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Rh(III)- and Ir(III)-Catalyzed Direct C–H Bond Transformations to Carbon–Heteroatom Bonds

Jeung Gon Kim, Kwangmin Shin, and Sukbok Chang

Abstract The direct manipulation of C–H bonds is now a powerful tool in chemical synthesis. In achieving the current high standard of research progresses, Rh(III) and Ir(III) complexes played an important role to understand the nature of C–H bond activation. While numerous stoichiometric reactions of hydrocarbons with Rh(III) or Ir(III) complexes were scrutinized, their use in catalytic transformations has been relatively undeveloped until recently. Given their outstanding reactivity in C–H activation, they are highly promising candidates for inducing mild C–H functionalizations. In spite of a short development history, numerous contributions from leading research groups made big strides in highly efficient and selective C–H bond transformations for the C–C and C–heteroatom bond formation. In this report, we specifically focus on the Rh(III)- or Ir(III)-mediated direct C–H functionalizations for the C–heteroatom bond formation that is now a rapidly growing area. This report presents the current status of such catalytic systems including scope of substrates and coupling partners as well as brief mechanistic descriptions.

Keywords C–H bond activation · C–heteroatom bond formation · Iridium(III) catalyst · Rhodium(III) catalyst

Contents

J.G. Kim, K. Shin, and S. Chang (✉)
Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, Republic of Korea

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea
e-mail: sbchang@kaist.ac.kr

1 Introduction

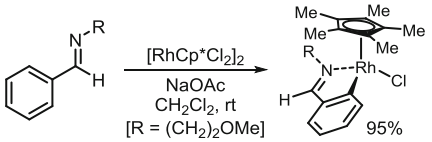
The direct functionalization of a carbon–hydrogen bond was not previously considered as a logical retrosynthetic disconnection mainly due to their high dissociation energy and omnipresence in organic molecules, thus resulting in a low level of efficiency and selectivity. Mainly due to the better understanding of the activation pathway, highly efficient catalytic systems have been developed during the last decades. Because of these tremendous research efforts on the direct C–H transformation, this strategy is now widely utilized in making functionalized molecules in various areas including organic synthesis, medicinal chemistry, and materials science. Direct use of abundant carbon–hydrogen connections could eliminate prefunctionalization steps, thus leading to atom and step economy in chemical synthesis. Therefore, transition metal-mediated C–H functionalization presents a high promise to chemo-, regio-, and stereoselective synthetic approaches, desirably under mild conditions [1–3]. In this regard, while significant achievements have been made by employing a wide range of transition metal catalysts, the group 9 metals of Co, Rh, and Ir have also played an important role in advancing the C–H functionalization routes [4–7]. Sufficiently high reactivity of Rh(III) and Ir(III) complexes made them suitable for studying the nature of C–H activation process since stoichiometric manipulations with hydrocarbons give an easy access to cyclometalated intermediates [8]. As the C–H bond cleavage of hydrocarbons can readily be achievable by tuning the ligated Rh and Ir species, the resultant mild catalytic C–H functionalization procedures are expected to have a high impact in broad research areas. Surprisingly, it was not until recently that their catalytic efficiency of group 9 metal complexes has successfully applied to the useful organic transformations. In this context, impressive achievements have been made recently to broaden the scope of Rh(III)- and Ir(III)-catalyzed construction of carbon–heteroatom bonds as well as carbon–carbon bonds.

The formation of carbon–heteroatom bonds is of special interest due to the fact that the introduction of heteroatom into molecules brings functions in addition to the structural modification [9–11]. In this direct C–H functionalization, although a wide range of catalytic systems have been developed, described herein are the recent advances achieved by Rh(III)- and Ir(III)-based catalytic systems. Since excellent reviews on the direct C–H borylation reactions are available due to their

extensive research efforts [12–14], this chapter does not cover the borylation chemistry.

2 Rh(III)-Catalyzed Reactions

In 2003, Davies and coworkers demonstrated that a Rh(III) complex generated from $[RhCp^*Cl_2]_2$ is capable of activating a C–H bond to form a metallacycle with an imine directing group (1) [15]. Derivatives of Cp*Rh(III) species turned out to be highly reactive enough to undergo the C–H activation process of various hydrocarbons under mild conditions, sometimes even at room temperature, which caught a special attention [5, 16]. After the Miura group's seminal report on the Rh(III)-based catalytic C–H bond functionalization to form C–C bonds [17–19], significant advances have been made in the Rh(III)-mediated C–H bond activation strategy for the C–C and C–heteroatom bond formations including B, N, S, Cl, Br, and I [4–6].

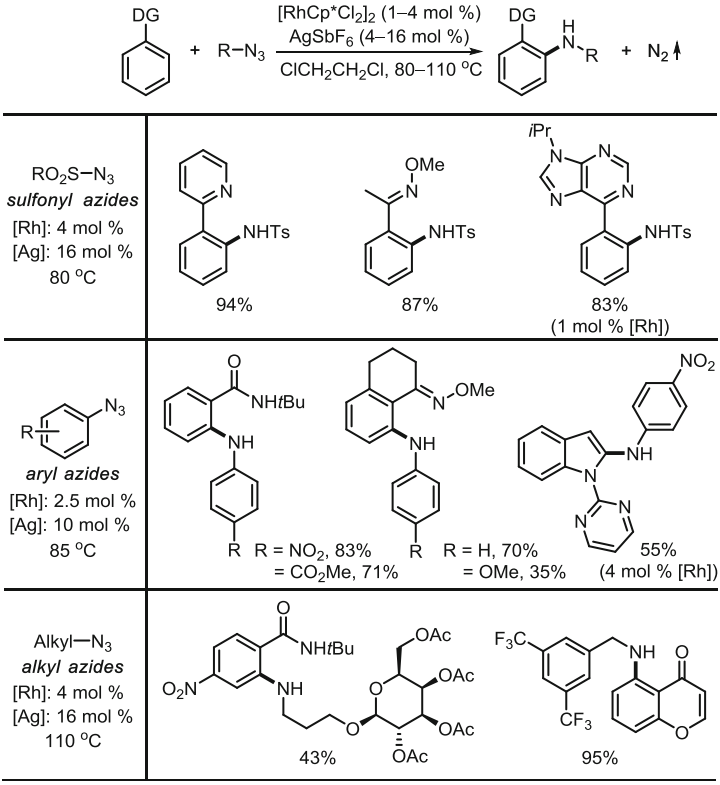


(1)

2.1 C–N Bond Formation

The direct amination of C–H bonds has been studied as an environmentally benign alternative to the Ullmann–Goldberg and Buchwald–Hartwig aminations, which employ (hetero)aryl halides or their equivalents to react with amines [20–26]. Significant research efforts are in progress for an ideal C–H amination system: coupling of unactivated hydrocarbons with readily available amino sources under mild conditions while producing minimal amounts of wastes [27, 28]. In 2012, Chang, Glorius, and Yu simultaneously reported Cp*Rh(III)-catalyzed direct C–H amination protocols with azides or *N*-chloroamines, operating under mild conditions in the absence of external oxidants. In contrast to the Rh(II)-catalyzed C–H aminations which undergo an initial metal-nitrenoid formation and subsequent insertion into C–H bonds (outer sphere mechanism) [29–32], Cp*Rh(III)-mediated C–H aminations are believed to proceed through sequential C–H activation and C–N bond formation (inner sphere pathway) [33].

Chang and coworkers presented the use of organic azides as a unique nitrogen source [34]. A cationic Cp*Rh(III) catalyst generated in situ from $[Cp^*RhCl_2]_2$ and silver additive was discovered to turnover C–N bond formation between 2-phenylpyridines and sulfonyl azides. This protocol does not require external oxidants and releases only nitrogen gas as sole by-product, enabling an environmentally benign catalytic process. This method displayed a high reactivity over a wide range of substrates and azides. Assorted types of directing groups [34–39]

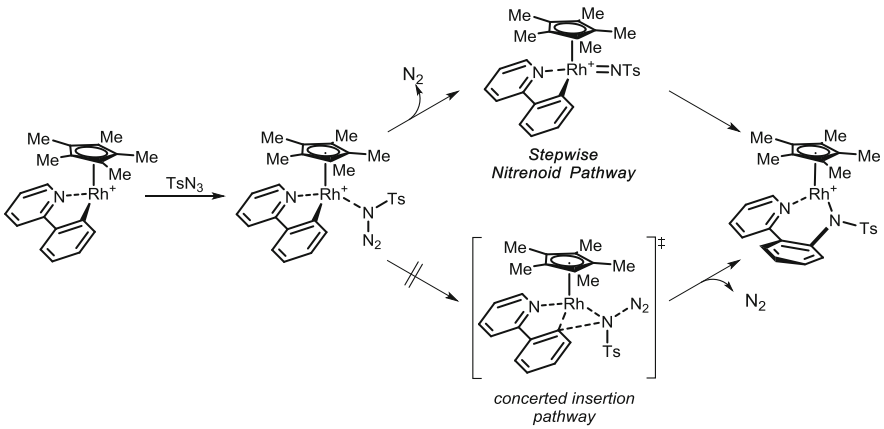


Scheme 1 Cp*Rh-catalyzed direct C–N bond-forming reactions using organic azides

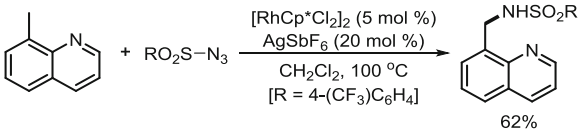
including pyridyl, azobenzene, imidate, amide, oxime, and ketone effectively underwent the direct C–H aminations with sulfonyl, alkyl [37], and aryl azides [38] (Scheme 1).

Detailed mechanistic studies and theoretical calculations were carried out by the Chang research group, especially clearing the mist in the C–N bond-forming step (Scheme 2) [40]. While two mechanisms, redox-active nitrenoid pathway and redox-neutral concerted pathway, were considered, DFT calculations pointed out that the stepwise pathway involving a Rh(V)-imido intermediate is energetically more feasible.

Wang and coworkers extended the scope of Cp*Rh(III)-catalyzed C–H amination protocol to sp^3 C–H bonds. A cationic Cp*Rh(III) species successfully activated benzylic C–H bonds of 8-methylquinolines and the resultant rhodacycles reacted with sulfonyl azides in moderate efficiency (2) [41].



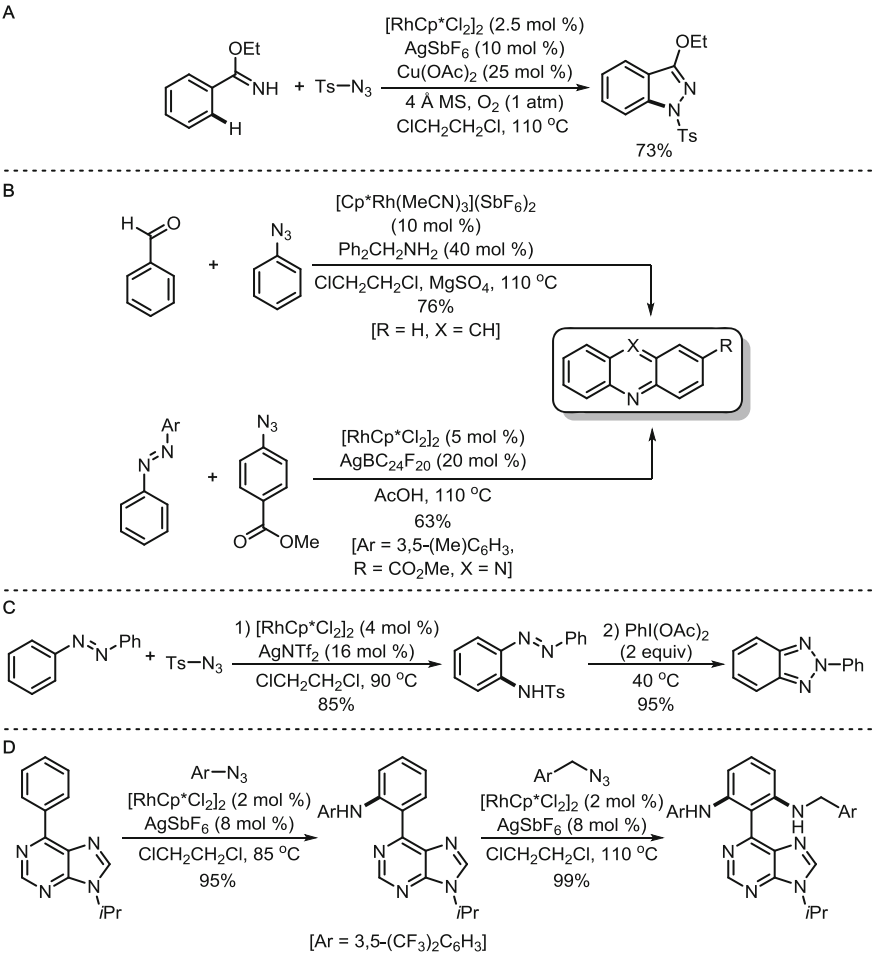
Scheme 2 Reaction mechanism of C–N bond formation step using organic azides



(2)

Aminated products obtained from the reaction with azides were shown to be a valuable motif for the preparation of many synthetic building blocks (Scheme 3). Syntheses of 1*H*-indazoles (Glorius, Scheme 3a) [42], acridines, phenazines (Bergman/Ellman, Scheme 3b) [43], 2-aryl-2*H*-Benzotriazoles (Lee, Scheme 3c) [35], and carbazoles (Chang) [38] showcased the synthetic versatility of aminated products. The Chang group also applied this method to 6-arylpurine functionalizations, an important unit in medicinal chemistry (Scheme 3d) [44].

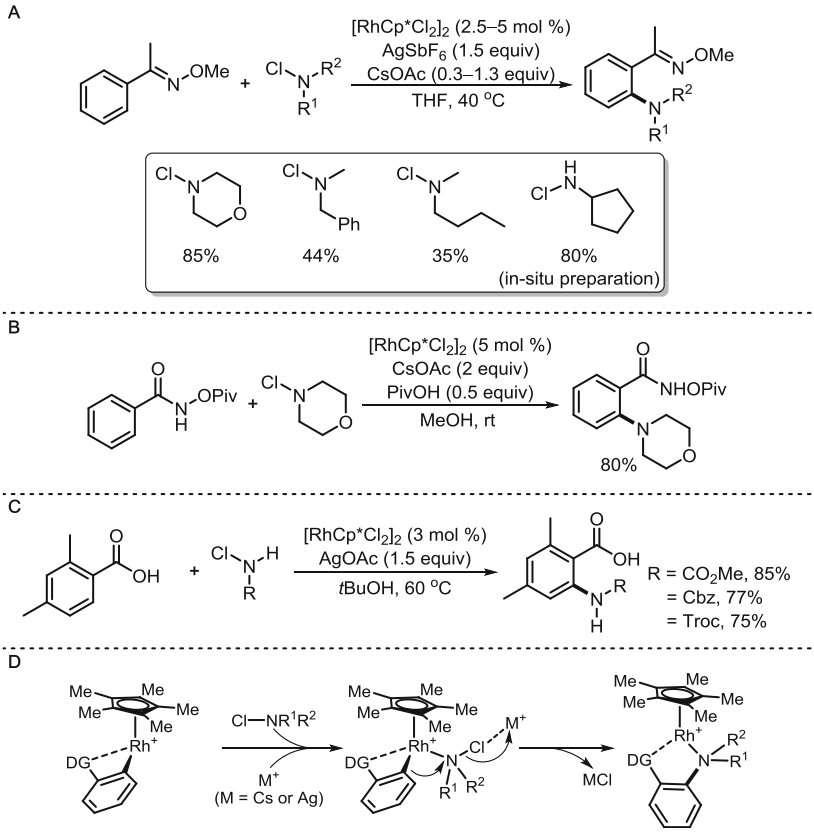
While *N*-chloroamines have been used for the electrophilic C–H amination of hydrocarbons by the action of various metal catalysts [45–47], it was proven to be especially well suited with the Rh(III) catalytic system (Scheme 4). In 2012, Glorius and Yu groups independently demonstrated that *N*-chloroamines would undergo a S_N-type reaction by utilizing chloride as a leaving group [48–50]. Oximes (Scheme 4a), hydroxamic acids (Scheme 4b), and benzoic acid derivatives (Scheme 4c) smoothly proceeded the desired C–H aminations under mild conditions. Whereas secondary *N*-chloroamines were used most efficiently, Yu and coworkers devised a method to tame reactive and unstable primary *N*-chloroamines. The presence of an external base or in situ generation of primary *N*-chloroamines led to the efficient production of secondary amine compounds [49]. Additionally, their recent works widened the synthetic scope by employing *N*-chlorocarbamates [50]. Both Glorius and Yu postulated that the extra Ag or Cs salts, which are required for high turnovers, facilitate chloride removal at the stage of C–N bond formation (Scheme 4d). Initial mechanistic studies revealed the electrophilic nature of this amination protocol although a Rh(V)-imido pathway could not be completely ruled out at the present stage.



Scheme 3 Synthetic applications of C-H aminations using organic azides: 1*H*-indazoles (**a**), acridines and phenazines (**b**), 2-aryl-2*H*-benzotriazoles (**c**), and functionalized 6-arylpurines (**d**)

A number of hydroxylamine derivatives were also shown to be effective in the Cp*Rh(III)-catalyzed amination reactions (Scheme 5) [51–55]. This C–H amination takes place upon the cleavage of N–O bond of aminating reagents to serve as an internal oxidant, thus making the procedure free from the use of stoichiometric amounts of external oxidants. An initial study was reported by Glorius and coworkers, where they hypothesized that an electron-deficient carboxylate would act as a leaving group (Scheme 5a) [51]. However, the exact reaction pathway is unclear especially in regard to whether a Rh(III) migratory insertion or a Rh(V)-nitrenoid pathway would be involved.

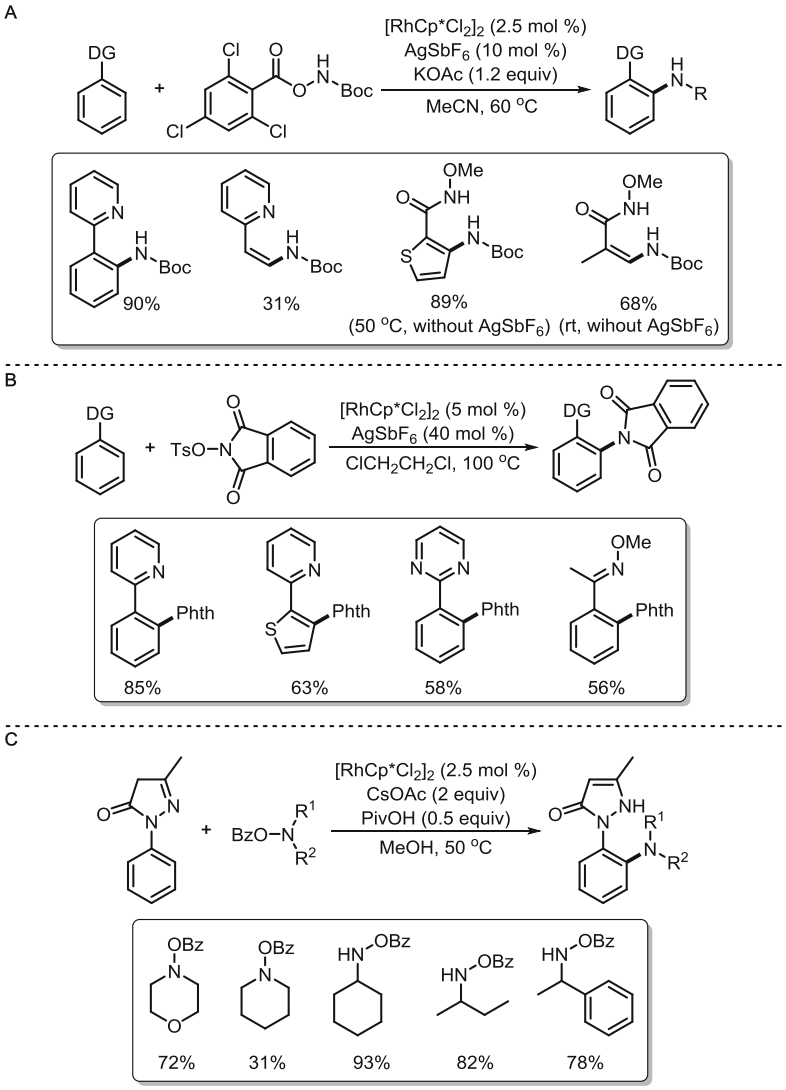
An analogous type of amidating source of *N*-arenesulfonated imides was developed by Li and coworkers, and it was successfully applied to the amidation of



Scheme 4 Cp*Rh(III)-mediated C-H amination with *N*-chloroamines of oxime (**a**), hydroxamic acid (**b**), and benzoic acid (**c**) derivatives and its mechanism (**d**)

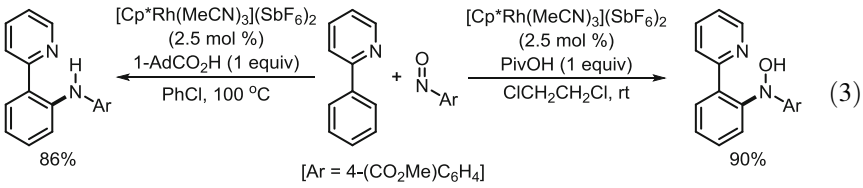
substrates containing pyridine or oxime directing groups (Scheme 5b) [52]. Zhang and coworkers utilized *N*-benzoylated alkylamines for the functionalization of phenidones and edaravone (neuroprotective drugs) analogues (Scheme 5c) [53, 54]. In 2015, Lu and coworkers developed a unique procedure of the Cp*Rh(III)-catalyzed amidation on water using *tert*-butyl 2,4-dinitrophenoxycarbamate as an amidating reagent [55]. $[RhCp^*Cl_2]_2$ was found to catalyze the directed C–N bond formation in water without additives. The authors proposed that an active cationic Rh(III) species would be formed by the hydroxyl group on water surface, thus replacing a silver salt that was used in most Cp*Rh(III)-catalyzed activations.

An interesting usage of nitroso compounds as an amino source was shown by Li and coworkers (3) [56–58]. An electrophilic nitrogen of nitrosobenzene was able to react with a rhodacycle species to afford *N*-diarylhydroxyamines at room temperature [56]. Later they established one-pot protocol of C–N bond formation and subsequent dehydroxylation to form diarylamines [57]. After the formation of *N*-diarylhydroxyamines, Rh(III) catalyst continues to promote dehydroxylation with



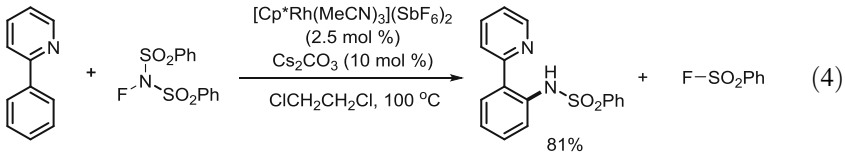
Scheme 5 Cp*Rh(III)-mediated C-H amination with *N*-substituted hydroxylamines of Aroyloxycarbamates (**a**) and *N*-arenesulfonated imides (**b**), and its application to edaravone functionalization (**c**)

an aid of molecular oxygen and carboxylic acid at elaborated temperature. The same research group extended this tandem protocol to in situ nitroso group formation. Three-step sequence of oxidation of *N*-hydroxylcarbamates to nitroso compounds, C–N bond formation, and dehydroxylation was realized in one pot to produce *N*-Boc protected arylamines [58].



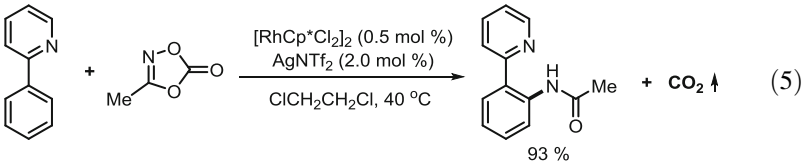
(3)

N-Fluorobenzenesulfonimide (NFSI), a well-known fluorination reagent, also participated in Rh(III)-catalyzed C–H functionalization as an amino source (4) [59, 60]. Yang and Li utilized NFSI as an electrophilic amidating reagent [61], exhibiting reasonable efficiency with 2-pyridyl-directed arenes.



(4)

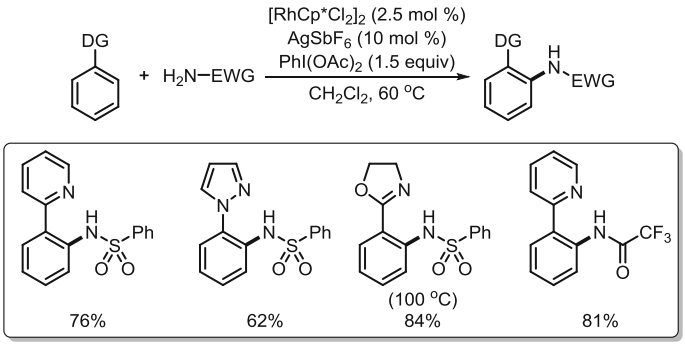
Chang and coworkers recently added another class of a highly reactive C–H amidating reagent, 1,4,2-dioxazol-5-one [62, 63]. During the mechanistic investigations on the Cp*Rh(III)-catalyzed direct C–H amination reaction, they revealed that an amino source with high coordination ability to metal center would increase the reaction rate. An acyl nitrene precursor, 1,4,2-dioxazol-5-one, showed high coordination affinity to the metal center, but with low activation energy in an imido-insertion process, which resulted in highly efficient amidation system, operating with as low as 0.5 mol% catalyst loading (5) [64].



(5)

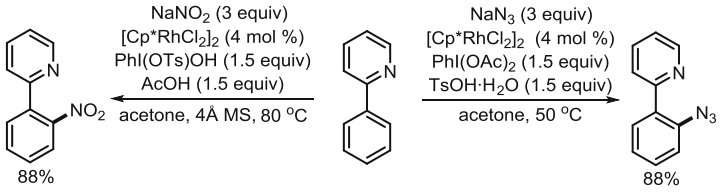
While various types of activated amine surrogates are in use for C–H aminations, the use of unmodified parent amines would be ultimately desirable for the step- and atom-efficient synthesis. Su and coworkers successfully applied the dehydrogenative coupling conditions by employing electron-deficient sulfonamides and acyl amides as amidating reagents (Scheme 6) [65]. Although stoichiometric amounts of oxidant such as $PhI(OAc)_2$ are required, this approach has an obvious advantage in that the reaction procedure does avoid an additional step of parent amine derivatization.

Along with the amination, C–H azidation and nitration were also developed [66]. Li and coworkers succeeded in the in situ formation of electrophilic azide source from NaN_3, which was then reacted with a rhodacycle to produce aryl azide products. An electrophilic azidation reagent of $PhI(N_3)OTs$ was obtained from a mixture of $PhI(OAc)_2$, TsOH, and NaN_3. Similar to azidation, the formation of an



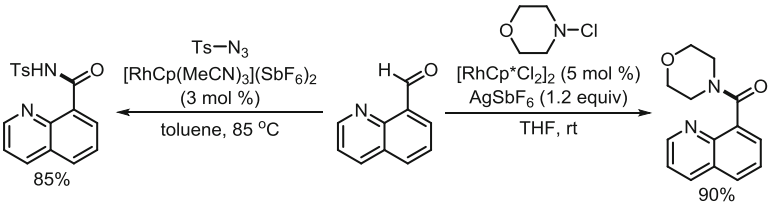
Scheme 6 Rh(III)-catalyzed dehydrogenative C–H amidation

electrophilic nitration source was achieved from the reaction of $NaNO_2$ with hyperiodine reagent. For both azidation and nitration, high conversion was observed over various substrates bearing rather strong directing groups such as pyridine and its analogues (6).



(6)

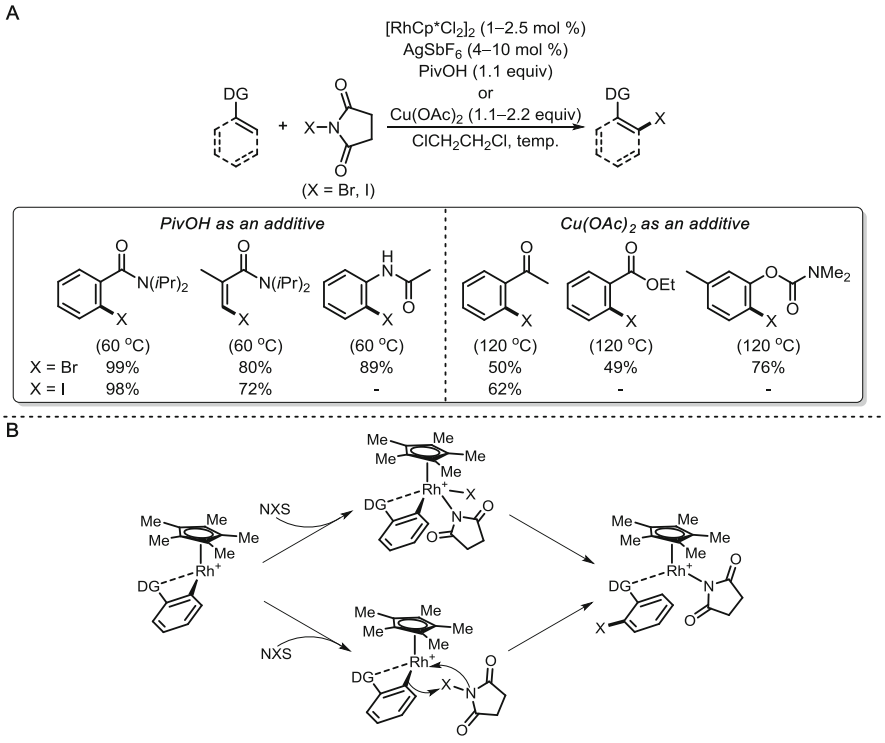
While the majority of known examples have focused on the (hetero)arene C–H bond activation and subsequent functionalization, several groups paid attention to other types of C–H bonds such as aldehydes [67–69]. Direct transformation of carbonyl C–H bonds into other functional groups such as ketones, amides, or esters would be highly valuable in synthetic chemistry. In this regard, Li group successfully developed the Cp*Rh(III)-catalyzed amide synthesis starting from aldehydes (7) [70, 71]. It was proposed that a cationic Cp*Rh(III) species activates a carbonyl C–H bond of 8-quinolinecarbaldehyes or 2-(methylthio)benzaldehydes to form a rhodium acyl intermediate that then reacts with amino sources including *N*-chloroamines and azides to deliver the desired amide products.



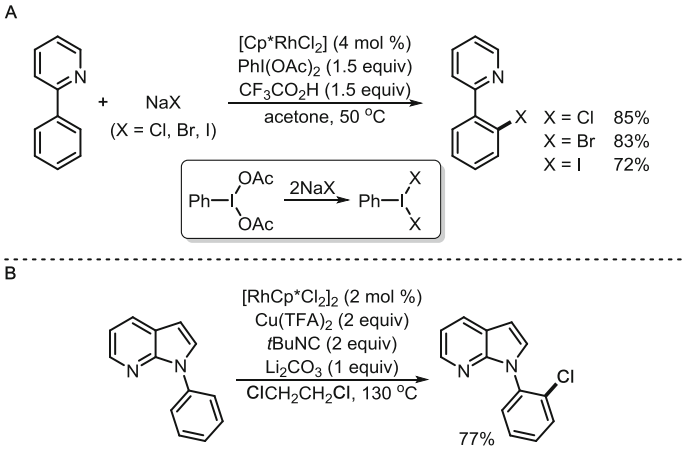
(7)

2.2 C–X (X = Cl, Br, and I) Bond Formation

With the aim of site selective halogenation, electrophilic halide sources such as *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) were successfully added to the list of reactive coupling partners. The Glorius group found that a cationic Cp*Rh(III) species is capable of coupling NBS and NIS with a broad range of arene substrates to produce *ortho*-halogenated arenes, which are otherwise difficult to obtain regioselectively via conventional halogenation methods (Scheme 7) [72–74]. It is notable that this halogenation reaction is facile with substrates containing ketone, ester, and carbamate directing groups where Cp*Rh(III)-based catalysis does not work efficiently for other types of C–H functionalizations [72]. The replacement of an additive from PivOH to $Cu(OAc)_2$ was key to success for substrates bearing enolizable ketones and esters as a directing group. In addition to aromatic C–H bonds, olefinic C–H bonds were also shown to be feasible for this halogenation protocol to give synthetically valuable (*Z*)-halogenated acrylamides [73]. In the presence of Cp*Rh(III) catalyst, non-catalyzed halogenation (background reaction) was effectively suppressed. Glorius and coworkers extended this method to the halogenation of important heterocycles such as furans, thiophenes,



Scheme 7 Rh(III)-catalyzed C-H halogenation using NBS and NIS: scope (**a**) and mechanism (**b**)

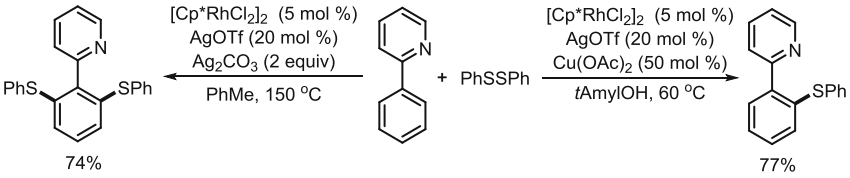


Scheme 8 Cp*Rh(III)-catalyzed halogenation using sodium halides (**a**) and 1,2-dichloroethane (**b**)

pyrazoles, quinolines, and chromones [74]. Recently, Chang and coworkers developed the selective halogenation at the C-8 position of quinoline *N*-oxides [75]. Wang and coworkers improved the synthetic utility of this approach by using readily available sodium halide salts as a halogen source (Scheme 8a) [76]. They proposed that the in situ formation of an active iodobenzene dihalide from $PhI(OAc)_2$ and sodium halide is a key to success. The achievement of chlorination is an additional merit, while NCS is not reported yet to be effective with Cp*Rh(III) catalysis. In addition, Xu and coworkers revealed an interesting reactivity of 1,2-dichloroethane as a chlorinating agent (Scheme 8b) [77]. In the functionalization of 7-azaindoles, 1,2-dichloroethane, which is a conventional solvent for numerous C–H functionalization reactions, was proven to be a facile chlorine source although its mechanism is unclear at the present stage.

2.3 C–S Bond Formation

Li and coworkers reported that the formation of a C–S bond could be achieved by using a Cp*Rh catalyst (8) [78]. Given that the sulfur atom can strongly bind to metals and, as a result, deactivate metal catalysts, the development of metal-catalyzed sulfenylation has been challenging. In the presence of extra oxidants, both mono- and di-thiolation were optimized to give thioethers with directing groups of pyridine, pyrimidine, pyrazole, and oxime.



(8)

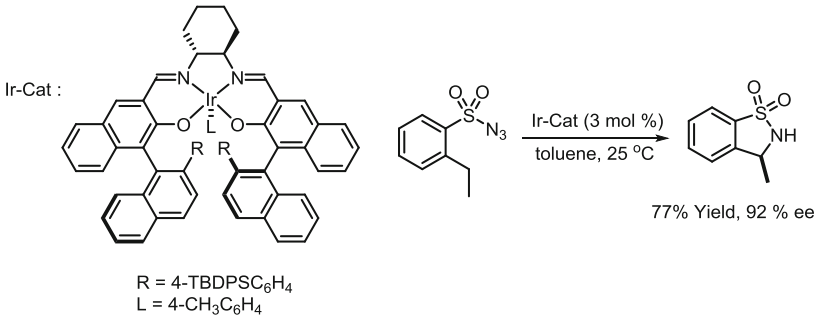
3 Ir(III)-Catalyzed Reactions

Whereas iridium complexes have been shown to be highly active for the *stoichiometric* C–H bond activation, their use in catalytic reactions was challenging [16, 79, 80]. The high stability of iridacycles, especially of half-sandwich complexes, hampered their catalytic turnovers. Thus, while their group 9 neighbor Cp*Rh (III) system has been widely applied to various C–H functionalizations, only a handful of Cp*Ir(III)-based catalytic methods have been developed in the area of C–C bond formation and H/D exchange [81–84]. As the difference in reactivity and mechanistic pathway between Ir(III) and its congeners is not fully understood yet [85], a number of notable achievements have been made in catalytic C–N and C–O bond formation in recent years.

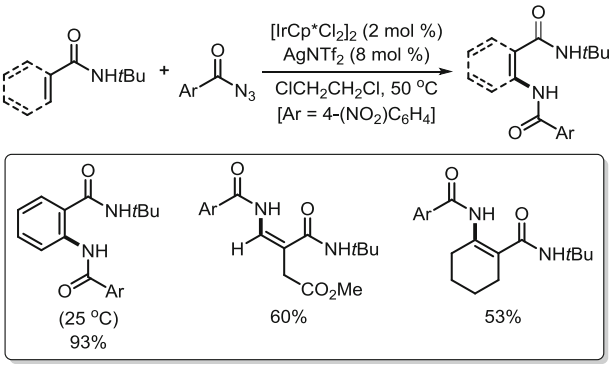
3.1 C–N Bond Formation

Iridium(III)-catalyzed C–N bond formation was previously investigated for an intramolecular asymmetric amination. Katsuki and coworkers prepared a series of chiral Ir(III)–salen catalysts for the intramolecular C–H amination to produce optically active benzosultams (Scheme 9) [86]. High level of enantioselectivity was achieved with catalyst loading as low as 3 mol% under mild conditions.

In case of intermolecular amination, Cp*Ir(III)-based catalytic systems showed excellent reactivity with various amino sources such as organic azides,



Scheme 9 (Salen)Ir(III)-catalyzed asymmetric intramolecular C–H amidation

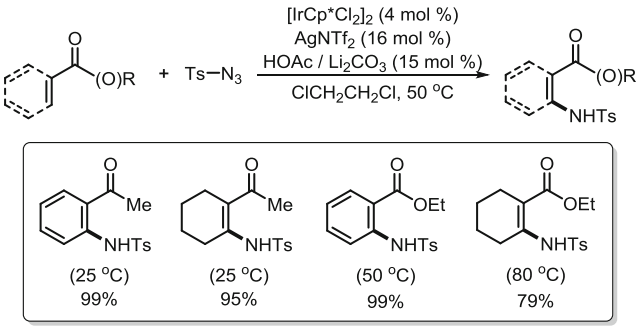


Scheme 10 Ir(III)-catalyzed C–H amidation using acyl azides

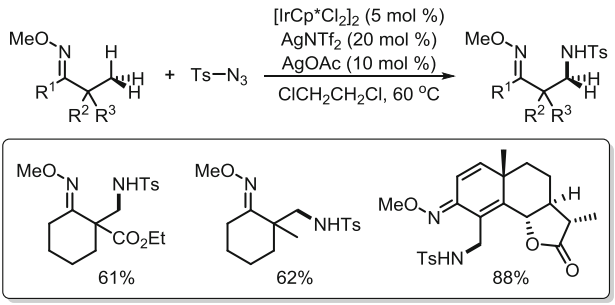
acetoxycarbamates, and anilines. As described above, the use of organic azides is environmentally benign due to the fact that no external oxidants are required and that N_2 is released as a single by-product. In this context, while Cp*Ir and Cp*Rh are both facile, Cp*Ir(III) system displayed a distinctive reactivity. Indeed, whereas Cp*Rh(III)-mediated aminations with azides require moderate- to high-temperature conditions (>80°C), the reactivity of Cp*Ir(III) catalyst is high enough to allow the reaction to run even at room temperature. In 2013, Chang and coworkers reported the first example of Ir(III)-catalyzed amidation of aryl and olefinic C–H bonds with acyl azides as the amino source [87, 88]. The fact that the mild reaction conditions permitted the use of this labile type of azides for the C–H amidation is significant because acyl azides easily undergo thermal Curtius rearrangement producing isocyanates (Scheme 10).

Another distinct feature of the Cp*Ir(III) catalytic system is in its high reactivity for substrates bearing weak directing groups [89]. As many C–H functionalizations require relatively strong coordination groups to facilitate the formation of a metallacycle intermediate, the use of weakly coordinating groups for the direct C–H activation has been a challenging task. While Cp*Rh(III) catalyst allowed the direct C–H amination of benzamides and aryl ketones at high temperature (>80°C), Cp*Ir(III) could form the C–N bonds by the action of ester or ketone directing groups at ambient temperature with the help of AcOH/Li_2CO_3 additives (Scheme 11).

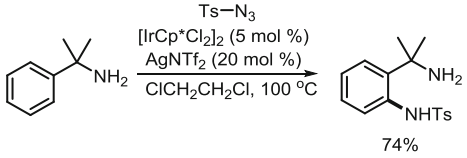
In 2015, the research team of Genentech reported an Ir(III)-catalyzed C–H sulfonamidation of arenes by using benzylic amine as a directing group (9) [90]. The Cp*Ir(III)-derived catalyst was found to be more effective over Rh (III) and Ru(II) with tertiary benzylic amines.



Scheme 11 Ir(III)-catalyzed C–H amidation with weakly coordinating carbonyl directing groups under mild conditions



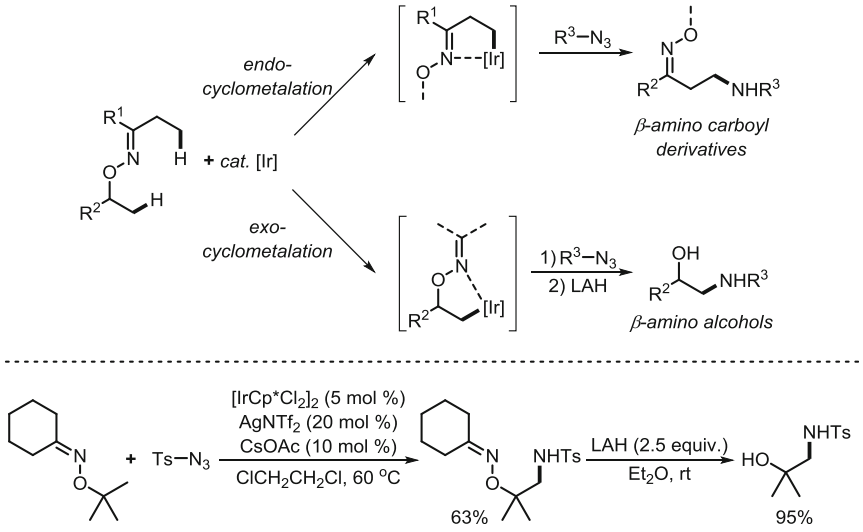
Scheme 12 Ir(III)-catalyzed amidation of unactivated sp^3 methyl C–H bonds



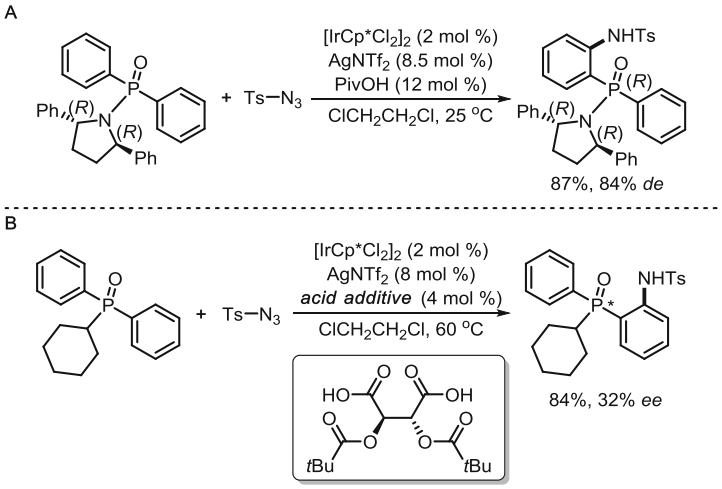
(9)

Excellent reactivity of Cp*Ir(III) complexes in the C–H activation process allowed for the functionalization of unactivated sp^3 C–H bonds [91, 92]. While Cp*Rh(III) catalyzed only activated benzylic C–H amidation of 8-methylquinolines, Cp*Ir(III) promoted the amidation of unactivated sp^3 methyl C–H bonds with the help of acetate additive. With a ketoxime directing group, their β-position was selectively amidated with various sulfonyl azides under mild conditions (Scheme 12) [91]. The same research group of Chang also devised a facile synthetic route accessing 1,2-amino alcohols by using direct C–H amidation reactions (Scheme 13) [92].

Asymmetric induction via C–H functionalization is a highly desirable but a challenging goal [93–95]. Chang and coworkers investigated a diastereoselective C–H amidation of diarylphosphoryl substrates bearing a chiral auxiliary (Scheme 14a) [96]. With a C_2-symmetric chiral pyrrolidine moiety, *P*-stereogenic center was newly generated by the Cp*Ir(III)-mediated diastereoselective



Scheme 13 Synthesis of 1,2-aminoalcohols via *exo*-directed sp^3 activation



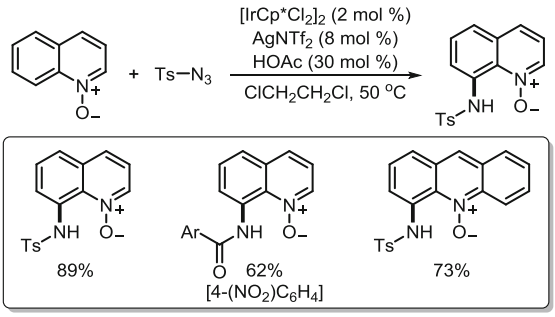
Scheme 14 Ir(III)-catalyzed diastereo-(**a**) and enantio-selective (**b**) C-H amidations of diarylphosphoryl compounds

amidation with notable selectivity. In the course of diarylphosphoryl amidation, detailed mechanistic studies revealed that Cp*Ir(III)–monoacetate is a reactive species, thus leading the authors to postulate that an introduction of chiral carboxylic acids would form a chiral Cp*Ir(III) intermediate for the asymmetric catalysis. Based on this assumption, they explored an enantioselective C–H amidation approach (Scheme 14b) [97]. Although various types of chiral carboxylic acids

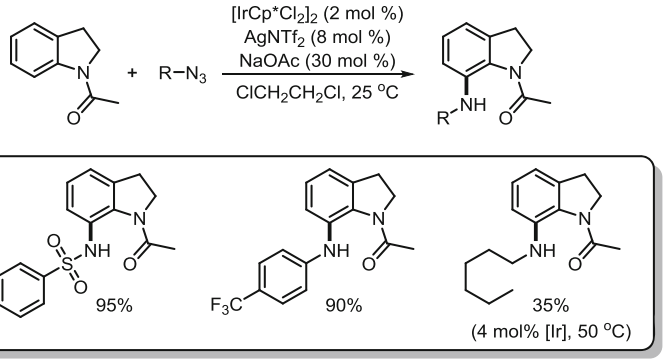
were examined for this purpose, the level of enantioselectivity is remained still low to moderate.

High reactivity of Cp*Ir(III) catalyst in the direct C–H amination with organic azides was successfully utilized in the synthesis of valuable products. Chang and coworkers proved that 8-aminoquinoline *N*-oxides could readily be obtained by a Cp*Ir(III)-catalyzed reaction of quinoline *N*-oxides with sulfonyl or acyl azides (Scheme 15) [75]. As most other metal systems were known to provide functionalization at the 2-position, the unique activation mode of the Cp*Ir(III) system at the C-8 position significantly improved quinoline derivatization. Later, they also demonstrated that a one-pot protocol of C8 functionalization of quinolines would be feasible and, therefore, a series of tandem processes was optimized consisting of *N*-oxide formation from quinolines, C–H functionalization at the C-8 position, and then deoxygenation of functionalized *N*-oxides [98].

The selective C-7 amination of indolines was achieved with Cp*Ir(III) catalyst. Chang and Li independently scrutinized the selectivity as well as reactivity of the indoline moiety that is an important structural core in pharmaceutical chemistry (Scheme 16) [99, 100]. Cp*Ir(III)-catalyzed C-7 amination proceeded efficiently

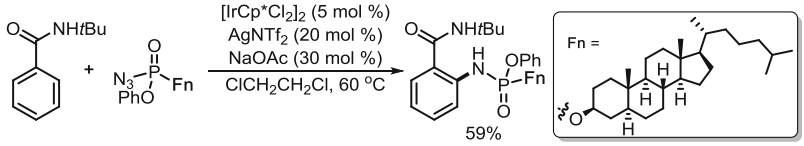


Scheme 15 Synthesis of C-8 functionalized quinoline derivatives



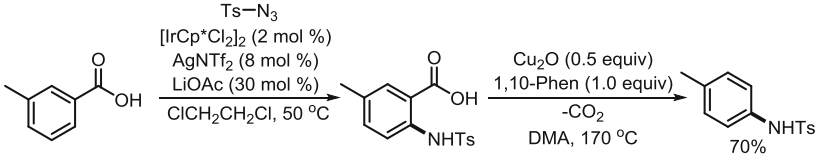
Scheme 16 Ir(III) catalyzed C–H amination with *N*-acetylindoline

under mild conditions and the scope of azides was broad including aryl, alkyl, and sulfonyl groups. In addition, a new synthetic route to phosphoramidates was developed using an intermolecular C–H amidation by the action of cationic Cp*Ir (III) catalyst with phosphoryl azides (10). As a result, this carbon–nitrogen bond formation strategy allows a quick access to a library of biologically important compounds [101, 102].



(10)

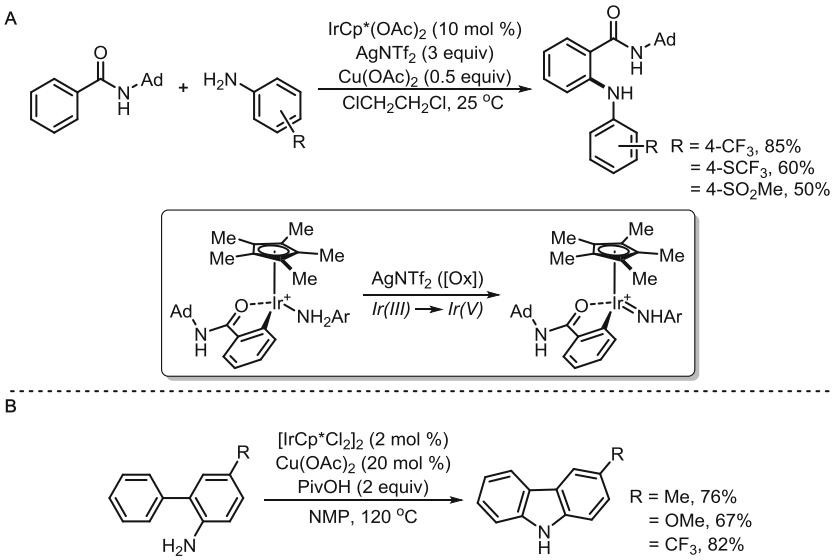
The Chang group recently developed a method installing an amino group at the *meta*- or *para*-position of arenes via the direct C–H amidation of substituted benzoic acids followed by tandem decarboxylation [103]. Traceless directing group approach consisting of sequential amidation by Cp*Ir(III)-based catalyst and one-pot Pd or Cu-promoted decarboxylation procedure provided a novel route to *meta*- or *para*-aniline products [104–107]. Remote steric effects by preexisting *meta*-substituents in benzoic acids made this method unique to produce *para*-amidated compounds exclusively, which are inaccessible by other C–H activation approaches (11).



(11)

Amino sources other than organic azides were also examined for the direct C–H amidation reactions. Chang and coworker successfully utilized *N*-substituted hydroxylamines as highly efficient amidating reagents with a Cp*Ir(III) catalyst system. Aryloxy- and acryloxycarbamates were found to undergo the C–H amidation over an assorted array of arene substrates at room temperature [108].

The high catalytic activity of Cp*Ir(III) species toward direct C–N bond-forming reactions enabled the use of anilines as an amino source in the inter- and intramolecular C–H amination reactions. In 2014, Chang group reported the first example of iridium-catalyzed oxidative C–H amination of benzamides with anilines (Scheme 17a) [109]. In a stark contrast to the conventional cross-dehydrogenative coupling reactions, this amination proceeds even at room temperature to prove the excellent performance of the iridium(III) catalyst toward C–H amination. Although the exact mechanism still needs to be explored at the present stage, the authors suggested the intermediacy of high-valent Ir(V) species formed by the assistance of an external oxidant $AgNTf_2$. Later, Miura and coworkers reported an intramolecular version of this Ir-catalyzed C–H amination of arenes leading to the synthesis of *N*–H carbazoles (Scheme 17b) [110]. Although, in contrast to the intermolecular

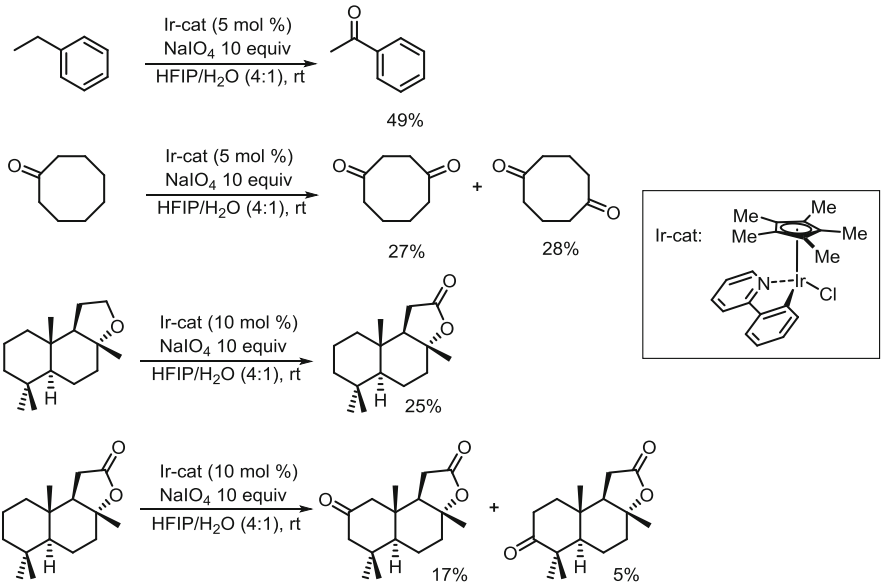


Scheme 17 Cp*Ir(III)-catalyzed dehydrogenative coupling between arenes and anilines: intermolecular (**a**) and intramolecular (**b**) C-H aminations

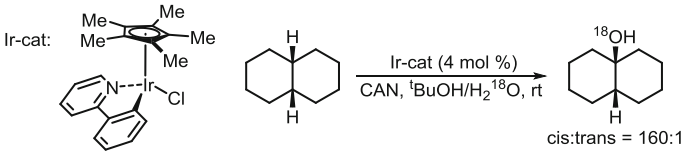
C–H amination with anilines, this procedure requires elevated temperature, the intramolecular reaction operates efficiently without the need of external oxidants, implying that this reaction may proceed via Ir(III)/Ir(I) catalytic cycle.

3.2 C–O Bond Formation

Cp*Ir(III)-based complexes have gained intense interests for their high catalytic activity in water oxidation [111–113]. In 2010, Crabtree and coworkers found that an iridacycle species could promote C–H hydroxylation with ceric ammonium nitrate (CAN) as the terminal oxidant and water as an oxygen source (12) [114]. Detailed mechanistic studies indicated that an alkane substrate is oxidized by an Cp*Ir(V)-oxo species, which is formed upon the oxidation of Cp*Ir(III)–H_2O complex with CAN [115]. While a radical pathway is ruled out, theoretical and experimental investigations support an oxygen insertion pathway, which is consistent with the observed retention of stereochemistry of *cis*-decaline and 1,4-dimethylcyclohexane.



Scheme 18 Cp*Ir (III)-catalyzed C–H oxidations



(12)

Later, $NaIO_4$ was introduced as a milder, but more efficient oxidant than CAN [116, 117] (Scheme 18). An array of functional groups was found to be compatible with the employed oxidative reaction conditions. In this context, functionalization of biologically relevant molecules such as (−)-ambroxide and sclareolide were successfully demonstrated.

In addition, molecular oxygen was shown to be an effective oxidant for the C–H oxidation with the Ir(III)-based catalyst system. In 2013, Yan and coworkers developed an aerobic oxidation system under solvent-free conditions [118]. The catalyst generated in situ from $[Cp^*IrCl_2]_2$, picolinic acid, and iodobenzene efficiently performed the reaction by using atmospheric O_2 with high turnover numbers up to 20,000 to furnish benzoic acids and aryl ketones via the selective benzylic C–H oxidation.

4 Outlook

Highly robust catalytic systems of Cp*Rh(III) and Cp*Ir(III) are expected to continue broadening their scope and improving their efficiency and selectivity in the direct C–H functionalizations and related transformations. Considering that many reactions presented in this report have not been fully understood, more detailed mechanistic elucidations of the C–H bond activation and functional group transfer steps would be crucial for the next level advance in terms of scope, reactivity, and selectivity. Particularly, a better understanding of the difference in reactivity between rhodium and iridium catalyst systems would provide a driving force to develop more practical C–H functionalization reactions even including their congener: cobalt catalyst system.

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