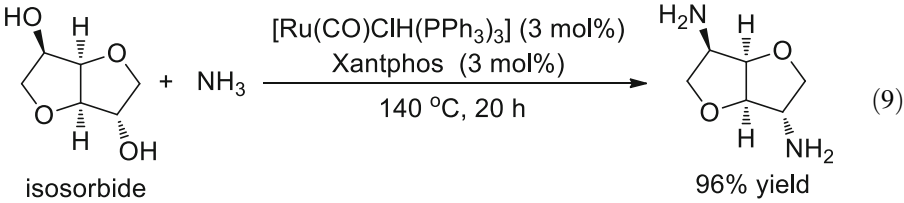
Scheme 18 Possible active Ru complexes in Milstein's method [73, 74]



Scheme 19 Possilble mechanism for Ru-catalyzed *N*-alkylation of indoles with alcohols

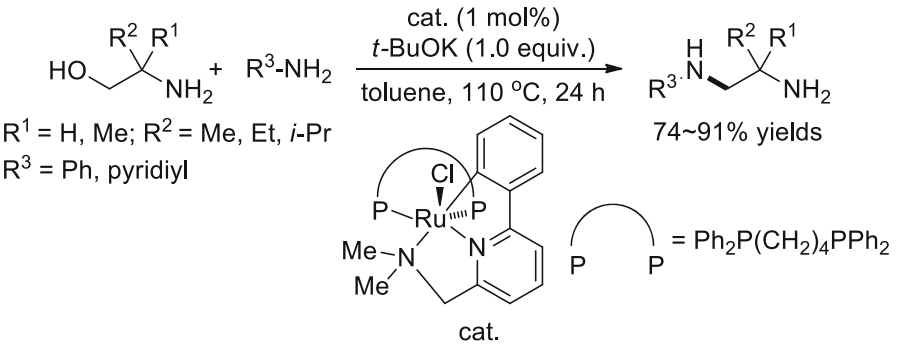


(8)



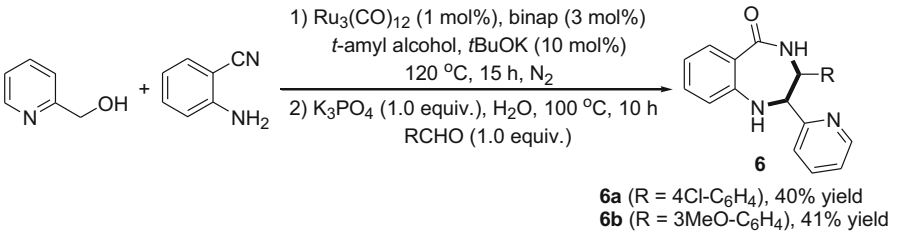
(9)

In 2012, Martín-Matute and co-workers [83] reported another pincer ruthenium(II) complex-catalyzed selective *N*-alkylation of (hetero)arylamines with primary alcohols. When the method was extended to aliphatic amines, the authors found that the aliphatic amine moiety could not be oxidized or alkylated. Inspired by this finding, aminoalcohols were later used as the alkyl source for *N*-alkylation of (hetero)aromatic amines. *N*-Arylated diamines were selectively obtained in excellent yield (Eq. 10).



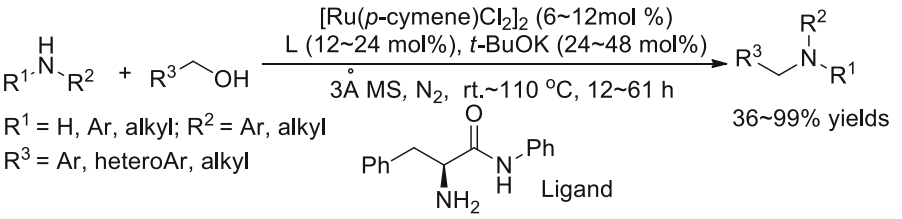
(10)

In 2014, Zhang and co-workers [84] reported the $[Ru_3(CO)_{12}]$/binap-catalyzed alkylation of 2-aminobenzonitriles with pyridylmethanols. An important structural unit, 1,2,3,4-tetrahydrobenzo[e][1, 4]diazepin-5-one (**6**), could be achieved by this straightforward one-pot method (Eq. 11).

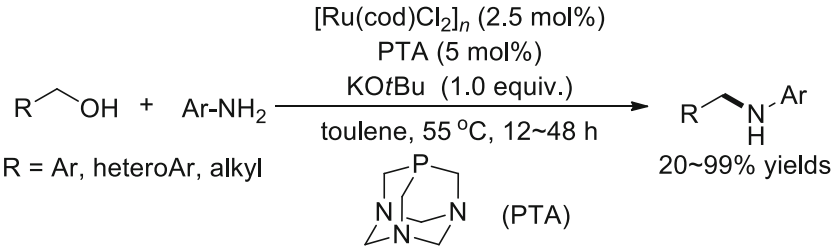


(11)

Some highly efficient catalytic systems enabling *N*-alkylation reactions to work under mild conditions even at room temperature have also been developed. In 2014, Enyong and co-workers [85] described ruthenium complex-catalyzed *N*-alkylation of primary and secondary amines with simple alcohols under mild conditions (Eq. 12). The authors found that when the substrate alcohol was used as the solvent, the reactions could be achieved at 40–60 °C and even at room temperature; whereas when using stoichiometric amounts of alcohol, higher temperatures, mostly 110 °C, were required. In 2015, Taddei and co-workers [86] reported a rather mild $[Ru(cod)Cl_2]_n$/PTA/*t*-BuOK-catalyzed *N*-alkylation of aromatic amines with primary alcohols at 55 °C (Eq. 13). This may be the mildest *N*-alkylation reaction catalyzed by ruthenium complexes described so far.

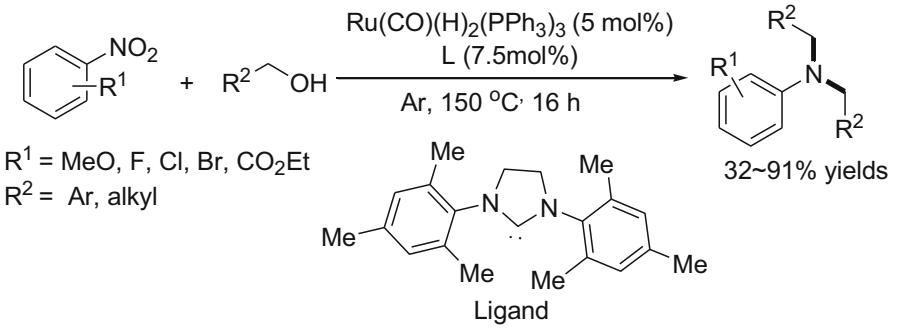


(12)

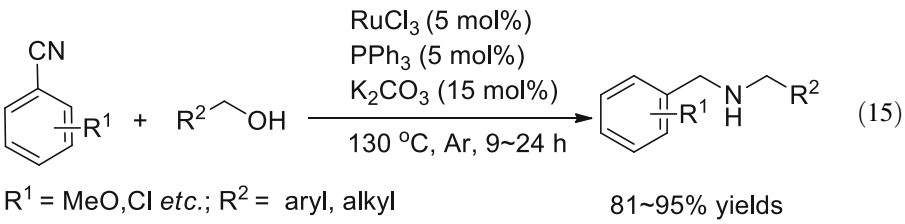


(13)

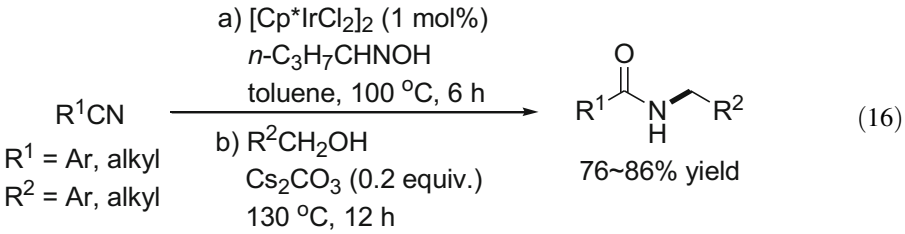
Nitroarenes and nitriles could also be employed as amine precursors. In 2010, Li and co-workers reported a ruthenium complex-catalyzed synthesis of tertiary amines by *N*-alkylation of nitroarenes with alcohols (Eq. 14) [87]. In this method, large excess amounts of the alcohols (mostly 7.5 equiv.) are necessary to reduce the nitroarenes to anilines prior to *N*-alkylation. In 2011, Shi and co-workers also developed an amination reaction for secondary amine synthesis from nitro or nitrile compounds (Eq. 15) [88]. In the same year, Deng and co-workers reported a ruthenium-catalyzed method for tertiary-amine synthesis from nitriles and primary alcohols [89]. In 2013, Beller and co-workers reported another *N*-alkylation reaction of nitrile compounds with secondary alcohols [90].

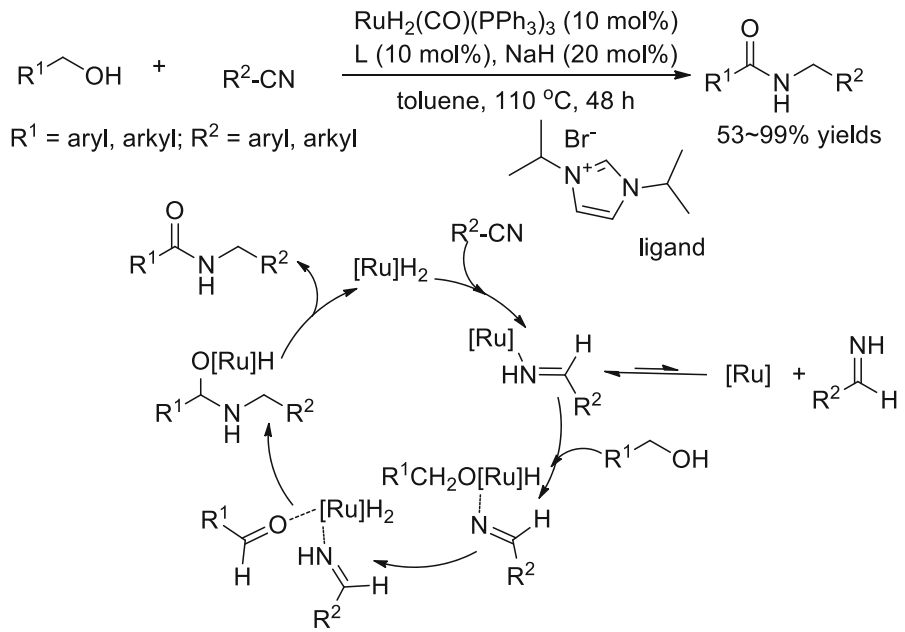


(14)



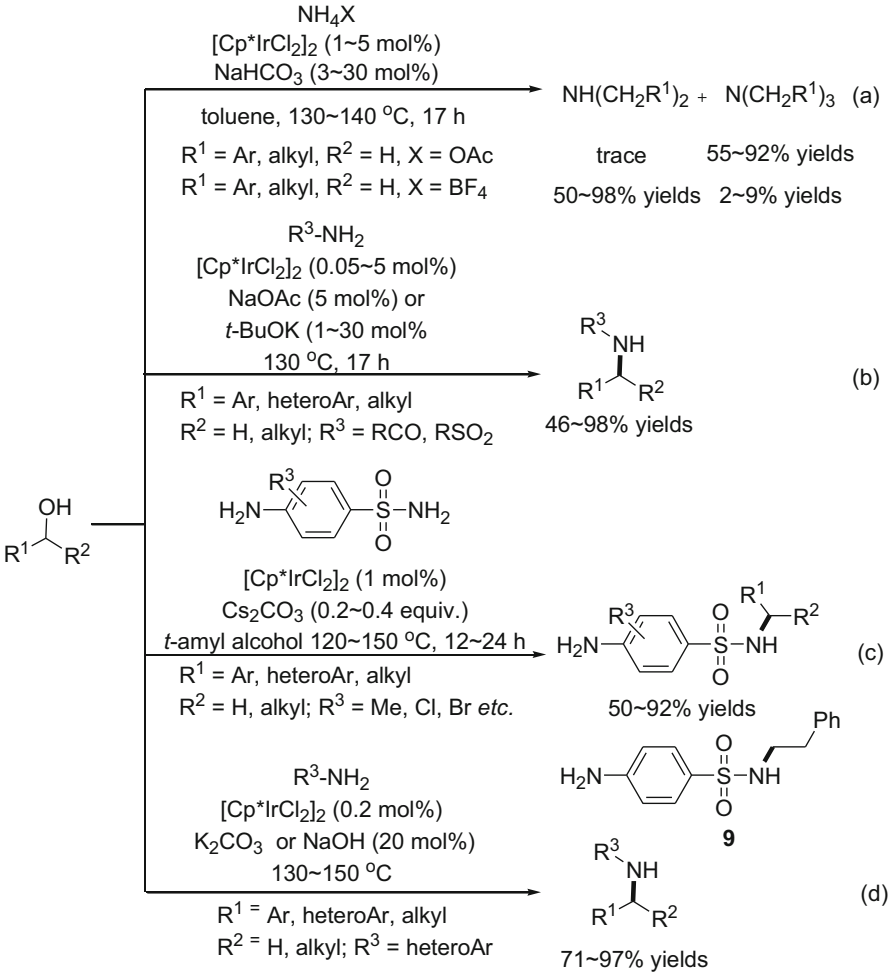
In 2014, Li and co-workers reported a direct synthesis of *N*-alkylated amides via tandem hydration/*N*-alkylation of nitriles and aldoximes with alcohols catalyzed by $[Cp^*IrCl_2]_2$ with a low catalyst loading (1 mol%) (Eq. 16) [91]. Control experiments revealed that nitriles were initially hydrated by aldoximes to give amides, which then reacted with alcohols to give *N*-alkylated amide products.





Scheme 20 Proposed catalytic cycle for the reversed and redox-neutral *N*-alkylation reaction of nitriles for amide synthesis

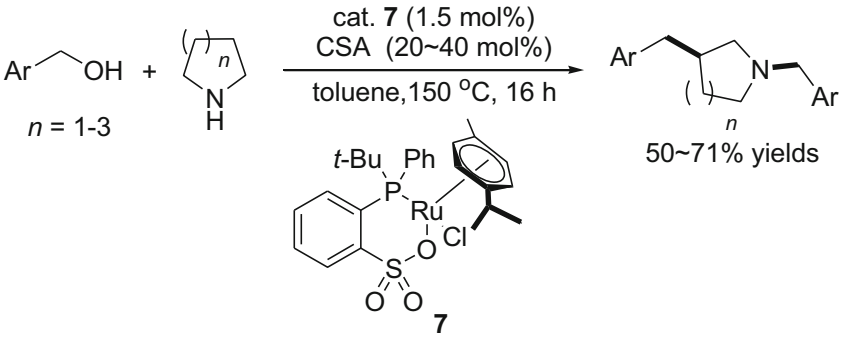
In 2013, Hong and co-workers reported a Ru-catalyzed reversed and redox-neutral *N*-alkylation reaction of nitriles and alcohols to afford *N*-alkylated amides with high atom efficiency (Scheme 20) [92]. Unlike the preceding reactions of alcohols and nitriles [88–91], in this reaction the alcohol serves as the acyl moiety of the amide product rather than the alkyl moiety. This also differs from the Ritter reaction, in which the alcohol serves as the alkyl source [22, 23]. In contrast, in this reaction the cyano moiety of the nitrile was reduced to become the alkyl moiety of the amide product. As shown in Scheme 20, the cyano moiety is initially hydrogenated by the dihydridoruthenium species RuH_2 to form a Ru-imine complex. The alcohol is then dehydrogenated to aldehyde by Ru to give another RuH_2 species, followed by imine reduction by RuH_2 and addition of the generated amine intermediate to aldehyde to give the hemiaminal intermediate. The last



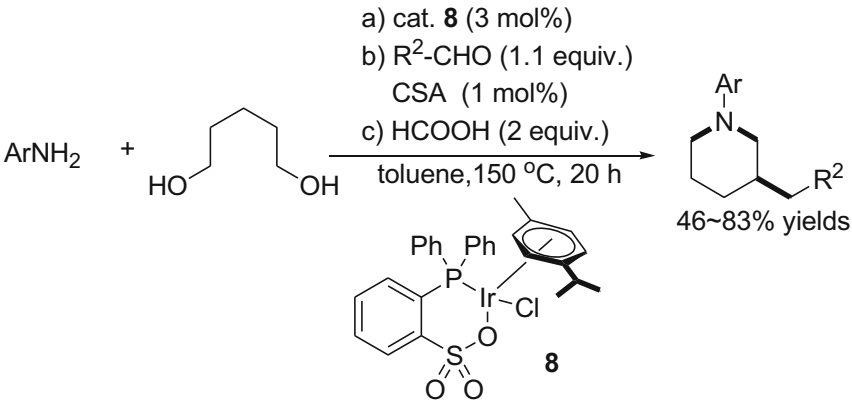
Scheme 21 $[Cp^*IrCl_2]_2$-catalyzed amination of alcohols with ammonium salts, carbamates, amides, sulfonamides and primary heteroarylamines

dehydrogenation of hemiaminal by Ru gives the corresponding *N*-alkylated amide product and regenerates the catalyst. In 2014, the authors extended the method to the synthesis of cyclic imides [93].

In 2010, Bruneau and co-workers described an unprecedented cascade *N*- and C(3)-dialkylation of unactivated cyclic amines with benzylic and aliphatic alcohols using a new (arene)ruthenium (II) complex **7** bearing a phosphinosulfonate ligand as the catalyst (Eq. 17) [94]. In 2012, they achieved a three-component *N*- and C-dialkylation reaction of the easily accessible anilines, diols, and aldehydes through tandem hydrogen transfer reactions in the presence of iridium complex **8** (Eq. 18) [95].



(17)

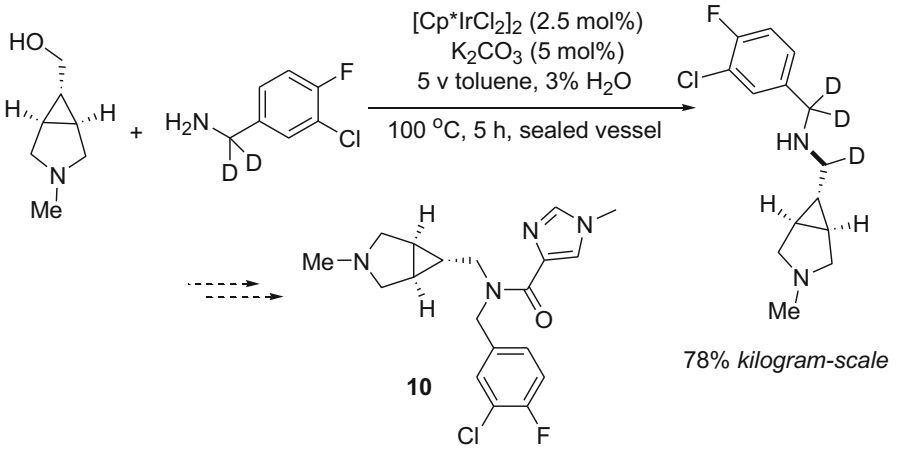


(18)

In 2008, Fujita, Yamaguchi and co-workers reported an efficient solvent-free synthesis of secondary and tertiary amines by $[Cp^*IrCl_2]_2$-catalyzed multi-alkylation of ammonium salts with primary or secondary alcohols [96]. The authors found that the type of ammonium salts greatly affected the selectivity of the reaction (Scheme 21a). Secondary 5- and 6-membered cyclic amines could also be prepared from ammonium tetrafluoroborate and diols by the same method.

In 2009, these authors also reported a similar transformation at 10 mmol scale, which makes the method more practical [97]. In the same year, the same authors again extended the method to *N*-alkylation of carbamates and amides, and in 2010 to *N*-alkylation of sulfonamides with catalyst loading as low as 0.05 mol% (Scheme 21b) [98, 99]. In 2014, Trudell and co-workers reported a microwave-mediated $[Cp^*IrCl_2]_2$-catalyzed *N*-alkylation of amides under solvent- and base-free conditions [100]. In 2015, Li and co-workers reported a direct synthesis of amino-(*N*-alkyl)benzenesulfonamides via *N*-alkylation of aminobenzenesulfonamides with alcohols catalyzed by $[Cp^*IrCl_2]_2/Cs_2CO_3$ (Scheme 21c) [101]. Notably, biologically active **9**, a histone arginine methyltransferase inhibitor, could be obtained in 80 % yield by this method. In 2012–2013, Li and co-workers also realized the *N*-alkylation reactions of primary heteroarylamines such as 2-aminothiazoles, 2-aminoimidazoles, 2-aminopyrimidines, 2-aminoquinazolines, and the corresponding secondary amines could be obtained in moderate to excellent yields (Scheme 21d) [102–104].

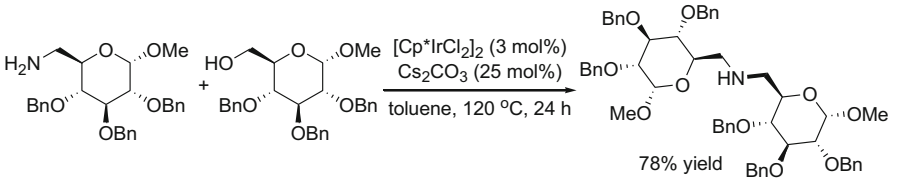
In 2011, by employing the iridium-catalyzed "borrowing hydrogen" reaction as the key step, Berliner and co-workers achieved the first kilogram-scale synthesis of **10**, a GlyT1 inhibitor for treatment of schizophrenia (Eq. 19) [105]. In a smaller 10 g scale reaction, the catalyst loading could even be reduced to less than 0.05 mol% Ir (S/C >2000), while still affording the product in a good yield of 84 %.



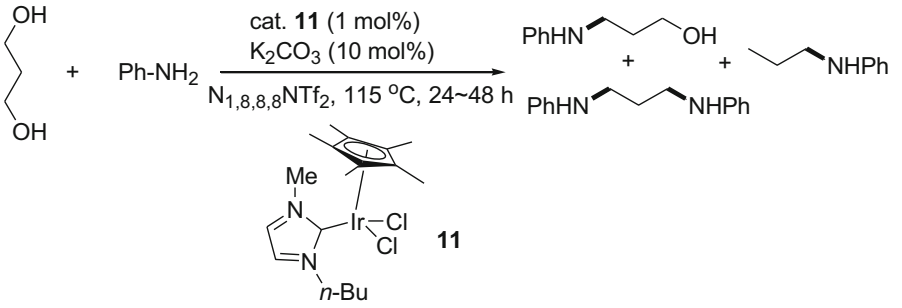
(19)

Biomass-based alcohols could also be employed directly as substrates in *N*-alkylation reactions, making the hydrogen autotransfer method more practical. In 2011, Martín-Matute and co-workers reported a $[Cp^*IrCl_2]_2$-catalyzed method for synthesis of secondary aminosugars from primary aminosugars with simple alcohols and primary carbohydrate alcohols (Eq. 20) [106]. In 2009, Stephens, Marr and co-workers reported that a one-pot bio- and chemo-catalytic process could be used for direct conversion of crude glycerol from biodiesel production to valuable secondary amines in a biphasic system without intermediate separation of 1,3-propanediol

[107]. In 2012, Marr and co-workers achieved an amination reaction of pure 1,3-propanediol in the presence of an Ir complex **11** (Eq. 21) [108].

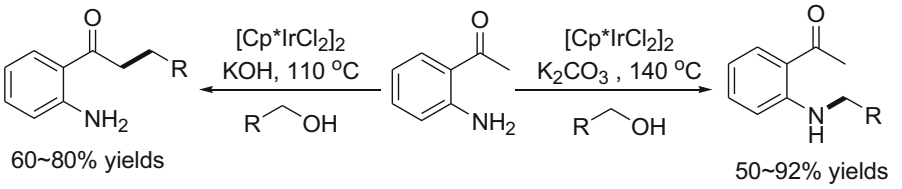


(20)



(21)

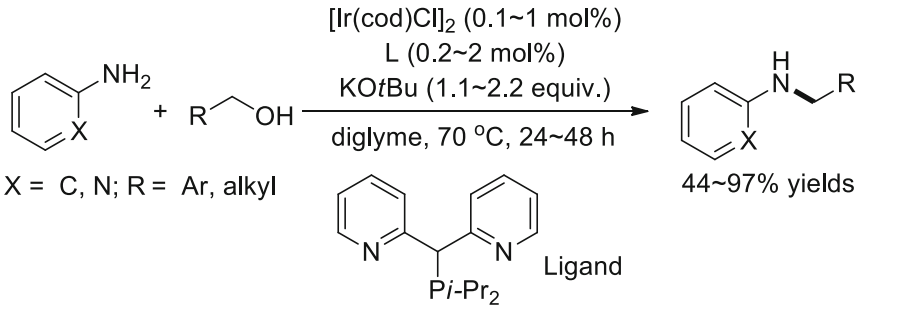
In 2012, Sridharan and co-workers reported a selective C- or *N*-alkylation of 2-aminoacetophenone catalyzed by $[Cp^*IrCl_2]_2$ under microwave irradiation conditions (Eq. 22) [109]. C-Alkylation takes place in the presence of $[Cp^*IrCl_2]_2$/KOH at 110 °C, while *N*-alkylation could be achieved using $[Cp^*IrCl_2]_2/K_2CO_3$ at 140 °C. By using different bases under different conditions, clean C- or N-selectivity could be achieved.



(22)

By using certain ligands to improve the activity of the metal catalyst, the *N*-alkylation reactions could also be performed under milder conditions. In 2009, Kempe and co-workers reported that a $[Ir(cod)Cl]_2$/P,N-ligand complex could enable the *N*-alkylation of (hetero)arylamines with alcohols under mild conditions of only 70 °C with a catalyst loading as low as 0.1 mol% (Eq. 23) [110]. In 2010, the same group designed a new P,N-ligand stabilized iridium complex **12** (Scheme 22) for efficient alkylation of anilines with alcohols under mild conditions

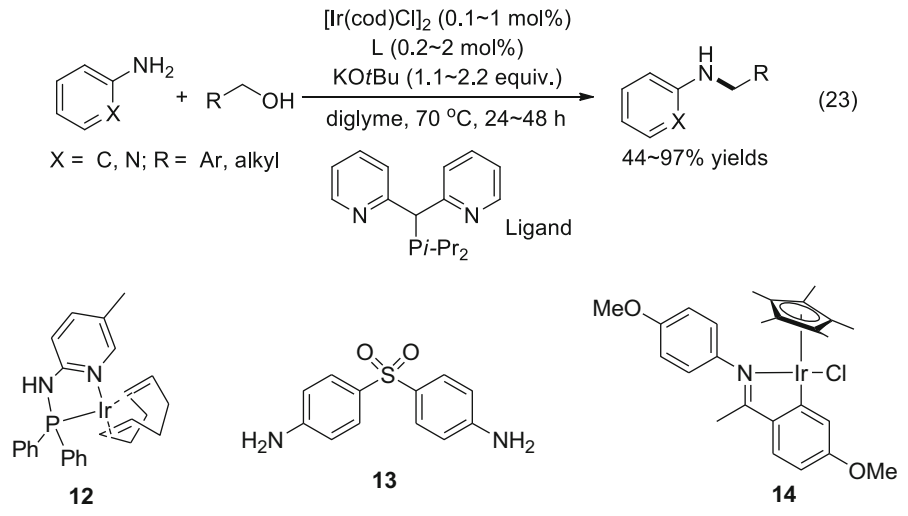
(70 °C) with catalyst loadings as low as 0.05 mol% [111]. In 2012, the Kempe group extended the method to the synthesis of symmetrical and unsymmetrical alkylated diamines under mild conditions (70 °C) [112]. For example, 4,4′-sulfonyldianiline (**13**), effective antibiotic medicaments used in the treatment of leprosy or malaria, could be symmetrically and unsymmetrically *N*-alkylated by this method.



(23)

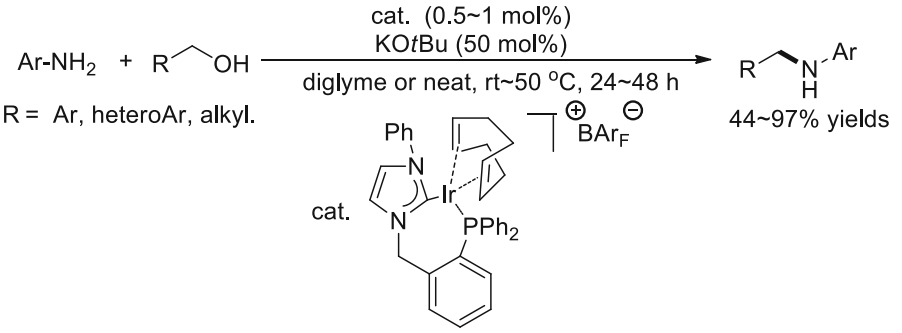
In 2015, Xiao and co-workers reported an iridium complex (**14**)-catalyzed *N*-alkylation of amines with alcohols under mild conditions (100 °C) (Scheme 22) [113]. Anilines, heteroarylamines, *N*-alkyl-*N*-arylamines, and sulfonamides could serve as *N*-nucleophiles. The same method can also be applied to amine-based *N*-alkylation reactions (vide infra).

In 2013, Andersson and co-workers reported an iridium NHC-phosphine complex-catalyzed solvent-free, and selective *N*-alkylation of anilines with alcohols under mild conditions even at room temperature (Eq. 24) [114]. Intramolecular *N*-



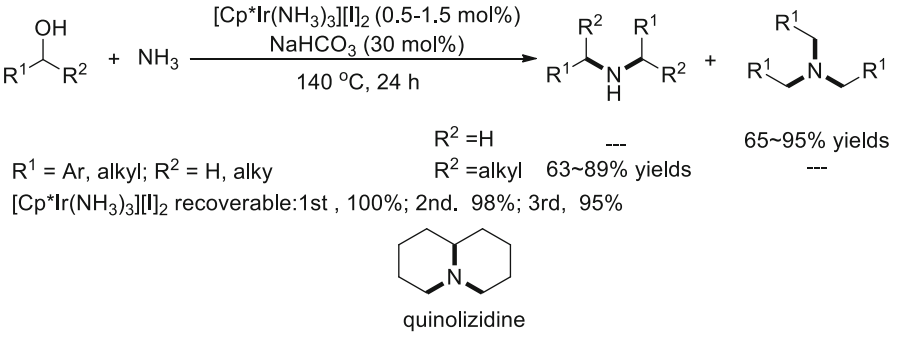
Scheme 22 Iridium complex **12** and **14** and 4′4-sulfonyldianiline **13**

heterocyclization of aminoalcohols could also be achieved to afford indole or 1,2,3,4-tetrahydroquinoline products.



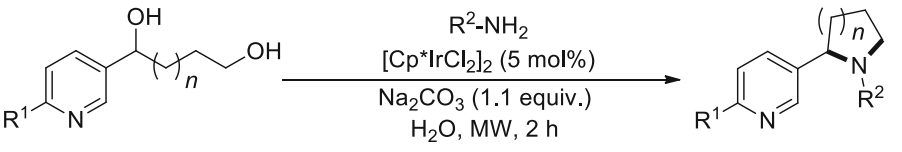
(24)

Some water-soluble and water-tolerant iridium catalysts have also been developed in recent years. In 2010, Williams and co-workers found [Cp*IrI_2] is a water-tolerant catalyst for *N*-alkylation of primary and secondary amines and sulfonamides in aqueous media [115]. In the same year, Fujita, Yamaguchi and co-workers also reported a water-soluble and air-stable [Cp*$Ir(NH_3)_3$][I]$_2$-catalyzed multi-alkylation of aqueous ammonia with alcohols (Eq. 25) [116]. The catalyst could be recycled by an easy procedure that still maintains high activity. Moreover, quinolizidines could also be achieved from the reaction of aqueous ammonia and a water soluble triol employing the same method.



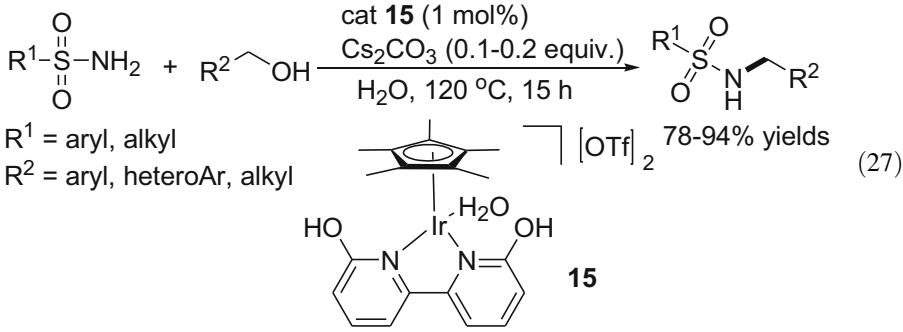
(25)

In 2012, Madsen and co-workers reported a [Cp*$IrCl_2$]$_2$-catalyzed method for the synthesis of piperazines from amines and 1,2-diols in toluene or water [117]. In 2013, Trudell and co-workers realized a microwave-assisted [Cp*$IrCl_2$]$_2$-catalyzed synthesis of nicotine and anabasine derivatives in water media (Eq. 26) [118]. In 2014, Li and co-workers reported an iridium complex **15**-catalyzed *N*-alkylation of sulfonamides with alcohols in aqueous media (Eq. 27) [119].



n = 1, 2. R^1 = H, MeO. R^2 = Me, Bn, 4-$MeOC_6H_4$ 50-78% yields

(26)

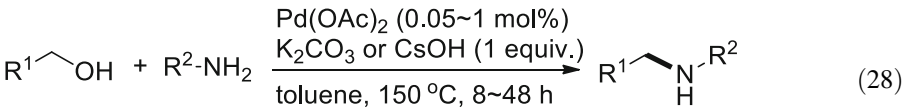


R^1 = aryl, alkyl
R^2 = aryl, heteroAr, alkyl

78-94% yields

(27)

In 2011, Ramón and co-workers reported a $Pd(OAc)_2$-catalyzed *N*-alkylation of poor nucleophilic heterocyclic amines, carboxamides, and *N*-(triphenylphosphoranylidene)aniline with alcohols with catalyst loading as low as 0.5 mol% (Eq. 28) [120]. In 2013, Seayad and co-workers reported a powerful $PdCl_2$/dppe-catalyzed *N*-alkylation of various primary and cyclic secondary amines with primary alcohols at 90–130 °C under neat conditions [121]. Besides, a 10 mmol scale reaction of aniline and benzyl alcohol was performed using 0.1 mol% of the catalyst at 100 °C, with up to 90 % yield of the product and a turnover number (TON) of 900 obtained.

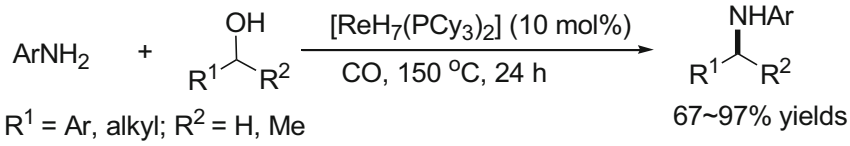


R^1 = Ar, alkyl; R^2 = RSO_2, RCO, Ar, alkyl *etc.* 5~99% yields

(28)

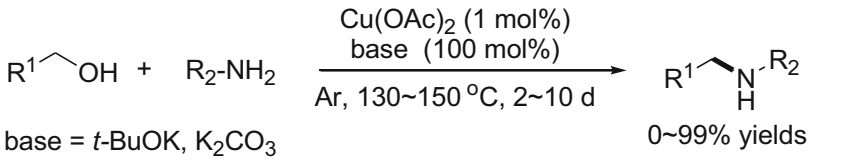
Some *N*-alkylation reactions catalyzed by other noble metal catalysts have also been reported. In 2011, Gusev and co-workers reported an Osmium complex-catalyzed *N*-alkylation of amines at 200 °C with a low catalyst loading (0.1 mol%) [122]. In 2014, Zhu and co-workers disclosed a $[ReH_7(PCy_3)_2]$-catalyzed amination of alcohols with anilines under CO atmosphere (Eq. 29) [123]. The authors proposed that coordination of CO with Re might lead to decomposition of $ReH_7(PCy_3)_2$ to a rhenium carbonyl complex, which was believed to be the active

catalyst. In 2014, Cheng reported a [Ph_3PAuCl]/AgOTf-catalyzed *N*-alkylation of primary amines with alcohols under a moderate temperature of 100 °C [124].



(29)

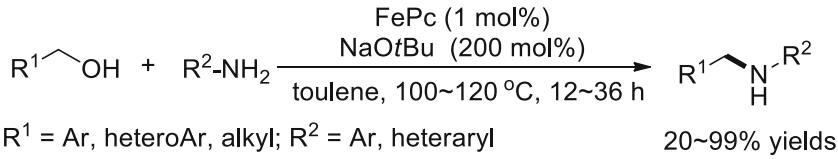
Several non-noble metal-catalyzed *N*-alkylation reactions have also been reported in recent years. In 2010, Ramón, Yus and co-workers reported $Cu(OAc)_2$-catalyzed *N*-alkylation of poor nucleophilic amine derivatives and alcohols (Eq. 30) [125]. Control experiments indicated that a base was indispensable in the reaction to force the alcohol dehydrogenation step, which was later confirmed by DFT calculations reported by Liu, Huang and co-workers [63]. In 2011, Ramón and co-workers reported the results of their own mechanistic studies and proposed two possible catalytic cycles [126]. The main aldehyde-free cycle, depicted with plain arrows, requires the presence of a base. The minor cycle, depicted in dashed arrows, may proceed when an aldehyde exists in the reaction media (Scheme 23). In the same year, Li and co-workers also disclosed a CuCl-catalyzed *N*-alkylation of heteroarylamines [127].



(30)

In 2010, Shi, Deng and co-workers reported the first $FeCl_2/K_2CO_3$-catalyzed *N*-alkylation of sulfonamides with alcohols through the borrowing hydrogen method (Scheme 24) [128]. Tentative mechanism studies were performed to show that the alcohol dehydrogenation step was the rate-determining step.

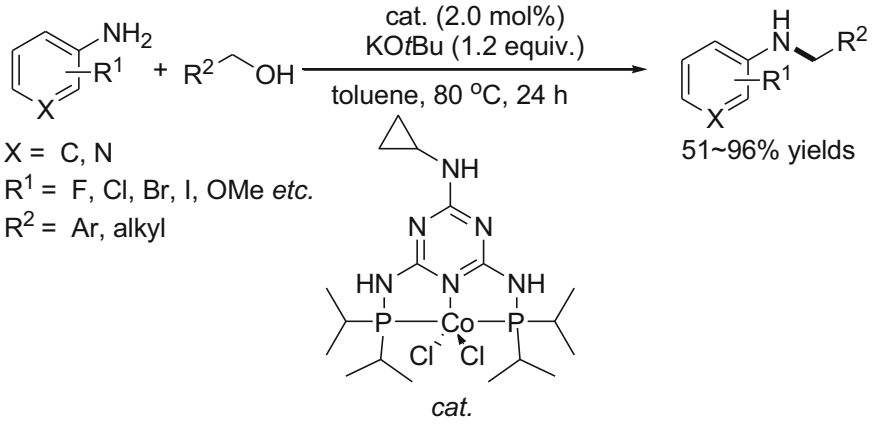
In 2013, Singh and co-workers also reported an iron(II) phthalocyanine (FePc)-catalyzed *N*-alkylation of heterocyclic amines (Eq. 31) [129]. In most cases, the reactions of benzyl alcohols could give moderate to excellent yields, but aliphatic alcohols gave only poor yields of the products.



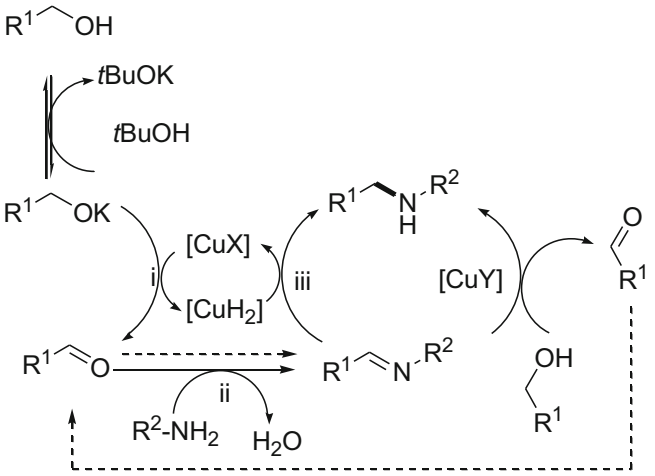
(31)

In 2014, Feringa, Barta and co-workers reported an *N*-alkylation reaction of amines with aliphatic alcohols catalyzed by an iron cyclopentadienone complex **16** [130]. A catalytic cycle was proposed based on in situ NMR studies (Scheme 25). Complex **16** was first transformed to the active complex **17** by addition of oxidant Me_3NO. Complex **17** was then reduced to **18** by the alcohol. **16** and **18** acted as the catalysts to dehydrogenate the alcohol and hydrogenate the imine intermediates. In 2015, Zhao and co-workers realized an AgF-assisted amination of secondary alcohols using complex **16** as the catalyst [131]. In the same year, Wills and co-workers demonstrated a similar iron complex for *N*-alkylation of amines with alcohols [132].

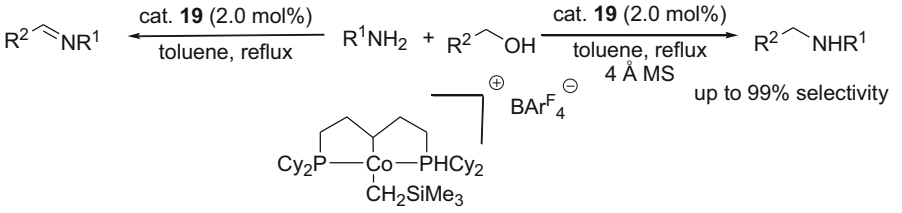
In 2015, Kempe and co-workers reported the first cobalt-catalyzed *N*-alkylation of (hetero)arylamines with alcohols under mild conditions (80 °C) with a relatively low catalyst loading (2 mol%) (Eq. 32) [133]. In 2016, Zhang and co-workers developed another pincer cobalt complex **19**, which is an active catalyst for both imination and *N*-alkylation reactions of aromatic and aliphatic amines with alcohols under base-free conditions [134]. By using complex **19**, monoalkylated amine products rather than the imines can be selectively achieved by simply adding 4 Å molecular sieves to the reaction mixture (Eq. 33).



(32)



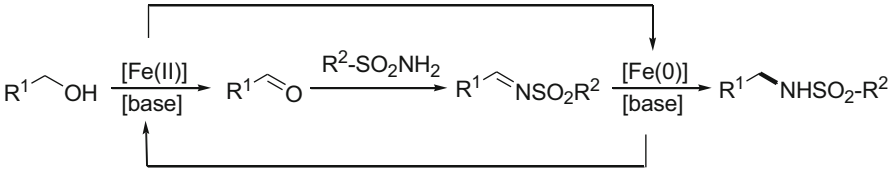
Scheme 23 Tentative catalytic cycles for Cu-catalyzed *N*-alkylation reactions



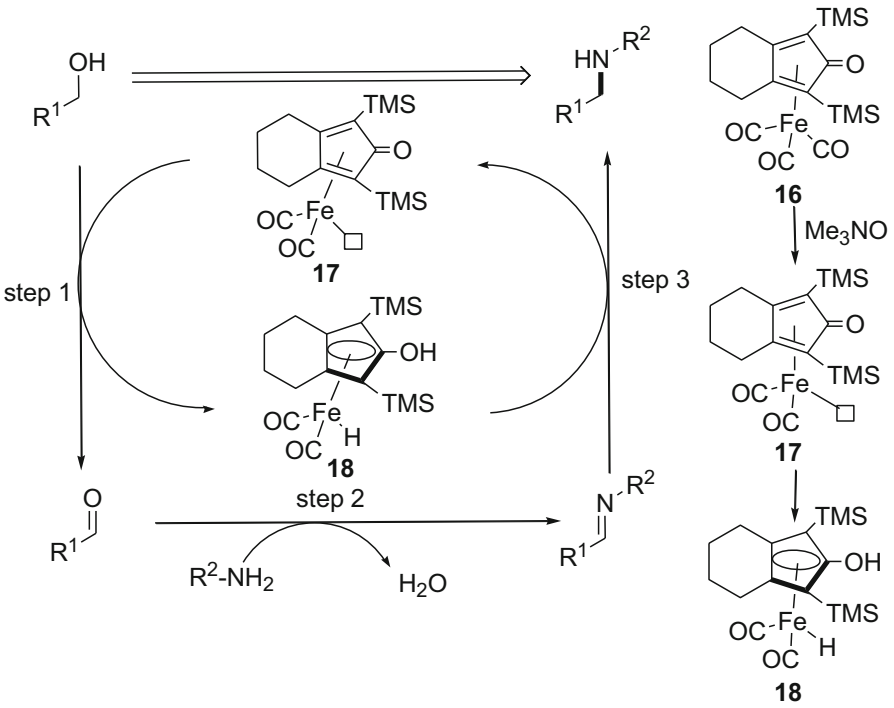
(33)

2.3 Recent Advances in Heterogeneous TM-Catalyzed *N*-Alkylation Reactions

Homogeneous TM catalysts, especially those of noble metals are usually expensive and toxic, and have problems of low availability, low stability, metal residue contaminant in the products, non-recoverability, and, therefore, low potential in large scale and industrial synthesis. In addition, the capricious ligands used are, in



Scheme 24 Proposed mechanism for iron-catalyzed alkylation of sulfonamide with alcohol

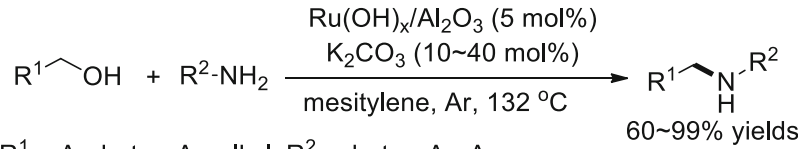


Scheme 25 Proposed mechanism for iron cyclopentadienone complexes-catalyzed *N*-alkylation reactions

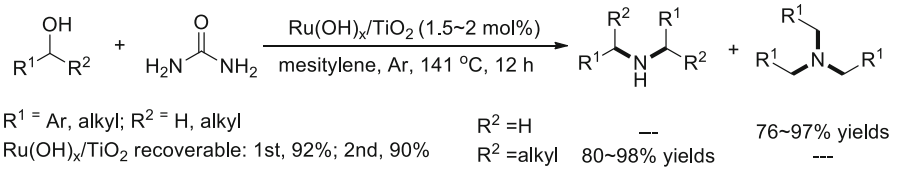
many cases, less available and more expensive than the TM pre-catalysts. To solve the problems and reduce the cost, recoverable and reusable heterogeneous catalysts are considered to be promising substitutes for the corresponding homogeneous catalysts. Consequently, various kinds of heterogeneous TM catalysts have also been developed and are used in *N*-alkylation reactions [10–12]. Most of the early heterogeneous methods require harsh conditions and suffer from problems of limited substrate scope, low selectivity, or the need for H_2 [10, 11]. In recent years, more and more active heterogeneous catalysts that can be used under milder or additive-free conditions, with higher catalytic performance and recoverability, have been developed. These include various types of supported Ru, Ir, Pt, Pd, Ag, Cu, and Ni catalysts.

Owing to the high activities of the homogeneous Ru and Ir catalysts in *N*-alkylation reactions, many heterogeneous Ru and Ir catalysts have been developed. In 2009, Mizuno and co-workers reported an effective *N*-alkylation of (hetero)arylamines with benzylic and aliphatic alcohols catalyzed by $Ru(OH)_x/Al_2O_3$ complex without any co-catalysts or additives (Eq. 34) [135]. The catalyst is recoverable and reusable without obvious loss of activity (1st, 89 %; 2nd, 87 %). Later in the same year, the authors reported another additive-free method for synthesis of secondary and tertiary amines from alcohols and urea catalyzed by $Ru(OH)_x/TiO_2$ (Eq. 35)

[136]. The catalyst could be reused at least twice while still maintaining high activity (1st, 92 %; 2nd, 90 %). In 2010, the Mizuno group further extended the method to *N*-alkylation of other nitrogen sources such as ammonium salt, ammonia, primary amines and secondary amines [137].



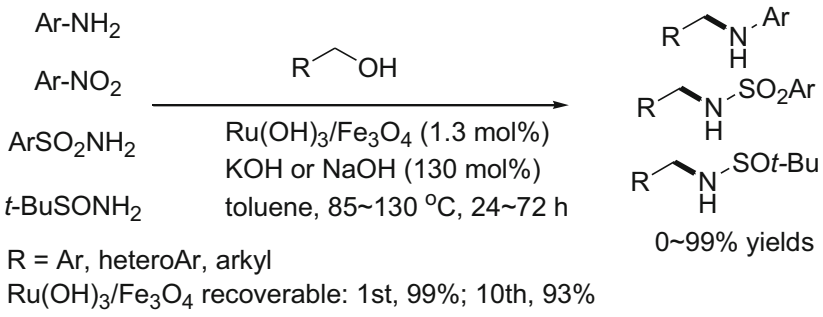
(34)



(35)

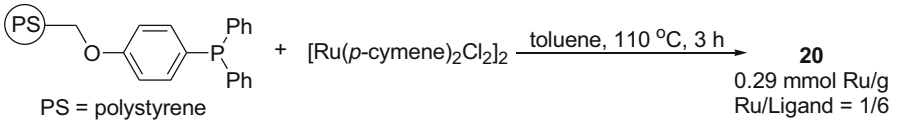
Continuing their work on the previously reported magnetite-catalyzed *N*-alkylation of aryl amines [138], in 2011 Ramón and co-workers reported $Ru(OH)_3/Fe_3O_4$-catalyzed *N*-alkylation reactions of poor nucleophilic amines/amides, such as aromatic and heteroaromatic amines, sulfonamides, sulfinamides, and nitroarenes (Scheme 26) [139]. The catalyst could be easily removed from the reaction mixture by magnet and reused up to ten times, showing the high activity of the catalyst (1st, 99 %; 10th, 93 %).

In 2014, Ramalingam and co-workers reported an additive-free reaction of primary and secondary amines with alcohols catalyzed by a supported ruthenium complex **20**, which was prepared from polystyrene-supported phosphine ligand and $Ru(p\text{-cymene})_2Cl_2]_2$ (Eqs. 36,37) [140]. The authors found the ratio of the

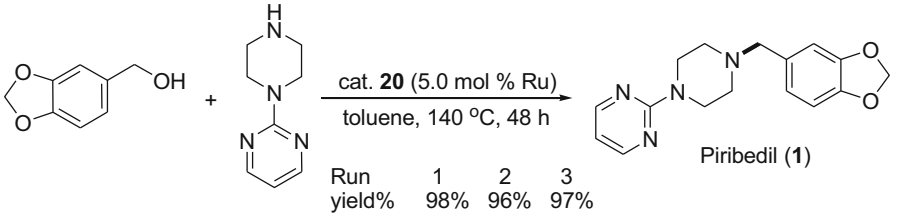


Scheme 26 $Ru(OH)_3/Fe_3O_4$-catalyzed *N*-alkylation reactions of poor nucleophilic amines/amides

phosphine ligand and Ru to be crucial to the high activity of the catalyst and low ruthenium leaching. Piribedil (**1**) could also be obtained in high yield by this method (1st, 98 %; 3rd, 97 %). The catalyst was also found effective for *N*-alkylation of piperidine under flow conditions.

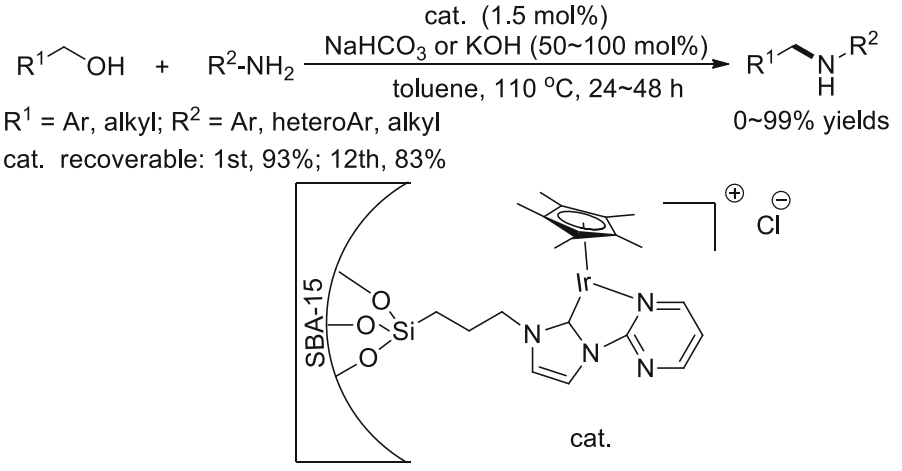


(36)



(37)

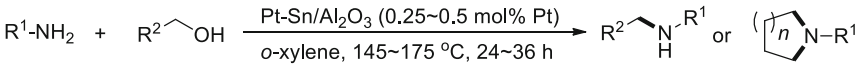
In 2013, Gao, Hou, and co-workers reported a mesoporous silica (SBA-15) supported iridium complex-catalyzed *N*-alkylation of primary amines with benzyl alcohols (Eq. 38) [141]. The catalyst could be recovered easily and reused at least 12 times without notable decrease in catalytic efficiency (1st, 93 %; 12th, 83 %).



(38)

In 2011, Yu and co-workers reported additive-free *N*-alkylation and *N*,*N*′-dialkylation reactions of amines and alcohols catalyzed by Pt–Sn/γ-Al_2O_3 with

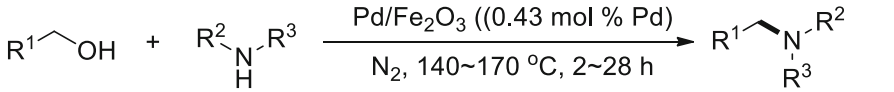
catalyst loading as low as 0.25 mol% (Eq. 39) [142]. Later in the same year, the Yu group extended the method to the direct synthesis of diamines by *N*,*N*′-dialkylation of amines with diols [143]. The recovered catalyst could be reused three times with the same activity. The same method can also be applied to amine-based *N*-alkylation reactions (vide infra).



R^1 = Ar, heteroAr, alkyl; R^2 = Ar, heteroAr, alkyl, $(CH_2)_mOH$; *n* = 1, 2, 3, 4
Pt-Sn/Al_2O_3 recoverable: 1st, 95%; 3nd, 95%

(39)

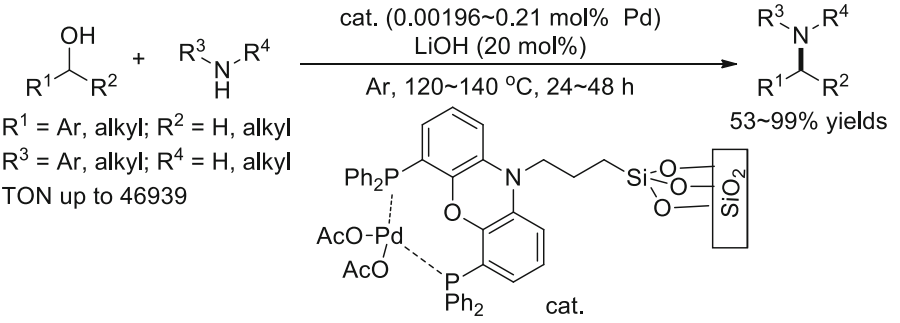
In the same year, Shi and co-workers reported the *N*-alkylation of anilines, aliphatic amines and indoles with alcohols catalyzed by Pd/Fe_2O_3 under base- and ligand-free conditions with a low catalyst loading (0.43 mol%) (Eq. 40) [144]. In 2013, Pera-Titus and co-workers reported the *N*-alkylation of anilines catalyzed by another heterogeneous Pd catalyst Pd/K-OMS-2 (Pd-substituted octahedral molecular sieve) [145].



R^1 = Ar, heteroAr, alkyl; R^2 = Ar, heteroAr, alkyl; R^3 = Ar, alkyl

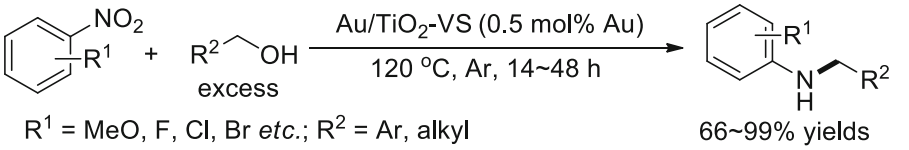
(40)

In 2015, Seayad and co-workers reported a silica supported palladium complex-catalyzed solvent-free *N*-alkylation of amines with catalyst loading as low as 0.00196 mol% and TON as high as 469390 (Eq. 41) [146]. The catalyst could be recycled at least four times without obvious loss of activity.

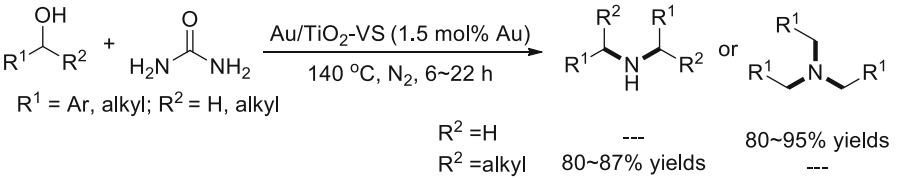


(41)

In 2010, Cao and co-workers reported the ligand- and base-free *N*-alkylation of anilines, aliphatic primary amines and pyrrolidine with alcohols catalyzed by very small (VS) Au nano particles: Au/TiO_2-VS [147]. The authors reported that 0.0083 mol% of the catalyst is efficient enough to catalyze a 100 mmol reaction of aniline and benzyl alcohol under solvent-free conditions, giving 96 % yield of the product. In 2011, the same group extended the method to reductive *N*-alkylation of nitrobenzenes with excess alcohols (8.0 equiv.) without external reducing reagents (Eq. 42) [148]. In 2012, the Cao group further extended their method to the synthesis of tertiary and secondary amines from alcohols and urea (Eq. 43) [149]. A 60 mmol scale solvent-free amination reaction of benzyl alcohol and urea gave the product in 92 % yield.

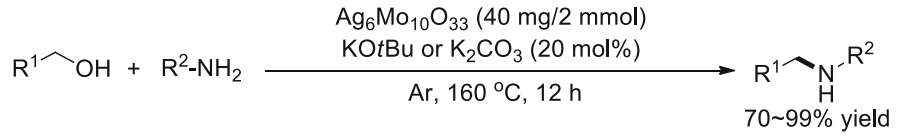


(42)



(43)

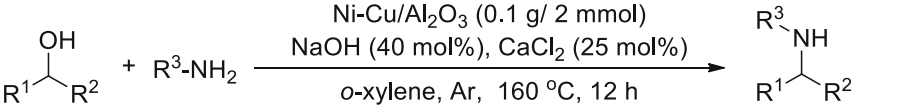
In 2009, Shimizu and co-workers found that Ag/Al_2O_3-$FeCl_3$ is highly active for the *N*-alkylation of anilines with benzylic alcohols [150]. The reactions using recovered catalyst led to only a slight decrease in product yields (1st, 94 %; 2nd, 85 %; 3rd, 86 %). In 2012, Jaenicke and co-workers also described the *N*-alkylation of aniline with linear aliphatic alcohols catalyzed by Ag/Al_2O_3-Cs_2CO_3 [151]. The recovered catalyst still exhibited high catalytic activity (1st, 99 %; 3rd, 97 %). In 2011, Shi and co-workers reported an $Ag_6Mo_{10}O_{33}$-catalyzed *N*-alkylation of amines, carboxamides, sulfonamides, and aromatic ketones with alcohols (Eq. 44) [152]. No deactivation occurred when the catalyst was recovered and reused twice (1st, 93 %; 2nd, 95 %).



R^1 = Ar, heteroAr, alkyl; R^2 = RSO_2, RCO, Ar, heteroAr
$Ag_6Mo_{10}O_{33}$ recoverable: 1st, 93%; 2nd, 95%

(44)

In addition to above noble metal catalysts, many *N*-alkylation reactions catalyzed by heterogeneous non-noble metal catalysts have also been reported. In 2012, Li and co-workers reported a Ni-Cu/γ-Al_2O_3-catalyzed *N*-alkylation of amines with alcohols (Eq. 45) [153]. The reactions using recovered catalyst led to slight decrease in product yields (1st, 90 %; 2nd, 84 %).

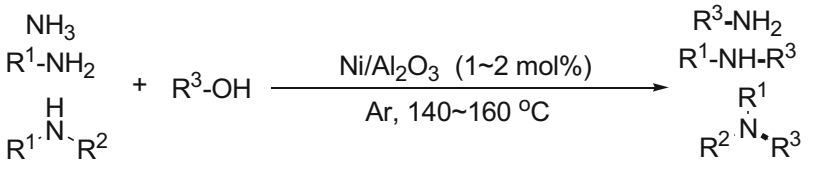


R^1 = aryl, alkyl; R^2 = H, Me, Et; R^3 = aryl, heteraryl, alkyl

(45)

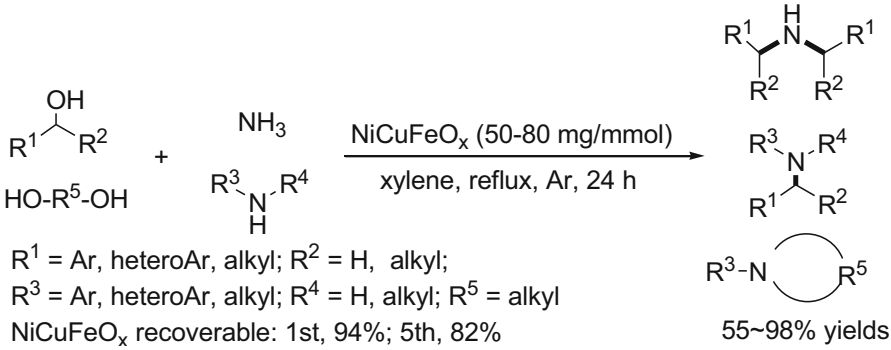
In 2013, Shimizu and co-workers first reported an additive-free Ni/Al_2O_3-catalyzed synthesis of primary amines from alcohols and ammonia (Scheme 27) [154]. The recovered catalyst could be reused at least twice without losing catalytic activity (1st, 88 %, 3rd, 89 %). Later in 2013, the authors extended the method to amination of alcohols with anilines and aliphatic amines (Scheme 27) [155]. In 2014, the Shimizu group also described a Ni/$CaSiO_3$-catalyzed amination reaction of alcohols with ammonia, anilines and aliphatic amines [156].

In 2013, Shi and co-workers reported a base- and ligand-free *N*-alkylation of ammonia, primary amines and secondary amines with alcohols catalyzed by an air- and moisture-stable $NiCuFeO_x$ catalyst (Scheme 28) [157]. The catalyst can be recovered easily and reused at least 5 times (1st, 94 %; 5th, 82 %). A 10 mmol scale



R^1 = Ar, heteroAr, alkyl; R^2= alkyl; R^3 = Ar, alkyl
Ni/Al_2O_3 recoverable: 1st, 88%; 3nd, 89%

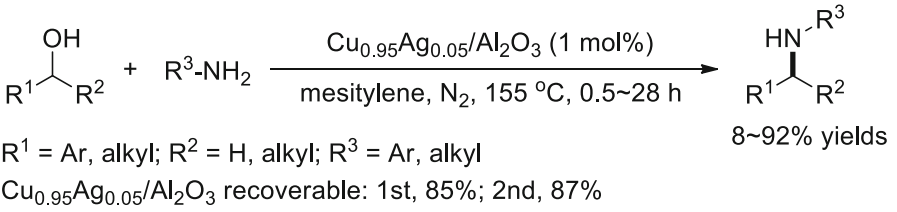
Scheme 27 Ni/Al_2O_3-catalyzed amination of alcohols with ammonia, anilines, and aliphatic amines



Scheme 28 $NiCuFeO_x$ complex-catalyzed *N*-alkylation of ammonia and primary and secondary amines with alcohols

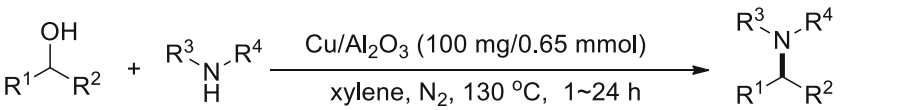
solvent-free reaction of aniline and benzyl alcohol afforded the product in 85 % GC yield. In addition, the same method could also be applied to self-*N*-alkylation of primary amines (vide infra). In 2014, Nandan and coworkers reported a Raney nickel-catalyzed *N*-alkylation of anilines, primary aliphatic amines, cyclic secondary amines and azole with alcohols [158]. The recovered catalyst showed a very good activity comparable to the fresh catalyst (1st, 91 %; 3rd, 88 %).

In 2009, Mizuno and co-workers reported a base- and ligand-free $Cu(OH)_x/Al_2O_3$-catalyzed *N*-alkylation of *N*-nucleophiles including urea, ammonia, anilines and alkylamines [159]. In 2011, Shimizu and co-workers reported an additive-free $Cu_{0.95}Ag_{0.05}/Al_2O_3$-catalyzed *N*-alkylation of anilines and aliphatic amines with benzylic and aliphatic alcohols with a low catalyst loading (1 mol%) (Eq. 46) [160]. The recovered catalyst could be reused without losing catalytic activity (1st, 85 %; 2nd, 87 %).



(46)

In 2012, Ravasio and co-workers also reported an additive-free *N*-alkylation of amines with benzyl and aliphatic alcohols catalyzed by Cu/Al_2O_3 [161]. In 2014, the authors extended the method to the *N*-alkylation of anilines with a wide range of alcohols (Eq. 47) [162]. In 2013, Mishra and co-workers reported an additive-free *N*-alkylation of primary amines with primary and secondary alcohols catalyzed by copper–aluminium hydrotalcite (CuAl-HT) [163].



R^1 = Ar, alkyl; R^2 = H, alkyl; R^3 = Ar, alkyl; R^4 = H, alkyl

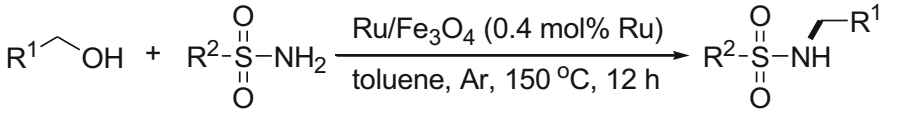
32.8~99.6% yields

(47)

2.4 Miscellaneous Catalytic *N*-Alkylation Reactions

In addition to the homogeneous and heterogeneous TM catalysts discussed above, other catalysts/methods such as nano catalysts, carbon materials, enzymes, chiral catalysts and continuous flow techniques have also been developed successfully and applied in *N*-alkylation reactions of amines/amides with alcohols.

In 2009, Beller and co-workers reported the *N*-alkylation of sulfonamides with benzylic alcohols catalyzed by nano-Ru/Fe_3O_4 with catalyst loading as low as 0.4 mol% (Eq. 48) [164]. A high 96 % yield of product could still be obtained even when the catalyst was reused 5 times and with TON up to 1100.



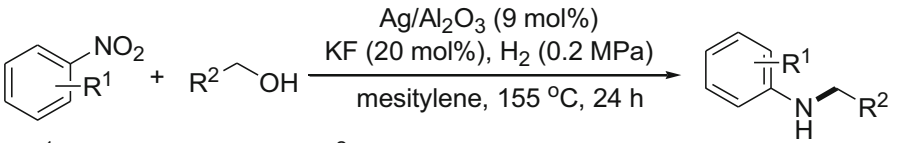
49~98% yields

R^1 = Ar, heteroAr R^2 = Ar, heteroAr, alkyl

Ru/Fe_3O_4 recoverable: 1st, 97%; 5th, 96%. TON up to 1100

(48)

In 2010, Shimizu and co-workers reported a nano-Ag/Al_2O_3-catalyzed one-step synthesis of *N*-substituted anilines from nitroarenes and stoichiometric benzyl alcohols under H_2 atmosphere (Eq. 49) [165], in which H_2 was employed to reduce the nitroarenes to anilines.



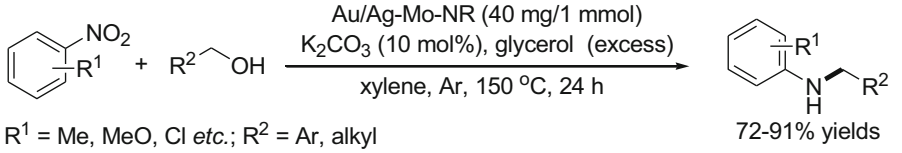
R^1 = MeO, F, Cl, Br *etc.*; R^2 = Ar,

80~94% yields

(49)

In 2012, Shi and co-workers reported another reductive *N*-alkylation of nitrobenzenes with stoichiometric alcohols (1.0 equiv.) catalyzed by nano-Au/

Ag–Mo nano-rods (Eq. 50) [166]. Unlike Shimizu's work using as H_2 [165], in Shi's work excess glycerol was employed as the reductant.

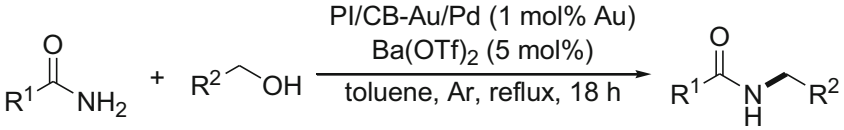


R^1 = Me, MeO, Cl *etc.*; R^2 = Ar, alkyl

(50)

Later in 2012, Corma, Sabater and co-workers reported a nano-Au/CeO_2-catalyzed *N*-alkylation of amines with alcohols [167]. In 2014, De Vos and co-workers reported a nano-Ag/Al_2O_3/Ga_2O_3-catalyzed amination of alcohols with a variety of aliphatic and aryl amines under mild conditions [168]. The catalyst remained active for at least three runs (1st, TOF = 1.01/h; 3rd, 1.02/h).

In 2015, Kobayashi and co-workers reported a PI/CB-Au/Pd (PI/CB, polymer-incarcerated metal nanoparticle catalyst with carbon black as a secondary supporter) complex-catalyzed *N*-alkylation of amides with alcohols (Eq. 51) [169]. The catalyst could be reused 11 times without appreciable loss of catalytic activity (1st, 99 %; 11th, 95 %).

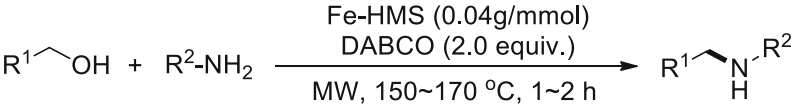


R^1 = Ar, heteroAr, alkyl; R^2 = Ar

PI/CB-Au/Pd recoverable: 1st, 99%; 11th, 95%

(51)

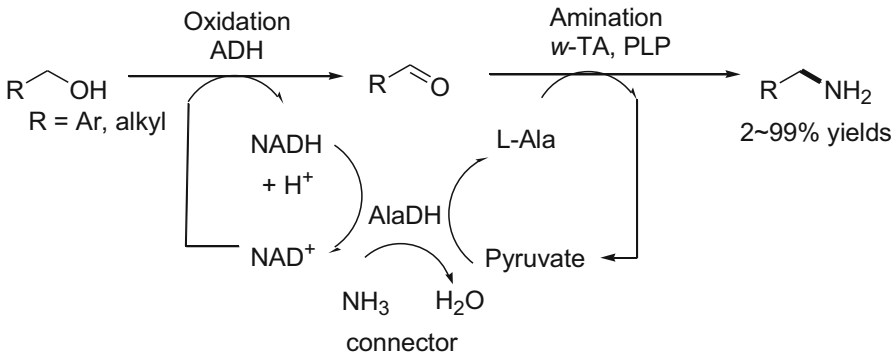
In 2010, Luque and co-workers were the first to report a microwave-assisted *N*-alkylation of amines with benzylic alcohols catalyzed by nano-Fe-HMS (HMS, hexagonal mesoporous silica) (Eq. 52) [170]. The authors found that base may be crucial in deprotonation/dehydrogenation of the alcohols.



R^1 = Ar; R^2 = Ar, heteroAr, alkyl

(52)

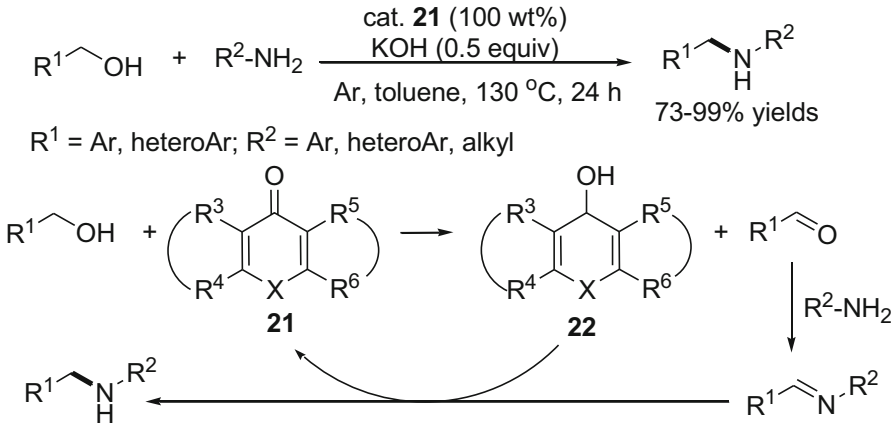
In 2010, Kolaczkowski and co-workers described a continuous flow *N*-benzylation of morpholine with benzyl alcohol catalyzed by a heterogeneous ruthenium complex with a product yield of 98 %, providing an efficient route for



Scheme 29 Proposed mechanism for the artificial multi-enzyme-catalyzed bioamination of primary alcohols

synthesis of *N*-benzyl morpholine [171]. In 2013, Kocsisin and co-workers also reported a Raney nickel-catalyzed *N*-alkylation of amines and pyrrole with alcohols in a continuous flow process [172]. In most cases the effective residence time was less than 1 min.

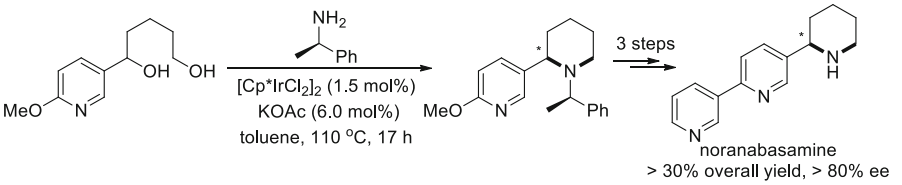
In 2012, Kroutil and co-workers reported the first amination reaction of primary alcohols with ammonium chloride by an artificial multi-enzyme-catalyzed cascade method (Scheme 29) [173]. The authors assumed that the reaction might proceed by two steps. Initially, the alcohol was oxidized by an alcohol dehydrogenase (ADH), consuming NAD^+ and leading to the formation of the aldehyde and NADH. Then, the aldehyde intermediate was aminated with an amine donor L-alanine by a *w*-transaminase (*w*-TA). Finally, by combining ADH-hT (ADH from *Bacillus stearothermophilus*) with CV-*w*-TA (*w*-TA from *Chromobacterium violaceum*), the amination of various primary alcohols successfully afforded the corresponding primary amines in 2–99 % yields.



Scheme 30 Tentative mechanism for amination of alcohols catalyzed by carbon material **21**

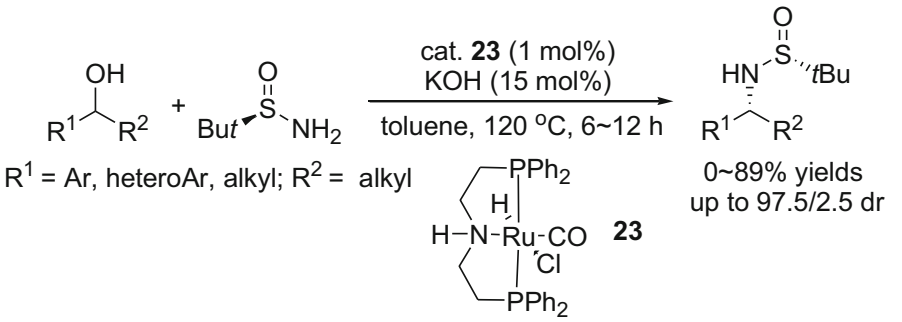
In 2015, Shi and co-workers reported a carbon material (**21**)-catalyzed amination of (hetero)benzylic alcohols with (hetero)aryl amines and aliphatic amines (Scheme 30) [174]. A tentative mechanism was proposed. First, hydrogen was transferred from the alcohol to the carbon catalyst **21** to give aldehyde intermediate and reduced catalyst **22**. Then, condensation of aldehyde and amine to imine and subsequent reduction by **22** led to the desired *N*-alkyl amine products and regeneration of carbon catalyst **22**.

The more challenging asymmetric *N*-alkylation reactions of amines with alcohols was also developed in recent years. In 2009, by employing an Ir-catalyzed *N*-heterocyclization reaction as the key step, Trudell and co-workers first achieved the enantioselective total synthesis of both enantiomers of noranabasamine with >30 % overall yields and >80 % ee (Eq. 53) [175].



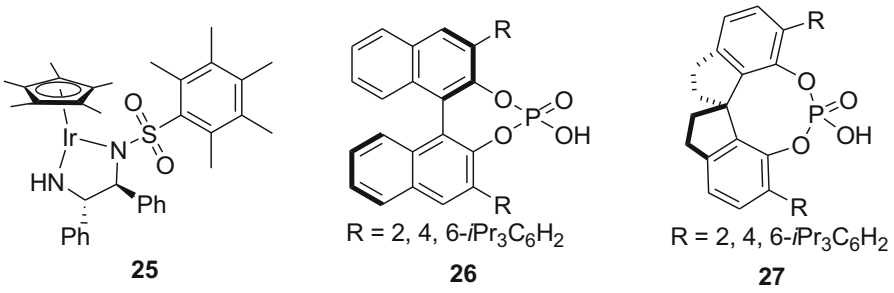
(53)

In 2014, Guan and co-workers reported the direct synthesis of α-chiral *tert*-butanesulfinylamines from the reaction of racemic alcohols and Ellman's sulfinamide catalyzed by ruthenium (II) pincer catalyst **23** (Eq. 54) [176], providing an effective method for the synthesis of chiral amine derivatives.

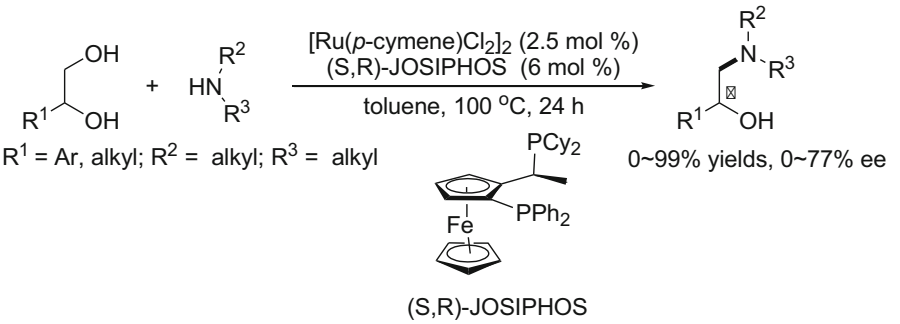


(54)

In 2013, Oe and co-workers achieved the first enantioselective synthesis of β-amino alcohols from the reaction of 1,2-diols and secondary amines catalyzed by $[Ru(p\text{-cymene})Cl_2]_2$/(*S*,*R*)-JOSIPHOS with moderate enantioselectivity (Eq. 55) [177].

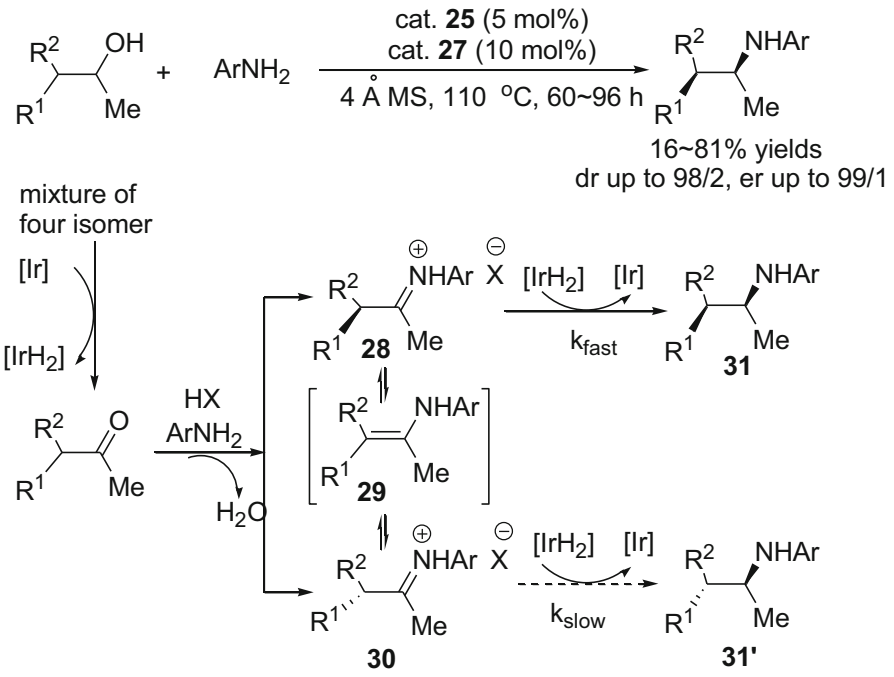


Scheme 31 Iridium complex **22** and chiral phosphoric acids **23** and **25**

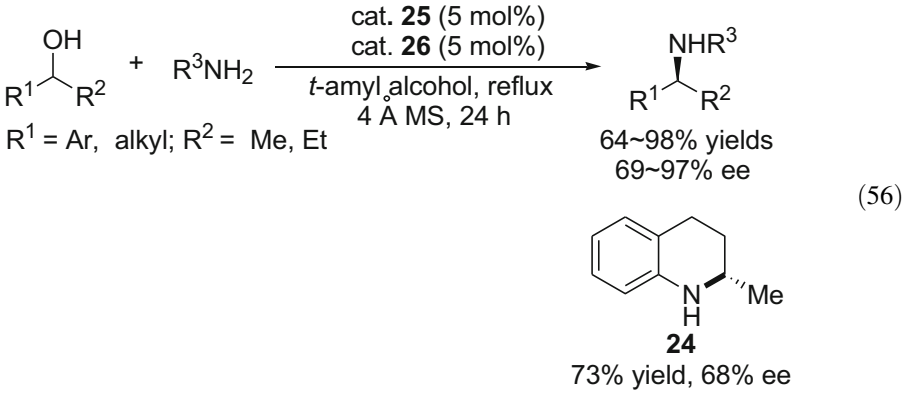


(55)

In 2014, by employing the hydrogen autotransfer method, Zhao and co-workers reported the first enantioselective amination of alcohols to chiral secondary arylamines in high yields and high ee up to 97 % (Eq. 56, Scheme 31) [178]. Intramolecular amination could also be achieved to give quinoline **24** with 68 % ee. The authors proposed that the high enantioselectivity might be attributed to the cooperation of the iridium complex **25** and the chiral phosphoric acid **26**.

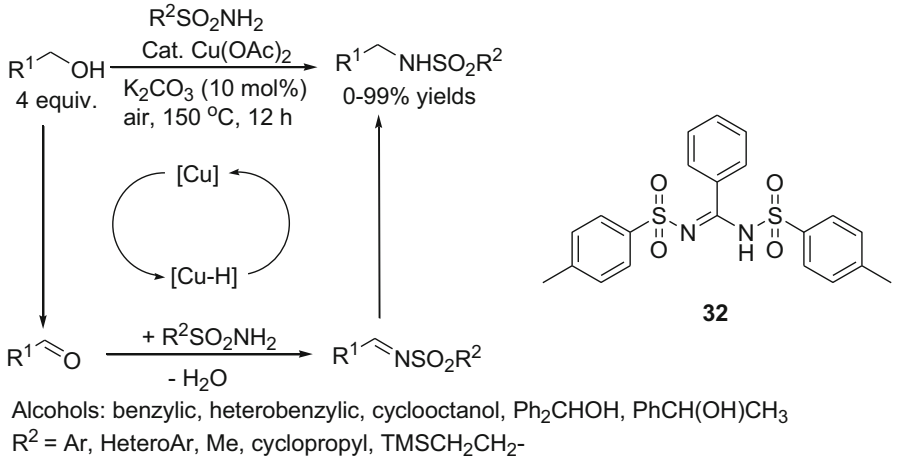


Scheme 32 Proposed mechanism for the dynamic kinetic asymmetric amination of alcohols



(56)

In 2015, Zhao and co-workers described the first dynamic kinetic asymmetric amination of alcohols via borrowing hydrogen methodology under the cooperative catalysis of iridium complex **25** and chiral phosphoric acid **27** (Schemes 31, 32) [179]. The authors proposed that, initially, the two stereocenters in the alcohols were both racemized to ketone by the first oxidation, followed by tautomerization of the iminium intermediates **28** and **30** through enamine intermediate **29**. Then, the



Scheme 33 Proposed mechanism for Cu-catalyzed *N*-alkylation of sulfonamides with alcohols under air

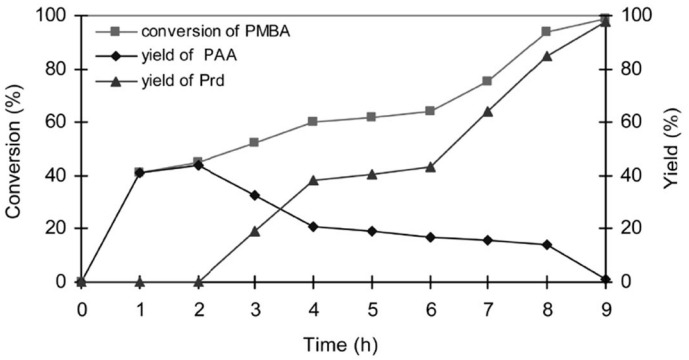
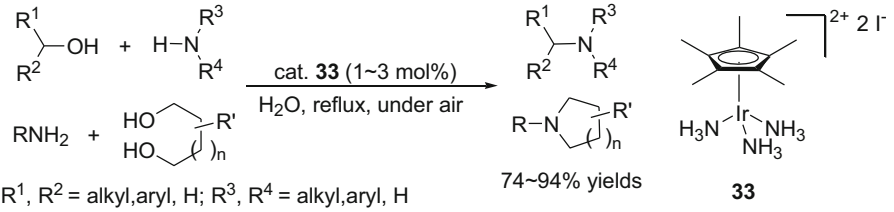


Fig. 1 PAA and *N*-alkylated product over time in the CuAl-HT_2/K_2CO_3-catalyzed amination of PMBA with benzylamine (BA) (160 °C, 9 h). *PAA* *p*-anisaldehyde, *PMBA* *p*-methoxybenzyl alcohol, *Prd* product

different reaction rates of the two stereoisomers towards hydrogenation by [IrH_2] led to the major product **31**.

2.5 TM-Catalyzed Aerobic *N*-Alkylation Reactions (Reactions Under Air)

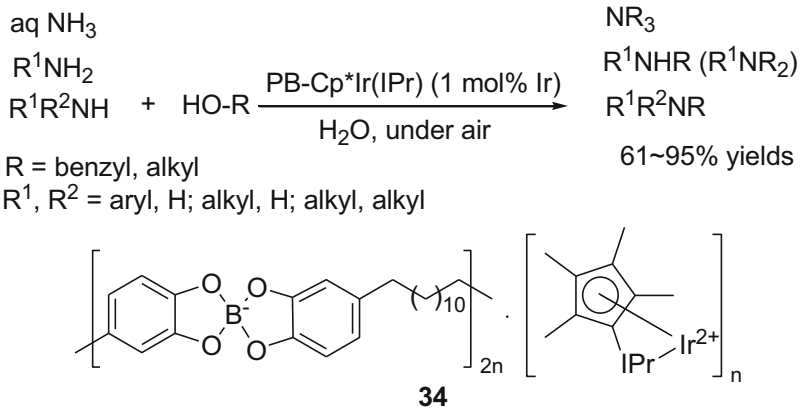
In addition to the above *N*-alkylation reactions carried out under inert conditions via anaerobic dehydrogenative activation of alcohols, some TM-catalyzed aerobic *N*-alkylation reactions carried out under air have also been reported in recent years. As they require no inert atmosphere protection, and use air-stable TM catalysts under aerobic conditions, these reactions may be operationally simpler and more practical.



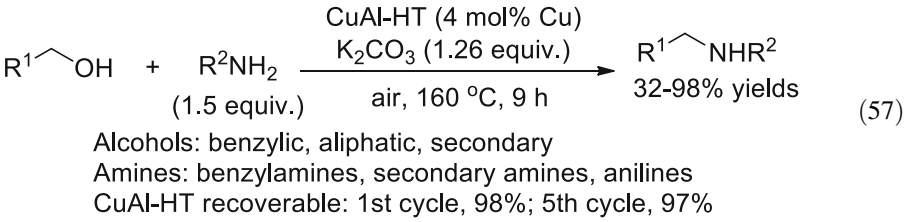
Scheme 34 Cp*Iridium complex (**33**)-catalyzed *N*-alkylation of amines with alcohols under air

In 2009, Shi, Beller and co-workers reported the first homogeneous $Cu(OAc)_2$-catalyzed aerobic *N*-alkylation of sulfonamides with alcohols (Scheme 33) [180, 181]. In condition screening, the authors found the reaction under air was comparatively more efficient (93 % conversion) than those under argon (48 %) or CO_2 (51 %). This method is thus a good alternative for *N*-alkylation of sulfonamides for using the cheaper Cu catalyst under aerobic conditions. The substrates seemed to be limited to sulfonamides only. In the cases of secondary alcohols, no base was required and the more Lewis acidic $Cu(OTf)_2$ was found to be a much better catalyst than $Cu(OAc)_2$. According to the mechanistic study, since bissulfonylated amidine **32** could only be generated in situ in reactions performed under air, the authors concluded that **32** should act as the stabilizing ligand to activate the Cu catalyst for dehydrogenation/hydrogenation processes, and, subsequently, the reaction proceeded through the hydrogen autotransfer/borrowing hydrogen mechanism involving [CuH] species (Scheme 33).

In the same year, Likhar and co-workers also reported a heterogeneous copper–aluminium hydrotalcite (CuAl-HT)-catalyzed amination of alcohols under air (Eq. 57) [182]. Benzylic, aliphatic, and secondary alcohols, benzylamines, secondary amines, and anilines could be tolerated in this method. Notably, the CuAl-HT catalyst can be recovered for reuse by simple filtration for at least five cycles without obvious loss of activity (5th cycle, 97 %). In mechanistic studies, the authors observed an initiation period in which the aldehyde intermediate was first generated in considerable amounts (before 2 h) prior to the formation of product, which remained in consideraable amounts until completion of the reaction (Fig. 1). The aldehyde could also be obtained in 98 % yield in a control reaction with the alcohol alone. Since no alkylated amine product was observed in the reaction of aldehyde and amine with CuAl-HT2, the authors concluded that, by an oxidation/imination/reduction sequence, an in situ generated momo(hydrido)copper species generated by a hydrogen transfer process from alcohols to Cu should be responsible for the second hydrogen transfer to imine intermediates to give the products.



Scheme 35 Boron-iridium heterobimetallic complex (**32**)-catalyzed *N*-alkylation reaction of ammonia and primary, secondary, and cyclic amines with alcohols under air



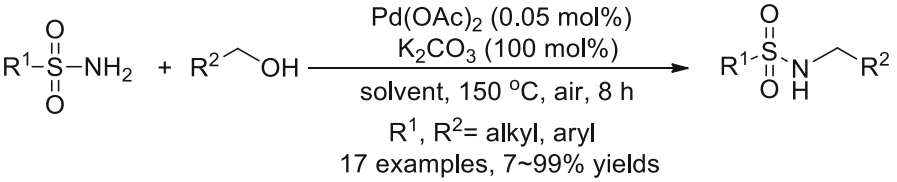
(57)

In 2011, Fujita, Yamaguchi and co-workers reported a water-soluble Cp*Iridium complex (**33**)-catalyzed base-free *N*-alkylation of amines with alcohols in water (Scheme 34) [183]. Since the catalyst is air-stable, the reactions could be readily carried out under air. Primary and secondary benzylamines, aliphatic amines, cyclic amines, anilines, as well as benzylic, aliphatic, secondary alcohols can be used to synthesize secondary and tertiary amines. Cyclic amines could also be achieved by *N*-alkylation of amines with diols. The authors also proposed a mechanism with hydrogen transfers from alcohols to form [Ir-H] complexes and finally to the product amines.

Later in the same year, Uozumi, Yamada, and co-workers also reported an in-water dehydrative *N*-alkylation reaction under air using a heterogeneous boron-iridium heterobimetallic Polymeric Catalyst **34** (Scheme 35) [184]. This method is suitable for the reactions of benzylic and aliphatic alcohols with ammonia, and primary, secondary, and cyclic amines. Different to usual hydrogen autotransfer reactions, which require basic conditions, the reactions of benzylic, aliphatic, and secondary amines and ammonia require a pH 4 aqueous buffer solution under microwave conditions. The catalyst can be recovered and reused at least twice without loss of activity.

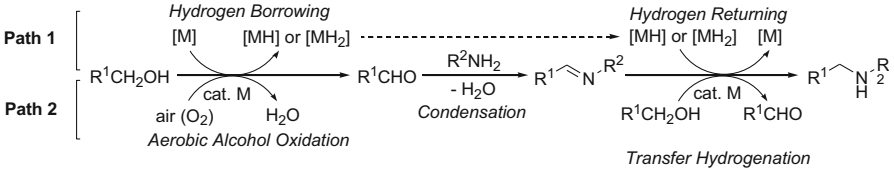
In the $Pd(OAc)_2$-catalyzed *N*-alkylation reactions reported in 2011 [120], Ramón and co-workers found the reactions of sulfonamides and alcohols under air were

more efficient than those under argon, and $Pd(OAc)_2$ could be used at a very low-loading of 0.05 mol% (Eq. 58).

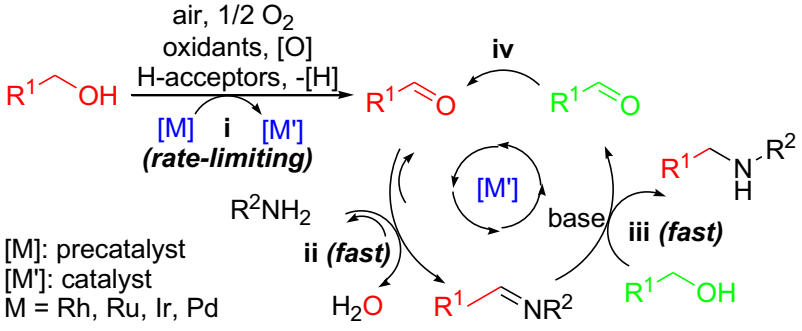


(58)

Also in 2011, Xu and co-workers reported a comparatively general TM-catalyzed aerobic *N*-alkylation reaction of sulfonamides, anilines, heteroarylamines, and carboxamines with benzylic, heterobenzylic, alkyl and allylic alcohols under air (Eq. 59) [185, 186]. Both ligated and ligand-free TM catalysts such as $Rh(PPh_3)Cl$, Ru, Ir, and Rh halides, and even the noble metal oxides, could be used as catalysts under air. In contrast to previous aerobic *N*-alkylation reactions that had not investigated air's influence on the reactions [120, 180–184], the authors were the first to observe air's promoting effect on the reaction. Thus, no reaction was observed, or only trace to low yields of the products, could be detected in parallel anaerobic reactions, while under air the same reactions could afford much higher yields of the products. As the authors found out, this is due to TM catalyst deactivation/poisoning by substrate amines/amides, making the alcohol activation process the rate-limiting step of the whole reaction. Air then participated in the reaction as a new way to oxidize the alcohols to the more active aldehydes. Similarly,

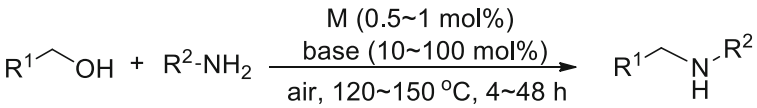


Scheme 36 Possible tandem processes for one-pot/multi-step *N*-alkylation reactions



Scheme 37 Proposed mechanism for air-promoted metal-catalyzed aerobic *N*-alkylation reactions (aerobic relay race mechanism)

if TM oxides, usually used as oxidants in conventional oxidation reactions, including oxidation of alcohols [37–42], were used as catalysts under anaerobic conditions, better results, up to moderate yields of the products, than with other catalysts could be obtained, most likely due to alcohol oxidation by metal oxides. The authors also found that, under the anaerobic conditions typical of the borrowing hydrogen and hydrogen autotransfer reactions, the same TM catalysts could also catalyze *N*-alkylation reactions, but required much higher temperatures; otherwise, addition of ligands is necessary to promote the originally ineffective reactions to occur to yield the desired products. Obviously these aerobic *N*-alkylation reactions proceeded via an alternative mechanism other than the typical borrowing hydrogen and hydrogen autotransfer mechanism (Scheme 3).



(59)

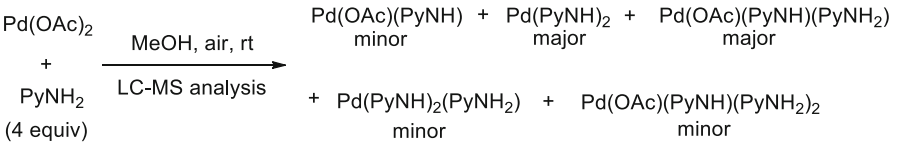
M = $Rh(PPh_3)_3Cl$, $RhCl_3{\cdot}3H_2O$, Rh_2O_3, $Rh_2(OAc)_4$,
$RuCl_3{\cdot}nH_2O$, RuO_2, $IrCl_3$, IrO_2, MnO_2, etc.
R^1 = aryl, heteroaryl, alkyl, allyl; R^2 = RSO_2, RCO, heteroaryl, aryl

After a detailed and careful study of the individual reactions and the reaction mechanism, Xu and co-workers proposed that, in addition to the known anaerobic dehydrogenation method (Scheme 36, path 1), TM-catalyzed aerobic oxidation of alcohols to aldehydes [36–41] (path 2) should be a good alternative for alcohol activation. Consequently, a new mechanism different from the usual hydrogen autotransfer process was proposed for the air-promoted TM-catalyzed aerobic *N*-alkylation reactions (Scheme 37). Thus, alcohols were first oxidized by air under TM catalysis to give aldehydes, which then condense with amines/amides to give imine intermediates. Imines were finally reduced by alcohols to product amines via a transfer hydrogenation process [46–51], generating meanwhile, as the authors proved, 1 equiv. of aldehydes as the byproduct. Since the byproduct aldehyde can be recovered to participate in next mechanism cycle, a small amount of air (ca. 10–20 mol% O_2) was adequate to generate the catalytic amount of aldehdye and initiate the whole reaction, resolving the rate-limiting issue in the alcohol activation step. In addition, the latter alcohol (in green), after transferring its hydrogen atoms to the preceding alcohol (in red, in its imine form via aldehyde intermediate), will (also in its imine form via aldehyde intermediate) receive new hydrogen atoms from an even later alcohol in next mechanism cycle, which is analogous to the relay race game with "handing off" of hydrogen atoms. Hence, the authors termed it the "relay race" mechanism.

In fact, the significant role of air in aerobic alkylation reactions had already been observed by the groups of Uozumi [187, 188] and Crabtree [189]. In 2006, Uozumi and co-workers noted that other mechanisms might participate in their aerobic C-alkylation reaction of ketones and alcohols because one reviewer pointed out that metal hydride intermediates are prone to react with molecular oxygen. In 2010, Crabtree and co-workers hypothesized that their C-alkylation reaction of secondary and primary alcohols under air most possibly underwent a procedure involving

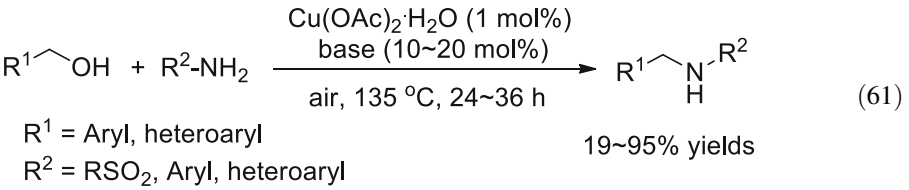
participation of air in the reaction, especially the oxidation of primary and secondary alcohols to aldehydes and ketones for next aldol condensation step.

Xu's air-promoted protocol could even be extended to non-noble metal oxides such as MnO_2 [190] and Pd catalysts [191]. In the latter work, the authors also observed the clear coordination between [Pd] and amines, leading to deactivation of the catalyst (Eq. 60) [191]. Therefore, aerobic reactions catalyzed by Pd were also found to be much more efficient and afforded higher yields of the products than the corresponding anaerobic reactions.

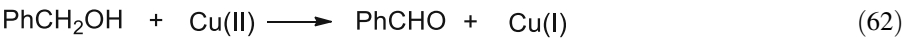


(60)

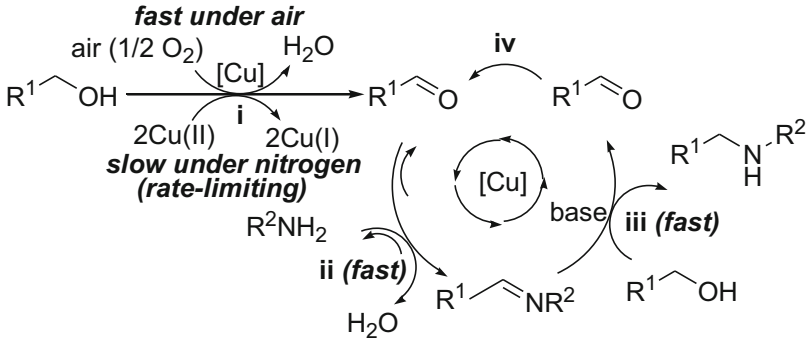
In 2012, Xu and co-workers continued to report a Cu-catalyzed aerobic *N*-alkylation reaction of sulfonamides, anilines and heteroarylamines with alcohols under air (Eq. 61) [192]. The authors evaluated the effects of the additives on the reaction. They not only observed the promoting effect of air, but also found that aldehyde contamination in substrate alcohols could also lead to more efficient reactions either under either air or under nitrogen. Besides, they observed the successful oxidation of alcohol by Cu(II) under anaerobic conditions (Eq. 62).



(61)



(62)



Scheme 38 Proposed mechanism for air-promoted Cu-catalyzed aerobic *N*-alkylation reactions

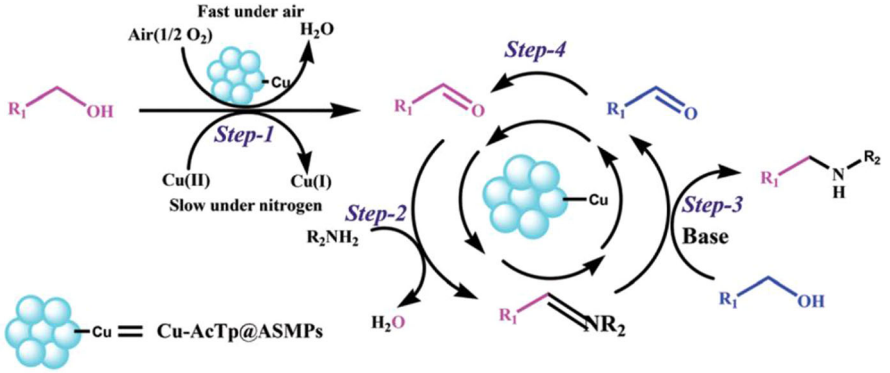
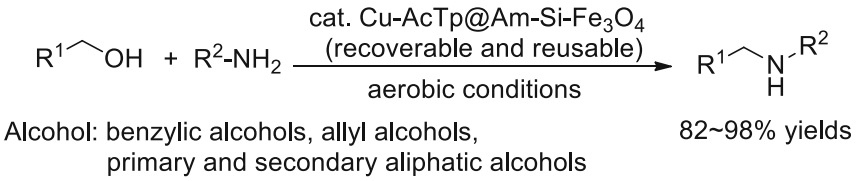


Fig. 2 Proposed mechanism for air-promoted Cu-AcTp@Am–Si-Fe_3O_4-catalyzed aerobic *N*-alkylation reactions

$$PhCH_2OH + Cu(I) \not\rightarrow PhCHO + Cu(0) \quad (63)$$

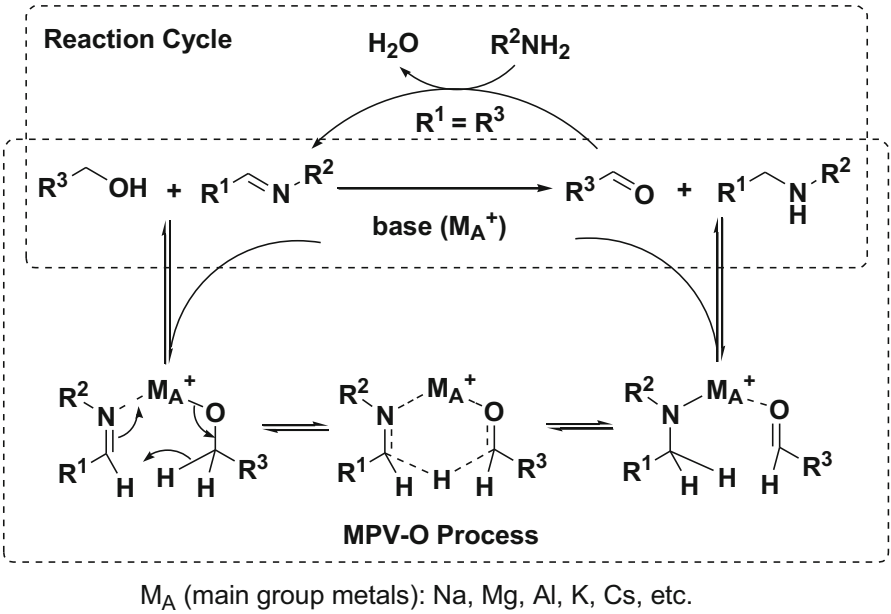
Since no alcohol oxidation was detected with Cu(I) salts under anaerobic conditions (Eq. 63), the authors proposed that the observed catalytic effect of Cu catalyst in anaerobic *N*-alkylation reactions might be attributed to the oxidation of alcohols by Cu(II) to give aldehydes and Cu(I) salts (Eqs. 62, 63), as Cu(II) has also been frequently used as an oxidant in organic reactions. As with the formation of [CuH] species, these authors pointed out that literature reports had indicated that generation of [CuH] species usually requires harsh conditions, such as using strong coordinating phosphine ligands and strong hydride-donating silanes under inert conditions, and that they are prone to be destroyed by molecular oxygen [193–195]. Therefore, the authors proposed a new mechanism for the Cu-catalyzed aerobic *N*-alkylation reactions under air (Scheme 38), in which the alcohol oxidation step is a slow step under inert conditions but a fast process under air. A similar Cu-catalyzed aerobic alkylation method can be extended to C-alkylation reactions of secondary alcohols and methyl ketones with primary alcohols [196].

In 2013, Sharma and co-workers reported another aerobic *N*-alkylation of anilines with benzylic, allylic, and primary and secondary aliphatic alcohols using a magnetite (Fe_3O_4) silica-based organic-inorganichybrid copper(II) nanocatalyst (Cu-AcTp@Am–Si-Fe_3O_4) (Eq. 64) [197]. Since Am–Si-Fe_3O_4 was used as the support for the active Cu catalysts, the Cu-AcTp@Am–Si-Fe_3O_4 catalyst can be readily recovered using a magnet for separation and reused at least ten times without obvious loss of catalytic activity. The authors also observed the promoting effect of air on the alkylation reaction. Thus, only trace product was observed under anaerobic conditions but a high yield of product could be obtained in reactions under air. Along with other findings, the authors proposed a mechanism following a preceding mechanism proposed for the air-promoted TM-catalyzed aerobic *N*-alkylation reactions (Fig. 2).

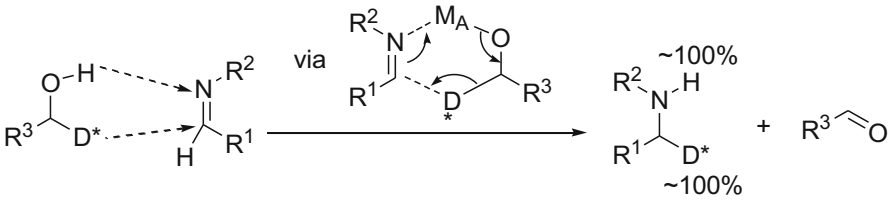


(64)

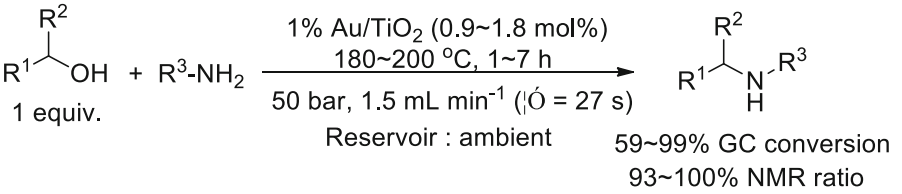
In 2012, Hellgardt, Hii, and coworkers achieved a base-free *N*-alkylation method for anilines, aliphatic and secondary amines and benzylic, aliphatic and secondary alcohols by using a heterogeneous Au/TiO_2 catalyst in a continuous flow reactor (Eq. 65) [198]. By employing the flow chemistry protocol, this provided not only a potentially greater reaction space, but also showed that higher reactivity and selectivity of the reactions can be achieved than using the batch reactors. In addition, the substrates in the reservoir can be stored readily under ambient conditions without the need for specialized inert atmosphere protection, making the method much simpler and more practical.



Scheme 39 Possible reaction mechanism for MPV-O *N*-alkylation reactions



Scheme 40 Deuterium labeling of MPV-O reactions



(65)

2.6 TM-Free *N*-Alkylation Reactions

TM-free *N*-alkylation reactions were first reported more than 100 years ago [4]. More reports with other methods appeared later [5–9], but these methods require rather harsh reaction conditions. Hence TM-catalyzed methods attracted much more attention and developed rapidly thereafter. It had previously been generally held that TM catalysts and dehydrogenative alcohol activation via formation of [MH]/[MH_2] species was indispensible in alcohol-based dehydrative alkylation reactions. The fact that TM-free catalysts can also be used in the same transformations seems to have been overlooked in recent decades.

2.6.1 Mechanistic Aspects of TM-Free N-Alkylation Reactions

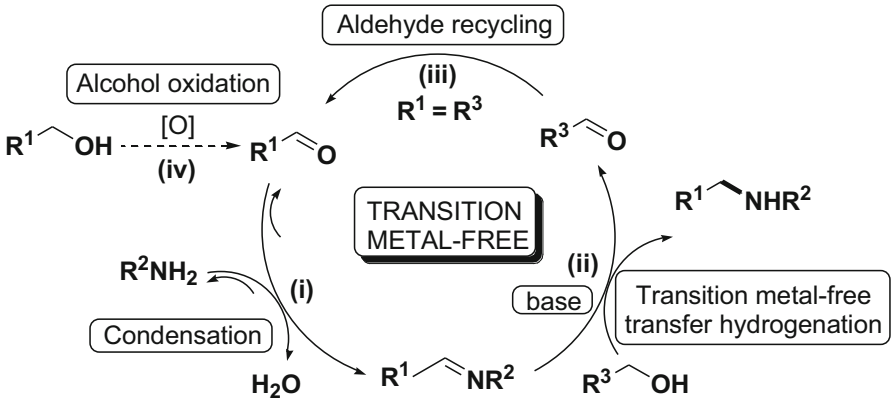
In TM-free *N*-alkylation reactions through hydrogen autotransfer processes, the key step of the reaction mechanism is the transfer hydrogenation of the imine intermediates by alcohols. The Meerwein-Pondorf-Verley reduction of carbonyl compounds by alcohols such as isopropanol, and the Oppenauer oxidation of alcohols by carbonyl compounds such as acetone, namely MPV-O redox reactions, are well known and are widely used for the preparation of given alcohols or carbonyl compounds. It is commonly accepted that MPV-O reactions proceed by hydrogen transfer from the alcohol to the carbonyl moiety via the key six-membered cyclic transition states [52, 53]. It was proposed that, analogous to these MPV-O reactions, transfer hydrogenation of imine intermediates by alcohols most likely proceed via similar MPV-O type six-membered cyclic transition states (Scheme 39, the lower MPV-O Process) [54], in which a key main group metal cation coordinates the imine and alchol moeties in close proximity, to accomplish a concerted hydrogen transfer from the alcohol to the imine C=N bond, affording the

alkylated amine product and the carbonyl byproduct. As shown in Scheme 39 (the upper Reaction Cycle), if byproduct R^3CHO can be recovered to condense with substrate amines as the alkyl source (R^1=R^3) to afford new imines, then a TM-free catalytic *N*-alkylation cycle via a hydrogen autotransfer process can be achieved. Consequently, it can be inferred that, if a deuterium-labeled alcohol is used as the hydrogen source (Scheme 40), both the β–C–D* and O–H of the alcohol can be transferred selectively to become β-C-D* and N–H in the product amine. This is also the same as with the direct hydrogen transfer (Scheme 6) and monohydride (Scheme 8) routes in TM-catalyzed reactions, so that it is difficult to distinguish between them using deuterium labeling methods.

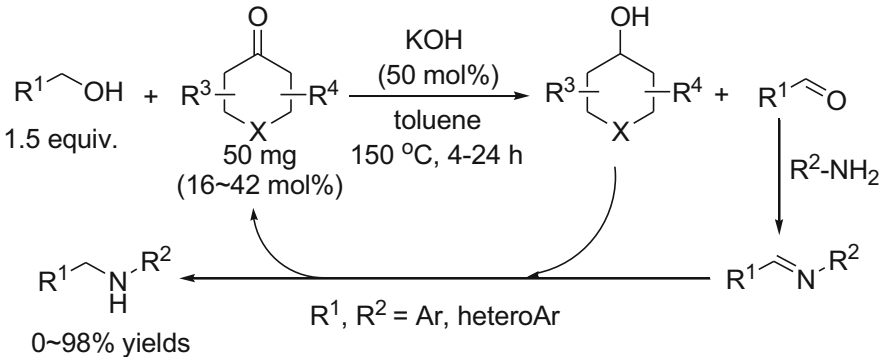
As in the alcohol activation step, like the TM-catalyzed direct hydrogen transfer route (Schemes 5, 14), the MPV-O process cannot provide carbonyl compounds directly according to the reaction mechanism (Scheme 39). This may make the alcohol activation reaction the rate-limiting step of the whole process. Most probably for this reason, the early TM-free *N*-alkylation reactions [4–9] were performed under harsh conditions to facilitate the initial formation of aldehydes by high temperature dehydrogenation of the alcohols. Otherwise, alternative ways for alcohol activation should be adopted (vide infra).

2.6.2 Recent Advances in TM-Free N-Alkylation Reactions

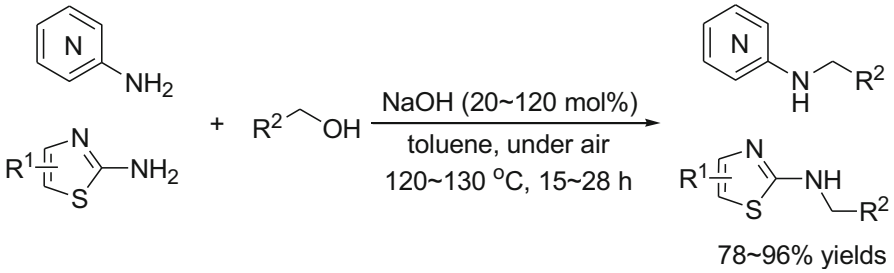
In 2013, based on their previous air-promoted TM-catalyzed aerobic *N*-alkylation reactions and the finding of aldehyde contaminant-accelerated reactions, Xu and co-workers further discovered that addition of external aldehydes can be a new way for alcohol activation. Thus, an efficient TM-free aldehyde-catalyzed *N*-alkylation reaction of sulfonamides, sulfinamides, anilines, heteroarylamines with benzylic and heterobenzylic alcohols was developed (Eq. 66) [54]. Since air does not affect the reactions, they could be performed readily in either air or inert atmosphere. The reactions are so efficient that they can be scaled up to at least 50 mmol scale.



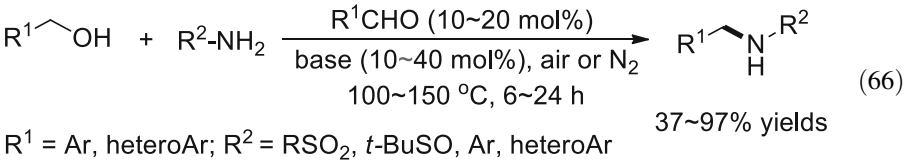
Scheme 41 Proposed mechanism for TM-free aldehyde-catalyzed *N*-alkylation reactions (TM-free relay race mechanism)



Scheme 42 Proposed mechanism for TM-free conjugated ketones-catalyzed *N*-alkylation reactions

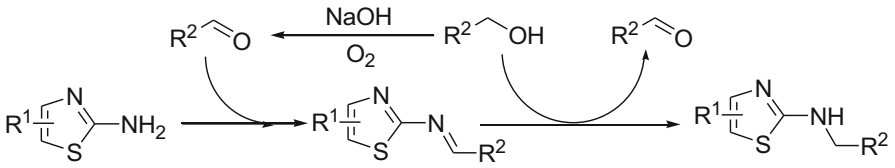


Scheme 43 NaOH-catalyzed *N*-alkylation reaction of heteroaryl amines with alcohols under air

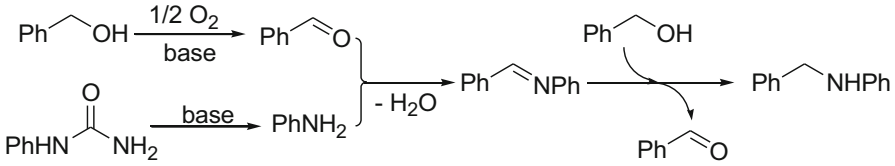


(66)

Since no reaction occurred at all in the absence of either the aldehyde catalyst or the base or both of them, as well as other proofs such as control reactions using high purity bases (>99.99 % purity), the authors concluded that the reaction is a true TM-free transformation. In addition to the aldehydes' catalytic effect, the authors proved that imine intermediates and other TM-free oxidants could also be employed to initiate the reaction, which is consistent with, and further supports, the TM-free *N*-alkylation mechanism (Scheme 39). Along with other results of mechanistic studies, the authors proposed a mechanism for the aldehyde-catalyzed *N*-alkylation reaction (Scheme 41). Firstly, the external aldehydes condense with amines/amides to give imine intermediates, which were then reduced by alcohols via a TM-free MPV-O transfer hydrogenation process to give product amines and regenerate byproduct aldehydes as the new alkyl source in next reaction cycle. In the key TM-free transfer



Scheme 44 Proposed mechanism for TM-free NaOH-catalyzed *N*-alkylation reactions

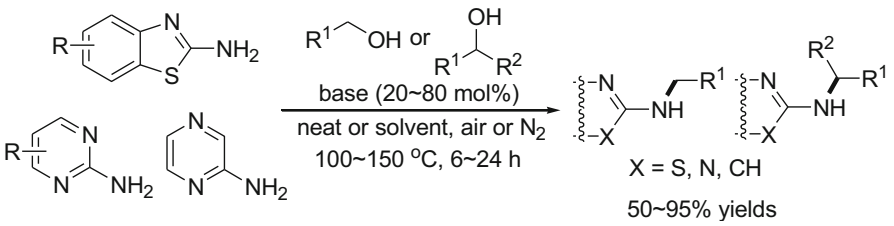


Scheme 45 Possible mechanism for base-mediated synthesis of amines from *N*-arylureas and alcohols under air

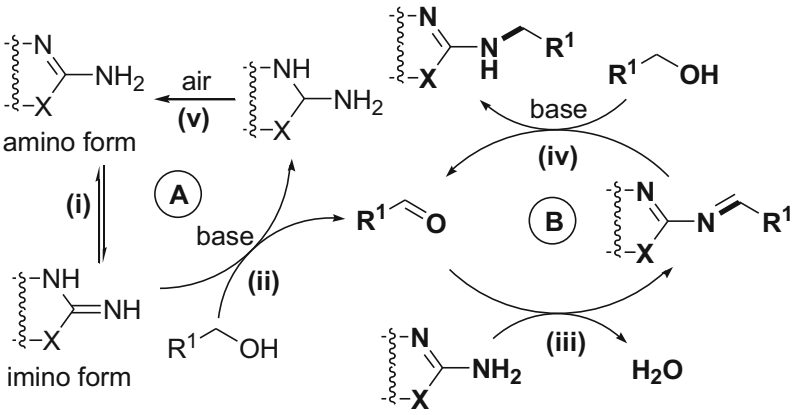
hydrogenation step, the existence of imine intermediates and generation of 1 equiv. of aldehyde to the product amine were clearly observed in ^{1}H NMR study of the reaction mixture, showing that aldehyde catalyst can be regenerated quantitatively in the process.

After discovering the catalytic activity of aldehydes, Xu and co-workers later extended the method to TM-free aldehyde-catalyzed C-alkylation of secondary alcohols with primary alcohols [199] and catalyst-free C-alkylation reactions of methyl ketones with alcohols [200]. In 2013, Wu and co-workers also reported a closely related TM-free ketone-initiated C-alkylation of indole and pyrrole with secondary alcohols [201]. Similarly, Shi and co-workers employed conjugated ketones to catalyze the TM-free *N*-alkylation reaction of amines with alcohols in 2015 (Scheme 42) [202], which is mainly suitable for benzylic and heterobenzylic alcohols, and anilines and heteroarylamines. Different ketones showed variant activities in the reaction (the catalysts were added in the same amount of 50 mg regardless of their molecular weights). In mechanistic studies such as the control reactions of the ketone catalyst and the substrate alcohol, up to 92 % ratio of the corresponding alcohol derived from reduction of the ketone catalyst can be detected in addition to formation of aldehdye intermediates derived from substrate alcohol.

In 2013, Adimurthy and co-workers reported a TM-free NaOH-catalyzed *N*-alkylation reaction of 2-aminothiazoles, 2-aminobenzothiazoles, aminopyrimidines, and aminopyridines with benzylic and heterobenzylic alcohols under air (Scheme 43) [203]. In condition optimization, the authors found the model reaction of 2-aminobenzothiazole and 4-chlorobenzylalcohol under air afforded a higher yield of the product (93 %) than the one under nitrogen (90 %). Therefore, along with other results of mechanistic studies and the authors' own previous work on based-catalyzed imine synthesis from alcohols and amines [204], they proposed that alcohol oxidation to aldehyde by air in the presence of bases is the initiation step of



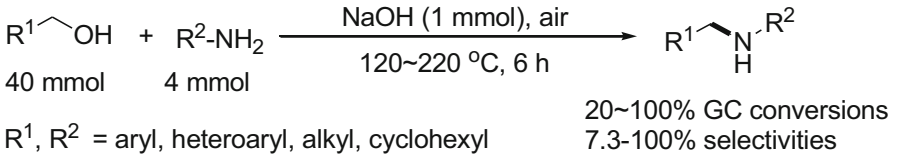
Scheme 46 Autocatalyzed *N*-alkylation of heteroaryl amines with primary and secondary alcohols



Scheme 47 Proposed mechanism for TM-free substrate heteroarylamine-autocatalyzed *N*-alkylation reactions

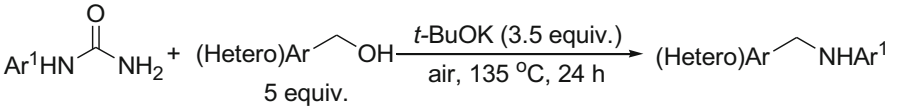
the *N*-alkylation reaction, followed by the condensation with amines and reduction of imine intermediate by the alcohol to give the final amine product (Scheme 44).

In 2014, Xia and co-workers also reported a base-catalyzed solvent-free *N*-alkylation of amines with alcohols under air (Eq. 67) [205]. Both aromatic and aliphatic amines and alcohols are suitable substrates. In this method, alcohols are used in large excess amounts (10 equiv.) as both the reactant and solvent, and some reactions have to be heated at high temperatures up to 220 °C. The authors also observed the significant accelerating effects of both aldehyde and imine on the reaction, concluding that they are actual intermediates of the reaction.



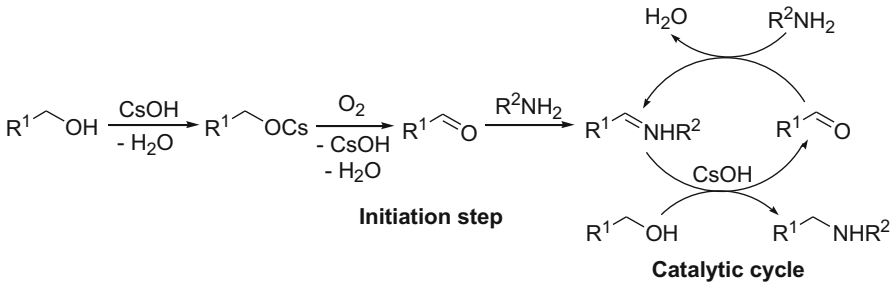
(67)

In the same year, Bhanage and co-workers reported a base-mediated synthesis of amines and imines from *N*-arylureas and benzylic alcohols or heteroaryl methanols under air (Eq. 68) [206]. The authors proposed base-mediated *N*-arylurea decomposition and aerobic alcohol oxidation processes for generation of the starting anilines and aldehydes, followed by condensation to imines and transfer hydrogenation by the alcohols to give the final amines (Scheme 45).

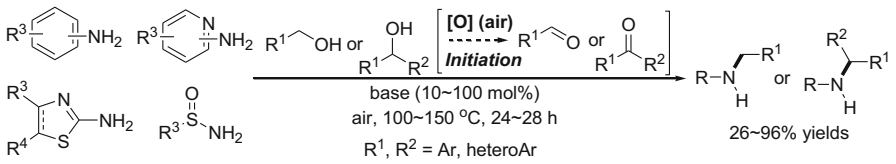


(68)

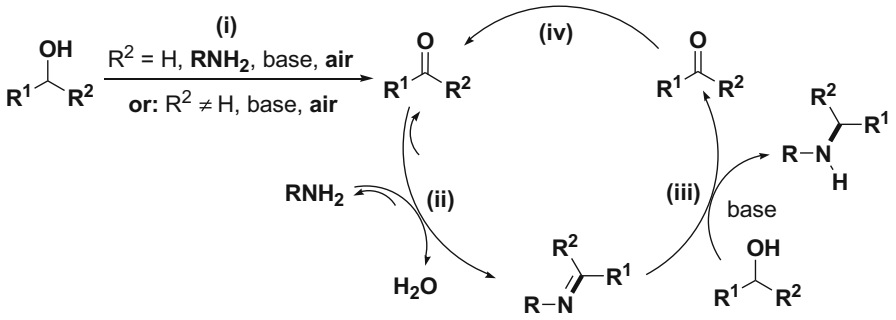
In 2015, Xu and co-workers reported a catalyst-free autocatalyzed *N*-alkylation of certain heteroaryl amines with primary and secondary alcohols (Scheme 46) [207]. Like methyl ketones in catalyst-free C-alkylation reactions [200], the authors hypothesized that certain amines with the typical $RC(=X)NH_2$ structural unit (X=O or N, etc.) may also undergo TM-free MPV-O reactions with alcohols to give the initiating aldehydes in the absence of external catalysts, which may further catalyze the target *N*-alkylation reaction. Indeed, 2-aminobenzothiazoles, 2-aminopyrimidines, and 2-aminopyrazine are active amines under critical catalyst-free conditions (pure aldehyde-free alcohol, strict degassing, and N_2 atmosphere protection). The model reaction of 2-aminobenzothiazole and benzyl alcohol gave a high 90 % yield of the product under the critical conditions; whereas the reaction under air slightly improved the product yield to 93 %, revealing that the autocatalyzed *N*-alkylation process



Scheme 48 Proposed mechanism for TM-free O_2-induced base-catalyzed *N*-alkylation reactions



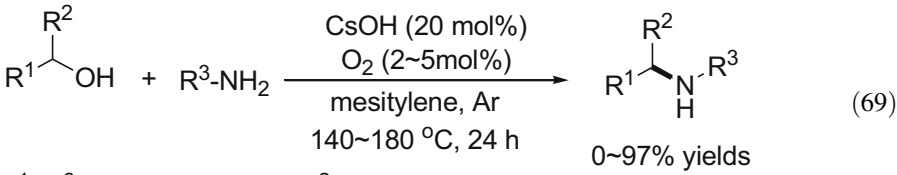
Scheme 49 TM-fee aerobic *N*-alkylation of anilines, certain heteroarylamines, and sulfinamides with alcohols under air



Scheme 50 Proposed mechanism for catalyst-free-like air-initiated *N*-alkylation reactions

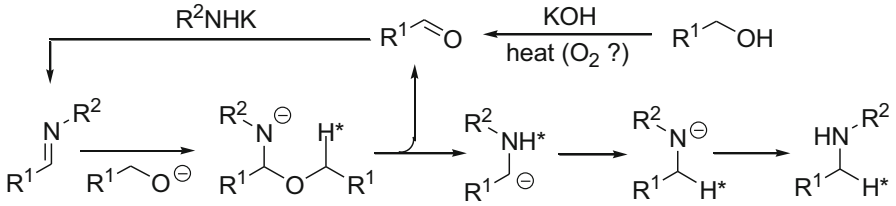
contributed to most of the product yield. Since base-mediated aerobic alcohol oxidation by air is not possible under the critical catalyst-free conditions, they concluded that tautomerization of the heteroarylamines and MPV-O reaction of the in situ formed imino tautomer with the alcohols led to the formation of the initiating aldehydes, which then resulted in efficient *N*-alkylation reactions (Scheme 47).

In 2015, Yao, Zhao, and co-workers reported a base-catalyzed *N*-alkylation of anilines and heteroarylamines with benzylic, heterobenzylic, aliphatic alcohols using catalytic amounts of O_2 as the initiator (Eq. 69) [208]. They found air or O_2 play important roles in the reactions because the reactions under O_2 or in open air led to formation of imines in high ratios. The authors further optimized the reaction conditions and found that adding 2–5 mol% O_2 to the reaction vessel was the best, giving high yields and selectivies of the product amines. Therefore, they proposed a mechanism for the *N*-alkylation reaction that was initiated by base-catalyzed aerobic alcohol oxidation by O_2 to the aldehydes (Scheme 48).



(69)

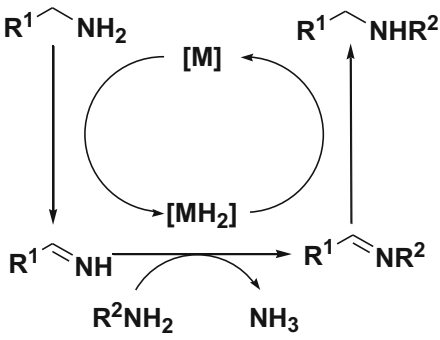
In 2016, Xu and coworker reported another TM-fee aerobic *N*-alkylation method for anilines, some heteroarylamines, and sulfinamides with alcohols (Scheme 49) [209]. As described in their work, these amines are not effective substrates under anaerobic catalyst-free autocatalyzed conditions, so an oxidant has to be employed to initiate the reaction. Differing from Yao and Zhao's protocol by adding O_2 to an argon atmosphere [208], they found that a catalytic amount of air is active enough to initiate the reaction. In addition to primary alcohols, secondary alcohols can also be used as the alkyl source. In mechanistic studies, the authors observed that primary and secondary alcohols underwent different initiation processes, i.e., primary alcohols require the presence of the amine to facilitate the aerobic oxidation to



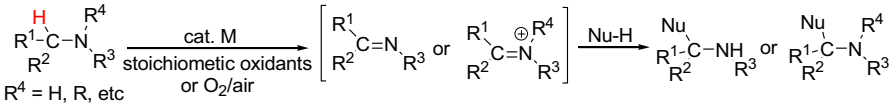
Scheme 51 Proposed mechanism for TM-free base-mediated *N*-alkylation reactions

aldehydes, while secondary alcohols can be transformed directly to ketones by air in the presence of a base (Scheme 50).

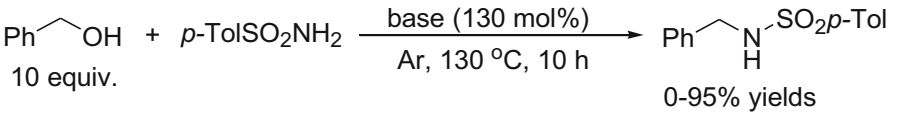
In 2015, Kang and coworkers reported another TM-free base-mediated *N*-alkylation reaction of sulfonamides and alcohols under argon (Eqs. 70, 71, 72) [210]. The authors found that the stronger base KOH is a better base for the reaction, and large excess alcohol was used as both reactant and solvent (Eq. 70); whereas, if corresponding basic salt potassium sulfonamides were employed instead, KOH can be used in catalytic amounts (Eq. 71). The reactions of anilines, heteroarylamines, and heterobenzylic and aliphatic alcohols also yielded corresponding alkylated amines efficiently in the presence of excess alcohols and 3 equiv. of base (Eq. 72). Since potassium sulfonamides were used as the reactant, and the reaction conditions are rather different (much stronger basicity) to previous aldehyde-catalyzed methods using only catalytic amounts of weak base K_2CO_3 [54], and no imine intermediates were detected in the present reactions, the authors excluded the possibility of an aldehyde-catalyzed mechanism and the MPV-O transfer hydrogenation process [52–54], and proposed a new mechanism (Scheme 51) involving the addition of potassium alcoholate to the imine intermediates to give hemiaminal intermediates. As to the initial aldehyde formation step, the authors proposed that oxidation of the alcohols by trace O_2 in the reaction systems might be a possible means of aldehyde generation [although alcohols with aldehyde contaminants (<0.1 %) were used, and trace amounts of H_2 were detected by GC in control reactions under the argon atmosphere as described in the work].



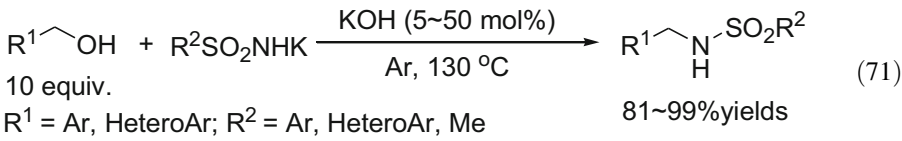
Scheme 52 General mechanism for amine-based hydrogen autotransfer reactions



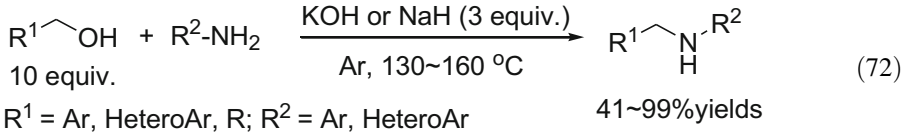
Scheme 53 General reaction routes for cross-dehydrogenative-coupling (CDC) reactions



(70)



(71)



(72)

3 Hydrogen Autotransfer *N*-Alkylation Reactions Using Amines as the Alkylating Reagents

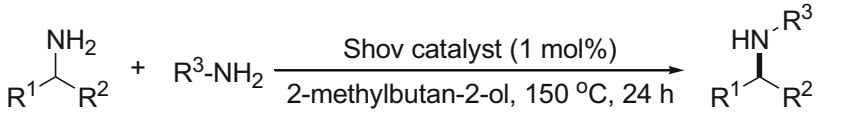
Like alcohols, amines could also be used as alkylating reagents to react with another amine to give *N*-alkylated amine products [10, 26], librating NH_3 as the byproduct instead of H_2O as in the case of alcohols. It is also held that amine activation proceeds via a hydrogen autotransfer process similar to that of alcohol activation. As shown in Scheme 52, the primary amine is first dehydrogenated, and then condenses with another amine to give different imine intermediates sequentially, which are reduced to give product amines. In addition to primary amines, secondary and tertiary amines could also be used as alkylating reagents.

It should be pointed out that this type of amine activation by anaerobic dehydrogenation resembles the cross-dehydrogenative-coupling (CDC) reactions [42, 43], in which the amine substrates, usually the secondary and tertiary amines, were also dehydrogenated/oxidized to give imines or iminium intermediates under oxidative conditions as the substrate activation protocol (Scheme 53). The difference is, in CDC reactions, no condensation/deamination reactions occur, and

the reaction proceeds via addition of nucleophiles, usually not an *N*-nucleophile, to give addition products.

Since the first homogeneous catalytic self-*N*-alkylation of amines reported by the groups of Laine and Concilio independently in the beginning of 1980s [211–213], more TM catalysts such as [Ru], [Ir], [Os], [Rh] and [Pt] have also been developed in the past two decades [10, 26]. More recently, effective cross-*N*-alkylation of two different amines, with low catalyst loadings, or those at lower temperatures were also reported.

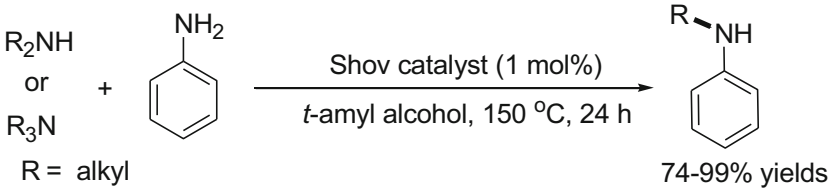
In 2007, Beller and co-workers described the first additive-free homogeneous *N*-alkylation of (hetero)aryl amines with aliphatic amines catalyzed by the Shvo complex with a low catalyst loading (1 mol%) (Eq. 73) [214]. The reactions of some challenging substrates, such as cyclic secondary amines, furan-, thiophene-, and indole-substituted amines, could also afford the corresponding products with good yields by this method.



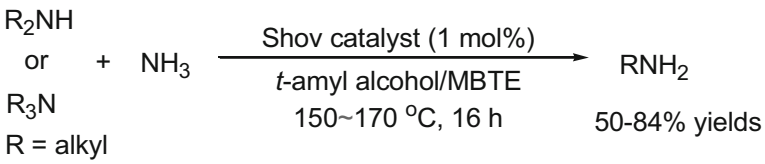
R^1 = Ar, alkyl; R^2 = H, alkyl; R^3 = aryl, heteroAr

(73)

In 2008, the Beller group extended the method to the *N*-alkylation of aryl amines with secondary amines and tertiary amines (Eq. 74) [215]. In the same year, they further applied the method to the *N*-alkylation of *tert*-alkylamines with aliphatic amines [216]. In 2011, the Beller group also reported the synthesis of primary amines by the reaction of secondary and tertiary amines with ammonia catalyzed by Shov catalyst (Eq. 75) [217].



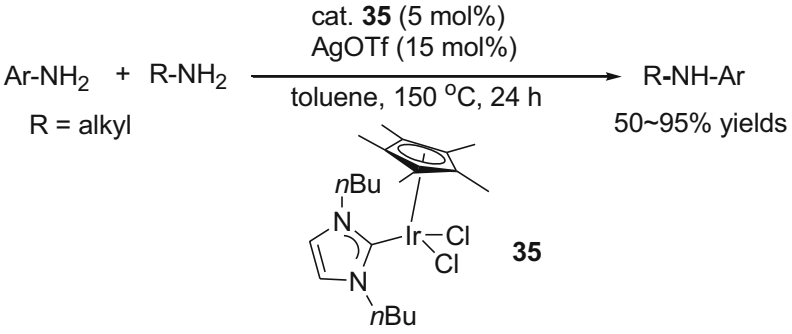
(74)



(75)

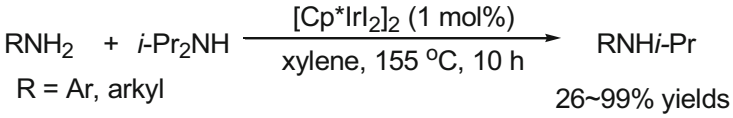
In 2008, Peris and coworkers developed an iridium complex (**35**)-catalyzed *N*-alkylation of anilines with alkyl amines (Eq. 76) [218]. The authors have previously

found that iridium complex **35** has similar activity with Shvo complex in the same year [219].



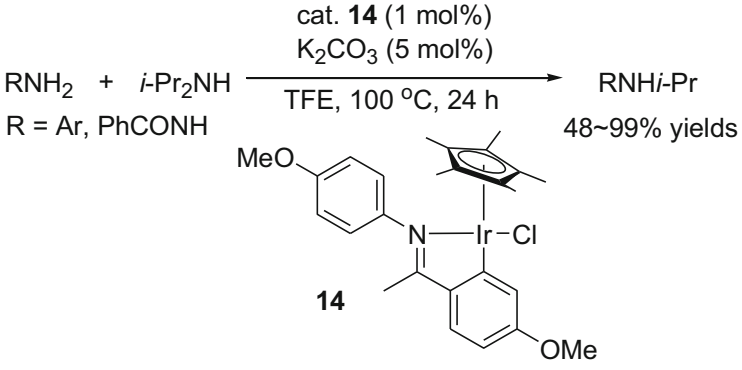
(76)

In 2009, Williams and co-workers described the $[Cp^*IrI_2]_2$-catalyzed *N*-alkylation of anilines, benzylic and aliphatic primary amines with diisopropylamine (Eq. 77) [220]. Although both substrate amines could be oxidized to give different imines and possibly different product amines, excellent selectivity could still be obtained. For example, the reaction of diisopropylamine and benzylamine gave exclusively *N*-isopropyl-*N*-benzylamine without any tertiary amine and dibenzylamine byproducts.



(77)

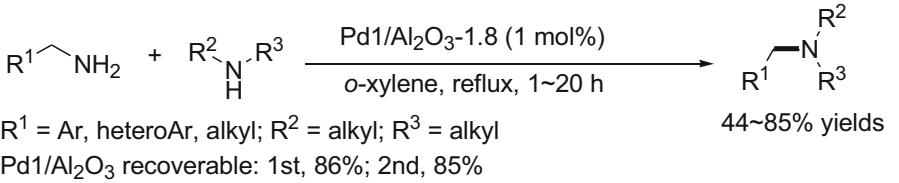
The aforementioned cyclometallated iridium complex **14** developed by Xiao and co-workers was also effective for *N*-alkylation of anilines and even benzohydrazide with diisopropylamine under mild conditions (Eq. 78) [113].



(78)

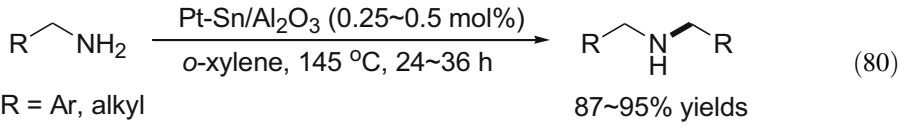
In addition to homogeneous TM catalysts, some heterogeneous TM catalysts, nano catalysts and even biomimetic and electrolytic catalysts have also been applied

successfully in the *N*-alkylation of amines using amines as the alkylating reagents. In 2011, Shimizu and co-workers reported a nano-Pd1/Al_2O_3-1.8-catalyzed cross-coupling of amines (Eq. 79) [221]. The recovered catalyst showed a very close catalytic activity with the fresh one (1st, 86 %, 2nd, 85 %). In the same year, Porcheddu and co-workers reported a microwave-assisted Pd/C-catalyzed *N*-alkylation of anilines with tertiary amines [222].



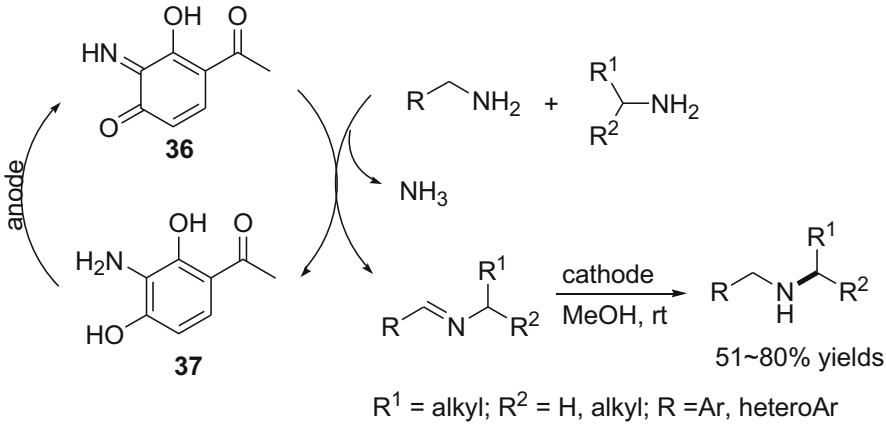
(79)

The aforementioned Pt–Sn/γ-Al_2O_3 catalyst developed by Yu and co-workers in 2011 was also effective for self-coupling of aliphatic primary amines with catalyst loading as low as 0.25 mol% (Eq. 80) [142]. In 2012, Shimizu and co-workers found nano-NaPt/SiO_2 and nano-SPt/SiO_2 are both effective catalysts for the *N*-alkylation of anilines, secondary and branched primary amines [223, 224]. In 2013, Shi and co-workers accidentally found that $NiCuFeO_x$ complex could catalyze the self-*N*-alkylation of primary amines [157].



(80)

In 2009, Largeron and co-workers reported a biomimetic electrolytic synthesis of secondary benzylic amines at room temperature (Scheme 54) [224]. An initial



Scheme 54 Proposed mechanism for biomimetic electrolytic synthesis of secondary amines

electrochemical oxidation of the benzylic amines by *o*-iminoquinone **36** and a subsequent condensation gave imine intermediates, which were then reduced to give the desired secondary amines along with the reoxidation of **37** to **36**.

4 Conclusion and Outlook

In summary, owing to their green and environmentally benign features, alcohols have been used widely as the alkylating reagents in the synthesis of amine and amide derivatives through dehydrogenative/oxidative activation to the more active carbonyl compounds and transfer of hydrogens to the products. Like alcohols, amines can also be used in a similar way as the alkylating reagents. This field developed rapidly in the past decades, being one of the hottest topics in the fields of organometallic catalysis, green chemistry, and even the pharmaceutical and industrial chemistry. More recently, in addition to TM-catalyzed anaerobic dehydrogenation methods, air-participated TM-catalyzed aerobic oxidative reactions using air-stable catalysts, nano and carbon materials, and biocatalysts have also been found to be new ways for alcohol activation and new catalysts. Some catalysts are so efficient that either bio-derived alcohols can be used as the alkylating reagents or the reactions can be performed under rather mild conditions at relatively lower temperatures (below 100 °C) or in an aqueous media. Meanwhile, new TM-free organocatalytic methods, including the use of aldehydes, substrate or external ketones, substrate amines, and the combination of air and base have also been developed as simple but efficient, economical and practical methods for *N*-alkylation of amines and amides with alcohols, and also represent meaningful advances to the early TM-free *N*-alkylation methods performed under harsh conditions [5–9]. Moreover, the recent development of asymmetric *N*-alkylation reactions for the successful synthesis of chiral amines and direct application of the *N*-alkylation method in pharmaceutical synthesis have also revealed the great potential of *N*-alkylation reactions. With the development of the new catalysts, new methods, and new protocols for alcohol activation, new concepts such as substrate-participated autocatalysis have also appeared in the field.

However, problems and bottlenecks still remain. Unlike the alcohols, new methods for using amines as alkylating reagents are still rare. This may be due to limited methods for amine activation. Like the newly developed aerobic oxidative activation of alcohols, advances in amines' cross-dehydrogenative coupling (CDC) reactions [42, 43] and amine oxidation reactions [226–229] may provide new possibilities for amine-based alkylation reactions. Besides, present mild and asymmetric reactions are still catalyzed by homogeneous metal complexes, so that developing efficient and recoverable heterogeneous methods would thus be another meaningful advance in the field. Moreover, most of the TM-free methods seemed to have limited scope for substrates, otherwise harsh conditions have to be applied. Therefore, developing new TM-free methods with relatively broad substrate scope and/or under mild reaction conditions remains a meaningful research topic in this field. Computational mechanistic studies of these TM-free reactions in order to acquire deeper insight and theoretical understanding of the reaction mechanism may

also help to develop new TM-free methods avoiding the use of expensive homogeneous catalysts and tedious preparation of heterogenous catalysts. In addition, mechanism elucidation in *N*-alkylation reactions by the hydrogen autotransfer processes remains a challenge, since: (1) there are mainly two mechanistic types in the reactions of amines/amides with alcohols (i.e., the direct nucleophilic substitution reactions and the hydrogen autotransfer processes), (2) there are at least four possible routes for hydrogen transfer from alcohols to products (direct hydrogen transfer, monohydride route, dihydride route, and MPV-O process), (3) similarities exist among the four routes of the hydrogen autotransfer reactions so that it is difficult to distinguish them as well as the reaction mechanism, and (4) mechanisms of specific reactions may vary depending on the substrates, catalysts, reaction conditions, even the settled conditions for mechanistic studies (e.g., in the sect. 2.1.3, the DFT studies of Ir-catalyzed *N*-alkylation reactions by different groups showed slightly different results). Mechanistic studies of the *N*-alkylation reaction are significant to this research also because they may afford new/deeper insights into the nature of the reactions, and provide new research opportunities and even conceptual and technical advances in the field. In a word, although there have been many meaningful advances in the field in recent decades, there still remains much room for improvement and extension of research. *N*-alkylation reactions by hydrogen autotransfer processes may have entered a new stage of development deserving of more attention and effort.

Acknowledgments We thank ZJNSF for Distinguished Young Scholars (LR14B020002), NNSFC (51502174), 580 Overseas Talents Program of Wenzhou, and Science and Technology Project of Shenzhen (JCYJ20150324141711616) for financial support.

References

1. Salvatore RN, Yoon CH, Jung KW (2001) Synthesis of secondary amines. Tetrahedron 57(37):7781–7785
2. Hofmann AW (1850) Researches regarding the molecular constitution of the volatile organic bases. Phil Trans R Soc Lond 140:93–141
3. McMurry J (2008) Organic chemistry, 7th edn. Thomson, Brooks/Cole, Boston
4. Nef JU (1901) Dissociationsvorgänge bei den einatomigen alkoholen, aethern und salzen. Liebigs Ann Chem 318(2–3):137–230
5. Lazier WA, Adkins H (1924) The alkylation of primary amines with aluminum alkoxides to give secondary amines free from tertiary amines. J Am Chem Soc 46(3):741–746
6. Sprinzak Y (1956) Reduction and benzylation by means of benzyl alcohol. II. *N*-benzylation. The preparation of secondary aromatic benzylamines. J Am Chem Soc 78(13):3207–3208
7. Miyano S (1965) Syntheses of *N*-(2-Pyridylmethyl)aniline and its derivatives. Chem Pharm Bull 13(9):1135–1137
8. Zvezdina EA, Pozharskii AF, Sokolov VI (1970) Imidazole derivatives containing potentially labile groupings attached to an *N*-atom. Chem Heterocycl Compd 6(3):389–391
9. Miyano S, Nakao M (1972) *N*-Alkylation of aromatic amines by means of alcohol. IV. Syntheses of *N*-alkylanilines and related compounds. Chem Pharm Bull 20(6):1328–1331
10. Guillena G, Ramón DJ, Yus M (2010) Hydrogen autotransfer in the *N*-alkylation of amines and related compounds using alcohols and amines as electrophiles. Chem Rev 110(3):1611–1641
11. Roundhill DM (1992) Transition metal and enzyme catalyzed reactions involving reactions with ammonia and amines. Chem Rev 92(1):1–27

12. Shimizu KI (2015) Heterogeneous catalysis for the direct synthesis of chemicals by borrowing hydrogen methodology. Catal Sci Technol 5(3):1412–1427
13. Grigg R, Mitchell TRB, Sutthivaiyakit S, Tongpenyai N (1981) Transition metal-catalysed *N*-alkylation of amines by alcohols. J Chem Soc, Chem Commun 12:611–612
14. Watanabe Y, Tsuji Y, Ohsugi Y (1981) The ruthenium catalyzed *N*-alkylation and *N*-heterocyclization of aniline using alcohols and aldehydes. Tetrahedron Lett 22(28):2667–2670
15. Murahashi S-I, Kondo K, Hakata T (1982) Ruthenium catalyzed synthesis of secondary or tertiary amines from amines and alcohols. Tetrahedron Lett 23(2):229–232
16. Muzart J (2005) Palladium-catalysed reactions of alcohols. Part B: formation of C-C and C-N bonds from unsaturated alcohols. Tetrahedron 61(17):4179–4212
17. Detz RJ, Hiemstra H, van Maarseveen JH (2009) Catalyzed propargylic substitution. Eur J Org Chem 36:6263–6276
18. Emer E, Sinisi R, Cozzi PG et al (2011) Direct nucleophilic SN1-type reactions of alcohols. Eur J Org Chem 4:647–666
19. Bandini M, Cera G, Chiarucci M (2012) Catalytic enantioselective alkylations with allylic alcohols. Synthesis 4:504–512
20. Chen L, Yin XP, Zhou J et al (2014) Catalytic functionalization of tertiary alcohols to fully substituted carbon centres. Org Biomol Chem 12(32):6033–6048
21. Plaut H, Ritter JJ (1951) A new reaction of nitriles. VI. Unsaturated amides1. J Am Chem Soc 73(9):4076–4077
22. Guérinot A, Reymond S, Cossy J (2012) Ritter reaction: recent catalytic developments. Eur J Org Chem 1:19–28
23. Hamid MHSE, Slatford P, Williams JMJ (2007) Borrowing hydrogen in the activation of alcohols. Adv Synth Catal 349(10):1555–1575
24. Nixon TD, Whittlesey MK, Williams JMJ (2009) Transition metal catalysed reactions of alcohols using borrowing hydrogen methodology. Dalton Trans 5:753–762
25. Watson AJA, Williams JMJ (2010) The give and take of alcohol activation. Science 329:635–636
26. Dobereiner GE, Crabtree RH (2010) Dehydrogenation as a substrate-activating strategy in homogeneous transition-metal catalysis. Chem Rev 110(2):681–703
27. Suzuki T (2011) Organic synthesis involving iridium-catalyzed oxidation. Chem Rev 111(3):1825–1845
28. Bähn S, Imm S, Beller M et al (2011) The catalytic amination of alcohols. ChemCatChem 3(12):1853–1864
29. Yang Q, Wang Q, Yu Z (2015) Substitution of alcohols by *N*-nucleophiles via transition metal-catalyzed dehydrogenation. Chem Soc Rev 44(8):2305–2329
30. Marr AC (2012) Organometallic hydrogen transfer and dehydrogenation catalysts for the conversion of bio-renewable alcohols. Catal Sci Technol 2(2):279–287
31. Hollmann D (2014) Advances in asymmetric borrowing hydrogen catalysis. ChemSusChem 7(9):2411–2413
32. Leonard J, Blacker AJ, Marsden SP et al (2015) A survey of the borrowing hydrogen approach to the synthesis of some pharmaceutically relevant intermediates. Org Pro Res Deve 19(10):1400–1410
33. K-I Fujita, Yamaguchi R (2005) Cp*Ir complex-catalyzed hydrogen transfer reactions directed toward environmentally benign organic synthesis. Synlett 4:560–571
34. Yamaguchi R, K-I Fujita, Zhu M (2010) Recent progress of new catalytic synthetic methods for nitrogen heterocycles based on hydrogen transfer reactions. Heterocycles 81(5):1093–1140
35. Xu Q, Li Q (2013) Recent advances of transition metal-catalyzed aerobic dehydrative reactions of alcohols and amines and related researches. Chin J Org Chem 33(1):18–35
36. Sheldon RA, Arends IW, Dijksman A et al (2002) Green, catalytic oxidations of alcohols. Acc Chem Res 35(9):774–781
37. Hashmi ASK (2007) Gold-catalyzed organic reactions. Chem Rev 107(7):3180–3211
38. Naota T, Takaya H, Murahashi SI (1998) Ruthenium-catalyzed reactions for organic synthesis. Chem Rev 98(7):2599–2660
39. Sigman MS, Jensen DR (2006) Ligand-modulated palladium-catalyzed aerobic alcohol oxidations. Acc Chem Res 39(3):221–229
40. Stahl SS (2004) Palladium oxidase catalysis: selective oxidation of organic chemicals by direct dioxygen-coupled turnover. Angew Chem Int Ed 43(26):3400–3420

41. Zhan BZ, Thompson A (2004) Recent developments in the aerobic oxidation of alcohols. Tetrahedron 60(13):2917–2935
42. Li CJ (2008) Cross-dehydrogenative coupling (CDC): exploring C–C bond formations beyond functional group transformations. Acc Chem Res 42(2):335–344
43. Scheuermann CJ (2010) Beyond traditional cross couplings: the scope of the cross dehydrogenative coupling reaction. Chem Asian J 5(3):436–451
44. Blackburn L, Taylor RJK (2001) In situ oxidation-imine formation-reduction routes from alcohols to amines. Org Lett 3(11):1637–1639
45. Guérin C, Bellosta V, Cossy J et al (2011) Mild nonepimerizing *N*-alkylation of amines by alcohols without transition metals. Org Lett 13(13):3534–3537
46. Zassinovich G, Mestroni G, Gladiali S (1992) Asymmetric hydrogen transfer reactions promoted by homogeneous transition metal catalysts. Chem Rev 92(5):1051–1069
47. Palmer MJ, Wills M (1999) Asymmetric transfer hydrogenation of C=O and C=N bonds. Tetrahedron Asymmetry 10(11):2045–2061
48. Gladiali S, Alberico E (2006) Asymmetric transfer hydrogenation: chiral ligands and applications. Chem Soc Rev 35(3):226–236
49. Bäckvall JE (2002) Transition metal hydrides as active intermediates in hydrogen transfer reactions. J Organomet Chem 652(1):105–111
50. Samec JS, Bäckvall JE, Andersson PG et al (2006) Mechanistic aspects of transition metal-catalyzed hydrogen transfer reactions. Chem Soc Rev 35(3):237–248
51. Muzart J (2015) Pd-Catalyzed Hydrogen-Transfer Reactions from Alcohols to C=C, C=O, and C=N Bonds. Eur J Org Chem 2015(26):5693–5707
52. Cha JS (2006) Recent developments in Meerwein-Ponndorf-Verley and related reactions for the reduction of organic functional groups using aluminum, boron, and other metal reagents: a review. Org Pro Res Deve 10(5):1032–1053
53. De Graauw CF, Peters JA, Huskens J et al (1994) Meerwein-Ponndorf-Verley reductions and Oppenauer oxidations: an integrated approach. Synthesis 10:1007–1017
54. Xu Q, Li Q, Zhu X et al (2013) Green and scalable aldehyde-catalyzed transition metal-free dehydrative *N*-alkylation of amides and amines with alcohols. Adv Syn Catal 355(1):73–80
55. Crabtree RH (2011) An organometallic future in green and energy chemistry? Organometallics 30(1):17–19
56. Gunanathan C, Ben-David Y, Milstein D (2007) Direct synthesis of amides from alcohols and amines with liberation of H_2. Science 317(5839):790–792
57. Balcells D, Crabtree RH, Eisenstein O et al (2008) Mechanism of homogeneous iridium-catalyzed alkylation of amines with alcohols from a DFT study. Organometallics 27(11):2529–2535
58. Fristrup P, Tursky M, Madsen R (2012) Mechanistic investigation of the iridium-catalysed alkylation of amines with alcohols. Org Biomol Chem 10(13):2569–2577
59. Zhao G-M, Liu H-L, Huang X-R et al (2015) Mechanistic study on the Cp* iridium-catalyzed *N*-alkylation of amines with alcohols. RSC Adv 5(29):22996–23008
60. Bartoszewicz A, González Miera G, Martín-Matute B et al (2015) Mechanistic studies on the alkylation of amines with alcohols catalyzed by a bifunctional iridium complex. ACS Catal 5(6):3704–3716
61. Nova A, Crabtree RH, Eisenstein O et al (2010) An experimental-theoretical study of the factors that affect the switch between ruthenium-catalyzed dehydrogenative amide formation versus amine alkylation. Organometallics 29(23):6548–6558
62. Zhao G-M, Liu H-L, Huang X-R et al (2014) DFT study on mechanism of *N*-alkylation of amino derivatives with primary alcohols catalyzed by copper(II) acetate. ACS Catal 4(7):2231–2240
63. Zhao G-M, Liu H-L, Huang X-R et al (2015) DFT study on the homogeneous palladium-catalyzed *N*-alkylation of amines with alcohols. ACS Catal 5(10):5728–5740
64. Hamid MHSA, Williams JMJ (2007) Ruthenium-catalysed synthesis of tertiary amines from alcohols. Tetrahedron Lett 48(47):8263–8265
65. Hamid MHSA, Allen CL, Williams JMJ et al (2009) Ruthenium-catalyzed *N*-alkylation of amines and sulfonamides using borrowing hydrogen methodology. J Am Chem Soc 131(5):1766–1774
66. Watson AJ, Maxwell AC, Williams JM (2011) Borrowing hydrogen methodology for amine synthesis under solvent-free microwave conditions. J Org Chem 76(7):2328–2331
67. Ma WMJ, James TD, Williams JMJ (2013) Synthesis of amines with pendant boronic Esters by borrowing hydrogen catalysis. Org Lett 15(18):4850–4853

68. Tillack A, Hollmann D, Beller M et al (2006) A novel ruthenium-catalyzed amination of primary and secondary alcohols. Tetrahedron Lett 47(50):8881–8885
69. Hollmann D, Tillack A, Beller M et al (2007) An improved ruthenium catalyst for the environmentally benign amination of primary and secondary alcohols. Chem-Asian J 2(3):403–410
70. Tillack A, Hollmann D, Beller M et al (2008) Salt-free synthesis of tertiary amines by ruthenium-catalyzed amination of alcohols. Eur J Org Chem 28:4745–4750
71. Imm S, Bahn S, Beller M et al (2010) An efficient and general synthesis of primary amines by ruthenium-catalyzed amination of secondary alcohols with ammonia. Angew Chem Int Ed 49(44):8126–8129
72. Pingen D, Muller C, Vogt D (2010) Direct amination of secondary alcohols using ammonia. Angew Chem Int Ed 49(44):8130–8133
73. Gunanathan C, Milstein D (2008) Selective synthesis of primary amines directly from alcohols and ammonia. Angew Chem Int Ed 47(45):8661–8664
74. Ye X, Plessow PN, Hofmann P (2014) Alcohol amination with ammonia catalyzed by an acridine-based ruthenium pincer complex: a mechanistic study. J Am Chem Soc 136(16):5923–5929
75. Pingen D, Vogt D (2014) Amino-alcohol cyclization: selective synthesis of lactams and cyclic amines from amino-alcohols. Catal Sci Technol 4(1):47–52
76. Bahn S, Williams JMJ, Beller M (2010) Selective ruthenium-catalyzed *N*-alkylation of indoles by using alcohols. Chem-Eur J 16(12):3590–3593
77. Whitney S, Grigg R, Keep A (2007) [Cp* $IrCl_2]_2$-catalyzed indirect functionalization of alcohols: novel strategies for the synthesis of substituted indoles. Org Lett 9(17):3299–3302
78. Zhang M, Imm S, Beller M et al (2011) Synthesis of alpha-amino acid amides: ruthenium-catalyzed amination of alpha-hydroxy amides. Angew Chem Int Ed 50(47):11197–11201
79. Imm S, Bahn S, Beller M et al (2011) Improved ruthenium-catalyzed amination of alcohols with ammonia: synthesis of diamines and amino esters. Angew Chem Int Ed 50(33):7599–7603
80. Baumann W, Spannenberg A, Deutsch J (2013) Utilization of common ligands for the ruthenium-catalyzed amination of alcohols. Chem-Eur J 19(52):17702–17706
81. Pingen D, Lutz M, Vogt D (2014) Mechanistic study on the ruthenium-catalyzed direct amination of alcohols. Organometallics 33(7):1623–1629
82. Pingen D, Lebl T, Vogt D et al (2014) Catalytic activity and fluxional behavior of complexes based on $RuHCl(CO)(PPh_3)_3$ and Xantphos-type ligands. Organometallics 33(11):2798–2805
83. Agrawal S, Lenormand M, Martín-Matute B (2012) Selective alkylation of (hetero)aromatic amines with alcohols catalyzed by a ruthenium pincer complex. Org Lett 14(6):1456–1459
84. Chen M, Zhang M, Jiang H et al (2014) Ruthenium-catalyzed *N*-alkylation for the synthesis of 2-*N*-pyridylmethyl benzonitriles and an exploration of its synthetic utility. ChemCatChem 6(10):2993–2997
85. Enyong AB, Moasser B (2014) Ruthenium-catalyzed *N*-alkylation of amines with alcohols under mild conditions using the borrowing hydrogen methodology. J Org Chem 79(16):7553–7563
86. Jumde VR, Gonsalvi L, Taddei M et al (2015) A ruthenium-based catalytic system for a mild borrowing-hydrogen process Eur J Org Chem 2015(8):1829–1833
87. Feng C, Deng G, Li C-J et al (2010) Ruthenium-catalyzed tertiary amine formation from nitroarenes and alcohols. Org Lett 12(21):4888–4891
88. Cui X, Shi F, Deng Y et al (2011) Ruthenium-catalyzed nitro and nitrile compounds coupling with alcohols: alternative route for *N*-substituted amine synthesis. Chem-Eur J 17(9):2587–2591
89. Liu S, Chen R, Deng GJ (2011) Ruthenium-catalyzed formation of tertiary amines from nitriles and alcohols. Chem Lett 40(5):489–491
90. Werkmeister S, Bornschein C, Beller M et al (2013) Ruthenium-catalyzed transfer hydrogenation of nitriles: reduction and subsequent *N*-monoalkylation to secondary amines. Eur J Org Chem 18:3671–3674
91. Wang N, Zou X, Li F et al (2014) The direct synthesis of *N*-alkylated amides via a tandem hydration/*N*-alkylation reaction from nitriles, aldoximes and alcohols. Chem Commun 50(61):8303–8305
92. Kang B, Fu Z, Hong SH (2013) Ruthenium-catalyzed redox-neutral and single-step amide synthesis from alcohol and nitrile with complete atom economy. J Am Chem Soc 135(32):11704–11707
93. Kim J, Hong SH (2014) Synthesis of cyclic imides from nitriles and diols using hydrogen transfer as a substrate-activating strategy. Org Lett 16(17):4404–4407

94. Sundararaju B, Tang Z, Bruneau C et al (2010) Ruthenium-catalyzed cascade *N*- and C(3)-di-alkylation of cyclic amines with alcohols involving hydrogen autotransfer processes. Adv Synth Catal 352(18):3141–3146
95. Yuan K, Jiang F, Bruneau C et al (2012) Iridium-catalyzed oxidant-free dehydrogenative C-H bond functionalization: selective preparation of *N*-arylpiperidines through tandem hydrogen transfers. Angew Chem Int Ed 51(35):8876–8880
96. Yamaguchi R, Kawagoe S, K-I Fujita et al (2008) Selective synthesis of secondary and tertiary amines by Cp*iridium-catalyzed multialkylation of ammonium salts with alcohols. Org Lett 10(2):181–184
97. K-I Fujita, Yamaguchi R, Mingwen Z et al (2009) A new atom-economical and selective synthesis of secondary and tertiary alkylamines by means of Cp*iridium complex catalyzed multiple *N*-alkylation of ammonium salts with alcohols without solvent. Synthesis 2009(07):1220–1223
98. K-I Fujita, Komatsubara A, Yamaguchi R (2009) *N*-alkylation of carbamates and amides with alcohols catalyzed by a Cp*Ir complex. Tetrahedron 65(18):3624–3628
99. Zhu M, K-I Fujita, Yamaguchi R (2010) Simple and versatile catalytic system for *N*-alkylation of sulfonamides with various alcohols. Org Lett 12(6):1336–1339
100. Apsunde T, Trudell M (2014) Solvent-free, base-free microwave-mediated iridium-catalyzed *N*-alkylation of amides with alcohols. Synthesis 46(02):230–234
101. Lu L, Ma J, Li F et al (2015) Effective recognition of different types of amino groups: from aminobenzenesulfonamides to amino-(*N*-alkyl)benzenesulfonamides via iridium-catalyzed *N*-alkylation with alcohols. Org Lett 17(10):2350–2353
102. Li F, Shan H, Chen L (2012) Direct *N*-alkylation of amino-azoles with alcohols catalyzed by an iridium complex/base system. Chem Commun 48(4):603–605
103. Li F, Kang Q (2012) Shan H (2012) Regioselective *N*-alkylation of 2-aminoimidazoles with alcohols to 2-(*N*-alkylamino)imidazoles catalyzed by the $[Cp^*IrCl_2]_2/K_2CO_3$ System. Eur J Org Chem 26:5085–5092
104. Li F, Chen L, Kang Q (2013) Regioselective *N*-alkylation with alcohols for the preparation of 2-(*N*-alkylamino)quinazolines and 2-(*N*-alkylamino)pyrimidines. New J Chem 37(3):624–631
105. Berliner MA, Dubant SPA, Makowski T (2011) Use of an iridium-catalyzed redox-neutral alcohol-amine coupling on kilogram scale for the synthesis of a GlyT1 inhibitor. Org Proc Res Deve 15(5):1052–1062
106. Cumpstey I, Agrawal S, Martín-Matute B et al (2011) Iridium-catalysed condensation of alcohols and amines as a method for aminosugar synthesis. Chem Commun 47(27):7827–7829
107. Liu S, Stephens G, Marr AC et al (2009) Adding value to renewables: a one pot process combining microbial cells and hydrogen transfer catalysis to utilise waste glycerol from biodiesel production. Chem Commun 45(17):2308–2310
108. Lacroix SD, Pennycook A, Marr AC et al (2012) Amination and dehydration of 1,3-propanediol by hydrogen transfer: reactions of a bio-renewable platform chemical. Catal Sci Technol 2(2):288–290
109. Bhat S, Sridharan V (2012) Iridium catalysed chemoselective alkylation of 2′-aminoacetophenone with primary benzyl type alcohols under microwave conditions. Chem Commun 48(39):4701–4703
110. Blank B, Michlik S, Kempe R (2009) Selective iridium-catalyzed alkylation of (hetero)aromatic amines and diamines with alcohols under mild reaction conditions. Chem-Eur J 15(15):3790–3799
111. Michlik S, Kempe R (2010) New iridium catalysts for the efficient alkylation of anilines by alcohols under mild conditions. Chem-Eur J 16(44):13193–13198
112. Michlik S, Hille T, Kempe R (2012) The iridium-catalyzed synthesis of symmetrically and unsymmetrically alkylated diamines under mild reaction conditions. Adv Synth Catal 354(5):847–862
113. Zou Q, Wang C, Xiao J et al (2015) Alkylation of amines with alcohols and amines by a single catalyst under mild conditions. Chem-Eur J 21(27):9656–9661
114. Li JQ, Andersson PG (2013) Room temperature and solvent-free iridium-catalyzed selective alkylation of anilines with alcohols. Chem Commun 49(55):6131–6133
115. Saidi O, Blacker AJ, Williams JMJ (2010) Borrowing hydrogen in water and ionic liquids: iridium-catalyzed alkylation of amines with alcohols. Org Proc Res Deve 14(4):1046–1049
116. Kawahara R, K-I Fujita, Yamaguchi R (2010) Multialkylation of aqueous ammonia with alcohols catalyzed by water-soluble Cp*Ir-ammine complexes. J Am Chem Soc 132(43):15108–15111
117. Lorentz-Petersen LLR, Nordstrøm LU (2012) Madsen R (2012) Iridium-catalyzed condensation of amines and vicinal diols to substituted piperazines. Eur J Org Chem 34:6752–6759

118. Trudell M, Apsunde T (2013) Microwave-assisted iridium-catalyzed synthesis of nicotine and anabasine derivatives. Synthesis 45(15):2120–2124
119. Qu P, Sun C, Li F et al (2014) The *N*-alkylation of sulfonamides with alcohols in water catalyzed by the water-soluble iridium complex {Cp*Ir[6,6′-$(OH)_2$bpy](H_2O)}$[OTf]_2$. Adv Synth Catal 356(2–3):447–459
120. Ramón D, Martínez-Asencio A, Yus M (2011) Palladium(II) acetate as catalyst for the *N*-alkylation of aromatic amines, sulfonamides, and related nitrogenated compounds with alcohols by a hydrogen autotransfer process. Synthesis 22:3730–3740
121. Dang TT, Ramalingam B, Seayad AM et al (2013) An efficient palladium-catalyzed *N*-alkylation of amines using primary and secondary alcohols. ACS Catal 3(11):2536–2540
122. Bertoli M, Choualeb A, Gusev DG et al (2011) PNP pincer osmium polyhydrides for catalytic dehydrogenation of primary alcohols. Dalton Trans 40(35):8941–8949
123. Abdukader A, Jin H, Zhu C et al (2014) Rhenium-catalyzed amination of alcohols by hydrogen transfer process. Tetrahedron Lett 55(30):4172–4174
124. Yang H, Mao R, Cheng G et al (2014) An efficient homogeneous gold(I) catalyst for *N*-alkylation of amines with alcohols by hydrogen autotransfer. Tetrahedron 70(46):8829–8835
125. Martínez-Asencio A, Ramón DJ, Yus M (2010) *N*-Alkylation of poor nucleophilic amine and sulfonamide derivatives with alcohols by a hydrogen autotransfer process catalyzed by copper(II) acetate. Tetrahedron Lett 51(2):325–327
126. Martínez-Asencio A, Ramón DJ, Yus M (2011) *N*-alkylation of poor nucleophilic amines and derivatives with alcohols by a hydrogen autotransfer process catalyzed by copper(II) acetate: scope and mechanistic considerations. Tetrahedron 67(17):3140–3149
127. Li F, Shan H, Kang Q et al (2011) Regioselective *N*-alkylation of 2-aminobenzothiazoles with benzylic alcohols. Chem Commun 47(17):5058–5060
128. Cui X, Shi F, Deng Y et al (2010) Fe(II)-catalyzed *N*-alkylation of sulfonamides with benzylic alcohols. Tetrahedron Lett 51(15):2048–2051
129. Bala M, Verma PK, Singh B (2013) Iron phthalocyanine as an efficient and versatile catalyst for *N*-alkylation of heterocyclic amines with alcohols: one-pot synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazoles. Green Chem 15(6):1687–1693
130. Yan T, Feringa BL, Barta K (2014) Iron catalysed direct alkylation of amines with alcohols. Nat Commun 5:5602. doi:10.1038/ncomms6602
131. Pan H-J, Ng TW, Zhao Y (2015) Iron-catalyzed amination of alcohols assisted by Lewis acid. Chem Commun 51(59):11907–11910
132. Rawlings AJ, Diorazio LJ, Wills M (2015) C–N bond formation between alcohols and amines using an iron cyclopentadienone catalyst. Org Lett 17(5):1086–1089
133. Rösler S, Ertl M, Kempe R et al (2015) Cobalt-catalyzed alkylation of aromatic amines by alcohols. Angew Chem Inl Ed 54(50):15046–15050
134. Zhang G, Yin Z, Zheng S (2016) Cobalt-catalyzed *N*-alkylation of amines with alcohols. Org Lett 18(2):300–303
135. Kim JW, Yamaguchi K, Mizuno N (2009) Heterogeneously catalyzed selective *N*-alkylation of aromatic and heteroaromatic amines with alcohols by a supported ruthenium hydroxide. J Catal 263(1):205–208
136. He J, Kim JW, Mizuno N et al (2009) Efficient catalytic synthesis of tertiary and secondary amines from alcohols and urea. Angew Chem Int Ed 48(52):9888–9891
137. Yamaguchi K, He J, Mizuno N et al (2010) The "borrowing hydrogen strategy" by supported ruthenium hydroxide catalysts: synthetic scope of symmetrically and unsymmetrically substituted amines. Chem-Eur J 16(24):7199–7207
138. Martínez R, Ramón DJ, Yus M (2009) Selective *N*-monoalkylation of aromatic amines with benzylic alcohols by a hydrogen autotransfer process catalyzed by unmodified magnetite. Org Biomol Chem 7(10):2176–2181
139. Cano R, Ramón DJ, Yus M (2011) Impregnated ruthenium on magnetite as a recyclable catalyst for the N-alkylation of amines, sulfonamides, sulfinamides, and nitroarenes using alcohols as electrophiles by a hydrogen autotransfer process. J Org Chem 76(14):5547–5557
140. Pei Shan S, Seayad AM, Ramalingam B et al (2014) Reusable supported ruthenium catalysts for the alkylation of amines by using primary alcohols. ChemCatChem 6(3):808–814
141. Wang D, Gao Z-W, Hou X-F et al (2013) An efficient and recyclable catalyst for *N*-alkylation of amines and β-alkylation of secondary alcohols with primary alcohols: SBA-15 supported *N*-heterocyclic carbene iridium complex. Adv Synth Catal 355(6):1117–1125

142. He W, Wang L, Yu Z et al (2011) Pt-Sn/γ-Al_2O_3-catalyzed highly efficient direct synthesis of secondary and tertiary amines and imines. Chem-Eur J 17(47):13308–13317
143. Wang L, He W, Yu Z et al (2011) Heterogeneous bimetallic Pt–Sn/γ-Al_2O_3 catalyzed direct synthesis of diamines from *N*-alkylation of amines with diols through a borrowing hydrogen strategy. Tetrahedron Lett 52(52):7103–7107
144. Zhang Y, Shi F, Deng Y et al (2011) Palladium catalyzed *N*-alkylation of amines with alcohols. Tetrahedron Lett 52(12):1334–1338
145. Ousmane M, Perrussel G, Pera-Titus M et al (2014) Highly selective direct amination of primary alcohols over a Pd/K-OMS-2 catalyst. J Catal 309:439–452
146. Dang TT, Ramalingam B, Seayad AM et al (2015) An efficient heterogenized palladium catalyst for *N*-alkylation of amines and alpha-alkylation of ketones using alcohols. RSC Adv 5(53):42399–42406
147. He L, Cao Y, Fan KN et al (2010) Efficient and clean gold-catalyzed one-pot selective *N*-alkylation of amines with alcohols. Chem-Eur J 16(47):13965–13969
148. Tang CH, Cao Y, Fan KN et al (2011) Direct one-pot reductive *N*-alkylation of nitroarenes by using alcohols with supported gold catalysts. Chem-Eur J 17(26):7172–7177
149. He L, Fan KN, Cao Y et al (2012) Highly efficient heterogeneous gold-catalyzed direct synthesis of tertiary and secondary amines from alcohols and urea. ChemSusChem 5(4):621–624
150. Shimizu K, Nishimura M, Satsuma A (2009) γ-Alumina-supported silver cluster for *N*-benzylation of anilines with alcohols. ChemCatChem 1(4):497–503
151. Liu H, Chuah G-K, Jaenicke S (2012) *N*-alkylation of amines with alcohols over alumina-entrapped Ag catalysts using the "borrowing hydrogen" methodology. J Catal 292:130–137
152. Cui X, Shi F, Deng Y et al (2011) Organic ligand-free alkylation of amines, carboxamides, sulfonamides, and ketones by using alcohols catalyzed by heterogeneous Ag/Mo oxides. Chem- Eur J 17(3):1021–1028
153. Sun J, Jin X, Li R et al (2012) Ni–Cu/γ-Al_2O_3 catalyzed *N*-alkylation of amines with alcohols. Catal Commun 24:30–33
154. K-I Shimizu, Kon K, Onodera W et al (2013) Heterogeneous Ni catalyst for direct synthesis of primary amines from alcohols and ammonia. ACS Catal 3(1):112–117
155. K-I Shimizu, Imaiida N, Kon K et al (2013) Heterogeneous Ni catalysts for *N*-alkylation of amines with alcohols. ACS Catal 3(5):998–1005
156. K-I Shimizu, Kanno S, Kon K et al (2014) *N*-alkylation of ammonia and amines with alcohols catalyzed by Ni-loaded $CaSiO_3$. Catal Today 232:134–138
157. Cui X, Deng Y, Shi F et al (2013) Development of a general non-noble metal catalyst for the benign amination of alcohols with amines and ammonia. Chem-Eur J 19(11):3665–3675
158. Mehta A, Thaker A, Nandan SR et al (2014) Reinvestigating Raney nickel mediated selective alkylation of amines with alcohols via hydrogen autotransfer methodology. Appl Catal A: Gen 478:241–251
159. He J, Yamaguchi K, Mizuno N (2010) Selective synthesis of secondary amines via *N*-alkylation of primary amines and ammonia with alcohols by supported copper hydroxide catalysts. Chem Lett 39(11):1182–1183
160. K-I Shimizu, Shimura K, Nishimura M et al (2011) Silver cluster-promoted heterogeneous copper catalyst for *N*-alkylation of amines with alcohols. RSC Adv 1(7):1310–1317
161. Santoro F, Psaro R, Ravasio N et al (2012) Reductive amination of ketones or amination of alcohols over heterogeneous Cu catalysts: matching the catalyst support with the *N*-alkylating agent. ChemCatChem 4(9):1249–1254
162. Santoro F, Psaro R, Ravasio N et al (2014) *N*-Alkylation of amines through hydrogen borrowing over a heterogeneous Cu catalyst. RSC Adv 4(6):2596–2600
163. Dixit M, Mishra M, Joshi PA et al (2013) Clean borrowing hydrogen methodology using hydrotalcite supported copper catalyst. Catal Commun 33:80–83
164. Shi F, Tse MK, Beller M et al (2009) Green and efficient synthesis of sulfonamides catalyzed by nano-Ru/Fe3O4. J Am Chem Soc 131(5):1775–1779
165. K-I Shimizu, Miyamoto Y, Satsuma A (2010) Silica-supported silver nanoparticles with surface oxygen species as a reusable catalyst for alkylation of arenes. ChemCatChem 2(1):84–91
166. Cui X, Shi F, Deng Y et al (2012) Au/Ag-Mo nano-rods catalyzed reductive coupling of nitrobenzenes and alcohols using glycerol as the hydrogen source. Chem Commun 48(75):9391–9393

167. Corma A, Navas J, Sabater MJ (2012) Coupling of two multistep catalytic cycles for the one-pot synthesis of propargylamines from alcohols and primary amines on a nanoparticulated gold catalyst. Chem-Eur J 18(44):14150–14156
168. Geukens I, Vermoortele F, De Vos DE et al (2014) Ag nanoparticles on mixed Al_2O_3-Ga_2O_3 supports as catalysts for the *N*-alkylation of amines with alcohols. Appl Catal A: Gen 469:373–379
169. Choo GCY, Miyamura H, Kobayashi S (2015) Synergistic cascade catalysis by metal nanoparticles and Lewis acids in hydrogen autotransfer. Chem Sci 6(3):1719–1727
170. Gonzalez-Arellano C, Luque R, Gai PL et al (2010) Highly active and selective supported iron oxide nanoparticles in microwave-assisted *N*-alkylations of amines with alcohols. Green Chem 12(7):1281–1287
171. Lamb GW, Al Badran FA, Williams JMJ et al (2010) Production of pharmaceuticals: amines from alcohols in a continuous flow fixed bed catalytic reactor. Chem Eng Res Des 88(12):1533–1540
172. Sipos G, Kocsis L, Jones RV et al (2013) Important industrial procedures revisited in flow: very efficient oxidation and *N*-alkylation reactions with high atom-economy. J Flow Chem 3(2):51–58
173. Sattler JH, Fuchs M, Kroutil W et al (2012) Redox self-sufficient biocatalyst network for the amination of primary alcohols. Angew Chem Int Ed 51(36):9156–9159
174. Yang H, Deng Y, Shi F et al (2015) Carbon-catalysed reductive hydrogen atom transfer reactions. Nat Commun 6:6478. doi:10.1038/ncomms7478
175. Miao L, DiMaggio SC, Trudell ML et al (2009) Enantioselective syntheses of both enantiomers of noranabasamine. Org Lett 11(7):1579–1582
176. Oldenhuis NJ, Dong VM, Guan Z (2014) From racemic alcohols to enantiopure amines: Ru-catalyzed diastereoselective amination. J Am Chem Soc 136(36):12548–12551
177. Eka Putra A, Oe Y, Ohta T (2013) Ruthenium-catalyzed enantioselective synthesis of β-amino alcohols from 1,2-diols by "borrowing hydrogen". Eur J Org Chem 2013(27):6146–6151
178. Zhang Y, Lim CS, Zhao Y et al (2014) Catalytic enantioselective amination of alcohols by the use of borrowing hydrogen methodology: cooperative catalysis by iridium and a chiral phosphoric acid. Angew Chem Int Ed 53(5):1399–1403
179. Rong Z-Q, Zhang Y, Zhao Y et al (2015) Dynamic kinetic asymmetric amination of alcohols: from a mixture of four isomers to diastereo- and enantiopure α-branched amines. J Am Chem Soc 137(15):4944–4947
180. Shi F, Tse MK, Beller M et al (2009) Copper-catalyzed alkylation of sulfonamides with alcohols. Angew Chem Int Ed 48(32):5912–5915
181. Cui X, Shi F, Beller M et al (2009) Copper-catalyzed *N*-alkylation of sulfonamides with benzylic alcohols: catalysis and mechanistic studies. Adv Synth Catal 351(17):2949–2958
182. Likhar PR, Arundhathi R, Kantam ML et al (2009) Amination of alcohols catalyzed by copper-aluminium hydrotalcite: a green synthesis of amines. Eur J Org Chem 2009(31):5383–5389
183. Kawahara R, K-I Fujita, Yamaguchi R (2011) *N*-alkylation of amines with alcohols catalyzed by a water-soluble Cp* iridium complex: an efficient method for the synthesis of amines in aqueous media. Adv Synth Catal 353(7):1161–1168
184. Ohta H, Uozumi Y, Yamada YM et al (2011) In-water dehydrative alkylation of ammonia and amines with alcohols by a polymeric bimetallic catalyst. Org Lett 13(15):3892–3895
185. Feng SL, Liu CZ, Xu Q et al (2011) Rhodium-catalyzed aerobic *N*-alkylation of sulfonamides with alcohols. Chin Chem Lett 22(9):1021–1024
186. Liu C, Liao S, Xu Q et al (2011) Discovery and mechanistic studies of a general air-promoted metal-catalyzed aerobic *N*-alkylation reaction of amides and amines with alcohols. J Org Chem 76(14):5759–5773
187. Yamada YM, Uozumi Y (2006) A solid-phase self-organized catalyst of nanopalladium with main-chain viologen polymers: α-alkylation of ketones with primary alcohols. Org Lett 8(7):1375–1378
188. Yamada YM, Uozumi Y (2007) Development of a convoluted polymeric nanopalladium catalyst: α-alkylation of ketones and ring-opening alkylation of cyclic 1, 3-diketones with primary alcohols. Tetrahedron 63(35):8492–8498
189. Allen LJ, Crabtree RH (2010) Green alcohol couplings without transition metal catalysts: base-mediated β-alkylation of alcohols in aerobic conditions. Green Chem 12(8):1362–1364
190. Yu X, Liu C, Xu Q et al (2011) Manganese dioxide catalyzed *N*-alkylation of sulfonamides and amines with alcohols under air. Org Lett 13(23):6184–6187
191. Yu X, Jiang L, Xu Q et al (2012) Palladium-catalyzed *N*-alkylation of amides and amines with alcohols employing the aerobic relay race methodology. Chin J Chem 30(10):2322–2332

192. Li Q, Fan S, Xu Q et al (2012) Copper-catalyzed *N*-alkylation of amides and amines with alcohols employing the aerobic relay race methodology. Org Biomol Chem 10(15):2966–2972
193. Deutsch C, Krause N, Lipshutz BH (2008) CuH-catalyzed reactions. Chem Rev 108(8):2916–2927
194. Rendler S, Oestreich M (2007) Polishing a diamond in the rough:"Cu–H" catalysis with silanes. Angew Chem In. Ed 46(4):498–504
195. Lipshutz BH (2009) Rediscovering organocopper chemistry through copper hydride. It's all about the ligand. Synlett 2009(04):509–524
196. Liao S, Yu K, Xu Q et al (2012) Copper-catalyzed C-alkylation of secondary alcohols and methyl ketones with alcohols employing the aerobic relay race methodology. Org Biomol Chem 10(15):2973–2978
197. Sharma RK, Monga Y, Gaba G et al (2013) Magnetite (Fe_3O_4) silica based organic–inorganic hybrid copper (ii) nanocatalyst: a platform for aerobic *N*-alkylation of amines. Green Chem 15(10):2800–2809
198. Zotova N, Hellgardt K, Hii KKM et al (2012) Catalysis in flow: Au-catalysed alkylation of amines by alcohols. Green Chem 14(1):226–232
199. Xu Q, Chen J, Liu Q et al (2013) Aldehyde-catalyzed transition metal-free dehydrative β-alkylation of methyl carbinols with alcohols. Adv Synth Catal 355(4):697–704
200. Xu Q, Chen J, Tian H et al (2014) Catalyst-free dehydrative α-alkylation of ketones with alcohols: green and selective autocatalyzed synthesis of alcohols and ketones. Angew Chem Int Ed 53(1):225–229
201. Han X, Wu J (2013) Redox chain reaction-indole and pyrrole alkylation with unactivated secondary alcohols. Angew Chem Int Ed 52(17):4637–4640
202. Dai X, Deng Y, Shi F et al (2015) A conjugated ketone as a catalyst in alcohol amination reactions under transition-metal and hetero-atom free conditions. RSC Adv 5(54):43589–43593
203. Donthiri RR, Pappula V, Adimurthy S et al (2013) Sodium hydroxide catalyzed *N*-alkylation of (hetero)aromatic primary amines and N1, C5-dialkylation of 4-phenyl-2-aminothiazoles with benzyl alcohols. J Org Chem 78(13):6775–6781
204. Donthiri RR, Patil RD, Adimurthy S et al (2012) NaOH-catalyzed imine synthesis: aerobic oxidative coupling of alcohols and amines. Eur J Org Chem 24:4457–4460
205. Lu XH, Sun YW, Xia QH et al (2014) Solid base catalyzed highly efficient *N*-alkylation of amines with alcohols in a solvent-free system. Catal Commun 55:78–82
206. Yadav DKT, Bhanage B (2014) Base-mediated synthesis of imines and amines from *N*-phenylureas and alcohols. Synlett 25:1611–1615
207. Li S, Li X, Xu Q et al (2015) Structure-dependent tautomerization induced catalyst-free autocatalyzed *N*-alkylation of heteroaryl amines with alcohols. Green Chem 17(6):3260–3265
208. Wang C, Yao Y, Zhao Y et al (2015) Insight into O2-promoted base-catalyzed *N*-alkylation of amines with alcohols. Eur J Org Chem 13:2972–2977
209. Li X, Li S, Xu Q et al (2016) Efficient and practical catalyst-free-like dehydrative *N*-alkylation of amines and sulfinamides with alcohols initiated by aerobic oxidation of alcohols under air. Tetrahedron 72(2):264–272
210. Li QQ, Xiao ZF, Kang YB (2015) Direct alkylation of amines with alcohols catalyzed by base. Org Lett 17(21):5328–5331
211. Shvo Y, Laine RM (1980) Homogeneous catalytic activation of C–N bonds. Alkyl exchange between tertiary amines. J Chem Soc, Chem Commun 16:753–754
212. Bui The K, Concilio C, Porzi G (1981) A facile synthesis of symmetrical secondary amines from primary amines promoted by the homogeneous catalyst $RuCl_2(Ph_3P)_3$. J Organomet Chem 208(2):249–251
213. Bui The K, Concilio C, Porzi G (1981) Cyclization of alpha, omega aliphatic diamines and conversion of primary amines to symmetrical tertiary amines by a homogeneous ruthenium catalyst. J Org Chem 46(8):1759–1760
214. Hollmann D, Bahn S, Beller M et al (2007) A general ruthenium-catalyzed synthesis of aromatic amines. Angew Chem Int Ed 46(43):8291–8294
215. Hollmann D, Bahn S, Beller M et al (2008) *N*-dealkylation of aliphatic amines and selective synthesis of monoalkylated aryl amines. Chem Commun 44(27):3199–3201
216. Bähn S, Hollmann D, Beller M et al (2008) Ruthenium-catalyzed synthesis of secondary alkylamines: selective alkylation with aliphatic amines. Adv Synth Catal 350(13):2099–2103
217. Bahn S, Imm S, Beller M et al (2011) Synthesis of primary amines from secondary and tertiary amines: ruthenium-catalyzed amination using ammonia. Chem-Eur J 17(17):4705–4708

218. Prades A, Corberan R, Peris E et al (2008) [$IrCl_2Cp^*$(NHC)] complexes as highly versatile efficient catalysts for the cross-coupling of alcohols and amines. Chem-Eur J 14(36):11474–11479
219. Corberán R, Peris (2008) An unusual example of base-free catalyzed reduction of C=O and C=NR bonds by transfer hydrogenation and some useful implications. Organometallics 27(8):1954–1958
220. Saidi O, Marsden SP, Williams JM et al (2009) Selective amine cross-coupling using iridium-catalyzed "borrowing hydrogen" methodology. Angew Chem Int Ed 48(40):7375–7378
221. K-I Shimizu, Shimura K, Ohshima K et al (2011) Selective cross-coupling of amines by alumina-supported palladium nanocluster catalysts. Green Chem 13(11):3096–3100
222. Lubinu MC, De Luca L, Porcheddu A et al (2011) Microwave-promoted selective mono-*N*-alkylation of anilines with tertiary amines by heterogeneous catalysis. Chem-Eur J 17(1):82–85
223. K-I Shimizu, Shimura K, Kato K et al (2012) Electronic effect of Na promotion for selective mono-*N*-alkylation of aniline with di-iso-propylamine by Pt/SiO_2 catalysts. J Mol Catal A: Chem 353–354:171–177
224. K-I Shimizu, Shimura K, Tamagawa N et al (2012) Sulfur promoted Pt/SiO_2 catalyzed cross-coupling of anilines and amines. Appl Catal A: Gen 417–418:37–42
225. Largeron M, Fleury M-B (2009) A biomimetic electrocatalytic system for the atom-economical chemoselective synthesis of secondary amines. Org Lett 11(4):883–886
226. Schümperli MT, Hammond C, Hermans I (2012) Developments in the aerobic oxidation of amines. ACS Catal 2(6):1108–1117
227. Largeron M, Fleury MB (2013) Bioinspired oxidation catalysts. Science 339(6115):43–44
228. Largeron M (2013) Protocols for the catalytic oxidation of primary amines to imines. Eur J Org Chem 2013(24):5225–5235
229. Chen B, Wang L, Gao S (2015) Recent advances in aerobic oxidation of alcohols and amines to imines. ACS Catal 5(10):5851–5876