CHEMICAL REVIEWS

Review

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Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications

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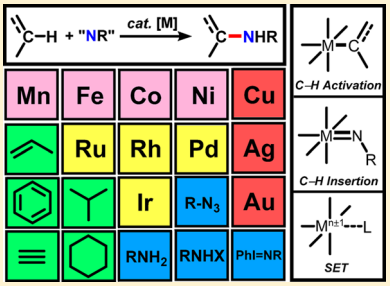
ABSTRACT: Catalytic transformation of ubiquitous C–H bonds into valuable C–N bonds offers an efficient synthetic approach to construct *N*-functionalized molecules. Over the last few decades, transition metal catalysis has been repeatedly proven to be a powerful tool for the direct conversion of cheap hydrocarbons to synthetically versatile amino-containing compounds. This Review comprehensively highlights recent advances in intra- and intermolecular C–H amination reactions utilizing late transition metal-based catalysts. Initial discovery, mechanistic study, and additional applications were categorized on the basis of the mechanistic scaffolds and types of reactions. Reactivity and selectivity of novel systems are discussed in three sections, with each being defined by a proposed working mode.



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1. INTRODUCTION

1.1. Introduction to Catalytic C–H Amination

The prevalence of nitrogen-containing molecules in natural products, synthetic intermediates, pharmaceutical agents, and functional materials has motivated synthetic chemists to develop convenient and mild amination reactions.[1] Whereas conventional organic transformations mainly rely on the inherent reactivity of functional groups, the introduction of transition metal catalysts provides novel strategies to construct covalent bonds, thus offering a great opportunity to derivatize raw chemicals with little functionality to synthetically versatile molecules.[2,3] Two general approaches for transition metal-catalyzed C–N bond formation are outlined in Scheme 1. A

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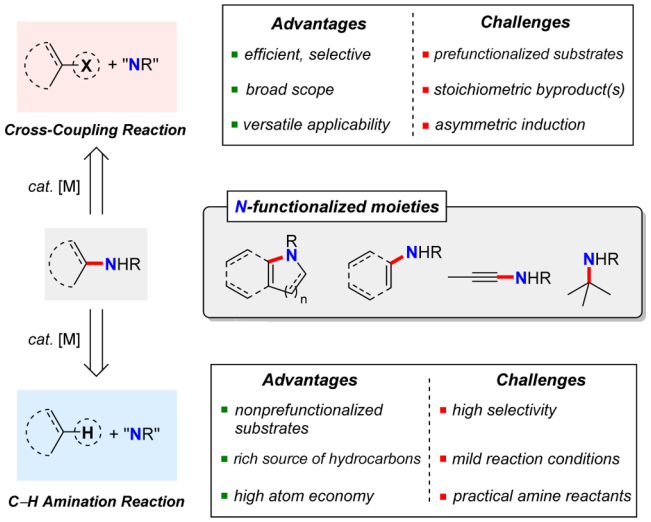
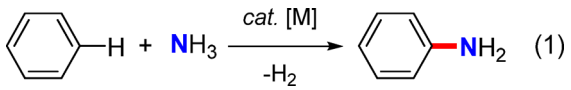
Scheme 1. Transition Metal-Catalyzed Approaches To Access *N*-Functionalized Molecules



conventional synthetic method is to utilize the cross-coupling reaction of aryl- or alkenyl (pseudo)halides with amines under optimal catalytic systems. The most representative example is the palladium-catalyzed Buchwald–Hartwig amination reaction.[4−10] While the reactivity of this coupling can be readily improved by fine-tuning of the steric and/or electronic property of ligands, the functional groups, such as halide moieties, need to be introduced prior to the amination. Moreover, the formation of stoichiometric amounts of byproducts, mainly halide salts, is inevitable. An alternative way to construct a C–N bond is to apply a C–H amination strategy that can directly functionalize a hydrocarbon substrate without preinstallation of a reactive group. It is often argued that a retrosynthetic scheme based on C–H functionalization is more straightforward along with offering high atom economy. The C–H amination strategy, however, is only viable under highly efficient catalyst systems, where the desired C–H bonds can be selectively targeted.

From a fundamental perspective, several essential factors in C–H amination can be illustrated with a simple reaction to obtain aniline: a cross-dehydrogenative coupling between benzene and ammonia (eq 1). This ideal reaction is



thermodynamically uphill as strong C–H (~113 kcal/mol) and N–H (~108 kcal/mol) bonds of reactants are converted to the weaker C–N (~103 kcal/mol) and H–H (~104 kcal/mol) bonds.[11,12] The high activation barrier in the aryl C–H bond cleavage also makes this amination kinetically sluggish. To properly address these fundamental issues, which are frequently encountered in analogous C–H aminations with other reactants, the following strategies can be envisaged: (i) the use of energetic substrates and/or aminating agents to drive the overall thermodynamics favorable, and (ii) the development of highly efficient catalytic systems to reduce the activation barriers based on mechanistic considerations.

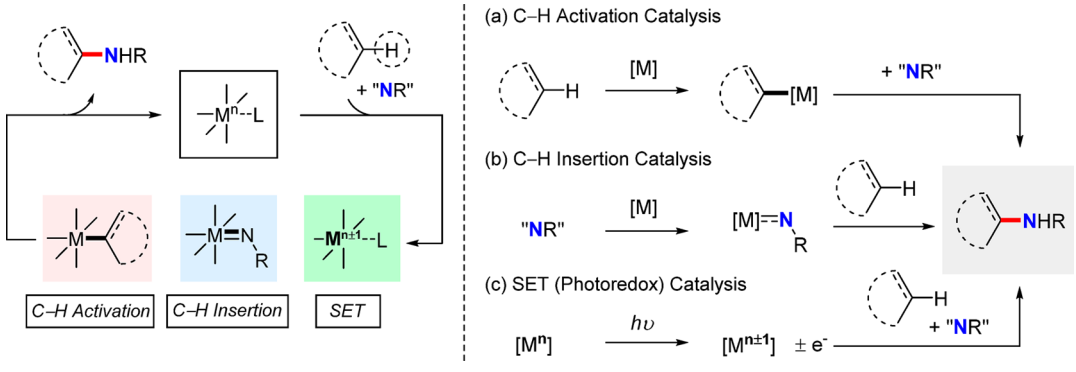
This work reviews recent progress in the transition metal-catalyzed C–H amination reactions. We adopt mechanistic manifolds as a prime consideration in classifying the rather comprehensive examples, and reaction types are also utilized as an index to categorize the reactions within the same mechanistic scaffold.

1.2. Mechanistic Manifolds in the Catalytic C–H Aminations

Transition metal-catalyzed C–H amination reactions can be classified into three categories, with each category being defined by a proposed intermediate on the reaction pathway (Scheme 2). A system denoted as "C–H activation catalysis" is postulated to generate an organometallic intermediate bearing a metal–carbon bond as a result of the carbon–hydrogen bond activation (Scheme 2a).[13,14] The cleavage of the C–H bond is facilitated by a close interaction between a metal center and the C–H bond of the hydrocarbon substrate.[13] The corresponding metallacyclic complexes engage a nitrogen source to eventually afford an aminated product.[15−19] The C–H cleavage operates mostly inside of the coordination sphere of the metal species (inner-sphere mechanism).[20−22] To achieve significant catalyst turnover under this mechanistic scaffold, the C–H metalation and subsequent C–N bond-forming step must be highly efficient and selective. In this regard, an appealing strategy is to utilize chelation-assisted C–H bond activation.[23−33] The coordinating group present in substrates readily binds to the metal center, thus enabling a regioselective cyclometalation in the presence of weak bases.[34,35]

The second mechanistic manifold involves "C–H insertion catalysis" as a key working mode. Instead of direct C–H activation of hydrocarbons by metal catalysts, an initially generated metal–nitrenoid species interacts with a substrate in either a concerted or a stepwise manner to result in C–N bond formation (Scheme 2b).[36−44] The C–H bond cleavage mostly takes place at the coordinating nitrene moiety, and hydro-

Scheme 2. General Mechanisms in Catalytic C–H Amination



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carbon substrates do not bind to the inner-sphere of the metal complex (outer-sphere mechanism). While the selectivity in this C−H insertion is highly dependent on the stereoelectronic nature of the putative metal−nitrenoid species,[45] C−H bonds at the benzylic, allylic, or tertiary position are prone to undergo facile insertion in general.

A newly emerging strategy in direct C−H amination is to use photoredox catalysis[46−51] via a single electron transfer pathway (Scheme 2c).[52] Upon irradiation of visible light, the photocatalyst mediates the formation of organoradical species that will react with coupling partners to furnish aminated products. The observed excellent level of functional group tolerance guides practical applications of this technology in the synthesis of complex molecules.[49,51]

1.3. Common Aminating Reagents

A wide range of aminating reagents have been utilized in the metal-catalyzed direct C−H amination reactions (Figure 1).

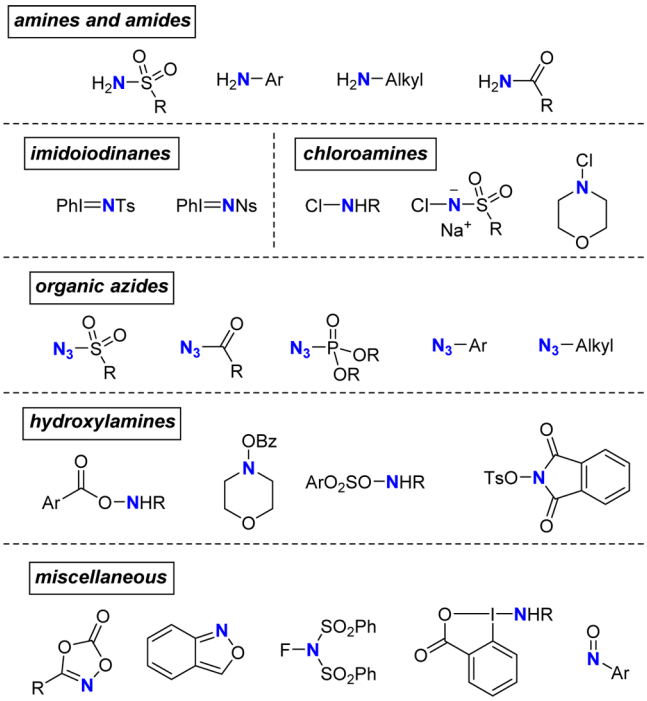

Figure 1. Representative examples of aminating reagents.

Although nonprefunctionalized amines or amides are the most desirable nitrogen sources, external oxidants are required to enable a catalytic C−H amination with these reactants.[15] Aminating reagents obtained from the derivatization of parent amines, usually possessing polarized N−X bonds, can be oxidatively cleaved by the action of metal catalysts. This allows an additional role of aminating reagents to serve as an internal oxidant, thus not requiring stoichiometric external oxidants in the catalytic process. Widely utilized aminating reagents are derivatives of iminoiodinanes,[53] chloroamines,[54] organic azides,[55] and hydroxylamines.[56] In addition, 1,4,2-dioxazol-5-ones,[57] anthranils,[58] *N*-fluorobenzenesulfonimide (NFSI),[59] amidobenziodoxolones,[60] and nitrosoarenes[61] were also recently demonstrated as new types of efficient amino group sources under individually optimized catalytic conditions.

1.4. Scope and Structure of This Review

Since the first report of Mn- and Fe-catalyzed direct C−H amination of cyclohexane using iminoiodinane as the amine source,[62,63] significant advances have been made in this area, especially during the past decade. Indeed, a range of new catalyst systems have been developed to enable amination under milder conditions with significant expansion of the substrate scope mainly by applying more effective aminating reagents. This Review is aimed at comprehensively summarizing the recent discoveries, synthetic applications, and mechanistic aspects in C−H amination catalyzed by transition metals, mostly in groups 8−11. In this Review, C−H amination reactions are categorized first on the basis of mechanistic considerations: C−H activation, C−H insertion, and single electron transfer pathways. Within the same mechanistic scaffold, they are additionally subclassified into inter- and intramolecular reactions based on aminating reagents. This classification may help the readers to navigate the relevant articles, guided by either mechanistic or synthetic interests. In the case of C−H aminations relying on an inner-sphere pathway, the presented examples are divided into two subsections by considering the strategy for C−H bond activation, in terms of whether it is driven by directing group-assistance or not. Within the category of single electron transfer pathway, recent advances achieved by means of photoredox catalysis are presented with mechanistic depiction. This will cover mainly the recent progress reported during the period of 2009 and the summer of 2016. Only a few seminal articles published before 2009 are highlighted with a mechanistic emphasis. Discoveries reported before 2009 are well-documented in other reviews.[21,22,64−67] Examples of a norbornene-assisted Catellani-type amination will not be covered because a detailed account was published recently.[68] Related C−H azidation or nitration reactions are not discussed herein.[69] C−H amination reactions based on cobalt−metalloporphyrin catalysis are covered by another article in this thematic issue of *Chemical Reviews*.

2. DIRECTING GROUP-ASSISTED C−H ACTIVATION CATALYSIS

The use of directing groups in the C−H functionalization approach allows a facile C−H metalation to give rise to metallacyclic complexes bearing covalent M−C bonds. The resultant nucleophilic character at the carbon center of the M−C bonds enables a subsequent reaction with aminating reagents, eventually releasing aminated products. In the case of the intramolecular reactions, an amino moiety of the substrate works as both a directing group and an amine source.[70−75]

2.1. Intramolecular C(sp^2)−H Amination

2.1.1. First-Row Catalysis. In 2008, Buchwald reported the synthesis of benzimidazoles via Cu-catalyzed intramolecular C−H amination of *N*-phenylbenzamidine (Scheme 3).[76] Copper(II) acetate was employed as a catalyst for this reaction with an acetic acid additive under an oxygen atmosphere. The authors found that amidines derived from unsubstituted aryl nitriles showed low conversion leading to the desired benzimidazoles mainly due to an inhibitory effect of the decomposed products. However, higher efficiency was obtained when amidines derived from *ortho*-substituted aryl nitriles were subjected irrespective of the electronic property. Three possible pathways were proposed for the C−N bond formation: (i) an electrophilic aromatic substitution to an amidine moiety with

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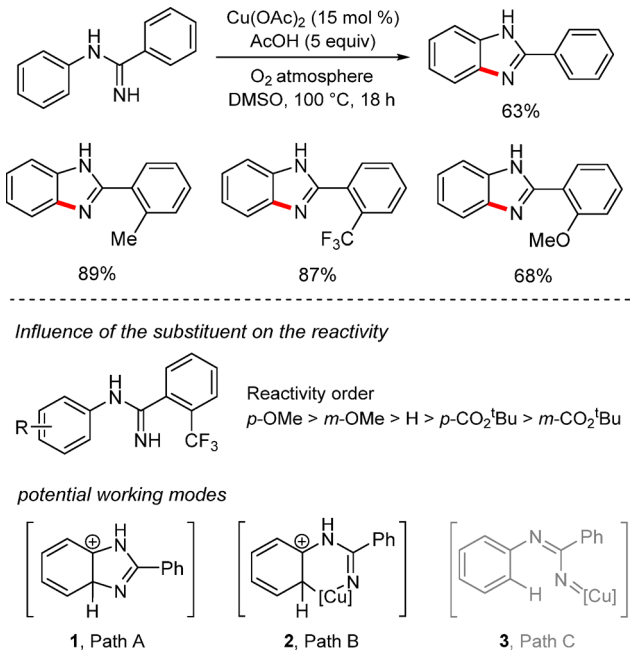
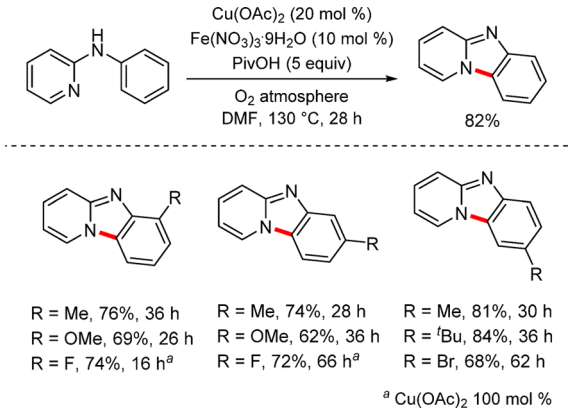
Scheme 3



concurrent release of a reduced copper species (path A), (ii) the formation of a metallacycle intermediate that undergoes reductive elimination and rearomatization (path B), and (iii) the intermediacy of Cu−nitrenoid species **3** to lead to concerted C−H insertion or electrocyclic ring closure and then a final 1,3-H-shift (path C). To gain mechanistic insight in the present amination reaction, the authors compared the conversion rate between electronically varied amidines in the formation of the corresponding benzimidazoles. The highest reactivity was observed from an amidine having a methoxy group at the *meta*-position, while an amidine with a $CO_2{}^tBu$ group at the same position was reacted slowly. Although this result is consistent with a typical pattern in the electrophilic substitution process, the reactivity difference is too small to conclude clearly. Nevertheless, the observed high reactivity from the electron-rich amidines was attributed to the stabilization of a plausible carbocation intermediate such as **1** or **2**.

The notable reactivity exhibited by the use of copper catalysts toward an intramolecular C(sp^2)−H amination was applied to the synthesis of various nitrogen-containing heterocycles. In 2010, Zhang (J.), Zhu, and co-workers reported a synthetic route to pyrido[1,2-*a*]benzimidazoles by using cocatalysts of copper/iron with pivalic acid additive under an O_2 atmosphere (Scheme 4).[77] When the relative reactivity of substrates was compared in regard to the electronic effects, anilines bearing electron-donating groups at the *meta*- or *para*-position were reacted faster than those having electron-withdrawing groups at the same position. This result implies that an electrophilic substitution process may operate in this reaction. In fact, the cyclization of electron-deficient substrates required stoichiometric amounts of catalyst with longer reaction time. In contrast to Zhang (J.) and Zhu's work,[77] new reaction conditions reported by Maes allowed electron-deficient substrates to react smoothly even with lower catalyst loading and shorter reaction time.[78] This cyclization approach was applied to the synthesis of a wide range of purine-fused

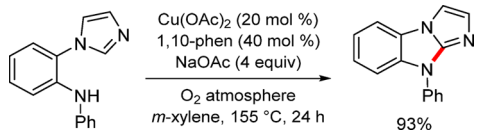
Scheme 4



polycyclic compounds starting from 6-anilinopurine nucleosides.[79]

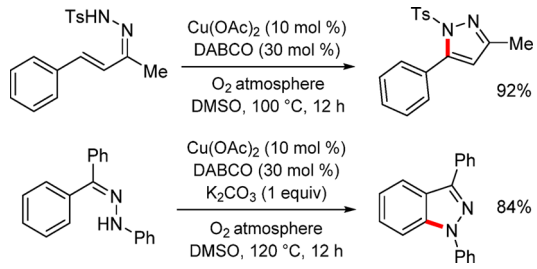
Fu and co-workers presented a synthetic route to prepare imidazobenzimidazole derivatives (Scheme 5).[80] In addition, notable examples of the copper-catalyzed intramolecular C−N bond formation to obtain a range of heterocycles were recently reported by Fu,[81] Qiao,[82] and Kaliappan.[83]

Scheme 5



Jiang and co-workers reported a direct access to pyrazoles and indazoles via a Cu-catalyzed oxidative C−H amidation (Scheme 6).[84] In this reaction, vinyl- or phenyl-substituted

Scheme 6



arylhydrazones were cyclized to the corresponding azaheterocyclic products with high efficiency. Interestingly, while a series of experiments were performed to confirm the involvement of a radical intermediate, the reaction was found to be unaffected by a variety of radical scavengers.

In 2014, Miura reported a picolinamide (PA)-directed intramolecular C−H amination by using a copper catalyst for the synthesis of carbazoles (Scheme 7a).[85] The reaction conditions required a stoichiometric manganese oxidant under microwave irradiation at high temperature. Considering that the removal of directing groups after the desired C−H functionalization is often problematic, the readily hydrolyzable picolinamide group is advantageous to give N−H carbazoles in high yield. Later, Miura applied this approach to the synthesis of indolines (Scheme 7b).[86] A putative intermediate **4** was

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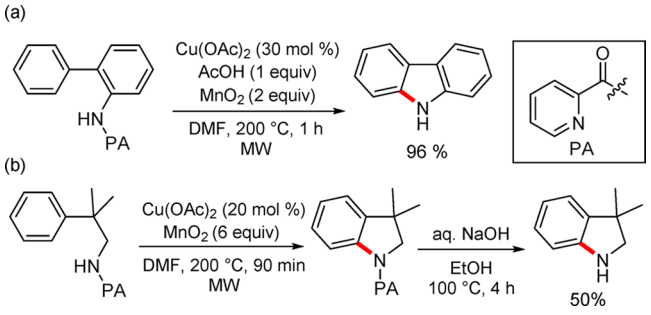
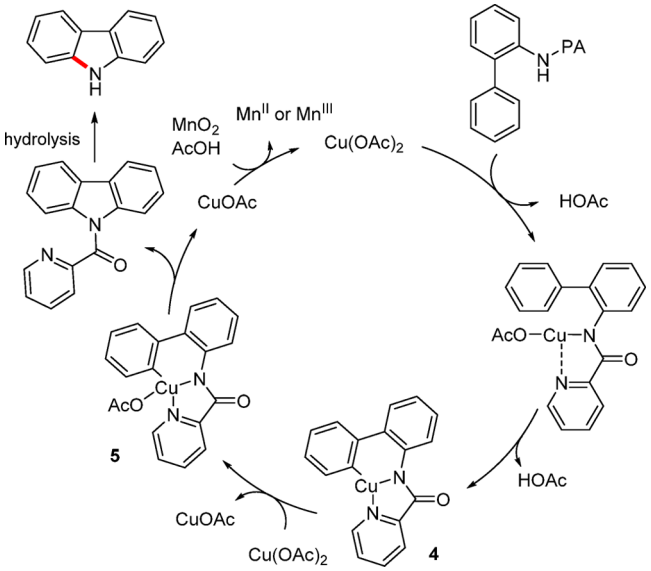
Scheme 7



proposed to form via C−H cupration of the substrates with the assistance of a bidentate directing group (Scheme 8). The disproportionation-induced formation of a Cu(III) species **5** would then facilitate subsequent reductive elimination, thus providing PA-coupled carbazole products.

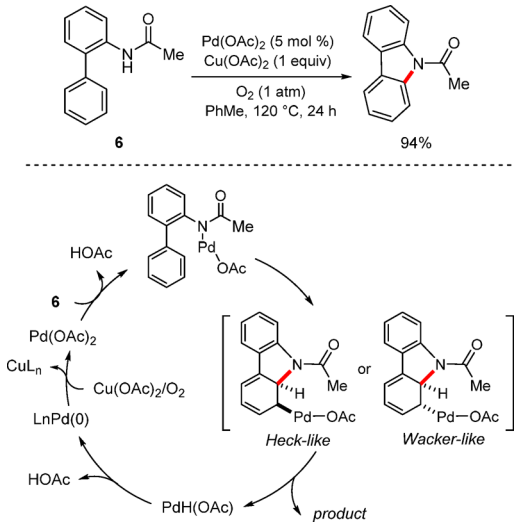
Scheme 8



2.1.2. Second- and Third-Row Catalysis. While an intramolecular version of the Buchwald-Hartwig *N*-arylation employs bifunctional substrates, amino-substituted aryl halides, recent progress in the C−H amination strategy allows the direct use of monofunctional compounds to obtain *N*-heterocycles. In 2005, Buchwald disclosed a Pd-catalyzed intramolecular C−H amination of acetaminobiphenyl **6** to obtain carbazole (Scheme 9).[87] With a stoichiometric copper acetate under an oxygen atmosphere, a catalytic cycle of Pd(II)/Pd(0) was assumed to operate. Although an electrophilic palladation pathway was initially proposed for the C−H bond cleavage, it was later found that the Heck- or Wacker-type intramolecular addition of Pd(II) species into arenes may occur to form the corresponding Pd(II) intermediate.[88] Subsequent *β*-hydride elimination provides carbazole products, and the reoxidation of resulting Pd(0) species by copper salts under an oxygen atmosphere regenerates Pd(II) catalysts.

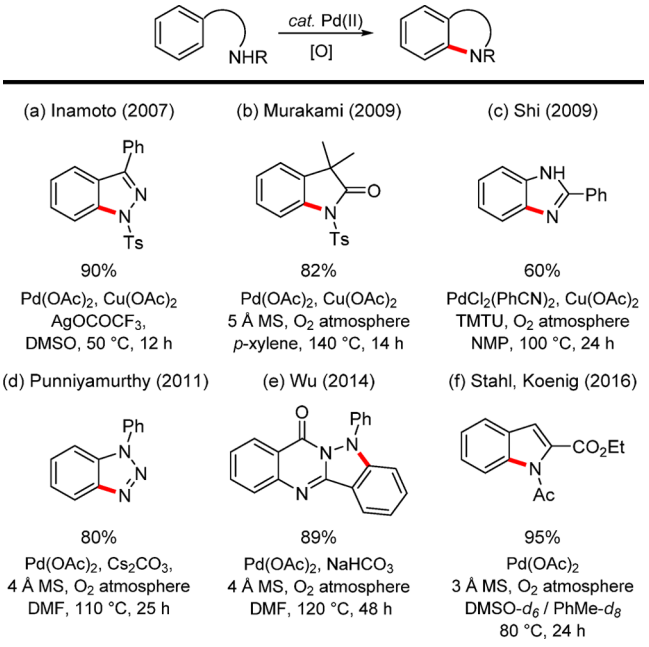
Since the earlier report of Buchwald on the oxidative cross-dehydrogenative coupling (CDC) between C(sp^2)−H and N−H bonds to obtain azaheterocycles,[87] extensive studies have been carried out by several research groups to widen the scope

Scheme 9



and/or to improve the reaction conditions. Indeed, the substrate scope was broadened to cover various heterocycles such as indazoles,[89] oxindoles,[90] 1*H*-benzo[*d*]imidazoles,[91] 1-aryl-1*H*-benzotriazoles,[92] *N*-arylindazole[3,2-*b*]-quinazolinones,[93] and indoles (Scheme 10).[94,95] Interestingly,

Scheme 10



this protocol turned out to be complementary to the oxidative palladium catalytic systems. For examples, Shi (Z.-J.)'s benzimidazole synthesis was distinct to the Buchwald's procedure, wherein amidines derived from *ortho*-substituted aryl nitriles were employed for achieving high product yields. In fact, Shi (Z.-J.)'s method did not require such *ortho*-substituents in amidine substrates.

Hartwig disclosed a new working mode in an intramolecular C(sp^2)−H amination with the use of *O*-acyloximes as an aminating source under Pd(0)/Pd(II) catalytic scaffold (Scheme 11).[96] The key to success was believed to be the facile oxidative N−O bond addition to Pd(0) followed by

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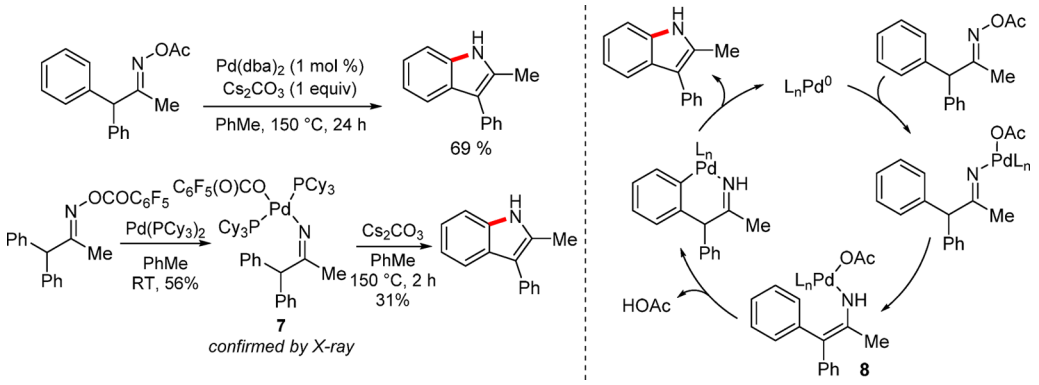
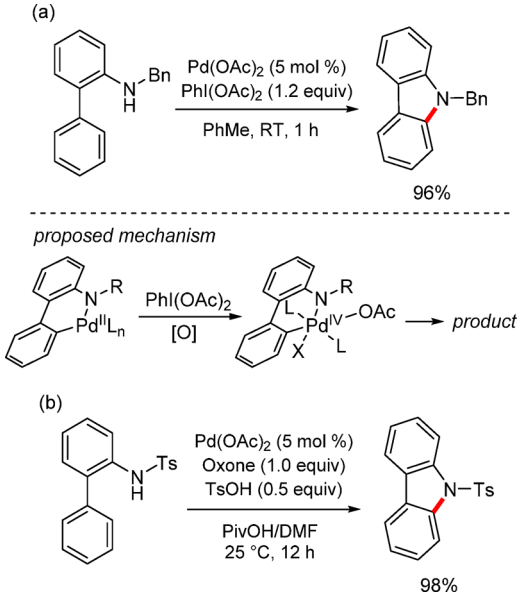
Scheme 11



tautomerization to generate an intermediate **8**, which then undergoes C−H bond cleavage leading to a palladacycle that is eventually reductively eliminated to indole products. Intermediate **7** derived from *O*-(pentafluoro)benzoyloxime was characterized by an X-ray crystallography analysis, and this Pd(II) complex **7** was converted to indole to support the proposed mechanistic pathway.

Another strategy for Pd-catalyzed C−H amination is to utilize a Pd(II)/Pd(IV) catalytic scaffold that can be induced to operative under mild oxidative conditions. In 2008, Gaunt reported a mild synthetic route to prepare carbazoles using $PhI(OAc)_2$ as the oxidant (Scheme 12a).[97] Notably, formation

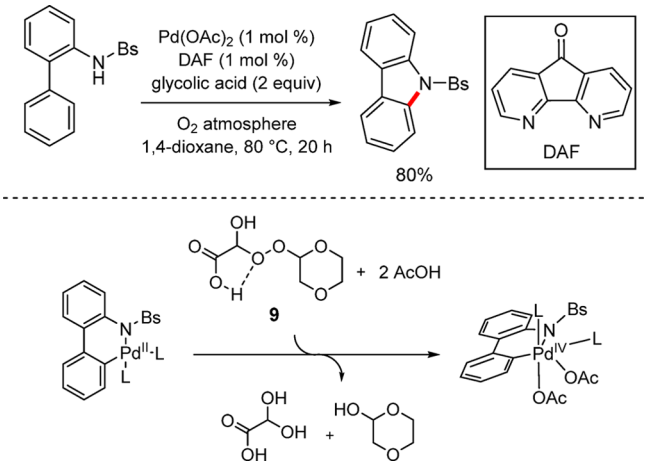
Scheme 12



of trinuclear carbopalladation complex was observed when a stoichiometric amount of an aniline substrate was exposed to palladium(II) acetate. Treatment of the trinuclear specie on $PhI(OAc)_2$ readily releases the carbazole product, suggesting that the oxidation to Pd(IV) species is facile and reductive elimination from the high-valent pallidum takes place smoothly. In 2011, Youn and co-workers employed biphenyl sulfonamides as a starting material for the preparation of electron-deficient carbazoles at room temperature (Scheme 12b).[98]

In 2014, Stahl reported an elegant procedure for Pd-catalyzed intramolecular aerobic C−H amination (Scheme 13).[99] While

Scheme 13



4,5-diazafluorenone (DAF) was used as a ligand, a peroxide-based oxidant **9** was proposed to form in situ from 1,4-dioxane solvent and O_2 in the presence of glycolic acid. A facile reductive elimination of a Pd(IV) intermediate, in situ generated by a peroxide-base oxidant, was suggested as a key step of the reaction.

Whereas the earlier procedures of C−H amination require stoichiometric amounts of strong oxidants, photoinduced single electron oxidation has recently arisen as a promising alternative that is thought to be environmentally benign. In 2015, Cho reported the preparation of carbazoles with the combined use of palladium and visible light photoredox catalysis (Scheme 14).[100] It was proposed that the reaction is initiated by a single electron transfer from a Pd(II) intermediate **10** to the photoexcited iridium species, thus affording the Pd(III) species **11** and one-electron reduced iridium catalyst. Reductive elimination of this Pd(III) intermediate gives a carbazole with Pd(I) species that is reoxidized to Pd(II) complex. On the other hand, an alternative pathway involving a Pd(IV)/Pd(II) catalytic cycle cannot be ruled out at the present stage, wherein one-electron oxidation occurs from Pd(III) species by the action of the photoexcited catalyst prior to the reductive elimination.

Indoline derivatives are recognized as an important azaheterocycle due to their ubiquity in numerous biologically active natural and synthetic compounds. In this regard, synthetic methods for the formation of indoline scaffolds have been actively pursued via an intramolecular catalytic C−H amination approach. In 2009, Yu (J.-Q.) reported a Pd-

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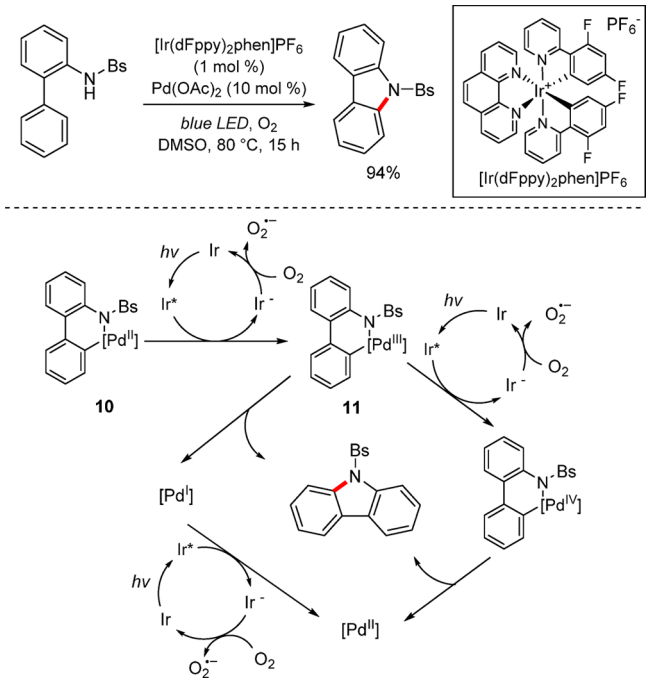
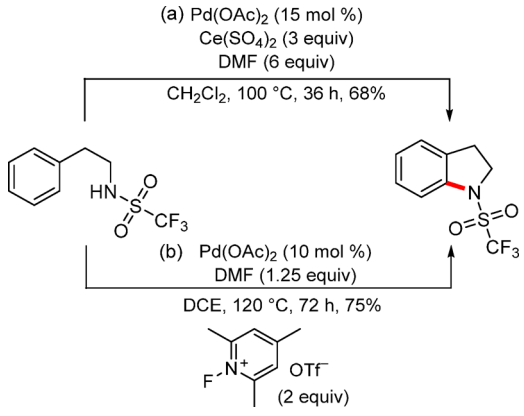
Scheme 14



catalyzed route to indolines starting from *N*-(2-phenyl)-ethyltriflamides using cerium sulfate as a one-electron oxidant (Scheme 15a).[101] In addition, 1-fluoro-2,4,6-trimethylpyridinium triflate also was used as a two-electron oxidant for the same conversion with superior reactivity and a broader substrate scope (Scheme 15b).

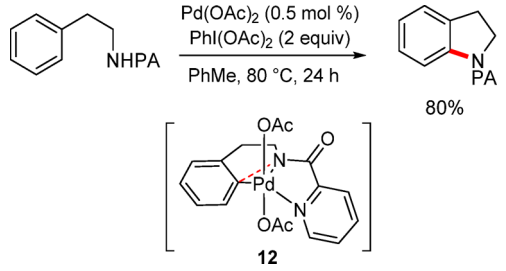
Scheme 15



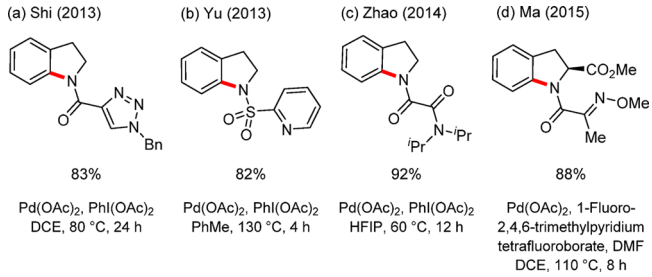
In 2012, Daugulis and Chen (G.) independently reported the synthesis of indolines from 2-phenylethyl amines bearing picolinamide (PA) auxiliary as a bidentate chelator, where the formation of high-valent Pd(IV) intermediates was proposed (Scheme 16).[102−104] Notably, the postulated six-membered intermediates **12** favored C−N bond-forming reductive elimination to give indolines rather than C−O formation.

Since the pioneering works of Daugulis and Chen (G.) demonstrating that bidentate auxiliaries are effective for oxidative cyclization under Pd(II)/Pd(IV) catalysis, a variety of bidentate directing groups have been examined in indoline synthesis. More specifically, the 1,2,3-triazole-4-carboxylate,[105] 2-pyridylsulfonyl,[106] oxalyl amide,[107] and 2-methoxyiminoacetyl[108] directing group have been employed for the oxidative synthesis of indolines under varied conditions (Scheme 17).

Scheme 16

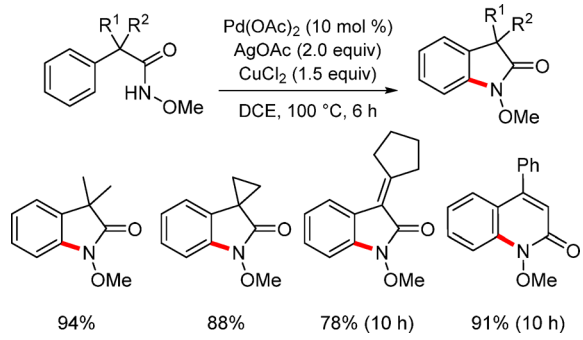


Scheme 17



A Pd-catalyzed intramolecular C−H amination was envisaged to provide lactams, an important structural motif of biological activity found in numerous natural and synthetic compounds. Yu (J.-Q.) and co-workers developed a synthetic route to yield γ- and δ-lactams using $Pd(OAc)_2$ catalyst in the presence of stoichiometric amounts of $CuCl_2$ and AgOAc (Scheme 18).[109]

Scheme 18



When *N*-methoxyhydroxamic acids were subjected to the optimized conditions, corresponding *N*-methoxy-indolin-2-ones were obtained in high yields, presumably via a six-membered palladacycle intermediate. The presence of geminal dialkyl and exocyclic vinyl groups was important in promoting the carbopalladation process, likely due to a conformational constraint. In addition, δ-lactams could also be obtained in good yield through the same approach.

Chen (G.) reported a more facile oxidative synthesis of γ-lactams by employing bidentate auxiliaries such as 8-amino-quinoline or 2-pyridylmethylamine (PM) groups (Scheme 19a).[110] As compared to Yu (J.-Q.)'s procedure described above,[109] Chen (G.)'s reaction facilitated C−H amination of substrates without geminal dialkyl substituents at the benzylic position. In 2016, Zhao (Y.) utilized a *N*,*O*-bidentate auxiliary,

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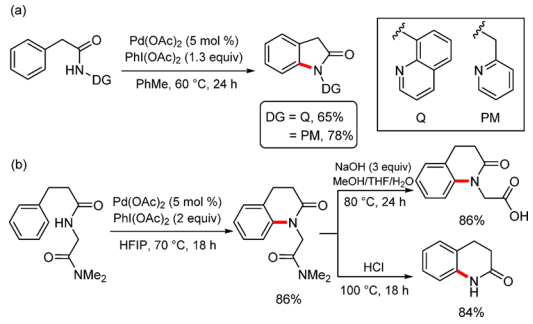
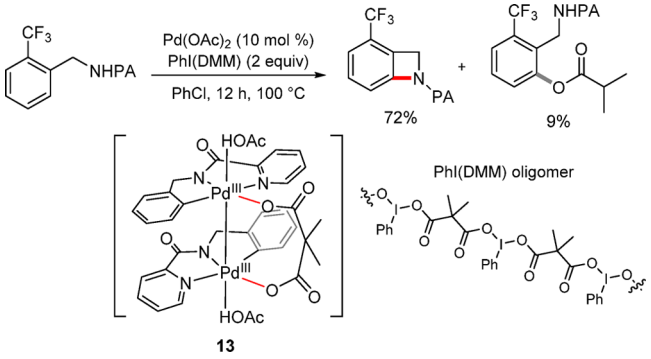
Scheme 19



specifically the glycine dimethylamide (GDMA) group in Pd-catalyzed oxidative cyclization to afford *δ*-lactam derivatives (Scheme 19b).[111]

More recently, Chen (G.) disclosed an elegant route to prepare benzazetidines via a Pd-catalyzed intramolecular C−H amination of picolinamide (PA)-protected benzylamines (Scheme 20).[112] The key to success was the use of a novel

Scheme 20



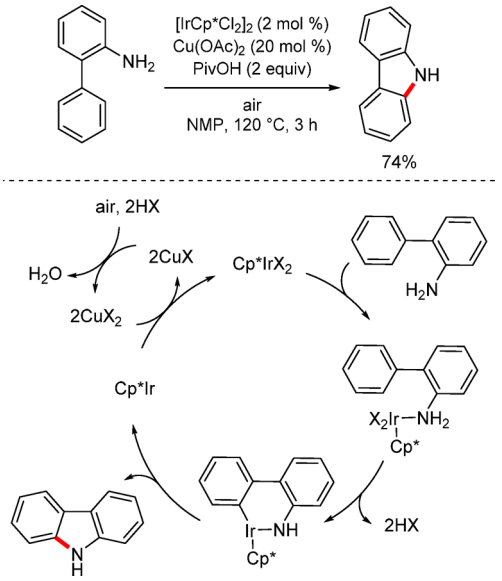
oxidant, phenyliodonium dimethylmalonate PhI(DMM), which is believed to facilitate a C−N bond-forming reductive elimination that is thermodynamically unfavorable in most other C−H aminations. At the same time, this oxidant was assumed to suppress the undesired C−O bond-forming process. DFT calculations revealed the formation of a bimetallic Pd(III)/Pd(III) intermediate **13** having DMM carboxylate ligands, and this bimetallic species undergoes reductive elimination leading to the desired C−N bond formation.

In 2015, Miura reported the synthesis of carbazoles via an Ir-catalyzed intramolecular dehydrogenative C−H amination of 2-aminobiphenyls (Scheme 21).[113] In stark contrast to other known metal catalyst systems requiring *N*-substituted amine substrates, Miura's conditions allowed the direct use of primary anilines without the need of *N*-substituents. Overall, the Ir(III)/Ir(I) catalytic cycle was proposed, where copper salt and atmospheric oxygen regenerate a catalytically active Cp*Ir(III) species.

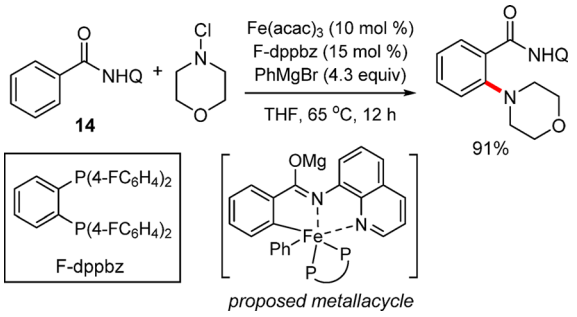
2.2. Intermolecular C(sp^2)−H Amination

2.2.1. First-Row Catalysis. *2.2.1.1. Iron Catalysis.* Utilization of iron-based catalysts in C−H functionalization is an appealing strategy considering their economic and environmental benefits. One inspiring example was reported by Ilies and Nakamura in a directed C−H amination with chloroamines as the aminating source (Scheme 22).[114] A Fe(III) catalyst system in the presence of a Grignard reagent, benzamides **14**

Scheme 21



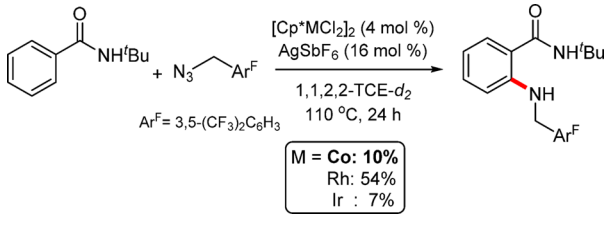
Scheme 22



having a quinolinyl ancillary group (Q) was efficiently aminated at the *ortho*-position. Extensive studies on the effects of directing groups and external ligands revealed that the reaction efficiency was influenced significantly by both of them: rigid bidentate groups and electron-deficient bis-phosphine ligands were especially effective for this amination. The authors hypothesized that a Fe-based metallacycle is formed via deprotonation of benzamides followed by base-mediated C−H bond cleavage. Recent computational studies on related systems indicated that spin-crossover could be involved in the C−H cleavage step.[115]

2.2.1.2. Cobalt Catalysis. Cobalt has received less attention in C−H activation catalysis until recently when compared to its group 9 congeners: rhodium and iridium. Chang and Musaev reported a comparative study to determine the difference in the catalytic activity of Cp*M(III) species (M = Co, Rh, and Ir) in the C−H amination of benzamides (Scheme 23).[116] DFT

Scheme 23



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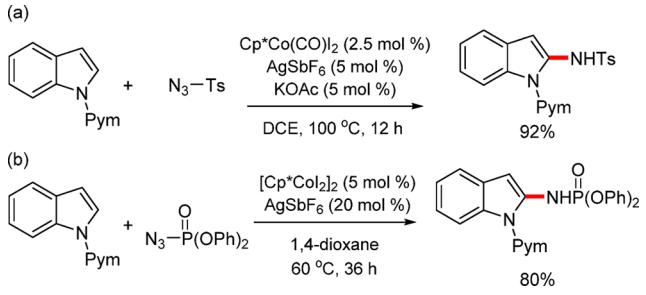
calculations suggested that the inferior catalytic activity of Co in the amination with alkyl azides can be ascribed to the kinetically and thermodynamically less favored C−H bond cleavage (concerted metalation-deprotonation, CMD process) than its Rh counterpart.

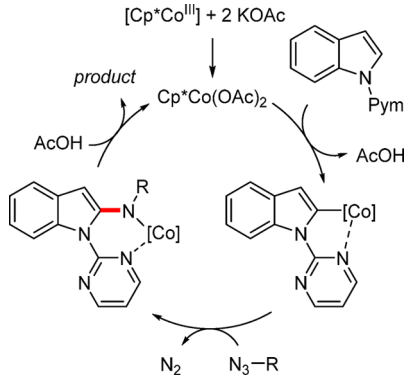
Kanai and co-workers revealed a pioneering example where $Cp^*Co(CO)I_2$ catalyst displays excellent reactivity in the amidation of *N*-pyrimidylindole with sulfonyl azides (Scheme 24a).[117] This air-stable half-sandwich cobalt species is readily

Scheme 24



prepared from a commercially available precursor of dicobalt octacarbonyl. The same research group further extended this amination to include phosphoryl azides (Scheme 24b),[118] where an exogenous acetate base was not required. Similar to the well-documented Cp*Rh(III) catalysis (see section 2.2.2), the proposed C−H amidation pathway consists of essentially the same elementary steps (Scheme 25). $Cp^*Co(OAc)_2$,

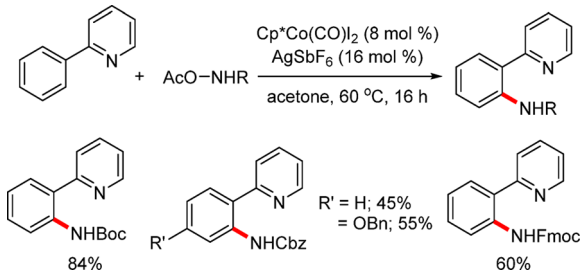
Scheme 25



generated in situ by a ligand exchange, was proposed to form a cobaltacyclic intermediate, and subsequent reaction with organic azides affords a Co(III)−amido species with release of molecular nitrogen. Finally, protonation of the cobalt amido complex will deliver the amidated product with the concomitant regeneration of a catalytically active species.

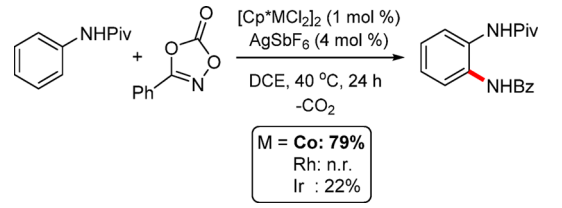
While organic azides were successfully applied to the Co(III) catalysis, a certain type of other aminating agent was also successfully used. In 2015, the Chang group proved the utility of acetoxycarbamates as a convenient and tunable amino group source for the Co(III)-catalyzed C−H amidation (Scheme 26).[119] Importantly, removable *N*-protected amino functionalities such as *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and fluorenylmethyloxycarbonyl (Fmoc) groups could be easily installed. The intermolecular KIE value (1.1) implied that the C−H bond cleavage may not be involved in the turnover-limiting stage.

Scheme 26



Chang and co-workers recently reported that 1,4,2-dioxazol-5-one can be employed as a highly efficient aminating reagent under the similar catalytic system.[120] As a robust amino source, 1,4,2-dioxazol-5-one was previously found to display superior reactivity as an acylnitrene precursor in the Rh(III)-catalyzed C−H amidation.[121] Interestingly, when *N*-pivaloylanilide was subjected to the amidation conditions, the cobalt catalyst displayed the highest reactivity for the C−H amidation among group 9 triads $[Cp^*MCl_2]_2$ (M = Co, Rh, and Ir, Scheme 27). Although the mechanistic origin of the superior reactivity is not fully understood to date, this example shows promise in the use of the first-row transition metal catalysis.

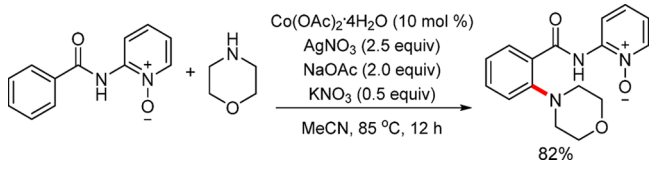
Scheme 27



The synthetic versatility of 1,4,2-dioxazol-5-ones was further proved by close examination of the substrate scope. Jiao and co-workers found that the Co(III)-catalyzed C−H amidation is viable in the presence of various directing groups including purine, pyridine, pyrimidine, ketoxime, and pyrazole moieties.[122] Ackermann and co-workers also described that an oxazolinyl group may direct the *ortho*-amidation of arenes by using 1,4,2-dioxazol-5-ones.[123] The Ackermann group reported Co-catalyzed one-pot synthesis of quinazolines from a reaction of benzimidates with dioxazolones.[124]

Because the cross-dehydrogenative coupling (CDC) allows a direct use of hydrocarbon substrates and nonprefunctionalized reactants, the application of this approach for C−H amination would be highly attractive. In 2016, a promising example was reported by Niu and Song using a Co(II) catalyst (Scheme 28),[125] where an arene $C(sp^2)$−H bond is aminated with alkyl amines in the presence of an external oxidant and a base. The key to success was the judicious choice of directing groups: while others were ineffective, 2-benzamidopyridine *N*-oxides

Scheme 28



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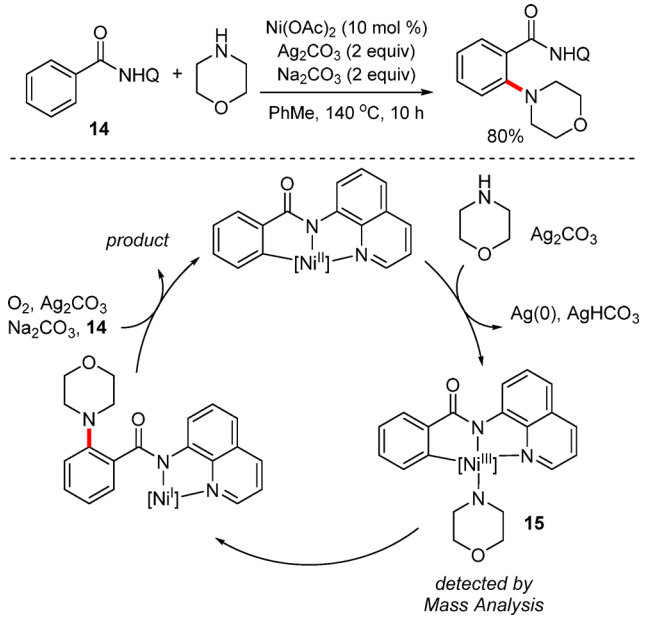
led to a highly efficient C−H amination. DFT calculations suggested that single electron transfer is involved in the catalytic pathway. In addition, the observed radical quenching and EPR analysis supported the existence of the single electron path. It is anticipated that, by developing more practical oxidants such as molecular oxygen, this Co-catalyzed amination procedure will find a versatile utility in synthetic chemistry in the near future.

2.2.1.3. Nickel Catalysis. A rare example of a Ni-based catalyst system for C−H amination was reported by Liu (Z.), Zhang (Y.), and co-workers (Scheme 29),[126] where benzamides

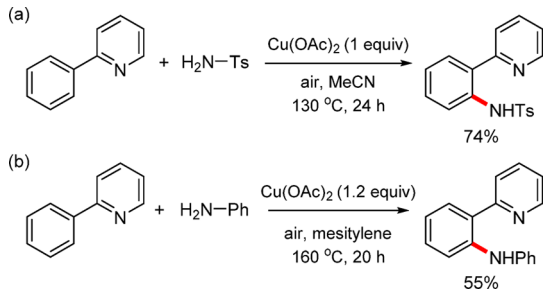
Scheme 29



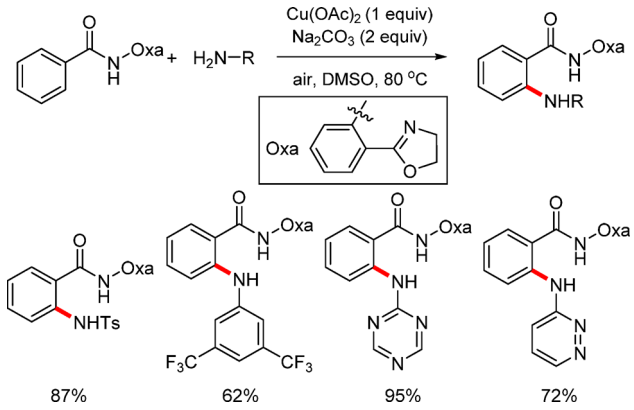
were reacted with alkyl amines in the presence of stoichiometric amounts of Ag(I) salt and carbonate base. 8-Aminoquinoline was employed as an effective directing group in this procedure. Although the reaction temperature was rather high, various functional groups such as acetal, carbamate, and ester were tolerated. The intermolecular KIE value (4.9) implied that the turnover-limiting stage is likely to involve C−H bond cleavage. Inhibitory effects by radical quenchers supported the single electron transfer pathway. The proposed catalytic cycle consists of C−H activation, single electron oxidation to Ni(III) species with amine binding, and reductive elimination followed by terminal oxidation. It is noteworthy that a key intermediate of Ni(III) amido **15** was observed by a mass spectroscopic analysis.

2.2.1.4. Copper Catalysis. Copper complexes constitute one of the earliest examples to show stoichiometric reactivity for directed C−H amination. In 2006, the Yu (J.-Q.)[127] and Chatani[128] groups independently reported $Cu(OAc)_2$-mediated C−H amination of 2-phenylpyridine (ppy) with tosyl amides and anilines, respectively (Scheme 30). The observation that no reaction took place with biphenyl indicates that the C−H amination is driven by chelation. While detailed mechanistic studies were not presented, Yu (J.-Q.) and co-workers proposed a single electron transfer (SET) pathway. The Yu (J.-Q.) group extended the scope of Cu(II)-mediated C−H amination to include benzamide substrates bearing an oxazoline directing group (Scheme 31).[129] This modification led to

Scheme 30



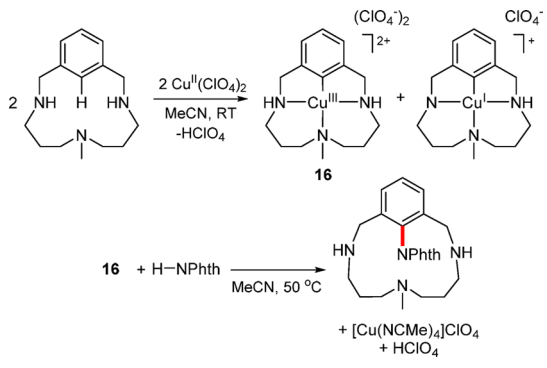
Scheme 31



milder reaction conditions (80 °C) with improved reaction efficiency as compared to their previous system.[127] In addition, an array of convenient amino sources could also be applied such as sulfonyl amides, anilines, and acyl amides. The oxazoline directing group in the aminated products can easily be removed under basic conditions to afford anthranilic acid derivatives.

Given that high-valent Cu(III) species had been proposed as key intermediates for numerous C−N coupling processes, Stahl and co-workers studied the reactivity of such complexes toward the key C−N bond-forming reductive elimination process (Scheme 32).[130,131] When copper(III) species **16** bearing a

Scheme 32



triazamacrocylic ligand, which can readily be prepared by aryl C−H activation via disproportionation of Cu(II) precursors,[132] was subjected to react with various nitrogen nucleophiles, facile reductive elimination occurred, leading to C−N bond formation under mild conditions. This study clearly demonstrated the amination activity of high-valent Cu(III) complex

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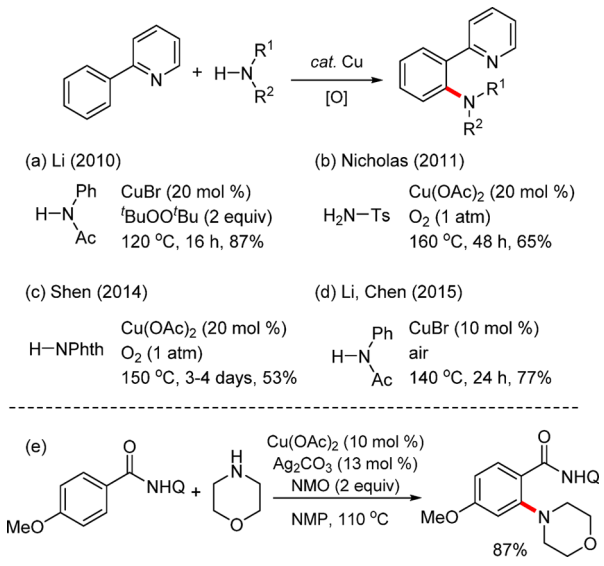
and its potential relevance in catalytic C−H functionalization. Indeed, combined experimental and computational investigations on the related C−H oxidation provided a clue that reductive elimination from Cu(III) complexes is operative in the catalytic cycle.[131,133]

On the basis of the mechanistic understanding of the stoichiometric C−H amination, extensive efforts have been made to develop their catalytic versions. As illustrated in Scheme 33, a range of catalytic systems were disclosed in the

Scheme 33



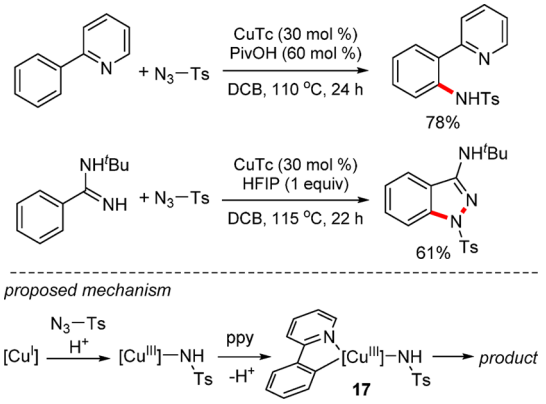
C−H amidation of 2-phenylpyridine, a representative substrate, by employing a small number of aminating reagents. In 2010, Li (C.-J.) and co-workers reported an example of a copper-catalyzed reaction,[134] wherein peroxide was used as an oxidant. Subsequently, several research groups of Nicholas,[135] Shen,[136] and Li (G.) and Chen (X.)[137] also demonstrated that O_2 can be used as an oxidant in copper catalyst systems. However, these Cu-catalyzed C−H amination reactions were operative only at high temperature (>120 °C), indicating that further improvements would be required to make these procedures more practical.

In 2013, Daugulis and co-workers found that bidentate directing groups are highly effective for Cu-catalyzed C−H amination (Scheme 33e).[138] Substrates bearing 8-aminoquinoline auxiliary were reacted with both cyclic and acyclic alkyl amines in the presence of *N*-methylmorphorine *N*-oxide (NMO) as an oxidant. More recently, the same research group established a more general procedure to use an O_2 oxidant with broader synthetic applicability to amidating reagents including sulfonamides, pyrazoles, indoles, and heteroaromatic amines.[139]

While 8-aminoquinoline derivatives are known to promote the C−H amination reactions highly effectively, other types of bidentate chelators also have been carefully examined as potential directing groups. Rodrigues and Arrayás reported that 2-picolinamide can facilitate a Cu-catalyzed amination of nonacidic C(sp^2)−H bonds at 130 °C.[140] Chen (G.) also uncovered the same oxidative C−H amination, but working at room temperature in the presence of $MgCl_2$ additive.[141]

Whereas the Cu-mediated aminations can facilitate cross-dehydrogenative coupling reactions using amine reactants, Zhu and co-workers reported a chelation-assisted C−H amidation of arenes with sulfonyl- or acyl azides (Scheme 34).[142] Whereas

Scheme 34



the reaction did not use external oxidants, satisfactory product yields were obtained at high temperature. When amidine or imine substrates were subjected to the reaction conditions, indazole products were isolated via a tandem process. It was proposed that an initial oxidation of Cu(I) species by organic azide and subsequent C−H cleavage give rise to a high-valent Cu(III)−amido intermediate **17**, which then undergoes a reductive elimination to afford the desired amidated product and Cu(I) species.

2.2.2. Second-Row Catalysis. *2.2.2.1. Ruthenium Catalysis.* Ruthenium complexes have been extensively examined in the area of inner-sphere C−H bond functionalization, possibly due to their facile formation of ruthenacycles under mild condition.[143] The notable progress in the Rh(III)-catalyzed C−H amination also ignited a search for isolobal Ru(II) catalysis, thereupon revealing a number of rather analogous examples. As summarized in Scheme 35, the C−H amidation conditions reported by several different research groups were surprisingly similar in that $[RuCl_2(p\text{-cymene})]_2$ was employed as a catalyst precursor in the presence of silver salts at 80−120 °C of reaction temperature to react with organic azides. In fact, Chang,[144] Jiao,[145] Sahoo,[146,147] and Ackermann[148] independently proved the viability of this approach. Various directing groups including *O*- or *N*-chelators were effective for these sp^2 C−H amidation reactions, thereby being readily applicable to biologically relevant heterocycles such as indolines,[149] xanthones,[150] 2-arylbenzothiazoles,[151] or 2-aryl-1,2,3-triazoles.[152] A notable extension of amino sources was reported by Chang, wherein benzoyl azides were successfully employed for C−H amidation in the presence of a Brønsted acid additive (Scheme 35f).[153]

Reaction paths of this ruthenium catalytic system were examined by Liang and co-workers. When a ruthenacyclic complex **18**, prepared from a reaction of 2-phenylpyridine with $[RuCl_2(p\text{-cymene})]_2$, was allowed to react with nosyl azide, a Ru(II)−amido complex was quantitatively generated (Scheme 36a).[154] Importantly, an olefin aziridination occurred when the catalytic amination was attempted in the presence of norbornene (Scheme 36b and c). Considering that olefin aziridination is viable in a system involving nitrene intermediates, the authors proposed the intermediacy of Ru−imido species **19** in a catalytic cycle. The proposed pathways in

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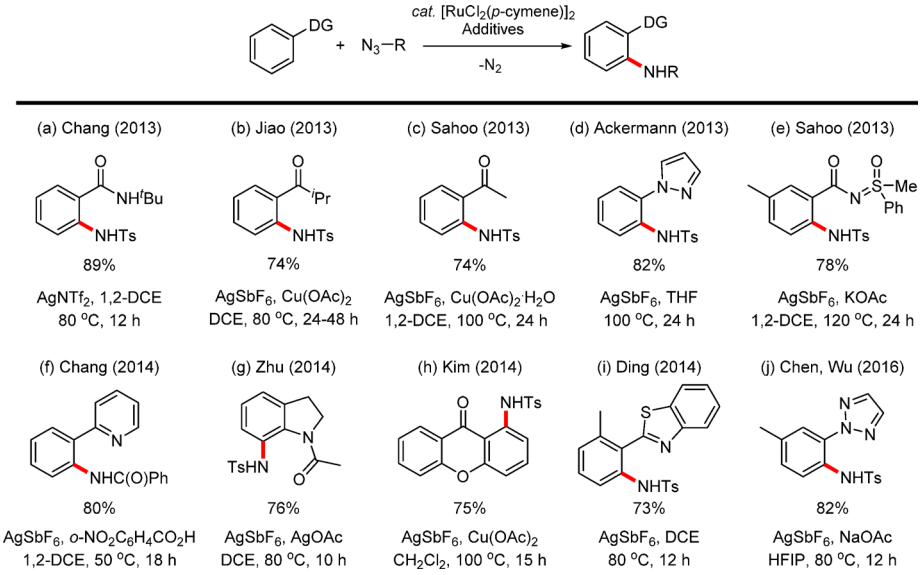
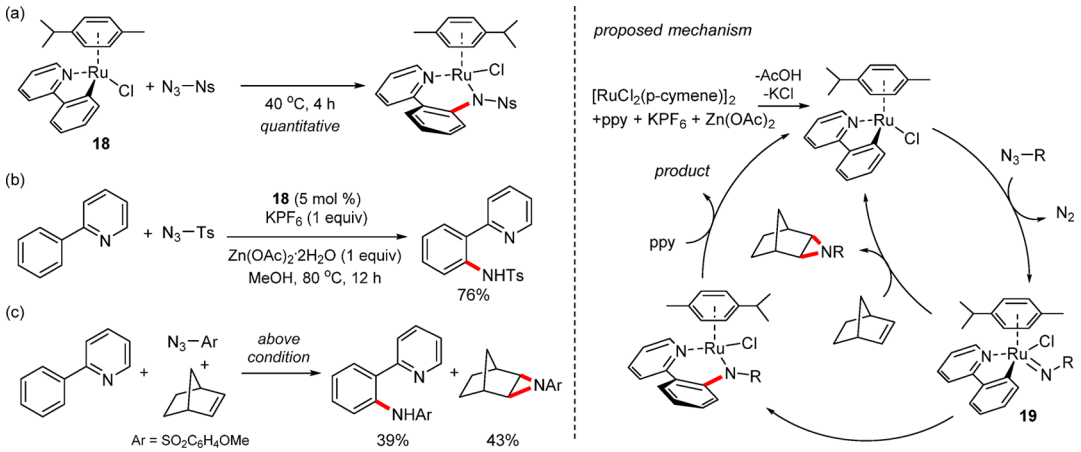
Scheme 35



Scheme 36

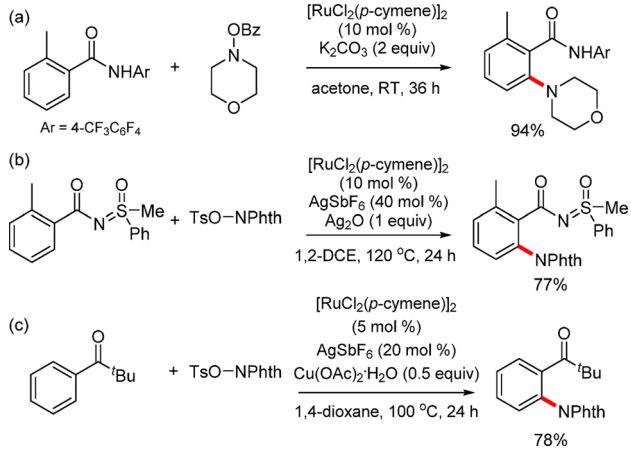


this Ru(II)-catalyzed amidation are quite similar to those in the corresponding Cp*Rh(III) catalysis.

An additional array of aminating reagents containing N−O bonds was examined under the ruthenium catalyst conditions. Yu (J.-Q.) and co-workers showed that benzamides bearing an electron-deficient *N*-aryl moiety underwent a C(sp^2)−H amination with *O*-benzoylhydroxylamines at room temperature (Scheme 37a).[155] Heteroarenes such as pyrazoles, benzothiophenes, and indoles were also competent with the Ru system. Sahoo showed that (*N*-OTs)phthalimide was an effective amino group source in the reaction of benzamides bearing a methyl phenylsulfoximine directing group (Scheme 37b).[156] Recently, Ackermann and co-workers scrutinized a ketone-directed C−H imidation with the same reagent (Scheme 37c), and they proved the synthetic feasibility of this approach to obtain various structural motifs.[157]

2.2.2.2. Rhodium Catalysis. Remarkable recent advances in the Rh(III)-catalyzed C−H functionalization approach have been successfully applied to the development of numerous C−C bond-forming reactions.[158] As a natural extension of this exciting achievement, researchers explored Rh(III)-catalyzed C−H amination reactions by assuming a similar mechanistic scaffold that a rhodacyclic intermediate may couple with proper

Scheme 37



amino precursors instead of carbon nucleophiles. In 2012, Yu (W.-Y.)[159,160] and Glorius[161] independently reported such transformations using chloroamines as the aminating reagents (Scheme 38a and b, respectively). Both tertiary and secondary chloroamines were amenable to react with arene substrates

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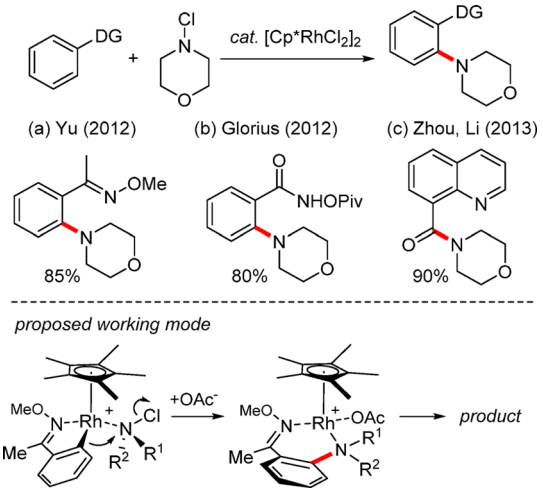
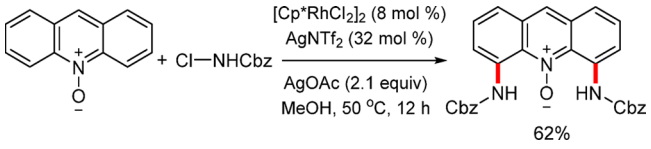
Scheme 38



bearing ketoxime or amide directing groups. Zhou, Li (Y.), and co-workers applied the same strategy to functionalize aldehydic C−H bonds to obtain amides at room temperature (Scheme 38c).[162] Because chloroamines are unstable and difficult to handle, the authors developed a one-pot procedure, where alkyl amines are chlorinated in situ and Rh(III)-catalyzed C−H amination is subsequently performed. Recently, Chang disclosed a convenient C−H amination protocol by using *N*-chlorocarbamates as the aminating reagent (Scheme 39).[163] Efficient installation of a protected amino moiety and subsequent facile deprotection were highlighted in this scalable procedure.

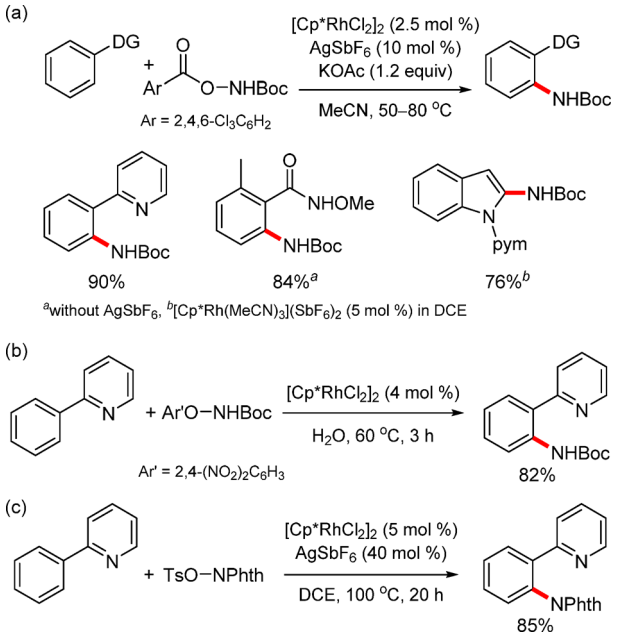
Scheme 39



Hydroxylamine derivatives were also envisioned to be an effective amino group source under the Rh(III) catalysis system. A systematic study carried out by Glorius revealed that *O*-(2,4,6-trichlorobenzoyl) hydroxylamines displayed notable reactivity toward C−H amination (Scheme 40a).[164] Both aryl and alkenyl C(sp^2)−H bonds were functionalized under relatively mild conditions. Xu, Yi, and co-workers further utilized this approach for the synthesis of 2-aminoindole derivatives.[165] Interestingly, Lu and co-workers demonstrated the high robustness of this reaction by conducting a C−H amidation in water (Scheme 40b).[166] While it did not require any additives, the authors proposed that the hydroxyl group on the water surface may work as a base. Wan, Li (X.), and co-workers utilized *N*-tosyloxyphthalimides as an amino group source under the Cp*Rh(III) catalyst system (Scheme 40c).[167] They proposed that the cleavage of a polarized N−O bond in those aminating reagents is crucial in enabling the external oxidant-free conditions. Later, Ding, Yao, and Zhang (A.) reported the C−H amidation of arenes with *O*-benzoyl hydroxylamines where acyl hydrazine and pyrazol-5(4*H*)-one worked as effective directing groups.[168]

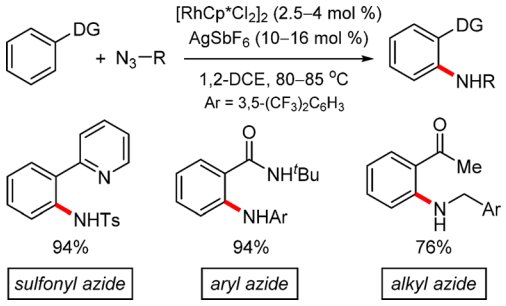
In 2012, the Chang group disclosed a new protocol of utilizing organic azides in C−H activation catalysis.[55] The

Scheme 40



authors demonstrated that various organic azides including sulfonyl,[55] aryl,[169] and alkyl[170] groups were successfully reacted with arene or alkene substrates bearing pyridine, amide, or ketone directing groups (Scheme 41). The reaction was

Scheme 41



operative in the absence of external oxidants to release N_2 as a single byproduct. A wide range of labile functional groups such as hydroxyls, ketones, or esters were compatible with the C−H amination conditions.[171] Further efforts were made to expand the scope to include 6-arylpurines,[172] 2-pyrimidiylindoles,[173] quinoline-8-carbaldehydes,[174] and 2,4-diarylquianolines.[175] Recently, Bach used a deprotectable amidating reagent, *tert*-butoxycarbonyl azide, in the total synthesis of quindoline and cryptolepine.[176] Lu reported a selective mono- or bis-amination of 2-phenylpyridine in the reaction with aryl azides in water.[177]

The mechanistic details were thoroughly investigated by the same research group.[57,178] When tosyl azide was reacted with a rhodacyclic intermediate **20**, insertion of an amide moiety into the Rh−C bond of the rhodacycle occurred smoothly to afford **21** in a high isolated yield (Scheme 42). Two plausible pathways explaining this outcome, which are denoted as concerted insertion and stepwise nitrenoid transfer, were evaluated by computational methods. Energetics derived from DFT calculations indicated that a stepwise nitrenoid transfer traverses with a lower activation barrier than the concerted

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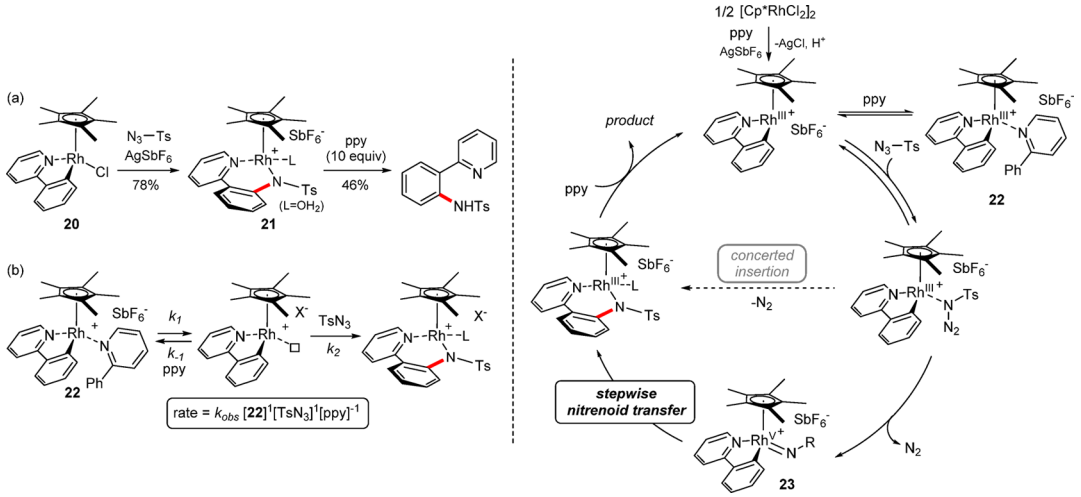
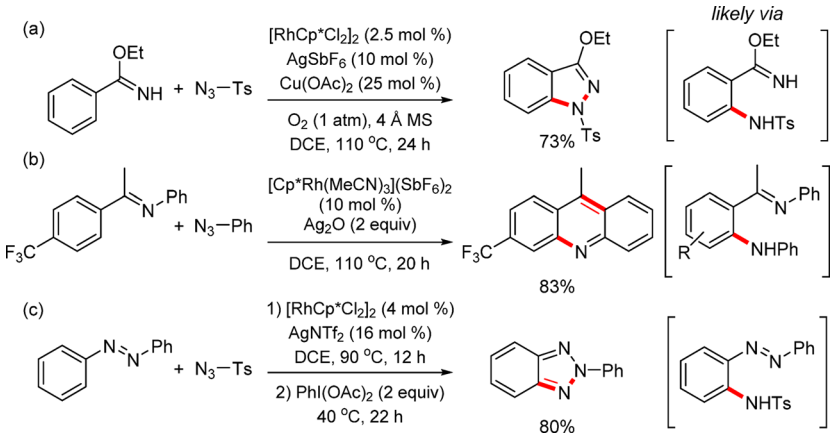
Scheme 42



Scheme 43



motion. As a result, the key intermediate in this process is a high-valent Rh(V)−nitrenoid species **23** that is envisaged to display high reactivity toward the subsequent insertion into the Rh−C bond of the rhodacycle. The final step in this catalytic cycle was suggested to be proto-demetalation by the second substrate to release an aminated product with the concomitant regeneration of a rhodacycle. On the basis of kinetic experiments, complex **22** was determined to be a resting species, and the C−N bond-forming step turned out to be rate-limiting (Scheme 42). All data including Hammett analysis, KIE experiments, and DFT calculations provided corroborating evidence for this mechanistic scaffold.

On the basis of this highly facile C−H amination protocol using organic azides, synthetic utility of the initially formed aminated products was further explored to enable subsequent transformations. For instance, Glorius reported a one-pot synthesis of substituted 1*H*-indazoles by tandem Rh-catalyzed C−H amidation of arylimidates followed by a Cu-mediated N−N coupling reaction (Scheme 43a).[179] Notably, a catalytic amount of copper species was sufficient for the postulated SET process. Ellman described the direct synthesis of unsymmetrical acridines and phenazines relying on Chang's protocol using aryl azides as the aminating reagent (Scheme 43b).[180] Upon the initial C−H amination, subsequent electrophilic aromatic substitution and then rearomatization afford the desired heterocyclic products. On the other hand, Lee (P.-H.) showed that the 2-aryl-2*H*-benzotriazoles can be readily obtained by a one-pot sequential process: C−H amidation of azobenzenes and oxidative cyclization of initially obtained *ortho*-amidated azobenzenes (Scheme 43c).[181]

The identification of organic azides as an excellent amino group source in the Rh(III)-based C−H activation catalysis led to the development of highly versatile C−H amination procedures with a fundamental mechanistic understanding of the C−N bond-forming process. However, elevated reaction temperatures higher than 80 °C were frequently required to obtain satisfactory product yields, thus causing a difficulty in employing thermally labile amino precursors such as acyl azides. In this regard, the Chang group managed to develop a new type of thermally stable, but highly reactive amidating source (Scheme 44).[121] A mechanistic study with benzoyl azides in a stoichiometric manner suggested that the C−N bond-forming step is rate-limiting. Given that lowering the activation barrier at the turnover-limiting step results in an increase of catalytic performance, the authors found that 1,4,2-dioxazol-5-one displays superior reactivity in the C−H amidation reaction. DFT calculations suggested that the higher performance of dioxazolone may have originated from both thermodynamic and kinetic advantages. More recently, a combined quantitative analysis of stoichiometric C−N couplings and computational investigations strongly suggested that putative Rh(V)− and Ir(V)−imido species will be involved

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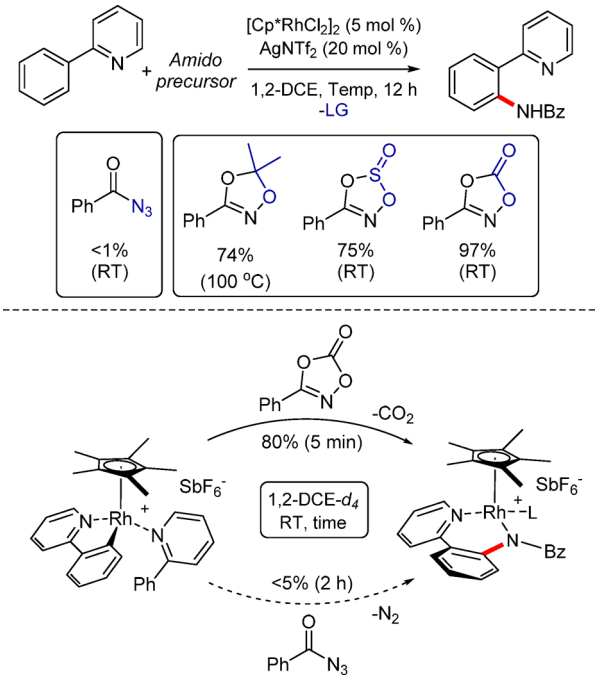
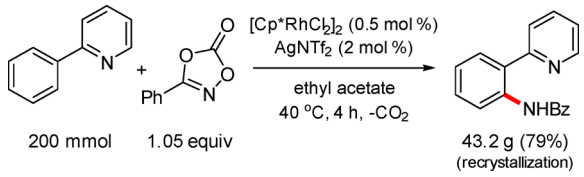
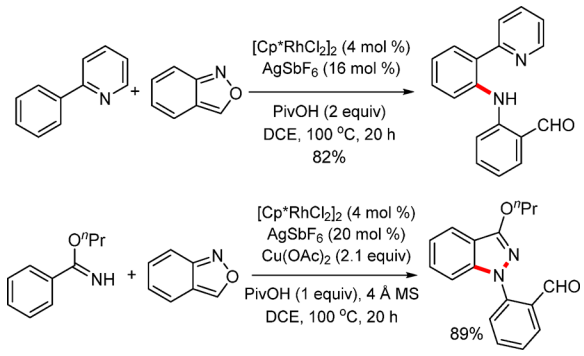
Scheme 44



Scheme 45



Scheme 46



as key intermediates when dioxazolones are used as the amide source.[182]

The Chang group also illustrated the practical aspects of the C−H amidation using 1,4,2-dioxazol-5-one in regard to scalability, safety, and benign reaction conditions.[183] While the measurement of differential scanning calorimetry (DSC) clearly indicated facile decomposition of benzoyl azide within the temperature range from −20 to 100 °C, 3-phenyl-1,4,2-dioxazol-5-one remained intact over three heating-and-cooling cycles within the same temperature span, thus suggesting its high thermal stability (Figure 2). In addition, amidation using this amino group source was readily scalable in ethyl acetate solvent, thus circumventing the use of halogenated solvents (Scheme 45).

Recently, Lan, Li (X.), and co-workers uncovered a bifunctional amidating reagent enabling the installation of two functionalities in products at the same time.[58] Anthranil was efficiently coupled with C(sp^2)− or C(sp^3)−H bonds under the Cp*Rh(III) catalyst system (Scheme 46). Notably, the obtained products possess a carboxaldehyde group that can be further converted to other synthetically valuable functionalities. Under oxidative conditions, indazole synthesis was also achieved in one-pot based on this amidation approach. DFT calculations indicated that the intermediacy of Rh−nitrenoid is energetically feasible. Jiao and co-workers independently reported a similar transformation, and they proposed an analogous Rh(V)−nitrenoid intermediate.[184] The Li (X.)[185] and Wang[186] research groups independently revealed a tandem process consisting of C−H amination and annulation by employing this bifunctional amidating reagent. After having the directed C−H amination mediated by Cp*Rh(III) catalyst, an intramolecular dehydrative cyclization was carried out to give condensed heteroaromatic products.

Zhou, Li (Y.), and co-workers disclosed that nitrosobenzene can serve as an efficient aminating source in the Rh-catalyzed direct C(sp^2)−H amination to afford *N*-diarylhydroxylamine products at room temperature (Scheme 47a).[61] Under slightly modified conditions, in situ cleavage of the *N*-hydroxyl group in products was also observed (Scheme 47b).[187] The Li (X.) group further applied this reaction to the development of a redox-neutral synthesis of indazole derivatives without requiring stoichiometric amounts of external oxidants.[188] Zhou, Yang (Y.), and co-workers showed that *N*-hydroxycarbamates can also work as an efficient aminating reagent,

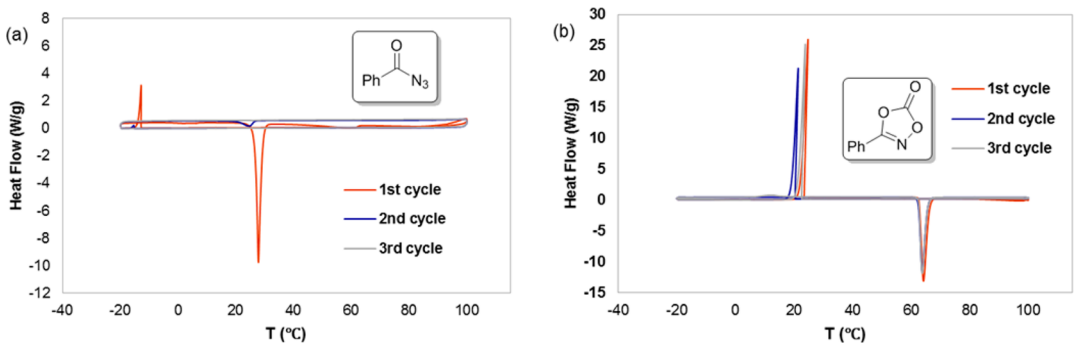


Figure 2. DSC measurement of (a) benzoyl azide and (b) 3-phenyl-1,4,2-dioxazol-5-one. Reproduced with permission from ref 183. Copyright 2015 American Chemical Society.

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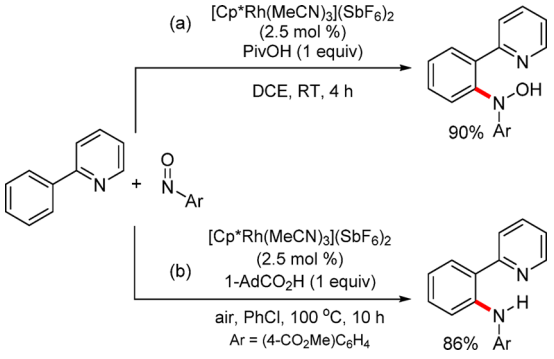
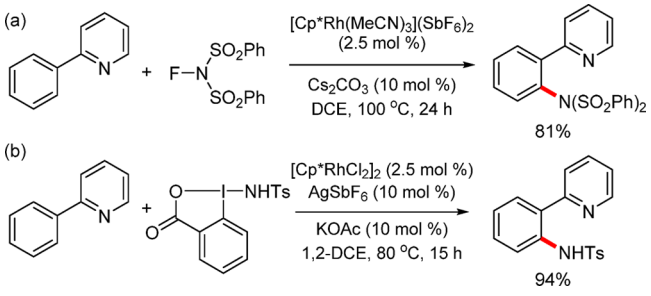
Scheme 47



where in situ prior oxidation of hydroxylcarbamates to nitrosoformates was proposed.[189]

Other types of prefunctionalized aminating sources bearing polarized and cleavable bonds were investigated. In 2013, Yang (L.), Li (C.-J.), and co-workers reported C(sp^2)−H amination with NFSI as the aminating reagent (Scheme 48a).[190] The

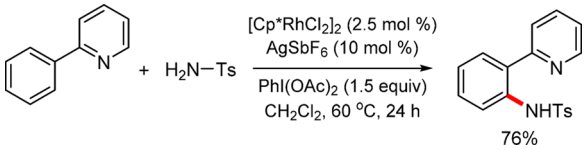
Scheme 48



authors proposed an electrophilic amidation pathway, where a rhodacyclic intermediate undergoes a substitution reaction with NFSI. Loh and co-workers recently utilized amidobenziodoxolones as an electrophilic amino group source in Cp*Rh(III)-catalyzed C−H amidation (Scheme 48b).[60] Complex organic molecules such as guanosine derivatives and camptothecin *N*-oxides were smoothly amidated under optimized condition.

While preoxidized amino precursors were extensively utilized for C−H amination, nonpreactivated amines (amides) were also scrutinized under various catalytic conditions. Su and co-workers reported a dehydrogenative coupling of aryl C(sp^2)−H bonds with sulfonamides by the use of Cp*Rh(III) catalyst and stoichiometric PhI($OAc)_2$ oxidant (Scheme 49).[191] A range of

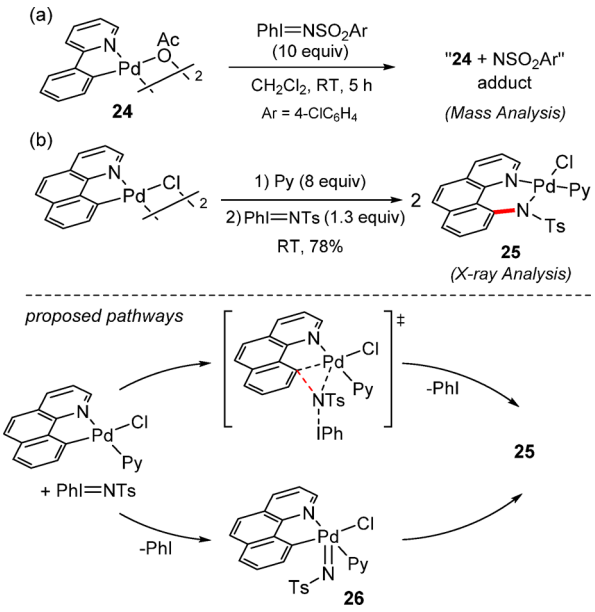
Scheme 49



N-coordinating groups such as pyridines, pyrazoles, and oxazolines were effective for this reaction. The observation that stoichiometric amidation of a rhodacyclic intermediate occurred by treatment of presynthesized iminoiodinane suggested a plausible formation of a nitrenoid species in situ under the catalytic conditions.

2.2.2.3. Palladium Catalysis. Initial attempts to extend the Pd-mediated C−H activation approach to amination reactions were made with several well-defined palladacyclic complexes. In 2006, Yu (W.-Y.) and Che found that a cyclometalated palladium dimer **24** reacted with iminoiodinane (Scheme 50a).[192] A mass spectroscopic analysis indicated the formation

Scheme 50



of an adduct composed of palladium and sulfonylnitrene moieties in the crude mixture. Sanford and co-workers independently reported a stoichiometric amidation of a benzo[*h*]quinoline-derived palladacycle to furnish a Pd(II)−amido complex that was characterized by a crystallographic analysis (Scheme 50b).[53] The authors proposed two possible pathways for this transformation: concerted and stepwise processes. In the concerted process, upon the initial coordination of iminoiodinane to the Pd(II) center of palladacycle, the loss of iodobenzene and the insertion of a sulfonamido moiety into Pd−C would take place at the same time to afford intermediate **25**. Alternatively, in the stepwise process, a prior liberation of iodobenzene gives rise to a discrete Pd(IV)−imido intermediate **26**, which can subsequently undergo an insertion to the Pd−C bond. Energetics calculated from DFT studies suggested preference for the stepwise pathway, and the electronic structure of the putative intermediate **26** was assigned to be a singlet Pd(IV)−imido species.[193] A protonation of complex **25** with HCl quantitatively released an *ortho*-amidated product, thus attesting the feasibility of a catalytic C−H amination reaction.

Indeed, Yu (W.-Y.) and Che pioneered a related catalytic C−H amidation with free amides in the presence of potassium persulfate as an external oxidant (Scheme 51a).[192] A number of amino sources such as carbamates, acetamides, sulfonamides, and cinnamides were successfully coupled with substrates bearing nitrogen-based chelators. In 2011, Liu (L.) and co-workers further developed an intermolecular C−H amidation of aromatic ketones utilizing *N*-fluoro-2,4,6-trimethylpyridinium triflate as an oxidant (Scheme 51b).[194] The use of electron-deficient Pd($OTf)_2$ was critical for efficient reaction, and the Pd−amine adduct **27** was characterized by an X-ray analysis. A stoichiometric conversion of **27** to the amidated

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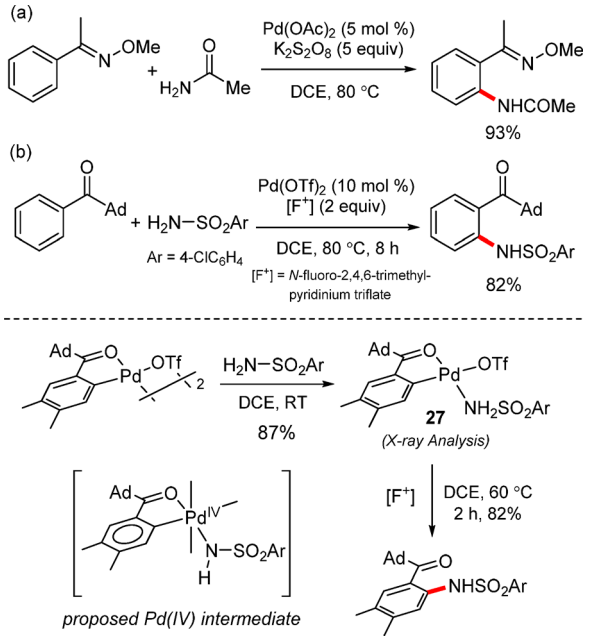
Scheme 51



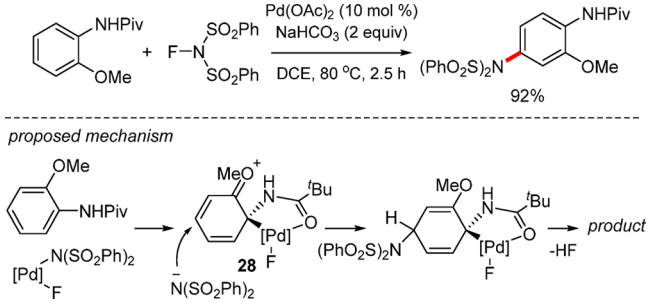
product was observed by adding the F^+ agent. On the basis of the observation that *N*-methyl sulfonamides worked as an amide source under the employed conditions, a nitrene intermediate was not suggested to be involved in this process. Instead, a Pd(IV) intermediate was proposed as a key intermediate for this catalytic C−H amination.

Yu (W.-Y.) and co-workers successfully utilized prefunctionalized aminating sources for Pd-catalyzed C−H amination reactions.[56] When ethyl *N*-nosyloxycarbamate was reacted with *N*-pivaloylanilide, palladium catalyst displayed notable activity without the need of external oxidants. The same group further applied this approach for the synthesis of anthranilic acid derivatives, by reacting ethyl mesitylsulfonyloxycarbamate with lithium 3,4-dimethylbenzoate under the optimized conditions to furnish *ortho*-amidated benzoic acids in a satisfactory yield.[195]

In 2011, Yu (J.-Q.) and co-workers reported an efficient catalytic system using *O*-benzoyl hydroxylamines as an amino group source (Scheme 52).[196] By employing an electron-deficient *N*-auxiliary (4-$CF_3C_6F_4$−) and stoichiometric amount of base, facile deprotonation of amide N−H bond was assumed to accelerate the formation of palladacyclic intermediate. The scope of directing groups was further expanded to include weakly coordinating moieties such as *N*-benzyl triflamides.[197] The reaction efficiency was significantly improved by adding 2,4,6-trimethoxypyridine as a supporting ligand. Two possible pathways were proposed on the C−N coupling step: (i) electrophilic amination and (ii) stepwise process that consisted of oxidative addition and reductive elimination. Recent DFT studies by Sunoj and Schaefer supported the latter mechanism involving a Pd(II)/Pd(IV) cycle, wherein a heterobimetallic Pd(μ-OAc)$_3$Ag complex was proposed as the active catalyst.[198,199]

Zhang (Q.) and co-workers developed a substrate-controlled chemoselective C−H amination of anilides using NFSI as the amino group source (Scheme 53).[59] While the *ortho*-amidated

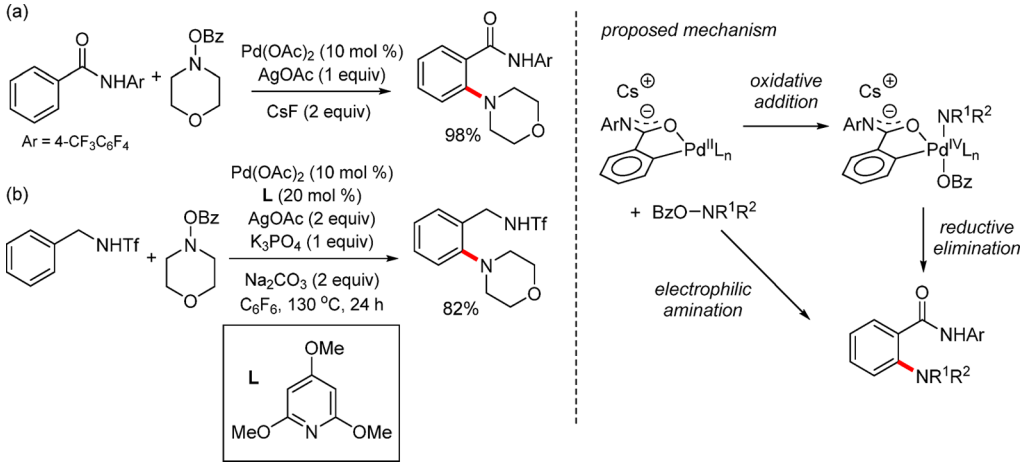
Scheme 53



products were obtained from a range of 4-substitutetd anilides, C−H amidation at the *para*-position was observed with 2-methoxy anilides under otherwise identical conditions. The authors proposed the formation of a spiro-type palladacyclic intermediate **28** when this particular substituent (−OMe) is present. Nucleophilic attack of an anionic imido species at the *para*-position to this unique palladacycle and subsequent deprotonation were assumed to afford the product. Although the proposed mechanism does not fit into the conventional C−H activation catalysis, it constitutes a rare example of Pd-catalyzed *para*-selective C−H amination.

2.2.3. Third-Row Catalysis. *2.2.3.1. Iridium Catalysis.* Because iridium complexes are known to display remarkable

Scheme 52



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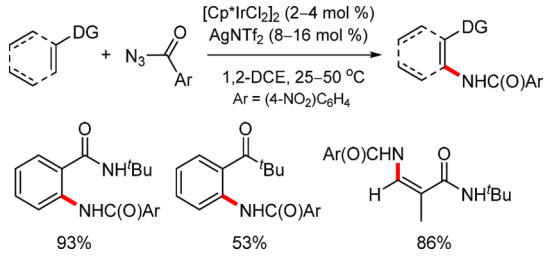
reactivity toward stoichiometric C−H activation of hydrocarbons,[200−204] it is tempting to investigate the corresponding catalytic functionalizations to introduce functional groups directly into inert molecules. Such a perspective, however, has been less explored, mainly due to the inherent stability of iridacyclic complexes. Inspired by significant advances in the Cp*Rh(III)-catalyzed C−H amination, the Chang group envisioned the use of a Cp*Ir(III) complex, group 9 congener, for analogous transformations.[205] Indeed, acyl azides displayed remarkable reactivity toward C−H amidation under Ir-catalyzed mild conditions (Scheme 54). Acyl azides were found to be a challenging amino group source in the Cp*Rh(III) catalysis because of their thermal instability, thus leading to poor amination efficiency. In contrast, the Cp*Ir(III) catalyst system allowed a highly efficient C−H amidation with acyl azides that were not decomposed to isocyanates via Curtius rearrangement under mild optimized conditions.

A broad range of combinations in regard to substrates and organic azides has been extensively investigated for the synthesis of valuable C−H aminated product motifs, as summarized in Table 1. Remarkably diverse substrates including aryl carbamates,[206] triarylphosphine oxides,[207,208] quinoline *N*-oxides,[209] benzoic acids,[210,211] alkyl benzoates,[212] indolines,[213] indoles,[214,215] acylsilanes,[216] aryl nitrones,[217] benzylic amines,[218] and 2-aryl-1,2,3-triazole *N*-oxides[219] were successfully coupled with sulfonyl azides as the amidating sources. In addition, azido formates,[220] phosphoryl azides,[221,222] aryl azides,[116,206] and alkyl azides[223] were also found to work as efficient amino precursors under the same catalytic system. Recently, Lu utilized this C−H amidation strategy for the synthesis of functionalized quinazoline-2,4(1*H*,3*H*)-diones, where a subsequent intramolecular cyclization was conducted.[224] Recently, Bolm disclosed a mechanochemical process for the Ir-catalyzed C−H amidation in solvent-free conditions.[225]

The half-sandwich iridium(III) catalyst displayed excellent reactivity toward C(sp^2)−H amidation using *N*-substituted hydroxylamines as the amino group source (Scheme 55).[226] Utilizing a cleavable N−O bond of the amidating reagents as an internal oxidant, various types of *N*-protected amino groups

Scheme 54



Scheme 55

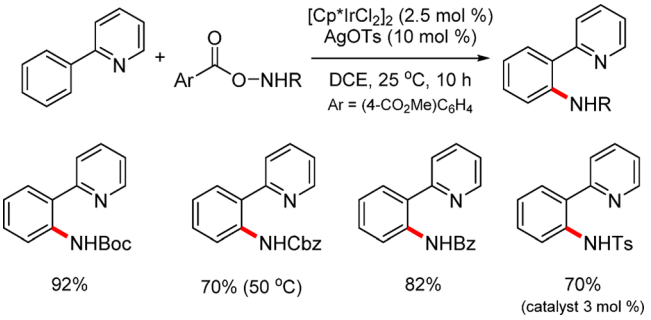
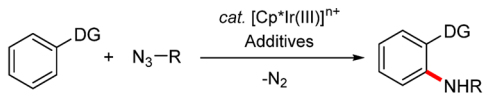
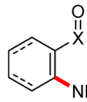
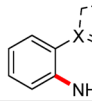
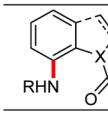
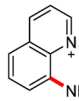
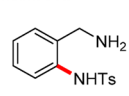
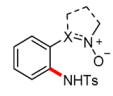


Table 1. Scope of the Ir(III)-Catalyzed C−H Amination with Organic Azides



	N_3−C(=O)−R	N_3−S(=O)2−R	N_3−C(=O)−OR	N_3−P(=O)(OR)2	N_3−Ar	N_3−Alkyl
	Ref 205	Ref 206, 225	Ref 220	Ref 221	Ref 116, 206	Ref 223
	Ref 205	Ref 206–208, 210–212, 216		Ref 221		
	Ref 205	Ref 206	Ref 220	Ref 221–222		
	Ref 213	Ref 206, 213–215	Ref 220	Ref 221	Ref 213	Ref 213
	Ref 209	Ref 209		**Miscellaneous**  Ref 218  Ref 217, 219		

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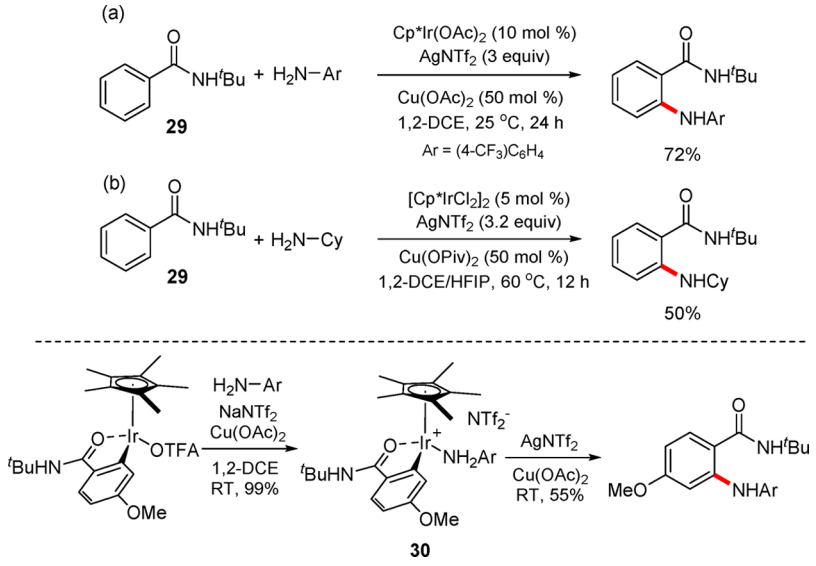
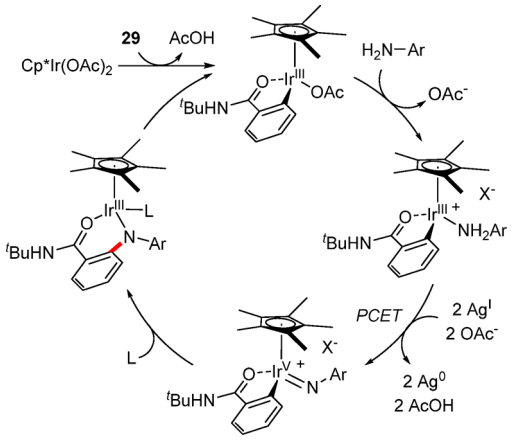
Scheme 56



were readily introduced to arenes. Notably, a broad range of labile functional groups such as esters, aldehydes, and ketones were tolerated under the employed catalytic conditions.

Chang and co-workers developed an Ir-catalyzed oxidative C−H amination in reaction with unactivated amines in the presence of silver(I) salt (Scheme 56). In this cross-dehydrogenative coupling, both anilines[227] and alkyl amines[228] smoothly reacted with benzamides **29** under mild conditions. Mechanistic insights were obtained by rendering a series of stoichiometric reactions. When a well-characterized iridacycle was allowed to react with aniline, an adduct **30** was formed quantitatively, which was characterized by an X-ray crystallographic analysis. While the subsequent addition of $AgNTf_2$ and $Cu(OAc)_2$ to the adduct afforded the *ortho*-aminated product, copper acetate alone did not mediate this conversion. On the basis of these results, the authors postulated a series of proton-coupled electron transfer (PCET) processes to access a high-valent Ir(V)−nitrenoid intermediate, which was previously postulated as a key intermediate in the C−H amination using organic azides as the aminating reagent (Scheme 57).

Scheme 57

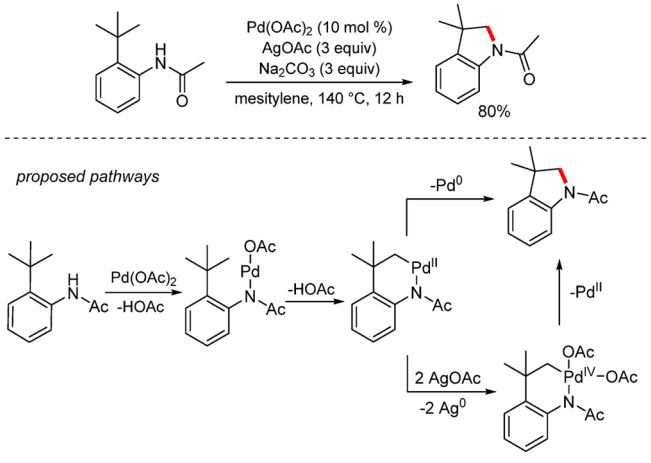


2.3. C(sp^3)−H Amination

Along with the notable advances in the direct C(sp^2)−H amination, considerable efforts have been made to extend its scope to more challenging substrates containing sp^3 C−H bonds. In addition to the high bond dissociation energy (BDE) of C(sp^3)−H bonds, the lack of empty low-energy orbitals or filled high-energy orbital, which may interact with the metal's orbitals, is attributed to lowered amination efficiency.[229] To deal with the inherently low reactivity and poor selectivity in the direct C(sp^3)−H bond functionalization, the use of directing groups at the proper sites relative to the targeted C−H bonds has been widely practiced. In this strategy, the facile formation of five- or six-membered metallacyclic intermediates is critical to achieve satisfactory efficiency of the transformation.

2.3.1. Intramolecular C−H Amination. In 2009, Glorius reported a synthetic route to prepare indolines via a Pd-catalyzed intramolecular C−H amination of *N*-(2-*tert*-butylphenyl)acetamides (Scheme 58).[230] Notably, the reaction took place selectively at C(sp^3)−H bonds even in the presence of C(sp^2)−H bonds. While a six-membered palladacycle could be a key intermediate, the authors suggested two possible

Scheme 58



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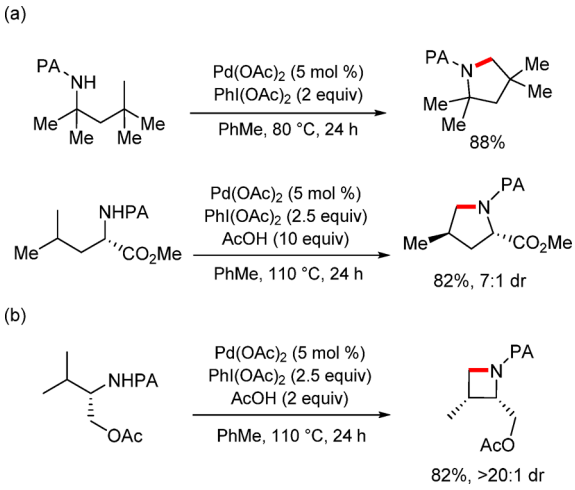
pathways leading to C−N bond formation: (i) a direct reductive elimination with reoxidation of the resultant Pd(0) species by Ag(I) salts, and (ii) Ag(I)-promoted oxidation of the palladacycle intermediate to Pd(IV) and then reductive elimination.[231]

An earlier investigation by Daugulis revealed that picolinamide (PA) displays a notable chelation-assistance effect to enable C(sp^3)−H functionalization including an arylation of primary or secondary alkyl moieties.[232] Using PA as a directing group, Daugulis[102] and Chen (G.)[103] independently reported Pd-catalyzed intramolecular amination to obtain five-membered pyrrolidines using $PhI(OAc)_2$ oxidant (Scheme 59a). More-

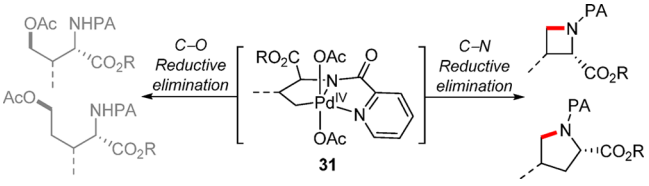
Scheme 59



over, Chen (G.) further extended this method to the production of four-membered azetidine compounds (Scheme 59b). Notably, a respectable diastereoselectivity was induced in this cyclization.

A catalytic cycle consisting of Pd(II)/Pd(IV) was proposed in these transformations, where a high-valent Pd(IV) intermediate **31** was assumed to facilitate reductive elimination step leading to C−N bond formation (Scheme 60). In this

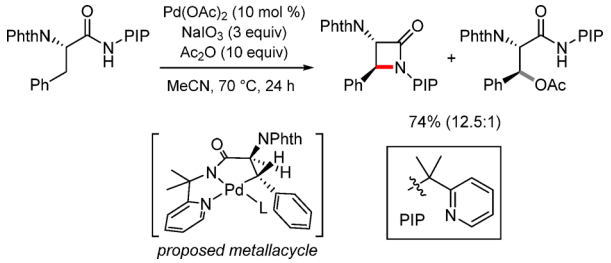
Scheme 60



context, it was proposed that the torsional strain on the putative intermediate **31** significantly affects the subsequent reductive elimination process. Although the observed product distribution is not fully understood, a conformational bias in the Pd(IV) intermediate was reasoned to be crucial, thus favoring the C−N bond formation in the case of having in-plane geometry while an out-of-plane geometry leads to the C−O bond formation.

Shi (B.-F.) demonstrated the utility of a modified bidentate directing group of 2-(pyridin-2-yl)isopropyl (PIP) in a Pd-catalyzed intramolecular C−H amination (Scheme 61).[233] Significantly, the reaction efficiently took place at the benzylic C(sp^3)−H bonds to furnish β-lactams along with the formation

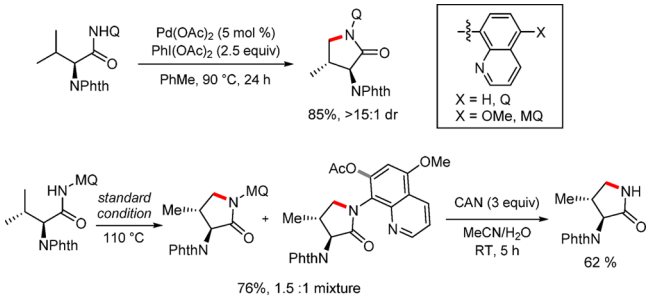
Scheme 61



of a small amount of β-acetoxylated byproduct. In this procedure, the combination of $NaIO_3$ with Ac_2O turned out to be effective for the oxidation of a cyclometalated Pd(II) intermediate to Pd(IV) species. The observed high diastereoselectivity was attributed to the involvement of a *trans*-palladacycle intermediate that undergoes reductive elimination to lead to the C−N bond formation.

In 2013, Chen (G.) proved that pyrrolidones can readily be accessed by the Pd-catalyzed intramolecular amination at the unactivated C(sp^3)−H bonds (Scheme 62).[110] The reaction

Scheme 62



proceeded via Q-directed activation of γ C−H bonds to afford γ-lactams with high diastereoselectivity. The 8-amino-5-methoxyquinoline (MQ) auxiliary was easily removed after the desired C−H functionalization with ceric ammonium nitrate (CAN) under mild conditions.

Since the first report by Daugulis on the use of 8-aminoquinoline as an efficient bidentate directing group,[232] it has been widely utilized in numerous C−H functionalization reactions. The beneficial effect of bidentate auxiliaries is not restricted to Pd-catalyzed C−H functionalizations. In fact, significant advances have been made recently in the first-row transition metal-catalyzed reactions employing bidentate directing groups. In 2014, Kanai reported a Cu-catalyzed intramolecular oxidative C−H amination using Ag_2CO_3 oxidant (Scheme 63a).[234] While C(sp^2)−H bonds are potentially feasible, C(sp^3)−H bonds were selectively reacted to afford β-lactam products presumably via a five-membered metallacycle intermediate. Interestingly, C−H amination was found to be favored at the benzylic β-methylene over β-methyl C−H bonds under the employed conditions. Similarly, Ge and co-workers also reported a Cu-catalyzed intramolecular amination with the use of a benzoate base and a duroquinone oxidant (Scheme 63b).[235] The amination reaction at the β-C−H bonds occurred with the following reactivity order: β-benzylic > β-methyl > β-methylene in ring > β-methylene in acyclic chain.

In 2014, Ge reported a Ni-catalyzed intramolecular C(sp^3)−H amination of aliphatic amides bearing a 8-aminoquinoline directing group (Scheme 63c).[236] Unlike the Cu-catalyzed

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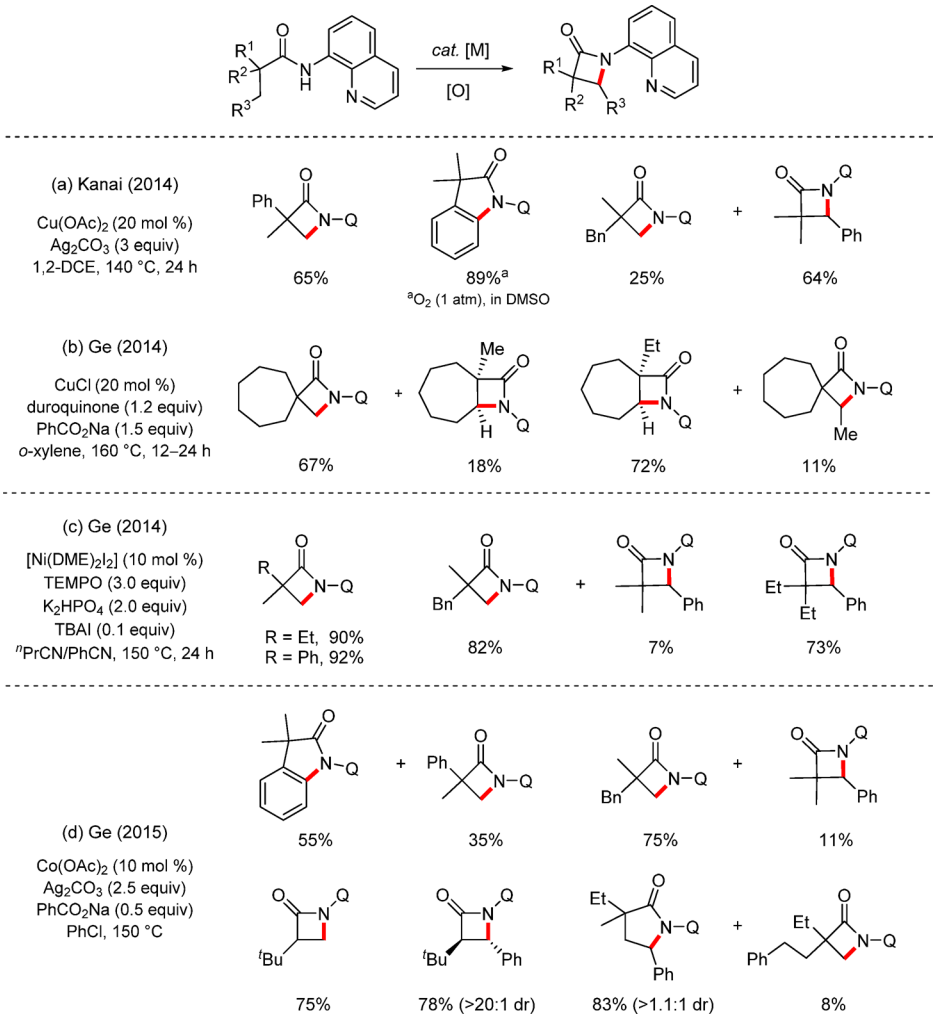
Scheme 63

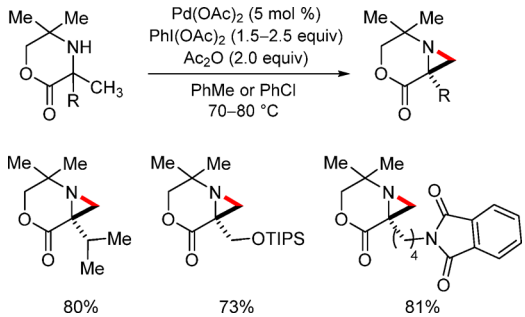


procedure, this nickel catalytic reaction proceeds predominantly at the β-methyl position to deliver β-lactam products while leaving the benzylic sp^3 C−H bonds intact. More recently, Ge also reported a Co-catalyzed intramolecular dehydrogenative amination with the assistance of the 8-aminoqunoline directing group to display some notable features (Scheme 63d).[237] For instance, aryl sp^2 C−H bonds are more reactive than sp^3 C−H bonds under this cobalt catalyst system, and α-monosubstituted propanamide derivatives were successfully cyclized. In addition, γ-benzylic C−H bonds were selectively reacted in the presence of β-methyl groups leading to γ-lactam products, which is the opposite reactivity pattern as compared to Kanai's catalyst system using the same substrate.[234]

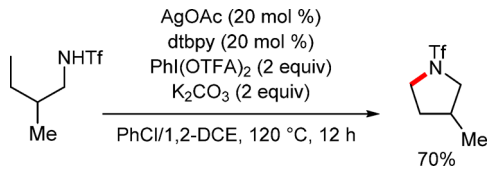
While the intramolecular amination of sp^3 C−H bonds has been feasible by the assistance of amide directing groups, a notable example of C−H amination with unprotected amines was recently reported by the Gaunt group (Scheme 64).[238] This Pd-catalyzed cyclization at the α-methyl sp^3 C−H bonds affords aziridine products in satisfactory yields by using PhI(OAc)$_2$ oxidant. A mechanistic pathway for this highly significant amination was later released.[239]

Interestingly, Shi (Z.-J.) reported a silver-catalyzed intramolecular amination of C(sp^3)−H bonds to form five-membered pyrroline products in the presence of a bipyridine ligand and PhI(OTFA)$_2$ oxidant (Scheme 65).[240] The substrate scope of the optimized catalytic system was broad, enabling the

Scheme 64



Scheme 65



direct amination of primary and benzylic C(sp^3)−H bonds to afford various types of azaheterocycles.

2.3.2. Intermolecular C−H Amination. In 2006, Yu (W.-Y.) and Che reported an intermolecular amination of

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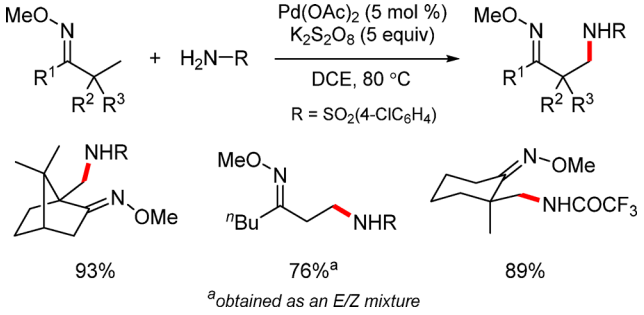
unactivated sp^3 C−H bonds by palladium catalysis (Scheme 66).[192] This Pd-catalyzed amination of aliphatic oxime

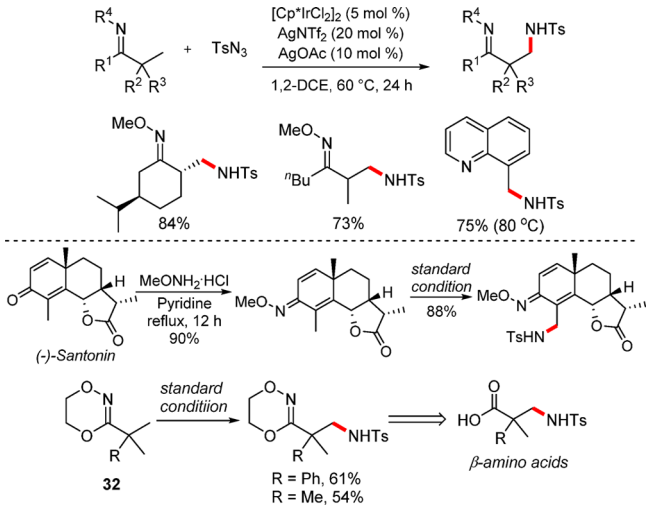
Scheme 66



substrates was efficient with primary sulfonamides or trifluoroacetamides as the amino source. The nitrenoid formation is believed to be facilitated by the use of potassium persulfate oxidant. While details of the nature of the nitrene species were not described, the authors proposed that a high-valent Pd(IV) species could be involved in the C−N bond-forming stage.

More recently, Chang and co-workers reported an Ir-catalyzed intermolecular amidation of sp^3 C−H bonds by using organic azides as a powerful amino group source (Scheme 67).[241] This amidation occurs selectively at the methyl sp^3 C−

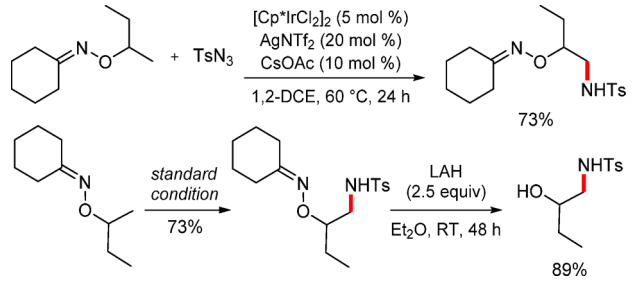
Scheme 67



H bonds in a wide range of substrates. Importantly, the reaction works highly efficiently under mild conditions and in the absence of external oxidants to release nitrogen gas as a single byproduct, thus making this protocol applicable to the late-stage C−H functionalization of complex compounds bearing labile functional groups. Indeed, amination of a ketoxime substrate derived from (−)-Santonin took place smoothly, and 5,6-dihydro-1,4,2-dioxazines **32** were readily amidated to give synthetically versatile products that can be further converted to β-amino acids. Wang reported similar Rh-[242] and Ru-catalyzed versions[243] of the amidation using organic azides.

The Ir-catalyzed amidation of sp^3 C−H bonds was also applied to the preparation of 1,2-amino alcohols starting from ketoximes derivatives (Scheme 68).[244] Taking advantage of the strong coordinating ability of the ketoxime directing group, the

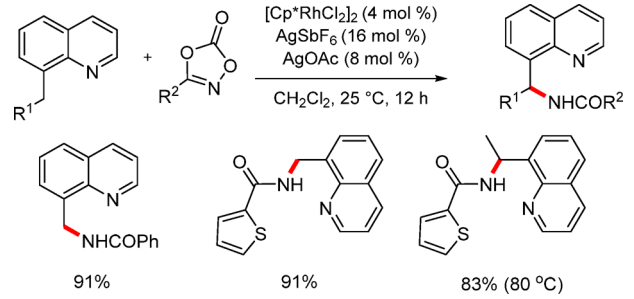
Scheme 68



amination was designed to occur at the β-methyl group selectively. Importantly, removal of the directing group was facile, leading to the corresponding β-hydroxyl sulfonamides in high yields.

On the basis of Chang's report that 3-substituted 1,4.2-dioxazol-5-ones display notable features as an amino group source when compared to organic azides,[121] Li (X.) and co-workers added one entry in the Rh-catalyzed intermolecular C(sp^3)−H amidation (Scheme 69).[245] Interestingly, they

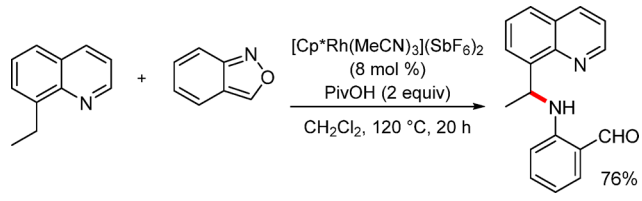
Scheme 69



showed that the amidation occurs selectively at the methylene C−H bonds of 8-ethylquinolines at 80 °C. This is a rare example to functionalize secondary C(sp^3)−H bonds with the assistance of directing groups.[192,241−243] More recently, Sundararaju reported that the amidation of 8-methylquinolines can be achieved by a cobalt catalyst system.[246]

Li (X.)[58] and Jiao[247] independently demonstrated the synthetic utility of anthranils as an efficient amino group source in an intermolecular amination of sp^3 C−H bonds (Scheme 70). The reaction allows a simultaneous installation of

Scheme 70



two functional groups in products: a nucleophilic amino moiety and an electrophilic formyl group. While the polarized character of a N−O bond in anthranils was postulated to play a critical role for the amidation efficiency, DFT studies indicated the intermediacy of a nitrenoid species.

In 2015, Yu (J.-Q.) and co-workers reported a Pd-catalyzed intermolecular sp^3 C−H amination to obtain β-amino amides, a versatile synthon (Scheme 71).[248] In this procedure, while *O*-

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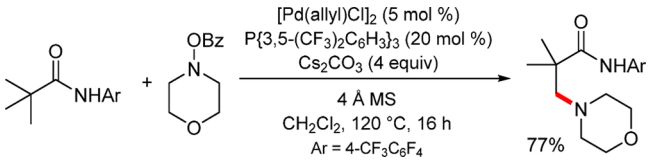
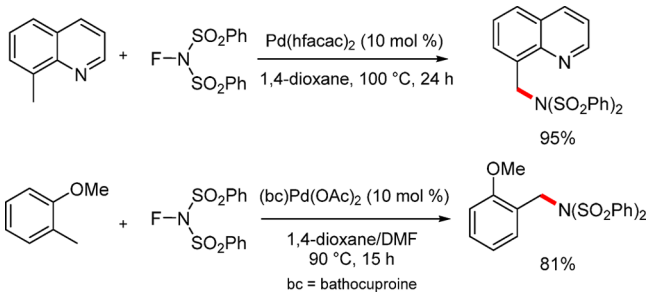
Scheme 71



benzoyl hydroxylamines were employed as the aminating reagent, the choice of weakly coordinating *N*-arylamide groups in substrates was found to be crucial for the reaction efficiency: a perfluorophenyl group was especially effective for this C−H amination. The amination works best with cyclic amine reactants albeit at rather high temperature.

Muñiz and co-workers utilized an NFSI as an amino source, thereby successfully developing Pd-catalyzed intermolecular sp^3 C−H amidation reactions (Scheme 72).[249] 8-Methylquinoline

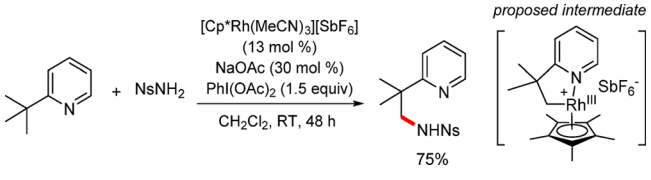
Scheme 72



was readily amidated by $Pd(hfacac)_2$ catalyst to give benzylic amidation products in good yields. Furthermore, the scope of the reaction was extended to substrates bearing labile coordinating groups such as methoxy. Indeed, it was found that the amination of 2-methylanisoles took place smoothly with NFSI under the combination of $Pd(OAc)_2$ and bathocuproine (bc).

Whereas activated amino precursors such as iminoiodinanes, organic azides, *N*-haloamides, or *N*-acyloxyamides are effectively utilized in the C−H amination reactions, the use of nonprefunctionalized parent amines has been much less explored, although a pioneering work of Che was reported in 2006.[192] In this context, this approach was revisited recently by You and co-workers (Scheme 73).[250] Rh-catalyzed intermo-

Scheme 73



lecular C(sp^3)−H amination of 2-(*tert*-butyl)pyridine with electron-deficient sulfonamides was operative at room temperature when $PhI(OAc)_2$ oxidant was employed. The authors proposed the intermediacy of a five-membered cationic rhodacycle in the catalytic cycle.

In 2015, Ge reported the Co-catalyzed intermolecular dehydrogenative C(sp^3)−H amination of *N*-(quinolin-8-yl)-propanamide derivatives with heptafluorobutanamide as an effective amidating reagent (Scheme 74).[237] The reaction required a number of stoichiometric additives and high reaction temperature. Interestingly, this amination occurred selectively at the β-methyl C−H bonds even in the presence of benzylic β-methylene sites. However, when α-phenyl-substituted propanamide was subjected to the present system, two products arising from sp^3 C−H and sp^2 C−H bond activation were formed in a moderate ratio.

3. DIRECTING GROUP-FREE C−H ACTIVATION CATALYSIS

While the directing group-assisted C−H amination allows a regioselective installation of an amino moiety at the directed sites, removal of such auxiliary groups after the main reaction is not straightforward, especially in many cases when heteroarene-based coordinating groups are employed, thus making the general application of this strategy problematic. In this context, direct C−H functionalization of hydrocarbons that do not bear the directing group is highly desirable, and is possibly an ideal transformation to pursue. However, a major challenge in this type of metal-catalyzed C−H functionalizations lies in its slow C−H metalation process, presumably due to the high kinetic barrier in the C−H bond cleavage step.[251,252] Selective recognition of specific C−H bonds in the absence of any functional group is an additional formidable issue. Nevertheless, a few notable examples of direct C−H amination have been recently reported by successfully managing the above difficulties.

3.1. Allylic C−H Amination

Allylic C−H amination[253,254] has been studied as a direct analogue of the corresponding allylic substitution reactions. Whereas the allylic substitution employs substrates bearing a leaving group at the allylic position, the C−H activation approach offers a direct route to functionalize unsaturated hydrocarbons without need to preinstall the leaving groups. Two distinctive mechanistic scaffolds are generally accepted in this allylic C−H amination (Scheme 75): (i) a tandem process consisting of nucleometalation and β-hydride elimination (path A);[255] and (ii) allylic C−H bond activation followed by reductive elimination (path B). While notable features in regard to the reactivity and selectivity are displayed in each mechanistic manifold, this section describes allylic C−H amination reactions occurring within the latter mechanistic scaffold only (path B in Scheme 75), which may involve π-allyl metal species **33** formed by the C−H bond activation. It is noteworthy that the allylic C−H activation takes advantage of chelation assistance by η^2-type coordination of olefins to the metal center, thus enabling facile formation of organometallic intermediates.

3.1.1. Intramolecular C−H Amination. In 2007, the White group reported a seminal example of an intramolecular allylic C−H amination (Scheme 76).[256] By using a Pd(II) catalyst of $(BisSO)Pd(OAc)_2$, homoallylic *N*-tosyl carbamate **34** was successfully cyclized to afford the corresponding oxazolidinone. The authors hypothesized that the tosyl substituent plays a critical role to tune the nucleophilicity of the carbamate moiety. When a substrate **34** was allowed to react with a stoichiometric amount of palladium species, the predominant formation of a Pd−π-allyl complex was clearly observed by ^{1}H NMR spectroscopy (Scheme 77). Subsequent addition of an external acetate base for deprotonation of N−H bond afforded a cyclized product with a similar level of diastereoselectivity, as seen in the catalytic reaction. The

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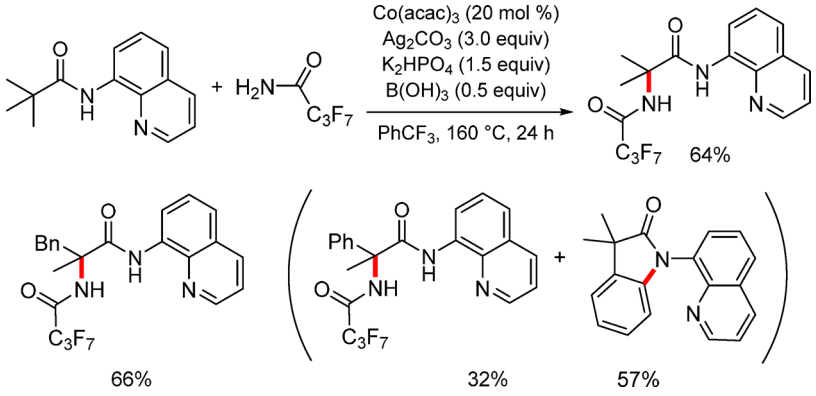
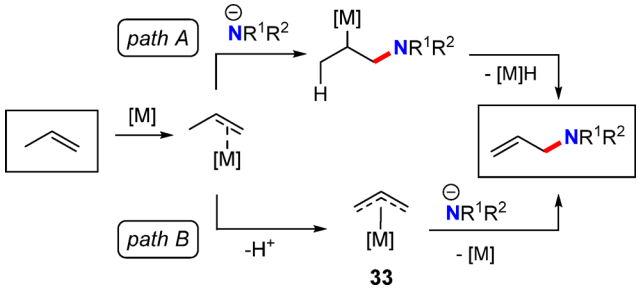
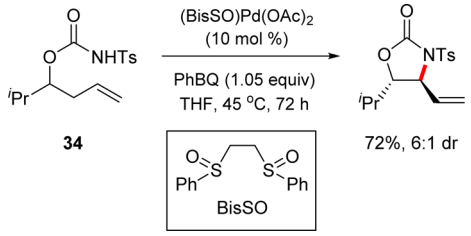
Scheme 74



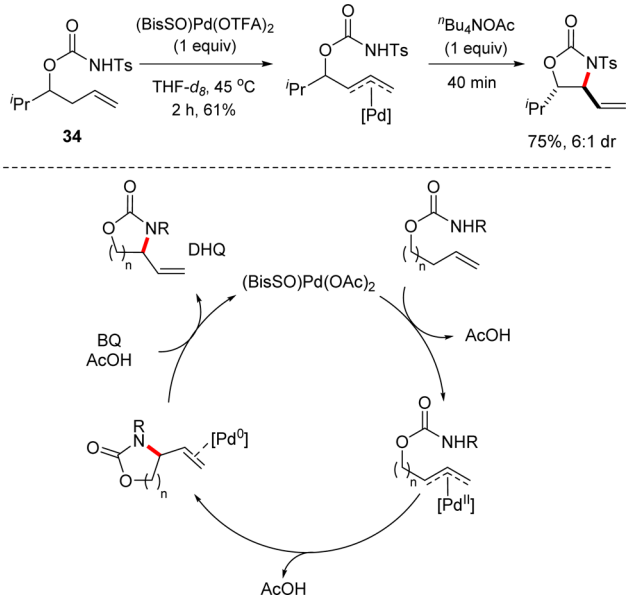
Scheme 75



Scheme 76



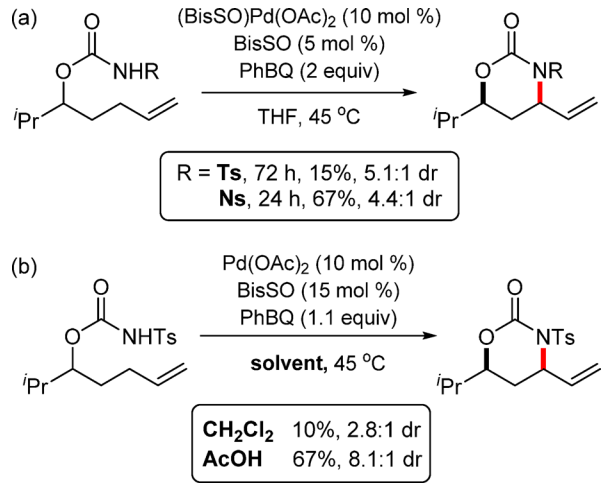
Scheme 77



proposed mechanism includes an electrophilic C−H activation affording a π-allyl palladium complex, subsequent *exo*-nucleophilic attack of carbamate, and reductive elimination to give the product and Pd(0) species that is reoxidized to Pd(II) by benzoquinone and acetic acid.

Additional efforts were made to improve the reaction scope of the allylic C−H amination and its synthetic applicability. The White group found that a *N*-nosyl substituent works better than the *N*-tosyl group for the formation of six-membered oxazinanone products, while a similar level of diastereoselectivity was observed in the two reactions (Scheme 78a).[257] On

Scheme 78



the other hand, choice of a solvent also exhibited a significant influence on the diastereoselectivity (Scheme 78b).[258] Given that protic activation of benzoquinone is required in the oxidation of Pd(0) to Pd(II) species,[259] the use of acetic acid as a solvent was reasoned to increase the product yields and diastreomeric ratio. DFT calculations suggested that a step involving either Pd(0) oxidation or allylic C−H activation would be turnover-limiting depending on the applied reaction conditions.[260] Having well-established amination conditions, a tandem procedure enabling sequential allylic C−H amination/vinylic C−H arylation was developed by White and co-workers.[261] By making two independent reactions operate in one-pot with the same catalyst, a synthetically valuable β-amino acid could be efficiently prepared.

A rare example affording a seven-membered lactam was reported by Liu (G.) and co-workers on the basis of the C−H

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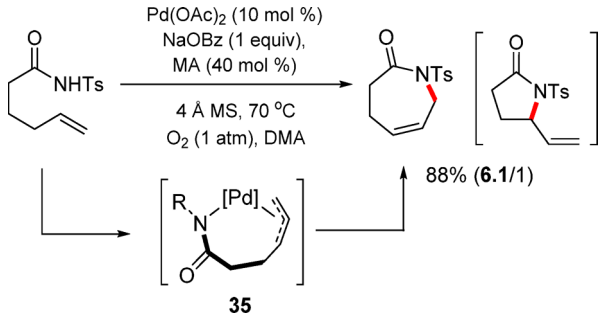
amination approach (Scheme 79).[262] To circumvent an *exo*-cyclization path leading to five-membered lactams, sodium

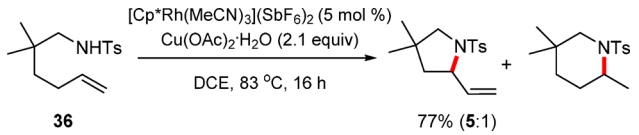
Scheme 79



benzoate was employed as a Brønsted base additive that can promote Pd–N bond formation, leading to an intermediate **35**. On the basis of the deuterium-labeling studies and KIE experiments, the authors concluded that the reaction follows a rate-limiting C–H activation and subsequent reductive elimination process.

While notable advances have been made recently in the allylic C–H amination by using Pd(II) catalysts, Rh(III) species were also observed to display an analogous catalytic activity. Cossy and co-workers demonstrated that ω-unsaturated *N*-sulfonyl amides **36** underwent a 5-*exo* cyclization by Cp*Rh-(III) catalyst in the presence of $Cu(OAc)_2$ oxidant (Scheme 80).[263] In situ generated $Cp^*Rh(OAc)_2$ was assumed to initiate

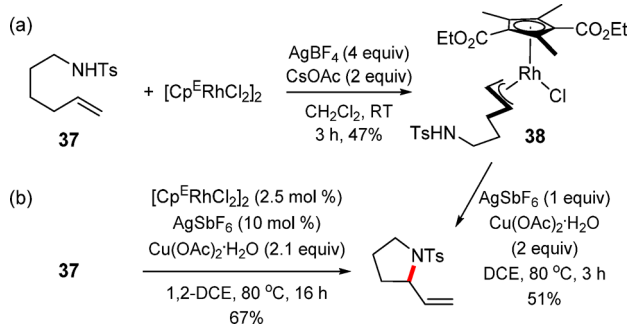
Scheme 80



the allylic C–H bond activation, leading to a Rh(III)–amido intermediate, which eventually undergoes a reductive elimination to afford a pyrrolidine product.

To prove the intermediacy of the π-allyl Rh(III) speies, Tanaka and co-workers synthesized such complexes and demonstrated that the species is indeed involved in the catalytic amination (Scheme 81).[264] In the presence of silver salt and cesium acetate, treatment of **37** with Rh(III) complex gave rise to a (π-allyl)Rh(III) complex **38** (Scheme 81a). The authors employed Rh(III) species bearing an ester-functionalized Cp derivative (Cp^E) for successful isolation. Intersetingly,

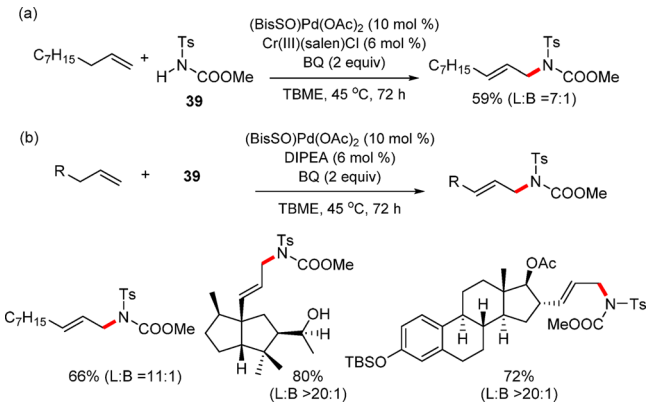
Scheme 81



no analogous complexation was observed with the more conventional Rh(III) complex having Cp* ligand. Subsequent addition of $AgSbF_6$ and $Cu(OAc)_2$ to the π-allyl Rh(III) species **38** furnished the corresponding pyrrolidine product in 51% yield. Because a similar conversion was also observed under catalytic conditions (Scheme 81b), the involvement of an allyl $C(sp^3)$–H activation was strongly suggested in the Rh-catalyzed allylic C–H amination reactions.

3.1.2. Intermolecular C–H Amination. As a logical extension of the fruitful intramolecular allylic amination, an intermolecular version was also investigated. The White group found that $(BisSO)Ph(OAc)_2$, which was an effective catalyst in the intramolecular amination, catalyzes an allylic C–H amination with *N*-(methoxycarbonyl)-*p*-toluenesulfonamide **39** serving as an amino group source in the presence of benzoquinone (Scheme 82a).[265] On the basis of the previous

Scheme 82

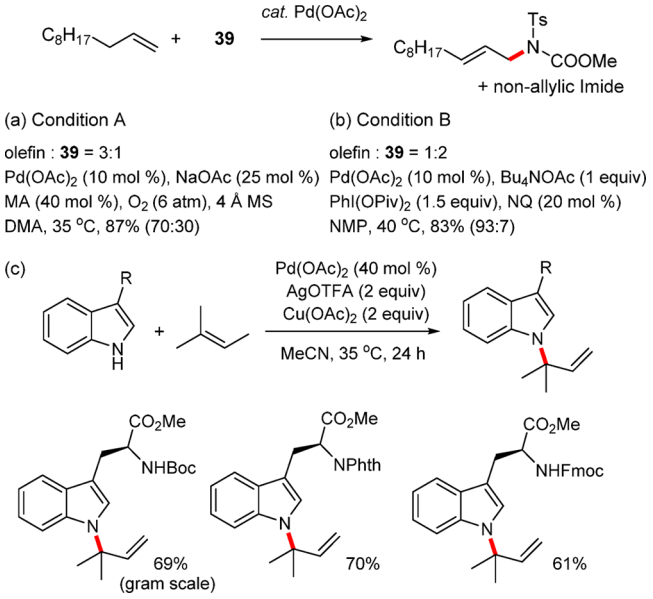


observation that certain Lewis acid additives faciliate the Pd-catalyzed allylic C–H acetoxylation,[266] a catalytic amount of Cr(III) (salen)Cl was added to the present catalytic system, thus leading to improvement in this C–H amination. While allyl amine products were obtained in moderate to good yields, linear isomers were highly favored over branched products. The results of the stoichiometric studies strongly suggested that the (π-allyl)Pd species will be an active intermediate in the C–H amination process. Further improvements in substrate scope were made by replacing the Lewis acid additive with a Brønsted base, *N*,*N*-diisopropylethylamine (Scheme 82b).[267] It was suggested that the role of the base additive is to increase the effective concentrations of an active nucleophile to proceed the reaction forward. Under the newly optimized intermolecular conditions, linear allylamines were selectively obtained in high yields to enable a late-stage introduction of an allyl amino group in complex molecules. Recently, further improvements of the reaction conditions were made by utilizing $BQ/Co(II)/O_2$-based redox-rely catalysis.[268]

Liu (G.) and co-workers reported an example of the intermolecular allylic C–H amination under aerobic oxidative conditions (Scheme 83a).[269] Notably, a catalytic amount of maleic anhydride (MA) was used in combination with 6 atm of O_2 to serve as terminal oxidants at ambient temperature. The same research group reported an additional procedure that employs $PhI(OPiv)_2$ in conjunction with 1,4-naphthoquinone (NQ, Scheme 83b).[270] Mechanistic studies revealed that the coordination of NQ to an active palladium species is crucial in the turnover-limiting stage.

DOI: 10.1021/acs.chemrev.6b00644
Chem. Rev. 2017, 117, 9247–9301

Scheme 83

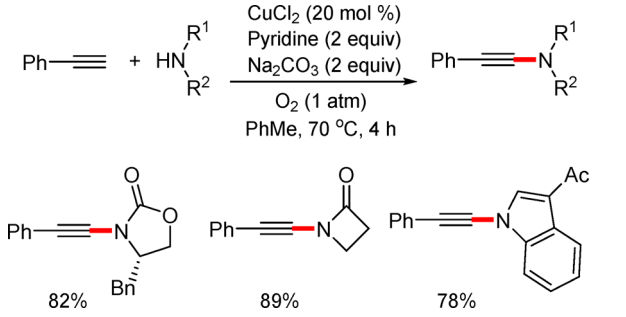


Baran and co-workers developed a highly efficient synthetic procedure of *N*-*tert*-prenylation of indoles based on the allylic C−H amination approach (Scheme 83c).[271] While other previously reported methods employ electron-deficient amino sources, Baran's reaction offers a unique opportunity to use indoles directly as the amino coupling partner. The authors proposed that an allylic C(sp^3)−H bond activation is crucial in affording the π-allyl−Pd species as a key intermediate.

3.2. Direct Amination of Acidic C−H Bonds

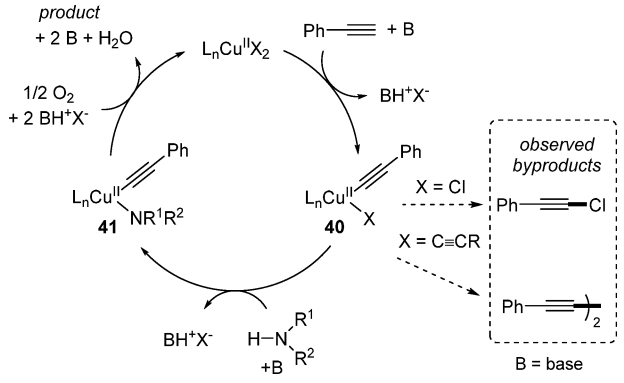
3.2.1. Alkynyl C(sp)−H Amination. A seminal report was presented by Stahl and co-workers on Cu(II)-catalyzed oxidative amidation of terminal alkynes in the presence of base additives (Scheme 84).[272] The reaction was highly efficient

Scheme 84



when amide protons have pK_a values in the range of 15−20 (in DMSO), and synthetically versatile ynamide products were obtained in respectable yields. As a key intermediate, a copper(II) alkynyl species **40** was proposed to form by a Cu-promoted C−H activation of terminal alkynes in the presence of a base (Scheme 85). The formation of alkynyl chloride and diyne as side products corroborated the involvement of a putative intermediate **40**. Subsequent formation of a Cu-(alkynyl) (amidate) intermediate **41** followed by reductive elimination will release the desired product. It is noteworthy that the formal oxidation state of proposed **41** is not clear to date because a recent mechanistic study of a related system

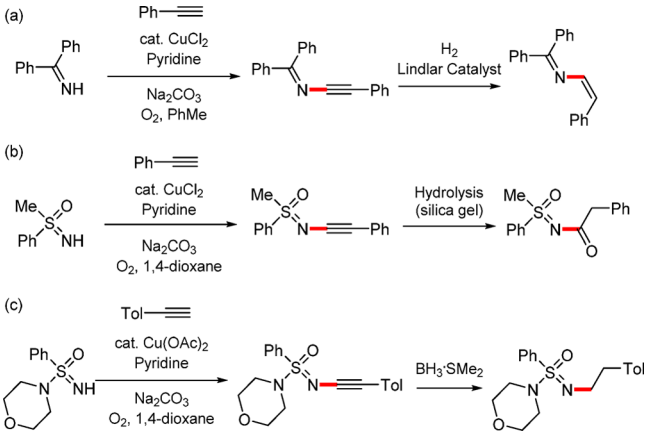
Scheme 85



indicates that the C−N bond formation might be initiated by reductive elimination from a high-valent Cu(III) intermediate (see sections 2.2.1 and 3.2.2).[130]

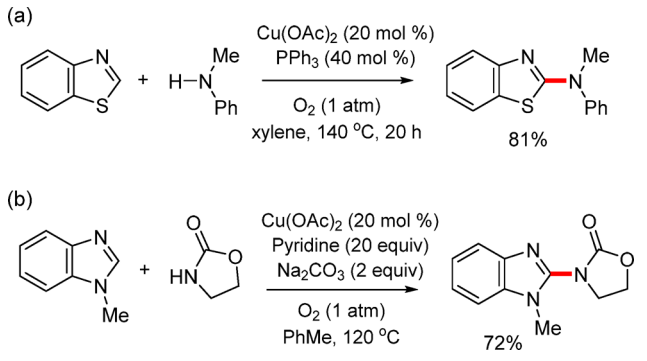
Stahl's amination procedure has been utilized to synthesize a wide range of valuable ynamide products using diaryl imines,[273] sulfoximines,[274] and sulfonimidamides[275] as efficient amino sources (Scheme 86).

Scheme 86



3.2.2. C(sp^2)−H Amination of Electron-Deficient (Hetero)arenes. In 2009, the Mori and Schreiber groups independently reported a Cu-catalyzed aerobic dehydrogenative coupling reaction between heterocyclic compounds and secondary amines (Scheme 87).[276,277] The most acidic C−H bond in substrates is selectively functionalized in this approach. Molecular oxygen at ambient pressure was employed as a

Scheme 87



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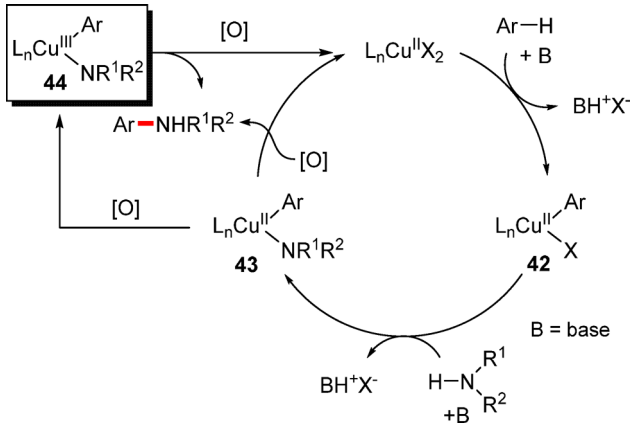
stoichiometric oxidant enabling the catalytic turnovers. Although the C−H amination is operated at relatively high temperatures, these works stimulated extensive subsequent efforts to functionalize heteroaromatic compounds to give biologically relevant products.

Subsequent investigations offered significantly improved reaction conditions of the C−H amination reaction with a broader scope of (hetero)arene substrates and amino sources. For instance, Bolm, Miura, and co-workers developed an amidation of 1,3,4-oxadiazoles with sulfoximines working at ambient temperature.[278] Su found that electron-deficient primary anilines readily react with heteroarenes when the amination is performed in the presence of TEMPO and O_2 as cooperative oxidants.[279] Direct C-2 amidations of quinoline *N*-oxides were reported by Cui,[280] Li (G.),[281] and Bolm[282] independently. Hirano, Miura, and co-workers developed a tandem process of C−H/N−H coupling and subsequent annulation to give *N*-azolylindoles in one-pot.[283]

A plausible mechanistic pathway of this type of C−H amination is depicted in Scheme 88.[279] An initially formed Cu−

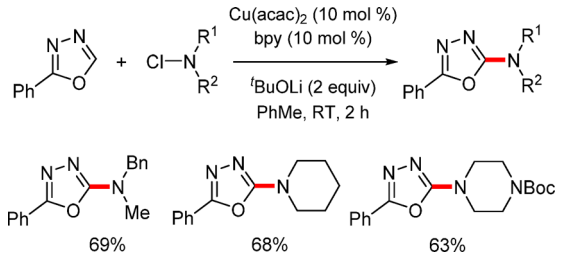
Scheme 88



Ar intermediate **42** engages with an amino reagent to give (Ar)Cu(II)−amido species **43** that will furnish an arylamine product and Cu(0) upon reductive elimination. Alternatively, the key intermediate **43** may be oxidized to a high-valent Cu(III) species **44** that undergoes reductive elimination to furnish an aminated product and Cu(I) complex. Recent mechanistic studies of this type of Cu-catalyzed C−H amination showed that the latter pathway with high-valent Cu(III) intermediates is favorable.[130,131,284]

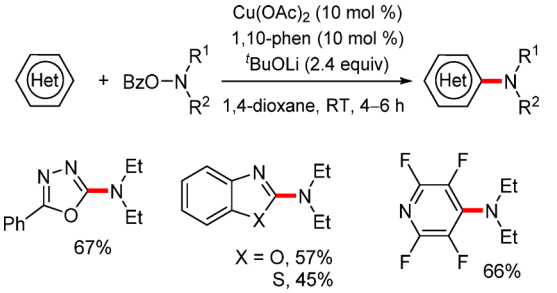
The requirement of superstoichiometric amounts of external oxidants in the direct C−H amination could be circumvented by using prefunctionalized amino sources that also work as an internal oxidant. Indeed, Miura and co-workers showed that *N*-chloroamines can be employed to play a dual role to serve as an amino group source and internal oxidant in the C−H amination of 1,3,4-oxadiazoles at ambient temperature (Scheme 89).[54] While the reaction scope and efficiency are promising, special care is needed in the preparation and storage of chloroamines. In this regard, the authors also developed a one-pot procedure, where amines are chlorinated with bleach and the C−H amination is followed in the same vessel. A recent study by Chang revealed that (NHC)Cu(I) species efficiently catalyze a direct C−H amination of (hetero)arenes with *N*-chlorocarbamates as practical amino reagents.[285]

Scheme 89



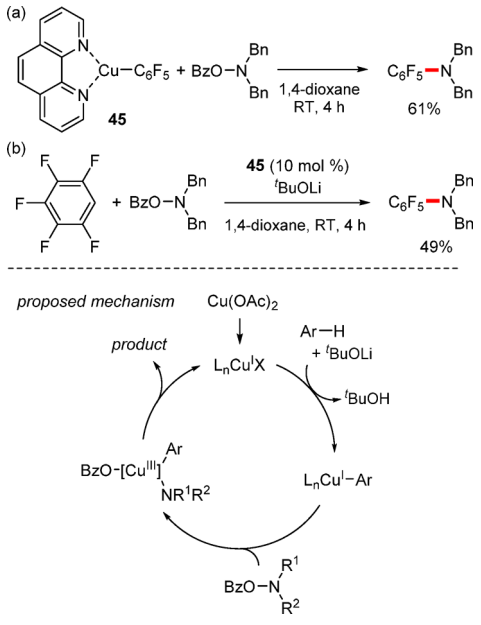
While mild reaction conditions could be applicable with chloroamines, the substrate scope was limited to a few types of heteroarenes. In this context, Miura introduced *O*-acylated hydroxylamines as a more robust and versatile amino group source in the Cu-catalyzed C−H amination (Scheme 90).[286]

Scheme 90



Separately prepared Cu(I)−pentafluorophenyl complex **45** was readily reacted with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine to afford a pentafluoroaniline product (Scheme 91a). In addition, complex **45** catalyzed the C−H amidation of pentafluorobenzene (Scheme 91b). It was proposed that, upon the initial reduction of $Cu(OAc)_2$ precursor to Cu(I) species presumably via a disproportionation process, C−H metalation takes place to afford a Cu(I)−aryl intermediate. The N−O bond of *O*-benzoyl hydroxylamines is postulated to undergo a facile

Scheme 91



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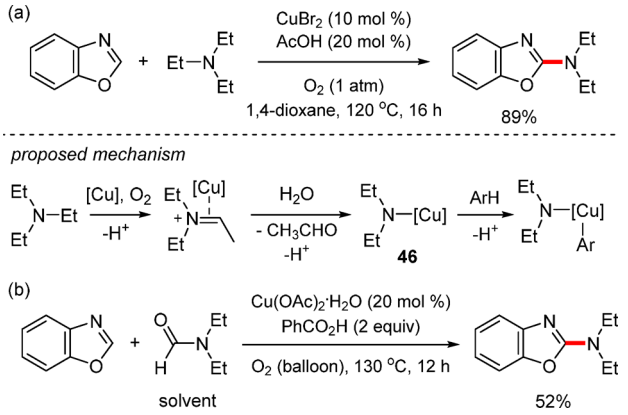
oxidative addition to this Cu(I)−aryl species to give an (aryl)Cu(III)−amido intermediate that is then reductively eliminated to release the desired product and Cu(I) complex. Additionally, 1,3,4-oxadiazoles, benzoxazoles, or benzothiazoles were also amidated readily with this electrophilic amidating reagent in the presence of alkoxide base.[287,288]

Interestingly, Huang and co-workers utilized triethylamine as an amino group source under the aerobic copper catalysis (Scheme 92a).[289] Given that copper salt can convert trimethyl-

Scheme 92

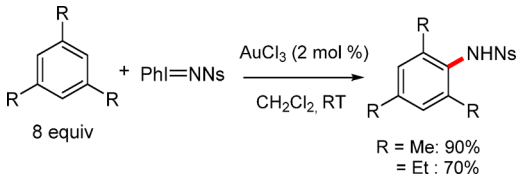


amine to the corresponding iminium species under aerobic conditions, the authors proposed the formation of a Cu−amido intermediate **46** via hydrolysis of copper−iminium adduct, which is followed by C−H metalation. Again, reductive elimination of this Cu−amido intermediate will release the aminated product. Under a similar mechanistic scaffold, formamide was also successfully used as the amino precursor in the presence of $Cu(OAc)_2$ under an oxygen atmosphere (Scheme 92b).[290] A putative Cu−amido intermediate like **46** was proposed to form via an acid-promoted decarbonylation of amides.

3.3. C−H Amination of Simple Arenes

Direct C−H functionalization of a simple hydrocarbon is a highly desirable but challenging task that is also the case in the field of C−H amination. In 2007, He and co-workers reported a Au-catalyzed direct C−H amidation of arene derivatives (Scheme 93).[291] Because of the unique capability of Au(III)

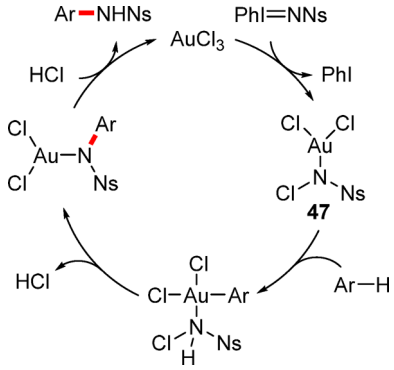
Scheme 93



complexes toward the electrophilic metalation of benzenes, the authors hypothesized that a resultant Au(III)−aryl intermediate may engage with aminating reagents to lead to C−N bond formation. Indeed, mesitylene and its derivatives were successfully converted to the corresponding arylamines by $AuCl_3$ catalyst at room temperature in the presence of iminoiodinane. The observation that other Lewis acidic metals or Brønsted acids were ineffective under otherwise identical conditions clearly demonstrates the superb reactivity of Au(III) catalyst employed herein. It is noteworthy that the amidation occurred exclusively at the aryl C−H bonds in the presence of benzylic hydrogens, thus offering a rare example to display selective C−H functionalization of aryl hydrogens over benzyl hydrogens. Because no kinetic isotope effect was measured, the authors concluded that the C−H auration process may not be involved in the turnover-limiting stage of the catalytic reaction.

In search of mechanistic details, Bao and Schaefer evaluated a putative reaction pathway by means of quantum chemical calculations (Scheme 94).[292] A reaction energy profile based on

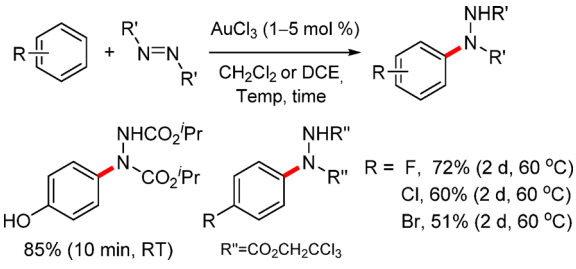
Scheme 94



the postulated C−H auration/imido insertion pathway, which was originally hypothesized by He and co-workers,[291] did not account for the experimentally observed KIE values. Several other possibilities, as a result, were additionally examined, leading the authors to propose a key intermediate **47** that enables the C−H bond activation. The nitrogen moiety in **47** was proposed to play a key role in assisting the deprotonation of aryl $C(sp^2)$−H bonds via σ-bond metathesis.

The Zhang (Y.) group utilized azodicarboxylates as an aminating reagent to synthesize aryl hydrazides under the analogous gold catalyst system (Scheme 95).[293] Whereas the

Scheme 95



previous reaction scope to use azodicarboxylates as the amino group source was limited to electron-rich arenes under strong Lewis acidic conditions, $AuCl_3$ catalyst allowed both electron-rich and -deficient aryl C−H bonds to undergo amination. The observed *para*-selective amination of phenol is indicative of an electrophilic aromatic metalation pathway.

The DeBoef group recently reported the Au(I)-catalyzed oxidative C−H amidation of alkyl benzenes by using phthalimide as an aminating source (Scheme 96).[294] Although the reaction requires superstoichiometric amounts of hypervalent iodine(III) oxidant and elevated temperatures (100 °C), the reaction proceeded with high regioselectivity. The authors proposed that the Au(I) precursor is oxidized to Au(III) in situ,

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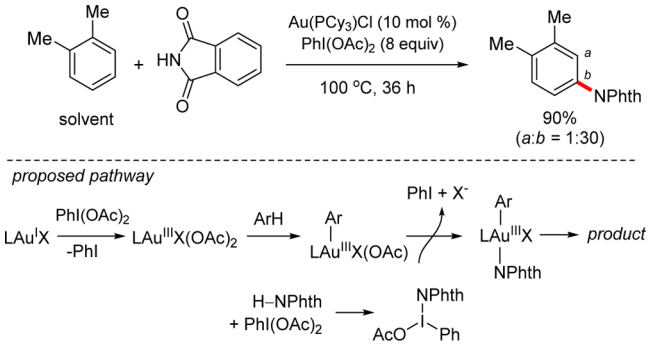
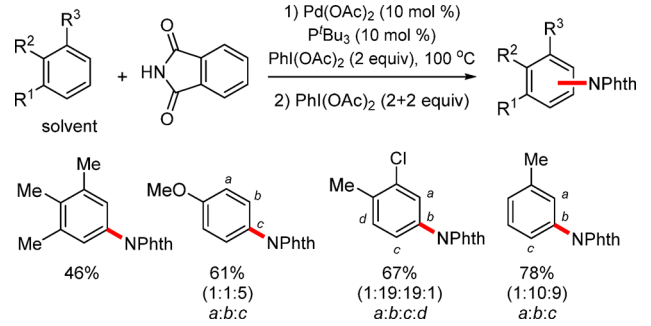
Scheme 96



which initiates an electrophilic aromatic C−H metalation. It was also suggested that phthalimide is converted to its iodane species, which is then transmetalated to an Au(III)−aryl intermediate to afford (aryl)Au(III)−amido species that will eventually undergo a reductive elimination to release an amidated product.

While Au(III) species display a remarkable catalytic activity toward the C−H amination of simple arenes at variable reaction temperatures, a few examples of palladium or copper catalyst systems have also been revealed. Hartwig and co-workers showed that Pd(II) catalyst in combination with hypervalent iodine oxidant can promote nondirected C−H imidation of arenes using phthalimide as the nitrogen source (Scheme 97).[295] Given that a similar transformation was

Scheme 97



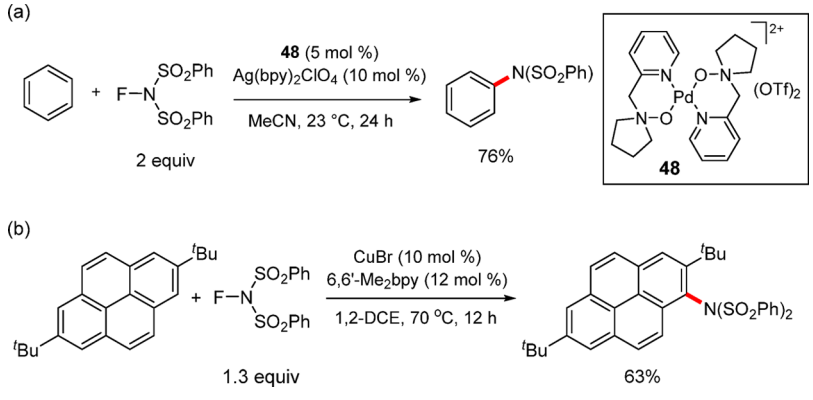
previously developed under metal-free conditions by Chang with the display of only statistical regioselectivity,[296] the enhanced selectivity exerted by palladium catalysis is noteworthy. Sterically more accessible sites such as *meta* or *para* C−H bonds of monosubstituted arenes were favored for the amidation. Interestingly, the observed regioselectivity in the C−H amidation was distinct from the reported selectivity in the related C−H acetoxylation reactions,[297−300] wherein *ortho*- and *para*-selectivity were predominantly observed. While a high level of KIE (4.1 ± 0.1) was indicative of the relevance of C−H bond cleavage to the rate-limiting stage, detailed understandings of a working mode in this nondirected C−H amination, particularly in regard to the disparate selectivity to the analogous C−H acetoxylation, will guide the future developments of more selective and practical catalyst systems.

In 2013, Ritter and co-workers devised a novel catalytic system enabling a catalytic C−H imidation of arenes with NFSI as the amino group source (Scheme 98a).[301] Pd(II) complex **48** bearing 1-(pyridin-2-ylmethyl)pyrrolidine 1-oxide was especially active in the presence of silver cocatalyst, and simple arenes, employed even as a limiting reactant, were imidated at room temperature. Subsequently, Itami and co-workers developed a Cu(I)-based catalyst system for a similar transformation (Scheme 98b).[302] 6,6′-Dimethylbipyridine (6,6′-Me_2bpy) was an especially effective ligand, and the substrate scope was broad, including heteroarenes and simple benzenes. Although mechanistic details remain elusive, inverse secondary KIE values for both Pd and Cu catalyst systems indicate that a rehybridization of arene substrates from sp^2 to sp^3 may be involved in the rate-determining stage.

4. C−H INSERTION CATALYSIS

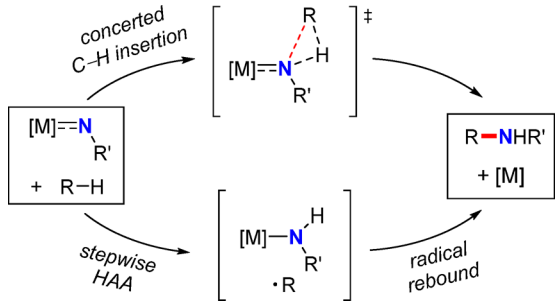
Catalytic transfer of a nitrene moiety was first demonstrated by Breslow in the tosylamidation of cyclohexane with a cytochrome P-450 model in 1982.[62,63] Subsequently, Mansuy demonstrated a catalytic olefin aziridination by utilizing iminoiodinane as a nitrenoid precursor with Mn- or Fe-porphyrin catalysts.[303] It was postulated that a key intermediate responsible for the C−H bond cleavage is a metal−nitrenoid species that is possibly formed by transferring a nitrene moiety in an aminating agent to the metal center. A few studies disclosed the characterization of such metal−nitrenoid species and their reactivity toward otherwise inert C−H bonds. With the action of key metal−nitrenoid species, the C−H bond cleavage of hydrocarbons may occur via two possible mechanisms: (i) a concerted C−H insertion and (ii) a stepwise process of hydrogen atom abstraction (HAA) and subsequent radical recombination (Scheme 99).[304] Unveiling the C−H cleaving pathway is of particular interest in this class of

Scheme 98



DOI: 10.1021/acs.chemrev.6b00644
Chem. Rev. 2017, 117, 9247−9301

Scheme 99



reactions as it provides useful information in designing more reactive and selective catalytic systems. To elucidate the mechanistic details, experimental data including kinetic isotope effect (KIE), a radical clock study, and stereochemical outcomes have been insightfully interpreted, often in combination with computational simulations.

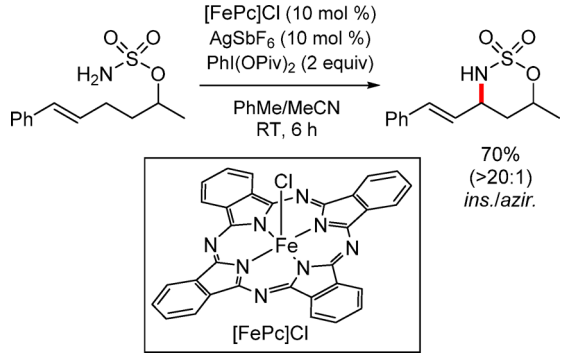
4.1. C(sp^3)–H Amination

4.1.1. First-Row Catalysis. Since the seminal reports on the Fe- and Mn-mediated nitrenoid transfer processes,[62,63,303] there have been extensive efforts to develop first-row transition metal catalyst systems that are applicable for more efficient and selective C–H amination reactions. The fact that these metals are earth-abundant and relatively nontoxic has made this research focus more rewarding. Whereas metalloporphyrin complexes were widely used to mediate the nitrenoid transfer, the utility of synthetically more accessible multidentate ligands bearing nitrogen or oxygen coordinating atoms was also extensively examined.

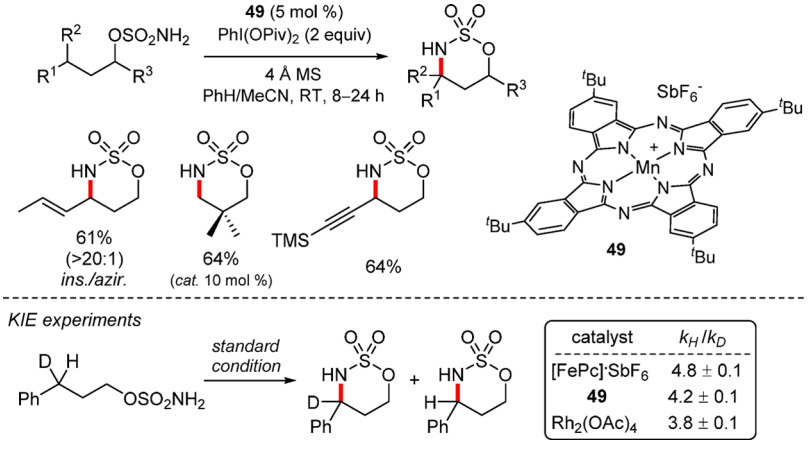
4.1.1.1. Manganese Catalysis. Early works on the manganese catalysis were mainly associated with porphyrin- or salen-based Mn(III) complexes. Che and co-workers described that electron-deficient Mn(III)–porphyrin catalyst is capable of catalyzing amidation of saturated C–H bonds with high turnover numbers.[305] Notably, enantioselective intra- and intermolecular C–H amidations were also disclosed with chiral (salen)Mn(III) catalysts.[306,307] Recently, White and co-workers developed an elegant catalyst system based on manganese *tert*-butylphthalocyanine ([Mn(^{t}BuPc)]·SbF_6, **49**), which displays high reactivity and excellent chemoselectivity toward an intramolecular C(sp^3)–H amidation (Scheme 100).[308] In general, a nitrenoid transfer process often suffers from poor chemoselectivity in that C–H amination and olefin aziridination reactions are sometimes competitive, especially when a substrate contains both reactive C–H bonds and π-acidic olefins. In this regard, it was noteworthy that by using **49** as a catalyst, a high level of preference for the C–H amidation was observed even toward the propargylic or primary C–H bonds. The authors carried out mechanistic studies to reason this unusual chemoselectivity exhibited by the catalyst **49**. KIE experiments revealed that the C–H insertion mode mediated by **49** may lie between the stepwise HAA/rebound process and concerted insertion pathway, which are usually operative in the known iron(III) and Rh_2(II) catalyst systems, respectively.

4.1.1.2. Iron Catalysis. Iron complexes have been examined as potential catalysts for a range of functional group transfer reactions because such reactivity is frequently found in enzymes containing iron-based active sites. In particular, cytochrome P-450 oxidase was found to catalyze C–H amination with iminoiodinane as the amine source,[62,63] and Che proved that analogues iron(III) porphyrins can work as efficient catalysts for the intramolecular amination reactions.[309] The formal C–H insertion in this case was proposed to proceed via HAA/rebound pathway due to the high spin state of nitrenoid intermediate. DFT calculations additionally supported the formation of a high-valent Fe(IV)=NR species.[310] Recently, a notable catalyst system of Fe(III)–phthalocyaninato ([FePc]-Cl) was developed by the White group (Scheme 101).[311] In the presence of a double bond adjacent to an allylic C–H bond, the C–H amidation was favored over the related aziridine reaction. The authors reasoned that a radical rebound step immediately

Scheme 101



Scheme 100



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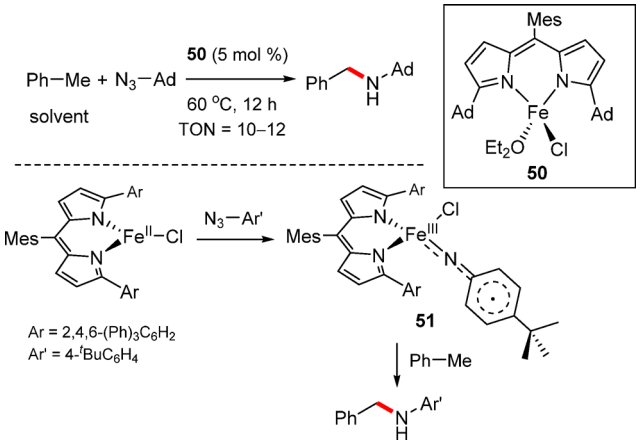
after the formation of an allyl radical is so rapid that other side reactions can be suppressed. The observed retention of stereochemistry and the absence of isomerization of double bonds in substrates additionally support this proposal.

A number of nonheme Fe-based catalysts have been extensively investigated on the basis of the C−H amination approach, especially in recent years. Among those, the Betley group's report on the utility of iron−dipyrromethane complexes is particularly noteworthy.[312] A high-spin Fe(II) complex **50** was shown to catalyze an amination of toluene solvent with alkyl azides at the benzylic C(sp^3)−H bonds (Scheme 102). Stoichiometric reactions enabled the isolation of

Scheme 102

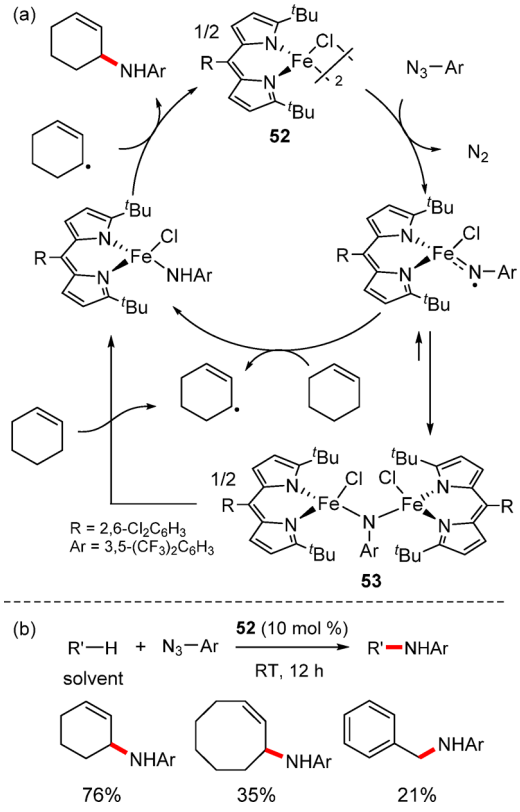


an iron complex **51**, and the spin state of this species was determined to be $S = 2$ with the aid of ^{57}Fe Mössbauer spectroscopy and also by theoretical calculations. The combined results indicated that the high-spin Fe(III) center is antiferromagnetically coupled to the imido-based ligand. Subsequent addition of toluene to **51** readily provided the C−H aminated product.

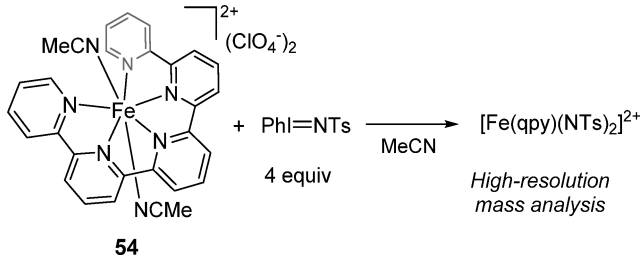
The same research group further characterized analogous iron complexes that are capable of catalyzing C−H amination processes. For instance, by having a sterically less-hindered *tert*-butyl substituent in the dipyrrinato ligand, a dimeric Fe(III) complex **52** bearing a bridging imido moiety was successfully isolated (Scheme 103a).[313] Spectroscopic analyses indicated the ground state of **53** is $S = 0$, presumably resulting from an antiferromagnetic coupling of two high-spin iron(III) species through the bridging imido ligand. Thermodynamic equilibrium between **53** and its monomeric form was monitored, and it was believed to be relevant for the hydrogen abstraction of substrates. The authors presented a catalytic C−H amination of cyclohexene and toluene in more details (Scheme 103b).

Che and co-workers synthesized a 7-coordinated iron complex **54** bearing a quinquepyridine (qpy) ligand that was shown to mediate a nitrene transfer when iminoiodinane was employed as the nitrogen source.[314] Not only activated C−H bonds of benzylic and allylic sites but also primary C−H bonds of saturated hydrocarbons were readily functionalized in both an inter- and an intramolecular manner. Notably, the formation of a putative iron−imido/nitrene bond was suggested to occur by treating **54** with an imido precursor in a stoichiometric manner (Scheme 104). This constitutes a unique example of C−H functionalization operated by 7-coordinate iron−imido/nitrene complexes.

Scheme 103

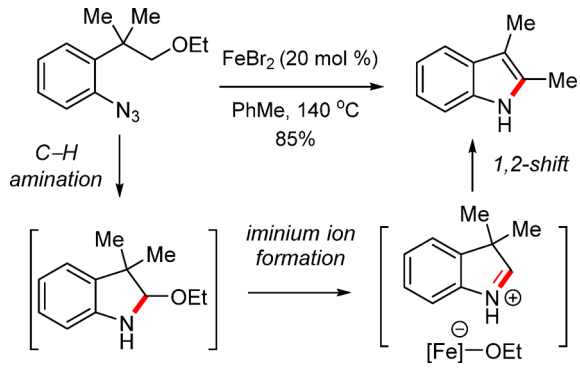


Scheme 104



Driver and co-workers reported an efficient synthetic route to 2,3-disubstituted indoles by utilizing an intramolecular C(sp^3)−H amination of *ortho*-alkoxylalkyl substituted phenyl azides (Scheme 105).[315] Iron(II) bromide triggers the extrusion of molecular nitrogen and subsequent ethereal C−H bond cleavage at elevated temperature. A proposal on this conversion

Scheme 105



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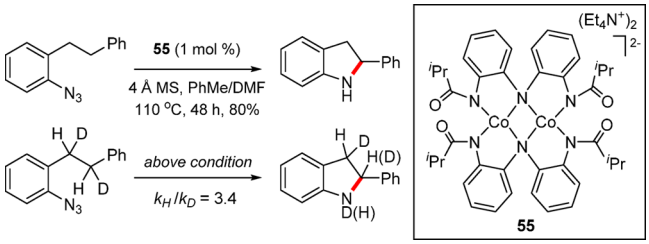
that consists of an iminium ion formation and subsequent 1,2-shift was supported by isolation of the corresponding indoline and 3*H*-indole intermediates, which subsequently undergo postulated 1,2-migration.

4.1.1.3. Cobalt Catalysis. Whereas the viability of the cobalt-mediated nitrene transfer was documented in 1999,[316,317] cobalt-based catalytic systems for C−H amination have not been intensively scrutinized until recently. Cenini and co-workers evaluated the reactivity of Co(II)−porphyrin species on the C−H amination and its mechanistic details.[318] In addition, the Zhang (X. P.) group proved the versatile catalytic reactivity of Co(II)−porphyrin complexes by using various amino precursors.[319−326] Detailed accounts on this topic can be found in this issue of *Chemical Reviews*, provided by Zhang (X. P.) and co-workers.

In 2015, Blakey and MacBeth revealed a novel catalyst system based on a dinuclear Co(II) complex **55** bearing redox-active anilide ligands (Scheme 106).[327] Given that the catalyst

Scheme 106

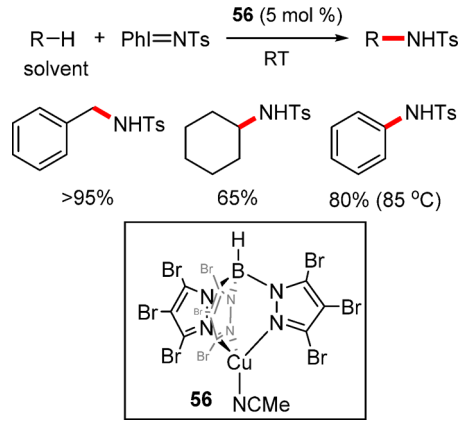


was effective for the catalytic oxygen atom transfer via multielectron processes,[328] the authors sought to investigate an analogous amino transfer process with organic azides. Using an aryl azide possessing a 2-homobenzyl substituent, an intramolecular C−H amination affording indoline products was successfully achieved. On the basis of the observed KIE value (3.4), the authors concluded that the HAA/radical recombination mechanism may be operative.

4.1.1.4. Copper Catalysis. Copper complexes were extensively studied as efficient catalysts for the nitrogen group transfer process.[329] Earlier promising results on the viability of olefin aziridination as a representative nitrenoid transfer reaction motivated researchers to study the relevant copper-mediated C−H insertion procedures.[330−334] In 1998, Taylor and co-workers reported an intermolecular catalytic amidation of benzylic or allylic C(sp^3)−H bonds with Cu(I) catalyst by employing chloroamine-T as the nitrogen source.[335] Although the synthetic scope was not extensively explored, it clearly proved the utility of copper complexes as a potential catalyst for the C−H amination reactions.

The Pérez group pioneered the nitrenoid insertion chemistry by devising an elegant copper catalyst **56** bearing a homoscorpionate ligand, thus allowing a direct C−H amination (Scheme 107).[336,337] A Tp ligand with perbromo substituents enabled the formal insertion of an imido moiety into not only methylene C(sp^3)−H bonds of cyclohexane but also C(sp^2)−H bonds of benzene. The same research group extended the synthetic utility of this C−H amination by successfully employing chloroamine-T as an aminating reagent.[337] Considering that functionalization of aromatic C−H bonds is challenging due to their high bond dissociation energy, this catalytic system allows an efficient and straightforward route to arylamines without any prefunctionalization. Computational

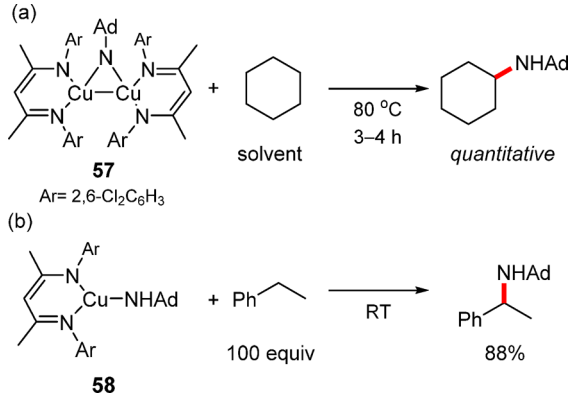
Scheme 107



studies were recently reported by Bao and co-workers to unveil the unique features of this catalysis.[338] Whereas the energy profile of the amidation reaction on the benzylic C−H bonds of toluene favors the HAA/rebound pathway in the insertion process, a higher activation barrier was shown for the analogous process with a benzene substrate. In this line, a novel pathway involving an initial aziridination of benzene followed by hydrogen atom abstraction was energetically more feasible. A putative key intermediate, Cu−nitrene complex, was successfully located, possessing a triplet ground state.

Warren and co-workers developed a catalytic system for the C(sp^3)−H amination by examining the stoichiometric reactivity of a dicopper complex (Scheme 108a).[339] When a dicopper

Scheme 108



complex bearing a *β*-diketiminate ligand was reacted with an equimolecular amount of alkyl azide, the formation of a dicopper nitrene species **57** was observed. An X-ray crystallographic analysis confirmed the structure of a symmetrically bridging nitrene moiety between two copper centers. Upon thermolysis of **57** in the presence of cyclohexane, the corresponding C−H amination product was formed in quantitative yield. Assuring the viability of these two key steps in the presumed catalytic cycle, the catalytic amination was disclosed, and several hydrocarbons were successfully employed. Notably, 1 equiv of substrate was sufficient to afford satisfactory product. Further kinetic and computational studies indicated that a terminal nitrene intermediate is possibly involved in the C−H insertion process.[304,339]

The same research group further extended this amination procedure to include primary alkyl amines as the amino group

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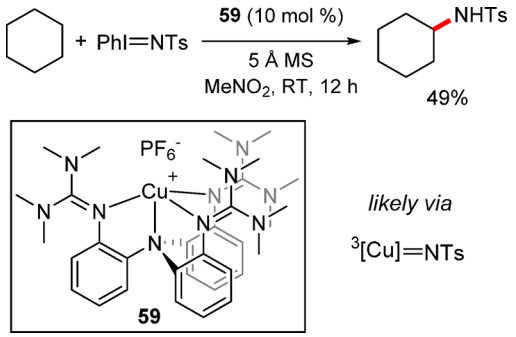
source.[340] When a large excess of ethylbenzene was added to a copper−amido complex **58**, the desired C−H aminated product was formed in 88% yield (Scheme 108b). The activation barrier calculated by DFT studies on the HAA/rebound pathway was well matched with the experimentally determined barrier. Clarifying the elementary steps eventually led to the development of a catalytic reaction. An additional study proved that a variety of aniline derivatives were also applicable under this catalyst system.

Stavropoulos and co-workers prepared a C_3-symmetric tripodal copper(I) complex **59** bearing a Lewis basic guanidinato ligand, and this copper species was found to catalyze the amino transfer reactions such as C−H amination and olefin aziridination (Scheme 109).[341] Mechanistic studies

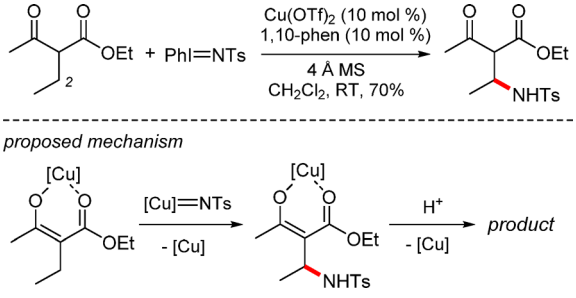
Scheme 109



including Hammett analysis, KIE, radical clock, and EPR experiments in addition to theoretical calculations allowed them to elucidate the active intermediates, and they thereupon proposed a working mode that carboradicals are involved in the C−H insertion process. It was shown that a putative triplet Cu−nitrene species is responsible for the observed reactivity.

An interesting outcome of regioselectivity was reported by Chan and co-workers in the Cu-catalyzed C−H amination of 1,3-dicarbonyl compounds (Scheme 110).[342] The amidation of

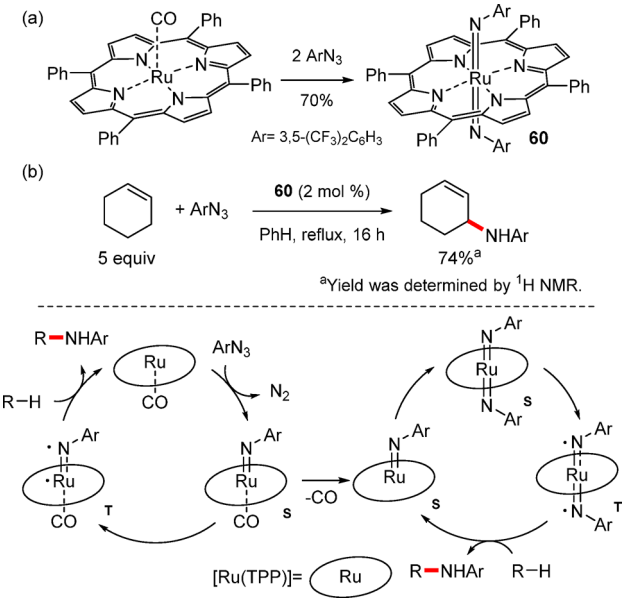
Scheme 110



ethyl 2-ethyl-3-oxobutanoate occurred at the C-2 position in the presence of iminoiodinane and Cu(II) catalyst. Because this site possesses an allylic character upon enolization, a posited nitrenoid moiety is believed to react at the seemingly unactivated C−H bond. The intermolecular KIE value was measured to be 1.9, thus implying that the C−H insertion proceeds presumably via a concerted manner. Because most copper catalysts display relatively large KIE values, being consistent with a HAA/rebound pathway, the mechanistic result of this particular reaction is informative. It is noteworthy that aziridination products can be selectively obtained when 2 equiv of nitrene precursors was employed.

4.1.2. Second-Row Catalysis. *4.1.2.1. Ruthenium Catalysis.* Earlier reports on the catalytic activity of the first-row metal complexes toward C−H amination and their mechanistic insights stimulated the development of Ru-based catalyst systems. Che and co-workers initiated this research by disclosing ruthenium(II) complexes bearing 1,4,7-trimethyl-1,4,7-triazacyclononane (Me_3tacn) as a supporting ligand.[343] Subsequently, the synthetic utility of Ru(II)−porphyrin catalysts in the amino group transfer was independently demonstrated by the groups of Cenini[316] and Che.[305] Importantly, the characterization of bis(tosylimido)Ru(VI) porphyrin, which is an active intermediate for the C−H insertion, established a clear mechanistic foundation in this type of reaction.[344−346] More recently, Gallo and co-workers synthesized an analogous Ru(VI) complex **60** that displayed its capability to catalyze C−H amination in reaction with aryl azides (Scheme 111a and b).[347,348] Taking advantage of the

Scheme 111



thermal stability of complex **60** (stable for a long period of time at room temperature), mechanistic studies such as spectroscopic characterization were carried out. DFT studies led the authors to propose that two distinct catalytic cycles may be operative: one involving a monoimido Ru(IV) species, and a second having a bisimido Ru(IV) intermediate.[349]

Du Bois and co-workers showed that a mixed-valent diruthenium(II/III) complex can catalyze an intramolecular allylic C−H amination (Scheme 112).[350] One advantage of using this catalyst system lies in its robustness toward oxidative conditions arising from the higher one-electron oxidation potential. Complex **61**, $Ru_2(hp)_4Cl$, displayed notable chemoselectivity as well as high efficiency for allylic C(sp^3)−H amidation in the presence of hypervalent iodine oxidant, wherein the allylic C−H bond was selectively reacted, leaving the olefin moiety intact. Computational calculations in combination with experimental analyses suggested the formation of a diruthenium−imidyl diradical species (quartet state) as a putative key intermediate being responsible for the

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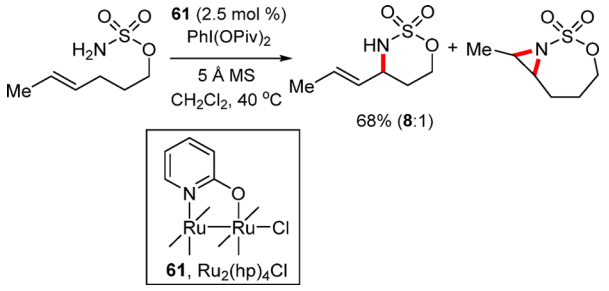
Scheme 112



observed chemoselectivity in both C−H amidation and olefin aziridination reactions.[351]

Asymmetric nitrenoid transfer to saturated C−H bonds is highly desirable in that it offers a straightforward route to chiral amino compounds from hydrocarbons. In 1999, Che and co-workers developed chiral Ru(porphyrin)-catalyzed asymmetric C−H amidation of ethylbenzene, achieving up to 58% ee.[352] This seminal example demonstrated the feasibility of an asymmetric induction by utilizing multidentate chiral ligands. In 2008, Blakey and co-workers utilized a Ru(II) (pybox) catalyst **62** to produce chiral sulfamates (Scheme 113a).[353] The reaction displayed a high level of reactivity as well as enantioselectivity under ambient conditions. Katsuki and co-workers disclosed a chiral (salen)Ru(II) catalyst system for the enantioselective intermolecular C(sp^3)−H amidation using SES−N_3 (2-(trimethylsilyl)ethanesulfonyl azide) as an amino group source (Scheme 113b).[354] While an analogous iridium catalyst does not provide satisfactory results, ruthenium species **63** displayed an excellent level of stereoselectivity in the C−H amidation. Mechanistic studies including radical clock and olefin isomerization tests suggested that the concerted C−H insertion path is more plausible, although a rapid HAA/rebound route cannot be completely ruled out.

4.1.2.2. Rhodium Catalysis. Among various catalytic systems previously utilized for the C−H insertion process, dirhodium tetracarboxylates displayed especially notable reactivity in transferring amino groups to unreactive C(sp^3)−H bonds. Early results on the use of hypervalent iminoiodinanes as a nitrenoid precursor stimulated subsequent investigations to develop more efficient procedures, thus enabling practical applications of this method to synthetic chemistry.[62,63,355,356] Most notably, the Du Bois[357−361] and Che[305] groups independently established an elegant protocol, the "PhI($OAc)_2$ + NH_2R" method, to generate a reactive iminoiodinanes species in situ by simply mixing primary amides and PhI($OAc)_2$ oxidant. The additive of MgO is frequently employed to quench an acid byproduct (AcOH) in the reaction mixture. Given that a separate preparation of iminoiodinane species is restricted to only a certain type of amides, this method dramatically expanded the amide scope to serve as direct nitrenoid precursors, thus establishing highly versatile and broad intramolecular C−H amination (Figure 3).[362] Detailed

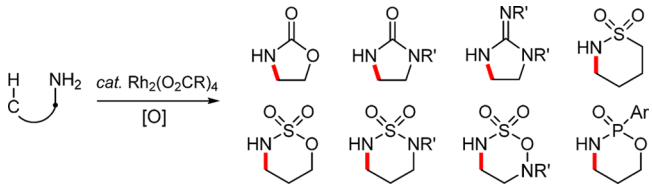
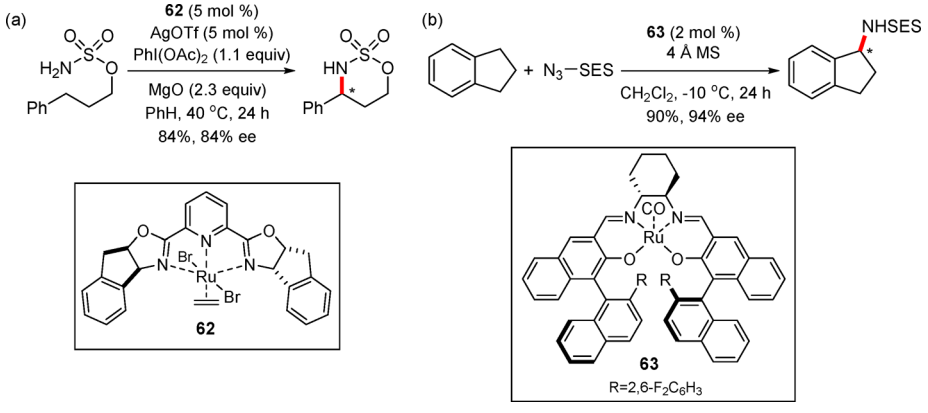


Figure 3. Heterocycle synthesis via Rh_2(II)-catalyzed intramolecular C−H amination. Reproduced with permission from ref 362. Copyright 2011 American Chemical Society.

discussions on this topic before the year 2009 were documented in the literature.[65,66] More recently, the Du Bois[363,364] and Dauban[365] groups independently summarized advances in the topic with emphasis on the synthetic and mechanistic studies.

Despite this early achievement, the "PhI($OAc)_2$ + NH_2R" method often suffers from catalyst degradation caused by an undesirable ligand exchange under oxidative conditions. To improve the stability of catalyst systems, the Du Bois group elegantly devised a strap-type ligand, where two carboxylates are connected to each other.[366] Tetramethylated *m*-benzenedipropionate (esp^{2-}) was employed to furnish a new catalyst system of bis{rhodium($\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate)}, commonly referred to as $Rh_2(esp)_2$, which displays superior catalytic activity and a broader substrate scope as compared to $Rh_2(OPiv)_4$.[367] Taking advantage of such notable features, recent advances with this novel catalyst system have been made to include diastereoselective synthesis of 1,3-diamines[368] and intramolecular amination of propargylic C−H bonds[369] (Scheme 114a and b). Remarkable catalytic performance was also demonstrated in an intramolecular cyclization of azido-2-(*tert*-butyl)benzenes to afford indoline products (Scheme 114c).[370] Notably, mechanistic tests using deuterium-labeled substrates provided supportive evidence that a stepwise C−H cleavage may be operating in this case (Scheme

Scheme 113



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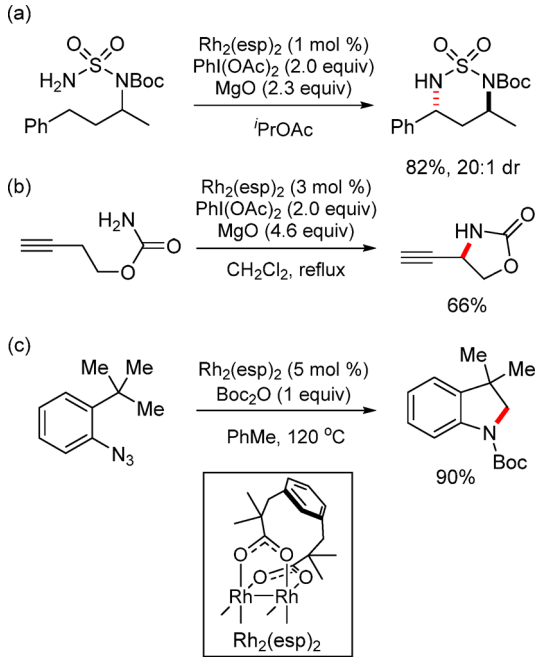
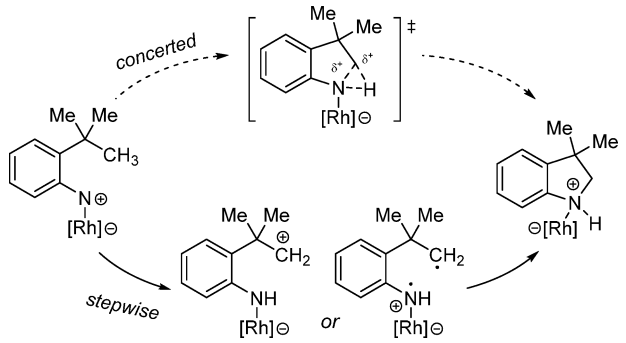
Chem. Rev. 2017, 117, 9247−9301

Scheme 114



115). While two stepwise pathways can be considered in the C−N bond-forming process (hydride transfer versus H atom

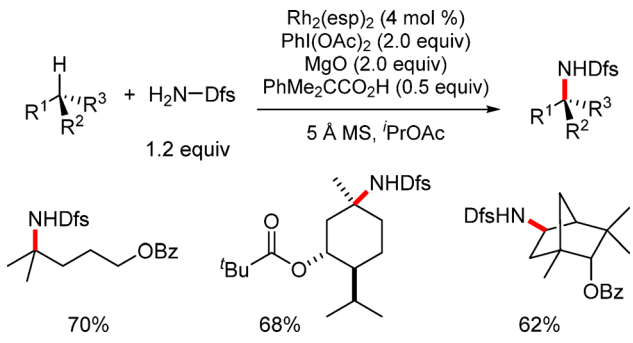
Scheme 115



abstraction), computational studies disclosed by Ke, Zhao (C.), and co-workers corroborated the latter pathway.[371]

Du Bois and co-workers reported another elegant example of an intermolecular C−H amination at the tertiary carbon centers with the established catalyst system of $Rh_2(esp)_2$ and $PhI(OAc)_2$/MgO (Scheme 116).[372] Notably, 2,6-difluorophen-

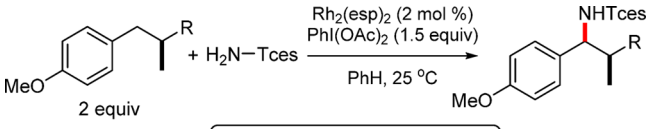
Scheme 116



yl sulfamate ($DfsNH_2$) was employed to display significant activity in this amination, where hydrocarbon substrates were used as a limiting agent. An excellent level of selectivity was observed even in the presence of multiple tertiary carbons in a substrate.

Bach and co-workers presented a notable example of diastereoselective intermolecular C−H amination by using the Rh catalyst system (Scheme 117).[373] By having a stereogenic

Scheme 117

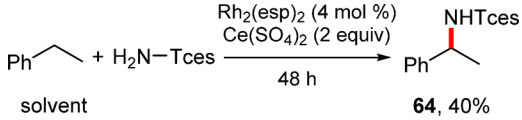


R	yield	dr (*syn*/*anti*)
CO_2Me	81%	82/18
$PO(OEt)_2$	65%	>95/5
SO_2Ph	56%	>95/5

center adjacent to the targeted C−H bonds, a high level of *syn*-selectivity was achieved in reaction with 2,2,2-trichloroethoxysulfonamide ($TcesNH_2$). They also performed mechanistic studies including DFT calculations to ascertain the origin of such high diastereoselectivity, especially by focusing on the conformational preferences.[374]

The influence of strapped ligands on the catalytic reactivity was further investigated by several analytical approaches. Importantly, the kinetic behavior clearly indicated the relative stability of $Rh_2(esp)_2$ in the presence of hypervalent iodine oxidants.[375] In contrast, when $Rh_2(O_2C^nPr)_4$ was subjected to the same oxidative conditions, a significant degree of complex degradation was observed, thus confirming a key role of the covalent connection between two carboxylates on the catalyst stability. The formation of $[Rh_2(esp)_2]^+$ species possessing mixed-valent dirhodium(II/III) centers was also observed under the employed oxidative conditions. In 2011, Berry and co-workers showed that mixed-valent dirhodium(II/III) species works as an active intermediate in an intermolecular C−H amination reaction.[376] Whereas the formation of a Rh−nitrenoid intermediate is generally accepted in the C−H amination of hydrocarbons, the authors speculated that the oxidized species $[Rh_2(esp)_2]^+$ facilitates a nitrenoid transfer presumably via sequential proton-coupled electron transfer (PCET) processes. On the basis of this hypothesis, a new procedure of the catalytic C−H amidation was developed by using single electron oxidants such as $Ce(SO_4)_2$ instead of hypervalent iodine species to afford amidated product **64** (Scheme 118).

Scheme 118



Given that mixed-valent dirhodium-carboxylate complexes are rather labile under oxidative conditions,[377] Berry and co-workers devised a new type of complex where carboxylates are substituted with carboxamides because nitrogen donors often stabilize more effectively high-valent metal complexes. Indeed, such displacement led to a significant improvement in terms of

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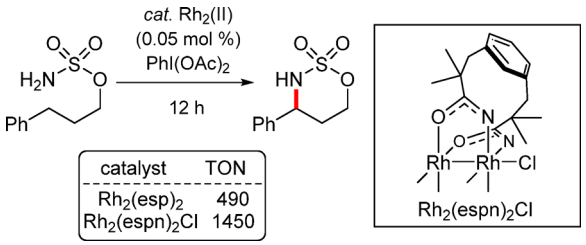
catalyst performance (Scheme 119).[377] In an intramolecular C−H amination of a model substrate, dirhodium complex

Scheme 119

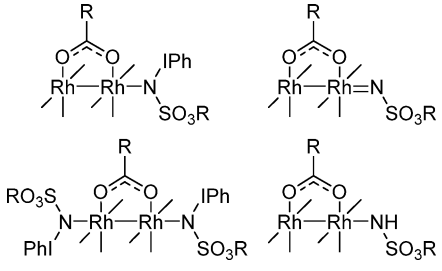


bearing carboxamide straps, $Rh_2(espn)_2Cl$, exhibited notable turnover numbers (1450), being much higher than those obtained with $Rh_2(esp)_2$ catalyst (490) under the same oxidative conditions. Combined theoretical and experimental investigations revealed that the ground state of a putative Rh−nitrenoid species is located at the quartet state and it can readily undergo spin crossover to maintain a concerted and asynchronous C−H insertion mode.[378]

Elucidation of a mechanistic working mode in the dirhodium-catalyzed C−H functionalization of hydrocarbons has been a long-standing interest. An early study by Müller and co-workers suggested that an intermolecular C−H amination by $Rh_2(OAc)_4$ catalyst follows a concerted C−H insertion pathway.[379] A similar conclusion was drawn by Du Bois on both intra- and intermolecular C−H amination reactions,[367,378,380] although recent studies on intermolecular reaction of tertiary C−H bonds suggested a stepwise HAA/rebound pathway.[372] Mechanistic interpretations of Hammett plotting, chirality transfer, radical clock test, and KIE values provided support for this postulate. Recent DFT studies corroborated the formation of Rh−nitrenoid species and a subsequent concerted asynchronous C−H insertion pathway.[381−383] However, despite these mechanistic descriptions, definite proof of the details of the C−N bond-forming process such as the isolation and characterization of key intermediates has been elusive to date. In this context, Du Bois and Zare tried to observe reactive intermediates by applying desorption electrospray ionization (DESI) mass spectroscopy to the catalytic C−H amination conditions.[384] With this DESI technique, they captured characteristic signals of several putative intermediates, critically including Rh−nitrenoid species having lifetimes of milliseconds or less (Scheme 120).

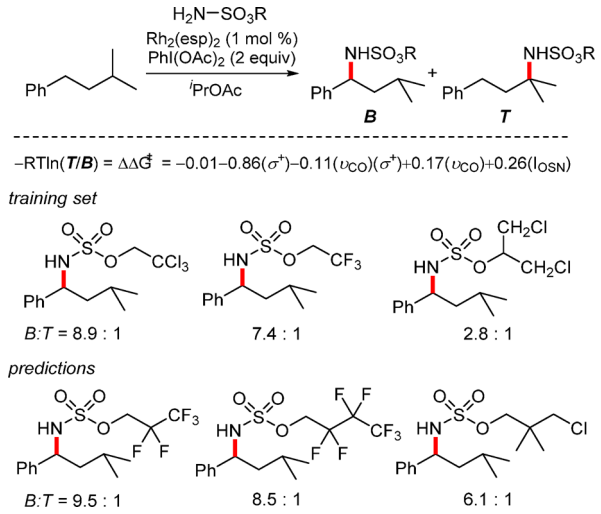
Selectivity control in the C−H functionalization is a critical issue especially when multiple reactive sites are present in a substrate. In fact, the dirhodium-mediated C−H insertion reaction often gives rise to a mixture of isomeric products. Sigman and Du Bois developed a model system to allow

Scheme 120



prediction of the isomeric ratio obtainable from the $Rh_2(esp)_2$-catalyzed C−H amidation (Scheme 121).[385] The Rh-catalyzed

Scheme 121



C−H amidation of isoamylbenzene gave two isomeric products, reacted at the benzylic and tertiary positions in each case. Because the isomeric ratio was found to be sensitive to the substrates employed, they carefully interrogated the benzylic-to-tertiary product ratios in a variety of substrates (23 entries) to establish a multiparameter-based free energy relationship. A comprehensive statistical treatment revealed that the electronic contributions reflected in the Hammett σ^+ values of isoamylbenzene derivatives and the computed infrared signals of sulfamate esters (υ_{CO}, I_{OSN}) were most critical to govern the selectivity. This model was further validated by another set of substrate combinations (38 entries), and, eventually, it was applied to predict the structure of substrates that may give rise to a high isomeric ratio.

Recently, remarkable progress has been made in the development of Rh-catalyzed asymmetric C−H insertion reactions, such that chiral amines can be installed with high site-selectivity.[36] A range of chiral carboxylates were utilized for the preparation of bimetallic chiral rhodium catalysts as shown in Scheme 122. Seminal reports by the Davies[386] and Du Bois[387] groups independently proved that intramolecular asymmetric aminations are highly viable with chiral catalysts **65** and **66**, which are derived from adamantylglycine and 2-piperidonate, respectively (Scheme 122a and b). Davies and co-workers presented an asymmetric intermolecular C−H amidation reaction with a chiral catalyst **66** (Scheme 122c).[386] Diastereoselective C−H amination reactions were also reported upon the combined use of chiral amides and catalyst **67** (Scheme 122d).[388,389] This method was applied to the amination of complex molecules bearing terpene, enol ether, or alkyne functionality.[390,391] In 2011, Lebel and co-workers utilized chiral carbamates for the diastereoselective intermolecular C−H amination with catalyst **68** (Scheme 122e).[392,393] The Bach group developed a notable asymmetric C−H amination by taking advantage of a secondary interaction between substrates and chiral catalyst **69** (Scheme 122f).[394] Hydrogen bonding was assumed to critically influence the stereodetermining C−H insertion step.

4.1.2.3. Silver Catalysis. While silver catalysts have rarely been utilized in C−H amination, notable exceptions are

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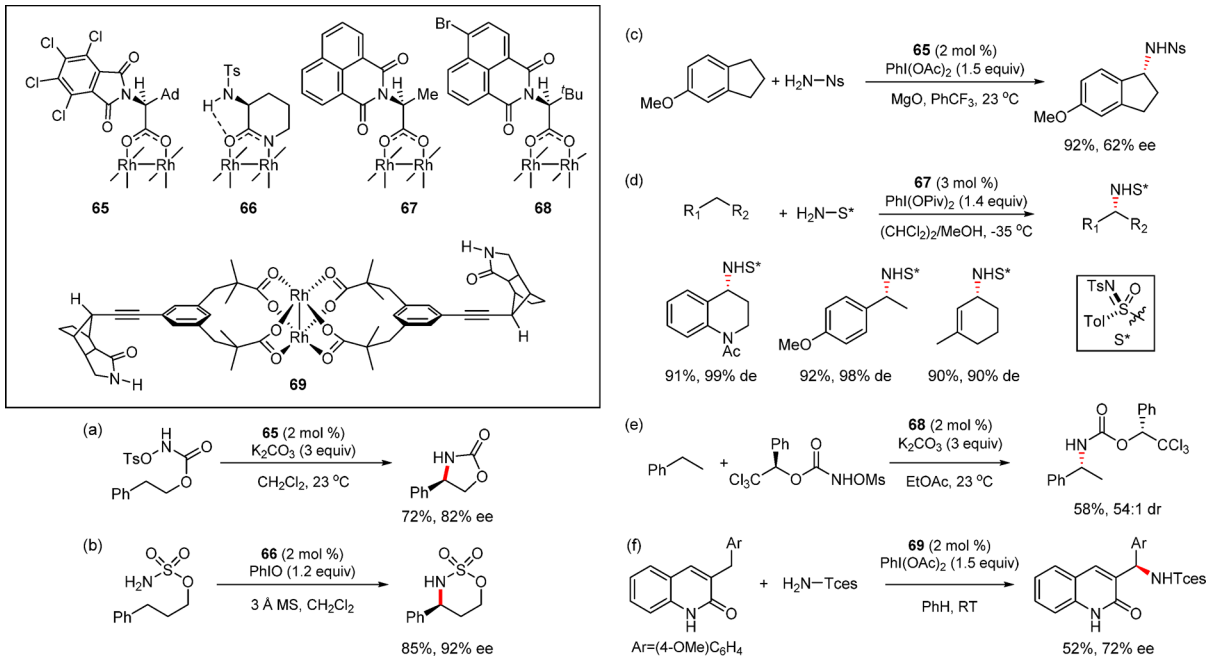
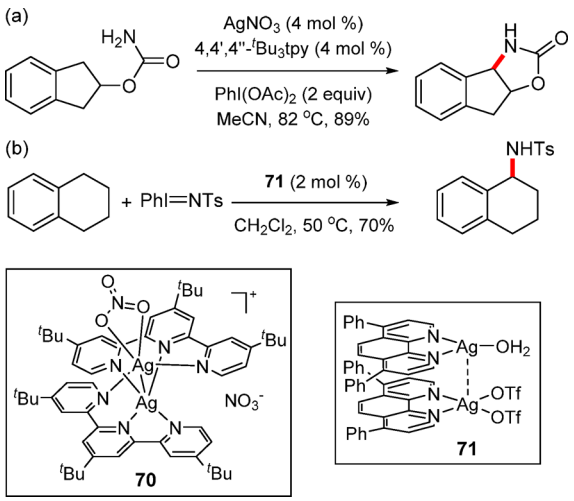
Scheme 122



recently revealed.[395] For instance, He and co-workers found that a dimeric silver(I) catalyst **70**, prepared in situ by mixing $AgNO_3$ and 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″terpyridine (4,4′,4″-^{t}Bu$_3$tpy), can dramatically improve the efficiency of a C−H amination, thus enabling an intramolecular C−H cyclization of carbamates (Scheme 123a).[396] Interestingly, the

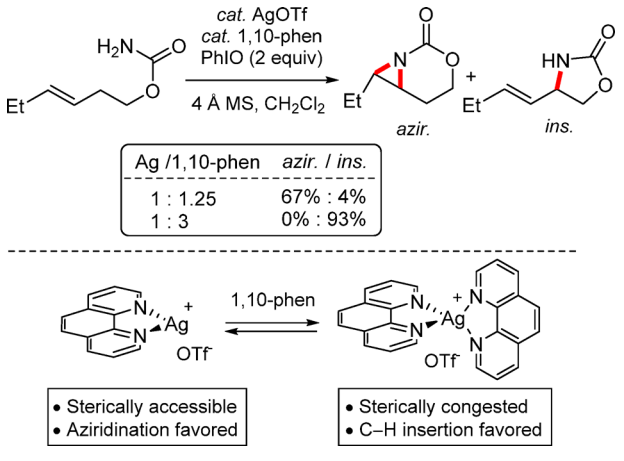
Scheme 123



use of analogous ligands such as pyridines or bipyridines resulted in much lower reactivity under otherwise identical conditions. The same research group later showed that a dimeric silver species **71** bearing bathophenanthroline ligands can smoothly catalyze an intermolecular C−H amination at the benzylic C(sp^3)−H bonds (Scheme 123b).[397] Interestingly, the crystallographic structure of complex **71** revealed an argentophilic interaction between two stacked silver(I) moieties. The authors posited that the conservation of this dimeric form during the catalytic reaction is important for achieving high reactivity by promoting the formation of a disilver(II)−nitrene intermediate and, at the same time, possibly inhibiting a radical process commonly observed in the Ag(I)-mediated reactions.

Chemoselectivity is an important issue in the nitrogen transfer chemistry because C−H amination and its relevant olefin aziridination can be mediated by the same metal−nitrenoid species. Given that the coordination geometry of silver(I) complexes depends on the ligands' concentrations, Schomaker and co-workers presented an interesting strategy to achieve ligand-controlled chemoselective nitrogen transfer (Scheme 124). They hypothesized that active intermediates

Scheme 124



in the catalytic cycle can be finely tuned by changing the ratio between metal and ligands.[398] When a bis-homoallyl carbamate was subjected to the AgOTf/1,10-phen (1:1.25) catalyst system, aziridination occurred predominantly. In contrast, an increase of the ligand to 3 equiv relative to the silver salt induced a reversal of the chemoselectivity, leading to C−H amination almost exclusively. It was rationalized that the steric bulk of the silver catalyst is responsible for this chemoselectivity

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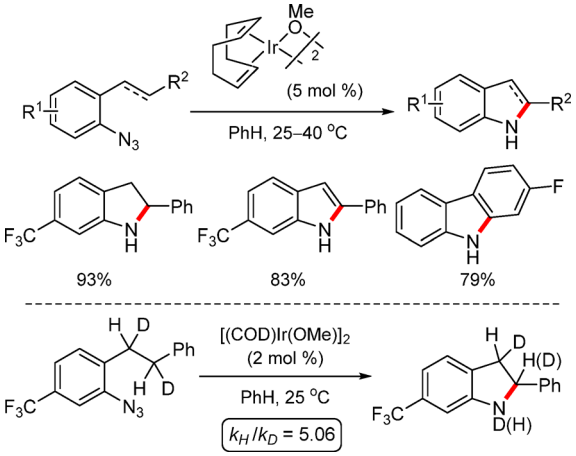
change: open coordination site promotes the olefin aziridination, whereas congested metal center favors the C−H insertion. A continuous research program by the same group also showed that silver-catalyzed regioselective C−H amination can be attained by the choice of ligands.[399] Thorough examination of different types of ligands revealed that the selectivity between benzylic and tertiary positions can be finely tuned by its coordination environment.

4.1.3. Third-Row Catalysis. *4.1.3.1. Iridium Catalysis.* The third-row transition metals have not received much attention in the area of the C−H insertion chemistry. Indeed, only a few examples of C−H aminations were known with iridium or gold catalysis. One notable procedure was disclosed by Driver and co-workers, who showed that $[(COD)Ir(OMe)]_2$ catalyst was effective for the mild intramolecular C−H amination of aryl azides giving rise to indolines, indoles, or carbazole products (Scheme 125).[400] Both benzylic C(sp^3)−H and olefinic or aryl

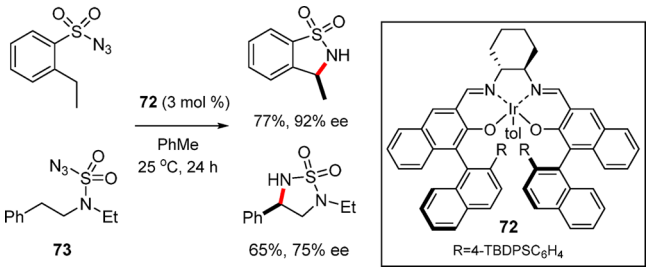
Scheme 125



C(sp^2)−H bonds were reactive toward the C−H insertion by interacting with putative iridium−nitrenoid intermediates at ambient temperature. Whereas an asynchronous concerted C−H insertion path was proposed on the basis of the intramolecular KIE value (5.06), further examinations would be required to rule out an alternative mechanism involving triplet nitrenoid intermediate.

Katsuki and co-workers prepared chiral (salen)iridium(III) complexes **72** for the asymmetric C−H amination in analogy to the corresponding Ru catalyst system,[354] which was developed by the same research group (Scheme 126).[401] An intramolecular C−H insertion at the benzylic *ortho* C−H bonds of sulfonyl azides was achieved in high enantiomeric excess to afford benzosultam products. The reaction scope was not

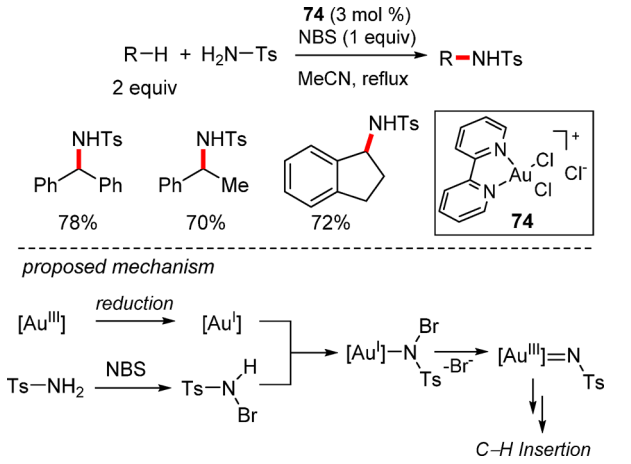
Scheme 126



limited to *ortho*-alkyl arylsulfonyl azides, and sulfamoyl azides **73** were also readily cyclized, albeit with moderate enantiomeric excess.

4.1.3.2. Gold Catalysis. A rare example of using gold catalysis was reported by Feng and co-workers (Scheme 127).[402] While a related aziridination with gold(I) catalyst

Scheme 127



was previously identified,[403] this study showed unique reactivity of gold species toward C−H amination of hydrocarbons. In the presence of gold(III) catalyst **74** and stoichiometric amounts of NBS, an intermolecular amination at the benzylic C(sp^3)−H bonds was achieved. Ligand effects on the reactivity were also observed: whereas triphenylphosphine was not effective, gold(III) species bearing pyridine or bipyridine ligands gave good to excellent product yields. *N*-Bromosulfonamide, formed in situ by the reaction of sulfonamide with NBS, was suggested to react with ethylbenzene to afford the C−H aminated products. The authors proposed that, upon the formation of *N*-bromosulfonamide, Au(I) species generated in situ from the Au(III) precursor reacts with the active amino group source to afford the Au(I)−amide adduct, which is then converted to a putative Au(III)−nitrenoid species, thus enabling the key C−H insertion.

4.2. C(sp^2)−H Amination

4.2.1. Intramolecular Amination via Metal−Nitrenoid Intermediate. Driver and co-workers pioneered the development of Rh_2(II)-catalyzed intramolecular C(sp^2)−H amination to obtain functionalized indoles (Scheme 128).[404−406] The authors found that dirhodium species bearing electron-deficient carboxylates catalyze the cyclization reaction of styryl- or aryl azides with neighboring aryl sp^2 C−H bonds to afford substituted indoles. As postulated in most C(sp^3)−H insertion aminations, the formation of a putative Rh−nitrenoid species was also proposed in Driver's reactions. Considering the importance of indoles as a privileged structure in medicinal and synthetic chemistry, this procedure is expected to have broad applications.

The mechanistic foundation for such novel reactivity was investigated using triaryl azide as a model substrate (Scheme 129).[407] While the Rh−nitrenoid species was proposed to form via the coordination of α-nitrogen of aryl azide to the rhodium center, three plausible pathways were envisioned in the subsequent C−N bond formation: (i) concerted C−H insertion of nitrenoid into aromatic C−H bonds, (ii)

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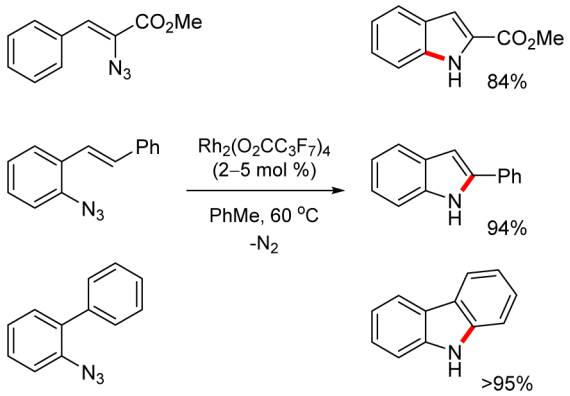
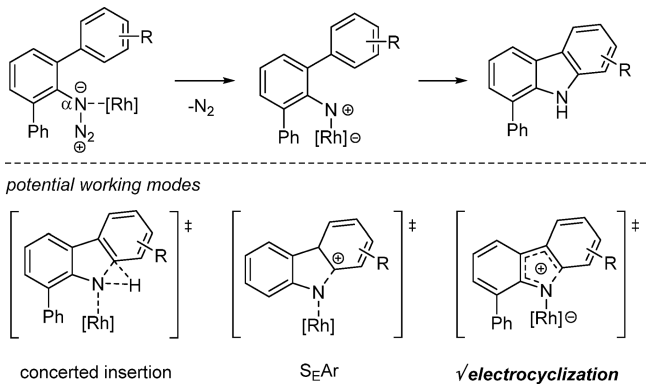
Scheme 128



Scheme 129

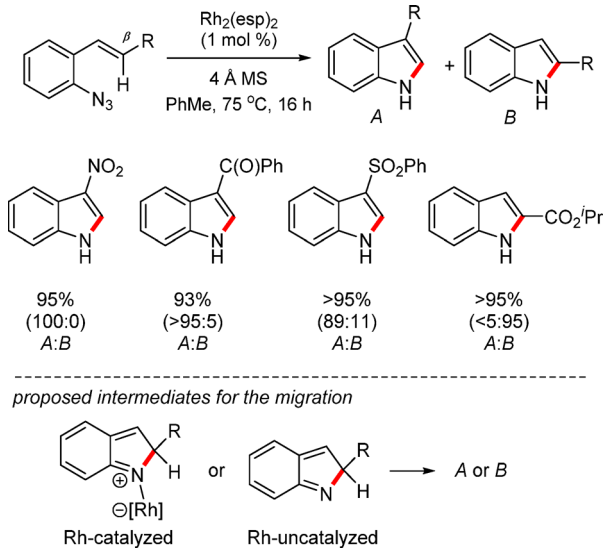


electrophilic aromatic substitution (S_EAr), and (iii) electrocyclization. Among them, the concerted C−H insertion and S_EAr mechanisms were excluded by the characteristic reactivity pattern observed in the competition studies. On the basis of a linear correlation between Hammett parameters and the product ratio, it was concluded that a planar nitrenoid species will undergo 4π-electron-5-atom electrocyclization leading to C−N bond. Recent computational studies corroborated a mechanistic scaffold involving a pseudoelectrocyclization process in the pericyclic transition state.[408] This proposal provides a novel working mode to involve a putative Rh−nitrenoid species because most of the known C−H aminations catalyzed by dirhodium complexes were proposed to undergo an insertion of C−H bonds via a concerted manner.

In 2011, Driver et al. reported a cascade process of C−H amination and subsequent nitro group migration to afford 3-nitroindoles when β-nitro styryl azides were subjected to the dirhodium catalytic system (Scheme 130).[409] The migration of C-2 substituents was not limited to nitro functionality, and various other electron-withdrawing groups including benzoyl or sulfonyl substituents were also viable. Interestingly, esters and amide moieties showed little reactivity toward the migration, suggesting that strong electronic bias is required. Combined mechanistic studies revealed that this migration proceeds even in the absence of dirhodium catalyst and that it is closely related to the intrinsic properties of substrates.[410] The same research group also applied the Rh(II) catalyst system for the total synthesis of (±)-horsfiline.[411]

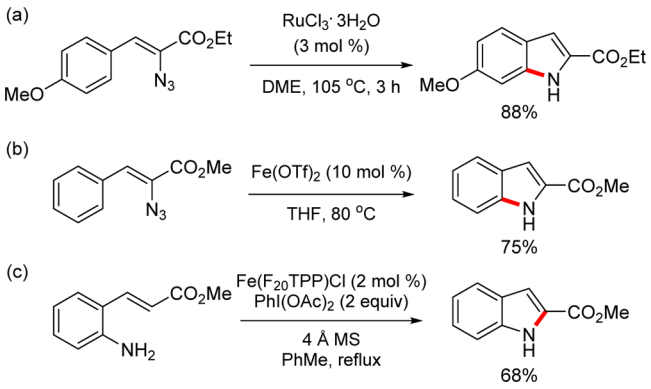
While a dirhodium catalyst system has been most frequently used for the intramolecular C(sp^2)−H amination of aryl- or vinyl azides, a few examples are known to employ other

Scheme 130



transition metal catalysts. For instance, Lin, Jia, and co-workers revealed the catalytic activity of $RuCl_3$ in the cyclization of β-styryl azides to afford indoles (Scheme 131a).[412] The Bolm

Scheme 131



group found that the same cyclization can be efficiently achieved with a commercially available $Fe(OTf)_2$ catalyst (Scheme 131b).[413] The reaction efficiency was changed depending on the solvents that were used, and ethers were the most effective to allow mild conditions. Che et al. also demonstrated that Fe(II) catalysts bearing electron-deficient porphyrin ligands can efficiently cyclize (*E*)-methyl 3-(*ortho*-amino-phenyl)acylate to furnish methylindole-2-carboxylate in the presence of $PhI(OAc)_2$ oxidant (Scheme 131c).[414] Interestingly, computational studies done by Li (J.) and co-workers indicated that the C−N bond formation in this iron-catalyzed cyclization does not follow the electrocyclization pathway, which was generally accepted in the Rh-catalyzed intramolecular reactions.[415] Instead, a hydrogen atom abstraction of C(sp^2)−H bonds and subsequent rebound pathway were calculated to be energetically more favorable to involve putative quartet or sextet intermediates.

Whereas the N_2 extrusion from organic azides is assumed to take place through the coordination of α-nitrogen to the most electrophilic metal centers, Plietker and Alt presented a novel working mode, where electron-rich iron complexes enable nucleophilic activation of aryl azides (Scheme 132).[416] Anionic

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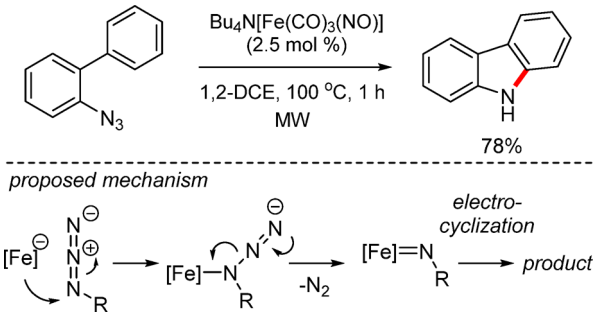
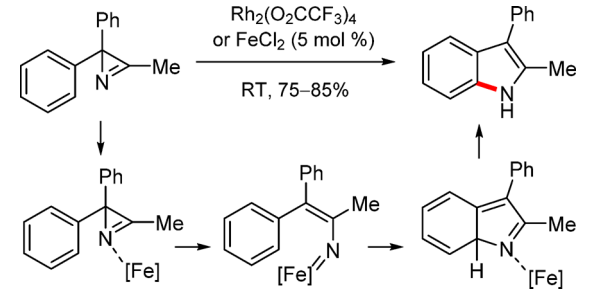
Scheme 132



iron complexes readily donate electrons to the α-nitrogen of azides to facilitate subsequent liberation of N_2, thus leading to a Fe−nitrenoid species. The optimized iron catalyst system was successfully applied to the cyclization of biphenyl azides, giving rise to carbazole products.

An interesting strategy for the intramolecular amination was established by using the 2*H*-azirine moiety as an amino precursor. Narasaka[417] and Zheng[418] independently proved this approach with dirhodium(II) and iron(II) catalysts, respectively (Scheme 133). DFT calculations by Li (J.), Yan, and co-

Scheme 133

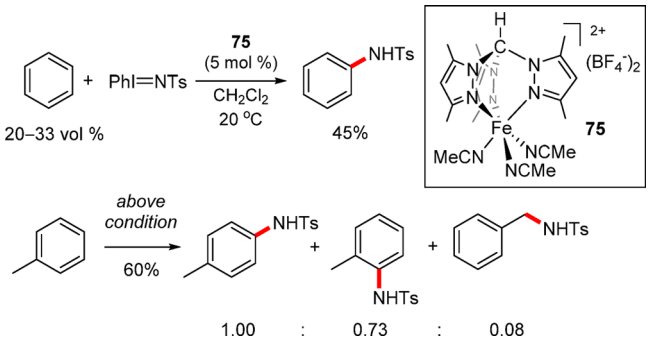


workers indicated that the catalytic cycle likely involves sequential processes of ring opening of 2*H*-azirines, C−N bond formation, and 1,2-hydride shift.[419] Reaction energy profiles of both Rh and Fe systems are directly compared to each other.

4.2.2. Intermolecular C−H Amination. Metal-catalyzed intermolecular C(sp^2)−H insertion is often highly challenging within the conventional mechanistic scaffolds involving direct C−H insertion or homolytic C−H bond cleavage. An alternative mechanistic consideration in the C−H amination of benzenes was described by Pérez with a TpCu(I) catalyst system (see section 4.1.1).[336,337] Although the fundamental basis for this proposal has not been clarified yet, DFT calculations suggested that it involves a tandem process: unusual aziridination of benzenes followed by H atom transfer and then rearomatization.[338] In 2013, Nicholas and co-workers reported a copper catalyst, (neocuproine)Cu(I), to enable a direct amination of simple arene at 140 °C by using *N*-tosyloxycarbamate as the aminating agent.[420] The authors proposed a putative copper(II)−imido species that will undergo an electrophilic addition to arenes.

The Jensen group found that, after a systemic screening of various complexes including manganese, iron, cobalt, and nickel, an Fe(II)−scorpionate species **75** is capable of catalyzing C−H amination of aromatic hydrocarbons (Scheme 134).[421] Reaction of toluene under the same conditions showed

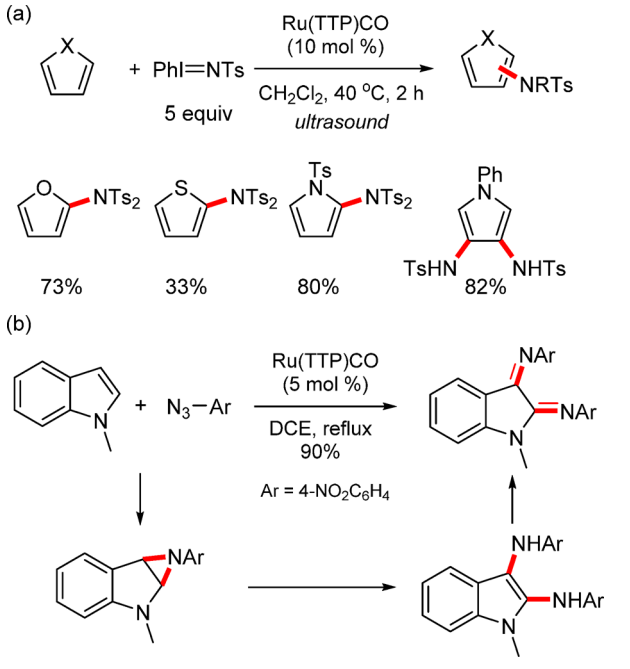
Scheme 134



a notable selectivity at the aryl C(sp^2)−H over the benzylic C(sp^3)−H bonds, but with moderate regioselectivity leading to *ortho*- and *para*-amidated products with a similar ratio.

Regioselectivity is a key issue in an intermolecular amination of substrates bearing seemingly analogous multiple C−H bonds. Che and co-workers utilized their Ru(II) porphyrin catalyst system for the selective C−H amination of a range of heterocycles (Scheme 135a).[422] When furan was allowed to

Scheme 135



react with iminoiodinanes in the presence of the ruthenium catalyst, an amidation took place selectively at the C-2 position. A similar selectivity pattern was also observed with thiophens and *N*-tosylpyrroles. However, when *N*-phenylpyrrole was employed, 3,4-bisamidated product was obtained in good yield without the formation of isomeric byproducts. The same research group further extended the scope of heteroarenes to include indoles (Scheme 135b).[423] (Porphyrin)Ru(II)-catalyzed C−H amination of *N*-alkylindoles was smooth in reaction with aryl azides to afford indolines products, being doubly imidated at the C-2 and C-3 positions. A potential involvement of anilines that could be derived from aryl azides as the amino group source was ruled out on the basis of a control experiment. Instead, this transformation was tentatively proposed to involve initial aziridination of the indole, followed

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by aziridine ring-opening, with subsequent C−H amination, and dehydrogenation to provide the diimine product.

5. PHOTOREDOX CATALYSIS

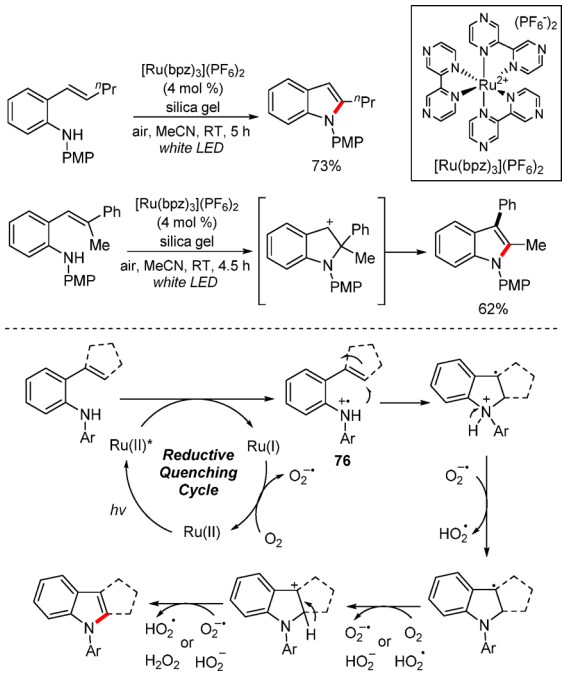
Significant recent advances have been made in the area of direct C−H amination through either nucleophilic or electrophilic mechanistic scaffolds that are facilitated by transition metal catalysts, thus leading to notable synthetic applications in medicinal and materials chemistry. However, from a mechanistic view, nitrogen-centered radicals have rarely been implicated in the direct C−N bond-forming procedures possibly due to their uncontrollable reactivity. Indeed, those reactive species are traditionally generated by thermolysis, short wavelength photolysis, or radical initiators that are usually incompatible with labile functional groups present in substrates, thereby making synthetic applications based on this approach rather difficult. Therefore, the development of preparative routes to nitrogen-centered radicals is highly desirable, especially in a predictable manner under more selective and mild conditions. In this context, the remarkable achievements in the single electron transfer process by visible light photoredox catalysis have extended the scope to the C−N bond-forming reactions by generating the required nitrogen-centered radicals under mild photoredox catalytic conditions.[424,425] Indeed, the visible light photoredox catalysis was found to generate the nitrogen-centered radicals easily with broad applications in the synthesis of nitrogen-containing compounds. In this section, recent notable advances in the direct C−H amination with this new mechanistic scaffold are described.

5.1. Intramolecular C−H Amination

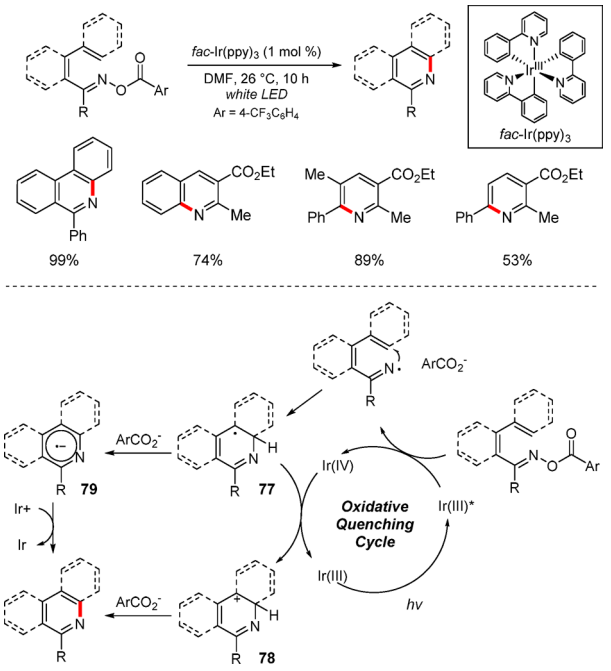
On the basis of the notable progress in the intramolecular C−H amination using photoredox catalysis, various azaheterocycles can now be prepared in a straightforward manner. In 2012, Zheng reported the synthesis of *N*-arylindoles from *ortho*-styryl anilines under a Ru-based photocatalyst system with visible light (Scheme 136).[426] Notably, the addition of silica gel was found to facilitate the absorption of molecular oxygen and to serve as a proton source. High efficiency in the cyclization was obtained especially when *p*-methoxyphenyl (PMP) was installed at the anilinic nitrogen atom. Interestingly, 2,3-disubstituted indoles were produced from *gem*-disubstituted styryl anilines, presumably via a 1,2-carbon shift of benzylic cation intermediates, wherein an aryl substituent is preferentially migrated over alkyl groups. According to this mechanistic depiction, an initial reductive quenching of a photoexcited Ru(II) species by styryl anilines gives rise to *N*-radical cation intermediate **76**, which then undergoes a series of electrophilic addition and aromatization to afford indoles. Subsequently, Xiao also reported the synthesis of 2-substituted indoles from styryl azides using visible light photocatalysis.[427]

In 2015, Yu (S.) and Zhang (Y.) reported an efficient intramolecular route to a wide range of heterocycles including phenanthridines, quinolines, and pyridines (Scheme 137).[428] In this approach, the key to success was the facile generation of nitrogen-centered radicals by iridium photocatalysis of acyl oxime substrates with visible light. In this reaction, electron-withdrawing substituents in acyl oximes improved the cyclization efficiency, presumably by enhancing the leaving group ability of carboxylate anions during the course of generating an imidyl radical that eventually undergoes an intramolecular homolytic aromatic substitution leading to a

Scheme 136



Scheme 137



carbon-centered radical intermediate **77**. This resulting *C*-radical **77** is oxidized by Ir(IV) species to give rise to a cationic intermediate **78**, which is then deprotonated to furnish *N*-heterocycles. Alternatively, **77** can also be transformed to an anionic radical intermediate **79**, which is then oxidized by Ir(IV) species to give the same product.

5.2. Intermolecular C−H Amination

In 2014, Sanford and co-workers reported a visible light photoredox catalyst system for the C−H amination of simple (hetero)arenes with *N*-acyloxyphthalimides as a precursor for nitrogen-centered radicals (Scheme 138).[429] The use of an

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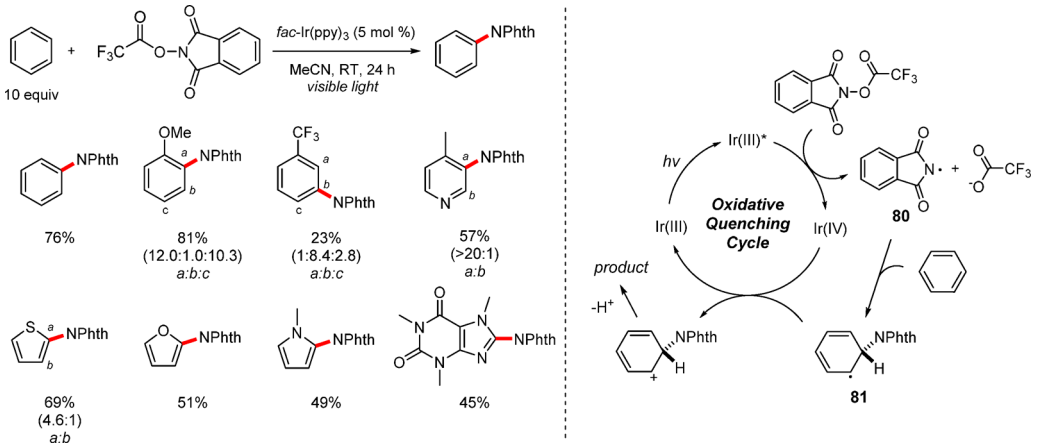
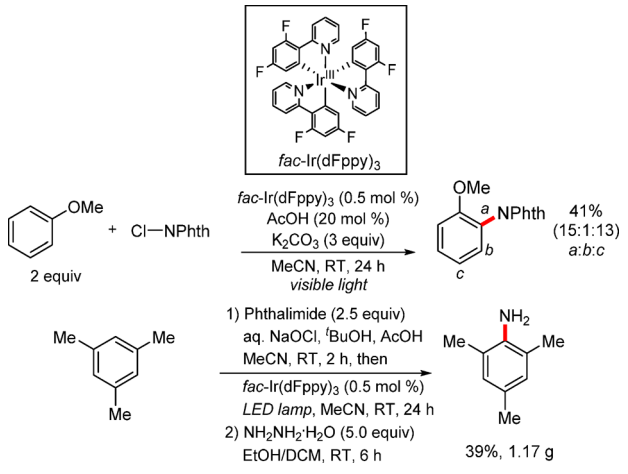
Scheme 138



electron-withdrawing trifluoromethyl substituent in *N*-acyloxyphthalimides enhanced the leaving group ability of the corresponding carboxylate anions, thus forming phthalimidyl radical more efficiently. Significantly, the desired aminated products could be obtained exclusively without C−O bond formation, thus suppressing the formation of byproducts. As the reaction follows an electrophilic aromatic substitution route, regioselectivity of this C−H amination closely reflects the electronic property of arene substituents. For examples, a high level of *ortho*/*para*-selectivity was observed with arenes bearing electron-donating groups, and a modest *meta*-selectivity was obtained when electron-withdrawing substituents are present. As depicted in Scheme 138, the catalytic cycle is assumed to begin with the photo irradiation of $Ir(ppy)_3$ catalyst that is readily excited to Ir(III)* species, which is then oxidatively quenched by *N*-trifluoromethylacyloxyphthalimide to release a nitrogen-centered radical intermediate **80**. This reactive radical species is added into arenes to form a carbon-centered radical intermediate **81**. A sequential process of single electron oxidation and deprotonation is then followed to afford the aminated products with the concomitant regeneration of a photoredox Ir(III) catalyst.

Lee (C.) and co-workers reported the visible light photocatalyzed C−H amination of (hetero)arenes using *N*-chlorophthalimides as an imidyl radical precursor (Scheme 139).[430] The reaction conditions were improved when

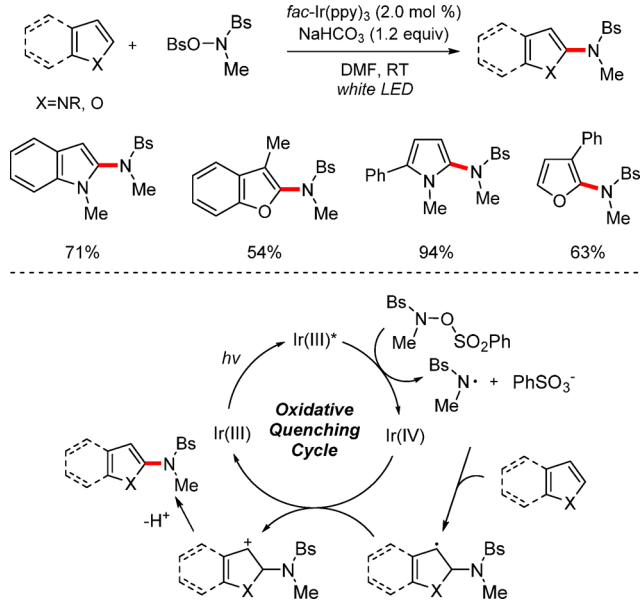
Scheme 139



compared to Sanford's procedure[429] in that only 2 equiv of substrate was employed with lower loading of iridium photo catalyst. Moreover, the author presented a gram scale one-pot procedure to perform *N*-chlorination, C−H imidation, and then deprotection to afford primary aniline products.

In 2014, Yu (S.) and co-workers reported another example of a photoinduced C−H amination of heteroarenes (Scheme 140).[431] While hydroxylamine derivatives were used as an

Scheme 140



amidyl radical source, the *N*-activating moiety on those precursors played a pivotal role for the reductive cleavage of N−O bonds, thus obtaining high amidation efficiency with the *N*-benzenesulfonyloxy group. In this approach, a range of heteroarenes including indoles, benzofurans, pyrroles, and furans underwent the desired C−H amidation in satisfactory yields. A series of control experiments was conducted to gain mechanistic insights including a radical inhibitory test and examination of model substrates blocked at a specific site. They proposed the formation of a carbocation intermediate at the C-3 position of indole substrates during the catalytic cycle.

Studer showed that *N*-aminopyridinium salts can be employed as precursors for the nitrogen-centered radicals to

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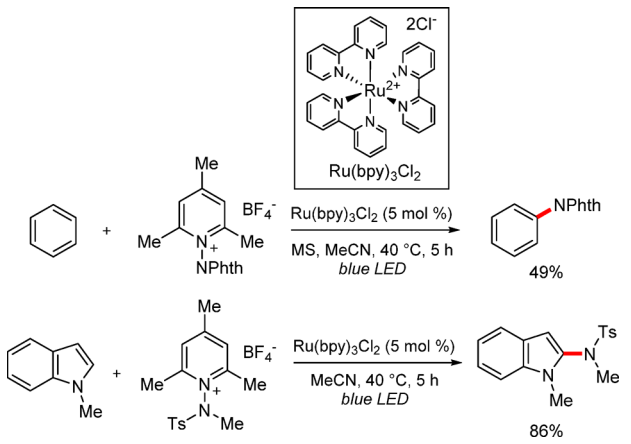
react with (hetero)arenes under a ruthenium photocatalyst system (Scheme 141).[432] Notably, *N*-aminopyridinium salts can

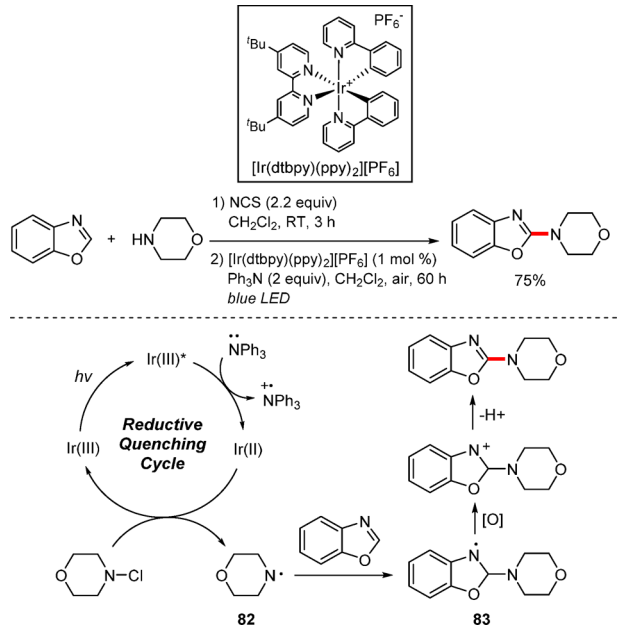
Scheme 141



readily be prepared from the corresponding pyrylium salts and hydrazine derivatives on a gram scale. A broad range of electron-rich (hetero)arenes were efficiently amidated with high regioselectivity, while electron-deficient substrates were rather sluggish.

Xue reported a synthetic route to prepare 2-amino-benzoxazoles under photoredox catalysis by directly utilizing secondary amines (Scheme 142).[433] Nonfunctionalized amines

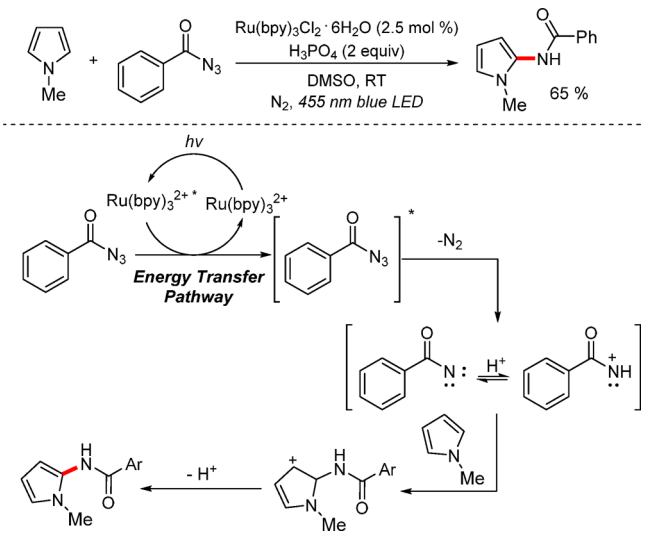
Scheme 142



were converted to their chloroamines in situ by reacting with stoichiometric amounts of *N*-chlorosuccinimide (NCS). In addition to morpholines, additional types of cyclic and acyclic secondary amines were successfully applied under this iridium photocatalyst system. In contrast to the previously reported analogous works,[429−432] a reductive quenching cycle was assumed to operate during the catalytic cycle: the excited Ir(III)* species is reductively quenched by triphenylamine to form an Ir(II) complex and triphenylammonium radical cation. This resultant Ir(II) species is capable of reducing the N−Cl bonds of amino group sources to generate a nitrogen-centered radical **82** that will be added to the benzoxazole substrate giving rise to a *N*-radical intermediate **83**. Finally, a tandem process consisting of single electron oxidation and deprotonation provides the desired aminated products.

In 2015, König and co-workers reported a C−H amination of heteroarene using benzoyl azide as the unique amino group source under the visible light ruthenium catalyst system in the presence of an acid additive (Scheme 143).[434] Interestingly, the

Scheme 143



reaction was proposed to proceed via an energy transfer pathway, wherein Ru species works as a triplet sensitizer for benzoyl azides upon the visible light irradiation. The energy transfer from an excited Ru(II)* species to benzoyl azides causes the loss of N_2 molecule to yield benzoyl nitrene, which is assumed to be protonated by the acid additive. Subsequently, the protonated nitrene species will react with electron-rich heteroarenes to give the corresponding aminated products.

6. CONCLUSION AND FUTURE OUTLOOKS

Metal-catalyzed direct C−H amination of hydrocarbons has become an important synthetic tool enabling the direct introduction of amino functional groups at the desired position of the substrates to produce nitrogen-containing molecules. In particular, late transition metal catalysts display notable performances in the amination reactions, giving rise to high reactivity as well as excellent selectivity over a broad range of substrates. Elucidation of mechanistic details shed light on the direction to design new catalyst systems to reinforce the above desirable features. Numerous examples of metal-catalyzed C−H amination reactions indicate that the critical steps determining the reaction efficiency and selectivity are closely related to both C−H bond cleavage and C−N bond formation. Interactions between metal centers and amino group sources are also crucial in certain mechanistic scaffolds. An additional research focus in the direct C−H amination is the development of the earth-abundant first-row metal catalysis by uncovering the relevance of the metal's spin state to the efficiency in the nitrenoid transfer process. Applications of more versatile amino group sources that are convenient and environmentally friendly are also important, especially from a practical point of view. While

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preactivated amino precursors are frequently utilized in the C−H amidation at present, the direct use of amines in reaction with hydrocarbons is more desirable if the corresponding dehydrogenative coupling conditions can remain mild. In this case, the use of environmentally benign external oxidants is another critical aspect that determines the overall efficiency of the C−H amination. It is envisioned that the scope of substrates in the direct C−H amination can be expanded to include not only simple hydrocarbons but also complex molecules enabling the late-stage introduction of amino functionality even in the presence of labile functional groups. Although several issues remain in making this method more practical and generally applicable to synthetic chemistry, remarkable advances accomplished in recent years will stimulate further developments, eventually making this approach one of the most valuable C−H functionalization technologies in the near future.

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ABBREVIATIONS

1,2-DCE	1,2-dichloroethane
1,1,2,2-TCE	1,1,2,2-tetrachloroethane
1,10-phen	1,10-phenanthroline
acac	acetylacetonate
Ad	adamantyl
azir	aziridination
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2′-bipyridine
BQ	1,4-benzoquinone
Bs	benzenesulfonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
Cp^E	1,3-bis(ethoxycarbonyl)-2,4,5-trimethylcyclopentadienyl
$Cp^*_{dichloroethane}$	pentamethylcyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclooctane
dba	dibenzylideneacetone
DCB	dichlorobenzene
Dfs	2,6-difluorophenyl
DFT	density functional theory
DG	directing group
DHQ	hydroquinone
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dtbpy	4,4′-di-*tert*-butyl-2,2′-bipyridyl
EPR	electron paramagnetic resonance
Fmoc	fluorenylmethyloxycarbonyl
$H_2F_{20}TPP$	*meso*-tetrakis(pentafluorophenyl) porphyrin
H_2TTP	*meso*-ditosylamido-2-furan
hfacac	hexafluoroacetylacetone
HFIP	hexafluoro-2-propanol
ins	insertion
KIE	kinetic isotope effect
LAH	lithium aluminum hydride
LG	leaving group
Mes	mesityl
MS	molecular sieve
Ms	methanesulfonyl
MW	microwave
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonamide
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorphorine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
PhBQ	phenyl-1,4-benzoquinone
PhthN	phthalimide anion
Piv	pivaloyl
PMP	*p*-methoxyphenyl
ppy	2-phenylpyridine
Py	pyridine
Pym	pyrimidyl
RT	room temperature
Tces	2,2,2-trichloroethoxysulfonyl
TBAI	tetrabutylammonium iodidie
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
Tc	thiophene-2-carboxylate
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf	triflyl, trifluoromethanesulfonyl
TFA	trifluoroacetyl
THF	tetrahydran

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TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMTU	*N*,*N*,*N*′,*N*′-tetramethylthiourea
Tol	4-methylphenyl
TON	turnover number
Tp	trispyrazolylborate
Ts	tosyl, *p*-toluenesulfonyl
XRD	X-ray diffraction

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