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Copper-Catalyzed Electrophilic Amination of Heteroarenes and Arenes by C–H Zincation**

Stacey L. McDonald, **Charles E. Hendrick**, and **Prof. Dr. Qiu Wang***

Department of Chemistry, Duke University Durham, NC 27708-0346 (USA)

Abstract

Direct amination of heteroarenes and arenes has been achieved in a one-pot C–H zincation/copper-catalyzed electrophilic amination procedure. This amination method provides an efficient and rapid approach to access a diverse range of heteroaromatic and aromatic amines including those previously inaccessible using C–H amination methods. The mild reaction conditions and good functional-group compatibility demonstrate its great potential for the synthesis of important and complex amines.

Keywords

amination; C–H functionalization; copper; heterocycles; synthetic methods

Heteroaromatic amines, especially 2-aminoazoles, are key structural motifs which are widely found in biologically important molecules and medicines.[1] For example, the 2-piperazinylbenzimidazole derivative lerisetron is currently in clinical trials for the treatment of nausea associated with cancer chemotherapy (Figure 1).[1a] Other classes of heteroaryl amines, such as anti-HIVagent HM13N,[1d] WRC-0571,[1b] and linagliptin,[1c] are also extensively used in drug discovery. Therefore, efficient methods for the synthesis of these important heteroaryl amines are highly valuable.

Complementary to the Buchwald–Hartwig amination from aryl halides,[2] direct C–H amination provides a new and potentially more effective C–N bond-formation approach for the synthesis of heteroaromatic amines. Several metal-free C–H/N–H coupling methods have been developed by an oxidative rearomatization pathway for the synthesis of 2-aminooxazoles.[3] Simultaneously, effective metal-catalyzed C–H aminations have also been achieved by various transition metals.[4,5] Despite these significant advances, the current methods often suffer from a limited arene scope and poor efficiencies, particularly on important skeletons including benzimidazoles, benzothiazoles, and thiazoles (Scheme 1A). This limitation is largely due to the challenging metalation step associated with the inherently high dissociation energy of sp^2 C–H bonds, and also leads to the common requirement of harsh reaction conditions (high temperatures, strong oxidants, and acidic or

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*qiu.wang@duke.edu.

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basic additives). A more general C–H amination method is needed to access those highly valuable aminated heteroarenes (Figure 1). Mild reaction conditions are desirable to broaden the scope of its applications.[6]

Herein we report a C–H zincation and copper-catalyzed electrophilic amination as a modular and facile amination approach to rapidly access a broad scope of important heteroaromatic and aromatic amines (Scheme 1B). Our approach is built on the use of strong and non-nucleophilic zinc bases,[7] such as $Zn(tmp)_2$ (tmp = 2,2,6,6-tetramethylpiperidide, pK_a of the conjugate acid = 37),[8] to generate the corresponding organozincates from a wide range of heteroarenes. Importantly, the resulting organozinc intermediates can serve as a more reactive surrogate of C–H bonds toward amination.[9] Thus, this strategy will overcome the narrow substrate scope and harsh reaction conditions of the previous C–H amination methods. In comparison to organozinc intermediates prepared from the heteroaryl halides and Grignard reagents,[10] our approach using the direct H–Zn exchange will make use of various arenes and heteroarenes as more convenient starting materials, and offer a better functional-group compatibility.[11] Based on this hypothesis, we have developed an operationally convenient one-step C–H amination procedure and examined its efficiency on a wide scope of heteroarenes and arenes, including both electron-rich and electron-deficient substrates. Particularly useful is its high efficacy for those substrates, such as benzimidazoles, pyridines, benzothiophenes, and less acidic C–H bonds, which were isolated in poor yields under previous amination conditions.[4b–k,12] The application of our chemistry has been demonstrated in the preparation of a diverse range of important heteroaromatic amines, including the potent antiemetic lerisetron.

Our studies began with the amination of *N*-methyl benzimidazole (**1a**) with the hydroxylamine **2** via the formation of its organozinc intermediate using $Zn(tmp)_2$ (Table 1). We focused on *O*-acylhydroxylamines as the electrophilic nitrogen source because of their easy availability and previous use in the electrophilic amination of different organometallic reagents.[9a–c,13] To our delight, the aminated product **3a** was formed upon treating the diarylzinc intermediate with **2** and a copper catalyst, among which $Cu(OAc)_2$ was most effective (entries 2–6). Without a copper catalyst, no aminated product was observed (entry 1). Furthermore, a stoichiometric amount of the diarylzinc intermediate was needed to fully convert **2** into **3a**, thus suggesting that the resulting monoarylzinc benzoate was ineffective for the amination under these reaction conditions (entries 7 and 8).[14]

One of the important attributes of this new amination approach is its potential to directly access a broad array of heteroaromatic amines, including those inaccessible from other C–H amination methods.[4b–k,12] Toward this end, we examined the amination reactions of different heteroarenes and arenes using **2** (Table 2). We first looked into simple heteroarenes, including both the electron-deficient benzothiazole **1b** and benzoxazole **1c**, and electron-rich benzofuran **1d** and benzothiophene **1e**. All the reactions successfully provided the aminated products (entries 2–5). Analogous reactions with the imidazole **1 f**, oxazole **1g**, and thiazole **1h** also occurred in excellent yields (entries 6–8). Next we examined the amination of functionalized arenes (entries 9–14), including the bromobenzoxazole **1i**, bromothiazoles **1j–k**, disubstituted oxazole **1l**, caffeine **1m**, and 1,3,4-oxadiazole **1n**. These reactions gave the corresponding aminated azoles in 82–96%

yields. In the examination of this method on pyridinyl C–H bonds, the reactions of the pyridines **1o–r** all proceeded smoothly, thus affording the aminated products **3o–r**, albeit at an elevated amination temperature (50 °C; entries 15–18). Lastly, the amination of the arene **1s** also proceeded smoothly (entry 19). The high regioselectivity observed in these aminated products is presumably derived from the selective zinc metalation. It is noteworthy that many functionalities were well tolerated, and include halide, ester, nitro, and nitrile groups. Many of these groups would be incompatible with the amination conditions by C–H lithiation to form organozinc intermediates.[13] Such a broad scope demonstrates the value of our amination protocol, which proceeds by C–H zinc metalation in comparison to other amination strategies.

The scope of the amines is also crucial for extensive utility of this amination method. Next we examined different *O*-benzoyl hydroxylamines derived from simple dialkylamines in the amination reactions with representative heteroarenes and arenes (Table 3). We were pleased to find that all the reactions proceeded smoothly in modest to excellent yields (67–97%), thus allowing the introduction of a variety of cyclic and acyclic alkylamino groups. Notably, the cleavage of the benzyl group or allyl group can additionally afford either a secondary amine or a primary amine (e.g., **13–17**).

Recognizing that the use of $Zn(tmp)_2$ would require the sacrifice of an additional equivalent of the arene moiety, we next exploited the amination of an alternative monoarylzinc intermediate using arenes as the limiting reagent and tmpZnCl·LiCl[15] in the C–H metalation (Table 4). Encouragingly, these reactions from both electron-deficient and electron-rich substrates all provided the aminated products in excellent yields, and included the azoles **4** and **19**, benzothiophene **20**, pyridines **21–22**, pyridazine **23**, and arenes **24–26**. These preliminary results suggest that arylzinc chloride was equally effective as a diarylzinc for electrophilic amination under the current reaction conditions and extend the synthetic utility of this amination with the flexibility of using heteroarenes as the limiting reagent.

Given the broad generality and operational simplicity of this amination reaction, its utility for the synthesis of medicinally valuable agents was demonstrated by the rapid synthesis of lerisetron (Scheme 2). This 5-HT_3 receptor antagonist was readily prepared from the simple benzimidazole **27** by using the standard amination conditions.

In summary, we have developed a direct and facile amination reaction of heteroarenes and arenes, including both electron-poor and electron-rich substrates. This transformation was achieved by a one-pot C–H zincation and copper-catalyzed electrophilic amination using *O*-acylhydroxylamines. It features broad substrate scope, high efficiency, mild reaction conditions, and good functional-group compatibility. It demonstrates great potential as a rapid and powerful way to access a variety of highly functionalized complex heteroaromatic amines which are of broad interest in organic synthesis and drug discovery. Furthermore, this work also provides insight into developing a modular C–H zincation/amination transformation for effective amination of sp^3 C–H bonds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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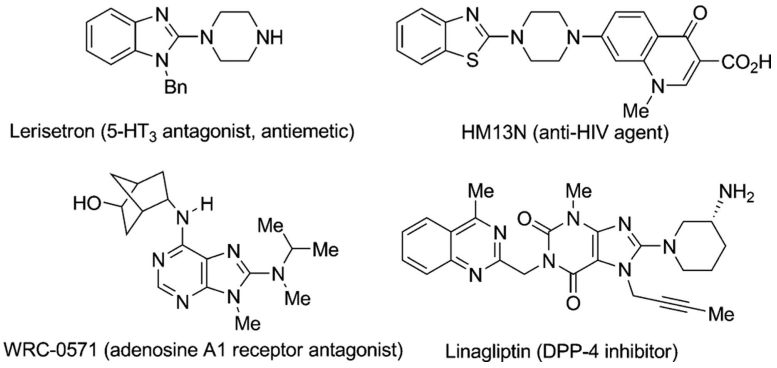
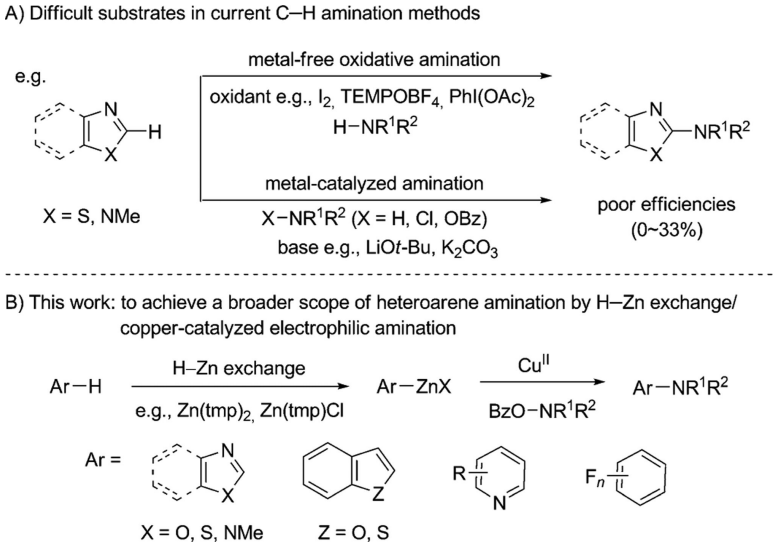
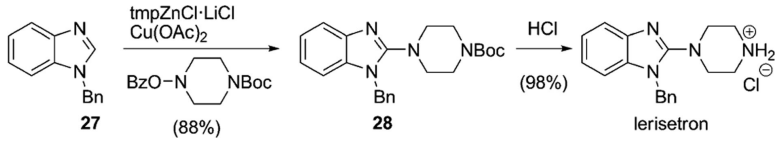


Figure 1.
Selected examples of bioactive heteroaromatic amines.



Scheme 1.

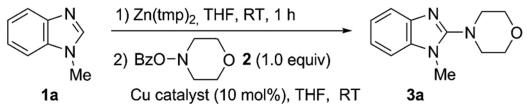
Direct C–H amination to access heteroaromatic amines. Bz= benzoyl, TEMPO= 2,2,6,6-tetramethyl-1-piperidinyloxy.



Scheme 2.
A rapid synthesis of lerisetron.

Table 1

Optimization studies for copper-catalyzed amination of benz-imidazole (**1a**) and **2**.[a]



Entry	1a (equiv)	$Zn(tmp)_2$ (equiv)	Copper catalyst	t[a] [h]	Yield [%][b]
1	2.1	1.0	-	24[c]	0
2	2.1	1.0	CuCl	4	88
3	2.1	1.0	CuOTf·tol	4	71
4	2.1	1.0	$CuCl_2$	3.5	89
5	2.1	1.0	$Cu(OTf)_2$	5	76
6	2.1	1.0	$Cu(OAc)_2$	5	99
7	1.4	0.6	$Cu(OAc)_2$	72[c]	56
8	1.05	0.5	$Cu(OAc)_2$	72[c]	40

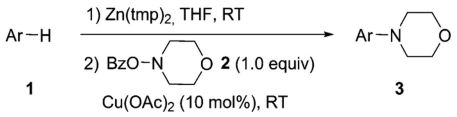
[a] Time required for complete consumption of 2 in step 2.

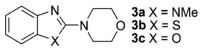
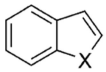
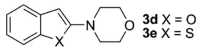
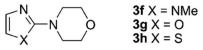
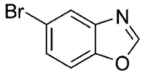
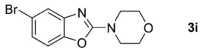
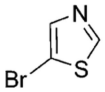
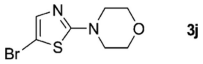
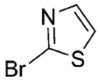
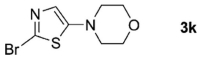
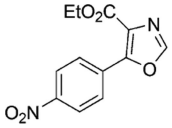
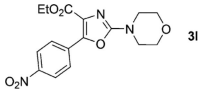
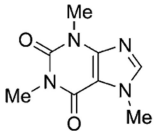
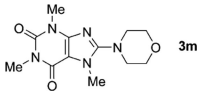
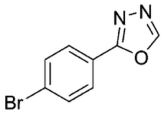
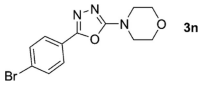
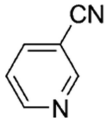
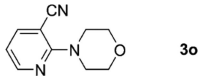
[b] Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

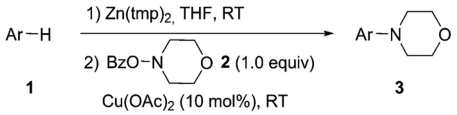
[c] 2 not fully consumed after 72 h. THF = tetra-hydrofuran.

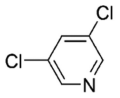
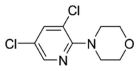
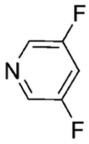
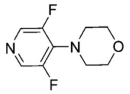
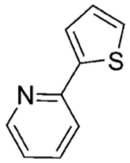
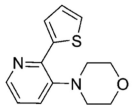
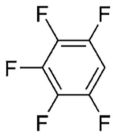
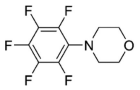
Table 2

Amination of heteroarenes and arenes.[a]



Entry	1	t [h][b]	3	Yield [%][c]
1	 **1a** X = NMe **1b** X = S **1c** X = O	1; 5	 **3a** X = NMe **3b** X = S **3c** X = O	96
2		1; 5		93
3		1; 5		95
4	 **1d** X = O **1e** X = S	1;[d] 5	 **3d** X = O **3e** X = S	71
5		1;[d] 5		70
6	 **1f** X = NMe **1g** X = O **1h** X = S	1; 12	 **3f** X = NMe **3g** X = O **3h** X = S	82
7		1; 12		92
8		1; 12		95
9	 **1i**	1; 24	 **3i**	96
10	 **1j**	1; 5	 **3j**	85
11	 **1k**	1; 5	 **3k**	90
12	 **1l**	1; 4	 **3l**	89
13	 **1m**	1;[e] 24	 **3m**	82
14	 **1n**	1; 4	 **3n**	91
15	 **1o**	2; 12[f]	 **3o**	81



Entry	1		*t* [h][b]	3		Yield [%][c]
16		**1p**	2; 12[f]		**3p**	79
17		**1q**	2; 12[f]		**3q**	91
18		**1r**	2; 12[f]		**3r**	74
19		**1s**	1; 12		**3s**	75

[a] Reactions typically run on 0.2 mmol scale. **1** (2.1 equiv), **2** (1.0 equiv, 0.08 M), $Zn(tmp)_2$ (1.0 equiv).

[b] Reaction time for deprotonation and amination step respectively.

[c] Yield of isolated product.

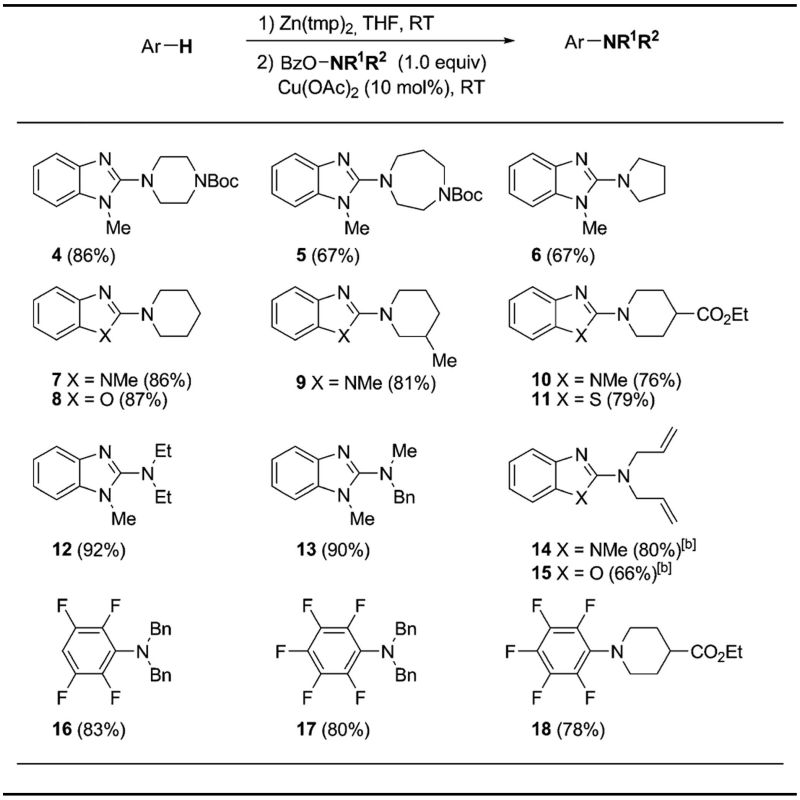
[d] $Zn\text{-}(tmp)_2\cdot LiCl\cdot MgCl_2$[4g] was used as base to form stable zincate intermediates.

[e] Deprotonation step run in CH_2Cl_2 because of the poor solubility of **1m** in THF.

[f] Amination step run at 50°C.

Table 3

Scope of *O*-benzoyl hydroxylamines.[a]

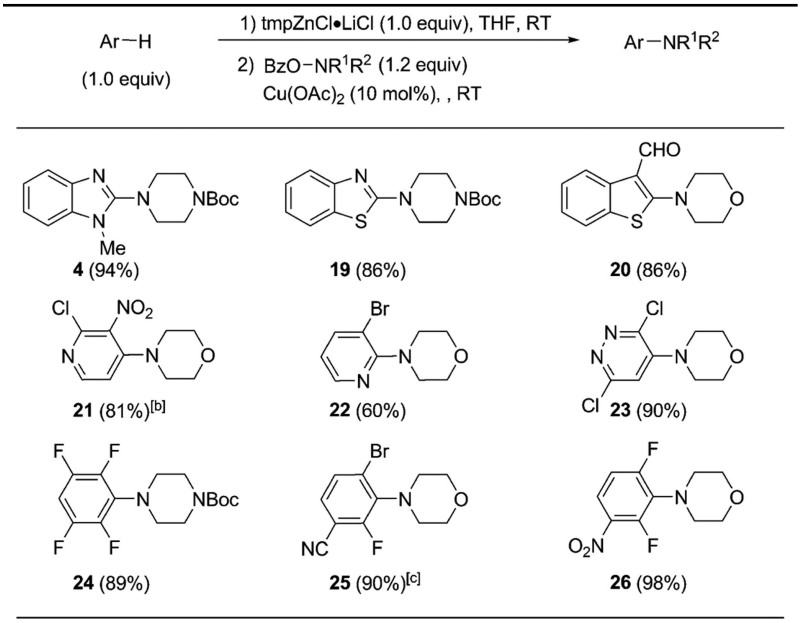


[b] Amination step run for 24 h. Boc=*tert*-butoxycarbonyl.

[a]Reactions run on 0.2 mmol scale. Conditions: Ar-H (2.1 equiv), $Zn(tmp)_2$ (1.0 equiv), RT, 1 h; $BzONR^1R^2$ (1.0 equiv, 0.08 M), $Cu(OAc)_2$ (10 mol%), RT, 5 h. Yields given are those of the isolated products.

Table 4

Direct amination using a tmpZnCl·LiCl-mediated metalation.[a]



[b] Amination step run at 50 °C.

[c] Deprotonation run at 65 °C.

[a] Reactions typically run on 0.2 mmol scale. Yields given are those of the isolated products.