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Iridium-Catalyzed Direct C−H Amination with Alkylamines: Facile Oxidative Insertion of Amino Group into Iridacycle

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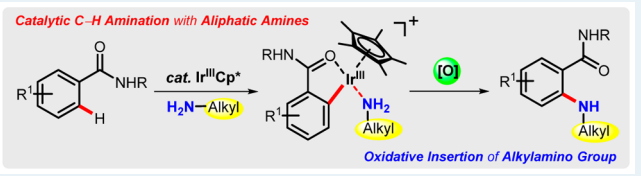
Supporting Information

ABSTRACT: Described herein is the development of Cp*Ir(III)-catalyzed direct arene C−H amination using alkylamines as an amino source. This C−N bond formation showcases a notable example of *cross-dehydrogenative coupling* to install an amino functionality at the *ortho*-position of benzamide substrates. Mechanistic studies including the isolation of an amine-bound iridacyclic intermediate along with a set of chemical oxidations demonstrated the Ir-catalyzed inner-sphere C−H amination with *primary alkylamines* for the first time.



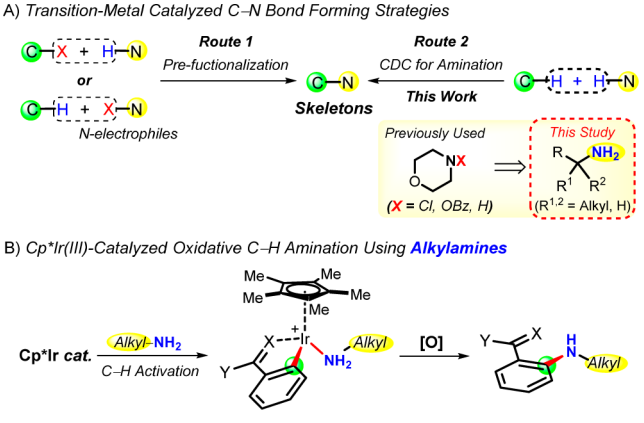
KEYWORDS: *iridium catalysis, C−H amination, alkylamines, oxidative coupling, cross-dehydrogenative coupling*

Construction of a carbon−nitrogen fragment, one of the most abundant building units in natural products, pharmacophores, and materials, has been a pivotal synthetic methodology, thus stimulating extensive research efforts to develop efficient and convenient C−N bond-forming reactions.[1] Among those methods, transition-metal-mediated procedures have come to the forefront, owing to their distinct advantages of ligand effects in achieving excellent reactivity, mild reaction conditions, and broad substrate scope.[2] Pioneered by the independent research of Buchwald and Hartwig, successful studies have been made in the N-arylation of organo-(pseudo)halides with a variety of amino sources based on the solid mechanistic understandings (Scheme 1A, top left).[3] Despite the remarkable advances achieved in this C−N cross-coupling approach, the prerequisite use of aryl (pseudo)-halides led synthetic chemists to consider the direct amination of nonprefunctionalized arenes by means of the C−H bond functionalization strategy.[4] Indeed, this perspective has guided the development of a handful of C−H amination procedures employing electrophilic aminating reagents as the coupling partner to react with arenes (Scheme 1A, bottom left).[4] In cases of displaying high reaction performance, its efficiency was attributed to the facile pseudonucleophilic character of metalated intermediates.[2f]

Although these approaches certainly bear attractive features, one limitation is the requirement of additional preparative steps for aryl (pseudo)halides or electrophilic amine precursors from arenes or amines, respectively. In this context, cross-dehydrogenative coupling (CDC)[2f,o] between arenes and amines would be an ideal alternative. However, there are several issues to consider in order to make this method more efficient and practical. For instance, metal catalysts are easily deactivated in the presence of superstoichiometric amounts of amine reactants. The requisite oxidative conditions may not be compatible with the designed catalyst system. In addition, over amination would also be a nontrivial issue especially when the amines are primary. In this regard, the direct utilization of various alkylamines as a coupling partner in metal-catalyzed C−H amination is a highly challenging task, albeit a highly desirable synthetic tool (Scheme 1A, Route 2).

In our continuing efforts to develop highly efficient direct C−H amination protocols, it was revealed that half-sandwich iridium(III) complexes exhibit notably superior performance toward catalytic C−H amination.[4g] We proved that a series of N-electrophiles work as effective amidating reagents under the exceptionally mild reaction conditions.[5] We also observed that cyclometalated half-sandwich iridium(III) complexes are compatible with certain terminal oxidants in performing catalytic C−H amination with anilines.[6] Encouraged by this result, we were prompted to advance our investigation to the

Scheme 1. Metal-Catalyzed C−N Bond Formation



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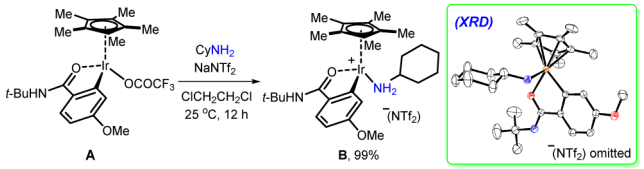
more challenging alkylamines by carefully tuning the catalytic system. Described herein is the first Ir-catalyzed inner-sphere C−H amination using *primary alkylamines* as the coupling partner (Scheme 1B), although intermolecular C−H amination with alkylamines has mostly been examined in the boundary of morpholine-type or secondary amines.[2f,7,8]

After a number of trials, we were able to isolate an amine-coordinated cationic iridacycle **B** quantitatively by treating cyclohexylamine with iridacycle **A** derived from *N*-(*t*-butyl)-4-methoxybenzamide in the presence of $NaNTf_2$ as a non-coordinating anion (Scheme 2). The structure of the key

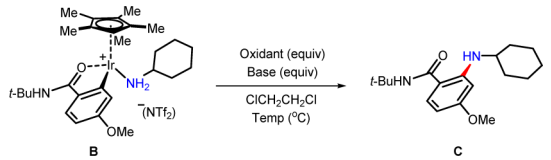
Scheme 2. Synthesis of Amine-Complexed Iridacycle



iridacycle species **B** was unambiguously characterized by X-ray crystallographic analysis. The nitrogen atom of cyclohexylamine in **B** is coordinated to the Ir metal center with a bond distance of 2.15 Å. We hypothesized that the newly synthesized *cationic* alkylamine complex needs to be readily oxidized in order to perform the subsequent C−N bond formation in accordance with our previous studies.[4g,6] This consideration prompt us to first examine a series of stoichiometric oxidations on this cationic amine adduct.

It was found that silver(I) oxidant was the most effective in this *stoichiometric* oxidative C−H amination study (Table 1).

Table 1. *Stoichiometric* Chemical Oxidation[a]



entry	oxidant (equiv)	base (equiv)	temp (°C)	yield (%)[b]
1	$AgNTf_2$ (3.2)	$Cu(OAc)_2$ (0.5)	60	40
2	**$AgNTf_2$ (3.2)**	**$Cu(OPiv)_2$ (0.5)**	**60**	**60**
3	$K_2S_2O_8$ (4.0)	$Cu(OPiv)_2$ (0.5)	60	n.r.
4	NFSI[c] (2.0)	$Cu(OPiv)_2$ (0.5)	60	n.r.
5	$PhI(OAc)_2$ (2.0)	$Cu(OPiv)_2$ (0.5)	60	n.r.
6	-	$Cu(OPiv)_2$ (0.5)	60	n.r.
7	-	$Cu(OPiv)_2$ (0.5)	120	n.r.

[a]**B** (0.2 mmol), oxidant and base in 1,2-dichloroethane (0.66 mL) for 12 h. [b]Yield based on ^{1}**H NMR** analysis of the crude reaction mixture using CH_2Br_2 as the internal standard. [c]*N*-Fluorobenzenesulfonimide.

Treatment of **B** with $AgNTf_2$ and acetate base $Cu(OAc)_2$ gave the desired *o*-aminated product **C** in 40% yield in $ClCH_2CH_2Cl$ at 60 °C (entry 1). The type of carboxylate base turned out to be critical, and $Cu(OPiv)_2$ was the most effective among several of the analogous species examined (e.g., entry 2).[9] Electron-transfer oxidants[10] other than silver(I) salts were shown to be detrimental for this transformation (entries 3−5). As predicted, **B** was not converted to the desired aminated product even at higher temperature (120 °C) in the absence of oxidant (entries 6−7). This result strongly indicates the plausible intermediacy of high-valent iridacycle species during the amino-group transfer.

To render the present C−H amination *catalytic* in the iridium species, we next optimized the reaction parameters of the initially found substoichiometric conditions (Table 2). Distinct from the stoichiometric conversion, however, the initial provisional catalytic conditions afforded the aminated product in significantly diminished yields even at elevated temperature (entries 1−2). Alternation of either base additive (entry 3) or electron-transfer oxidants (entries 4−6) did not affect the reaction efficiency. At this stage, we hypothesized that catalyst poisoning would be a main cause for the deviation in reactivity between stoichiometric and catalytic conditions. This reasoning led us to search for ways to alleviate the supposed metal deactivation by alkylamines. We paid special attention to the solvent effect in that perfluorinated alcohols, particularly 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), are known to form H-bonding to amines.[11] Indeed, Anderson et al. effectively correlated the interaction strength of HFIP-amine complexes to the enthalpy of H-bond formation measured by isothermal titration calorimetry.[11a] Taking this into consideration, we were pleased to find that improved reaction efficiency was realized by using HFIP/1,2-DCE as a cosolvent system (entries 7−9).

The choice of the *N*-alkyl group of the benzamides was observed to be another key parameter affecting the amination efficiency under the Ir-catalyzed conditions. This is not surprising in that the steric property of chelating groups is known to significantly influence the C−H bond cleavage step.[6,12] Among the assorted *N*-alkyl groups screened, the amination took place most efficiently when sterically bulky *N*-adamantylbenzamide was applied (entry 10). In a stark contrast, secondary amines such as *N*-methylcyclohexylamine were totally inert (entry 11) in accordance with our mechanistic consideration (vide infra).

On the basis of above experiments and precedent literature,[6,10,13] a mechanistic proposal of the present C−H amination with alkylamines is depicted in Scheme 3. First, a pregenerated iridium species (**I**) induces the C−H bond cleavage to generate a cyclometalated Ir(III) complex (**II**), presumably via a concerted metalation−deprotonation (CMD)[14] process. To preliminarily examine this C−H cleavage stage, kinetic isotope effect (KIE) studies were implemented. The KIE was not observed from parallel comparison reactions (k_H/k_D = 1.01), and no significant product distribution (P_H/P_D = 2.03) was measured in an intermolecular competition experiment. In addition, deuterium scrambling was shown to take place in both aminated products and recovered benzamide substrate, thus implying that the C−H cleavage is reversible and that it may not be involved in the rate-limiting stage (see SI for details).[15] This result is noteworthy in that significant KIE values (k_H/k_D = 1.83 and P_H/P_D = 5.70) were observed in the amination with anilines in our previous study.[6] Although more comprehensive mechanistic studies are required to reason this discrepancy, we assume at the present stage that the solvent effects may be responsible for this different outcomes. Although a complete mechanistic understanding for the C−N bond-forming process is beyond the scope of the present contribution, the oxidation of cationic amine iridacycle adduct (**III**) inducing an amino-group transfer is proposed to proceed presumably through a high-valent imido-iridium(V) intermediate (**V**) by the sequential oxidation by Ag^+ oxidant. Although the direct reductive elimination from **IV** also warrants consideration, we believe that it is less likely because of the

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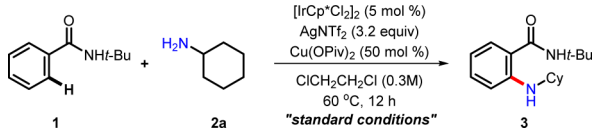
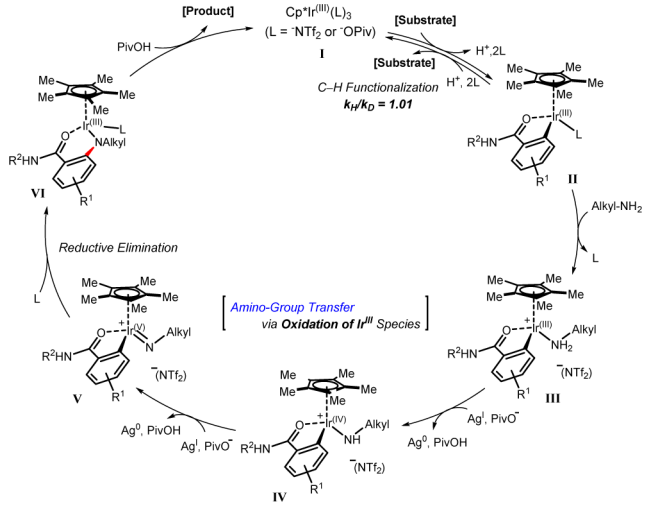
Table 2. Optimization of *Catalytic* Reaction Parameters[a]



entry	changes from the "*standard conditions*"	yield (%)[b]
1	none	28
2	conducted at 120 °C	16
3	KOPiv instead of $Cu(OPiv)_2$	22
4	$K_2S_2O_8$ instead of $AgNTf_2$	n.r.
5	NFSI[c] instead of $AgNTf_2$	n.r.
6	$PhI(OAc)_2$ instead of $AgNTf_2$	n.r.
7	$ClCH_2CH_2Cl$/HFIP(1:1) as a cosolvent	50
8	$ClCH_2CH_2Cl$/HFIP(2:1) as a cosolvent	46
9	HFIP as a sole solvent instead of $ClCH_2CH_2Cl$	45
10[c]	*N*-adamantylbenzamide instead of *N*-(*tert*-butyl)benzamide	**71(70)**
11[c]	*N*-methylcyclohexylamine instead of cyclohexylamine	n.r.

[a]**1** (0.2 mmol), **2a** (0.22 mmol), catalyst, oxidant and additive in solvent (0.66 mL) for 12 h. [b]Yield based on ^{1}**H NMR** analysis of the crude reaction mixture using CH_2Br_2 as the internal standard (isolated yield in parentheses). [c]$ClCH_2CH_2Cl$/HFIP (1:1) as a cosolvent. n.r. = no reaction.

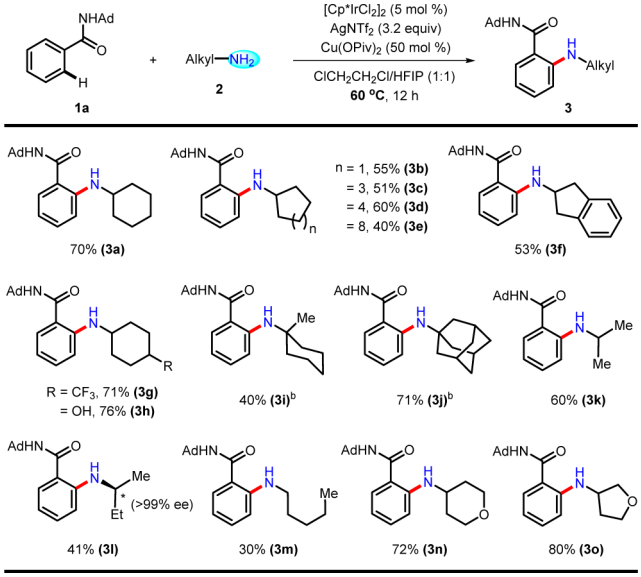
Scheme 3. Possible Mechanistic Pathway



observed poor reactivity of secondary amines (vide supra), thus leading us to propose the formation of an iridium(V) species that is also precedent in the literature.[13d] Finally, proto-demetalation of an amido-inserted iridium complex **VI** will occur to liberate the desired C−H amination product with the regeneration of a catalytically active iridium species (**I**).

With the optimized reaction conditions and mechanistic considerations in hand, we next investigated the scope of the present C−H amination procedure by employing various primary alkylamines (1.1 equiv) in reaction with *N*-adamantylbenzamide **1a** (Table 3). An array of cycloalkylamines with various ring sizes (5−12) were readily aminated to afford the desired products in good yields at 60 °C (**3a**−**e**). Benzofused alkylamine (**2f**) and cyclohexylamine containing a trifluoromethyl group (**2g**) participated in the amination without difficulty in HFIP/1,2-DCE cosolvent. Interestingly, cyclohexylamine bearing a free hydroxyl group (**2h**) also afforded the desired amination product in good efficiency, verifying high functional group tolerance. Moreover, the current amination proceeded efficiently with highly branched primary amines under slightly modified conditions employing KF instead $Cu(OPiv)_2$ (**3i**−**j**). Significantly, acyclic reactant

Table 3. Substrate Scope of Alkylamines[a]



[a]**1a** (0.2 mmol) and **2** (0.22 mmol) in 1,2-dichloroethane/HFIP (1:1, 0.66 mL) at 60 °C for 12 h (isolated yields). [b]**KF** (2.0 equiv) instead of $Cu(OPiv)_2$ in 1,2-dichloroethane (0.66 mL).

such as isopropylamine (**2k**) also smoothly underwent the amination. Notably, amination with optically pure (*S*)-(+)-*sec*-butylamine (**2l**) proceeded without epimerization, proving the excellent stereospecificity of the present C−H amination protocol. A reaction with linear amylamine (**2m**) was also successful, albeit in moderate yield. It should be noted that primary amines bearing heterocycles (**2n**−**o**) were reacted in good yields under the optimized conditions.

The scope of benzamides was next examined in reaction with cyclohexylamine (**2a**) to explore the generality of the present C−H amination procedure (Table 4). Benzamide bearing a potentially oxidizable methyl group at the *para*-position (**1b**) gave the desired product in good yield. Sterically bulky *t*-butyl substituent (**1c**) did not decrease the reactivity. As anticipated, the amination took place exclusively at the sterically less congested C−H bond in case of benzamide having a *meta*-

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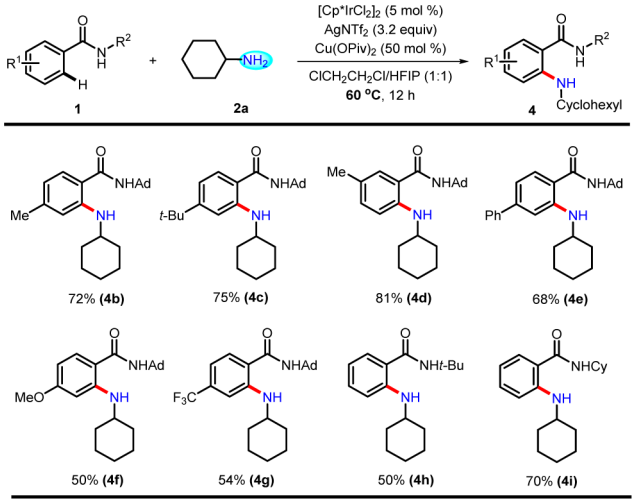
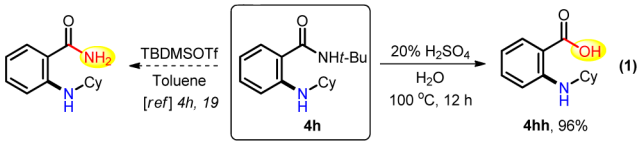
Table 4. Substrate Scope of Benzamides[a]



[a] **1** (0.2 mmol) and **2a** (0.22 mmol) in 1,2-dichloroethane/HFIP (1:1, 0.66 mL) at 60 °C for 12 h (isolated yields).

substituent (**4d**). It was revealed that the reactivity was not significantly deteriorated by the electronic variation of benzamides (**4e**–**g**). As aforementioned, the amination efficiency was maintained with sterically bulky *N*-alkyl substituents of benzamide substrates (**4h**–**i**).[16]

ortho-Aminated benzamide products obtained in this study were readily converted to synthetically[17] and biologically[18] valuable compounds according to the literature procedures, thus furnishing 2-(alkylamino)benzamide or *N*-alkylanthranilic acid (eq 1).[4h,19]



In conclusion, we have developed an oxidative Cp*Ir(III)-catalyzed direct C–H amination of arenes using primary alkylamines as a simple and abundant coupling partner. Mechanistic studies including a set of stoichiometric oxidation reactions revealed the critical role of external oxidants on the amino group insertion step, thus eventually leading to the Ir-catalyzed inner-sphere catalytic process with primary alkylamines for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02165.

General experimental procedures; characterization details; and ^{1}H, ^{13}C, and ^{19}F NMR spectra of new compounds (PDF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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(9) See the Supporting Information (SI) for detailed information.

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