# Transition-Metal-Catalyzed C−N Bond Forming Reactions Using Organic Azides as the Nitrogen Source: A Journey for the Mild and Versatile C−H Amination

Kwangmin Shin,[†,‡] Hyunwoo Kim,[†,‡] and Sukbok Chang*[‡,†]

[†]Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-338, Republic of Korea
[‡]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-338, Republic of Korea
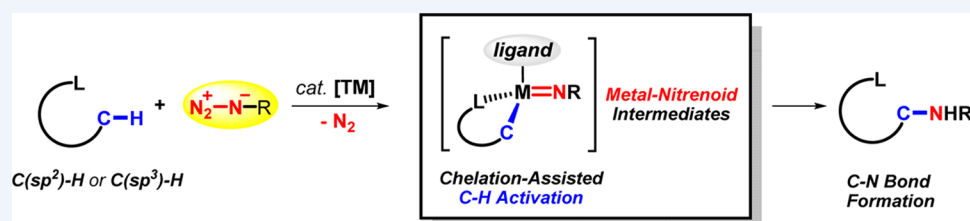
CONSPECTUS: Owing to the prevalence of nitrogen-containing compounds in functional materials, natural products and important pharmaceutical agents, chemists have actively searched for the development of efficient and selective methodologies allowing for the facile construction of carbon−nitrogen bonds. While metal-catalyzed C−N cross-coupling reactions have been established as one of the most general protocols for C−N bond formation, these methods require starting materials equipped with functional groups such as (hetero)aryl halides or their equivalents, thus generating stoichiometric amounts of halide salts as byproducts. To address this aspect, a transition-metal-catalyzed direct C−H amination approach has emerged as a step- and atom-economical alternative to the conventional C−N cross-coupling reactions. However, despite the significant recent advances in metal-mediated direct C−H amination reactions, most available procedures need harsh conditions requiring stoichiometric external oxidants. In this context, we were curious to see whether a transition-metal-catalyzed mild C−H amination protocol could be achieved using organic azides as the amino source. We envisaged that a dual role of organic azides as an environmentally benign amino source and also as an internal oxidant via N−N$_2$ bond cleavage would be key to develop efficient C−H amination reactions employing azides. An additional advantage of this approach was anticipated: that a sole byproduct is molecular nitrogen (N$_2$) under the perspective catalytic conditions.

This Account mainly describes our research efforts on the development of rhodium- and iridium-catalyzed direct C−H amination reactions with organic azides. Under our initially optimized Rh(III)-catalyzed amination conditions, not only sulfonyl azides but also aryl- and alkyl azides could be utilized as facile amino sources in reaction with various types of C(sp^2)−H bonds bearing such directing groups as pyridine, amide, or ketoxime. More recently, a new catalyst system using Ir(III) species was developed for the direct C−H amidation of arenes and alkenes with acyl azides under exceptionally mild conditions. As a natural extension, amidation of primary C(sp^3)−H bonds could also be realized on the basis of the superior activity of the Cp*Ir(III) catalyst. Mechanistic investigations revealed that a catalytic cycle is operated mainly in three stages: (i) chelation-assisted metallacycle formation via C−H bond cleavage; (ii) C−N bond formation through the in situ generation of a metal−nitrenoid intermediate followed by the insertion of an imido moiety to the metal carbon bond; (iii) product release via protodemetalation with the concomitant catalyst regeneration. In addition, this Account also summarizes the recent advances in the ruthenium- and cobalt-catalyzed amination reactions using organic azides, developed by our own and other groups. Comparative studies on the relative performance of those catalytic systems are briefly described.

1. INTRODUCTION

1.1. Metal-Catalyzed C−N Bond-Forming Reactions

The development of methods for introducing nitrogen functionality into organic frameworks has been one of the major research topics in synthetic chemistry owing to the ubiquity of amino compounds in natural products, synthetic intermediates, and pharmaceutical agents.[1] While traditional approaches to construct carbon−nitrogen bonds often require several steps, metal-mediated C−N bond formation has opened a new avenue in regard to efficiency and applicability (Scheme 1).[2] Aside from the seminal reports on the Cu-mediated C−N cross-coupling of aryl halides with amines by Ullmann and Goldberg,[2a] Buchwald and Hartwig[2b,c] independently developed palladium-catalyzed amination procedures with the help of suitable ligands. This method has been significantly advanced during the past decades and is now considered one of the most reliable synthetic routes to C−N bond construction (Scheme 1a).
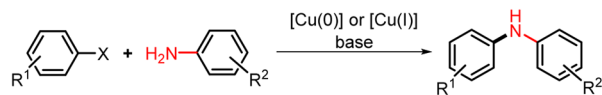
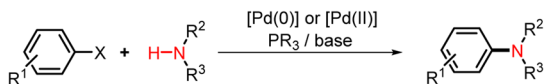**Scheme 1. Metal-Mediated C−N Bond Forming Reactions**

a) C-N Cross-Coupling Reactions

- Ullmann & Goldberg coupling (1903 &1906)
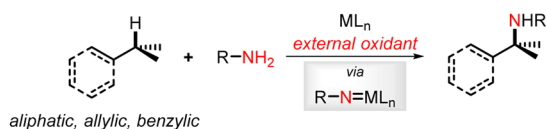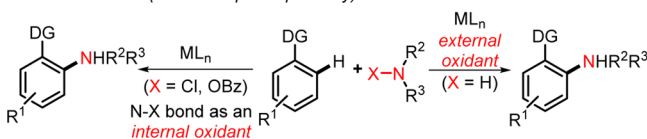

- Buchwald & Hartwig coupling (1995)

b) C-H Amination: Outer-sphere or Inner-sphere

- **C-H Insertion** (via outer-sphere pathway)


aliphatic, allylic, benzylic

- **C-H Activation** (via inner-sphere pathway)

Despite the notable features of the metal-catalyzed C−N cross-coupling reactions, this approach requires prefunctionalized starting materials such as aryl halides or their pseudohalides to react with amino sources. In this context, direct C−H amination methods have emerged as step- and atom-economical alternatives.[3] This method can be categorized to be outer or inner sphere pathways according to the method of forming C−N bonds. In the former approach, the C−N bond is produced via nitrene transfer from an initially generated metallonitrenoid to the targeted C−H bonds.[4] While this strategy has been successfully applied to the C(sp[3])−H amination, reactions at the C(sp[2])−H bonds, especially in the intermolecular version, are less explored.[5] On the other hand, the inner-sphere C−H amination proceeds via metal-catalyzed C−H activation of chelation-group-containing substrates initially leading to metallacyclic intermediates that react with aminating reagents to form a C−N bond.[6] This strategy is effective not only for C(sp[3])−H amination but also C(sp[2])−H reactions, thus offering complementary procedures for the "C−H insertion" approach. It needs to be addressed that the latter type of amination (inner-sphere pathway) employs either external[7] or internal oxidants[8] to facilitate the desired reaction, thus generating stoichiometric byproducts in most cases (Scheme 1b).
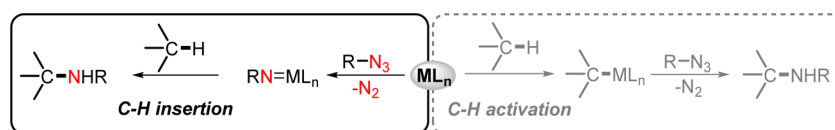
1.2. Organic Azides in C−H Amination Reactions

Since the first use, organic azides have been recognized as an efficient and convenient amino source in various types of C−N bond-forming reactions.[9] In fact, azides have such notable features as follows: (i) they are easy to prepare, (ii) a sole byproduct in the C−N bond-forming reactions and nitrogen transfer processes is molecular nitrogen (N_2), and (iii) the N−N_2 bond in azides may work as an internal oxidant to generate *in situ* high-valent metal species, thus frequently not requiring external oxidants to reoxidize metal catalysts. However, despite these unique aspects of organic azides as an amino source, they have not been widely utilized in direct C−H amination reactions. Although some examples of C−H insertion reactions employing azides were reported,[10] applications in the inner-sphere C−H amination reactions have been less explored (Scheme 2).

These considerations led us to investigate the possibility of using organic azides as an efficient nitrogen source in the transition-metal-catalyzed amination of chelation-group-containing substrates. At the beginning, we were hopeful to take advantage of the above-described features in our approach, thereby developing an environmentally friendly protocol that can be applied to a wide range of substrates in the absence of external oxidants to generate N_2 byproduct. We initially hypothesized that a plausible mechanistic pathway of this amination would involve three main steps: (i) cyclometalation via C−H activation, (ii) formation of metal nitrenoid species followed by insertion of nitrenoid moiety to cyclometalates,[11] and (iii) protodemetalation to release product with the regeneration of active catalyst (Scheme 3).

2. Rh(III)-CATALYZED C−H AMINATION USING ORGANIC AZIDES

In order to verify our working hypothesis, we first examined chelation-assisted regioselective C−H amidation of arenes by using metal catalysts that were known to mediate the *C−H insertion pathway*. A series of dirhodium species were chosen as catalysts for the desired transformation owing to their success in various types of C−N bond formation via outer-sphere pathway.[12] In a reaction of 2-phenylpyridine with *p*-toluenesulfonyl azide, we observed that some dimeric rhodium-(II) species indeed catalyzed the regioselective C(sp[2])−H amidation. However, the efficiency of the Rh(II)-catalyzed amidation was found to be rather low to afford only unsatisfactory product yields (Scheme 4a).

This result led us to turn our attention to the mechanistic alternative of the inner-sphere pathway. Inspired by the precedent studies that a Cp*Rh(III) catalyst system facilitates a wide range of C−H bond functionalizations,[13] we examined catalytic activity of $[RhCp*Cl_2]_2$ in a chelation-assisted C−H amidation approach. To our delight, screening of reaction conditions revealed that amidation of 2-phenylpyridine with tosyl azide was catalyzed highly efficiently by a cationic Cp*Rh(III) species generated *in situ* by treating $[RhCp*Cl_2]_2$ with a silver additive.[14a] Among various silver salts screened,

Scheme 2. Organic Azides in Metal-Catalyzed C−N Bond Formation

Scheme 3. Our Working Hypothesis

*chelation-assisted
C-H Activation*   *formation of metal-imido intermediate
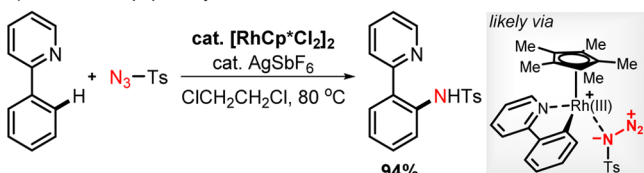   & nitrene insertion*

Scheme 4. C−H Amination Using Rh(II) or Rh(III) Catalysts

a) **Rh(II)** catalyst: amidation via **C-H insertion**
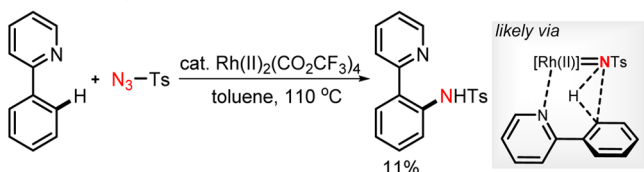
b) Cationic **Rh(III)** catalyst: amidation via **C-H activation**


AgSbF$_6$ was found to be most effective (Scheme 4b). Under the optimized conditions, 2-phenylpyridines substituted with various functional groups underwent the desired amidation smoothly with a range of sulfonyl azides in good yields, thus demonstrating the generality and high functional group tolerance of this procedure. In addition, substrates bearing directing groups other than 2-pyridine were also facile for this C−N bond-forming reaction (Scheme 5). The C−H amidation of arenes with sulfonyl azides could be performed in a multigram scale without difficulty.[14b] However, safety precautions should especially be taken when organic azides of small molecular weight $[(N_C + N_O)/N_N \leq 3]$ are reacted.[9]

After the initial discovery of the Rh-catalyzed C−H amidation of arenes using sulfonyl azides, it remained to be determined whether this reaction could be extended to additional types of azides with electronic or steric variation. In fact, the majority of organic azides utilized in the metal-catalyzed C−H amination were known to have electron-withdrawing properties, presumably because of facilitating the formation of a nitrene intermediate, and as a result, the use of electron-neutral or -donating organic azides in C−H amination is more challenging. In this line, we were pleased to observe

that aryl azides readily participated in the amination of benzamides and aryl ketoximes to yield the desired aminated products in moderate to good yields (Scheme 6).[15] It was also notable that aryl azides bearing electron-neutral or -donating groups underwent the amination in high efficiency.
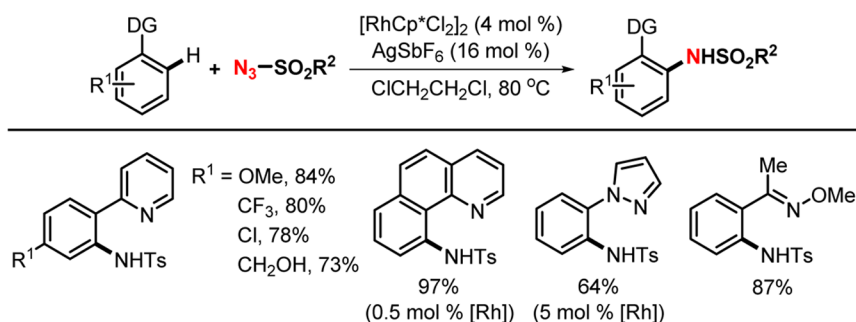
**Scheme 6. Scope of Rh-Catalyzed Amination Using Aryl Azides**
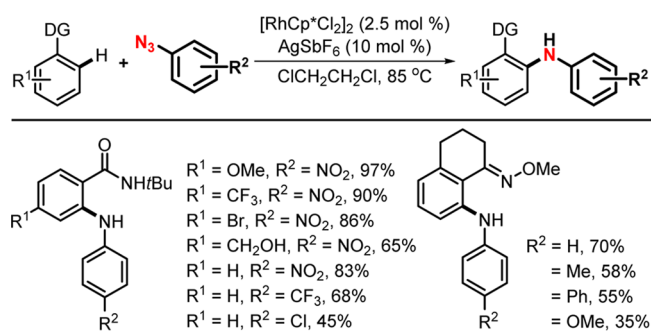
Subsequent investigations on the Rh-catalyzed C−H amination revealed that the scope of amino sources could further be extended to alkyl azides (Scheme 7).[16] Alkyl azides were used in a number of C−N bond-forming reactions such as aza-Wittig reaction, azide−alkyne cycloaddition ("click chemistry"), Schmidt rearrangement, and Staudinger ligation.[9] In this aspect, our result was significant especially considering the fact that the utilization of alkyl azides in metal-catalyzed C−H amination had rarely been reported.[10] Benzamides, aryl ketones, and ketoximes were readily reacted with benzyl azides to afford the alkyl-aminated products. Moreover, simple alkyl or functionalized aliphatic azides could also be applied successfully.

To understand the mechanistic details of the Rh-catalyzed C−H amination reaction with organic azides, we conducted a series of experiments using 2-phenylpyridine and tosyl azide as a model substrate and amino source, respectively.[17] Treatment of a pregenerated rhodacycle, **1**, with tosyl azide in the presence of a stoichiometric amount of a silver additive allowed us to

Scheme 5. Scope of Rh-Catalyzed Amidation Using Sulfonyl Azides

Scheme 7. Scope of Rh-Catalyzed Amination Using Alkyl Azides


$[Ar = 3,5-(CF_3)_2C_6H_3]$
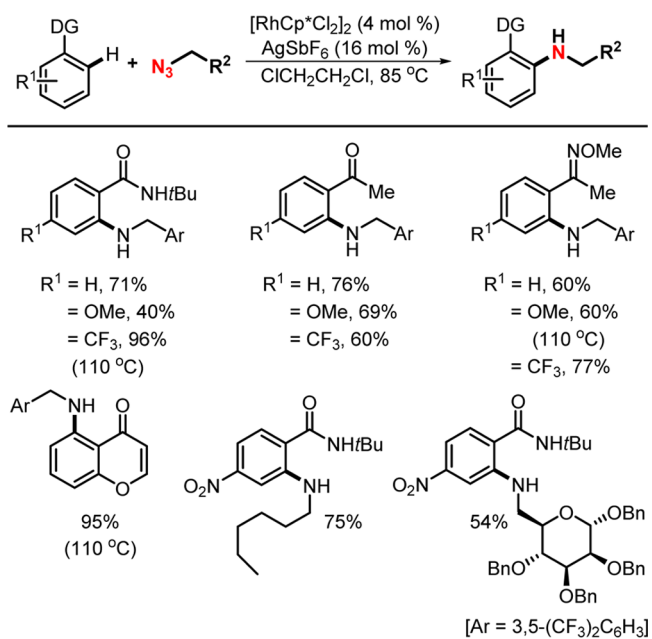
capture the corresponding rhodium-amido complex **7**, which is one of the key intermediates in the catalytic cycle (Scheme 8). It was revealed that the substrate works also as a proton source to facilitate the protodemetalation of rhodacyclic intermediate **7**, thus releasing amidated product. Kinetic studies showed that the amidation was first order on rhodacycle catalyst **3** and azide reactant each, while the reaction gave an inverse order on 2-phenylpyridine. Based on the kinetic data, a simplified catalytic pathway was proposed as shown in Scheme 8. Dissociation of 2-phenylpyridine from rhodacycle **3** (resting species) leaves one vacant site in the metal center (rhodacycle **2**), presumably in a reversible manner. Azide then interacts with the cationic rhodium complex **2** to form an azide-coordinated rhodacycle **4**, which would undergo subsequent C−N bond formation to afford the corresponding rhodium-amido complex **7**.

The key C−N bond-forming step was envisioned to proceed via either a concerted insertion or a stepwise pathway involving a discrete metal nitrenoid intermediate. Although more

comprehensive mechanistic studies are required to distinguish one from the other route, one clue was obtained by a stoichiometric reaction of rhodacycle **1** with a series of tosylamido precursors, which are known to readily generate metal nitrenoids. It was observed that the complex **1** underwent the amidation smoothly with these amido precursors to validate the stepwise nitrenoid pathway (Scheme 9). In addition,

Scheme 9. Stoichiometric Amidation Reactions with Various Nitrene Precursors
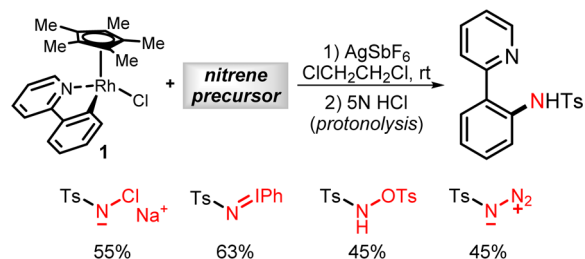
density functional theory (DFT) studies revealed that the activation energy of the stepwise nitrenoid pathway is more feasible than that of the concerted amido insertion route. These results led us to propose the intermediacy of a high-valent rhodium(V)-imido species in the Rh-catalyzed amidation.[18,19] A plausible catalytic cycle based on the experimental and computational studies is depicted in Scheme 10. Although the above mechanistic considerations describe the amidation with sulfonyl azides, we assume at the present stage that a similar pathway is also operative with aryl and alkyl azides.

The Rh catalyst system works efficiently especially when arene substrates bear nitrogen directing groups such as pyridine or ketoxime, whereas weak coordinating groups are less effective. The scope of azides was relatively broad to include sulfonyl, aryl, and alkyl azides, whereas acyl azides were not reactive with the Rh catalyst. While mechanistic details were fully investigated, the intermediacy of the proposed high-valent Rh(V)-imido species needs to be evidenced by spectroscopic tools.

Scheme 8. Simplified Reaction Pathway Based on Kinetic Studies

$$rate = k_{obs}[\mathbf{3}][TsN_3][\text{2-PhePy}]^{-1}$$
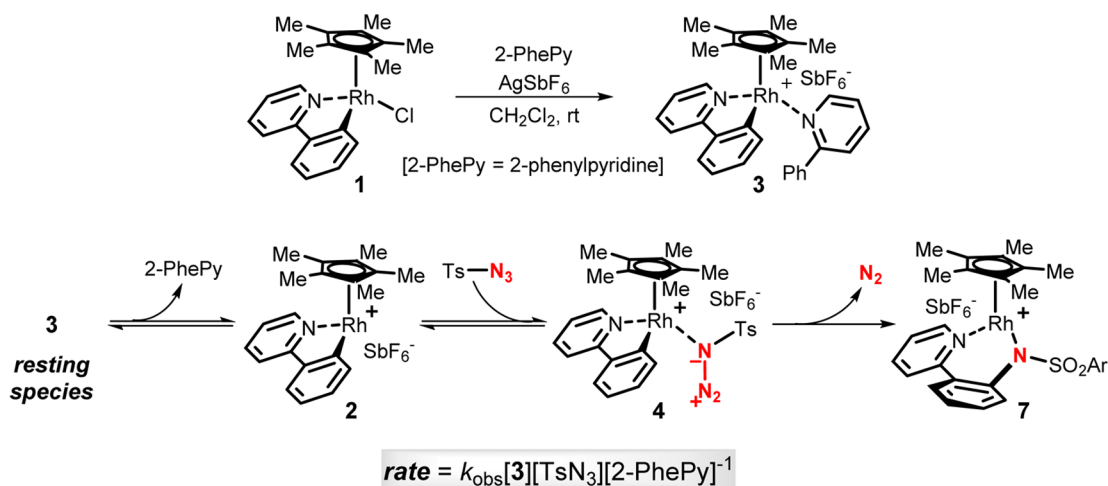
**Scheme 10. Mechanistic Proposal of Rh-Catalyzed C−H Amidation**
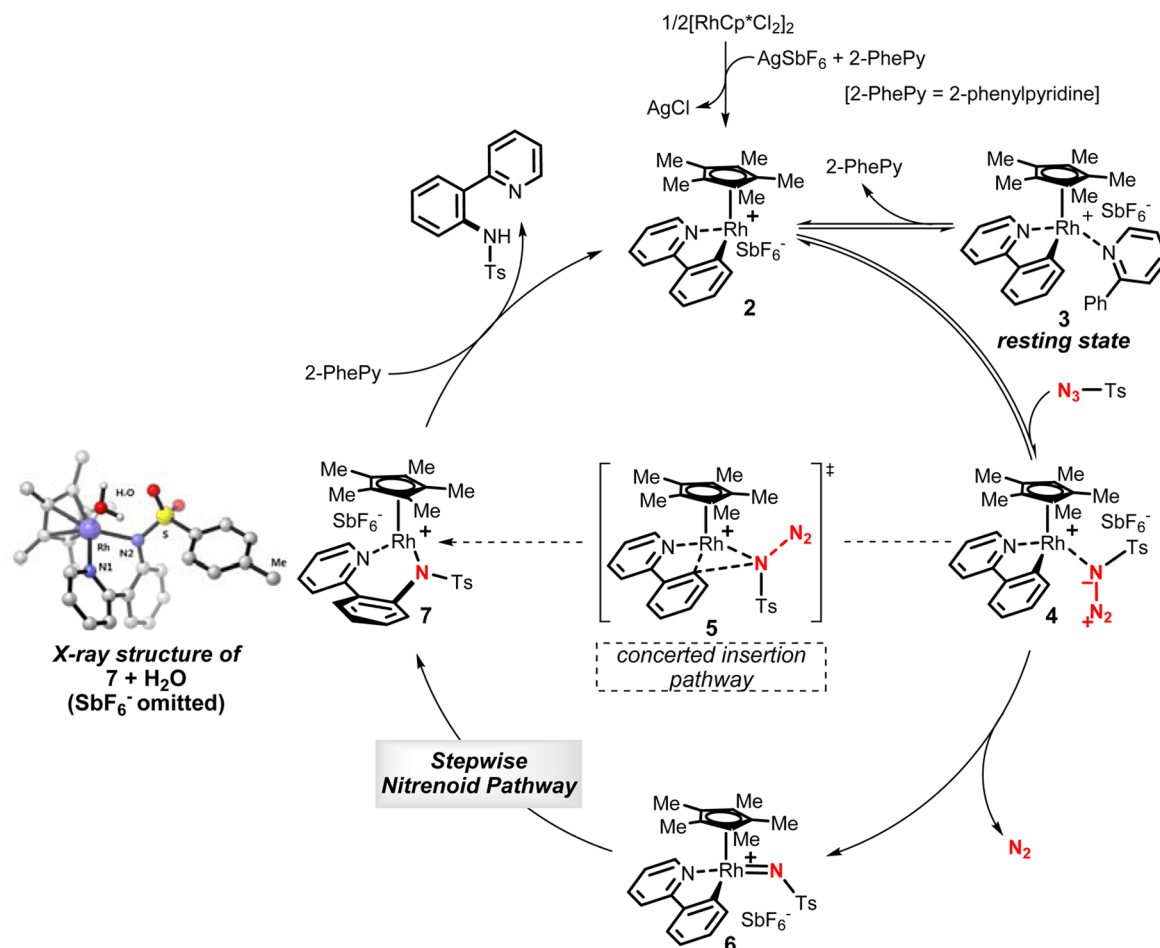
3. Ir(III)-CATALYZED C−H AMINATION USING ORGANIC AZIDES

After developing the Rh-catalyzed direct C−H amination of arenes with organic azides, we were curious to see whether a similar reaction could also be catalyzed by iridium, a group 9 congener in the periodic table. This perspective was based on the fact that iridium has stood out to display high performance toward C−H bond cleavage.[20] Indeed, it was known that iridium complexes react with a broad range of chelation-group-containing compounds to form iridacycles via C−H bond activation.[21] In particular, half-sandwich Cp*Ir(III)-metalacycles have attracted special attention owing to their excellent catalytic activity in a range of important organic transformations such as hydroamination, hydrogen transfer, oxidation, and reductive amination.[22] However, due to the high stability of the half-sandwich iridacyclic species, the installation of functional groups into the organic moiety (C−H functionalizations) has been difficult to achieve in most cases (Scheme 11).

Nevertheless, we envisioned that it would be plausible to develop Cp*Ir(III)-catalyzed C−H amination reactions using organic azides because a catalyst precursor, [IrCp*Cl₂]₂, is structurally and electronically similar to [RhCp*Cl₂]₂. In fact, a stoichiometric conversion of iridacycle 8 to an amido inserted complex 10 was previously reported using tosyl azide or PhINTs as the amido source in high yield at room temperature, and this transformation was proposed to proceed via a nitrenoid intermediate 9 (Scheme 12).[23]

**Scheme 11. Cyclometalated Cp*Ir(III) Complexes: Generation and Utilities**
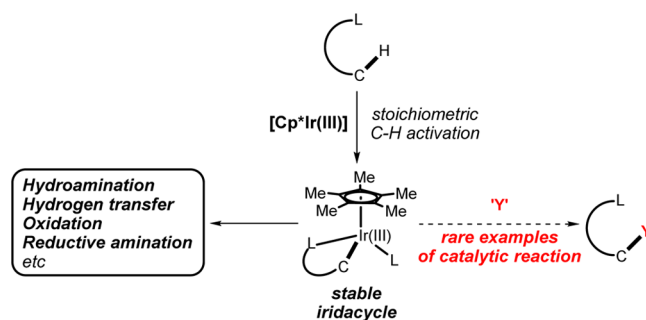
With this background, we examined the feasibility of Cp*Ir(III) species to catalyze the desired C−H amination using organic azides.[24] When [IrCp*Cl₂]₂ was employed as a catalyst in the presence of AgNTf₂ additive, catalytic amidation of arenes with acyl azides took place under very mild conditions.[25] Substrates with assorted directing groups such as benzamides, anilides, ketones, hydrazones, or amino esters were readily reacted with acyl azides bearing various functional groups to afford the desired amidated products in good to excellent yields (Scheme 13).

The Ir-based amidation procedure was successfully applied to the amidation of olefinic $C(sp^2)$−H bonds. For instance, acrylamides were reacted under the optimized conditions to afford (Z)-enamides with excellent regio- and stereoselectivity.

**Scheme 12. Stoichiometric Conversion of Iridacycle 8 with Nitrene Precursors**
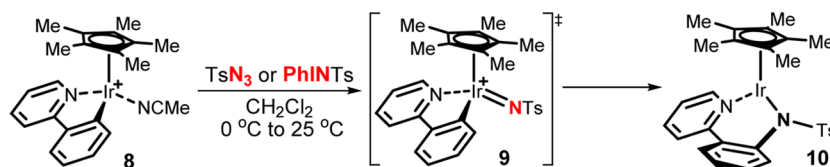
Scheme 13. Scope of Ir-Catalyzed Amidation Using Acyl Azides
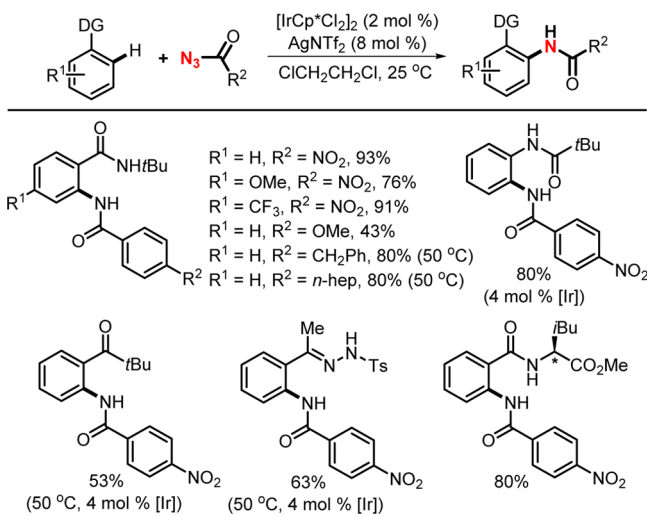
It should be noted that only Cp*Ir(III) species displayed significant performance toward direct C−H amidation of alkenes whereas Rh and Ru catalyst systems were ineffective (Scheme 14).[26] While this notable catalytic activity of Cp*Ir for

Scheme 14. Direct C−H Amidation of Alkenes: Catalyst Comparison
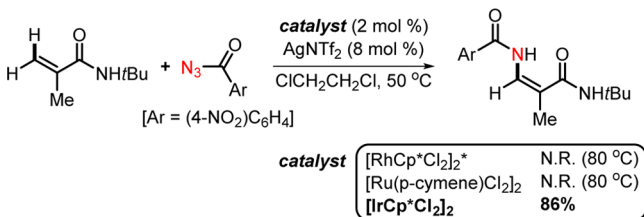
the olefinic C−H amidation is not fully understood at the present stage, when compared with other catalytic systems, it can be attributed to the high efficiency in the imido transfer process by iridium species.

Representative scope of the Ir-catalyzed amidation of olefinic substrates is presented in Scheme 15 to show that functionalized acrylamides as well as methacrylamides were highly facile leading to the corresponding enamide products. Variation on the N-alkyl moiety of secondary amides was found to be highly flexible, thus demonstrating excellent functional group tolerance.

Based on the superior performance of Cp*Ir(III) catalyst for the chelation-assisted C−H amidation, we examined more challenging substrates bearing weak directing groups. When ethyl benzoate was examined, the choice of additives turned out to be crucial for achieving high efficiency, and the combined use

of acetic acid and lithium carbonate was most effective (Scheme 16).[27]

It was reasoned that these two additives of acetic acid and lithium carbonate generate lithium acetate and lithium carbonate in situ and that lithium ion promotes the dissociation of acetate ligand from the iridium center, thus enabling more facile coordination of the weak directing group of ester to iridium. In addition, it was also postulated that the acetate ion works as a soluble basic species to mediate the base-assisted cyclometalation step, while the carbonate ion serves as an insoluble proton abstractor to drive the amidation reaction forward by making the C−H cleavage step irreversible.[28] A broad range of esters including bicyclic and olefinic C−H bonds was successfully amidated in good yields. Notably, acetophenone also underwent the amidation reaction to afford the desired products in excellent yields even at room temperature (Scheme 17).

The successful development of Ir-catalyzed amidation of weakly coordinating esters prompted us to investigate the synthesis of 8-aminoquinolines starting from quinoline N-oxides by utilizing N-oxide as a chelating group to guide the C(8)−H activation.[29] Optimization studies revealed that the desired C-8 amidation became facile in the presence of acid additives (Scheme 18).

A broad range of functionalized quinoline N-oxides smoothly underwent the C−N bond formation to afford C8-amidated products in satisfactory yields (Scheme 19). Interestingly, acridine N-oxide was reacted giving rise to a monoamidated product in reasonable yield. The reaction was highly regioselective at the C-8 position of quinoline N-oxides even in the presence of a potentially reactive phenyl group at the C-2 position. In addition, benzo[c]cinnoline monoxide was amidated exclusively at a C−H bond neighboring the N-oxide group.
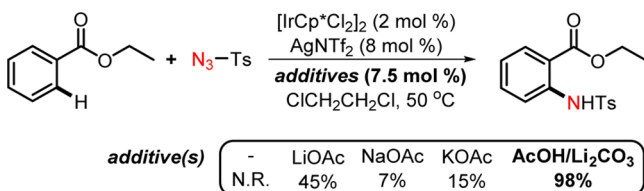
To rationalize the significant additive effects of carboxylic acids in the C−H amidation of quinoline N-oxides, mechanistic studies were conducted to delineate the mode of catalyst as well as the role of the acid additive. A small value of kinetic isotope effects ($k_H/k_D = 1.23$) indicated that the C−H bond cleavage may not be involved in the rate-determining step. The observation that the reaction was sensitive to the acidity of additives and that the initial rate of this amidation was first order in acid concentration led us to propose that the acid additive facilitates the final protodemetalation step,[30] which was postulated to be rate-determining (Scheme 20).

Along with this mechanistic understanding of the acid additives, we investigated a diastereoselective C−H amidation of diarylphosphoryl compounds bearing a chiral auxiliary (Scheme 21).[31] It was found that a C_2-symmetric chiral pyrrolidine moiety stood out to be the most effective chiral auxiliary to generate the P-stereogenic center up to 90% de. DFT calculations suggested that phenyl groups on the chiral pyrrolidine auxiliary may play a key role in the stereo-differentiation, presumably due to the different degree of $\pi-\pi$

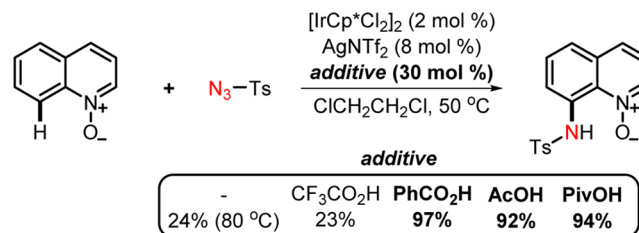**Scheme 15. Scope of Ir-Catalyzed Amidation of Olefinic Substrates**
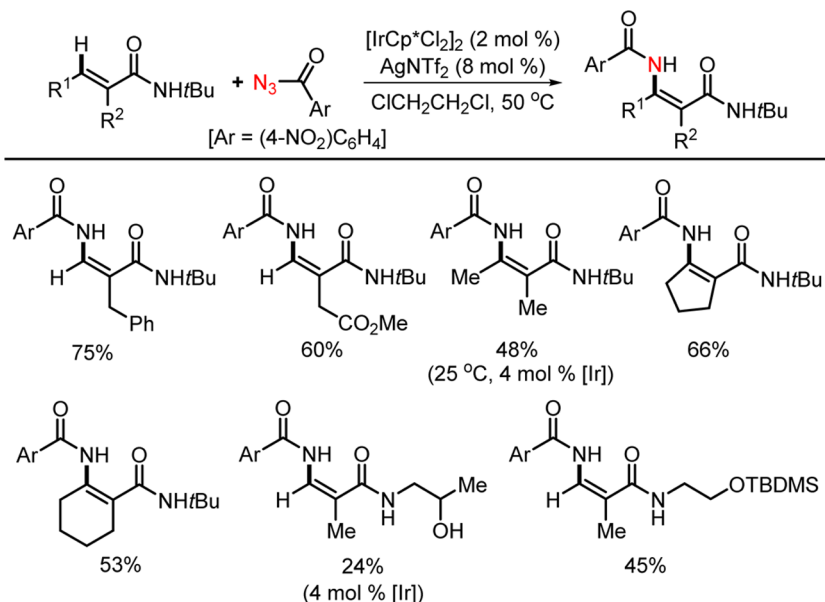
Scheme 16. Additive Effects in Ir-Catalyzed Amidation of Ethyl Benzoate

additive(s)	-	LiOAc	NaOAc	KOAc	**AcOH/Li₂CO₃**
	N.R.	45%	7%	15%	**98%**

Scheme 18. Additive Effects in Ir-Catalyzed Amidation of Quinoline N-Oxide

	-	CF₃CO₂H	**PhCO₂H**	AcOH	PivOH
additive	24% (80 °C)	23%	**97%**	92%	94%

interactions between two aryls bonded to the P atom and two phenyl substituents on the pyrrolidine auxiliary.[32]

One of the most notable features observed in the Ir-catalyzed C−H amidation was that this system could be applied to methyl C(sp³)−H bonds of ketoxime substrates in reaction with sulfonyl or acyl azides under mild conditions.[33] While the efficiency of this amidation was keenly dependent on the choice of additives, AgOAc proved to be most effective (Scheme 22). Variation in the O-alkyl moiety of ketoxime substrates little influenced the reaction efficiency, and the presence of potentially reactive olefinic double bonds did not deteriorate the selectivity. It was noteworthy that the amidation occurred exclusively at the methyl C(sp³)−H bond without reacting at the methylene C(sp³)−H bonds. Attractive features of this

amidation such as broad substrate scope and mild conditions led us to utilize it as a powerful tool for the late-stage functionalization of natural products or complex synthetic compounds (Scheme 23).

The high performance of the [Cp*IrCl₂]₂ catalyst in the C−N bond-forming reactions was also demonstrated in searching for additional organic azide reactants. In fact, phosphoryl azides were successfully employed as an efficient amino source to produce biologically interesting phosphoramidate compounds (Scheme 24).[34] A combination of *in situ* generated cationic iridium species with acetate additive facilitated the desired phosphoramidation in satisfactory yields. Interestingly, not only
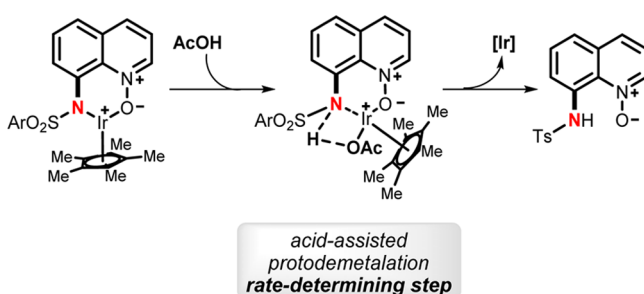
Scheme 17. Scope of Ir-Catalyzed Amidation of Ester and Ketone Derivatives
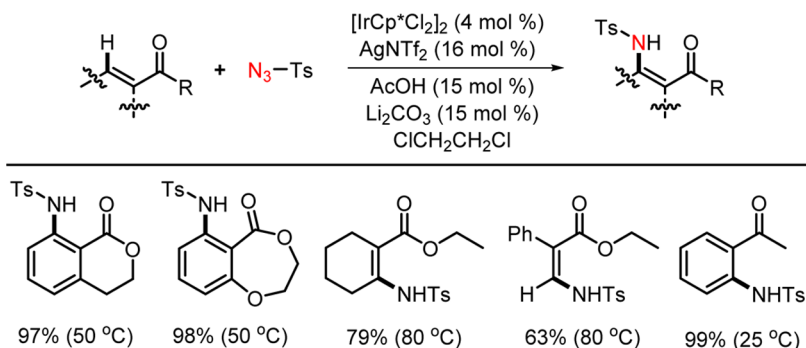
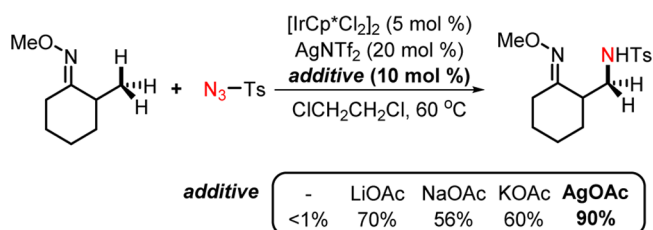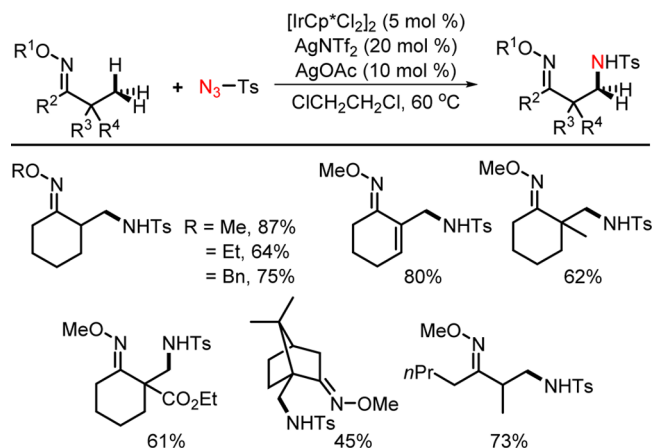**Scheme 19. Scope of Ir-Catalyzed Amidation of Quinoline N-Oxides**

R = Cl, 72%
OSi(iPr)₃, 86%

73%

71%

66%
(80 °C)
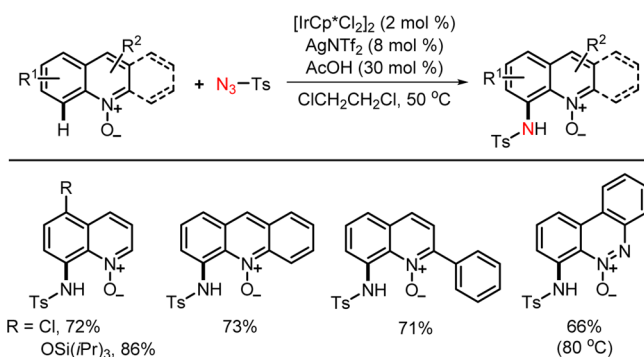
Scheme 20. Product Release in Ir-Catalyzed Amidation of Quinoline N-Oxides

acid-assisted protodemetalation
rate-determining step

C(sp²)−H but also benzylic C(sp³)−H bonds were efficiently amidated by employing this amidation procedure.

The observed individual performance of rhodium and iridium catalysts in the C−H amination with organic azides motivated us to compare these catalytic systems.[35] A series of amination reactions of N-tert-butylbenzamide with several types of azides was analyzed using Cp*Rh(III) and Cp*Ir(III) catalysts. In general, the iridium catalyst displayed much higher performance toward sulfonyl, aryl, and acyl azides, while rhodium catalyzed amination exhibited superior efficiency with alkyl azides. (Scheme 25).

Computational comparison between the Rh- and Ir-based amination reactions disclosed that the generation of a plausible metal nitrenoid intermediate **14** is more facile with Cp*Ir(III) than with the rhodium system (Scheme 26). This difference in catalytic activity between the two systems was reasoned by the intrinsically strong relativistic effects of iridium.[36] In other words, the relativistic contraction of the 6s orbital in iridium

Scheme 22. Effects of Acetate Additives in Ir-Catalyzed C(sp³)−H Amidation

additive	-	LiOAc	NaOAc	KOAc	**AgOAc**
	<1%	70%	56%	60%	**90%**

Scheme 23. Scope of Ir-Catalyzed C(sp³)−H Amidation

R = Me, 87%
= Et, 64%
= Bn, 75%

80%

62%

61%

45%

73%

Late-stage functionalizations

88%

75%
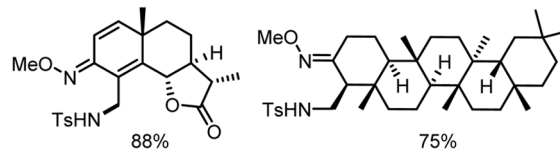
induces greater participation of p or d orbitals in metal−nitrenoid bonding, thus forming more stable metallonitrene species than the corresponding rhodium case. In this line, the inherent strong relativistic effects on iridium increase the electron density of the N atom in the metal−nitrogen bond of complex **16**, thereby reducing the energy required for the concerted metalation−deprotonation step in the catalytic cycle (steps from complex **16** to **19**, Scheme 26). These computational studies are in good agreement with the observed propensity that the Ir-catalyzed amination protocol displays much higher efficiency in most cases than the corresponding Rh-catalyzed system.

Scheme 21. C−H Amidation of Diarylphosphoryls: Diastereoselective C−H Amidation

62%, 48% *de* (55 °C)

87%, 84% *de*

92%, 90% *de*

93%, 90% *de*
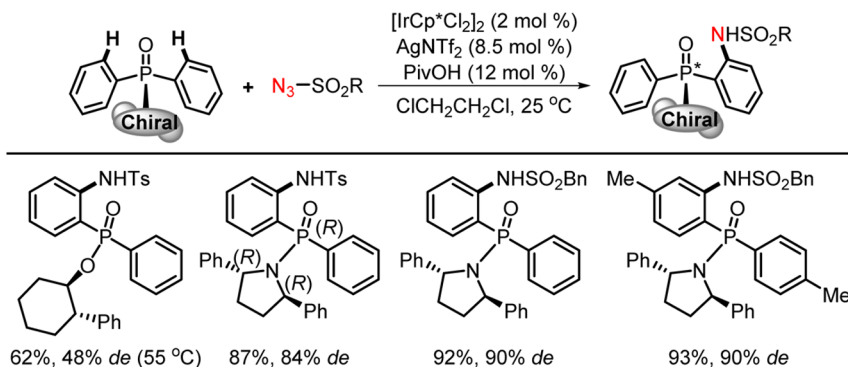
Scheme 24. Scope of Ir-Catalyzed C−H Amidation of Arenes with Phosphoryl Azides

4. DIRECT C−H AMINATION CATALYZED BY OTHER TRANSITION METALS

4.1. Ruthenium-Catalyzed C−H Amination Using Organic Azides

One of the major considerations in developing a practical synthetic method is the cost of reaction systems, as well as efficiency and selectivity. In this regard, although the devel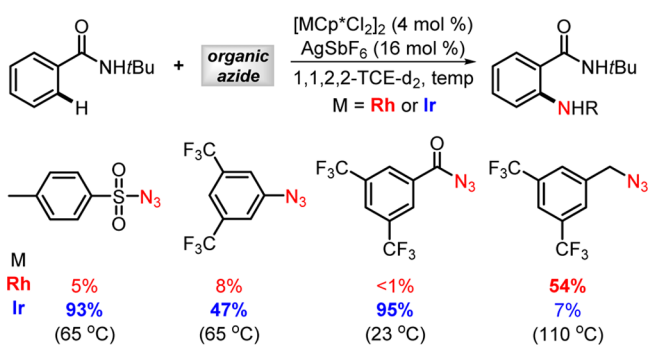oped Rh- and Ir-catalyzed C−H aminations using organic azides are highly efficient and applicable to various types of substrates, we were curious to find more economical alternatives to utilize a similar strategy.

We first examined the feasibility of a ruthenium system applicable to the C−H amination using organic azides. In fact, although the Ru-catalyzed C−H activation approach has been extensively studied, making it a powerful synthetic tool since the pioneering work of Murai and co-workers,[37] Ru-based C−H functionalizations are utilized mainly for C−C bond formation. In addition, while a few examples of Ru-catalyzed C−N bond-forming reactions are disclosed on the basis of the C−H insertion pathway,[38] intermolecular amination via an inner-sphere route was reported only recently by us and Sahoo's group independently (Scheme 27).[39a,b] Careful screen-
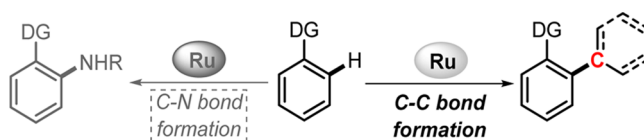
Scheme 25. Performance Comparison between Rh- and Ir-Catalyzed Amination

Scheme 27. Ru-Catalyzed C−H Functionalization

Whereas the Ir-catalyzed C−H amidation protocol operates efficiently over a broad range of substrates under milder conditions (25−50 °C), the amino source is rather limited to sulfonyl and acyl azides. Further extension of substrates (e.g., methylene sp³ C−H bonds) and amino sources (e.g., aryl and alkyl azides) will make this procedure more broadly applicable.

ing of reaction parameters revealed that [RuCl₂(p-cymene)]₂ catalyst exhibited excellent amination efficiency among a wide range of ruthenium species examined when a silver salt and NaOAc were added as additives (Scheme 28). Although the exact role of acetate additives is not fully elucidated yet, they may facilitate the C−H cleavage leading to a cyclometalate

Scheme 26. Comparative DFT Studies between Rh- and Ir-Catalyzed C−H Amination

Scheme 28. Scope of Ru-Catalyzed C–H Amidation Using Sulfonyl Azides

Scheme 30. Cobalt-Catalyzed Amidation of Indoles: Catalyst Optimization
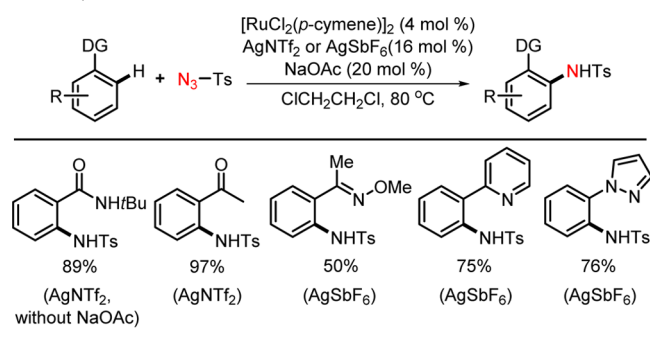
intermediate especially for substrates bearing weak directing groups.[40] Under the optimal conditions, substrates containing various directing groups such as amide, ketone, ketoxime, 2-pyridine, and pyrazole were readily reacted with sulfonyl azides to yield the desired amidated products in reasonable yields.

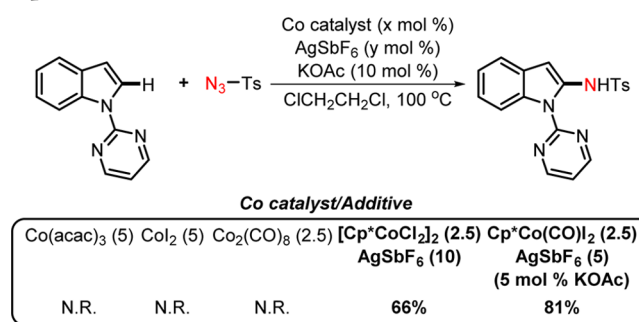To get mechanistic insights into this Ru-catalyzed amidation reaction, a series of experiments were conducted. For example, KIE studies showed that the C–H cleavage is rate-limiting in the catalytic cycle. In addition, although we failed to obtain experimental evidence to support the "stepwise nitrenoid pathway", Liang and co-workers were able to observe an aziridinated product by adding slightly excess amounts of norbonylene under their Ru-catalyzed amidation conditions (Scheme 29),[41] indicative of forming a ruthenium-imido species.

Although a Ru-catalyzed C–N bond-forming protocol is anticipated to be advantageous to other Rh or Ir catalyst systems from the practical point of view, more comprehensive studies are required to expand the current narrow scope of substrates and amino sources that can work under more ambient conditions.

4.2. Cobalt-Catalyzed C–H Amination Using Organic Azides

The use of first row transition metals in catalytic transformations has been receiving much attention in recent years owing to their abundance and relatively low cost.[42] Among those metals known to mediate C–H bond activation, cobalt, a congener of rhodium and iridium in the same family of group 9, has been utilized as an efficient catalyst in the C–H functionalizations.[43] In this context, Kanai and co-workers recently reported the Co-catalyzed amidation of indoles using sulfonyl azides as an amino source.[44] It was shown that both [Cp*CoCl$_2$]$_2$ and Cp*Co(CO)I$_2$ were effective catalyst precursors in the presence of a silver salt and KOAc additive, indicating that *in situ* generation of a cationic Cp*Co(III) species seems to be crucial (Scheme 30). Under the optimized conditions (100 °C), indoles having a 2-pyrimidyl directing group underwent the Co-catalyzed amidation to afford amidated products in good yields (Scheme 31). The Co-

catalyzed C–N bond formation is still in its infancy mainly due to the lack of mechanistic understanding, especially with regard to the imido transfer process. However, this catalyst system is expected to have high potential as a practical procedure upon the reasonable expansion of substrate scope.

5. SUMMARY AND OUTLOOK

As we hypothesized at the beginning of this journey for developing a mild and versatile C–H amination protocol, the idea of using organic azides as the unique amino source in metal-catalyzed C–H amination via an inner-sphere pathway has been realized successfully. As a result, a series of transition-metal-catalyzed direct C–N bond-forming reactions have been developed that can be operative without using external oxidants to release N$_2$ gas as a single byproduct. While the rhodium-catalyzed amination system was facile with several types of organic azides such as sulfonyl, aryl, and alkyl derivatives, changing the catalyst from Cp*Rh(III) to Cp*Ir(III) species allowed us to exploit the superior performance for the direct amidation of not only aryl and alkenyl C(sp^2)–H bonds but also more challenging unactivated primary C(sp^3)–H bonds. In addition, ruthenium- and cobalt-catalyzed amidation procedures have also been developed, thus offering cost-effective alternatives although the scope and efficiency still need to be further improved. Detailed mechanistic investigations of the Rh, Ir, and Ru catalyst systems led us to propose that the C–N bond-forming reactions proceed via a stepwise pathway involving a metal–nitrenoid intermediate. Although a significant advance in this area has been made by us and other groups, several challenges still remain for the future research directions. For example, the current amination reactions rely on the chelation-assisted C–H activation strategy to secure the regioselectivity, thus requiring certain types of directing groups. In this regard, it would be synthetically more valuable to develop a direct C–H amination procedure even for compounds that do not bear those chelation groups.[45] Second, although ruthenium-,[39] cobalt-,[44] and copper-catalyzed amination reactions have been scrutinized,[46] the reactivity and generality of these systems are still inferior to the

Scheme 29. Mechanistic Probe on the Viability of Metal Nitrenoid Intermediate
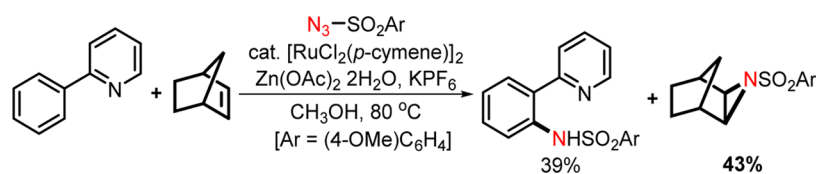
Scheme 31. Scope of Co-catalyzed Amidation of Indoles
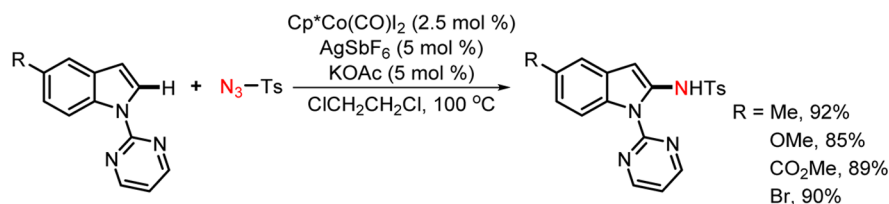
corresponding rhodium- or iridium-catalyzed protocols. Thus, the development of more versatile C−H amination reactions catalyzed by earth abundant first row transition metals is highly valuable. In addition, efforts should be made to understand more comprehensively mechanistic details of the direct amination reactions. In this context, physical evidence that supports the high-valent metal−nitrenoid intermediates would be most informative.

■ AUTHOR INFORMATION

Corresponding Author

*Sukbok Chang. Phone: +82-42-350-2841. Fax: +82-42-350-8180. E-mail: sbchang@kaist.ac.kr.

Author Contributions

The manuscript was written through equal contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

Notes

The authors declare no competing financial interest.

Biographies

Kwangmin Shin was born in Seoul, Republic of Korea, in 1990. He received his B.S. degree in Chemistry at KAIST in 2012. He is currently a Ph.D. candidate in Prof. Sukbok Chang's research group in KAIST. His research interests are focused on the development of new and practical transition-metal-catalyzed C−H bond functionalizations.

Hyunwoo Kim obtained his B.S. degree in Chemistry at KAIST in 2013. He is currently a Ph.D. candidate in Prof. Sukbok Chang's research group in KAIST. His research interests include the development of transition-metal-mediated organometallic reactions.

Sukbok Chang is Professor at the Institute for Basic Science (IBS) and Korea Advanced Institute of Science & Technology (KAIST). In 1996, he earned his Ph.D. degree in organic chemistry at Harvard University under the supervision of Professor Eric N. Jacobsen. After postdoctoral experience with Professor Robert H. Grubbs at Caltech, he joined Ewha Womans University (Seoul) as an assistant professor in 1998 and then moved to KAIST in 2002. Since 2012, he has been a director of the Center for Catalytic Hydrocarbon Functionalizations at IBS. His research interests are the development, understanding, and synthetic applications of transition metal catalysis.

■ REFERENCES

(1) (a) Hili, R.; Yudin, A. K. Making Carbon-Nitrogen Bonds in Biological and Chemical Synthesis. *Nat. Chem. Biol.* **2006**, *2*, 284−287. (b) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*, 1st ed.; Wiley-VCH: Weinheim, Germany, 2007.

(2) (a) Evano, G.; Blanchard, N.; Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **2008**, *108*, 3054−3131. (b) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (c) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361. (d) Bariwal, J.; Van der Eycken, E. C−N Bond Forming Cross-Coupling Reactions: An Overview. *Chem. Soc. Rev.* **2013**, *42*, 9283−9303.

(3) Collet, F.; Dodd, R. H.; Dauban, P. Catalytic C−H Amination: Recent Progress and Future Directions. *Chem. Commun.* **2009**, 5061−5074.

(4) Dequirez, G.; Pons, V.; Dauban, P. Nitrene Chemistry in Organic Synthesis: Still in Its Infancy? *Angew. Chem., Int. Ed.* **2012**, *51*, 7384−7395.

(5) (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. Intramolecular C−H Amination Reactions: Exploitation of the Rh$_2$(II)-Catalyzed Decomposition of Azidoacrylates. *J. Am. Chem. Soc.* **2007**, *129*, 7500−7501. (b) Zhang, Q.; Wu, C.; Zhou, L.; Li, J. Theoretical Studies on Intramolecular C−H Amination of Biaryl Azides Catalyzed by Four Different Late Transition Metals. *Organometallics* **2013**, *32*, 415−426.

(6) Louillat, M.-L.; Patureau, F. W. Oxidative C−H Amination Reactions. *Chem. Soc. Rev.* **2014**, *43*, 901−910.

(7) (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. Intermolecular Amidation of Unactivated sp^2 and sp^3 C−H Bonds via Palladium-Catalyzed Cascade C−H Activation/Nitrene Insertion. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. (b) Mei, T.-S.; Wang, X.; Yu, J.-Q. Pd(II)-Catalyzed Amination of C−H Bonds Using Single-Electron or Two-Electron Oxidants. *J. Am. Chem. Soc.* **2009**, *131*, 10806−10807.

(8) (a) Tan, Y.; Hartwig, J. F. Palladium-Catalyzed Amination of Aromatic C−H Bonds with Oxime Esters. *J. Am. Chem. Soc.* **2010**, *132*, 3676−3677. (b) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. Pd-Catalyzed Intermolecular C−H Amination with Alkylamines. *J. Am. Chem. Soc.* **2011**, *133*, 7652−7655. (c) Grohmann, C.; Wang, H.; Glorius, F. Rh(III)-Catalyzed Direct C−H Amination Using N-Chloroamines at Room Temperature. *Org. Lett.* **2012**, *14*, 656−659.

(9) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.

(10) (a) Kwart, H.; Khan, A. A. Copper-Catalyzed Decomposition of Benzenesulfonyl Azide in Cyclohexene Solution. *J. Am. Chem. Soc.* **1967**, *89*, 1951−1953. (b) Breslow, D. S.; Sloan, M. F. A New Synthesis of Sulfonylnitrenes. *Tetrahedron Lett.* **1968**, *51*, 5349−5352. (c) Gephart, R. T.; Warren, T. H. Copper-Catalyzed sp^3 C−H Amination. *Organometallics* **2012**, *31*, 7728−7752. (d) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. Organic Azides: "Energetic Reagents" for the Intermolecular Amination of C−H Bonds. *Chem. Commun.* **2014**, *50*, 11440−11453.

(11) Ke, Z.; Cundari, T. R. Palladium-Catalyzed C−H Activation/ C−N Bond Formation Reactions: DFT Study of Reaction Mechanisms and Reactive Intermediates. *Organometallics* **2010**, *29*, 821−834.

(12) Zalatan, D. N.; Du Bois, J. Metal-Catalyzed Oxidations of C−H to C−N Bonds. *Top. Curr. Chem.* **2010**, *292*, 347−378.

(13) Song, G.; Wang, F.; Li, X. C−C, C−O and C−N Bond Formation via Rhodium(III)-Catalyzed Oxidative C−H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678.

(14) (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. Rhodium-Catalyzed Intermolecular Amidation of Arenes

with Sulfonyl Azides via Chelation-Assisted C−H Bond Activation. *J. Am. Chem. Soc.* **2012**, *134*, 9110−9113. (b) Park, S. H.; Park, Y. S.; Chang, S. Rhodium-Catalyzed Direct Amination of Arene C−H Bonds Using Azides as the Nitrogen Source. *Org. Synth.* **2014**, *91*, 52−59.

(15) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. Rhodium-Catalyzed Direct C−H Amination of Benzamides with Aryl Azides: A Synthetic Route to Diarylamines. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904−9908.

(16) Shin, K.; Baek, Y.; Chang, S. Direct C−H Amination of Arenes with Alkyl Azides under Rhodium Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 8031−8036.

(17) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. Mechanistic Studies of the Rhodium-Catalyzed Direct C−H Amination Reaction Using Azides as the Nitrogen Source. *J. Am. Chem. Soc.* **2014**, *136*, 2492−2502.

(18) For selected examples on the generation of the metal−nitrene intermediate with azides during the C−H amination reaction, see: (a) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinmann, F. W.; Cundari, T. R.; Warren, T. H. Copper−Nitrene Complexes in Catalytic C−H Amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 9961−9964. (b) King, E. R.; Hennessy, E. T.; Betley, T. A. Catalytic C−H Bond Amination from High-Spin Iron Imido Complexes. *J. Am. Chem. Soc.* **2011**, *133*, 4917−4923. (c) Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. Mechanism of Cobalt(II) Porphyrin-Catalyzed C−H Amination with Organic Azides: Radical Nature and H-Atom Abstraction Ability of the Key Cobalt(III)−Nitrene Intermediates. *J. Am. Chem. Soc.* **2011**, *133*, 12264−12273.

(19) For selected examples describing Rh(V) species, see: (a) Vyboishchikov, S. F.; Nikonov, G. I. Rhodium Silyl Hydrides in Oxidation State +5: Classical or Nonclassical? *Organometallics* **2007**, *26*, 4160−4169. (b) McBee, J. L.; Escalada, J.; Tilley, T. D. High Oxidation State Rhodium and Iridium Bis(silyl)dihydride Complexes Supported by a Chelating Pyridyl-Pyrrolide Ligand. *J. Am. Chem. Soc.* **2009**, *131*, 12703−12713.

(20) (a) Choi, J.; Goldman, A. S. Ir-Catalyzed Functionalization of C−H Bonds. *Top. Organomet. Chem.* **2011**, *34*, 139−167. (b) Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. Designing Catalysts for Functionalization of Unactivated C−H Bonds Based on the C−H Activation Reaction. *Acc. Chem. Res.* **2012**, *45*, 885−898.

(21) Han, Y.-F.; Jin, G.-X. Cyclometalated [Cp*M(C^X)] (M = Ir, Rh; X = N, C, O, P) Complexes. *Chem. Soc. Rev.* **2014**, *43*, 2799−2823.

(22) Liu, Z.; Sadler, P. J. Organoiridium Complexes: Anticancer Agents and Catalysts. *Acc. Chem. Res.* **2014**, *47*, 1174−1185.

(23) Sau, Y.-K.; Yi, X.-Y.; Chan, K.-W.; Lai, C.-S.; Williams, I. D.; Leung, W.-H. Insertion of Nitrene and Chalcogenolate Groups into the Ir−C σ Bond in a Cyclometalated Iridium(III) Complex. *J. Organomet. Chem.* **2010**, *695*, 1399−1404.

(24) (a) Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. Intramolecular Ir(I)-Catalyzed Benzylic C−H Bond Amination of *ortho*-Substituted Aryl Azides. *Org. Lett.* **2009**, *11*, 3598−3601. (b) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 9884−9887.

(25) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. Ir(III)-Catalyzed Mild C−H Amidation of Arenes and Alkenes: An Efficient Usage of Acyl Azides as the Nitrogen Source. *J. Am. Chem. Soc.* **2013**, *135*, 12861−12868.

(26) For selected examples on the Cp*Rh(III)- or (*p*-cymene) Ru(II)-catalyzed C−H functionalization of olefin substrates, see: (a) Kuhl, N.; Schröder, N.; Glorius, F. Rh(III)-Catalyzed Halogenation of Vinylic C−H Bonds: Rapid and General Access to Z-Halo Acrylamides. *Org. Lett.* **2013**, *15*, 3860−3863. (b) Hu, X.-H.; Zhang, J.; Yang, X.-F.; Xu, Y.-H.; Loh, T.-P. Stereo- and Chemoselective Cross-Coupling between Two Electron-Deficient Acrylates: An Efficient Route to (Z,E)-Muconate Derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 3169−3172.

(27) Kim, J.; Chang, S. Iridium-Catalyzed Direct C−H Amidation with Weakly Coordinating Carbonyl Directing Groups under Mild Conditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 2203−2207.

(28) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. Investigation of the Mechanism of C(sp^3)−H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation Adjacent to Amides and Sulfonamides. *J. Am. Chem. Soc.* **2010**, *132*, 10692−10705.

(29) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. Regioselective Introduction of Heteroatoms at the C-8 Position of Quinoline N-Oxides: Remote C−H Activation Using N-Oxide as a Stepping Stone. *J. Am. Chem. Soc.* **2014**, *136*, 10770−10776.

(30) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. Autocatalysis for C−H Bond Activation by Ruthenium(II) Complexes in Catalytic Arylation of Functional Arenes. *J. Am. Chem. Soc.* **2011**, *133*, 10161−10170.

(31) Gwon, D.; Lee, D.; Kim, J.; Park, S.; Chang, S. Iridium(III)-Catalyzed C−H Amidation of Arylphosphoryls Leading to a P-Stereogenic Center. *Chem.—Eur. J.* **2014**, *20*, 12421−12425.

(32) Hunter, C. A.; Sanders, J. K. M. The Nature of π−π Interactions. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534.

(33) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. Iridium-Catalyzed Intermolecular Amidation of sp^3 C−H Bonds: Late-Stage Functionalization of an Unactivated Methyl Group. *J. Am. Chem. Soc.* **2014**, *136*, 4141−4144.

(34) Kim, H.; Park, J.; Kim, J. G.; Chang, S. Synthesis of Phosphoramidates: A Facile Approach Based on the C−N Bond Formation via Ir-Catalyzed Direct C−H Amidation. *Org. Lett.* **2014**, *16*, 5466−5469.

(35) Figg, T. M.; Park, S.; Park, J.; Chang, S.; Musaev, D. G. Comparative Investigations of Cp*-Based Group 9 Metal-Catalyzed Direct C−H Amination of Benzamides. *Organometallics* **2014**, *33*, 4076−4085.

(36) (a) Pyykkö, P. Relativistic Effects in Structural Chemistry. *Chem. Rev.* **1988**, *88*, 563−594. (b) Siegbahn, P. E. M. Comparison of the C−H Activation of Methane by M(C$_5$H$_5$)(CO) for M = Cobalt, Rhodium, and Iridium. *J. Am. Chem. Soc.* **1996**, *118*, 1487−1496.

(37) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient Catalytic Addition of Aromatic Carbon-Hydrogen Bonds to Olefins. *Nature* **1993**, *366*, 529−531. (b) Arokiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C−H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879−5918.

(38) (a) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M. *Chem. Commun.* **1999**, 2377−2378. (b) Fantauzzi, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Casati, N.; Macchi, P.; Cenini, S. The Key Intermediate in the Amination of Saturated C−H Bonds: Synthesis, X-ray Characterization and Catalytic Activity of Ru(TPP)(NAr)$_2$ (Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$). *Chem. Commun.* **2009**, 3952−3954. (c) Dong, H.; Latka, R. T.; Driver, T. G. Ruthenium-Catalyzed γ-Carbolinium Ion Formation from Aryl Azides; Synthesis of Dimebolin. *Org. Lett.* **2011**, *13*, 2726−2729. (c) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. C−H Nitrogenation and Oxygenation by Ruthenium Catalysis. *Chem. Commun.* **2014**, *50*, 29−39.

(39) (a) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. Sulfoximine Directed Intermolecular o-C−H Amidation of Arenes with Sulfonyl Azides. *Org. Lett.* **2013**, *15*, 1638−1641. (b) Kim, J.; Kim, J.; Chang, S. Ruthenium-Catalyzed Direct C−H Amidation of Arenes Including Weakly Coordinating Aromatic Ketones. *Chem.—Eur. J.* **2013**, *19*, 7328−7333. (c) Shin, K.; Ryu, J.; Chang, S. Orthogonal Reactivity of Acyl Azides in C−H Activation: Dichotomy between C−C and C−N Amidations Based on Catalyst Systems. *Org. Lett.* **2014**, *16*, 2022−2025.

(40) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315−1345.

(41) Zhang, L.-L.; Li, L.-H.; Wang, Y.-Q.; Yang, Y.-F.; Liu, X.-Y.; Liang, Y.-M. Ruthenium-Catalyzed Direct C−H Amidation of Arenes: A Mechanistic Study. *Organometallics* **2014**, *33*, 1905−1908.

(42) (a) Cenini, S.; Gallo, E.; Penoni, A.; Ragaini, F.; Tollari, S. *Chem. Commun.* **2000**, 2265−2266. (b) Lu, H.; Zhang, X. P. Catalytic C−H Functionalization by Metalloporphyrins: Recent Developments and Future Directions. *Chem. Soc. Rev.* **2011**, *40*, 1899−1909. (c) Hennessy, E. T.; Betley, T. A. Complex N-Heterocycle Synthesis via Iron-Catalyzed, Direct C−H Bond Amination. *Science* **2013**, *340*, 591−595.

(43) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C−H Functionalization. *Acc. Chem. Res.* **2014**, *47*, 1208−1219.

(44) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. Air-Stable Carbonyl (pentamethylcyclopentadienyl)cobalt Diiodide Complex as a Precursor for Cationic (Pentamethylcyclopentadienyl)cobalt(III) Catalysis: Application for Directed C-2 Selective C−H Amidation of Indoles. *Adv. Synth. Catal.* **2014**, *356*, 1491−1495.

(45) Rousseau, G.; Breit, B. Removable Directing Groups in Organic Synthesis and Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450−2494.

(46) Peng, J.; Xie, Z.; Chen, M.; Wang, J.; Zhu, Q. Copper-Catalyzed C(sp²)−H Amidation with Azides as Amino Sources. *Org. Lett.* **2014**, *16*, 4702−4705.