Recent Advances in Electrophilic Amination Reactions

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Abstract: Electrophilic nitrogen sources are an increasingly popular class of reagents for the formation of C–N bonds. Recently, a significant number of useful methodologies have been reported, in particular, examples using transition-metal catalysis. This review summarizes the latest developments in this field, with a focus on very recent advances.

Key words: amination, catalysis, heterocycles, C–H activation, organometallic reagents

Martin Corpet received his Licence de Chimie from the Université du Havre. He then moved to Université Pierre et Marie Curie, and received a JCEMolChem fellowship to spend a semester studying at the Université de Montreal, where he worked under the supervision of Professor Davit Zargarian. He completed his Masters at the Université Pierre et Marie Curie, working in Corinne Aubert's group, before joining Dr. Corinne Gosmini at Ecole Polytechnique, from where he received his PhD in 2013. Martin is now a postdoctoral fellow at the University of St Andrews, working in Professor Steven Nolan's group.

Corinne Gosmini was born near Paris in France. She obtained her PhD in chemistry at Université Pierre et Marie Curie under the supervision of Professor Jean F. Normant and Dr Raymond Sauvêtre. In 1993, she was appointed by the CNRS as Chargée de Recherches in the laboratory of Professor Jacques Périchon. She is currently CNRS Director of Research at the 'Laboratoire de Chimie Moleculaire' and Associate Professor at the Ecole Polytechnique in Palaiseau. In 2013, she became the director of the UMR 7653 and now of the UMR 9168. Her early interests were devoted toward the development of new electrochemical reactions catalyzed by nickel and cobalt complexes. Since 2003, her main research activities have been concerned with the development of new chemical coupling reactions, and the preparation of organometallic compounds catalyzed by cobalt complexes under versatile conditions in order to form C–C and C–N bonds.

1 Introduction

Most biologically active substructures and medicinal chemistry targets incorporate nitrogen atoms, hence the formation of C–N bonds remains an important area of study in organic chemistry. A large number of methodologies have been developed for the generation of C(sp^2)–N bonds. In the last decade, the transition-metal-catalyzed cross-coupling of electrophilic aryl halides with amines, a process more commonly known as the Buchwald–Hartwig amination,[1] has become an elegant and a powerful method for creating C–N bonds. These reactions normally involve palladium, copper, nickel or, more recently, cobalt centers, that are often supported by sophisticated and expensive ligands and generally require the use of a stoichiometric base and high reaction temperatures. Milder reaction conditions, with longer reaction times, can be accessed using other methods, such as the Chan–Lam copper-catalyzed oxidative coupling reaction of nucleophilic arylboronic species with amines.[2] Another method for generating C–N bonds involves an umpolung strategy that employs a nucleophilic organometallic reagent and an electrophilic nitrogen source (R_2N^+). This approach has traditionally received relatively little attention, but has recently been studied by several groups. A number of excellent reviews[3] covering the coupling chemistry of electrophilic nitrogen sources prior to 2012 are available in the literature; this review therefore focuses on more recent methodologies, and describes the reactions of electrophilic nitrogen sources involving either stoichiometric organometallic reagents, catalyzed C–H activation or enolate derivatives.

2 Reactions with Stoichiometric Organometallic Compounds

Several methodologies have been developed in which, instead of relying on an external oxidant (air or O_2), a hy-

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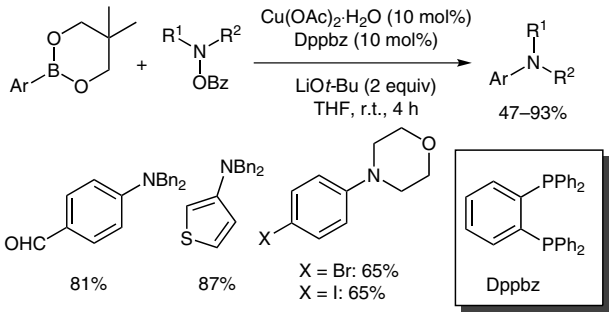
droxylamine derivative is used in the cross-coupling reaction. Transition-metal-catalyzed (Pd, Ni, Cu or Co), or metal-free electrophilic aminations of different organometallic reagents have thus received extensive attention for the preparation of different amines. In recent years, various organometallic species have been used, however, organoboron derivatives remain the most popular reagents.

2.1 Organoboron Nucleophiles

The amination of organoboron reagents using hydroxylamine-*O*-sulfonic acid was first reported by Brown,[4] but the uncatalyzed reaction could only be used to form primary amines. The use of catalysts, most notably those based upon copper, has allowed a much wider range of amines to be prepared from organoboron derivatives.

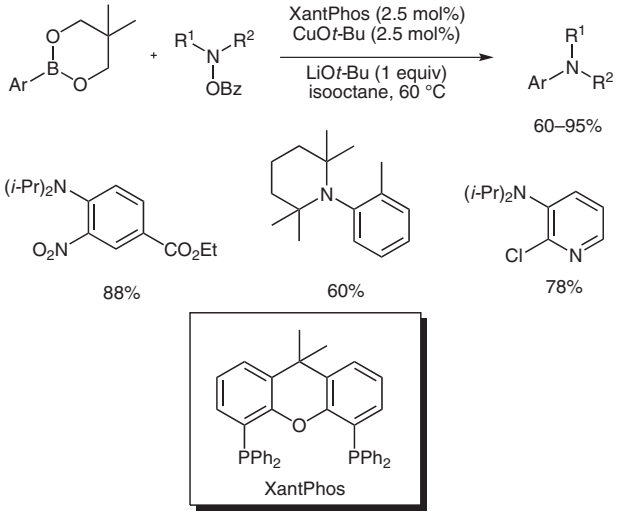
Recently, the group of Miura and Hirano reported that arylboronic acid derivatives could be coupled to *O*-benzoylhydroxylamines bearing alkyl groups, under mild conditions, by using an in situ generated copper(I)–diphosphine complex in the presence of lithium *tert*-butoxide (Scheme 1).[5] Moderate to good yields were obtained with a variety of functionalized compounds.



Scheme 1 Copper-catalyzed amination using Cu–Dppbz

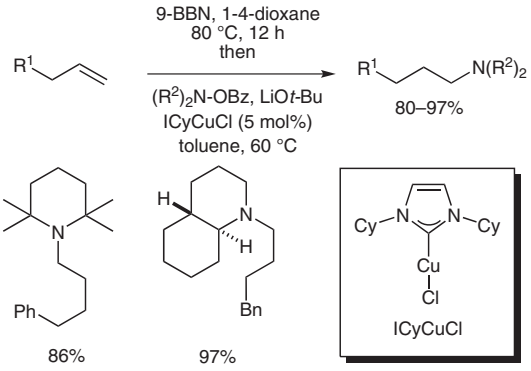
Lalic reported that the use of a ligand with a wider bite angle in a non-coordinating solvent allowed the reaction to proceed with higher efficiency (Scheme 2).[6] The reaction tolerated steric hindrance both on the amine moiety and on the aromatic group, and therefore allowed the formation of highly congested anilines in good to excellent yields. It has been proposed that a copper *tert*-butoxide complex is the catalytically active species, and that lithium *tert*-butoxide is necessary to prevent the formation of unreactive copper carboxylates. A copper–N-heterocyclic carbene (Cu–NHC) complex could also be used, albeit with reduced yields.

The same group showed that alkyl–9-BBN reagents also underwent amination, and that a copper–NHC complex was more efficient in this case (Scheme 3).[7] The alkylboron derivative was prepared by hydroboration of a terminal alkene and was used in situ for the subsequent cross-coupling step. This highly stereoselective protocol constitutes a convenient one-pot methodology for the anti-Markovnikov hydroamination of a double bond. This



Scheme 2 Copper–XantPhos-catalyzed amination with sterically demanding amines

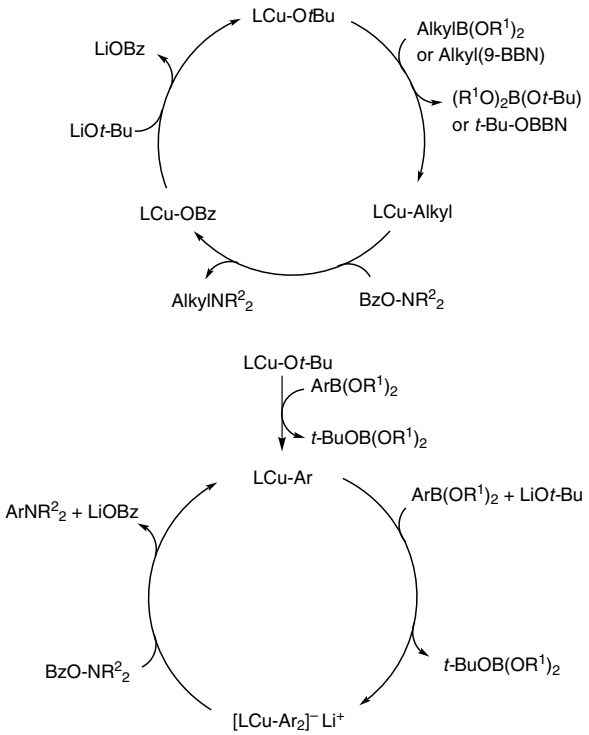
method is compatible with a wide range of functional groups and allows the preparation of sterically hindered amines.



Scheme 3 A hydroboration/amination sequence

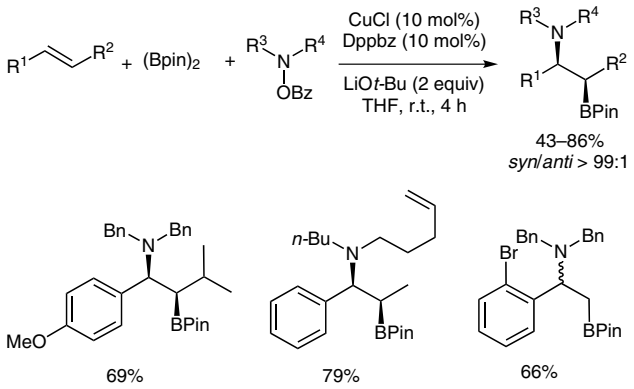
The coupling mechanism involves a copper *tert*-butoxide species that undergoes transmetallation with the organoborane to afford an organocopper derivative (Scheme 4). While Lalic believes that copper *tert*-butoxide is part of the catalytic cycle, Miura proposed that this step only allows entrance into the catalytic cycle.

Lalic showed that a monoaryl-copper species possessing a 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) ligand reacted efficiently with *O*-benzoylhydroxylamines to form the desired aniline derivatives.[7] However, experiments conducted by the Miura group indicated that a diarylcuprate might be the active species when sterically undemanding ligands were used.[8] In the former case, the reaction of the aryl-copper intermediate and counteranion exchange regenerated the copper *tert*-butoxide and liberated the arylamine. In the latter case, the diarylcuprate is proposed to react with the *O*-benzoylhydroxylamine to form the arylamine, with regeneration of the monoarylcopper species.



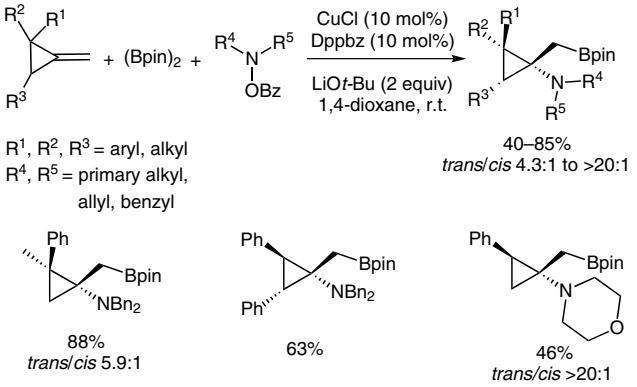
Scheme 4 Mechanisms proposed by Lalic (top) and Miura (bottom)

Miura and Hirano also applied their reaction conditions to a three-component copper-catalyzed aminoboration of styrenes, which used a combination of bis(pinacolato)diboron and *O*-benzoylhydroxylamines to allow the direct formation of β-boronated tertiary alkyl amines (Scheme 5).[8] This mild catalytic reaction worked equally well with terminal and internal double bonds, and proceeded with excellent regioselectivity, with the amine being introduced α with respect to the aromatic group.



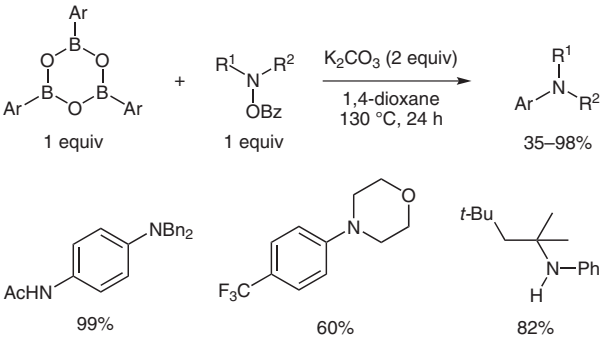
Scheme 5 Three-component *syn*-aminoboration

Very recently, the same group reported that such aminoborations could be applied to methylenecyclopropanes to give (borylmethyl)cyclopropylamines with good to excellent stereoselectivity (Scheme 6).[9] The products could be further functionalized, for instance, by Suzuki–Miyaura cross-coupling.



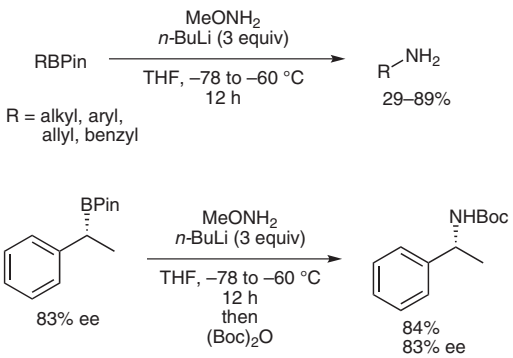
Scheme 6 Stereoselective aminoboration of methylenecyclopropanes

The use of an arylboroxine as a nucleophile in reactions with *O*-benzoylhydroxylamines in the presence of potassium carbonate as the base enabled metal-free aminations that gave the corresponding arylamines in moderate to excellent yields (Scheme 7).[10] A disadvantage was that relatively high temperatures were required and only one of the three aryl groups from the arylboroxine was transferred.



Scheme 7 Transition-metal-free amination of arylboroxines

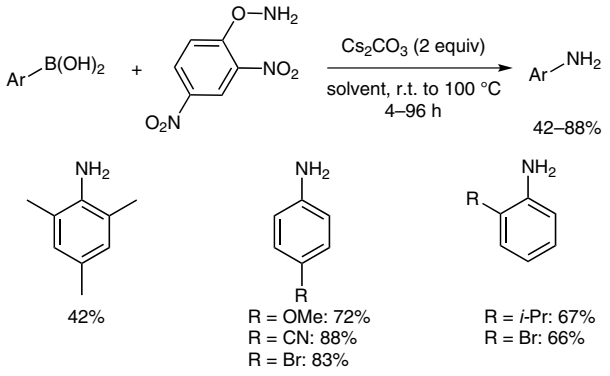
Generally, common boronic esters require transition metal catalysts in order to react with nitrogen electrophiles such as alkyl azides, chloroamines and hydroxylamine derivatives. However, Morken demonstrated a stereospecific amination of alkyl pinacolboronate esters by using a lithiated methoxylamine that gave rise to primary amines



Scheme 8 Enantiospecific amination using lithiated methoxylamine

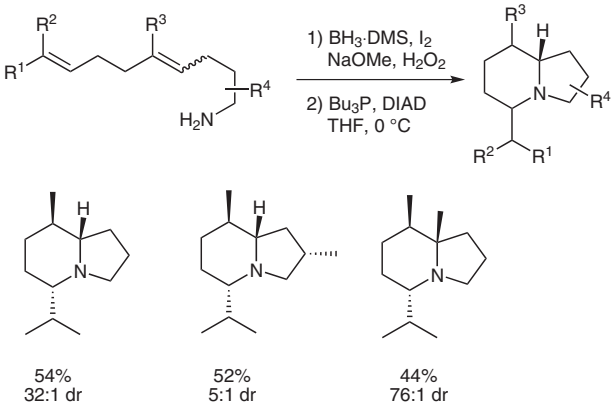
(Scheme 8).[11] *O*-Methylhydroxylamine was deprotonated in situ by *n*-butyllithium (*n*-BuLi), and the resulting ate complex furnished the corresponding amine in moderate to good yields, with retention of configuration at the boron-bearing carbon. Although the reaction was developed with alkyl-boron species, it was equally efficient with electron-rich aryl substituents. Finally, secondary alkyl pinacolboronate esters were well tolerated under these conditions.

Simultaneously, another method to access primary arylamines was reported by Kürti's group. They were able to effect the transition-metal-free amination of arylboronic acids under mild conditions by using hydroxylamines possessing an *O*-2,4-dinitrophenyl leaving group (Scheme 9).[12] Using cesium carbonate as a promoter, the amination proceeded with *O*-(2,4-dinitrophenyl)hydroxylamine, in 1,2-dichloroethane or toluene at a temperature below 100 °C, in moderate to good yields.



Scheme 9 Transition-metal-free amination using *O*-(2,4-dinitrophenyl)hydroxylamine

Finally, Shenvi has disclosed that dienamines take part in stereoselective intramolecular hydroamination reactions to provide indolizidines. The first step involved a directed double hydroboration with subsequent coordination of the amine to give a four-coordinate borane, and this was followed by oxidation of the amine to instigate alkyl transfer from the boron to nitrogen and complete the synthesis (Scheme 10).[13]

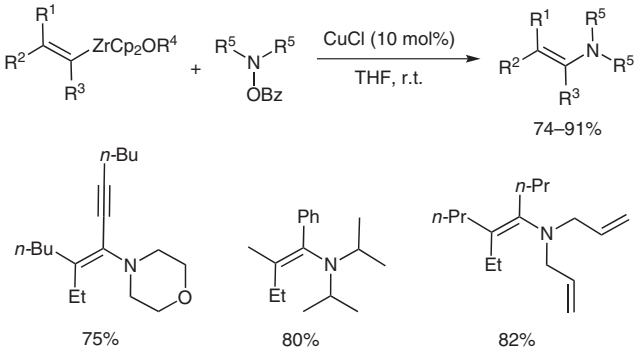


Scheme 10 Stereoselective hydroamination to access polysubstituted indolizidines

In summary, various organoboron compounds can be used efficiently to create C–N bonds by employing umpolung strategies. Generally, primary, secondary and sterically hindered tertiary amines are accessible using copper-catalyzed reactions. However, some metal-free aminations were also found to be efficient.

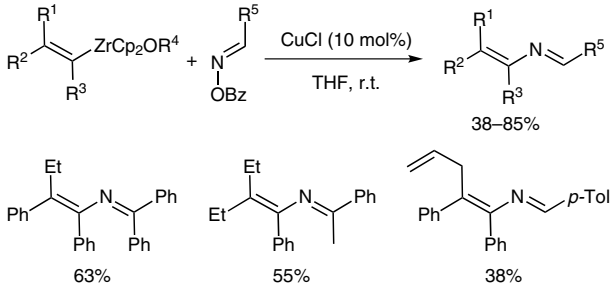
2.2 Zirconium Derivatives

Trisubstituted vinyl zirconocene species are easily prepared through carbozirconation of internal alkynes, and constitute attractive substrates for electrophilic amination. The resulting enamine is normally obtained as a single stereo- and regioisomer. Thus, Chen and Xi proposed the use of simple copper chloride salts to prepare trisubstituted enamines stereoselectively, via reaction of a vinylzirconocene with *O*-benzoylamines, under mild conditions (Scheme 11).[14] Even with a sterically hindered amine such as diisopropylamine, the reaction proceeded at room temperature in good to excellent yields. However, only a few functional groups were present on the substrates.



Scheme 11 Amination of vinylzirconium species

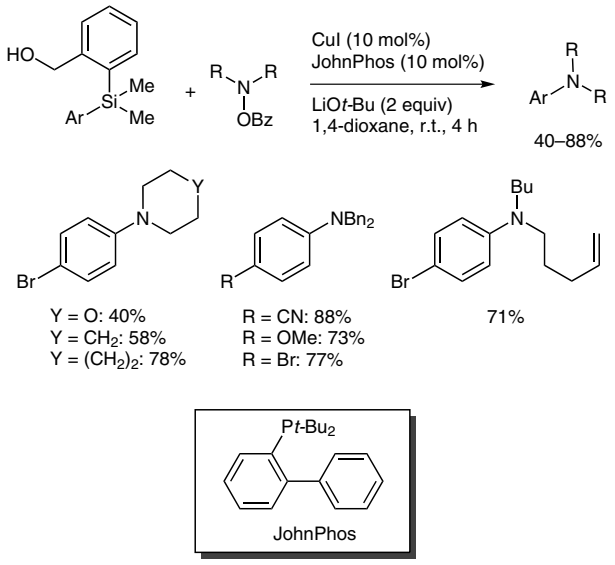
This methodology was extended to the electrophilic imination of alkenylzirconocenes with *O*-benzoyl ketoximes and aldoximes, which allowed various 2-azadienes to be prepared in moderate to good yields (Scheme 12).[15] However, the yields were generally lower than those obtained with *O*-benzoylamines.



Scheme 12 Imination of vinylzirconium species

2.3 Silicon Derivatives

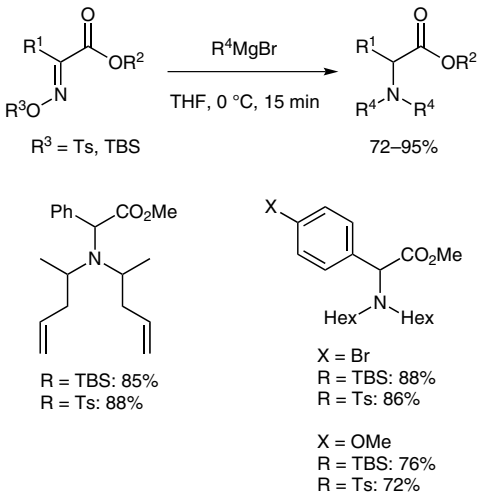
The use of silicon derivatives as coupling partners presents an attractive alternative to many other nucleophiles due to their stability, non-toxicity, and the natural abundance of silicon. Miura has described the use of *O*-benzoylamines as an electrophilic nitrogen source for the amination of [(2-hydroxymethyl)phenyl]dimethylarylsilanes into arylamines (Scheme 13).[16] The catalyst was formed in situ from copper iodide and the bulky monophosphine ligand, JohnPhos, and was found to work best in the presence of excess lithium *tert*-butoxide. The reaction tolerated a wide range of functional groups and occurred smoothly at room temperature in good to excellent yields. The presence of the benzylic alcohol functionality that assists in the desilylation step was essential.



Scheme 13 Copper-catalyzed amination of arylsilanes

2.4 Grignard Reagents

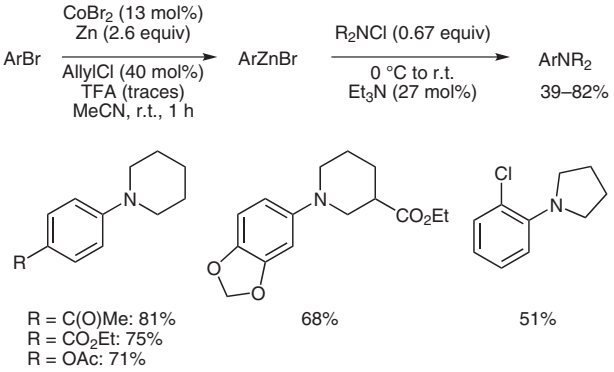
The first examples of transition-metal-catalyzed electrophilic amination reactions employed Grignard reagents as the nucleophile source,[17] and a wide range of catalysts (Cu,[18] Ni,[19] Ti[20]) have since been developed that allow Grignard reagents to be coupled to a variety of electrophilic amines (*N*-haloamines, *O*-acylhydroxylamines). Recently, Kakiuchi reported that Grignard reagents could be used to obtain α-dialkylaminoesters directly, in the absence of a catalyst, via a single-pot reaction that combined the nucleophilic substitution of oximes and a Michael-type addition to α-iminoesters (Scheme 14).[21] The reaction proceeded smoothly at 0 °C and the α-aminoester products were obtained in moderate to good yields. The authors also showed that the *E* configuration of the *O*-sulfonylimine was crucial for the reaction, with the *Z*-isomer being unreactive. The tosyl group could be replaced by a silyl group without impairing the reaction.



Scheme 14 Transition-metal-free formation of dialkylaminoesters

2.5 Organozinc Reagents

Johnson has conducted seminal work on electrophilic aminations using *O*-acylhydroxylamine with diarylzinc species and copper catalysts.[22] More recently, Jarvo described a nickel-catalyzed cross-coupling between diarylzinc species and *N*-chloroamines that resulted in anilines.[23] Interestingly, a one-pot methodology that eliminates the need to isolate the chloroamine was performed by reacting a dialkylamine with *N*-chlorosuccinimide in *N*,*N*-dimethylacetamide, and using the product electrophile directly in a nickel-catalyzed cross-coupling. Our group has prepared arylzinc reagents by a dissolving metal method that was catalyzed by cobalt salts,[24] and found that the residual cobalt was also able to catalyze the coupling of the arylzinc products with electrophilic nitrogen sources to produce C–N bonds (Scheme 15).[25] The arylzinc bromides formed by this type of cobalt catalysis could also react with in situ generated *N*-chloroamines obtained from the reaction of amines with *N*-chlorosuccinimide in toluene. The reaction tolerated a wide range of functional groups, and highly functionalized aniline derivatives could be obtained in moderate to excellent yields. In some cases, addition of catalytic triethylamine allowed the reaction to proceed more efficiently, although its role could not be clearly defined.



Scheme 15 Cobalt-catalyzed amination of arylzinc bromides

To summarize, the use of various organometallic species allows the formation of different amines by reaction with electrophilic nitrogen either under metal-catalyzed or metal-free conditions. Organoboron species are mainly used for these umpolung strategies, but other organometallic species bearing functional groups can also be successfully coupled.

3 Catalytic Organometallic Species

Over the past few decades, considerable research on catalysis has been directed successfully toward developing technology that eliminates the need for stoichiometric quantities of prefunctionalized nucleophiles, especially organometallic examples. The electrophilic amination reaction is no exception, and numerous methods to accomplish this objective have been reported in recent years.

3.1 C–H Activation Reactions

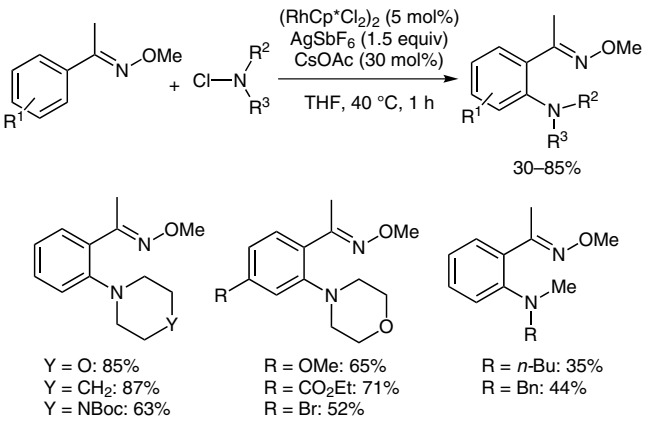
Tremendous progress has been made in developing catalytic transformations that rely upon the activation of C–H bonds.[26] This type of activation has two advantages: (1) stoichiometric organometallic reagents are no longer required and, (2) substrates for C–H activation are normally more readily available than the corresponding halide or pseudo halide. This research has been focused principally upon generating C–C bonds, but C–N bond formation, using either oxidative conditions or electrophilic nitrogen sources, has also been studied.[3b] Procedures for the formation of C–N bonds through C–H amination reactions that employ copper, rhodium or palladium catalysts have also appeared quite regularly since the report of the first example in 2010.[27]

3.1.1 Rhodium-Catalyzed

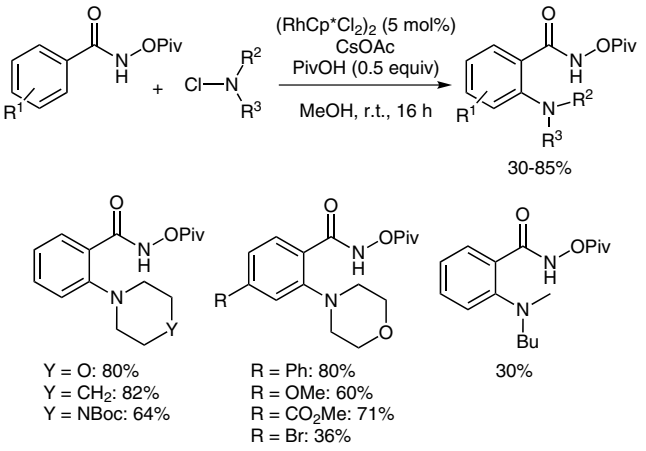
The ability of rhodium to activate C–H bonds has been studied in detail over the past decade. Previously, *N*-chloroamines were employed as electrophilic nitrogen sources in order to form amines by intermolecular C–N bond formation.[28] For example, Yu's group reported that excess silver hexafluoroantimonate ($AgSbF_6$), with a catalytic amount of cesium acetate as the base, allowed fast and efficient amination of benzoketoximes (Scheme 16).[28]

Glorius reported that a similar reaction occurred at room temperature with substoichiometric pivaloic acid, and cesium acetate as the base (Scheme 17).[29]

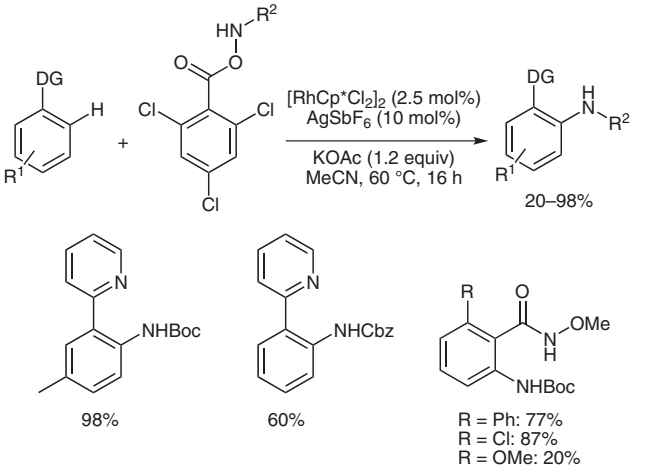
More recently, the same group proposed the use of *tert*-butyl (2,4,6-trichlorobenzoyl)oxycarbamate as the coupling partner (Scheme 18).[30] Using a rhodium catalyst, they were able to activate aromatic C–H bonds lying *ortho* to nitrogen-containing directing groups (pyridine or *O*-methylhydroxamic acid), and this allowed carbamate-protected anilines to be produced in good to excellent yields. The reaction was extended to other heteroaryl substrates, albeit with lower yields, and to vinylic C–H bonds. Secondary amines could not be used.



Scheme 16 Rhodium-catalyzed amination with *N*-chloroamines

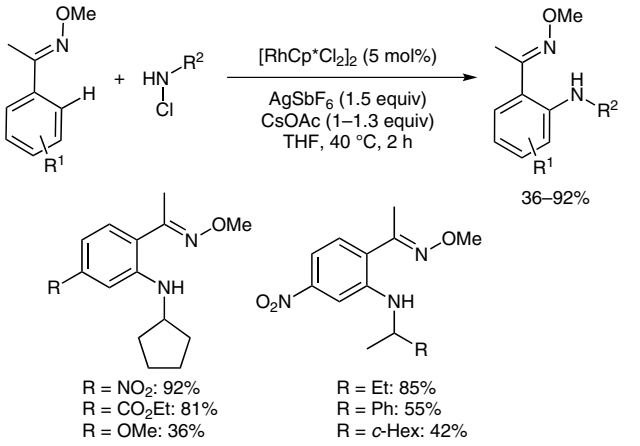


Scheme 17 Room-temperature rhodium-catalyzed amination



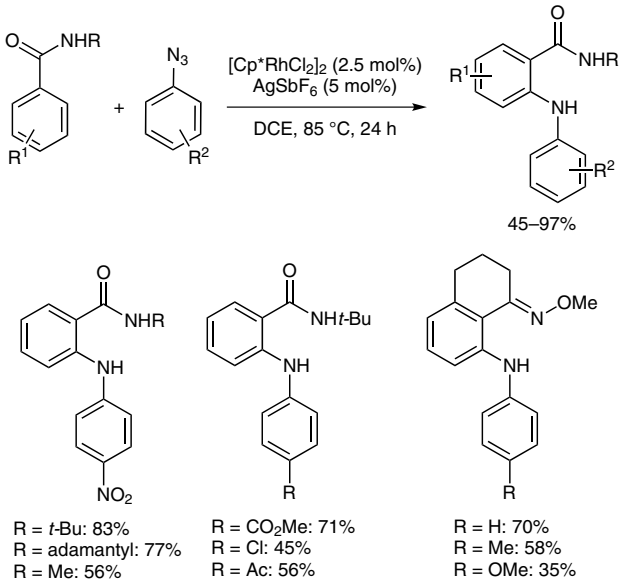
Scheme 18 Rhodium-catalyzed amination of aromatic C–H bonds; DG = 2-pyridine, *O*-methylhydroxamic acid

Using the same catalyst, Yu extended the methodology to primary *N*-chloroamines (Scheme 19).[31] Using acetophenone *O*-methyloxime, secondary anilines were obtained in moderate to good yields. However, formation of a substantial amount of residual chlorinated arylamine was observed when electron-rich aromatic substrates were used, and the yields were accordingly lower.



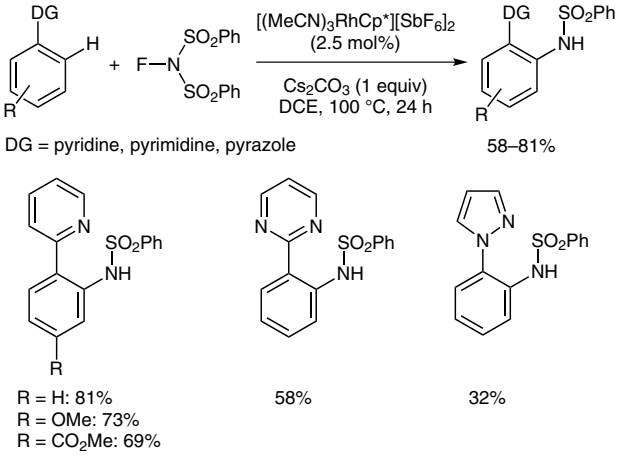
Scheme 19 Rhodium-catalyzed amination of aromatic C–H bonds using primary *N*-chloroamines

This catalyst was also employed by Chang for the direct C–H amination of benzamides with aryl azides as the electrophilic amination reagents, without stoichiometric base or silver salts (Scheme 20).[32] This methodology was restricted to the formation of diarylamines, but had the advantage of having nitrogen as the leaving group. This reaction used either a sterically hindered benzamide or a ketoxime as the directing group, and proceeded more efficiently in the case of electron-poor aryl azides.



Scheme 20 Rhodium-catalyzed amination of C–H bonds with aryl azides

Finally, Li's group showed that rhodium catalysis using *N*-fluorobenzenesulfonimide as the amination agent allowed sulfonamide groups to be introduced to aromatic rings bearing a suitable heteroaryl directing group (Scheme 21).[33] Unlike a previously reported palladium-catalyzed methodology,[34] only one of the two sulfonyl substituents on the nitrogen was present in the final product. The use of pyridine directing groups allowed formation of the products in good to excellent yields, but pyrazole or pyrimidines proved to be less efficient.

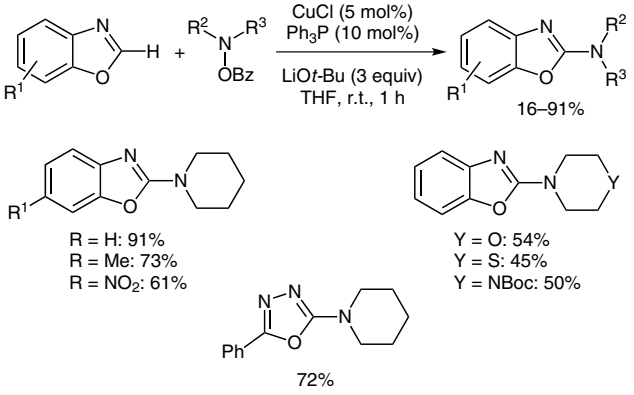


Scheme 21 Rhodium-catalyzed formation of arylsulfonamides

3.1.2 Other Metals

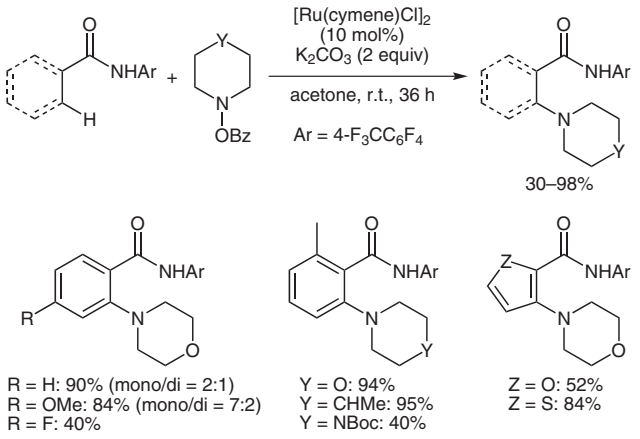
The amination of azole rings is highly important due to their biological and pharmaceutical applications.

Recently, Yotphan et al. reported milder conditions and showed that a system based upon triphenylphosphine (Ph_3P) and copper alone was adequate to effect the amination of various benzoxazoles when *O*-benzoylamines were used as the electrophile and lithium *tert*-butoxide as the base (Scheme 22).[35] Moderate to good yields were achieved only in the presence of a secondary amine. The methodology could be extended to oxadiazoles, but other azoles such as benzothiazole or *N*-methylbenzimidazole did not react under these conditions.



Scheme 22 Copper-catalyzed amination of benzoxazoles

A collaboration between Yu and Dai showed that ruthenium could also be used for the directed amination of C–H bonds.[36] The reaction, which was carried out in acetone at room temperature in the presence of potassium carbonate, employed a simple ruthenium–cymene dimer as the catalyst (Scheme 23). This method was used to introduce a cyclic amine moiety into classical aromatic and heteroaromatic substrates. Electron-rich substrates reacted much more efficiently, but a significant proportion of the product was bis-aminated in cases where two positions were accessible. The presence of a somewhat exotic aromatic group (4-$F_3CC_6F_4$) on the amide was necessary, although Yu had disclosed an efficient methodology to allow formation of the corresponding carboxylic acid in an earlier article.[37]



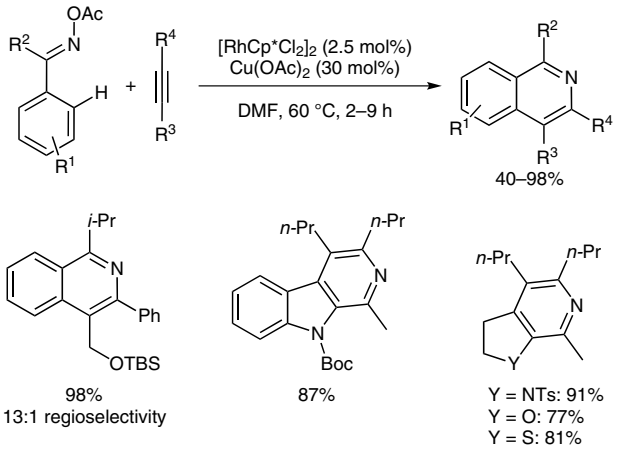
Scheme 23 Ruthenium-catalyzed amination of aromatic and heteroaromatic amides

3.2 Heterocycle Synthesis via Addition/Amination Sequences

Synthetic sequences that involve the reaction of a C–H-activated arene with a carbon–carbon multiple bond and a subsequent ring-closing amination step are particularly attractive, because they allow a convenient and modular access to densely functionalized heterocyclic structures. Most of the methodologies that have appeared in the last few years involve a single nitrogen center that serves as both the directing group and the electrophilic amination reagent.

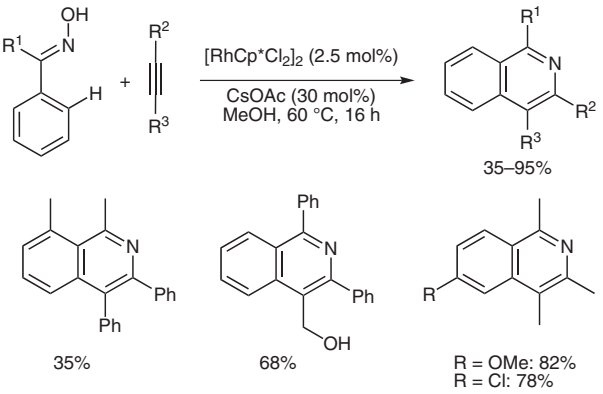
3.2.1 Rhodium-Catalyzed

Over the past six years, numerous rhodium-based addition/amination methods have been developed that employ a stoichiometric amount of oxidant.[38] However, research in the last three years has shown that the amount of oxidant can be reduced greatly, and in some cases, the oxidant can be eliminated completely if the amination step is electrophilic. The pioneering work in the area was performed by Chiba,[39] who was able to use a rhodium catalyst and a catalytic amount of a copper oxidant to prepare substituted isoquinolines from internal alkynes and aryl or heteroaryl *O*-acetyl oximes (Scheme 24). The reaction was carried out in *N*,*N*-dimethylformamide at 60 °C, and provided access to a wide range of heteroaromatic structures in yields which were moderate to excellent.



Scheme 24 Chiba's rhodium-catalyzed formation of isoquinolines

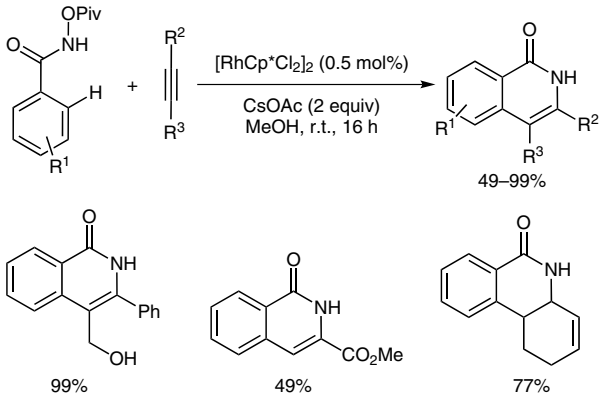
A similar reaction was used by Li to prepare isoquinolines from oximines (Scheme 25).[40] Moderate heating and longer reaction times were required, but the reaction proceeded efficiently in the presence of a catalytic amount of base.



Scheme 25 Formation of isoquinolines using oximines

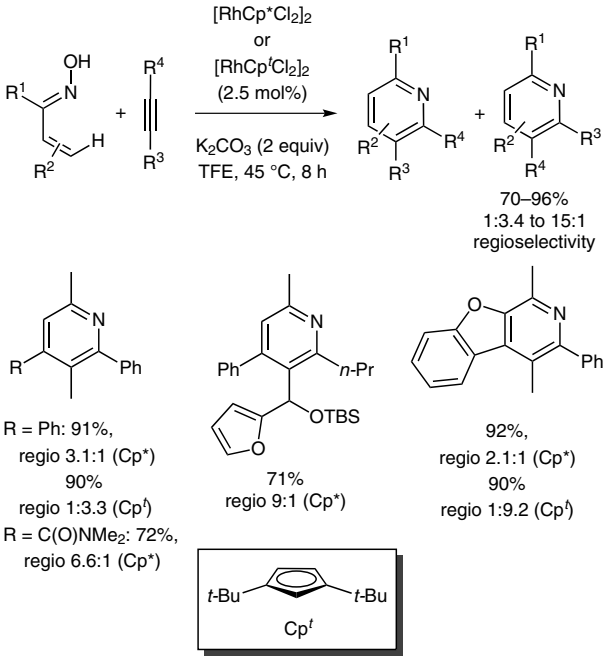
Fagnou's group extended their earlier work[38] to allow the synthesis of isoquinolones in a cycle which involved a rhodium-catalyzed C–H activation directed by an *O*-pivaloylbenzamide group (Scheme 26).[41] The key breakthrough in the electrophilic amidation employed in this work was that both internal and terminal alkynes could be used; previous methodologies of this type required the use of external oxidants, which effectively prevented the use of terminal alkynes. The reaction was regioselective, with the substituent on the alkyne located *ortho* relative to nitrogen. A variety of alkenes could also be used as substrates, such that the reaction could equally give rise to dihydroisoquinolones. Different leaving groups could be used, but the pivaloyl group was usually the most effective. The reaction mechanism was investigated by densi-

ty-functional theory (DFT) calculations, crossover experiments, kinetics and deuterium labeling experiments, and these allowed the influence of the leaving group, and the nature of the various deprotonation steps to be clarified.

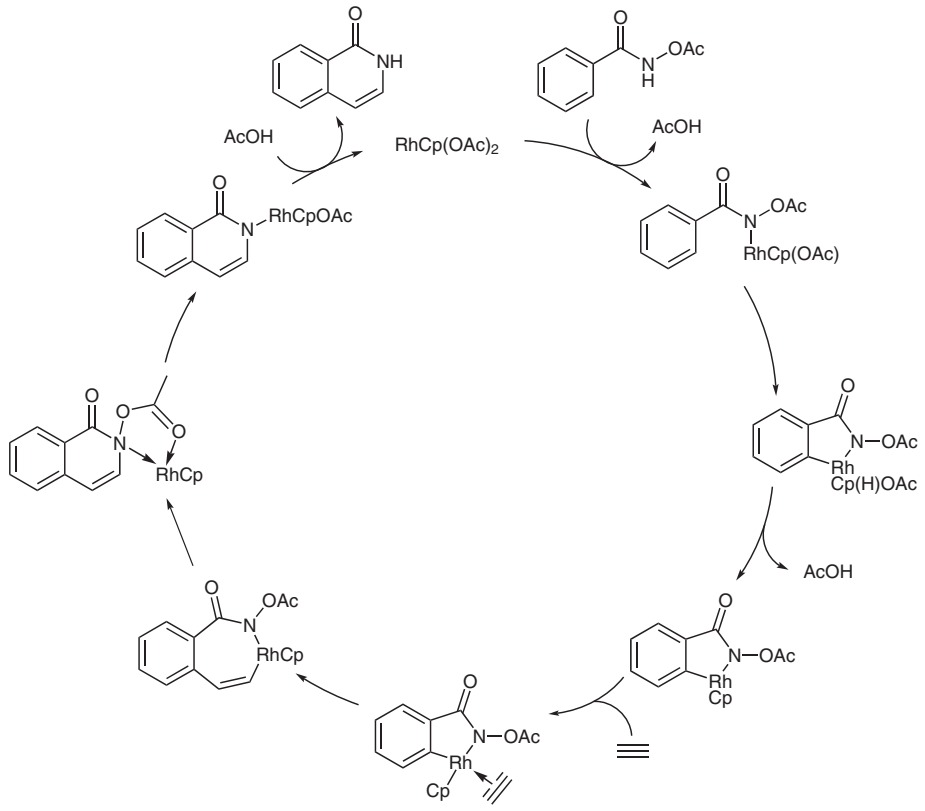


Scheme 26 Rhodium-catalyzed formation of isoquinolones

The mechanism was calculated using OAc as the leaving group, and acetylene as the alkyne, and is presented in Scheme 27. It begins with the formation of a rhodium(III) amido complex, followed by a concerted and rate-determining metalation–deprotonation. Subsequent reductive elimination of acetic acid from the rhodium-coordination sphere was followed by coordination and insertion of the alkyne into the rhodium–aryl bond to provide a seven-membered rhodacycle. Reductive elimination of a C–N bond then created the isoquinolone ring, the coordination complex of which at the rhodium center evolved rapidly through an oxidative insertion of the metal into the weak N–O bond. Protonation by acetic acid in the last step liberated the product and regenerated the starting rhodium(III) complex.



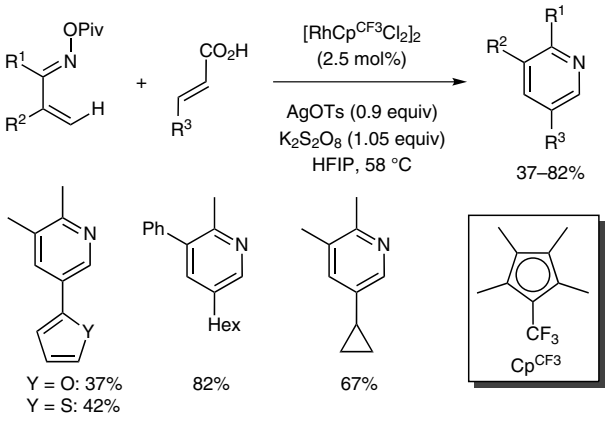
Scheme 28 Formation of pyridines by rhodium-catalyzed reactions of α,β-unsaturated oximines



Scheme 27 Calculated mechanism for the formation of isoquinolones

In 2011, Rovis reported that vinylic C–H bonds could also be activated using rhodium catalysts.[42] Thus, tetrasubstituted pyridines could be formed from conjugated oximines through a C–H activation/carbometallation/amination sequence (Scheme 28). The same catalytic system was also applied to aromatic and heteroaromatic C–H bonds for the preparation of isoquinolines. In all cases, the desired heterocycles were obtained in good to excellent yields at quite low temperature (45 °C). Interestingly, the appropriate choice of cyclopentadienyl ligands allowed the opposite regioisomer to be prepared, although the selectivity was consequently reduced.

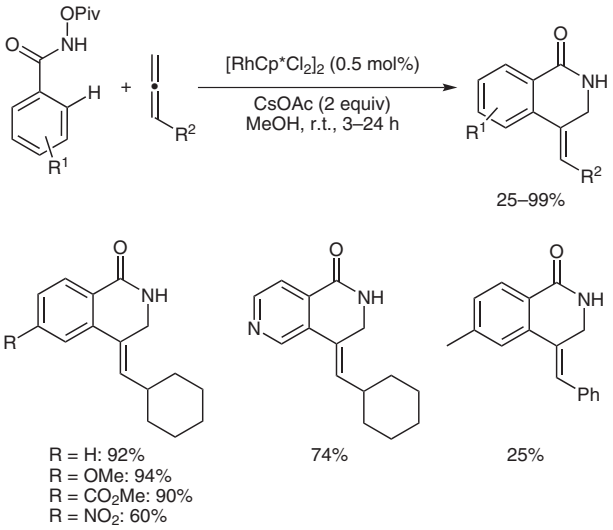
Very recently, Rovis reported that acrylic acids reacted with the same class of precursor to allow the formation of pyridines (Scheme 29).[43] This decarboxylative reaction was conducted in hexafluoroisopropanol (HFIP), and the classical pentamethylcyclopentadienyl ligand (Cp*) was replaced by the partially fluorinated analog, tetramethyl(trifluoromethyl)cyclopentadienyl (Cp^{CF3}). The reaction required a substoichiometric quantity of a silver salt and an additional external oxidant, and gave the desired trisubstituted pyridines in moderate to good yields, with perfect regioselectivity.



Scheme 29 Formation of pyridines using acrylic acids

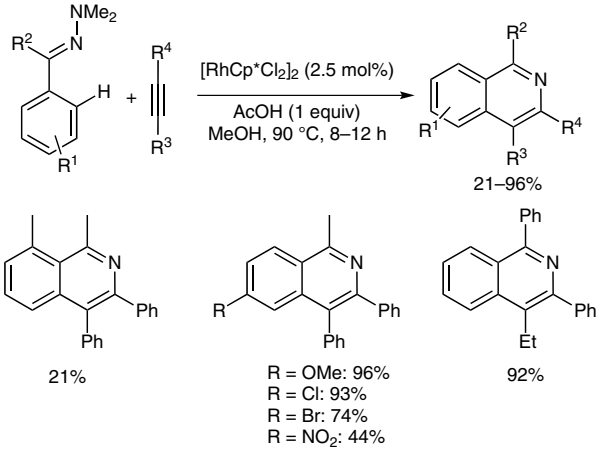
The Glorius group has developed an intermolecular annelation reaction of allenes with functionalized benzamide derivatives to give 3,4-dihydroisoquinolin-1(2*H*)-ones (Scheme 30).[44] In this reaction, an exocyclic double bond was installed. Both mono- and disubstituted allenes provided the desired products with predictable regioselectivity, and in good to excellent yields.

Finally, Cheng's group showed that oxygen-based leaving groups were not essential for effecting this type of chemistry (Scheme 31).[45] In this methodology, the oximine was replaced by an *N*,*N*-dimethylhydrazone and, instead of the basic conditions used in the methods presented above, the reaction was conducted in the presence of acid. The corresponding isoquinolines were obtained in moderate to excellent yields from arylhydrazones and alkynes through sequential C–C and C–N bond formation. A number of



Scheme 30 The use of allenes in the C–H activation/carbometallation/amination sequence

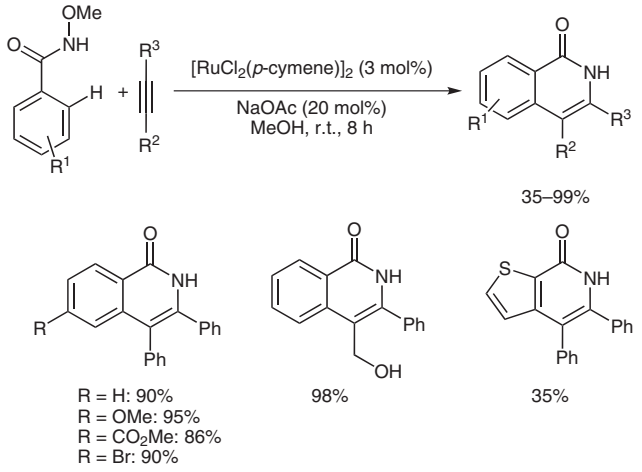
functional groups were found to be compatible with the somewhat harsher conditions used for this reaction. Only keto-derived hydrazones were suitable substrates; aldehyde-derived hydrazones did not participate in this reaction.



Scheme 31 Formation of isoquinolines with dimethylamine as the leaving group

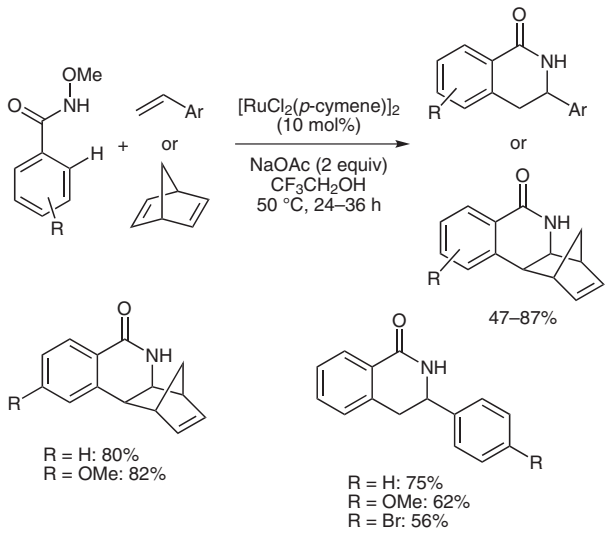
3.2.2 Other Metals

Although rhodium is the most widely used metal for C–H activation reactions, the Wang group showed that a ruthenium-based catalytic system could also be employed for the regioselective synthesis of isoquinolones, a method that demonstrated a broad substrate scope and gave good to excellent yields of products (Scheme 32).[46] The conditions were milder than those previously described by Ackermann using the same catalyst,[47] and were very similar to those used for the rhodium-catalyzed reactions.



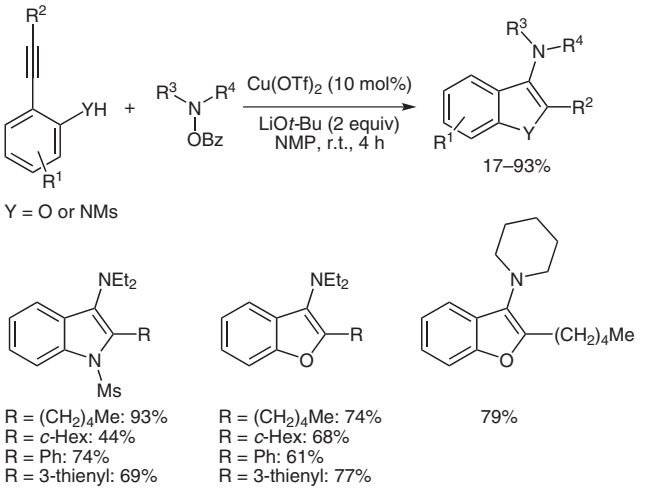
Scheme 32 Ruthenium-catalyzed formation of isoquinolines

This ruthenium-catalyzed C–H bond activation/carbometallation/amidation sequence has been extended to activated alkenes (norbornadiene or styrene), and these reactions gave dihydroisoquinolones upon annelation in 2,2,2-trifluoroethanol (Scheme 33).[48] The amination step failed with electron-poor olefins such as acrylates in methanol; the leaving group on the nitrogen was lost but only the Heck product was obtained.



Scheme 33 Ruthenium-catalyzed C–H activation/carbometallation/amination with activated alkenes

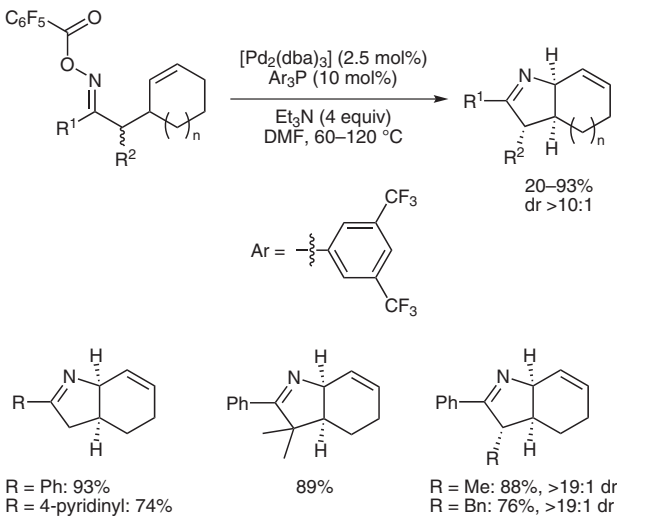
Hirano and Miura have developed a related copper-catalyzed annelative amination that gave 3-aminobenzofurans and -indoles in moderate to excellent yields starting from *ortho*-alkynylphenols and -anilines, respectively (Scheme 34).[49] It is noteworthy that the efficient catalytic formation of both C–Y (Y = O or NMs) bonds featured in these reactions.



Scheme 34 Copper-catalyzed formation of 3-aminobenzofurans and -indoles

3.3 Narasaka–Heck (or Amino-Heck) Reactions

The use of oxime esters as electrophiles in Heck-type reactions was pioneered by Narasaka at the end of the 20th century.[50] An example of a diastereoselective intramolecular Narasaka–Heck reaction was reported recently by Bower (Scheme 35).[51] Bicyclic nitrogen-containing products were obtained in moderate to excellent yields and excellent diastereoselectivity when a pentafluorobenzoyloxime was used as the electrophilic nitrogen center in a catalytic annelation that employed a palladium–tri(3,5-bistrifluorophenyl)phosphine based system in *N*,*N*-dimethylformamide.

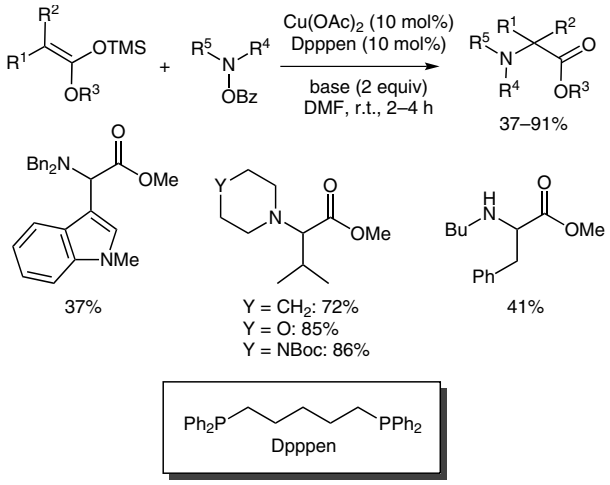


Scheme 35 Diastereoselective intramolecular Narasaka–Heck reaction

4 Enolates as Nucleophiles

The electrophilic amination reaction is of particular interest when applied to enolate derivatives, because it can lead to unnatural α-amino acid derivatives in a straightforward manner. In fact, several methodologies have been reported over the years, using transition metal catalysts,[52] or organocatalysis.[53] However, the scope remained limited, especially with respect to the amine moiety, due to the electrophiles used (azodicarboxylates, chloramine T, nitrosoarenes, etc.).

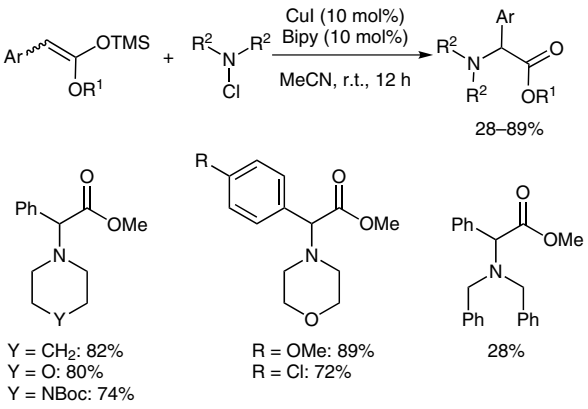
Hirano and Miura showed that, in the presence of various additives, *O*-benzoylhydroxylamine was an effective electrophilic amination reagent for forming a C–N bond with ketene silylacetals under catalysis by a copper(II)–1,5-bis(diphenylphosphino)pentane complex (Scheme 36).[54] A number of α-aminoesters were prepared in moderate to excellent yields under mild conditions. Various chiral phosphine ligands were tested in attempts to access chiral α-amino acids, but were unsuccessful. However, the use of readily available L-menthol as a chiral auxiliary on the enolate resulted in modest stereoinduction.



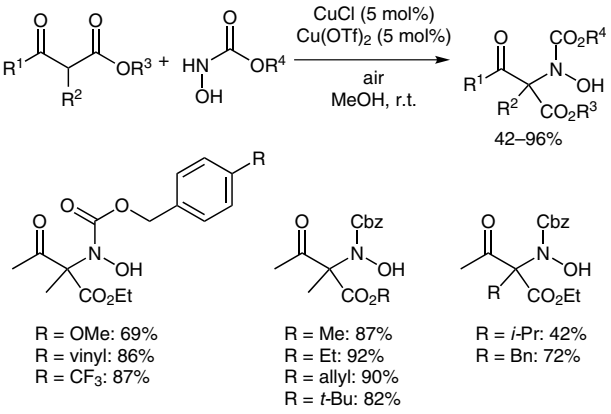
Scheme 36 Copper-catalyzed formation of α-amino acids from ketene silyl acetals

Ketene silylacetals of this type also reacted with *N*-chloroamines in the presence of a copper (I)–bipyridine complex to give α-amino-α-aryl esters in modest to excellent yields (Scheme 37).[55] A one-pot procedure was proposed that was especially welcome in cases where the required *N*-chloroamine was instable; based upon the formation of the *N*-chloroamine using *N*-chlorosuccinimide in acetonitrile and its direct use in the electrophilic amination step, this procedure significantly broadens the scope in terms of the amine moiety.

In a reaction that circumvents the need to preform both the enolate and the electrophilic nitrogen source, Read de Alaniz reported the use of β-keto esters as substrates and nitrosoformates as the source of electrophilic

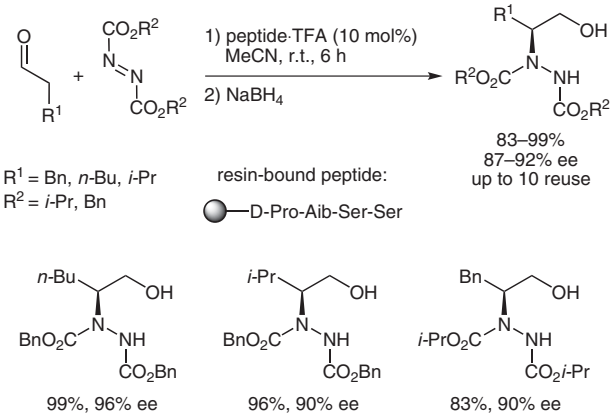


Scheme 37 Formation of α-amino-α-aryl esters using *N*-chloroamines



Scheme 38 Oxidative amination of β-keto esters using *N*-hydroxycarbamates

nitrogen; the latter reagents were obtained in situ through the aerobic oxidation of *N*-hydroxycarbamates (Scheme 38).[56] A combination of copper(I) and copper(II) salts allowed an *N*-hydroxycarbamate moiety to be introduced smoothly into the acetylacetonates at room temperature in good to excellent yields.

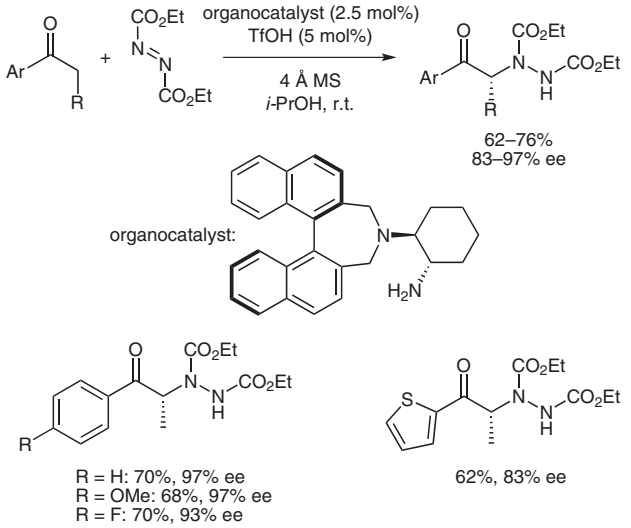


Scheme 39 Organocatalytic α-amination of aldehydes using a resin-supported peptide

The use of azodicarboxylate esters as nucleophiles for the organocatalytic α-amination of aldehydes was pioneered by Jørgensen and List using a proline catalyst.[57] Subsequently, a variety of organocatalysts have allowed the reaction to be extended, notably to α-branched aldehydes, and to ketones. However, these reactions typically require high catalyst loadings, and recent efforts have therefore been focused, to a large degree, upon recoverable or more efficient catalysts.

Kudo and Tanaka reported a resin-supported peptide that allowed the organocatalytic reaction to proceed in high yields and enantioselectivities, and which could be reused up to 10 times without loss of activity (Scheme 39).[58]

Organocatalysis has also been used for the amination of aromatic ketones.[59] A mixture of a BINOL-derived organocatalyst and catalytic triflic acid allowed aromatic ketones to be α-aminated in moderate to good yields and with good enantioselectivity (Scheme 40).



Scheme 40 Organocatalytic stereoselective α-amination of aromatic ketones

5 Conclusion

In conclusion, various approaches have been developed for accessing C–N bonds through the reaction of electrophilic amination reagents with organometallic species, enolates or C–H-activated arenes, and the numerous strategies that are now available for forming intermolecular or intramolecular C–N bonds allow the synthesis of a broad range of functionalized amines. Generally speaking, the advances in this area have been very significant, but the introduction of aromatic amines through approaches based upon electrophilic nitrogen sources remains an interesting problem because of the dearth of suitable precursors. Further advances in this area can be confidently expected.

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