



Substitution of alcohols by N-nucleophiles via transition metal-catalyzed dehydrogenation

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ARTICLE

Substitution of alcohols by N-nucleophiles via transition metal-catalyzed dehydrogenation

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Transition metal-catalyzed substitution of alcohols by N-nucleophiles (or N-alkylation of amines and related compounds with alcohols) avoids the use of alkylating agents by means of borrowing hydrogen (BH) activation of the alcohol substrates. Water is produced as the only by-product, which makes the “BH” processes atom-economic and environmentally benign. Diverse types of homogeneous organometallic and heterogeneous transition metal catalysts, and substrates such as N-nucleophiles including amines, amides, sulfonamides and ammonia, and various alcohols, can be used for this purpose, demonstrating the promising potential of “BH” processes to replace the procedures using traditional alkylating agents in pharmaceutical and chemical industries. Borrowing hydrogen activation of alcohols for C-N bond formation has recently been paid more and more attention, and a lot of new and novel procedures and examples have been documented. This critical review summarizes the recent advances in “BH” substitution of alcohols by N-nucleophiles since 2009. “Semi-BH” N-alkylation processes with or without an external hydrogen acceptor is also briefly presented. Suitable discussion of the “BH” strategy provides new principles for establishing green processes to replace the relevant traditional synthetic methods for C-N bond formation.

1. Introduction

Construction of a C-N bond is one of the most important tasks for synthetic chemists. Substitution, addition, cycloaddition, and cross-coupling reactions, etc. can be employed to form this chemical bond. Transition metal-catalyzed cross-coupling reactions have recently been made great progress in C-N bond formation. However, in the traditional cross-coupling alkylation to form a C-N bond various organic or organometallic coupling

partners such as halides, tosylates, triflates, sulfonates, organo-boron, -tin, and -zinc reagents, are usually required, and in some cases dangerous peroxides and diethyl azodicarboxylate have to be used as the coupling partners.¹ Although a variety of alkylating compounds have been successfully explored, the need to develop readily available alkylating agents as well as the corresponding effective catalytic systems is still strongly desired in N-alkylation of amines and the related compounds.

Alcohols are readily available chemicals in bulks and are considered as potential alkylating agents. However, alcohols are rather unreactive as alkylating agents because the hydroxyl moiety in an alcohol molecule can not be easily replaced by a nucleophilic reagent. Alcohols are usually involved in reactions in the forms of their corresponding halides, tosylates, triflates, and sulfonates, etc. by converting the OH functionality to a better

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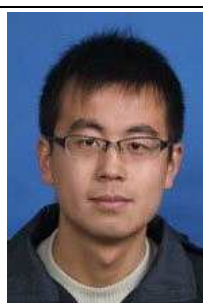
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Qin Yang

Qin Yang studied chemistry at Central China Normal University, Wuhan, China, and received her BSc degree in July 2007. In September 2008, She joined Prof. Zhengkun Yu's group at Dalian Institute of Chemical Physics, Chinese Academy of Sciences (CAS) to pursue a PhD degree. Her current research interest is focused on iron-catalyzed cyclization and related homogeneous catalysis.

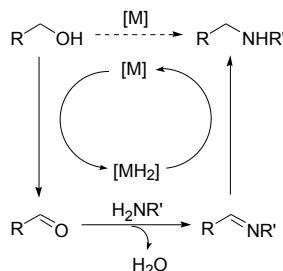


Qingfu Wang

Qingfu Wang studied chemistry at Hua Zhong University of Science and Technology, Wuhan, China, and received his BSc degree in July 2011. He then joined Prof. Zhengkun Yu's group at Dalian Institute of Chemical Physics, Chinese Academy of Sciences (CAS) to pursue a PhD degree. His current research interest is centered on transition metal complex-promoted homogeneous catalysis and synthetic methodologies.

leaving group. Based upon the principle of atom-economy in chemical transformations, the above-mentioned alternative methods to utilize alcohols lack of efficiency and produce a lot of undesired wastes.² For modern synthetic chemistry in both the academic laboratories and industry, green chemistry-featured environmentally benign processes are always expected.

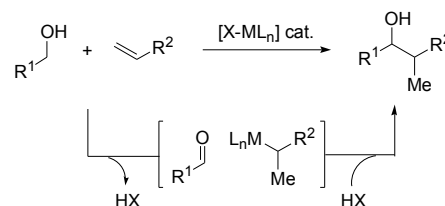
In the pioneering work by Grigg,³ and Watanabe,⁴ alcohols were directly used as the alkylating agents for the N-alkylation of amines under transition metal catalysis, which presents the first examples of alcohol substitution by N-nucleophiles. Since then, continuous efforts have been contributed to N-alkylation of amines as well as the related reactions by activating alcohols through the so-called borrowing hydrogen (BH)⁵⁻¹⁰ or hydrogen autotransfer (HA)^{2,11,12} strategy. Diverse catalytic systems have been established for the catalytic N-alkylation reactions with alcohols as the alkylating agents.¹³⁻¹⁷ A borrowing hydrogen (or hydrogen autotransfer) process can be generally depicted by the substitution of an alcohol with an amine (or N-alkylation of an amine with an alcohol) (Scheme 1). In the BH (or HA) process, an alcohol is temporarily removed hydrogen to form the corresponding aldehyde or ketone intermediate by a transition metal catalyst, rendering the alcohol as an alkylating agent. Such an intermediate is transformed to an imine by condensation with an amine *in situ*. Subsequent hydrogen return to the imine intermediate from the transition metal catalyst affords the amine product with a newly formed C-N bond, producing water as the only by-product. Such a “BH” strategy avoids use of organic halides or other derivatives of alcohols as the alkylating agents, featuring an atom-economic and green chemical process.



Scheme 1 Borrowing hydrogen (BH) strategy for the substitution of alcohols by N-nucleophiles.

Since 2009, transition metal-catalyzed N-alkylation of amines and related compounds with alcohols through borrowing hydrogen activation of the alcohol substrates has been paid more and more attention.⁸⁻¹⁰ Various homogeneous organometallic and heterogeneous transition metal catalysts, challenging substrates such as amides, ammonia, and polyols, related transformations in aqueous phase, and asymmetric BH processes as well as scale-up preparation of industrially useful amines have been successfully applied in this prosperous area. A lot of potentially useful new and novel N-alkylation examples have been documented. It is noted that an alternative strategy for alcohol activation by temporary oxidation to an aldehyde has been developed by Krische, et al.¹⁸ Dehydrogenation of primary alcohols in the presence of π -unsaturated reactants provides aldehyde-organometal pairs that combine to form products of carbonyl addition in the absence of stoichiometric organometallic reagents. In this aspect, elegant examples have recently been reported.¹⁹⁻²² Scheme 2 differentiates Krische’s “C-H functionalization” from the “BH” substitution of alcohols by N-nucleophiles. This review only summarizes the progress in “BH” substitution of alcohols by

N-nucleophiles under homogeneous organometallic and heterogeneous transition metal catalysis since 2009.



Scheme 2 C-H functionalization of alcohols by redox-triggered carbonyl addition.¹⁸

2. Homogeneous transition metal-catalyzed substitution of alcohols by N-nucleophiles

2.1 Substitution of alcohols by amines

Amine synthesis may have received much more attention than the preparation of many other functional compounds in organic chemistry because amines are widely used as the organic intermediates in academic laboratories, chemical and pharmaceutical industries, and they can also be employed for the synthesis of various biologically active materials.²³ Substitution of alcohols by amines or ammonia (or N-alkylation of amines or ammonia with alcohols) is considered as a promising alternative route to access new higher-order amines. In general, substitution of alcohols by amines through a BH strategy is catalyzed by organometallic ruthenium, iridium, copper, iron, and palladium catalysts, etc. Relatively unreactive amides, sulfonamides, and ammonia can also be used as the N-nucleophiles. Starting from primary amines higher-order amines such as secondary and tertiary amines, cyclic tertiary amines by means of diols, and N-heterocyclic compounds by employing functionalized amine substrates, were obtained. In a similar manner, secondary amines and ammonia were applied for the same purpose.

2.1.1 Ruthenium catalysts

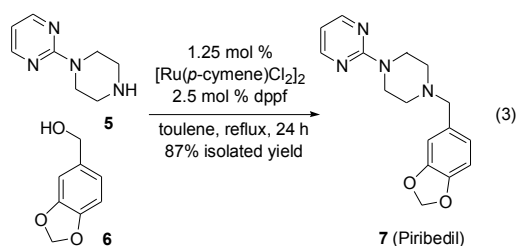
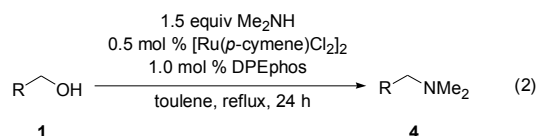
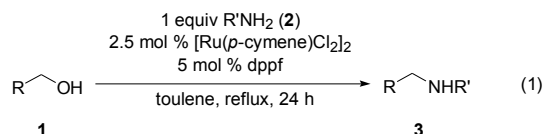
Ruthenium complexes are typically effective catalysts for substitution of alcohols by amines through a borrowing hydrogen mechanism. By using $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ with bidentate phosphine dppe or DPEphos as the catalyst the alkylation of amines



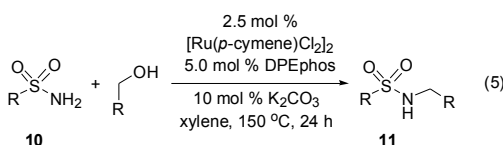
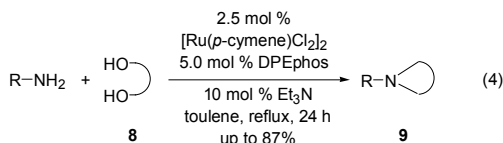
Zhengkun Yu

Prof. Zhengkun Yu obtained his PhD degree at Dalian Institute of Chemical Physics (DICP), CAS in July of 1995. During October 1995-January 2003 he worked as a post-doctoral fellow or research associate in the labs of Prof. Rudolf Aumann (University of Münster, Germany), Prof. John G. Verkade (Iowa State University, USA) and Prof. Chuck Winter (Wayne State University, USA) and in Japan Corporation of Science and Technology (Tokyo, Japan). He returned to DICP as a “Hundred Talents Program of CAS” professor in February 2003. Since then he has been a full professor at DICP where his research interests are focused on novel organometallic complex catalysts and catalytic inert chemical bond activation.

by alcohols was achieved.²⁴ *t*-Butylamine, 1-phenylethylamine, anilines, and 2-aminopyridine were alkylated to give the corresponding secondary amines by benzylic alcohols or 2-arylethanol (eqn (1)), respectively, reaching up to 100% conversions for alcohols **1** and up to 89% isolated yields for the target products **3**. In the cases using cyclic or acyclic secondary amines, tertiary amines were formed as the products. The conversion of alcohols into *N,N*-dimethylamino compounds **4** was realized by using dimethylamine as a solution in toluene (eqn (2)). This methodology was applied to prepare the drug for the

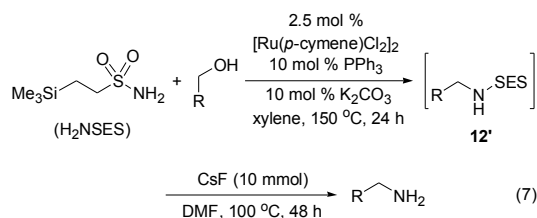
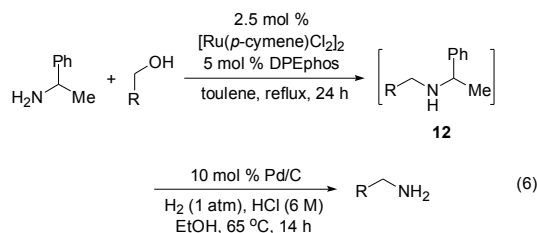


treatment of Parkinson's disease, that is, Piribedil (**7**), by the reaction of commercially available piperidine (**5**) with piperonyl alcohol (**6**) (eqn (3)). Through adjusting the reaction parameters and introducing a base into the reaction system, the above catalytic system could be employed for the synthesis of cyclic amines from the reactions of diols **8** with primary amines (eqn (4)), and *N*-alkylation of the very challenging substrates, that is, sulfonamides **10** (eqn (5)). The preparation of *N*-alkylated sulfonamides **11** is very important for drug development as well as for protecting a nitrogen functionality. Solvent-free conditions could also be used for the same reactions.²⁵

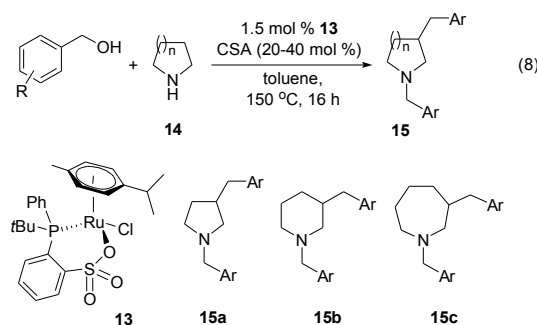


A formal transamination was achieved by *in situ* deprotecting the resultant secondary amine product (eqn (6) and (7)).²⁶ By means of 10% Pd/C as the catalyst and H₂ (1 atm) as the reductant, the secondary alkyl moiety was removed from the resultant

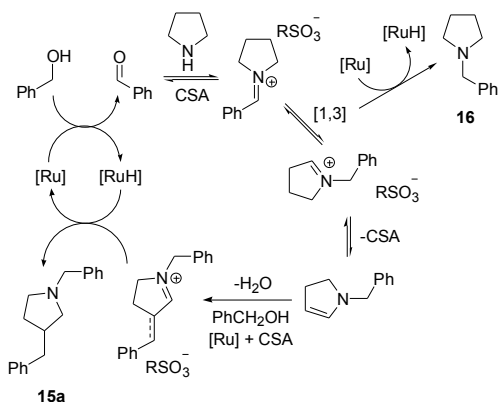
secondary amine intermediate **12**, giving a primary amine product (eqn (6)). Trimethylsilyl ethanesulfonamide group (SES) is one of the most readily removed protecting groups in amine protection and activation by converting an amine into the corresponding sulfonamide.²⁷ Thus, SES-protecting amine **12'** was prepared and then deprotected *in situ* with CsF base, affording the target amine product (eqn (7)). A combination of



Ru₃(CO)₁₂ and *N*-phenyl-2-(dicyclohexyl-phosphanyl)pyrrole performed efficiently for the monoamination of vicinal diols by secondary amines or anilines.²⁸ With the exception of ethylene glycol, monoamination of the diols produced the corresponding amino alcohols in good yields. Such a catalyst system was also effective for the amination of primary and secondary alcohols by primary amines to form secondary amines.²⁹

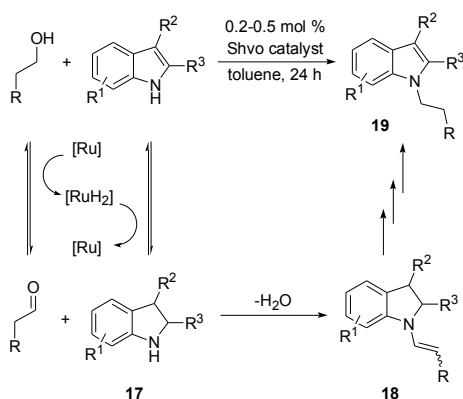


An (arene)ruthenium(II) complex combined with camphorsulfonic acid (CSA) promoted the *N*- and C(3)-dialkylation of unactivated amines by a cascade reaction via a borrowing hydrogen pathway (eqn (8)).³⁰ The reaction was highly regioselective and water was produced as the only side product. Benzylic alcohols reacted with pyrrolidine, piperidine, or azepane to form various *N*- and C(3)-dialkylation products of types **15a-15c**, respectively. A BH mechanism is proposed in Scheme 3. In the overall catalytic cycle, species of type **16** may be formed as the side product. Using aromatic *N*-heterocyclic compounds such as indoles as the substrates, ruthenium-catalyzed *N*-alkylation was also achieved in the presence of Shvo complex as the catalyst (Scheme 4).³¹ Phenylethanol, benzylic alcohols, and aliphatic alcohols were used as the alkylating agents. Based upon the proposed mechanism, species **17** and **18** are considered as the

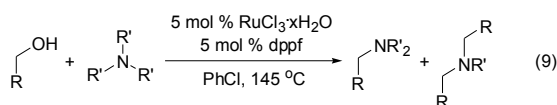


Scheme 3 A proposed BH mechanism for substitution of benzylic alcohols by unactivated amines.³⁰

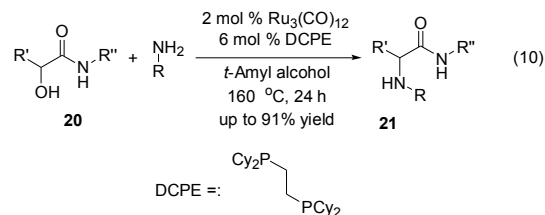
reaction intermediates. The simple ruthenium salt, that is, $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$, could also act as the catalyst in the presence of 1,1'-bis(diphenyl-phosphino)ferrocene (dppf) as the ligand to promote the direct amination of alcohols with aliphatic tertiary amines, producing unsymmetric tertiary amines in up to 87% yields and exhibiting obvious ligand and solvent effects (eqn (9)).³²



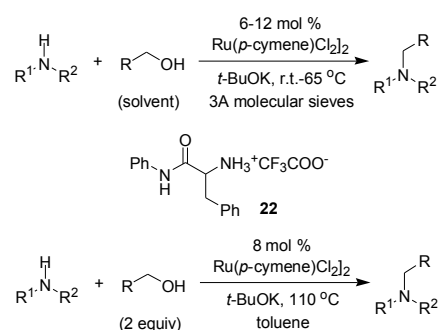
Scheme 4 N-Alkylation of indoles with alcohols.³¹



With 2 mol % $\text{Ru}_3(\text{CO})_{12}$ and 6 mol % 1,2-bis(dicyclohexylphosphino)ethane (DCPE) as the catalyst, α -hydroxyl amides **20** were aminated by anilines, aliphatic primary and secondary amines, and ammonia to afford α -amino acid amides **21**, a class of very important amino acid derivatives with potential bioactivity (eqn (10)).³³ For the amination reaction to occur, the choice of the ligand and solvent is crucial. Among the tested bidentate phosphine ligands, DCPE acted as the most effective one, and *tert*-amyl alcohol was the most suitable solvent. This atom-efficient amination protocol proceeded efficiently with the commercially available $\text{Ru}_3(\text{CO})_{12}$ /DCPE catalyst system without using any special equipment. A combination of $\text{Ru}_3(\text{CO})_{12}$ /BINAP/*t*-BuOK (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) was used as the catalyst system for the synthesis of 2-N-pyridylmethyl benzonitriles in moderate to good yields.³⁴ These resultant functionalized benzonitrile derivatives were effi-

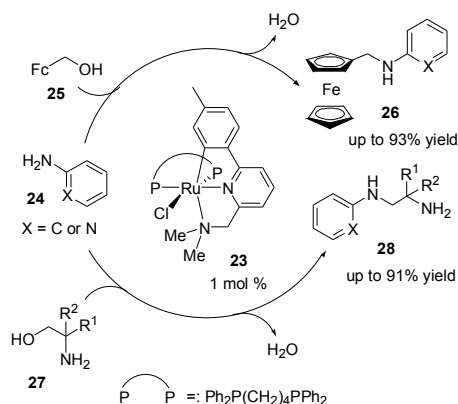


ciently applied in the preparation of biologically interesting 2,3-diaryl-1,2,3,4-tetrahydrobenzo[*e*][1,4]diazepin-5-ones. Using a simple amino amide ligand **22** in the salt form ruthenium-catalyzed one-pot alkylation of primary and secondary amines with simple alcohols was achieved under various conditions. With an alcohol as the solvent as well as the substrate the reaction underwent under mild conditions, even as low as room temperature, and at high temperature in an organic solvent the reaction was carried out with high selectivity by means of stoichiometric amount of the alcohol (Scheme 5).³⁵



Scheme 5 Ru(II)/amino amide-catalyzed N-alkylation.³⁵

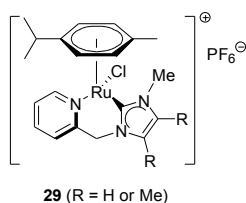
In the presence of ruthenium(II) pincer complex **23**, the selective monoalkylation of heteroaromatic amines **24** with a range of primary alcohols including pyridine-, furan-, and thiophene-substituted alcohols efficiently underwent to afford the corresponding secondary amines as the only products (Scheme 6).³⁶ This protocol is featured with no tertiary amine formation



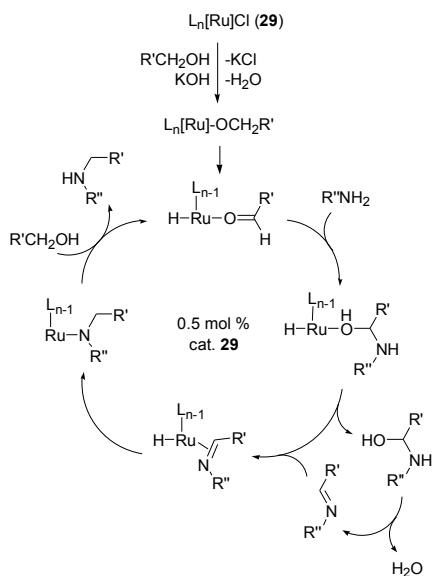
Scheme 6 Selective N-monoalkylation of N-heteroaromatic amines.³⁶

via polyalkylation of the amine substrates. Using ferrocenyl-substituted alcohol **25** as the alkylating agent, secondary amine products **26** were obtained in up to 93% yields. Aliphatic amines such as benzylamine and hexylamine did not react under the

same optimal conditions, which opens the possibility of using aliphatic amino alcohols **27** as the alkylating agents. Thus, diamines **28** were obtained in good to excellent yields. It is noteworthy that the reactions were carried out in refluxing toluene in the presence of *t*-BuOK base (1 equiv) and 4A molecular sieves. Ruthenium(II) carbonyl complexes with phosphine-functionalized PNS-type thiosemicarbazole ligands effected the N-alkylation of N-heteroaromatic amines with alcohols.³⁷ Ruthenium(II) picolyl-NHC complexes **29** showed good catalytic activity for N-alkylation of amines in the presence of KOH base (50 mol %), and a general mechanism reveals that the *in-situ* generated ruthenium hydride species is the catalytically

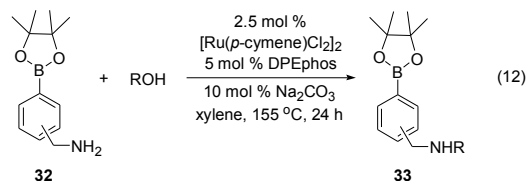
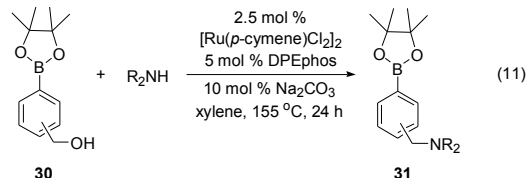


active species (Scheme 7).³⁸ A similar mechanism was also proposed for N-alkylation of various amines with alcohols by Williams, et al.²⁴ Half sandwich ruthenium(II) complexes bearing a benzimidazole moiety were used for the same purpose.³⁹ With functionalized substrates such as *para*- and *meta*-boronic ester group-bearing alcohols **30** or amines **32**, Ru(II)-catalyzed amine alkylation reactions underwent to form boronic ester group-functionalized amines **31** and **33**, respectively, which may be used as molecular sensors (eqns (11) and (12)).⁴⁰

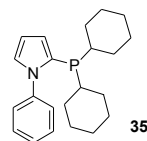
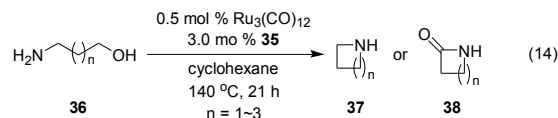
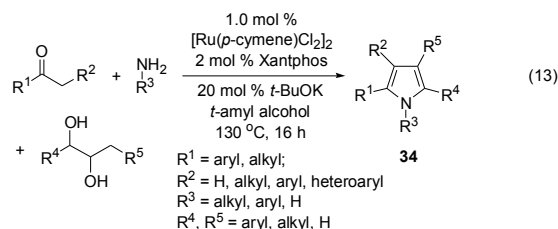


Scheme 7 A proposed mechanism for Ru(II)-NHC-catalyzed substitution of alcohols by amines.³⁸

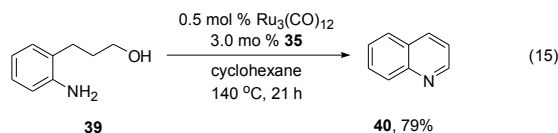
A general and highly regioselective synthesis of pyrroles via ruthenium(II)-catalyzed three-component reaction of ketone, amine, and vicinal diol was reported (eqn (13)).⁴¹ The catalyst system was composed of the commercially available [Ru(*p*-cymene)Cl₂]/*t*-BuOK, and a variety of aryl and alkyl ketones as well as α -functionalized and activated benzylic ones were reacted with various amines (anilines, alkyl amines, and ammonia) and

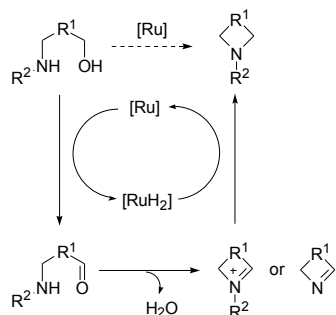


vicinal diols to give the corresponding heterocyclic products, pyrroles **34**. Because stoichiometric amounts of additives or bases are not necessary, this synthetic protocol has the potential to be used frequently. With 1 mol % Ru₃(CO)₁₂ as the precatalyst in the presence of 20 mol % K₂CO₃, similar results were obtained.⁴² In the overall catalytic cycle, borrowing hydrogen pathways were involved and water was formed as the by-product.



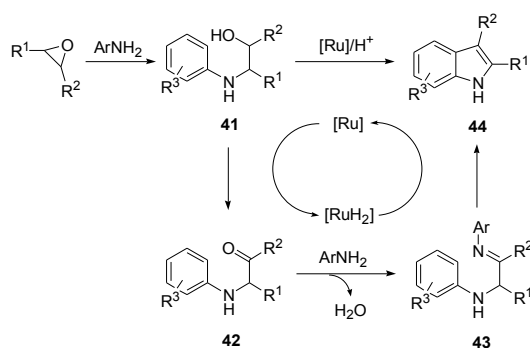
By means of an amination catalyst effective for the direct synthesis of amines from alcohols and ammonia, that is, Ru₃(CO)₁₂/CatCXium® PCy (**35**),⁴³ *n*-amino-alcohols **36** underwent intramolecular N-alkylation to be selectively cyclized to either the cyclic amine or amide (eqn (14)).⁴⁴ Presence of water led to amine **37** as the major product, whereas using a sacrificial ketone as the hydrogen acceptor resulted in amide product **38**. A “BH”-type cyclization mechanism is depicted in Scheme 8. In the absence of an additive, only a mixture of **37** and **38** could be obtained, and N-substituted amino-alcohols gave the amines as the only products, while the reaction of α -aminoaryl-substituted *n*-propanol **39** produced quinoline **40** (79%) as the major product (eqn (15)).





Scheme 8 Intramolecular amino-alcohol cyclization via a "BH" mechanism.⁴⁴

Epoxide can be applied as the temporary alkylating agent to undergo a BH reaction with an aniline, constructing an indole core (Scheme 9).⁴⁵ Such an indole synthetic protocol follows a domino sequence. The first reaction is ring-opening of the epoxide by the aniline, *in situ* forming the corresponding 1,2-amino-alcohol. Intermediate **41** undergoes a BH reaction to successively generate species **42** and **43**. Eventually, indole **44** is produced from the dehydrogenative/deaminative cyclization of intermediate **43** under ruthenium catalysis. Good yields were

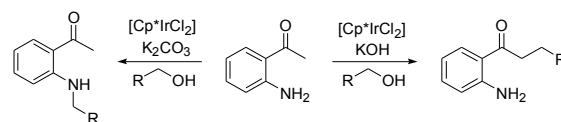
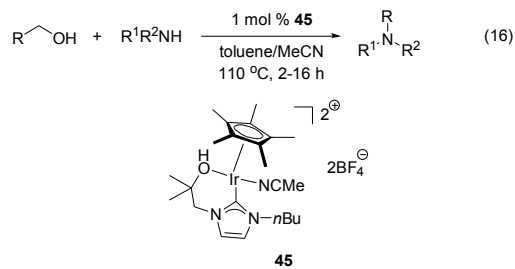


Scheme 9 Indole synthesis using epoxides and amines.⁴⁵

obtained for the indole products by using $\text{Ru}_3(\text{CO})_{12}/\text{dppf}$ as the catalyst system. Water and hydrogen were generated as the only stoichiometric by-products, rendering this method highly atom-economic. It should be noted that the efficiency of BH substitution of alcohols by amines through transition metal-catalyzed dehydrogenation is often strongly dependent on metals,⁴⁶ ligand/solvent and selection,⁴⁷ and other factors.⁴⁸

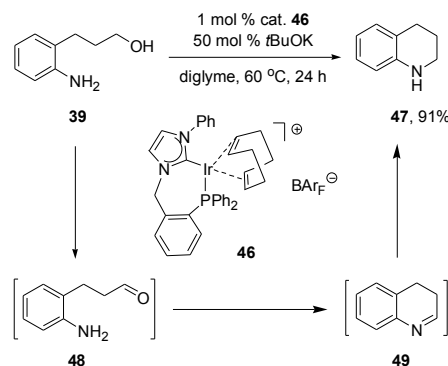
2.1.2 Iridium catalysts

Iridium complex catalysts have been paid much attention in substitution of alcohols by N-nucleophiles (or N-alkylation of amines and related compounds with alcohols) as the alkylating agents.^{49,50} In this aspect, iridium N-heterocyclic carbenes (NHCs) have been paid much more attention.⁵¹ A series of bifunctional iridium(III) complexes containing bidentate N-heterocyclic carbenes functionalized with an alcohol or ether group (NHC-OR, R = H or Me) were prepared, and exhibited high catalytic activity for the N-alkylation of amines with alcohols.⁵² In particular, the reactions of amines and alcohols catalyzed by Ir(III) complex $\text{Cp}^*(\text{NHC-OH})\text{Ir}(\text{MeCN})(\text{BF}_4)_2$ (**45**) afforded the corresponding higher-order amine products in up to >99% yields (eqn (16)). The reactions were also performed in toluene/ CH_2Cl_2 at 50 °C over a longer time (48-60 h). Iridium(III)-catalyzed chemoselective al-



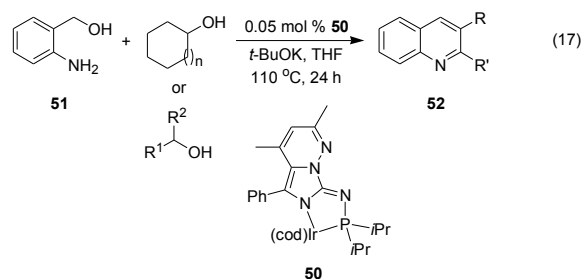
Scheme 10 N- and C-alkylation of 2'-aminoacetophenone with benzylic alcohols.⁵³

kylation of 2'-amino-acetophenone with benzylic alcohols under microwave conditions formed either the corresponding N- or C-alkylation products in good yields (Scheme 10).⁵³ The iridium(I) complex coordinated with a PNP-pincer-type phosphalkene ligand⁵⁴ and Cp*-iridium(III) half sandwich complexes⁵⁵ exhibited high catalytic activity for the N-alkylation of amines with alcohols.



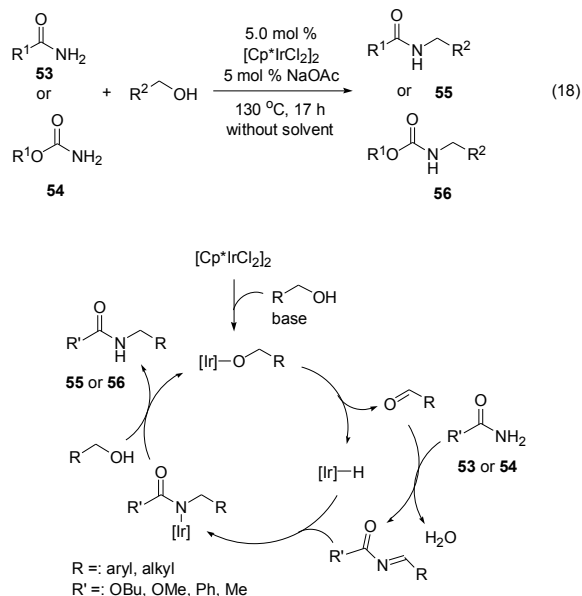
Scheme 11 An intramolecular borrowing hydrogen process.⁵⁶

An intramolecular borrowing hydrogen process occurred in amino-alcohols **39** in the presence of a bidentate iridium NHC-phosphine complex catalyst **46**, affording N-heterocyclic compounds **47** as the products under mild conditions (Scheme 11).⁵⁶ In the catalytic cycle, aldehyde **48** and imine **49** are the possible reactive intermediates. It is noteworthy that **39** underwent intramolecular N-alkylation with a Ru(0) catalyst to form quinoline as the product (eqn (15)).⁴⁴ By means of P,N-chelated iridium(I) complex **50** as the catalyst substitution of ben-



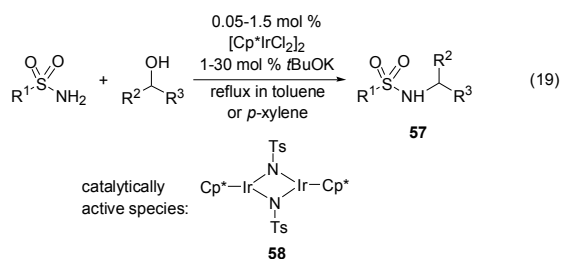
zyl alcohol with anilines was efficiently realized under mild conditions (70 °C, 24 h) to give the secondary amine products, while *o*-aminobenzyl alcohols (**51**) reacted with primary alcohols at 110 °C produced quinolines (**52**) through acceptorless dehydrogenative condensation (eqn (17)).⁵⁷

Amides and the related compounds can be N-alkylated with alcohols under iridium catalysis. A combination of [Cp*IrCl₂]₂ and NaOAc acted as the effective catalyst system for the N-alkylation of amides **53** and carbamates **54** with alcohols as the alkylating agents under solvent-free conditions (eqn (18)).⁵⁸ Iridium alkoxy and hydride species are proposed to be formed *in situ* in the catalytic cycle, following a borrowing hydrogen pathway (Scheme 12).



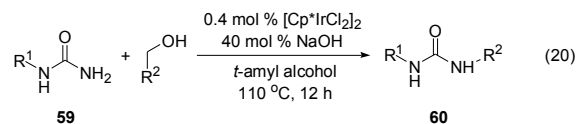
Scheme 12 Iridium-catalyzed substitution of alcohols by amides and carbamates.⁵⁸

Iridium(III)-catalyzed substitution of alcohols by sulfonamides occurred efficiently in refluxing toluene or *p*-xylene, affording N-alkylated sulfonamides **57** in good to excellent yields (eqn (19)).⁵⁹ Mechanistic studies revealed that the key catalytic species was a sulfonylimido-bridged unsaturated diiridium complex [(Cp*Ir)₂(μ-NTs)₂] (**58**). The [Cp*IrCl₂]₂/NaOH system behaved the same for the N-alkylation of these sulfonamides with alcohols.⁶⁰ Through a similar BH mechanism regioselective N-

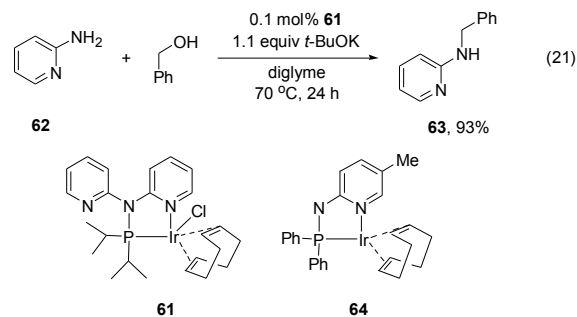


alkylation of N-monosubstituted ureas **59** with alcohols was conducted to produce N,N'-alkyl aryl ureas and N,N'-dialkyl ureas **60** in 70-93% yields under iridium catalysis (eqn (20)).⁶¹ The synthetic protocol is featured that no isomeric N1-alkylated

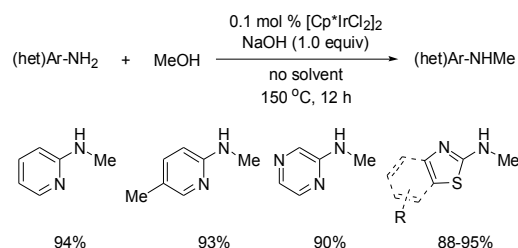
and N3-dialkylated products were formed in all the cases. Due to the high atom efficiency and formation of water as the only side product, the present method is highly attractive in functionalizing ureas.



Heteroaryl amines are another kind of amine substrates which can be N-alkylated with alcohols by iridium complex catalysts. In the presence of 0.1 mol % iridium complex **61** containing an anionic P,N ligand, N-alkylation of 2-aminopyridine (**62**) was achieved under mild conditions to give N-(2-pyridyl)benzylamine (**63**) in 93% yield (eqn (21)).⁶² Using 0.05-0.4 mol % **61** or **64** as the catalyst efficient N-alkylation of anilines by alcohols was also conducted under these conditions.⁶³ The anionic P,N ligand-bearing iridium(I) complex catalyst **64** exhibited a much



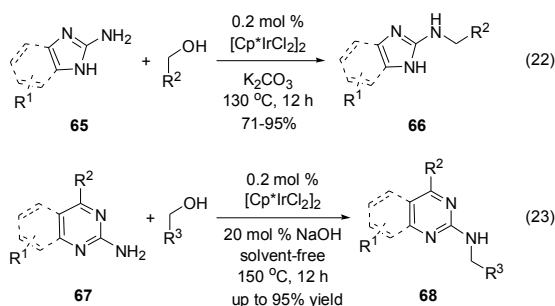
higher catalytic activity than the Ir(I) complex catalyst **61** supported by a neutral P,N ligand, and was featured a good stability. With complex **64** as the catalyst symmetrically and unsymmetrically N-alkylated diamines were obtained from the reactions of unsubstituted diamines with alcohols (70 °C, 48 h).⁶⁴ Methanol was used as a methylating agent for arylamines and arylsulfonamides in the presence of [Cp*IrCl₂]₂/NaOH at 150 °C under the solvent-free conditions.⁶⁰ In the same fashion, N-methylation of N-heteroaromatic amines with methanol was effi-



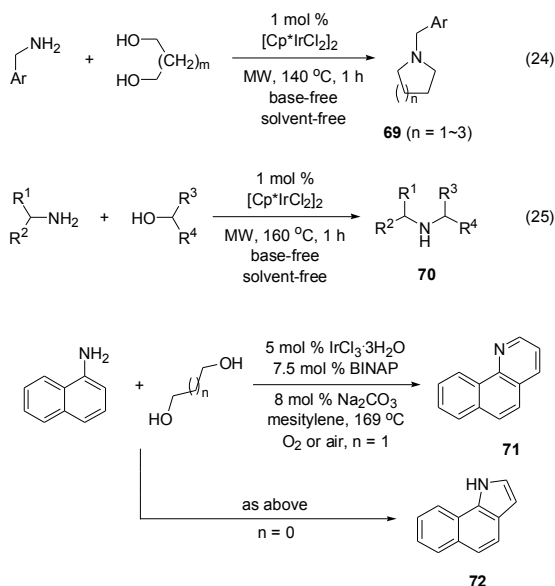
Scheme 13 Iridium-catalyzed substitution of methanol by N-heteroaromatic amines.⁶⁰

ciently performed, affording the target products in 88-95% yields (Scheme 13). During the reaction, excessive amount of methanol was required as both the alkylating agent and solvent. This method avoids the poor selectivity towards the N-monomethylation and limited substrate scope by using other procedures. The [Cp*IrCl₂]₂/K₂CO₃ catalyst system worked very

efficiently for the regioselective N-alkylation of 2-aminoimidazoles **65** with alcohols, forming 2-(N-alkylamino)imidazoles **66** (eqn (22)).⁶⁵ A catalytic amount of the relatively weak K_2CO_3 base (10 mol %) was necessary, rendering the synthetic reactions highly selective. Elevating temperature to 150 °C made N-alkylation of 2-aminoquinazolines and 2-aminopyrimidines **67** occur under solvent-free conditions, giving 2-(N-alkylamino)quinazolines and -pyrimidines **68** in 71-96% yields (eqn (23)).⁶⁶



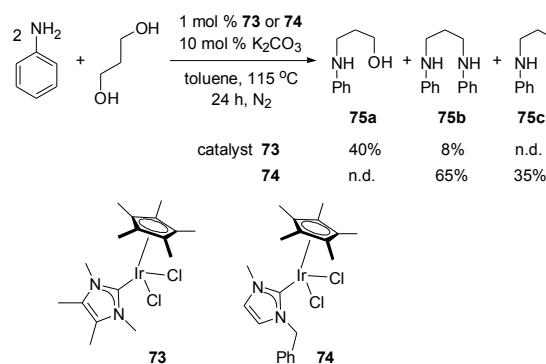
Under the microwave conditions, iridium(III)-catalyzed N-alkylation of amines with alcohols occurred without solvent and a base.⁶⁷ Such alkylation reactions were green, atom-economic, and effective for mono-, di-, and trialkylation of amines, and reasonable yields of the trialkylated products were obtained by means of 4 equiv alcohols. In the case using diols as the alkylating agents, cyclic tertiary amines **69** were obtained (eqn (24)), and secondary alcohols could also be employed as the alkylating agents (eqn (25)). Benzoquinoline derivatives **71** were efficiently synthesized by iridium-catalyzed N-heterocyclization



Scheme 14 Synthesis of benzoquinolines and benzindoles.⁶⁸

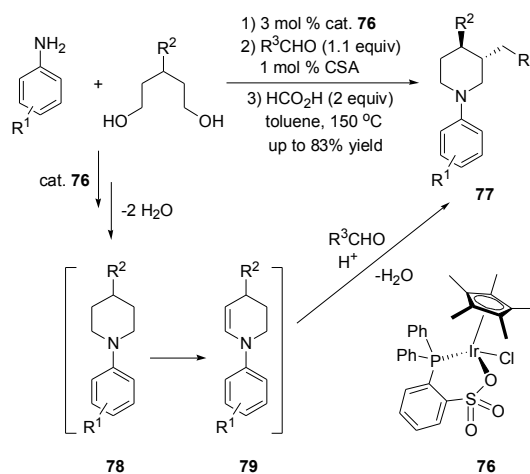
of naphthylamines with diols by using the $IrCl_3 \cdot 3H_2O$ /BINAP catalyst system (Scheme 14).⁶⁸ The N-heterocyclization reaction was found to be remarkably influenced by the ligands employed. With the same protocol, benzindoles **72** were obtained. Treatment of 1,3-propanediol with 2 equiv of aniline in the presence of Ir-NHC complex **73** or **74** gave a mixture of

mono- and diamination products **75a** and **75b** or a mixture of the diamination and reductive mono-amination products **75b** and **75c** (Scheme 15).⁶⁹ The iridium complex catalysts played a crucial role in the product selectivity. Iridium- and ruthenium-catalyzed synthesis of 2,3-disubstituted indoles was realized from the BH reactions of anilines with vicinal diols.⁷⁰ Using either $[Cp^*IrCl_2]_2$ /MsOH or $RuCl_3 \cdot xH_2O$ /phosphine (phosphine = PPh_3 or Xantphos) gave various indole derivatives with water and hydrogen as the side products. Iridium(III) complex **76** featuring a phosphane-sulfonate chelate exhibited good catalytic efficiency for the direct



Scheme 15 Amination of 1,3-propanediol with aniline.⁶⁹

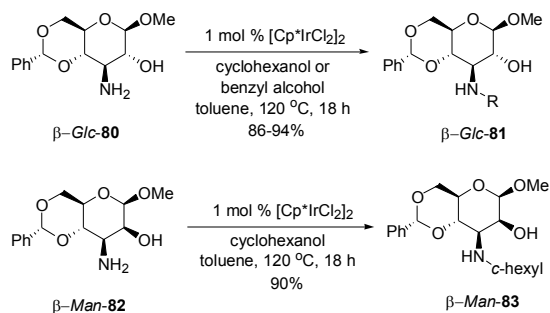
endo dehydrogenation of piperidine, allowing the tandem protocol for the three-component preparation of diverse N-aryl piperidine derivatives **77** from the easily accessible primary amines, diols, and aldehydes (Scheme 16).⁷¹ In the overall catalytic cycle, species **78** and **79** were confirmed as the reaction intermediates, and three hydrogen auto-transfers and one hydrogen transfer occurred with the sole precatalyst, that is, complex **76**.



Scheme 16 Tandem hydrogen-transfer processes.⁷¹

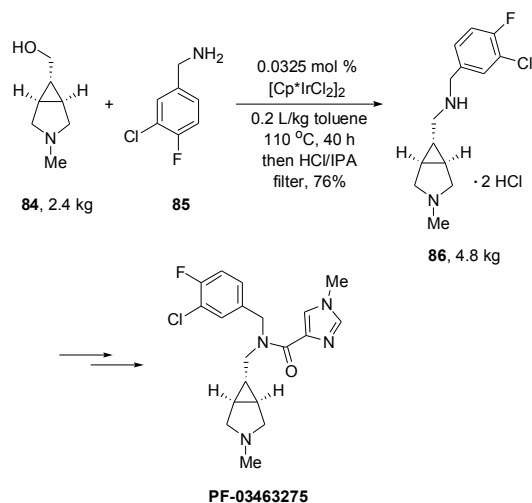
The BH N-alkylation strategy can be applied for the functionalization of carbohydrates. The iridium-catalyzed condensation of alcohols and amines was applied as a method for aminosugar synthesis (Scheme 17).⁷² Primary carbohydrate amines at primary and secondary carbons were alkylated by alcohols in the presence of $[Cp^*IrCl_2]_2$. Hexopyranosides with a primary amine at C3 and with a secondary alcohol unprotected (*viz* β -Glc-**80** and β -Man-**82**) underwent efficient N-alkylation

with cyclohexanol or benzyl alcohol. Products due to redox epimerisation or amination of the unprotected secondary alcohol groups were not detected.



Scheme 17 Iridium-catalyzed alkylation of C3 carbohydrate amines with alcohols.⁷²

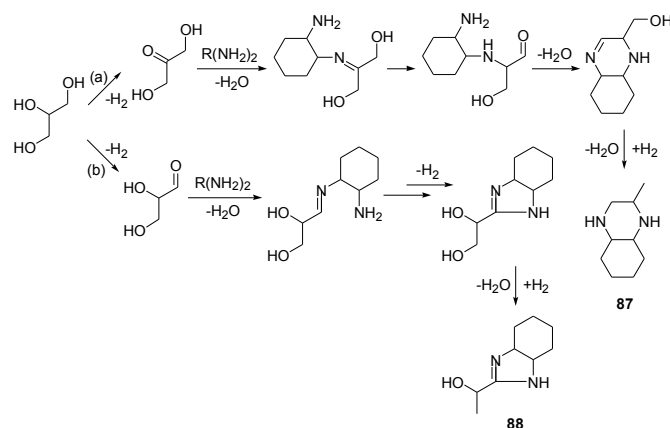
The first kilogram-scale application of the borrowing hydrogen strategy, that is, transition metal-catalyzed redox-neutral coupling of an alcohol with an amine, was achieved to synthesize **PF-03463275**, a GlyT1 inhibitor developed for the treatment of schizophrenia (Scheme 18).⁷³ Less than 0.05 mol % $[\text{Cp}^*\text{IrCl}_2]_2$ was used as the catalyst. Water and a tertiary amine were essential for the high catalytic activity, resulting in dramatically increased reaction rates as compared to the known protocols. The drug intermediate, that is, amine **86**, was thus synthesized on a kilogram scale, which shortened the traditional four-step medicinal procedure to a one-pot process to access it.



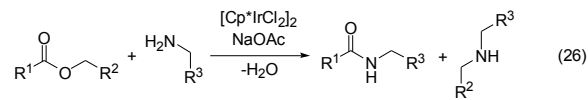
Scheme 18 Scale-up preparation of drug intermediate **86**.⁷³

Conversion of biomass to value-added chemicals is strongly desired.⁷⁴ Glycerol as a bio-renewable alcohol was successfully used for N-alkylation of 1,2-diaminocyclohexane in water, catalyzed by $[\text{Cp}^*\text{IrCl}_2]_2$, and the reaction gave a mixture of 2-methyldecahydroquinoxaline (**87**) and hexahydro-1H-benzimidazole (**88**).⁷⁵ A preliminary mechanism is proposed in Scheme 19. Following path *a*, dehydrogenation of the secondary hydroxyl group of glycerol leads to an intermediate in which coordinated dihydroxyacetone undergoes amine attack with formation of the imine; cyclization, dehydration, and returning of hydrogen results in product **87**. In the case that the primary hydroxyl group of glycerol coordinates to iridium, glycerol undergoes first dehydro-

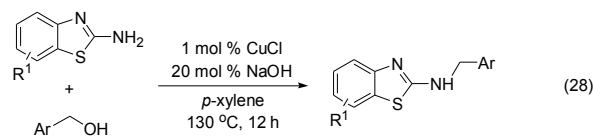
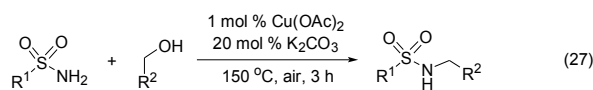
genation to form glyceraldehyde, then attack by the amine, and the resultant imine is cyclized and dehydrogenated to the N-heterocyclic core which is further dehydrated and reduced by the *in-situ* generated hydrogen to produce **88** (path *b*).



Scheme 19 Iridium-promoted amination of glycerol with a diamine.⁷⁵



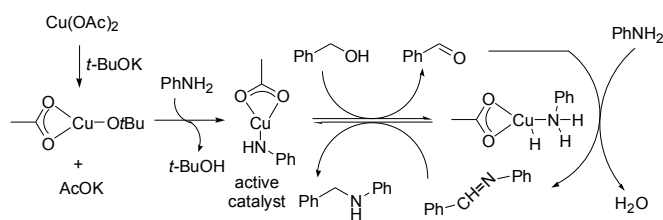
The BH strategy can also be used to trap a reaction side-product to make it value-added and thus render the process more atom-economic. Iridium(III)-catalyzed tandem synthesis of amides and amines from esters under solvent-free conditions was realized.⁷⁶ The combination of $[\text{Cp}^*\text{IrCl}_2]_2$ and NaOAc mediated the reaction of an ester with a primary amine, affording the target amide and secondary amine $\text{R}^2\text{CH}_2\text{NHCH}_2\text{R}^3$ (eqn (26)). The new amide was formed by ester-amide exchange which released alcohol R^2OH *in situ* and subsequently transformed to the secondary amine through interaction with the excessive primary amine $\text{R}^3\text{CH}_2\text{NH}_2$ substrate *via* borrowing hydrogen. Eventually, water was produced as the sole by-product. This method expands the synthetic versatility of ester transformation.



2.1.3 Copper catalysts

Copper compounds have also been reported to catalyze the borrowing hydrogen substitution of alcohols by N-nucleophiles. $\text{Cu}(\text{OAc})_2$ acted as the effective catalyst for the substitution of alcohols by sulfonamides (eqn (27)),⁷⁷ it also promoted the N-monoalkylation of poor nucleophilic amines such as aromatic and heteroaromatic amines as well as carboxamides, phosphinamides, and phosphazenes with primary alcohols.⁷⁸⁻⁸⁰ A combination of CuCl and NaOH was used as the catalyst system for the regiose-

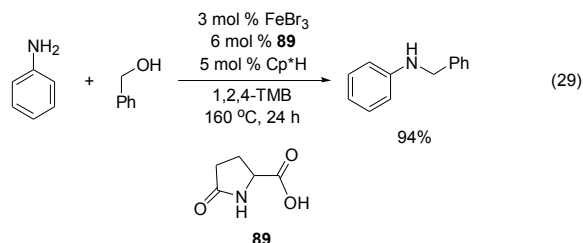
lective N-alkylation of 2-aminobenzothiazoles with benzylic alcohols, forming secondary amines in good to excellent yields (eqn (28)).⁸¹ DFT calculations were carried out to explore the mechanism of Cu(OAc)₂-catalyzed substitution of primary alcohols by amines.⁸² The study reveals that *t*-BuOK base is necessary for the generation of the catalytically active species from Cu(OAc)₂, and the catalytic cycle consists of three sequential steps: (1) Cu(II)-catalyzed alcohol oxidation to form the corresponding aldehyde and copper hydride; (2) aldehyde-amine condensation to generate an imine intermediate; (3) imine reduction by the copper hydride to yield the desired secondary amine product and regenerate the active catalyst (Scheme 20).



Scheme 20 Cu(OAc)₂-catalyzed substitution of primary alcohols by amines.⁸²

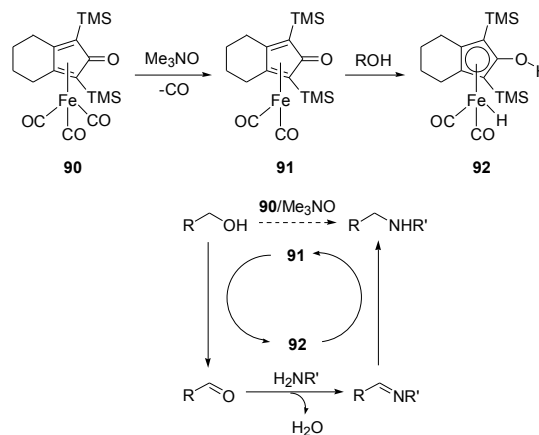
2.1.4 Iron catalysts

Readily available unmodified magnetite (Fe₃O₄) catalyzed selective N-monoalkylation of aromatic amines with benzylic alcohols to give secondary amines through a BH pathway, and the catalyst (20 mol %) could be recycled for up to eight times without losing effectiveness.⁸³ The FeCl₂/K₂CO₃ catalyst system catalyzed the N-alkylation of sulfonamides with benzylic alcohols to form the corresponding N-monoalkylated sulfonamides in > 90% yields.⁸⁴ The XPS analysis suggests a possible catalytic



cycle between Fe(II) and Fe(0) species. Treatment of a 1,2,4-trimethylbenzene (1,2,4-TMB) solution of aniline (6 mmol) with benzyl alcohol (3 mmol) in the presence of FeBr₃ (3 mol %) and DL-pyroglutamic acid (ligand **89**, 6 mol %) at 160 °C for 24 h gave the corresponding monoalkylated amine product (eqn (29)).⁸⁵

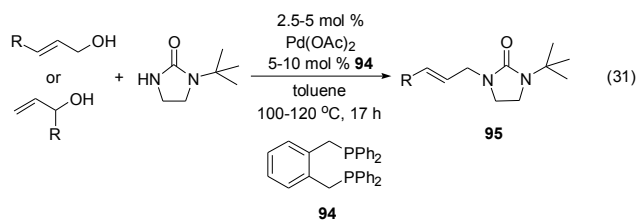
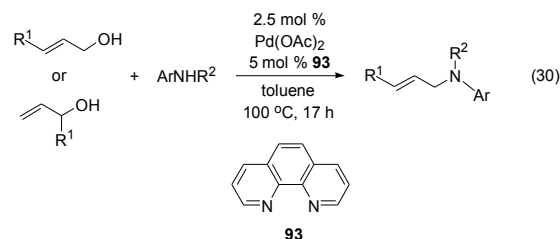
Direct C-N bond formation with an iron complex catalyst is also possible through a borrowing hydrogen mechanism if the catalytic complex is bifunctional in nature and can exhibit suitable activity for both alcohol dehydrogenation and imine hydrogenation in the overall BH process. Iron(0) complex **90** was successfully employed as the precatalyst for the substitution of alcohols with amines via the *in-situ* generated bifunctional iron species **91**, which can be converted to its reduced, hydride form **92** (Scheme 21).⁸⁶ Such a synthetic methodology is effective for the monoalkylation of anilines and benzyl amines with various alcohols, and five to seven-membered nitrogen heterocycles were also obtained by using diols as the alkylating agents.



Scheme 21 Iron(0) complex-catalyzed substitution of alcohols by amines.⁸⁶

2.1.5 Palladium catalysts

Efficient amination of allylic alcohols with aryl and alkyl amines was achieved by means of Pd(OAc)₂/1,10-phenanthroline (**93**) as the catalyst, affording allylic amines (eqn (30)).⁸⁷ The reactions of cinnamyl and other allylic alcohols with 1-*tert*-butylimidazolidin-2-one and derivatives may also follow a BH mechanism, forming N-allylated N-heterocycles **95** (eqn (31)).⁸⁸ Notably, compound 1,2-bis(diphenylphosphinomethyl)benzene **94** was

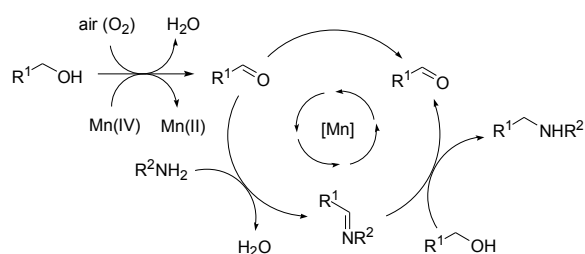


identified as the most effective ligand. Palladium acetate also worked as a versatile catalyst for the selective N-monoalkylation of amino derivatives with poor nucleophilic character, such as aromatic and heteroaromatic amines as well as carboxamides, sulfonamides, and phosphazenes, in all cases, by using primary alcohols as the initial source of the electrophile through a borrowing hydrogen or hydrogen autotransfer process.⁸⁹ Both the Pd(OAc)₂/K₂CO₃ in air⁹⁰ and PdCl₂/dppe/LiOH⁹¹ systems have been documented for the N-alkylation of amides and amines with alcohols using the aerobic relay race methodology and the N-alkylation of amines with primary and secondary alcohols.

2.1.6 Other transition metal catalysts

Osmium hydride complexes usually possess good air, moisture, and thermal stability, and are promising catalysts for substitution

of alcohols by amines.^{92,93} $\text{ReH}_7(\text{PCy}_3)_2$ was also reported to promote the amination of alcohols via a BH pathway, and a carbon monoxide atmosphere was crucial to the N-alkylation of primary amines with a variety of primary and secondary alcohols.⁹⁴ $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ with an oxidant (O_2 , etc.) effected the N-alkylation reactions of amines and amides with alcohols.⁹⁵ In this case, a direct amination pathway can not be excluded and the N-alkylation might proceed via allylated rhodium species. Manganese dioxide catalyzed the N-alkylation of sulfonamides and amines with alcohols under air.⁹⁶ A base was necessary and the reaction became slow under a nitrogen atmosphere. It was confirmed that the imine intermediate underwent transfer hydrogenation from the alcohol substrate to form the secondary amine product as well as the corresponding aldehyde (Scheme 22). It is noteworthy that bimetallic alloys and complexes such as Raney nickel⁹⁷ and Ir-[N3]-M-type ($\text{M} = \text{Pd}, \text{Ir}$) complexes⁹⁸ can be employed for the same purpose. A highly efficient homogeneous $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgOTf}$ catalyst was developed for the BH substitution of benzylic alcohols with amines.⁹⁹ This catalytic system exhibited excellent selectivity for the monoalkylation of primary amines with these alcohols.



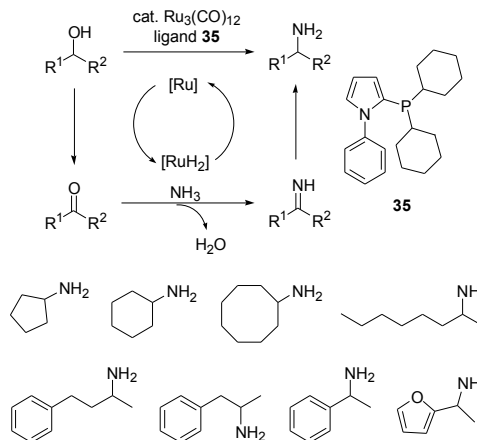
Scheme 22 MnO_2 -catalyzed N-alkylation of amines with alcohols.⁹⁶

2.2 Substitution of alcohols by ammonia

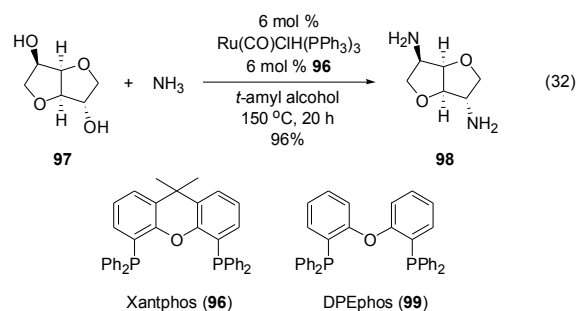
2.2.1 Ruthenium catalysts

Primary amines are very useful intermediates for further derivation reactions. Although numerous synthetic procedures including reduction of nitro and nitrile compounds have been developed for such a task, synthesis of primary amines is still an active area in academic laboratories. The borrowing hydrogen methodology has been widely employed to synthesize higher-order amines from primary amines, but this method has not been paid considerable attention for the preparation of primary amines.¹⁰⁰ Almost at the same time, Beller¹⁰¹ and Vogt⁴³ reported $\text{Ru}_3(\text{CO})_{12}$ -catalyzed amination of secondary alcohols with ammonia in the presence of the pyrrole phosphine ligand, i.e., **35**, directly affording primary amines (Scheme 23). With 6–10 mol % $\text{Ru}_3(\text{CO})_{12}$ as the catalyst, **35** as the ligand, and *t*-amyl alcohol or cyclohexane as the solvent, the reaction of a secondary alcohol with liquid ammonia was conducted in a stainless-steel autoclave at 140–150 °C to form the corresponding primary amine product. Various primary amines were thus prepared in up to 86% yields.

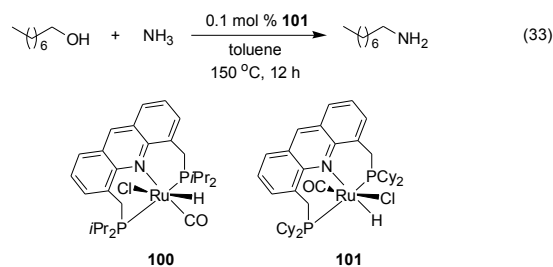
With $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3/\text{Xantphos}$ (**96**) as the catalyst, isosorbide (**97**) was diaminated by ammonia in *t*-amyl alcohol at 150 °C for 20 h (eqn (32)).¹⁰² In addition, other primary and secondary alcohols as well as diols including hydroxyl-substituted esters could be efficiently converted to the corresponding amines or diamines in good to excellent yields. A combination of the same Ru(II) precatalyst and DPEphos (**99**) played the same role in amination of various alcohols with



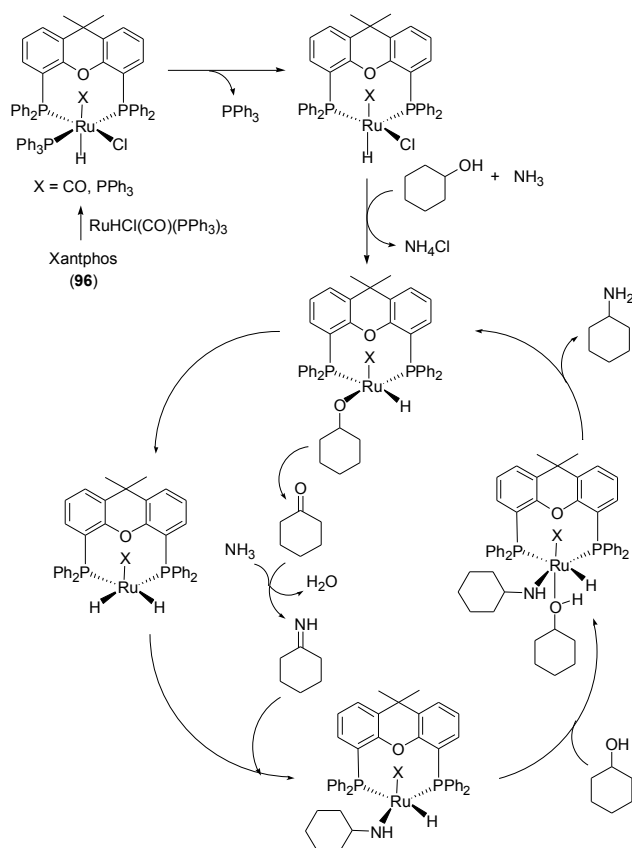
Scheme 23 Synthesis of primary amines from secondary alcohols and ammonia.^{43,101}



ammonia.¹⁰³ The selective catalytic diamination of other primary and secondary diols with ammonia was also realized to give the corresponding diamines in good yields and high selectivity. These results are in compliance with the publication of Milstein's pioneering work,¹⁰⁰ and one of the possible RuH intermediate species has been confirmed.¹⁰⁴



The mechanistic details were investigated for the amination of alcohols with ammonia catalyzed by a structurally modified congener of Milstein's acridine-based PNP-pincer Ru(II) complex **100**, that is, complex **101** (eqn (33)).¹⁰⁰ The experimental results and DFT calculations about the catalytically active species as well as the behaviors of the substrates and intermediates have suggested that no metal-ligand cooperation is required for the high catalyst activity and selectivity.¹⁰⁵ The amination of cyclohexanol with ammonia catalyzed by $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3/\text{Xantphos}$ (**96**) was investigated in order to gain a mechanistic insight (Scheme 24).¹⁰⁶ The NMR studies revealed that the reaction of the Ru(II) complex/**96** with alcohol in the presence of a strong base initially formed an inactive dihy-



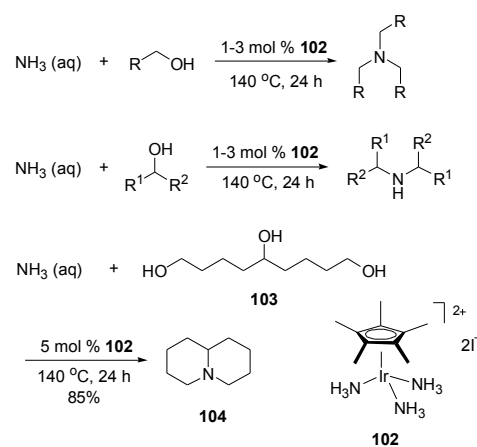
Scheme 24 Amination of alcohols with NH_3 by using $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3/\text{Xantphos}$ (**96**) catalyst.¹⁰⁶

drido ruthenium species. Addition of a ketone made the dihydride (re)activated by means of the *in-situ* generated imine from condensation of the ketone with NH_3 as the activator. The subsequent reaction occurring at the metal center thus resulted in the target primary amine product and generated the catalytically active $\text{Ru}(\text{II})$ -alkoxide species. Such a mechanism was very closely related to the known transfer hydrogenation mechanism.¹⁰⁷ It was observed that the catalyst systems consisting of $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ and fluxional Xantphos-type ligands exhibited very different catalytic activities for the direct amination of cyclohexanol with ammonia, depending on the different structures of the slightly bent backbones of the ligands.¹⁰⁸

2.2.2 Iridium catalysts

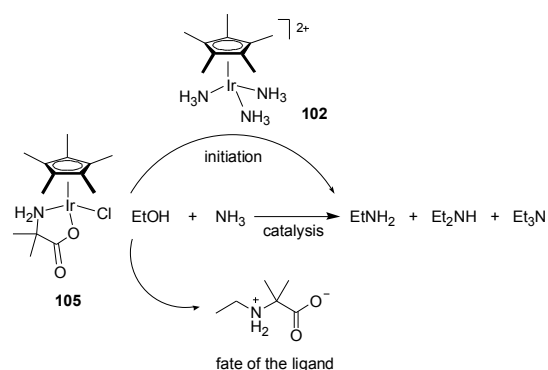
Iridium complexes are also effective catalysts to promote the amination of alcohols with ammonia. By means of water-soluble $\text{Cp}^*\text{Ir}(\text{NH}_3)_3\text{I}_2$ (**102**), the 28% aqueous solution of ammonia was applied for the synthesis of higher-order amines from alcohols (Scheme 25).¹⁰⁹ A variety of secondary and tertiary amines were synthesized by the multialkylation of aqueous ammonia with theoretical equivalents of primary and secondary alcohols. The catalyst could be recycled by a facile procedure maintaining high activity. The reaction of aqueous ammonia with 1,5,9-nonanetriol (**103**) was performed at 140 °C for 24 h in the presence of **102** (5 mol %), affording quinolizidine (**104**) in 85% yield. This method provides a rapid approach to quinolizidine in a one-flask operation.

The use of aminoacidato $\text{Cp}^*\text{Ir}(\text{III})$ -complexes in the catalytic alcohol amination reactions of primary and secondary alcohols with amines permits to carry out these transformations under very

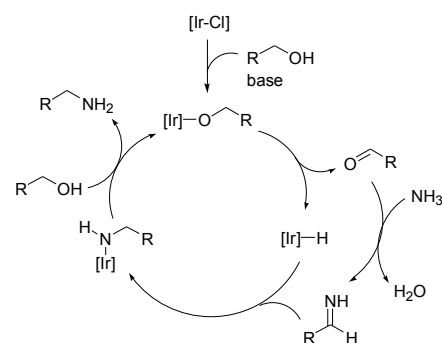


Scheme 25 Amination of alcohols using 28% aqueous ammonia.¹⁰⁹

mild conditions without use of an additional base.¹¹⁰ Dissociation of the chelating ligand from complex **105** occurred during the initiation period of the reaction to generate the more active species **102**, which promoted amination of short-chain ethanol with ammonia, forming a mixture of EtNH_2 , Et_2NH , and Et_3N (Scheme 26). The amination pathway is depicted in Scheme 27, which is similar to that by using a $\text{Ru}(\text{II})$ complex catalyst (Scheme 24).¹⁰⁶



Scheme 26 Amination of ethanol by ammonia.¹¹⁰

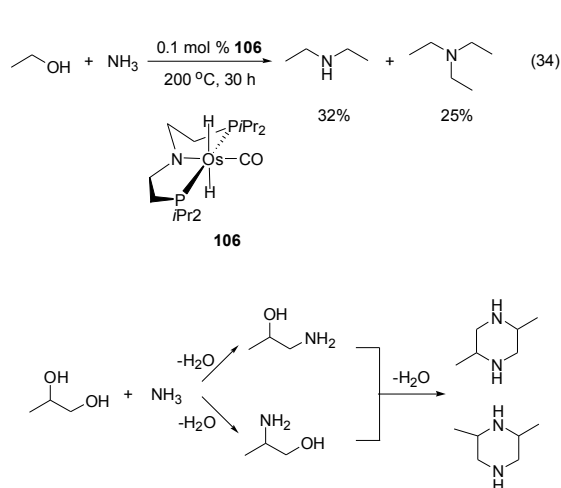


Scheme 27 A proposed mechanism for iridium-catalyzed amination of alcohols by ammonia.¹¹⁰

2.2.3 Other transition metal catalysts

The osmium hydride complex **106** mediated the reaction of ethanol with ammonia at 200 °C to form diethylamine (32%) and

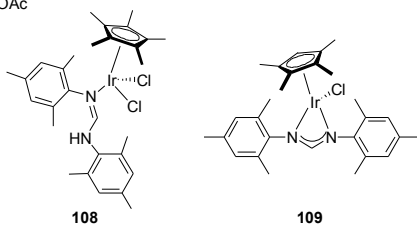
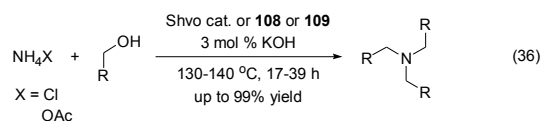
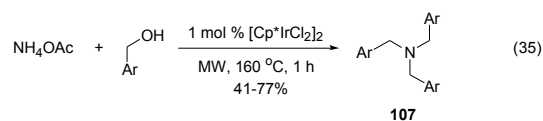
triethylamine (25%), exhibiting a potential application in the preparation of short-chain aliphatic primary amines (eqn (34)).⁹² The Rh-In bimetallic catalysts supported on carbon were applied for the amination of alcohols with ammonia in an aqueous phase,¹¹¹ and the reaction of 1,2-propanediol with NH₃ was conducted at 180 °C for 24 h under 5 MPa hydrogen atmosphere, affording a mixture of 1-amino-2-propanol, 2-amino-1-propanol, and dimethylpiperazines (Scheme 28).^{111,112}



Scheme 28 Amination of 1,2-propanediol using ammonia.^{111,112}

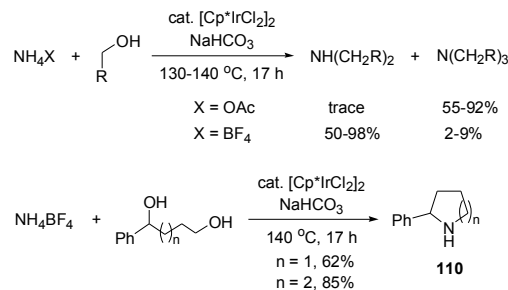
2.2.4 Using ammonium salts

The surrogates of ammonia, that is, ammonium salts, were also used as the nitrogen source for the synthesis of higher-order amines with alcohols as the alkylating agents. Trialkylation of ammonium acetate was conducted with excessive amount of benzylic alcohols at 160 °C in the presence of 1 mol % [Cp*IrCl₂]₂ under microwave conditions (eqn (35)),⁶⁷ giving tertiary amines **107** as the products. Both Shvo's catalyst and



[Cp*IrCl₂(amidine)] (**108**) promoted the reactions of NH₄X (X = Cl, OAc) with primary alcohols, efficiently affording the corresponding tertiary amine products (eqn (36)).¹¹³ The high catalytic activity of complex **108** may be attributed to the presence of an NH moiety in the amidine ligand, which renders the formation of species **109** *in situ* to act as the precatalyst. Both

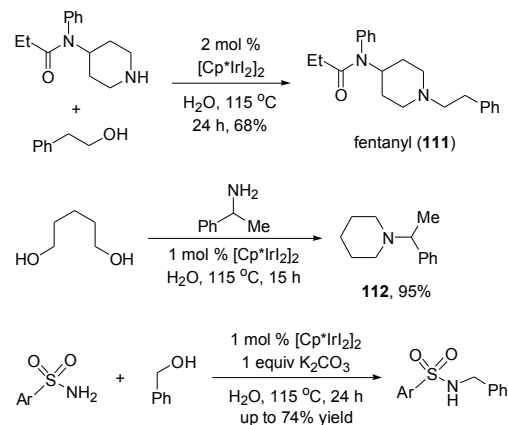
NH₄OAc and NH₄BF₄ were used as the nitrogen sources under solvent-free conditions: the reactions of ammonium acetate with alcohols gave tertiary amines exclusively, whereas those of ammonium tetrafluoroborate afforded secondary amines selectively (Scheme 29).¹¹⁴ Using this method, five- and six-membered cyclic amines **110** were synthesized from ammonium tetrafluoroborate and diols in one pot.



Scheme 29 Multialkylation of ammonium salts with alcohols.¹¹⁴

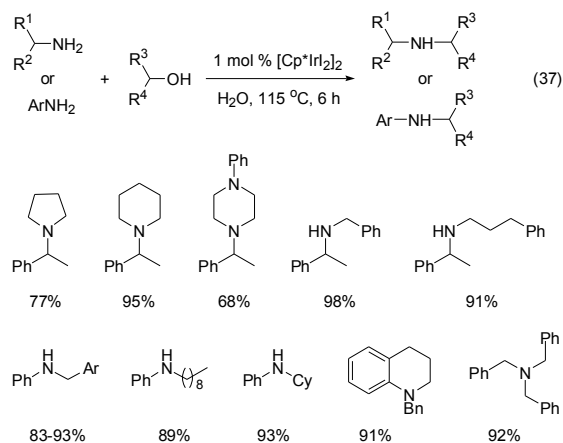
2.3 Substitution of alcohols by N-nucleophiles in aqueous phase

Substitution of alcohols by N-nucleophiles (or N-alkylation of amines with alcohols and related compounds) can be performed in aqueous phase. [Cp*IrI₂]₂ was found to be an efficient catalyst for the alkylation of amines with alcohols in water.^{115,116} Primary amines could be converted to secondary amines, and secondary amines to tertiary amines in the absence of a base. The protocol was successfully applied for the synthesis of the analgesic fentanyl (**111**), and the conversion of primary amines into N-heterocycles **112** by their reactions with diols was realized, along with the N-alkylation of sulfonamides (Scheme 30).

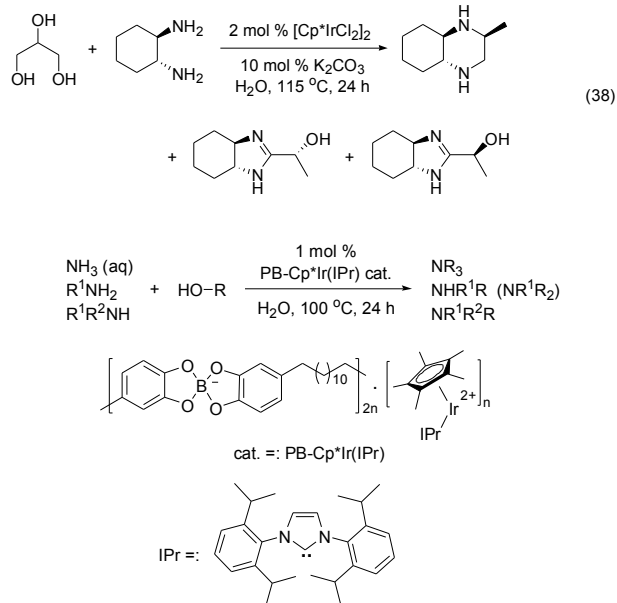


Scheme 30 Substitution of alcohols by amines in water.^{115,116}

Short-chain isopropanol was used as the alkylating agent to form N-isopropylamines. With water-soluble and air-stable iridium-amine complex [Cp*Ir(NH₃)₃]₂ (**102**) as the catalyst, various secondary and tertiary amines were synthesized by the N-alkylation reactions of theoretical equivalents of amines and alcohols in water without a base under air.^{117,118} In this case, versatile alcohols and amines were employed to undergo the BH-type reactions, giving the target higher-order amine products (eqn (37)).



N-Alkylation of poor nucleophilic sulfonamides with alcohols was performed in water by means of water-soluble iridium complex $\{Cp^*Ir[6,6'-(OH)_2-bpy](H_2O)\}_2(OTf)_2$.¹¹⁹ The OH functionality is crucial for the catalytic activity of the complex. Polyols could be employed for the preparation of N-heterocycles in water.¹²⁰⁻¹²² Glycerol was aminated by 1,2-diaminocyclohexane in water in the presence of 2 mol % $[Cp^*IrCl_2]_2$ and 10 mol % K_2CO_3 , affording a mixture of N-heterocyclic products within 24 h (eqn (38)).⁷⁵ Under aerobic conditions, the boron-iridium heterobimetallic polymeric catalyst, that is, PB- $Cp^*Ir(IPr)$, was applied for the N-alkylation of ammonia and

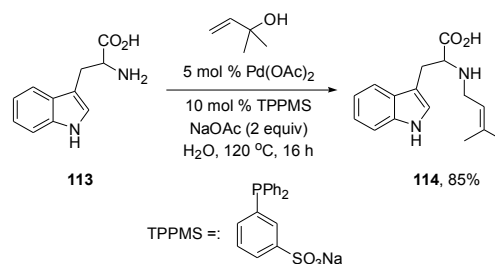


Scheme 31 N-Alkylation of amines with alcohols in water using a polymeric heterobimetallic catalyst.^{122,123}

amines with alcohols in water without the use of organic solvents, giving the corresponding alkylated amines (Scheme 31).^{122,123}

Palladium-catalyzed N-alkylation of unprotected amino acid **113** with 1,1-dimethylallyl alcohol was performed in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % water-soluble ligand sodium diphenylphosphinobenzene-3-sulfonate (TPPMS), and NaOAc (2 equiv) in water at 120 °C for 16 h, selectively producing N-monoalkylated amino acid **114** in 85% yield (Scheme 32).¹²⁴ Other catalyst systems were also reported for substitution of

alcohols by N-nucleophiles in water.^{55,100,109} These results have demonstrated promising applications of the synthetic protocols in green synthesis.

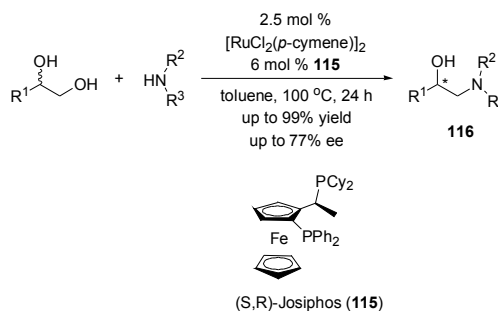


Scheme 32 N-Alkylation of amino acid with tertiary alcohol in water.¹²⁴

2.4 Enantioselective substitution of alcohols by amines

2.4.1 Ruthenium catalysts

Chiral amines are widely used in pharmaceutical and fine chemical industries. Many methods have been developed to prepare them. Asymmetric hydrogenation of ketimines or reductive amination of ketones are known to reach this goal. However, external reductants such as hydrogen gas, Hantzsch esters, silanes, and formic acid have to be used for these processes. The recently well-developed BH or HA strategy has begun to be paid attention in asymmetric catalysis.^{125,126} Ruthenium-catalyzed enantioselective synthesis of β -amino alcohols from 1,2-diols by using $[RuCl_2(p\text{-cymene})]_2/(S,R)\text{-Josiphos (115)}$ catalysis was reported.¹²⁷ Treatment of the racemic diols with secondary amines afforded the corresponding optically active β -amino alcohols **116** in up to 99% yield with 77% ee (Scheme 33).

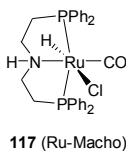
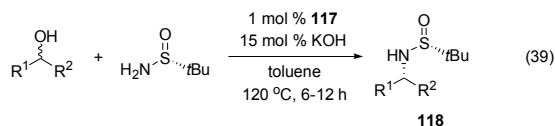


Scheme 33 Asymmetric substitution of diols by amines.¹²⁷

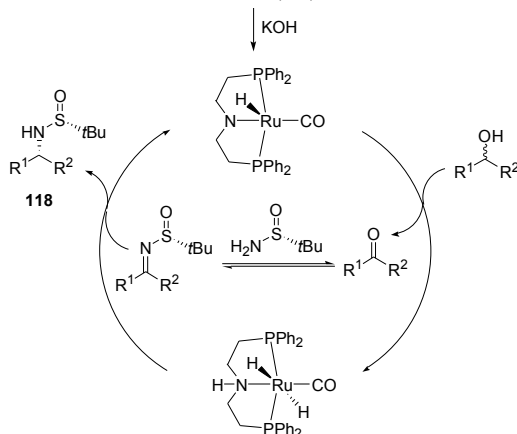
Commercially available ruthenium(II) PNP-type pincer complex catalyst (Ru-Macho, **117**) promoted the formation of α -chiral *tert*-butanesulfinylamines (**118**) from racemic secondary alcohols and chiral *tert*-butanesulfinamides in up to 89% yields with > 95:5 dr via a hydrogen borrowing strategy (eqn (39)).¹²⁸ A simplified BH mechanism is proposed in Scheme 34. This study offers an effective synthetic protocol to access chiral amines by means of the widely used Ellman's sulfinamide auxiliary and the inexpensive and industrially relevant Ru-Macho catalyst.

2.4.2 Iridium catalysts

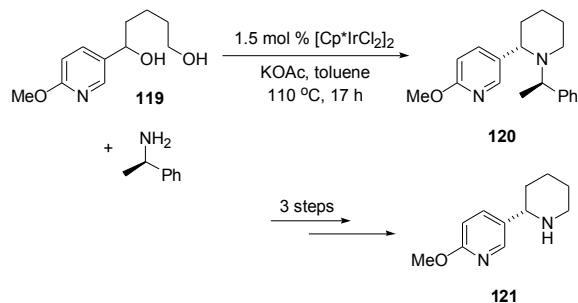
The combination of $[Cp^*IrCl_2]_2$ and KOAc promoted the enan-



Ru-Macho (117)

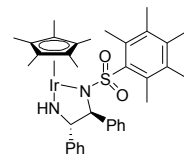
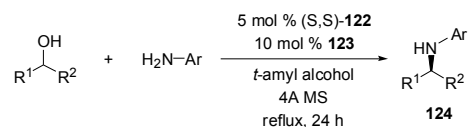
**Scheme 34** Asymmetric amination of alcohols using Ellman's sulfinamides.¹²⁸

tioreselective N-heterocyclization of 1-(5-methoxypyridin-3-yl)-1,5-pentanediol (**119**) with either (*R*)- or (*S*)-1-phenylethyl-amine, generating 2-(pyridin-3-yl)piperidine ring system **120** in 69-72% yield (Scheme 35).¹²⁹ Compound **120** can be used for the preparation of the *R* and *S* enantiomers of the amphibian alkaloid

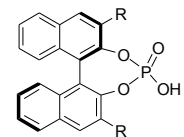
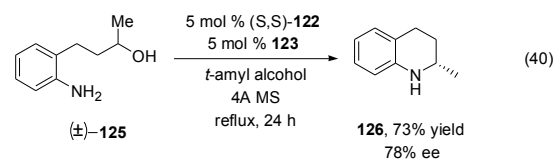
**Scheme 35** Enantioselective amination of diols via BH N-alkylation of amines.¹²⁹

noranabasamine (**121**). Asymmetric amination of alcohols through the borrowing hydrogen methodology was achieved in the presence of a chiral phosphoric acid under iridium catalysis.¹³⁰ By combining iridium complex **122** supported by a chiral ligand with chiral phosphoric acid **123**, the asymmetric amination of secondary alcohols with aromatic amines was established to produce chiral amines **124** with up to 97% ee (Scheme 36).¹³⁰ In a similar manner, the intramolecular amination in (\pm)-**125** was achieved, affording the chiral quinoline product **126** bearing a simple methyl substituent (eqn (40)). It is noted that the higher loading of ligand **123** relative to the precatalyst **122** was not necessary, suggesting that the intramolecular imine-condensation

step was efficient enough, even in the absence of the external acid cocatalyst.

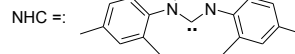
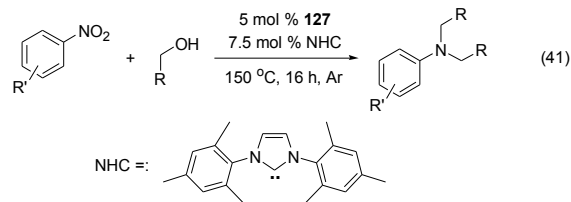


(S,S)-122

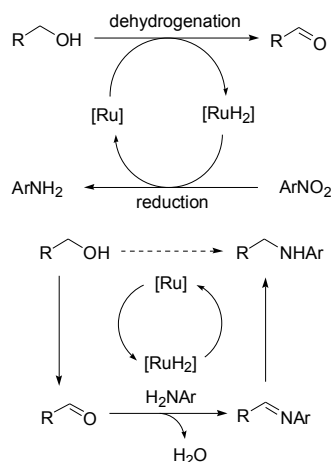
123 (R = 2,4,6-IPr₃C₆H₂)**Scheme 36** Asymmetric N-alkylation of amines with alcohols.¹³⁰

2.5 Reductive N-alkylation with alcohols

Nitroarenes are cheap and readily available in bulks and the reduction of nitro compounds is a key step in the preparation of many pharmaceuticals and fine chemicals. Based on the above-established synthetic systems using alcohols, it is reasonable to envision the synthesis of secondary amines through a BH strategy by using the commercially available and inexpensive nitroarenes and alcohols as the starting materials. For such a transformation the alcohol may serve as both the hydrogen source for nitro reduction and the alkylating agent for the *in-situ* generated amine intermediate through a borrowing hydrogen pathway. Because amine is temporarily formed during the reaction and subsequently consumed by its condensation with the aldehyde intermediate generated *in situ* from the alcohol substrate, the relevant discussion is included in this section. Although excessive amount of alcohol is required, such a protocol is still considered as a convenient and simple approach to access secondary amines. In this aspect, homogeneous and heterogeneous transition metal catalysts have recently been reported.

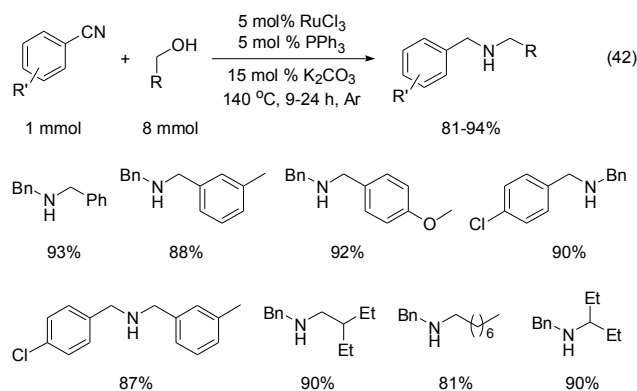


With the Ru(II) complex catalyst, that is, Ru(CO)(H)₂(PPh₃)₃ (**127**)/NHC, nitroarenes reacted with excessive amount of primary alcohols (7.5 equiv) at 150 °C under an argon atmosphere afforded the corresponding tertiary amines (eqn (41)).¹³¹ Such a process combined two catalytic cycles: the nitro reduction to amine, and N-alkylation of the resultant amine with the alcohol through a borrowing hydrogen pathway. That is, the alcohol oxidation, nitro reduction and imine reduction were realized in a

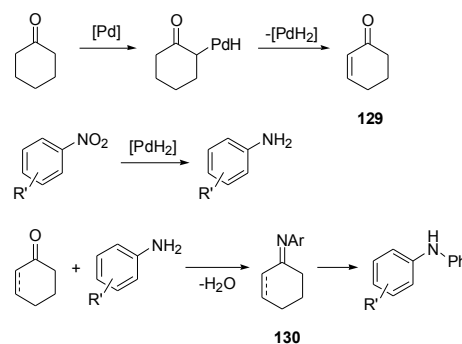
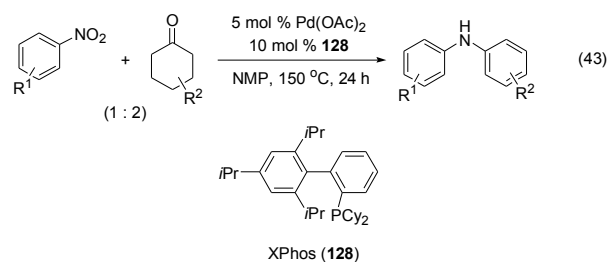


Scheme 37 Ruthenium-catalyzed direct amination of alcohols with nitroarenes.¹³¹

cascade (Scheme 37). When benzyl alcohol and other primary alcohols were used as the alkylating agents/hydrogen donors, the target tertiary amine products were obtained in moderate to excellent yields. It should be noted that excessive alcohol up to 7.5 equiv was required to get the decent yields for the target products. In the presence of a base, i.e., K_2CO_3 , 2.5 mol % $[Ru(p\text{-cymene})Cl_2]/dppb$ ($dppb = Ph_2P(CH_2)_4PPh_2$) promoted the reactions of nitroarenes with primary alcohols at 130 °C under an argon atmosphere to yield the corresponding secondary amines in 70-95% isolated yields.¹³² However, in the case of using benzonitriles as the substrates, more harsh conditions were applied to produce the same secondary amine products (eqn (42)).



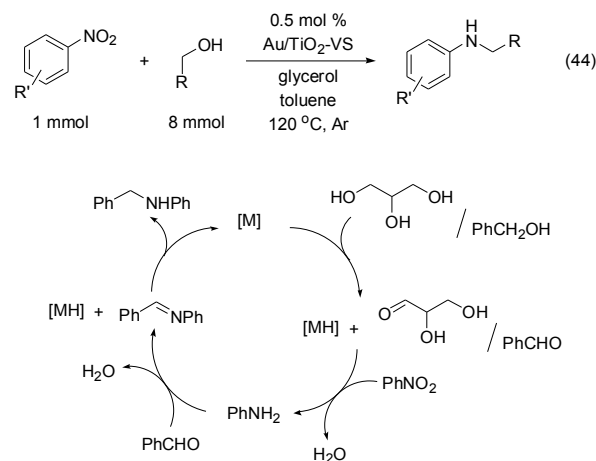
A similar catalyst system mediated the synthesis of tertiary amines from nitriles and alcohols.¹³³ By means of $Ru(acac)_3/dppe/KHCO_3$ as the catalyst, secondary amines were also obtained from the reactions of nitroarenes in the presence of excessive primary alcohols.¹³⁴ With $Pd(OAc)_2/Xantphos$ (**96**) or $XPhos$ (**128**) as the catalyst, the reactions of nitroarenes with cyclohexanone, the oxidized form of cyclohexanol, formed diarylamines in good to excellent yields (eqn (43)).¹³⁵ The nitro reduction, cyclohexanone dehydrogenation, imine formation and reduction were performed in a cascade without using any external reducing reagent and oxidant. A simplified mechanism is proposed in Scheme 38. The palladium catalyst activates cyclohexanone to undergo dehydrogenation to form cyclic enone **129** through β -elimination. Nitrobenzene is reduced to the corresponding aniline, which continues the aldol condensation with the *in-situ* generated



Scheme 38 Palladium-catalyzed one-pot diarylamine formation.¹³⁵

cyclic enone or cyclohexanone itself to produce imine **130**. Subsequent dehydrogenation and reduction of the imine intermediate **130** affords the diarylamine product. It is noted that $XPhos$ (**128**) worked as efficiently as $Xantphos$ (**96**) did.

With very small Au NPs (approximately 1.8 nm) deposited on TiO_2 ($Au/TiO_2\text{-VS}$) as the catalyst, nitroarenes could be efficiently alkylated to the corresponding secondary amines in the presence of 8 equiv of primary alcohols (eqn (44)).¹³⁶ Up to 99% yields were reached from the reactions performed in toluene at 120 °C. A highly efficient $Au/Ag\text{-Mo}$ nano-rods catalyst ($Au/Ag\text{-Mo-NR}$) was developed to promote the one-pot synthesis of amines and imines by using equivalents of nitrobenzenes and

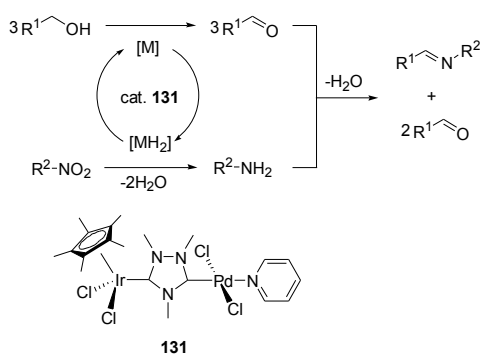


Scheme 39 Reductive coupling of nitrobenzenes with alcohols using glycerol as the hydrogen source.¹³⁷

alcohols as the starting materials, and bio-based glycerol as the hydrogen source.¹³⁷ Formation of the amine and imine products depended on the temperature. When the 1:1 molar ratio reaction of a nitrobenzene with an alcohol was carried out in refluxing

toluene in the presence of K_2CO_3 base and glycerol for 24 h, the corresponding imine was formed in up to 98% yields. In refluxing xylene at 150 °C, the amine product was obtained in up to 91% yields. A plausible mechanism is depicted in Scheme 39. Variation of the reaction parameters led to the intermediate as the major product.

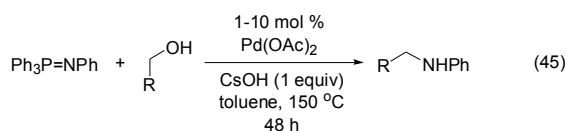
In the presence of 1.3 mol % $CuO-Fe_3O_4$ catalyst and 300 mol % NaOH, nitrobenzene reacted with benzylic alcohols in toluene at 130 °C for 3 days to afford the corresponding imines ($ArCH=NPh$) as the major products (61-84%).¹³⁸ An Ir-Pd heterobimetallic complex catalyst (**131**) and its [Ir-Ir] and [Pd-Pd] analogues catalyzed the reactions of nitroarenes with excessive amount of benzylic alcohols in the presence of Cs_2CO_3 base at 100 °C efficiently afforded the corresponding imines and aldehydes.¹³⁹ Such a transformation can be considered as a variation of the well-defined borrowing hydrogen substitution process of alcohols by amines (or N-alkylation of amines with alcohols) (Scheme 40).



Scheme 40 Reductive BH process for N-alkylation of nitrobenzenes with alcohols.¹³⁹

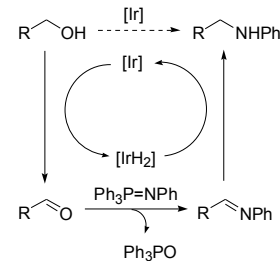
2.6 Indirect Wittig amination of alcohols

Palladium was reported as the catalyst for the alkylation of nitrogenated compounds through a BH or hydrogen transfer process. The indirect aza-Wittig reactions of N-(triphenylphosphoranylidene)aniline with alcohols (2 equiv), 1-10 mol % palladium(II) acetate, and cesium hydroxide (1 equiv) in toluene at 150 °C for 48 h gave the target secondary amine products in up to 97% yields (eqn (45)).¹⁴⁰ $[Ir(COD)Cl]_2$ was also documented for the same purpose.¹⁴¹ The relevant mechanism is demonstrated in Scheme 41.



3. Heterogeneous transition metal-catalyzed substitution of alcohols by N-nucleophiles

As reported in the literatures, most of the successful catalyst systems for substitution of alcohols by N-nucleophiles (or N-alkylation of amines and the related compounds with alcohols) are transition metal complex-based homogeneous catalyst systems, which are usually inapplicable for scale-up production because of the problem of catalyst reusability and/or the indis-

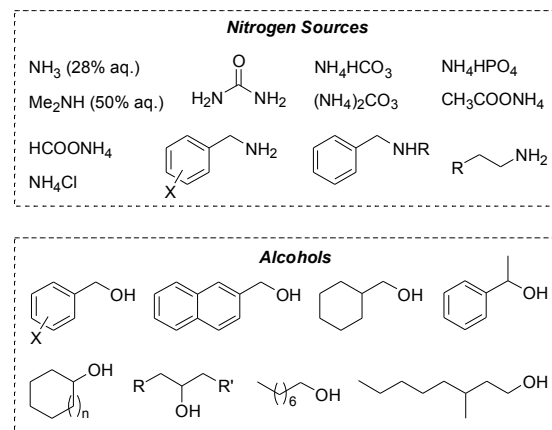
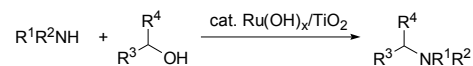


Scheme 41 Indirect Wittig amination of alcohols.^{140,141}

ispensable use of large amounts of additives or co-catalysts. Heterogeneous transition metal catalysts can overcome some of the drawbacks of homogeneous catalysts, but they often have to suffer from harsh reaction conditions, low turnover numbers and frequencies, limited substrate scope, and use of excessive amount of alcohols to obtain satisfactory yields. Thus, exploration of efficient heterogeneous transition metal catalyst systems has recently aroused considerable attention for borrowing hydrogen or hydrogen autotransfer processes.

3.1 Ruthenium catalysts

Heterogeneous ruthenium catalysts have been known for the BH substitution of alcohols by N-nucleophiles. Substitution of primary alcohols by aromatic and heteroaromatic amines could be efficiently promoted by a supported ruthenium hydroxide catalyst $Ru(OH)_x/Al_2O_3$.¹⁴² A variety of primary aromatic and heteroaromatic amines were selectively converted to the corresponding secondary amines in moderate to excellent yields without using any co-catalyst such as a base and stabilizing ligand. Monitoring the reaction of benzyl alcohol (1.5 equiv) with

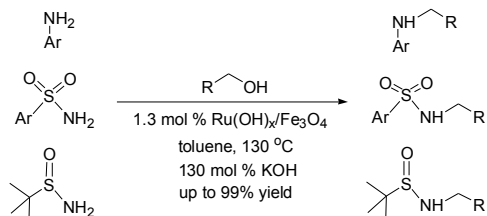


Scheme 42 $Ru(OH)_x/TiO_2$ -catalyzed N-alkylation of amines with alcohols.¹⁴³

aniline in mesitylene at 132 °C under an argon atmosphere by GC analysis revealed that in the presence of $Ru(OH)_x/Al_2O_3$ catalyst (5 mol % Ru) an imine intermediate was initially formed and then transformed to the target secondary amine product.

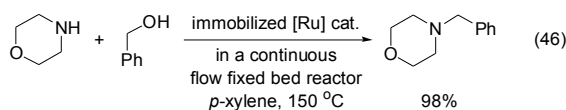
N-Alkylation of ammonia (or its surrogates, such as urea, NH_4HCO_3 , and $(NH_4)_2CO_3$), and amines with alcohols, including primary and secondary alcohols, was efficiently established under

anaerobic conditions by the supported ruthenium hydroxide catalyst, that is, $\text{Ru}(\text{OH})_x/\text{TiO}_2$ (Scheme 42).¹⁴³ Notably, the catalytic activity of a physical mixture of $\text{Ru}(\text{OH})_x \cdot n\text{H}_2\text{O}$ and TiO_2 powders was usually comparable to that of $\text{Ru}(\text{OH})_x \cdot n\text{H}_2\text{O}$, and much lower than that of $\text{Ru}(\text{OH})_x/\text{TiO}_2$, suggesting that the highly dispersed ruthenium hydroxide species is essential for a decent catalyst performance.



Scheme 43 $\text{Ru}(\text{OH})_x/\text{Fe}_3\text{O}_4$ -catalyzed substitution of alcohols by amines.¹⁴⁴

Impregnated ruthenium on magnetite (Fe_3O_4) could behave as a recyclable catalyst for the selective N-monoalkylation of amino derivatives with poor nucleophilic character, such as aromatic and heteroaromatic amines, sulfonamides, sulfonamides, and nitroarenes, with alcohols (Scheme 43).¹⁴⁴ The alkylation of amines in the presence of KOH base rendered the N-monoalkylated amines, and the same protocol using NaOH yielded the related imines. Such a catalyst could be easily removed by a simple magnet and was reused for up to ten times, exhibiting the same catalytic activity. A nano-Ru/ Fe_3O_4 catalyst was applied for the efficient synthesis of N-monoalkylated sulfonamides from the BH reactions of unsubstituted sulfonamides with primary alcohols.¹⁴⁵ The mechanistic studies suggests dehydrogenation of the alcohol to be the rate-determining step. Ru^{3+} immobilized on a calcium hydroxyapatite (HAP) support was used to catalyze the substitution of alcohols by amines without the need for base co-catalysts, base pretreatment of the catalyst, or ligands.¹⁴⁶ In general, the catalytic activities of $\text{Ru}(\text{OH})_x/\text{Al}_2\text{O}_3$ and $\text{Ru}(\text{OH})_x/\text{TiO}_2$ were much higher than that of Ru/HAP.^{142,143} Ruthenium catalysts supported by polystyrene- or silica-supported phosphine ligands exhibited good to excellent catalytic activity towards the substitution of primary alcohols by both primary and secondary amines at 120–140 °C, affording the target products in 62–99% yields.¹⁴⁷ These catalysts could be recycled with low ruthenium leaching.

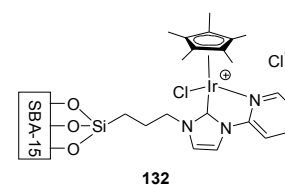
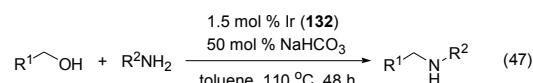


The continuous flow substitution of alcohols by amines was tested by using the supported catalysts in a column reactor. The *anti*-Parkinson agent Piribedil (**7**) was thus synthesized in 98% yield. For real industrial scale-up production, a continuous reaction process is always desired. Using a heterogeneous ruthenium catalyst in a continuous flow fixed bed catalytic reactor, substitution of benzyl alcohol by morpholine was realized (eqn (46)).¹⁴⁸ The 1:1 molar ratio reaction was thus conducted in such a continuous flow reactor, where the catalytic polymer beads were retained in the bed. Operating at 150 °C and using *p*-xylene as the solvent, the conversion into the desired tertiary amine was shown to be as high as 98%. This approach is

very promising for clean and atom-economic scale-up production of secondary and tertiary amines in the pharmaceutical industry.

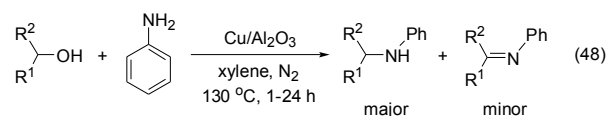
3.2 Iridium catalysts

Mesoporous silica (SBA-15)-supported pyrimidine-substituted N-heterocyclic carbene iridium complex **132** was used as the catalyst for the environmentally benign substitution of primary alcohols by amines (eqn (47)), giving the secondary amine products in 52–99% yields.¹⁴⁹ The catalyst was reused for more than nine times without notable decrease in its catalytic efficiency. A bifunctional Ir-Zr based metal-organic framework (MOF) heterogeneous catalyst was also applied for the substitution of alcohols by amines,¹⁵⁰ and the catalyst worked well even in air in the absence of a base.



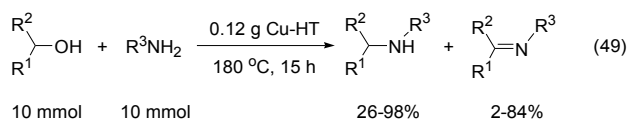
3.3 Copper catalysts

Heterogeneous copper catalysts are another type of effective catalysts for the BH substitution of alcohols by amines. Supported copper hydroxide $\text{Cu}(\text{OH})_x/\text{TiO}_2$ (or Al_2O_3) could act as the catalyst for the synthesis of secondary amines via N-alkylation of the primary amines and ammonia with alcohols.¹⁵¹ Diverse symmetrically and unsymmetrically substituted tertiary amines were thus synthesized. The $\text{Cu}/\text{Al}_2\text{O}_3$ catalyst was used for the N-alkylation of anilines with benzylic alcohols to furnish secondary amines.¹⁵² It should be noted that this process did not require any additive, was intrinsically safe and produced no waste. However, in most cases imines were formed as the minor products (eqn (48)). The Al_2O_3 -supported copper-silver bimeta-



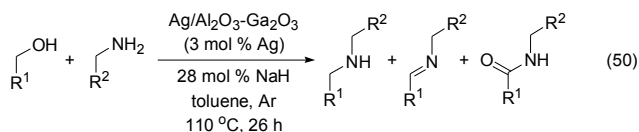
llic catalyst with a Cu/Ag molar ratio of 95/5 ($\text{Cu}_{0.95}\text{Ag}_{0.05}/\text{Al}_2\text{O}_3$) effected the substitution of various alcohols (benzylic and aliphatic alcohols) by anilines and aliphatic amines.¹⁵³ A simple non-noble metal catalyst NiCuFeO_x was designed and prepared for the N-alkylation of ammonia or amines with alcohols.¹⁵⁴ In the absence of organic ligands and bases, primary amines were efficiently transformed into secondary amines and N-heterocyclic compounds, and secondary amines could be N-alkylated to form tertiary amines. In particular, primary and secondary amines can be produced through a one-pot reaction of ammonia with alcohols. Using a Mg-Al hydrotalcite supported copper catalyst (Cu-HT, Mg/Al molar ratio = 2:1), the substitution of primary and secondary alcohols by anilines and primary amines afforded a mixture of the target secondary amine products (26–98%) and

the imine intermediates (2-84%).¹⁵⁵ This route is featured a solvent-, ligand-, and base-free process for clean BH production of amines and imines (eqn (49)).



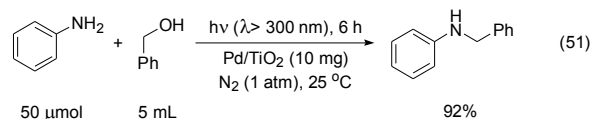
3.4 Silver catalysts

The silver catalysts immobilized on various supports such as the Ag/Mo hybrid material with specific $\text{Ag}_6\text{Mo}_{10}\text{O}_{33}$ crystal structure¹⁵⁶ and $\text{Ag}/\text{Al}_2\text{O}_3$ ¹⁵⁷ catalyzed the substitution of alcohols by amines, carboxamides, and sulfonamides. Relatively weak bases, that is, K_2CO_3 , Cs_2CO_3 and K_3PO_4 , were usually necessary as the additives. The reactions were conducted at up to 160 °C under solvent-free conditions by using excess of the alcohol substrates, affording the target products in up to 99% isolated yields. Silver nanoparticles generated from AgNO_3 and NaH were immobilized on the mixed Al_2O_3 - Ga_2O_3 supports to promote alcohol amination under mild conditions.¹⁵⁸ TEM characterization revealed a close interaction of the Ag NPs and the gallium oxide phase. Using the optimal molar ratio of alcohol:amine (2:1) this hybrid material catalyzed the reactions of primary alcohols with amines to produce the target secondary amines, imines, or amides as the products, and the product selectivity was strongly primary amine-dependent (eqn (50)).



3.5 Palladium catalysts

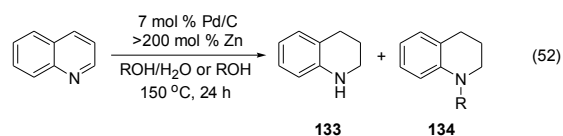
N-Monoalkylation of amines with alcohols occurred on TiO_2 loaded with palladium nanoparticles, giving secondary amines in nearly quantitative yields.¹⁵⁹ The process proceeded via tandem photocatalytic and catalytic reactions: (i) Pd-assisted alcohol oxidation on the photoactivated TiO_2 ; (ii) condensation of the formed aldehyde and amine on the TiO_2 surface; and (iii) hydrogenation of the formed imine by the surface hydrogen atoms on the Pd particles. The rate-determining step is the imine hydrogenation, and the reaction strongly depended on the size of the palladium nanoparticles. In order to reach high yields for the secondary amine products, low concentration of the starting amine substrates (50 μmol) was applied (eqn (51)).



A new Pd-substituted octahedral molecular sieve (Pd/K-OMS-2) was prepared and employed for the direct amination of alcohols with primary amines operating under the borrowing hydrogen mechanism.¹⁶⁰ The catalyst offered full conversion and high selectivity towards N-benzylaniline in the model alkylation

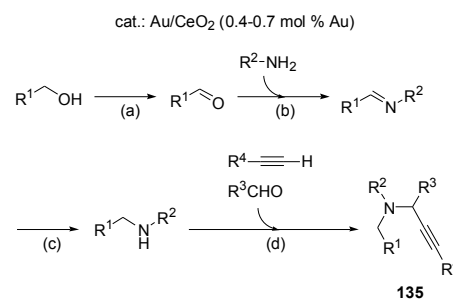
reaction of aniline with benzyl alcohol at 160 °C for 3 h, producing neither of the tertiary amine nor toluene. Pd/K-OMS-2 performed as a tandem tri-functional catalyst, first oxidizing benzyl alcohol to benzaldehyde, then behaving as a Lewis acid for imine formation, and finally reducing the imine intermediate to the corresponding secondary amine. An iron oxide immobilized palladium catalyst effected the N-alkylation of amines with alcohols under base- and organic ligand-free conditions, forming secondary and tertiary amines in up to 99% isolated yields.¹⁶¹

Palladium nanoparticles (Pd NPs) generated *in situ* from complex (dippe)PdMe₂ were used as the efficient catalyst for the N-alkylation of amines with aliphatic alcohols using the neat conditions, under hydrogen atmosphere.¹⁶² Using short chain alcohols led to di- and trialkylated amines in >80% yields, while use of bulky alcohols afforded the corresponding mono-alkylated amines. The Pd/C/Zn system mediated the N-alkylation of quinolines with alcohols (eqn (52)).¹⁶³ The reaction is featured a BH process and afforded 1,2,3,4-tetrahydro-quinolines **133** and N-alkylated tetrahydroquinolines **134** in excellent yields in one step by varying the loading of zinc dust and the category of alcohols.



3.6 Other metal catalysts

By means of Au/ TiO_2 -VS (VS = very small, *ca.* 1.8 nm Au NPs) as the catalyst, N-alkylation of aniline with primary and secondary alcohols underwent in toluene at 120 °C under 5 atm N_2 atmosphere, giving the secondary amine products in up to 95% yield.¹⁶⁴ Coupling of the two multistep catalytic cycles for

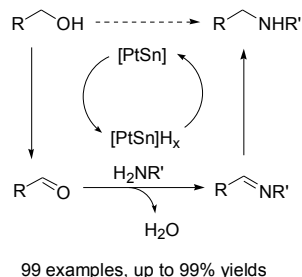


Scheme 44 Au/ CeO_2 -catalyzed one-pot synthesis of propargylamines.¹⁶⁵

the one-pot synthesis of propargylamines **135** from primary amines and alcohols on the nanoparticulated gold catalyst Au/ CeO_2 (2.5 wt % Au) was achieved (Scheme 44).¹⁶⁵ The three-step cycle (a-c) follows a BH pathway to give the N-monoalkylated product. The nature of R^3CHO and alkyne ($\text{R}^4\text{C}\equiv\text{CH}$) had a critical influence on the global reaction. The best combination was to use a benzylalcohol and benzylamine for steps a-c, then a cyclic aliphatic aldehyde and an aromatic terminal alkyne for step d.

The commercially available heterogeneous bimetallic Pt-Sn/ γ - Al_2O_3 catalyst (Pt:Sn = 1:3, 0.5 wt % Pt) exhibited a very high catalytic activity for the substitution of alcohols by amines (Scheme 45).^{166,167} The support effect, Pt:Sn molar ratio, and

reaction atmosphere are crucial for the high catalytic activity and selectivity. A wide substrate scope of 99 examples was presented and the target products were obtained in up to 99% isolated yields. The catalyst could be recycled for three times without loss of its catalytic activity and Pt metal leaching, demonstrating the potential for application in the direct production of secondary and tertiary amines.

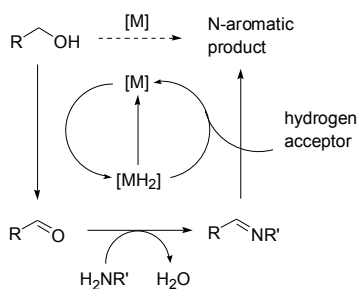


Scheme 45 Pt-Sn/ γ -Al₂O₃-catalyzed substitution of alcohols by amines.¹⁶⁶

Nickel nanoparticles (Ni NPs) loaded on various supports have been shown diverse catalytic activity to promote N-alkylation of amines with alcohols.¹⁶⁸⁻¹⁷⁰ Colloidal nickel and cobalt catalysts enabled the N-alkylation of amines with primary alcohols.¹⁷¹ Sulfated tungstate as a heterogeneous catalyst for N-alkylation of amines with alcohols could eliminate overalkylation of the amine substrates, selectively producing N-monoalkylated higher-order amine products.¹⁷²

4. Semi-borrowing hydrogen N-heterocyclization

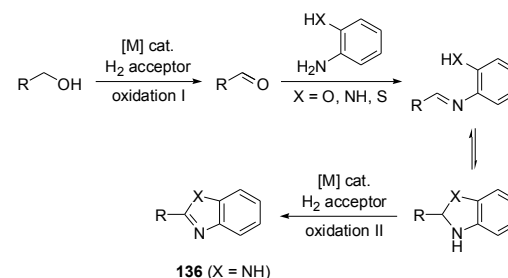
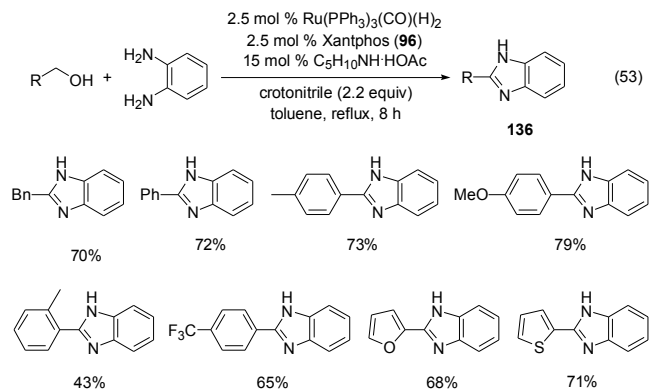
In this paper, a *semi*-borrowing hydrogen sequence is defined as a process in which the initial oxidation reaction of alcohol liberates hydrogen, and the released hydrogen is not returned to the target product, but consumed by an external hydrogen acceptor or returned to a side product during the reaction (Scheme 46). Unsaturated compounds are usually used as the external hydrogen acceptors.¹⁷³⁻¹⁷⁵



Scheme 46 *Semi*-borrowing hydrogen substitution of alcohols by amines.

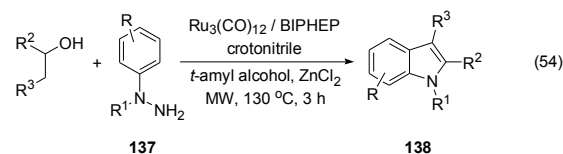
By means of Ru(PPh₃)₃(CO)(H)₂/Xantphos (**96**) as the catalyst in the presence of piperidinium acetate and crotonitrile (2.2 equiv) the reactions of primary alcohols with *o*-aminoaniline in refluxing toluene afforded benzimidazoles (**136**) in moderate to good yields (eqn (53)).¹⁷⁶ The sacrificial agent (hydrogen acceptor), that is, crotonitrile, played a crucial role in promoting the desired reaction. A general *semi*-BH mechanism is demonstrated in Scheme 47. Ruthenium(III) complexes bearing a

cystamine-based disulfide ligand also acted the same way for the N-alkylation of *o*-substituted anilines, giving various benzimidazoles.⁴⁸



Scheme 47 *Semi*-BH mechanism for benzimidazole synthesis.¹⁷⁶

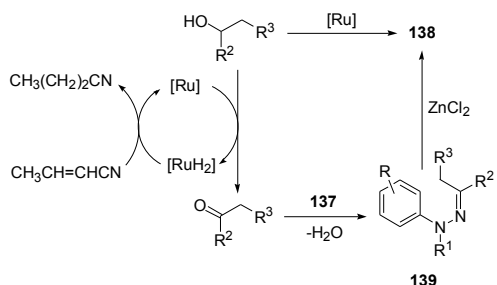
A new version of Fischer indole synthesis was developed in which primary and secondary alcohols were catalytically oxidized in the presence of arylhydrazines **137** and protic or Lewis acids under microwave-assisted ruthenium catalysis (eqn (54)).¹⁷⁷ Such a BH-based protocol efficiently afforded N-alkylated indoles **138**. The addition of phosphine ligands improved the yields, and use of BIPHEP (2,2'-bis(diphenylphosphanyl)-1,1'-biphenyl) led to the best results in terms of yield and purity of the



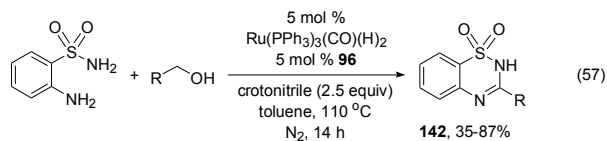
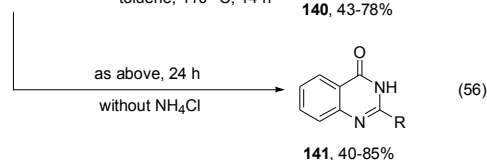
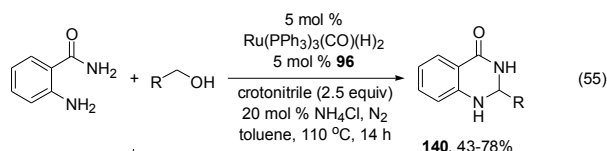
reaction mixture. In addition, microwave irradiation significantly increased the reaction rate enhancing the final indole yields. This method provides an easy route to access functional indoles. The overall reaction was accomplished in one step, and the use of alcohols instead of aldehydes or ketones as the starting materials has shown several advantages in terms of a large selection of reagents, easy handling, and safety of the process (Scheme 48).¹⁷⁷

Ruthenium-catalyzed *semi*-BH strategy has also been successfully applied for the conversion of primary alcohols into either 2,3-dihydroquinazolines **140** or quinazolines **141** and **142** by means of *o*-aminobenzamides and *o*-aminobenzenesulfonamides (eqn (55)-(57)).¹⁷⁸ The addition of 20 mol % NH₄Cl switched formation of the two heterocycle products. Using this protocol, the products could be purified by recrystallization from the

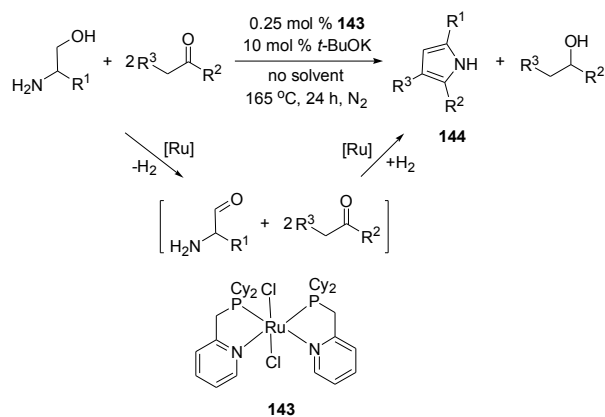
reaction mixture with no need for column chromatography.



Scheme 48 Ruthenium(0)-catalyzed synthesis of indoles in the presence of a hydrogen acceptor.¹⁷⁷



N-Unsubstituted pyrroles **144** through the ruthenium-promoted reactions of fully unmasked α -amino alcohols with ketones were synthesized. The α -amino alcohol was converted to the corresponding aldehyde which underwent cyclization with the ketone substrate (Scheme 49).¹⁷⁹ One additional equivalent of the ketone acted as the hydrogen acceptor during the reaction, and the overall reaction was salt-free and externally acceptorless. This process is featured high atom-, step-, and pot-economy, and avoids usually difficult multistep operations involving protection/deprotection.



Scheme 49 Salt-free synthesis of pyrroles.¹⁷⁹

5. Summary and outlook

The advances in transition metal-catalyzed “borrowing hydrogen” substitution of alcohols by N-nucleophiles (or N-alkylation of amines and related compounds with alcohols) since 2009 has been summarized. Diverse homogeneous organometallic and heterogeneous transition metal catalyst systems, challenging substrates such as amides and ammonia, transformations in aqueous phase, and asymmetric “BH” processes as well as scale-up preparation of industrially useful compounds are presented. Suitable discussions of the “BH” or “HA” strategy will bring chemists some new principles for activating substrates and establishing promising green processes to replace the relevant traditional synthetic methods for C-N bond formation.¹⁸⁰⁻¹⁸³

6. Acknowledgements

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