Organic LETTERS

Letter

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N-Substituted Hydroxylamines as Synthetically Versatile Amino Sources in the Iridium-Catalyzed Mild C−H Amidation Reaction

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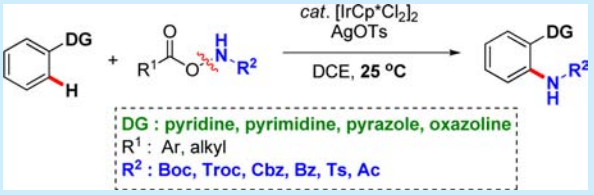
Supporting Information

ABSTRACT: *N*-Substituted hydroxylamines such as aroyloxy- or acyloxycarbamates were successfully employed as synthetically versatile amino precursors in the iridium-catalyzed direct C−H amidation of arenes. The reaction proceeds smoothly at room temperature over a broad range of substrates with high functional group tolerance to afford *N*-substituted arylamine products.



Arylamines are a versatile building unit in synthetic chemistry, and they are also an important pharmacophore in numerous natural products and synthetic compounds displaying interesting biological activities.[1] As a result, extensive research efforts have been focused toward the development of efficient synthetic procedures to introduce an amino group into (hetero)arenes.[2] In this regard, the Buchwald−Hartwig reaction has been established as a standard protocol for the amination of aryl halides.[3] More recently, a new strategy based on metal-catalyzed C−H activation has been scrutinized as a more straightforward method employing arenes as a substrate in lieu of aryl halides.[4] Although this direct C−H amination approach takes advantage of using arenes without prefunctionalization, it frequently suffers from harsh reaction conditions, a narrow substrate scope, and the need for external oxidants.[5] In fact, this reaction often works best with arene substrates that bear certain activating or directing groups under oxidative conditions.[6] In addition, a range of amine precursors have been examined such as chloroamines,[7] hydroxylamines,[8] *N*-fluorobenzenesulfonimide (NFSI),[9] or sulfonamides.[10] In this regard, we also have investigated organic azides as a readily available and convenient amino source in the direct C−H amination reactions using Rh,[11a−d] Ru,[11e] and Ir[11f−i] catalytic systems.[12] Glorius et al. recently reported an elegant example of Rh(III)-catalyzed direct C−H amidation of arenes using aroyloxycarbamates as an amino source to obtain *N*-Boc protected arylamine.[13] Zhou et al. also developed the Rh-catalyzed direct amination using nitrosobenzenes or *N*-hydroxycarbamates to give synthetically valuable products.[14]

Continuing our efforts to develop efficient and selective direct C−H amination procedures,[11,15] we envisioned employing aroyloxycarbamates and their derivatives as aminating sources under our previously developed iridium catalytic systems.[11f−i] We were also curious about testing a postulate that amidation efficiency might be related to the N−O bond strength of the amino precursors. In this aspect, we have successfully applied a range of aroyloxy- and acyloxycarbamates to an Ir-catalyzed direct amidation of arenes, thus allowing a significant expansion of direct C−H amination approaches to afford synthetically versatile *N*-substituted aniline products.

At the outset of our studies, we screened optimal amidation conditions in a model reaction of 2-phenylpyridine **1a** with 1.1 equiv of *N*-Boc-substituted benzoylhydroxyamine[16] **2a**. The desired amidation took place smoothly with an iridium precursor, $[IrCp^*Cl_2]_2$ (2.5 mol %), in the presence of a $AgNTf_2$ additive (10 mol %, Table 1, entry 1). In addition to a monoamidated product (**3a**), a bis-amidated minor compound (**4a**) was also formed (**3a**/**4a**, 76:9). While the amidation proceeded efficiently even at rt (entry 2), it became quite sluggish without a silver salt (entry 3). Among various silver additives screened, air stable AgOTs (entry 5) turned out to be the most effective in view of the selectivity (see the Supporting Information (SI) for details). When KOAc was used in lieu of

Table 1. Optimization of the Ir-Catalyzed Amidation[a]

entry	catalyst	additive	*t* (°C)	yield[b] (**3a**/**4a**, %)
1	$[IrCp^*Cl_2]_2$	$AgNTf_2$	50	76:9
2	$[IrCp^*Cl_2]_2$	$AgNTf_2$	25	74:7
3	$[IrCp^*Cl_2]_2$	none	25	11:0
4	$[IrCp^*Cl_2]_2$	AgOAc	25	68:5
5	$[IrCp^*Cl_2]_2$	AgOTs	25	81:5
6[c]	$[IrCp^*Cl_2]_2$	KOAc	25	18:0
7[d]	$[IrCp^*Cl_2]_2$	AgOTs	25	96:0 (92)
8	$[RhCp^*Cl_2]_2$	$AgSbF_6$	25	44:0
9	$[Ru(p\text{-cymene})Cl_2]_2$	$AgNTf_2$	80	<10:0
10[c]	$Pd(OAc)_2$	$PhI(OAc)_2$	80	0:0

[a]Reaction conditions: **1a** (0.1 mmol) and **2a** (1.1 equiv) in 1,2-dichloroethane (DCE, 0.5 mL). [b]Yield and ratio were based on ^1H NMR of crude reaction mixture ($Cl_2CHCHCl_2$ as an internal standard). [c]100 mol % of additive was used. [d]**1a** (1.2 equiv) and **2a** (0.1 mmol) for 10 h; isolated yield is in parentheses.

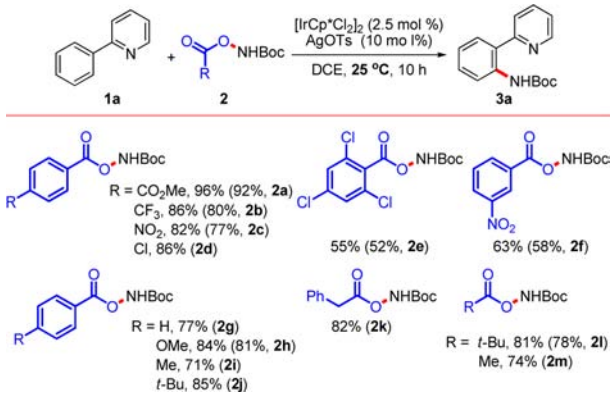
Received: May 9, 2014
Published: June 5, 2014

   dx.doi.org/10.1021/ol501338h | *Org. Lett.* 2014, 16, 3328−3331

silver species, only a poor yield was obtained (entry 6). The reaction efficiency and selectivity were also sensitive to the choice of solvents, and 1,2-dichloroethane (DCE) was selected for the subsequent study. The formation of a bis-amidated compound (**4a**) could be suppressed by changing the stoichiometry of two reactants. Indeed, a monoamidated product **3a** was obtained exclusively without **4a** when substrate **1a** was employed in slight excess relative to an amidating reagent **2a** (**1a**/**2a**, 1.2:1; entry 7). Interestingly, the amidation was much poorer when other catalyst systems were used. For instance, whereas a Rh species [Cp*Rh(III)] catalyzed the reaction in moderate efficiency (entry 8), the amidation was not effective with Ru or Pd catalysts (entries 9−10).

With the optimized conditions in hand, we next investigated the scope of various amidating reagents in reaction with 2-phenylpyridine at rt (Scheme 1). It was observed that a wide

Scheme 1. Scope of Various Electrophilic Amidating Agents[a]

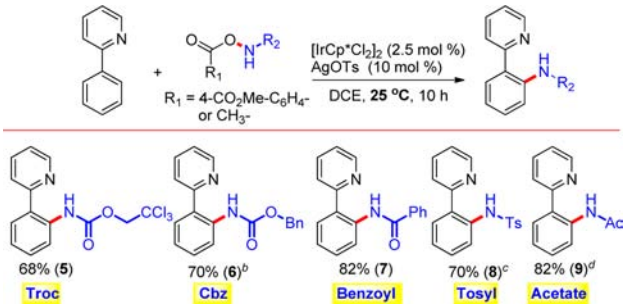


[a]Reaction conditions: **2** (0.2 mmol) and **1a** (1.2 equiv) in 1,2-dichloroethane (0.5 mL); yields are based on NMR of crude reaction mixture ($Cl_2CHCHCl_2$ as an internal standard); percentages given in parentheses are isolated yields.

range of amidating reagents could be employed with high efficiency irrespective of their electronic properties at the benzoyl side: electron-withdrawing (**2a**−**2f**), neutral (**2g**), or donating groups (**2h**−**2j**) gave comparable product yields. Not only benzoyloxy derivatives but also acyloxy analogues such as phenylacetyl (**2k**), pivaloyl (**2l**), and acetyl (**2m**) readily participated in the reaction as efficient amidating reagents, thus significantly expanding the scope of the present protocol.

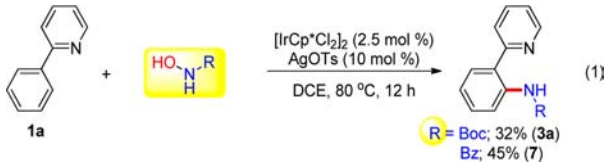
Next, we investigated the feasibility of introducing various types of *N*-carbamates at arene C−H bonds using *N*-substituted aroyloxyamines (Scheme 2). We were pleased to see that a range of synthetically useful *N*-substituents could readily be employed for this purpose to furnish the desired products in high yields. Trichloroethyl carbamate (Troc, **5**) and carboxybenzyl (Cbz, **6**) were introduced satisfactorily. Other derivatives such as those that include the benzoyl (Bz, **7**) and tosyl (Ts, **8**) group were also synthesized efficiently. When *N*-acetoxyacetamide was reacted with 2-phenylpyridine, the desired acetamidation proceeded highly efficiently to afford **9** at 25 °C, releasing acetic acid as a byproduct. The fact that various *N*-substituted aniline products could be accessed through the present procedure offers synthetic flexibility in the utilization of the obtained products. In fact, *N*-substituents can be removed under acidic (*N*-Boc), basic (*N*-Ac and *N*-Bz), or hydrogenation conditions (*N*-Cbz).[17]

Scheme 2. Scope of Amidating Reagents[a]



[a]Reaction conditions: **1a** (0.2 mmol) and **2** (1.2 equiv) in 1,2-dichloroethane (0.5 mL), R^1 = 4-CO_2Me-C_6H_4-. [b] At 50 °C. [c] 3 mol % of catalyst and 12 mol % of $AgNTf_2$ at 60 °C. [d] R^1 = $-CH_3$.

With the successful application of *N*-substituted *O*-benzoyl or *O*-acyloxyamines as efficient amino sources, we were also curious about whether *N*-substituted "*free*" hydroxylamines could be employed for the direct C−H amidation. When *N*-Boc-hydroxylamine was reacted with 2-phenylpyridine, the desired product (**3a**) was obtained in low yield even at 80 °C (eq 1). The efficiency was slightly improved when *N*-benzoylhydroxylamine was used leading to **7** in 45% yield.

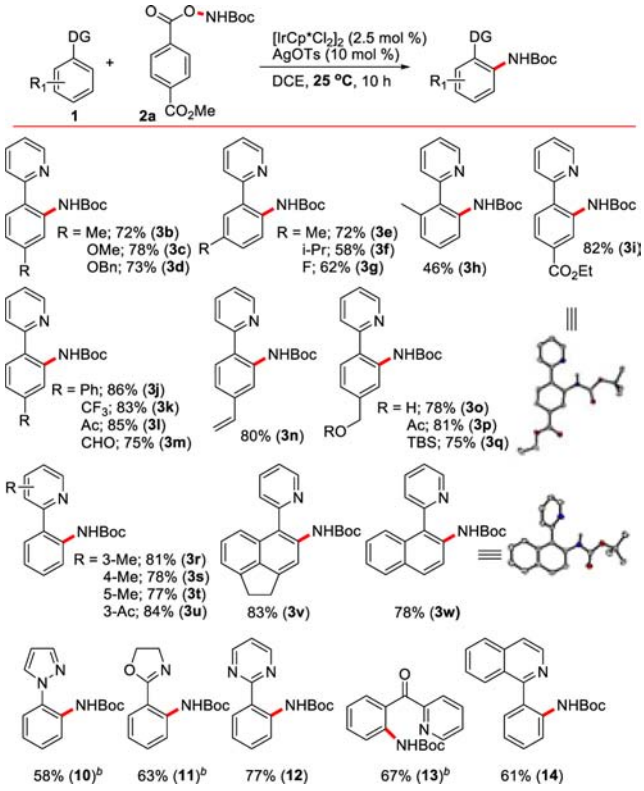


With the optimal conditions and preliminary results of the reactivity dependence on amidating reagents in hand, we subsequently examined the scope of substrates in reactions with *N*-Boc-substituted aroyloxyamine **2a** (Scheme 3). Overall, the amidation proceeded efficiently at rt irrespective of electronic and/or steric variation in substrates. Indeed, 2-phenylpyridine derivatives bearing electron-donating groups such as alkyl and alkoxy (**3b**−**3f**, **3h**) underwent the amidation in good yields. Likewise, electron-withdrawing substituents including fluoro (**3g**), ester (**3i**), phenyl (**3j**), trifluoromethyl (**3k**), and acetyl (**3l**) groups did not deteriorate the reaction efficiency. The structure of product **3i** was unambiguously confirmed by an X-ray diffraction.

Sensitive groups such as aldehyde (**3m**) and olefin (**3n**) were compatible with the present conditions. Functional group tolerance was excellent as demonstrated by the successful reaction of substrates bearing free hydroxyl (**3o**), acetyl (**3p**), and silyl (**3q**) groups. It needs to be mentioned that the amidation is highly selective occurring at the *ortho*-position relative to the 2-pyridinyl moiety even in the presence of ester or ketone (**3i**, **3l**), which were shown by us to work as effective chelating groups under the Ir-catalyzed C−H functionalzia-tion.[11h] Variation of the type of substituents and/or their position in the pyridyl moiety of 2-phenylpyridine substrates was viable as seen in the facile formation of **3r**−**3u**. Direct amidation at fused arenes such as 1,2-dihydroacenaphthylene (**3v**) and naphthyl (**3w**) was also smooth under the present conditions. The structure of **3w** was confirmed by an X-ray crystallographic analysis. The current amidation was convenient for a scale-up process without difficulty. For example, amidation of **1k** with **2a** could be performed in gram quantity using 1 mol

dx.doi.org/10.1021/ol501338h | *Org. Lett.* 2014, 16, 3328−3331

Scheme 3. Substrate Scope for the Ir-Catalyzed Amidation[a]



[a] **2a** (0.2 mmol), **1** (1.2 equiv), $[IrCp^*Cl_2]_2$ (2.5 mol %), and AgOTs (10 mol %) in 1,2-dichloroethane (0.5 mL). [b] $AgNTf_2$ was used instead of AgOTs at 50 °C.

% of the [Ir] catalyst to afford **3k** in 78% yield (see the SI for details).

Heterocyclic compounds other than pyridine were next examined as plausible chelating groups in the present direct C−H amidation approach (Scheme 3). 2-Phenylpyrazole, 2-phenyl-2-oxazoline, 2-phenylpyrimidine, and 2-benzolypyridine were readily amidated to afford the corresponding products (**10**−**13**) in high yields. 1-Phenylisoquinoline (**14**) was also a facile substrate for the present direct C−H amidation.

To obtain mechanistic insights into the present direct C−H amidation reaction, a series of preliminary experiments were carried out. A small value for primary kinetic isotope effects (*KIE* = 1.19) was measured in a parallel experiment (Scheme 4a), implying that the C−H bond cleavage may not be involved in the rate-limiting stage.[14b,18] Two iridacyclic species (**15** and **16**), prepared separately (Scheme 4b), catalyzed the amidation with similar efficiency (Scheme 4c), suggesting that those complexes could be involved in the catalytic cycle under the corresponding conditions. Interestingly, an iridacycle **16** was found to contain an additional molecule of acetic acid, being connected to an acetato ligand through the H-bond, and its structure was unambiguously confirmed by X-ray crystallographic analysis.

Because it was intriguing to see the effects of the electronic property of the leaving group on the reaction progress, initial amidation rates were compared among amidating reagents bearing electronically different substituents. Although electron-donating groups induced the reaction to be slightly faster compared to electron-withdrawing substituents (Figure 1), the difference was not significant, implying that the cleavage of a

Scheme 4. Preliminary Mechanistic Investigation

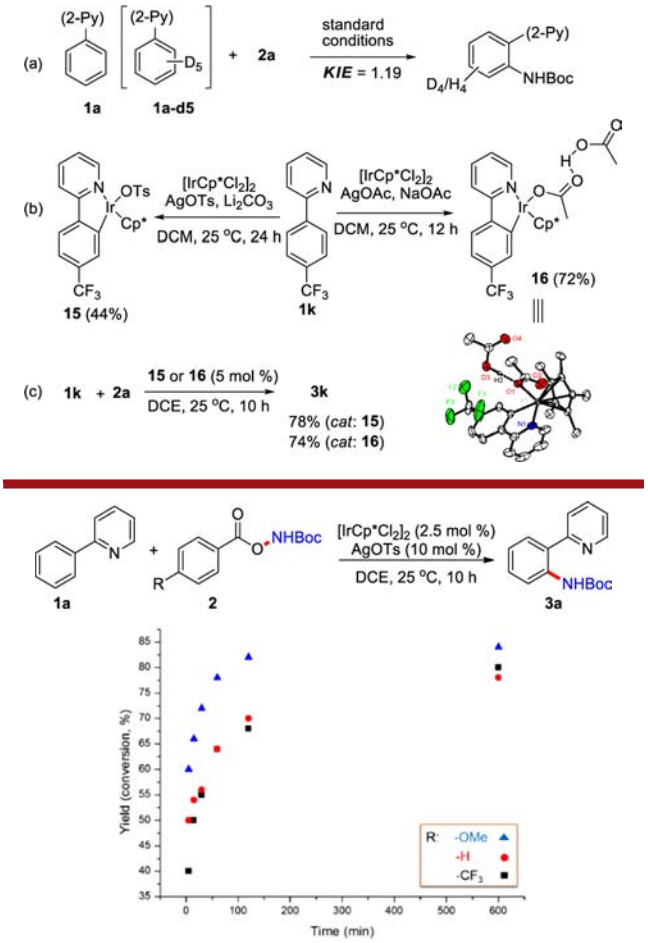


Figure 1. Initial reaction rates with amidating reagents bearing electronically different *p*-substituents.

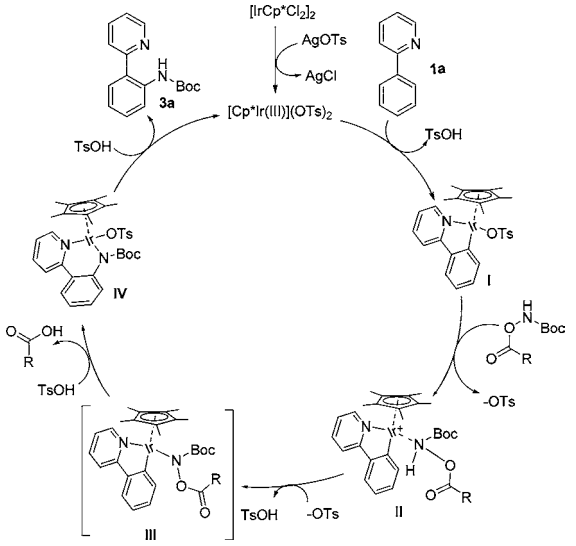
benzoyl leaving group from the amidating reagents does not affect the rate-controlling stage of the catalytic cycle.

Based on the above-mentioned mechanistic studies and precedent literature,[19] a catalytic cycle of the present Ir(III)-catalyzed direct C−H amidation is proposed in Scheme 5, using 2-phenylpyridine as a model substrate. It is assumed that a dimeric iridium species is converted to its monomeric sulfonato complex upon the addition of the AgOTs additive. An iridacycle **I** will be generated by the reaction of a substrate with the *in situ* generated monomeric iridium species. As a next step, a ligand exchange is believed to occur leading to **II** that undergoes a migratory insertion to give an iridium amido complex (**IV**) with the concomitant release of a carboxylic acid presumably via **III**. Alternatively, a pathway involving Ir(V), formed by the oxidative addition of the N−O bond to Ir(III), cannot completely be ruled out at the present stage. Finally, product **3a** is formed by protodemetalation of **IV** with the regeneration of a metal catalyst.

In summary, we developed an efficient iridium-catalyzed direct C−H amidation of arenes using aroyloxy- or acyloxycarbamates as amino sources. A range of arene substrates was selectively amidated at rt in high efficiency with excellent functional group tolerance. The amidation procedure does not require external oxidants or bases, and it can be scaled up without difficulty. Various types of synthetically versatile *N*-substituted aniline products were accessed including *N*-Boc, *N*-

dx.doi.org/10.1021/ol501338h | *Org. Lett.* 2014, 16, 3328−3331

Scheme 5. Plausible Catalytic Cycle



Cbz, *N*-Troc, *N*-Bz, *N*-Ts, and *N*-Ac groups, thus offering a powerful tool that allows versatility and flexibility, which would be potentially useful in organic synthesis, medicinal chemistry, and materials science.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Institute of Basic Science (IBS) in Korea.

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