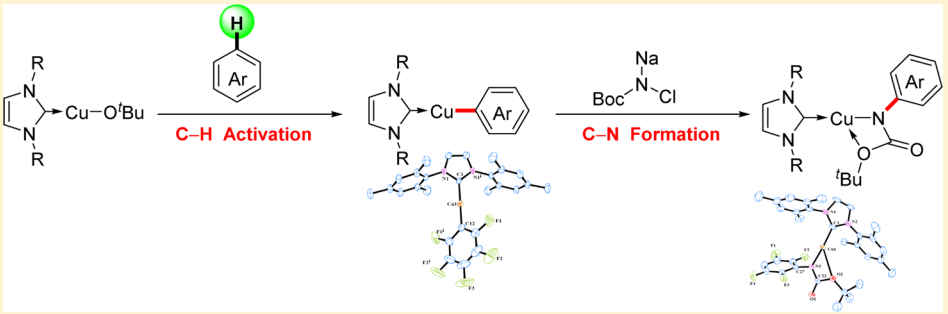
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

(NHC)Cu-Catalyzed Mild C−H Amidation of (Hetero)arenes with Deprotectable Carbamates: Scope and Mechanistic Studies

Weilong Xie,[†,‡] Jung Hee Yoon,[†,‡] and Sukbok Chang*[,†,‡]

[†]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, South Korea
[‡]Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-701, South Korea

Supporting Information



ABSTRACT: Primary arylamines are an important unit broadly found in synthetic, biological, and materials science. Herein we describe the development of a (NHC)Cu system that mediates a direct C−H amidation of (hetero)arenes by using *N*-chlorocarbamates or their sodio derivatives as the practical amino sources. A facile stoichiometric reaction of reactive copper-aryl intermediates with the amidating reagent led us to isolate key copper arylcarbamate species with the formation of a C−N bond. The use of ^{t}BuONa base made this transformation catalytic under mild conditions. The present (NHC)Cu-catalyzed C−H amidation works efficiently and selectively on a large scale over a range of arenes including polyfluorobenzenes, azoles, and quinoline *N*-oxides. Deprotection of the newly installed carbamate groups such as Boc and Cbz was readily performed to afford the corresponding primary arylamines.

INTRODUCTION

Functionalized arylamines are versatile compounds to show broad utility in various fields such as organic synthesis, medicinal chemistry, and materials science (Figure 1).[1] For instance, cefdinir is a third-generation antibiotic for treating infections caused by Gram positive and negative bacteria,[1c] and triphenylamines (TPA) draw interest in the field of organic light-emitting diodes (OLEDs).[1f−h] As a result, various preparative methods have been developed for the synthesis of arylamines.[2] Among those, whereas a tandem procedure of nitration followed by reduction is the most conventional route,[2,3] it often requires dealing with issues of selectivity and functional tolerance. In this context, transition-metal-catalyzed construction of C−N bonds has attracted special attention.[4] In particular, Pd-catalyzed N-arylation of aryl (pseudo)halides is now well-established with broad applications by the pioneering contributions of Buchwald and Hartwig.[4,5] On the other hand, as an alternative approach, direct C−H amination of arenes has recently been scrutinized with the use of several late transition metals such as Pd, Ru, Rh, and Ir.[6] The direct C−H amination approach has also been examined by using first-row transition metals due to their abundance, cost efficiency, and environmental compatibility.[7] In this line, copper has been investigated in the C−H amination that occurs through an oxidative coupling pathway[8] as well as in the conventional nucleophilic amination.[9]

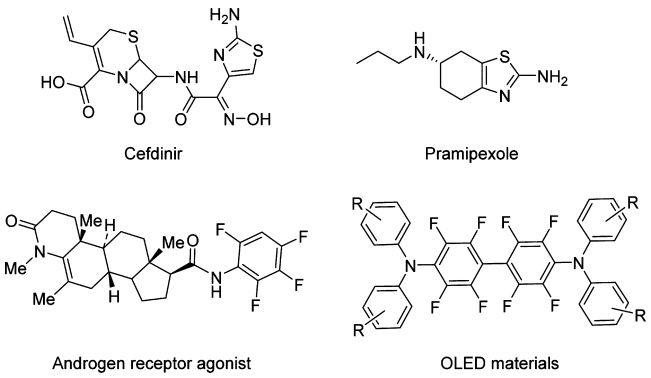


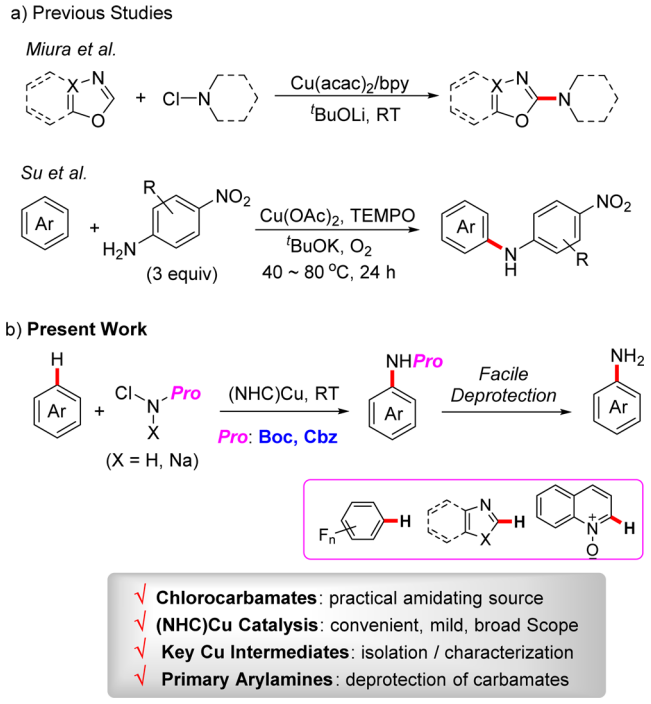
Figure 1. Selected examples of arylamines in applications.

Recently, Miura et al. introduced secondary chloroamines as a highly efficient electrophilic aminating source for the copper-catalyzed C−H amination of azoles (Scheme 1a, top).[10] Those amino precursors were subsequently utilized in the Rh- or Fe-catalyzed *ortho*-amination of arenes.[11] In addition, *O*-acyl

Received: July 20, 2016
Published: September 1, 2016

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

Scheme 1. Cu-Catalyzed C−H Amination of (Hetero)arenes



hydroxylamine derivatives were also shown to be an efficient aminating source in the C−H amination by the action of several metal catalysts including Pd,[12a−d] Rh,[12e] Co,[12f] or Cu.[12g,h] Su et al. proved that electron-deficient anilines can be directly reacted with (hetero)arenes by copper catalyst in the presence of TEMPO and alkoxide base under aerobic oxidative conditions to afford secondary diraylamines (Scheme 1a, bottom).[13] We previously showed that silver, cobalt, or manganese species can effectively mediate a nondirected C−H amination of azoles.[14] Detailed mechanistic studies of these reactions revealed that they involve an oxidative rearomatization process as a key element, thus giving rise to difficulty in expanding the substrate scope beyond azoles.[15]

Continuing our interests in the direct C−H amination reactions,[16] we herein present the development of (NHC)Cu-catalyzed C−H amidation of (hetero)arenes by using *N*-chlorocarbamates or their sodio derivatives as the practical amino sources. Stoichiometric studies to fully characterize two key copper intermediates led us to optimize mild catalytic conditions that were successfully applied to various substrates including fluoroarenes, azoles, and quinoline *N*-oxides. Facile deprotection of initially introduced carbamate groups readily delivered primary arylamines.

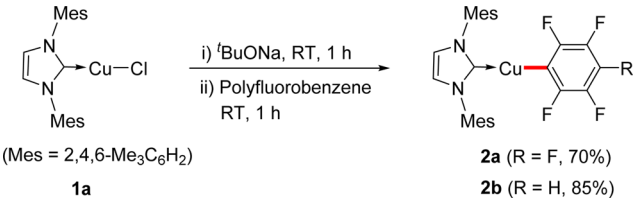
RESULTS AND DISCUSSION

Stoichiometric Amidation: Characterization of Key Copper Intermediates. Recently, N-heterocyclic carbene (NHC)-copper complexes have been fruitfully utilized in various important catalytic reactions.[17] Along with this methodology development, detailed mechanistic investigations have been made mainly by the characterization of key intermediates bearing NHC as a stabilizing ligand.[18] Inspired by Nolan and Hou's independent studies,[19,20] we recently reported a (NHC)Cu-catalyzed C−H allylation and homoallylation of polyfluoroarenes or heteroarenes.[21] Subsequently, we were curious if a similar catalyst system of (NHC)Cu can also be applied to the direct C−H amination of (hetero)arenes.

We decided to initiate this prospective program first by figuring out key plausible intermediates in a stoichiometric transformation to see whether the envisioned C−H amination would indeed be feasible. We, therefore, attempted the characterization of a (NHC)Cu-aryl species that would serve as a precursor in a subsequent C−N bond formation.

A NHC-bound copper complex, [(IMes)CuCl] [**1a**, IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene], was treated with sodium *tert*-butoxide (1.0 equiv) in benzene, and then 1.0 equiv of pentafluorobenzene was added at room temperature (Scheme 2). The reaction was completed within 2 h to

Scheme 2. Synthesis of Reactive Copper-Aryl Complexes



afford a new copper species that was isolated (70%), and its structure was determined by NMR to be [(IMes)Cu-(C_6F_5)] (**2a**). Similarly, an analogous copper-aryl species, [(IMes)Cu-(2,3,5,6-C_6F_4H)] (**2b**), could be isolated in 85% yield by employing 1,2,4,5-tetrafluorobenzene in THF solvent.

Pleasingly, the molecular structure of **2a** was confirmed by an X-ray crystallographic analysis to display that this copper complex is monomeric (Figure 2). The angle of C_{NHC}−Cu−

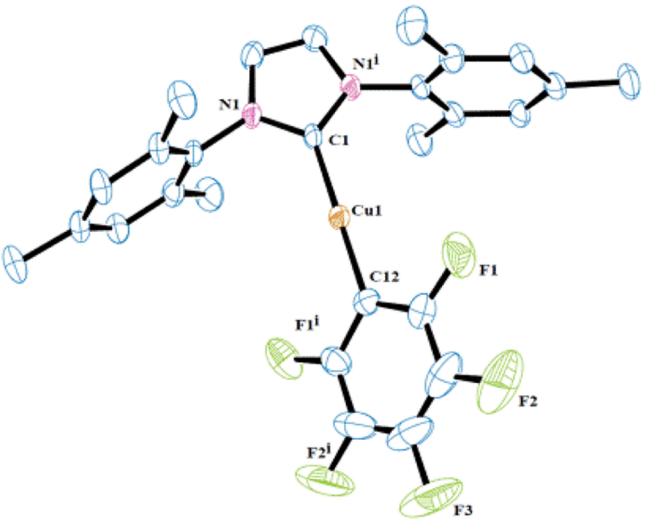


Figure 2. ORTEP of **2a** with thermal ellipsoids set at 50% probability level (H atoms and benzene solvent are omitted for clarity). Selected bond lengths (Å) and angles (deg): Cu1−C1, 1.888(6); Cu1−C12, 1.907(6); C1−Cu1−C12, 180.0.

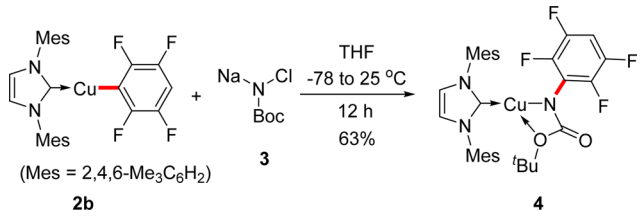
C_{aryl} bonds is 180.0° to indicate that the bonding configuration is completely linear. Bond lengths of Cu−C_{NHC} and Cu−C_{aryl} are 1.888(6) and 1.907(6) Å, respectively. The Cu−C_{aryl} bond in this complex turns out to be shorter when compared to that of Cu−C_{aryl} in a previously reported tetrameric pentafluorophenyl copper species [1.962(2) to 2.007(2) Å],[22a] but slightly longer than that of a pentafluorophenyl copper-pyridine

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

complex [1.8913(17) Å].[22b] The Cu−C_{aryl} bond length in complex **2a** is similar to that in a dimeric complex of (4-methoxy-2,3,5,6-tetra-fluorophenyl)copper-phenanthroline reported by the Daugulis group, where the corresponding bond length is 1.932(2) Å.[19d] It should be noted that complex **2a** represents *the first example of structurally characterized NHC-bound copper polyfluoroaryl species* to our best knowledge. In fact, while polyfluoroarenes are known to readily react with (NHC)Cu complexes to afford the corresponding copper-aryl species which were proposed as the key intermediate in a number of reactions,[19a,20a,b,21] these species have not been crystallographically characterized while the {(IPr)Cu[C_6H_4(4-OMe)]} complex obtained from a reaction of [(IPr)Cu(O^tBu)] with arylboronic ester was known [IPr = *N,N′*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene].[18b]

With these isolated copper-aryl complexes [(NHC)Cu-Ar_F] in hand, we next examined the feasibility of copper-mediated C−N bond formation by reaction with amino precursors. Regarding plausible amino sources, we first chose *N*-chlorocarbamate derivatives since they are easy to prepare and convenient to handle. Moreover, we envisioned that, upon deprotection of initially formed carbamate-bearing products, the corresponding primary arylamines can readily be accessible. To our delight, when [(IMes)Cu-(2,3,5,6-C_6F_4H)] (**2b**) was allowed to react with *N*-chloro-*N*-sodio-*tert*-butylcarbamate [(Boc)N(Na)(Cl)] (**3**), easily prepared from Boc-NH_2 (*vide infra*), the aryl group was smoothly transferred from the copper center to the nitrogen atom of the carbamate group to deliver [(IMes)Cu-N(Boc)(2,3,5,6-C_6F_4H)] (**4**) in THF solvent (63%), thus *generating a new C−N bond* (Scheme 3). This complex was fully characterized by NMR and X-ray analysis to disclose that complex **4** is also monomeric (Figure 3).

Scheme 3. Stoichiometric C−N Bond Formation



The carbamate group is shown to be bound to the copper center in an η^1-N−η^1-O fashion forming a three-coordinate copper species. Interestingly, an alkoxy group instead of carbonyl oxygen is weakly coordinated to the copper center (Cu1—O2: 2.838 Å). Bond lengths of Cu—C_{NHC} and Cu—N are 1.8720(13) and 1.8742(11) Å, respectively. The Cu—C_{NHC} bond length in complex **4** is slightly shortened compared to that in complex **2a**, and the Cu—N bond length is slightly longer than the reported Cu—N distance in the copper anilido complex [1.846(2) Å].[23] The angle of C1—Cu1—N3 is 173.53(6)°, only slightly distorted from linearity. Interestingly, weak interactions of C—H···F—C and C—H···O═C were displayed from the crystal packing of this complex (see Table S14 in the Supporting Information for details). To our best knowledge, this copper complex [(IMes)Cu-N(Boc)(2,3,5,6-C_6F_4H)] (**4**) is *the first characterized copper species obtained from a copper-mediated C−N bond forming-process*.

***N*-Choro-*N*-sodio-carbamates as the Practical Amidating Reagent.** The above stoichiometric reactions demonstrated that copper-aryl complexes, generated from copper-

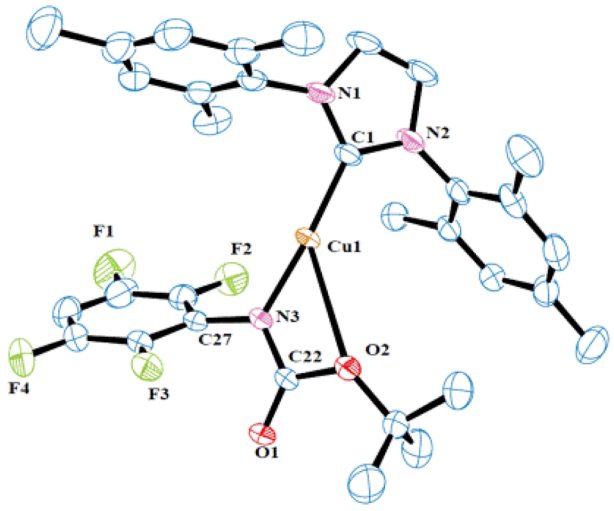
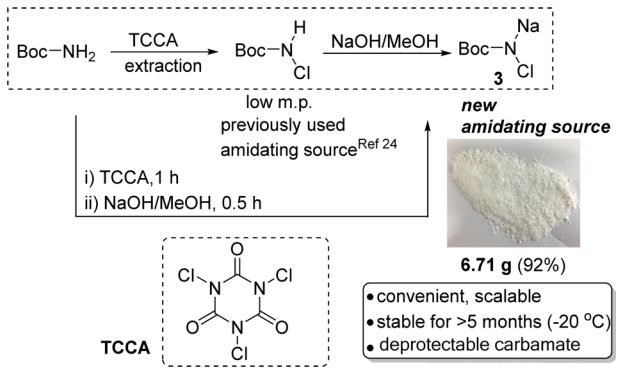


Figure 3. ORTEP of **4** with thermal ellipsoids set at 50% probability level (H atoms are omitted for clarity). Selected bond lengths (Å) and angles (deg): Cu1−C1, 1.8720(13); Cu1−N3, 1.8742(11); C1−N1, 1.3609(19); C1−N2, 1.3594(18); N3−C22, 1.3529(18); C1−Cu1−N3, 173.53(6); N1−C1−Cu1, 128.15(11); N2−C1−Cu1, 127.55(11).

mediated C−H activation of (hetero)arenes, readily react with *N*-chloro-*N*-sodio-*tert*-butylcarbamate (**3**) forming a *new C−N bond*. This result led us to anticipate that the development of a direct C−H amination with the (NHC)Cu system would be highly feasible. First, we tried to establish a preparative procedure of the amidating precursor. While we recently reported a Rh-catalyzed C-8 amidation of quinoline *N*-oxides by using *N*-chlorocarbamates,[24] these amino presursors are often difficult to handle because of troublesome physical properties (e.g., *tert*-butyl chlorocarbamates: mp 39 °C[24]).

In this text, we desired to employ a more convenient and practical type of amino sources for the C−H amination. Previously, it was reported that *N*-chloro-*N*-sodio-*tert*-butylcarbamate was readily prepared by the reaction of *tert*-butylcarbamate (Boc-NH_2) with ^{t}BuOCl followed by treatment with NaOH/MeOH.[25] In our case, the same product could be obtained in high yield by a reaction of Boc-NH_2 with trichloroisocyanuric acid (TCCA) followed by a treatment with NaOH/MeOH (Scheme 4). It should be mentioned that trichloroisocyanuric acid is cheap and the byproduct (isocyanuric acid) is nontoxic. This reaction could be performed on a large scale to produce *N*-chloro-*N*-sodio-*tert*-butylcarbamate

Scheme 4. Preparative Route to *N*-Chloro-*N*-sodio-*tert*-butylcarbamate (3)

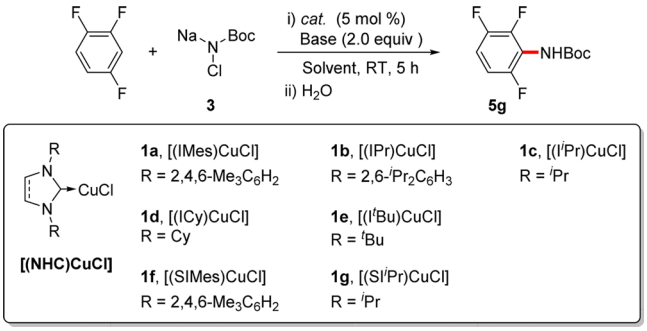


DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

(3). The isolation process is also easy: a conventional workup provides the analytically pure solid product in high yield (see the Supporting Information for details). Importantly, *N*-chloro-*N*-sodio-*tert*-butylcarbamate (3) is convenient to handle and stable to store without decomposition for a few months at −20 °C.

Catalytic C−H Amidation with (NHC)Copper System. Encouraged by the above stoichiometric transformations, we initiated an optimization study of the (NHC)Cu-catalyzed C−H amidation of 1,2,4-trifluorobenzene[26] in reaction with 1.1 equiv of *N*-chloro-*N*-sodio-*tert*-butylcarbamate (3) (Table 1).

Table 1. Optimization for the Amidation Conditions[a]



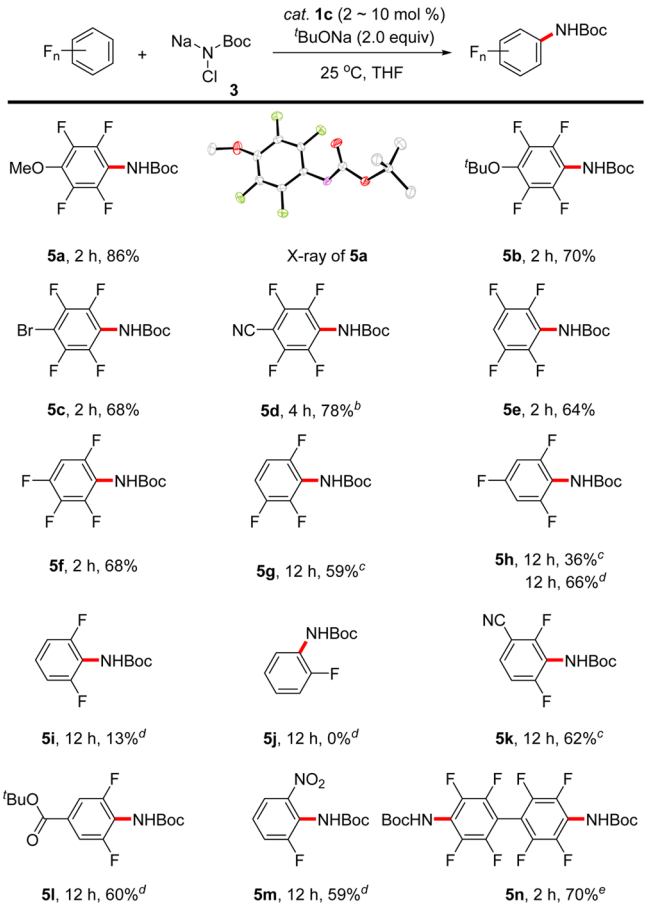
entry	catalyst	base	solvent	yield[b] (%)
1	**1a**	^{t}BuONa	THF	43
2	**1b**	^{t}BuONa	THF	12
3	**1c**	^{t}BuONa	THF	57
4	**1d**	^{t}BuONa	THF	48
5	**1e**	^{t}BuONa	THF	51
6	**1f**	^{t}BuONa	THF	42
7	**1g**	^{t}BuONa	THF	56
8	CuCl	^{t}BuONa	THF	14
9	–	^{t}BuONa	THF	<1
10	**1c**	–	THF	<1
11	**1c**	^{t}BuOLi	THF	3
12	**1c**	^{t}BuOK	THF	12
13	**1c**	^{t}BuONa	1,4-dioxane	45
14	**1c**	^{t}BuONa	toluene	<1
15	**1c**	^{t}BuONa	$ClCH_2CH_2Cl$	<1
16[c]	**1c**	^{t}BuONa	THF	58
17[d]	**1c**	^{t}BuONa	THF	65
18[d,e]	**1c**	^{t}BuONa	THF	63

[a]1,2,4-Trifluorobenzene (0.2 mmol), **3** (1.1 equiv), base (2.0 equiv), catalyst (5.0 mol %), and dibenzyl (0.5 equiv, internal standard) in THF (0.5 mL). [b]Crude NMR yields. [c]Performed in dark conditions. [d]For 12 h. [e]*tert*-Butyl *N*-chlorocarbamate was used as the amidation source with 3.0 equiv of base.

When pregenerated (NHC)Cu catalysts (5 mol %) were examined in the presence of 2 equiv of ^{t}BuONa, the desired amidation was found to proceed more efficiently at room temperature with IMes or I^{i}Pr [I^{i}Pr = 1,3-diisopropylimidazol-2-ylidene] ligands when compared to IPr (entries 1−3). Other copper NHC complexes including ICyCuCl (**1d**) or I^{t}BuCuCl (**1e**) displayed slightly lower efficiency compared to I^{i}PrCuCl (**1c**) (entries 4−5). In addition, copper catalysts bearing saturated NHCs such as SIMes (**1f**) or SI^{i}Pr (**1g**) were also effective for the present amidation (entries 6−7). A reaction with CuCl alone took place only in low efficiency (entry 8) while no conversion was observed in the absence of copper species or base (entries 9−10). Counter cations of *tert*-butoxide base were influential for the amidation efficiency to reveal that lithium or potassium was less effective than sodium (compare entries 3 and 11−12). While the use of 1,4-dioxane solvent led to a slightly decreased yield than THF (compare entries 3 and 13), other nonpolar solvents were totally ineffective (entries 14−15). When the reaction was carried out in dark conditions, no noticeable change was observed (entry 16) to imply that the amidation is not affected by visible light as sometimes observed in the copper-catalyzed reactions.[27] The amidation gave a similar yield when *tert*-butyl *N*-chlorocarbamate [Boc-NH(Cl) in Scheme 4] was employed as an amino source, but with higher loading of ^{t}BuONa (entry 18).

Substrate Scope of the (NHC)Cu-Catalyzed C−H Amidation. With the optimized conditions in hand, a range of polyfluoroarenes were next examined. Pleasingly, substrates bearing various substituents were amidated with *N*-chloro-*N*-sodio-*tert*-butyl carbamate (3, 1.1 equiv) in satisfactory yields at room temperature (Table 2). Tetrafluoroanisole was reacted to give the desired product (**5a**, 86% in 2 h) using 2.0 mol % of catalyst **1c**. The structure of **5a** was confirmed by an X-ray crystallographic analysis. Likewise, a substrate bearing a *tert*-butoxy group reacted smoothly (**5b**). Labile substituents such as bromo or cyano groups were compatible with the present conditions (**5c**−**5d**). Two isomeric tetrafluorobenzenes were

Table 2. Scope of Fluoroarenes in the C−H Amidation[a]



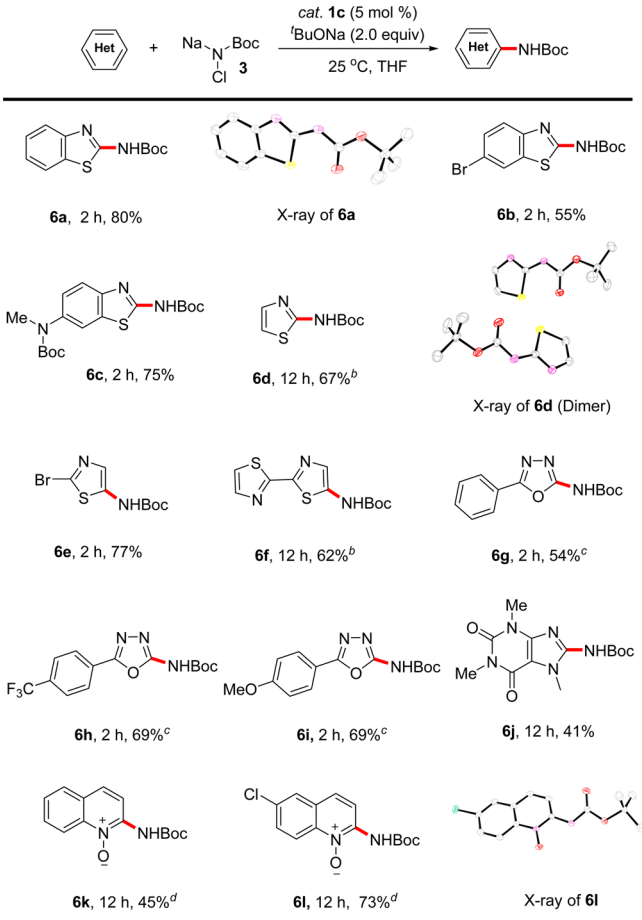
[a]Fluoroarenes (0.5 mmol), **3** (1.1 equiv), ^{t}BuONa (2.0 equiv), and **1c** (2.0 mol %) in THF (0.5 mL); isolated product yields shown. [b]Li O^{t}Bu used as the base. [c]**1c** (5.0 mol %). [d]**1c** (10.0 mol %). [e]2.5 equiv of **3** and 4.0 equiv of ^{t}BuONa.

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

amidated without difficulty (**5e**–**5f**). Not surprisingly, substrates bearing less acidic C–H reactive sites were found to exhibit lower reactivity. Trifluorobenzenes were amidated in moderate yields with higher loading of copper catalyst (**5g**–**5h**). It needs to be mentioned that the position of amidation is controlled by the relative acidity of the potentially reactive C–H bonds present (**5g**).[28] On the other hand, challenging substrates including di- or monofluorobenzene were sluggish under the present conditions (**5i**–**5j**). However, we were pleased to see that electron-withdrawing groups other than fluoro can also be effective substituents for the present copper-catalzyed C–H amidation. Indeed, benzenes substituted with cyano, ester, and nitro groups were readily amidated under the present catalyst system to afford the corresponding products in satisfactory yields (**5k**, **5l**, and **5m**, respectively). It should be noted that *tert*-butyl 3,5-difluorobenzoate was selectively amidated at the C-4 position (**5l**). Interestingly, a biphenyl substrate bearing octafluoro substituents was smoothly amidated at both C–H bonds leading to a bisamidated product (**5n**), a potentially valuable compound in materials science.[1f,g]

With the successful results on polyfluoroarenes, we subsequently turned our attention to the C–H amidation of heteroarenes (Table 3). Benzothiazole was efficiently amidated at the C-2 position (**6a**) with *N*-chloro-*N*-sodio-*tert*-butyl carbamate (**3**, 1.1 equiv) by using catalyst **1c** (5 mol %), and

Table 3. Scope of Heteroarenes in the C–H Amidation[a]



[a]Heteroarenes (0.2 mmol), **3** (1.1 equiv), ^{t}BuONa (2.0 equiv), and **1c** (5.0 mol %) in THF (0.5 mL); isolated product yields shown. [b]At 60 °C. [c]LiO^tBu was used as the base. [d]1,4-Dioxane was used as the solvent.

the structure of **6a** was confirmed crystallographically. Derivatives having bromo or amido substituents also underwent the desired amidation without difficulty (**6b**–**6c**). Thiazole was reacted selectively at the C-2 position[28] to afford synthetically valuable 2-amidothiazole (**6d**).[29] Again, the structure of **6d** was confirmed by an X-ray crystallographic analysis. Significantly, the position of C–H bonds in the amidation of thiazoles was found to be altered by the presence of the pre-existing substituents. For instance, 2-bromothiazole was selectively amidated at the C-5 position leaving the C4–H bond intact while the labile bromo group remained untouched (**6e**). Monoamidation of 2,2′-bithiazole was achieved by using 1.1 equiv of *N*-chloro-*N*-sodio-*tert*-butyl carbamate (**3**) at slightly higher temperature in good yield (**6f**). It needs to be mentioned that Daugulis and co-workers succeeded in the direct C-2 arylation of thiazoles with iodobenzene by using a copper/phenanthroline catalyst system.[19c,d]

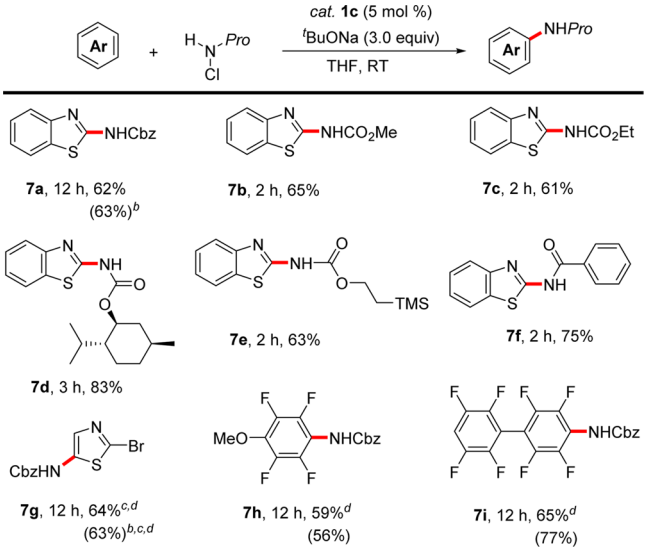
Oxadiazoles were amidated effectively by employing ^{t}BuOLi base in these substrates (**6g**–**6i**). Electronic variation at the 2-phenyl moiety of 1,3,4-oxadiazoles little influenced the amidation efficiency. Significantly, caffeine, a structural motif found in important biomolecules,[30] underwent the desired reaction to afford 8-amidocaffeine (**6j**). In addition, quinoline *N*-oxides were observed to be amidated selectively at the C-2 position. When quinoline *N*-oxide was allowed to react with *N*-chloro-*N*-sodio-*tert*-butyl carbamate (**3**, 1.1 eqiuv) in 1,4-dioxane, the corresponding amidated product (**6k**) was obtained in moderate yield (25 °C, 12 h). A derivative bearing a chloro group at the C-6 position underwent the C–H amidation more efficiently to give the desired product (**6l**), and its structure was confirmed by X-ray analysis.

It should be mentioned that the present copper catalyst system for the C-2 amidation of quinoline *N*-oxides turns out to be complementary to the previously reported C–H amidation routes *with regard to the regioselectivity*. We recently showed that quinoline *N*-oxides can be amidated selectively at the *C-8 position* under the Ir or Rh catalyst systems by employing sulfonyl azides or *N*-chlorocarbamates as the amino sources.[16d,24] In this approach, the *N*-oxide moiety of quinoline *N*-oxide substrates works as a directing group to guide the remote C8–H bond activation by forming the corresponding metallacyclic intermediates. This aspect is clearly distinct for the present approach wherein the most acidic C–H bond is selectively amidated without the need of directing groups in substrates.

In addition to the scope of (hetero)arenes, we also briefly investigated the feasibility of synthetically valuable carbamates as additional types of deprotectable amidating sources. We were pleased to see that a wide range of *N*-chlorocarbamates were readily employed with the present (NHC)Cu catalyst system under mild conditions (Table 4). For instance, *N*-benzyloxycarbonyl (Cbz) could be introduced at the 2-position of benzothiazole (**7a**). In addition, the alkoxy group in carbamates was found to be flexible to include methyl, ethyl, and chiral menthyl groups (**7b**–**7d**). Trimethylsilylethyl carbamate was also installed in satisfactory yield (**7e**) that has been widely used as an amino-protecting group as well as in the synthesis of glycosides.[31] We were pleased to observe that *N*-chlorobenzamide could serve as an efficient amidating precursor in a reaction with benzothiazole (**7f**). In addition, the application of benzyl *N*-chlorocarbamate (Cbz) was successful with several (hetero)arenes such as 2-bromothiazole (**7g**), tetrafluoroanisole (**7h**), and polyfluorobiphenyl (**7i**). It is noteworthy that the C–

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605–12614

Table 4. Scope of *N*-Chlorocarbamates[a]



[a](Hetero)arenes (0.2 mmol), amidation source (1.1 equiv), ^{t}BuONa (3.0 equiv), and **1c** (5.0 mol %) in THF (0.5 mL); isolated product yields. [b]Using *N*-chloro-*N*-sodio benzylcarbamate (1.1 equiv) and ^{t}BuONa (2.0 equiv); the values in parentheses refer to the NMR yields. [c]**1c** (10.0 mol %). [d]At 60 °C.

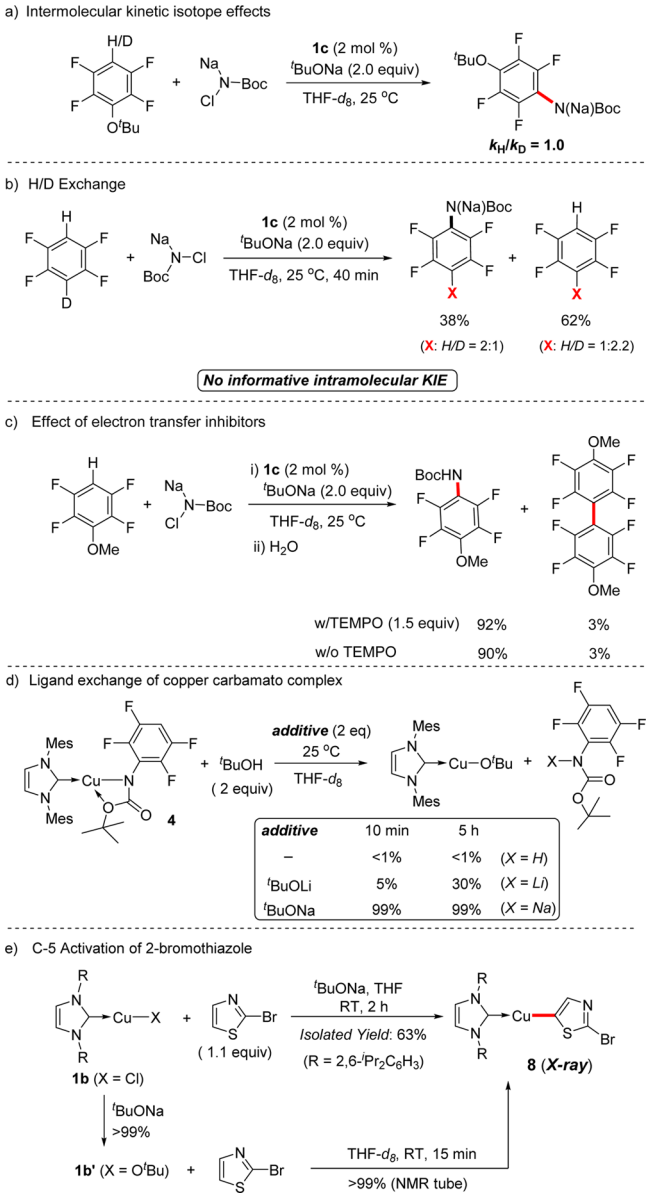
H amidation of heteroarenes was also examined with *isolated N*-chloro-*N*-sodio benzylcarbamate [(Cbz)N(Na)(Cl)] as the amidating reagent. Pleasingly, the reaction efficiency was observed to be similar when compared to the product yields obtained from amidation with [(Cbz)NH(Cl)] (**7a**, **7g**, **7h**, and **7i**).

Mechanistic Studies. To shed light on the present C−H amidation pathway, a serious of mechanistic experiments were performed. No measurable kinetic isotope effect (KIE) was observed in competition reactions between (tetrafluoro)-alkoxybenzene and its deuterated derivative (Scheme 5a). The absence of intermolecular kinetic isotope effect (KIE) suggests that the C−H bond cleavage of arenes may not be related to the rate-determining step.

When 1,2,4,5-tetrafluorobenzene-*d* was subjected to the amidation conditions, a H/D exchange was observed in this substrate leading us to conclude that no informative intramolecular KIE values can be obtained (Scheme 5b). Notably, a small amount of a byproduct, 1,1′-biphenyl, was detected in NMR and GC−MS analysis from an amidation of 2,3,5,6-tetrafluoroanisole under the current catalyst system. On the basis of the precedent examples, this result can be interpreted to consider that a higher order of oxidation state of copper species may be involved.[32] Moreover, a radical pathway could be ruled out since the addition of TEMPO did not affect the reaction outcome (Scheme 5c).

We were also curious about the final stage in the catalytic cycle: the regeneration of catalytically active copper species with product release (Scheme 5d). When an isolated copper carbamato complex [(IMes)Cu-N(Boc)(2,3,5,6-C_6F_4H)] (**4**) was allowed to react with ^{t}BuOH (2.0 equiv) that is generated *in situ* from the copper-aryl formation, no conversion (<1%) was observed, thus indicating that protonolysis of the [(IMes)Cu-N(Boc)(Ar_F)] intermediate is less likely. However, when ^{t}BuOLi (2.0 equiv) was added to this solution, [(IMes)Cu(O^tBu)] started to form slowly at room temperature, and the conversion reached 30% after 5 h at the same

Scheme 5. Preliminary Mechanistic Studies



temperature. Significantly, the same conversion was completed within 10 min by the addition of sodium base (^{t}BuONa, 2.0 equiv) under otherwise identical conditions to form [(IMes)-Cu(O^tBu)] quantitatively along with [(Na)N(Boc)(Ar_F)] (see the Supporting Information for details). These results suggest that the copper carbamato complex [(NHC)Cu-N(Boc)(Ar_F)] readily exchanges the amido ligand with *tert*-butoxide to relase product with the regeneration of catalytically active copper species [(IMes)Cu(O^tBu)], and its efficiency is dependent on the counter cations although the exact reason is not clear at the present stage.

In addition, a Cu(I) aryl complex **8** generated from the C−H activation at the C-5 position of 2-substituted thiazoles was confirmed crystallographically for the first time (Scheme 5e). When [IPrCuCl] (**1b**) was reacted with 2-bromothiazole in the presence of sodium *tert*-butoxide, a new copper complex was isolated in 63% yield (in 2 h at 25 °C). It was also proved that [(IPr)Cu(O^tBu)] (**1b′**) was formed quantitatively from its chloro precursor **1b** with ^{t}BuONa, and that **1b′** was

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

subsequently reacted with 2-bromothiazole affording the same complex **8** also in quantitative yield. Structure of **8** was characterized by an X-ray analysis (Figure 4) to reveal that the Cu−C_{NHC} and Cu−C_{aryl} bond lengths are 1.897(2) and 1.895(2) Å, respectively, and the angle of C1−Cu1−C28 is 173.15(10)°.

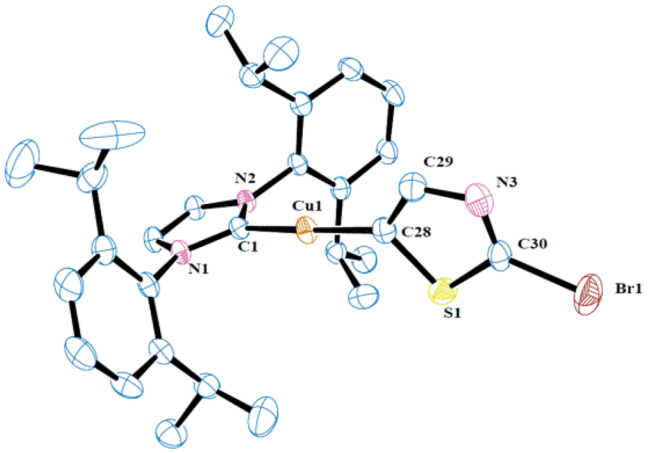


Figure 4. ORTEP of **8** with thermal ellipsoids set at 50% probability level (H atoms and diethyl ether solvent are omitted for clarity). Selected bond lengths (Å) and angles (deg): Cu1−C1, 1.897(2); Cu1−C28, 1.895(2); C28−C29, 1.360(4); C28−S1, 1.717(3); C29−N3, 1.385(3); C1−Cu1−C28, 173.15(10).

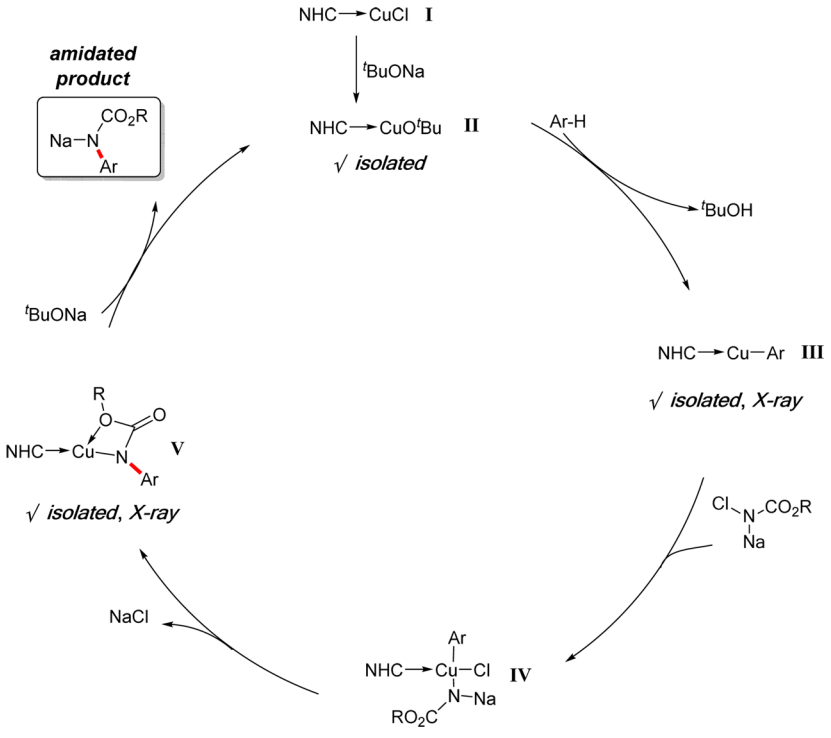
On the basis of the above mechanistic studies and literature precedents,[17−21,32,33] a proposed pathway of the (NHC)Cu-catalyzed C−H amidation of (hetero)arenes is presented in Scheme 6. First, a catalyst precursor [(NHC)Cu−Cl] (**I**) exchanges its chloro ligand with alkoxide base to form an isolable [(NHC)Cu−O^{t}Bu] complex (**II**) that will subsequently react with arene substrates (Ar−H) with the generation of a structurally fully characterized copper-aryl intermediate (**III**). We propose that an oxidative insertion of an amidating reagent (*N*-chloro-*N*-sodio-alkyl carbamates or *N*-chlorocarbamates) at the Cu(I) center of **III** will occur, thus forming a Cu(III) complex (**IV**). In fact, copper-aryl species were known to react with chloroamines or *O*-acyl hydroxylamines to form Cu(III) complexes according to the independent studies of Buchwald, Miura, and others.[10,12g,33] Moreover, Stahl provided a solid evidence for the involvement of the Cu(I)/Cu(III) cycle in the C−N bond formation with the isolation of a well-defined Cu(III) complex.[32c]

Again, it is believed that the reactive Cu(III) species **IV** will undergo a transfer of an aryl group to the carbamate moiety affording a Cu(I) carbamato intermediate (**V**) by forming the desired C−N bond as characterized in the above study. Finally, this copper species **V** will exchange a ligand with base, sodium *tert*-butoxide, thus delivering the amidation product with concurrent regeneration of catalytically active copper species **II**.

Synthesis of Primary Aromatic Amines. Synthetic utility of the present (NHC)Cu catalyst system was briefly demonstrated as shown in Scheme 7. The C−H amidation was highly convenient even on a gram scale where the catalyst loading could be lowered without affecting the efficiency (Scheme 7a). As anticipated, the newly introduced carbamate groups were readily deprotected under the well-established conditions to afford primary arylamines. For instance, after the initial C−H amidation of benzothiazole, the NH-Boc group was removed by acid to give 2-aminobenzothiazole (**9a**) in 80% yield over 2 steps (Scheme 7b).

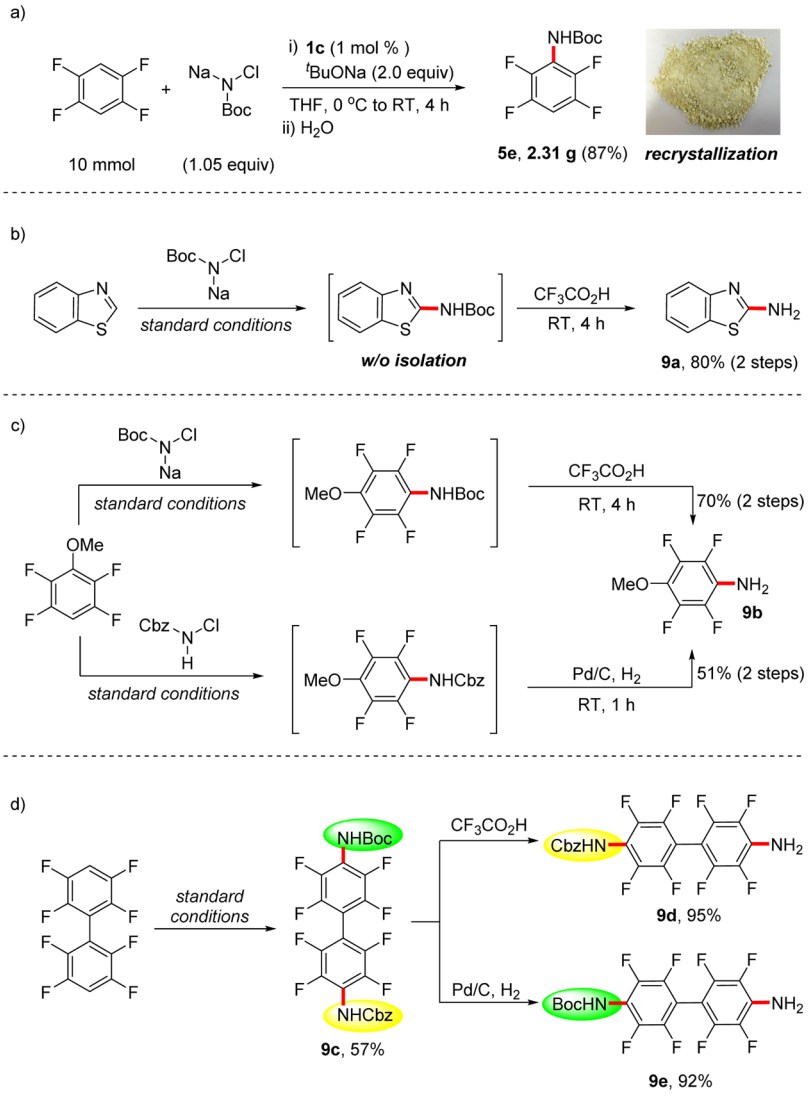
The present amidation approach is highly flexible in choosing amidating precursors as proved in the synthesis of an aniline derivative (Scheme 7c). Two amino sources (Boc- and Cbz-carbamates) can be efficiently utilized in the C−H amidation, and the corresponding amidated compounds were subsequently

Scheme 6. Proposed Mechanism



DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

Scheme 7. Synthetic Application



subjected to the individual deprotection conditions to afford 2,3,5,6-tetrafluoro-4-methoxyaniline (**9b**). Finally, this catalytic system can be applied as an orthogonal route to install multiamino moieties with different protecting groups (Scheme 7d). For instance, a double C−H amidation of octafluorobiphenyl occurred through a tandem manner to afford a bisamidated compound (**9c**) bearing two different carbamate groups (Boc and Cbz). Importantly, each protecting group could selectively be removed without affecting the other carbamate moiety (**9d** and **9e**).

CONCLUSIONS

We have developed the (NHC)Cu-catalyzed C−H amidation of (hetero)arenes using *N*-chlorocarbamates or their sodio derivatives as the amidating sources. In particular, the latter one (*N*-chloro-*N*-sodio-carbamates) was found to be convenient to handle, easy to scale up, stable to store, and environmentally friendly, giving rise to NaCl as a single byproduct in the present C−H amidation system. In stoichiometric reactions, two types of key copper intermediates were isolated and fully characterized for the first time which subsequently led us to optimize the catalytic conditions. The developed amidation protocol works highly efficiently and selectively over a broad range of substrates to include polyfluorobenzenes, azoles, and quinoline *N*-oxides. The installed carbamate groups can readily be deprotected to deliver primary arylamines, thus anticipating an immediate application in synthetic, medical, and materials chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07486.

Detailed experimental procedures and characterization of new compounds, mechanistic study, and X-ray analyses (PDF)

Crystallographic data for **2a** (CIF)

Crystallographic data for **4** (CIF)

Crystallographic data for **5a** (CIF)

Crystallographic data for **6a** (CIF)

Crystallographic data for **6d** (CIF)

Crystallographic data for **6l** (CIF)

Crystallographic data for **8** (CIF)

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614

AUTHOR INFORMATION

Corresponding Author

*sbchang@kaist.ac.kr

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This article is dedicated to Professor Masahiro Murakami on the occasion of his 60th birthday. This research was supported by the Institute for Basic Science (IBS-R010-D1) in Korea.

REFERENCES

(1) (a) *Amines: Synthesis, Properties and Applications*; Lawrence, S. A., Ed.; Cambridge University Press: Cambridge, 2005. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (c) Cabri, W.; Ghetti, P.; Pozzi, G.; Alpegiani, M. *Org. Process Res. Dev.* **2007**, *11*, 64. (d) *The Chemistry of Anilines, Parts 1 and 2*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 2007. (e) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008. (f) Hirata, S.; Totani, K.; Zhang, J.; Yamashita, T.; Kaji, H.; Marder, S. R.; Watanabe, T.; Adachi, C. *Adv. Funct. Mater.* **2013**, *23*, 3386. (g) Zacharias, P.; Gather, M. C.; Rojahn, M.; Nuyken, O.; Meerholz, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4388. (h) Yuan, W. Z.; Gong, Y.; Chen, S.; Shen, X. Y.; Lam, J. W. Y.; Lu, P.; Lu, Y.; Wang, Z.; Hu, R.; Xie, N.; Kwok, H. S.; Zhang, Y.; Sun, J. Z.; Tang, B. Z. *Chem. Mater.* **2012**, *24*, 1518.

(2) (a) Blaser, H. U.; Siegrist, U.; Steiner, H.; Studer, M. Aromatic Nitro Compounds. In *Fine Chemicals through Heterogeneous Catalysis*; Sheldon, R. A., van Bekkum, H., Eds.; Wiley-VCH: Weinheim, 2001; p 389. (b) Mallat, T.; Baiker, A.; Kleist, W.; Koehler, K. Amination Reactions. In *Handbook of Heterogeneous Catalysis*, 2nd ed.; Ertl, G., Knozinger, H., Schuth, F., Weitkamp, J., Eds.; Wiley-VCH: Weinheim, 2008; p 3548.

(3) (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: Weinheim, Germany, 1989. (b) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035. (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(4) For selected reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(5) (a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

(6) For selected reviews, see: (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (c) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (d) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. (e) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610. (f) Kim, H.; Chang, S. *ACS Catal.* **2016**, *6*, 2341.

(7) For recent reviews, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (b) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (c) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (d) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498. (e) Wan, J.-P.; Jing, Y. *Beilstein J. Org. Chem.* **2015**, *11*, 2209. (f) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. - Asian J.* **2016**, *11*, 168.

(8) For the selected references, see: (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (c) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. (d) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601. (e) Li, G.; Jia, C.; Chen, Q.; Sun, K.; Zhao, F.; Wu, H.; Wang, Z.; Lv, Y.; Chen, X. *Adv. Synth. Catal.* **2015**, *357*, 1311. (f) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. *Org. Lett.* **2014**, *16*, 1840. (g) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (h) Xu, H.; Qiao, X.; Yang, S.; Shen, Z. *J. Org. Chem.* **2014**, *79*, 4414.

(9) For the selected references, see: (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174. (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (c) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211. (d) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (f) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

(10) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900.

(11) (a) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646. (b) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656. (c) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272.

(12) (a) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (b) Zhu, D.; Yang, G.; He, J.; Chu, L.; Chen, G.; Gong, W.; Chen, K.; Eastgate, M. D.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 2497. (c) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350. (d) Gou, Q.; Liu, G.; Liu, Z.-N.; Qin, J. *Chem. - Eur. J.* **2015**, *21*, 15491. (e) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014. (f) Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853. (g) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (h) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, *44*, 1792.

(13) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301.

(14) (a) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (b) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899.

(15) (a) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11511. (b) Li, Y.; Liu, J.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *Org. Biomol. Chem.* **2012**, *10*, 3715. (c) Wang, R.; Liu, H.; Yue, L.; Zhang, X.-K.; Tan, Q.-Y.; Pan, R.-L. *Tetrahedron Lett.* **2014**, *55*, 2233.

(16) (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (b) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492. (c) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534. (d) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 10770.

(17) For recent reviews, see: (a) Gaillard, S.; Cazin, C. S. J.; Nolan, S. P. *Acc. Chem. Res.* **2012**, *45*, 778. (b) Egbert, J. D.; Cazin, C. S. J.; Nolan, S. P. *Catal. Sci. Technol.* **2013**, *3*, 912. (c) Lazreg, F.; Cazin, C. S. J. In *N-Heterocyclic Carbenes—Effective Tools for Organometallic Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Mannheim, 2014; pp 199–242. (d) Lazreg, F.; Nahra, F.; Cazin, C. S. J. *Coord. Chem. Rev.* **2015**, *293*, 48.

(18) Selected examples for the isolation of Cu(NHC) intermediates, see: (a) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* **2008**, *130*, 16486. (b) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (c) Takatsu, K.; Shintani, R.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 5548. (d) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314. (e) Suess, A. M.; Uehling, M. R.; Kaminsky, W.; Lalic, G. *J. Am. Chem. Soc.* **2015**, *137*, 7747.

(19) (a) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674. (b) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (d) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

(20) (a) Lesieur, M.; Lazreg, F.; Cazin, C. S. J. *Chem. Commun.* **2014**, *50*, 8927. (b) Fortman, G. C.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2010**, *29*, 3966. (c) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2990. (d) Makida, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4122.

(21) Xie, W.; Chang, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 1876.

(22) (a) Sundararaman, A.; Lalancette, R. A.; Zakharov, L. N.; Rheingold, A. L.; Jäkle, F. *Organometallics* **2003**, *22*, 3526.

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605–12614

(b) Sundararaman, A.; Zakharov, L. N.; Rheingold, A. L.; Jäkle, F. *Chem. Commun.* **2005**, 1708.
(23) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpont, A. W.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* **2006**, *45*, 9032.
(24) Gwon, D.; Hwang, H.; Kim, H. K.; Marder, S. R.; Chang, S. *Chem. - Eur. J.* **2015**, *21*, 17200.
(25) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2710.
(26) In the report of Miura et al., $Cu(OAc)_2$/phen-catalyzed amination of 1,2,4-trifluorobenzene with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine generated 3% of the desired amination product, see ref 12g.
(27) Photoinduced C−N bond formation via a radical pathway was reported by Fu et al., see: Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647.
(28) For pK_a values, see: Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.
(29) (a) Khalil, A.; Edwards, J. A.; Rappleye, C. A.; Tjarks, W. *Bioorg. Med. Chem.* **2015**, *23*, 532. (b) Navarre, J.-M.; Guianvarc'h, D.; Farese-Di Giorgio, A.; Condom, R.; Benhida, R. *Tetrahedron Lett.* **2003**, *44*, 2199.
(30) (a) Saladino, R.; Mincione, E.; Crestini, C.; Negri, R.; Di Mauro, E.; Costanzo, G. *J. Am. Chem. Soc.* **1996**, *118*, 5615. (b) Michelson, A. Z.; Chen, M.; Wang, K.; Lee, J. K. *J. Am. Chem. Soc.* **2012**, *134*, 9622.
(31) (a) Isidro-Llobet, A.; Álvarez, M.; Albericio, F. *Chem. Rev.* **2009**, *109*, 2455. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436. (c) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732.
(32) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190. (c) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (d) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78. (e) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (f) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.
(33) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38.

DOI: 10.1021/jacs.6b07486
J. Am. Chem. Soc. 2016, 138, 12605−12614