C–N Bond Formation

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Silver-Mediated Direct Amination of Benzoxazoles: Tuning the Amino Group Source from Formamides to Parent Amines**

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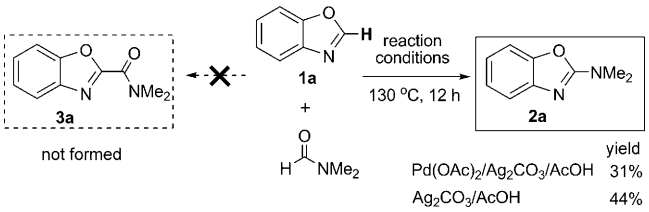
Dedicated to Professor Sunggak Kim

The construction of C–N bonds of heteroaromatic compounds is a highly important transformation in synthetic chemistry since it can offer nitrogen-containing molecules of great interest in biological, pharmaceutical, and materials sciences.[1] During the past decades, remarkable progresses have been made in the metal-facilitated C–N bond-forming reactions such as hydroamination[2] or oxidative amidation[3] of double or triple bonds as well as the Buchwald–Hartwig-type cross couplings.[4] Despite these significant advances, direct installation of amino groups or their surrogates on aryl or alkyl C–H bonds is still challenging. To meet this demand, a new approach involving oxidative addition of amino or amido moieties into hydrocarbons has been extensively studied.[5,6] In particular, site-selective amination of preorganized arenes through catalytic C–H bond activation was recently developed.[6] An *ortho*-selective amination of naphthols through thermal cleavage of disubstituted hydrazines was also reported.[7] Most recently, Mori and co-workers have reported an oxidative amination of azoles using copper salts at high temperature ($\approx$140 °C).[8] Herein, we describe an unprecedented silver-mediated C–N bond formation of benzoxazoles by decarbonylative coupling with formamides. On the basis of mechanistic considerations, we have also developed a direct amination protocol with parent amines under very mild reaction conditions.[9]

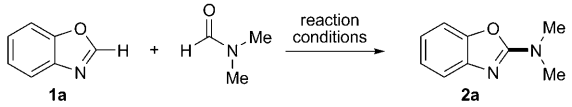
In line with our recent efforts on metal-catalyzed C–H bond functionalization,[10] we wondered whether subjection of electron-rich heteroarenes to Pd/Ag-catalytic systems in the presence of formamides could provide amidated products (Scheme 1).[11] To our surprise, when benzoxazole (**1a**) was treated with *N*,*N*-dimethylformamide (DMF) using the Pd(OAc)$_2$/Ag$_2$CO$_3$ system in the presence of an acetic acid additive, 2-aminated benzoxazole **2a** was obtained as a single product, albeit in moderate yield. In contrast, no amidated product **3a** was observed under other reaction conditions examined.[12] Subsequent studies revealed that the unexpected decarbonylative amination reaction also proceeded even in the absence of the palladium catalyst and with slightly higher yields.



Scheme 1. Decarbonylative amination of benzoxazole (**1a**).

Encouraged by these preliminary result, we subsequently tried to optimize the decarbonylative amination conditions using benzoxazole (**1a**) in neat DMF (40 equiv),[13] as shown in Table 1. Although no desired product was obtained in the absence of the silver salt or the acid additives (entries 1 and 2), addition of certain types of carboxylic acids promoted the transformation in the presence of silver salts (entries 3–8).[14] Among various acids examined, *p*-anisic acid turned out to be most effective for the amination reaction (entry 8). Catalytic amounts of Ag_2CO_3 did not furnish the desired product (entry 9), thus indicating that the use of stoichiometric amounts of silver salts is essential for smooth conversion under these reaction conditions.[15] In addition, other silver sources such as Ag_2O, AgOAc, AgOTf (Tf = triflate), or AgF (entry 10) were less effective when compared to Ag_2CO_3.[13]

Table 1: Optimization of reaction conditions.[a]



Entry	Silver salt	Acid additive	Yield [%][b]
1	none	none	<1
2	Ag_2CO_3	none	<1
3	Ag_2CO_3	CF_3CO_2H	<1
4	Ag_2CO_3	CH_3CO_2H	44
5	Ag_2CO_3	$C_6H_5CO_2H$	58
6	Ag_2CO_3	(4-NO_2)$C_6H_4CO_2H$	54
7	Ag_2CO_3	(4-Me)$C_6H_4CO_2H$	71
8	**Ag_2CO_3**	**(4-MeO)$C_6H_4CO_2H$**	**78**
9[c]	Ag_2CO_3	(4-MeO)$C_6H_4CO_2H$	<1
10[d]	AgF	(4-MeO)$C_6H_4CO_2H$	30

[a] Reaction conditions: **1a** (0.5 mmol), DMF (40 equiv), Ag salt (2.0 equiv), acid additive (5.0 equiv) at 130 °C for 12 h. [b] Yield is based on ^{1}H NMR spectroscopy. [c] 0.1 equivalents of Ag_2CO_3 were used relative to **1a**. [d] 4 equivalents of Ag salt were used.

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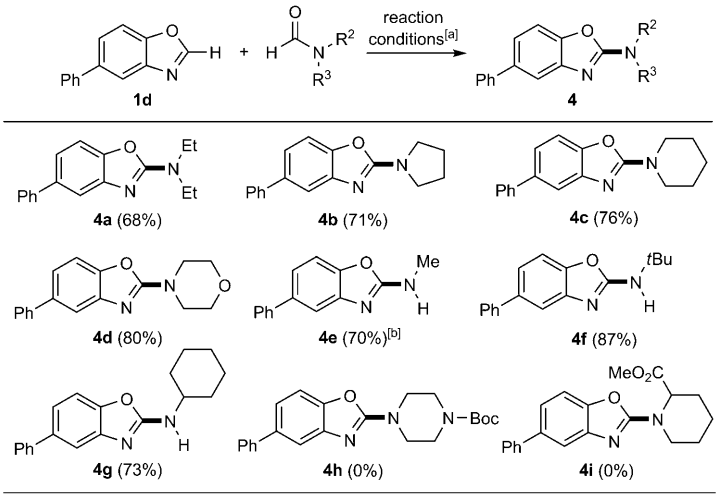
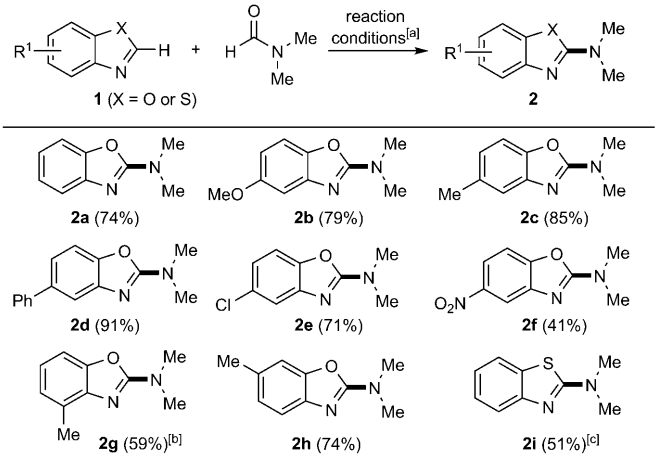
Under the optimized reaction conditions, we explored the substrate scope of benzoxazoles in the decarbonylative amination using DMF (Scheme 2). Benzoxazoles bearing substituents with diverse electronic properties such as methoxy (**2b**), methyl (**2c**), and phenyl groups (**2d**) all smoothly reacted with DMF to provide the desired products in high yields. No significant rate difference was observed between these substituted substrates. Interestingly, a labile substituent such as chloro group (**2e**) at the C5 position of benzoxazole was tolerated under the present reaction conditions. However, a reaction with 5-nitrobenzoxazole (**2f**) afforded the corresponding product with a slightly lower yield.

2-Aminobenzoxazoles bearing substituents at the C4- or C6-positions were also readily obtained with similar efficiency (**2g** and **2h**). Notably, when benzothiazole was subjected to the reaction conditions, a C2-aminated product (**2i**) was selectively obtained in a synthetically acceptable yield, thus demonstrating



Scheme 3. Decarbonylative amination with formamides. [a] Reaction conditions: **1d** (0.5 mmol), formamide (25 equiv), Ag_2CO_3 (2.0 equiv), *p*-anisic acid (5.0 equiv) at 130 °C for 12 h. Yield of isolated product shown in brackets. [b] 40 equivalents of formamide was used. Boc = *tert*-butoxycarbonyl.

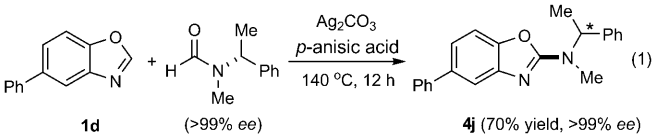


Scheme 2. Decarbonylative amination with heteroarenes. [a] Reaction conditions: **1** (0.5 mmol), DMF (40 equiv), Ag_2CO_3 (2.0 equiv), *p*-anisic acid (5.0 equiv) at 130 °C for 12 h. Yield of isolated product shown in brackets. [b] The reaction was carried out for 36 h. [c] 4-Toluic acid (5.0 equiv) was used.

that the present protocol can be readily extended to other types of heteroarenes.[16]

We next examined the scope of formamides in the silver-mediated amination of benzoxazoles (Scheme 3). Various types of formamides were readily employed and afforded products bearing 2-(*N*,*N*-diethylamino) (**4a**), pyrrolidinyl (**4b**), piperidinyl (**4c**), and morpholinyl (**4d**) groups in good yields. High efficiency in the amination reaction was maintained even in the case of *N*-monoalkylformamide substrates. For instance, 2-aminobenzoxazole derivatives substituted with *N*-methyl (**4e**), *tert*-butyl (**4f**), or cyclohexyl (**4g**) groups were easily obtained, thus offering an additional opportunity for further manipulation of the products obtained. However, no product was afforded with formamide substrates bearing an amido or ester functional group (**4h** and **4i**).

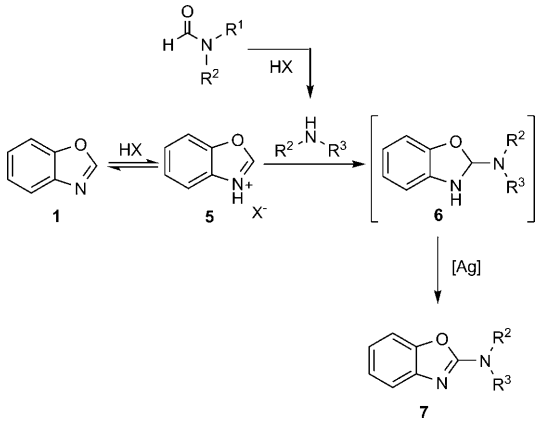
Meanwhile, we were pleased to observe that when an optically active formamide, (*R*)-*N*-methyl-*N*-(1-phenylethyl)-formamide, was treated with 5-phenylbenzoxazole (**1d**), the corresponding product **4j** was obtained in good yield without racemization [Eq. (1)].[17] This result is significant since the



present procedure can also be utilized for the introduction of an optically active amino group onto heteroarenes. 2-Aminobenzoxazole derivatives are of great interest in medicinal chemistry, and they have been important targets in combinatorial approaches.[18]

Although comprehensive studies are required to elucidate the mechanistic details of the present reaction, a tentative proposal is presented in Scheme 4. It is envisioned that the formamide substrates are first decarbonylated by the action of carboxylic acid additives to afford amines (or their salts),[19] which subsequently react with protonated benzoxazoles **5** leading to a putative 2-aminobenzoxazoline intermediate **6**. Rearomatization of **6** could be facilitated by a silver species, presumably through a single electron transfer to afford the 2-aminated product **7**.[15,20] Kinetic isotope competition experiments were carried out for the reaction of 5-methylbenzoxazole and its 2-deuterated derivative with DMF to reveal the intermolecular kinetic isotope effects ($k_{H/D}$) to be 0.9,[13] thereby implying that a silver-mediated C–H activation pathway is less likely.

On the basis of the proposed mechanism, we envision that amines (or their salts) could be directly employed in the



Scheme 4. A proposed pathway of the amination reaction.

amination of benzoxazoles. Moreover, milder reaction conditions were also anticipated by the direct use of amines because the involvement of slow decarbonylation of formamides can be avoided in this case (as compared to the use of formamides).

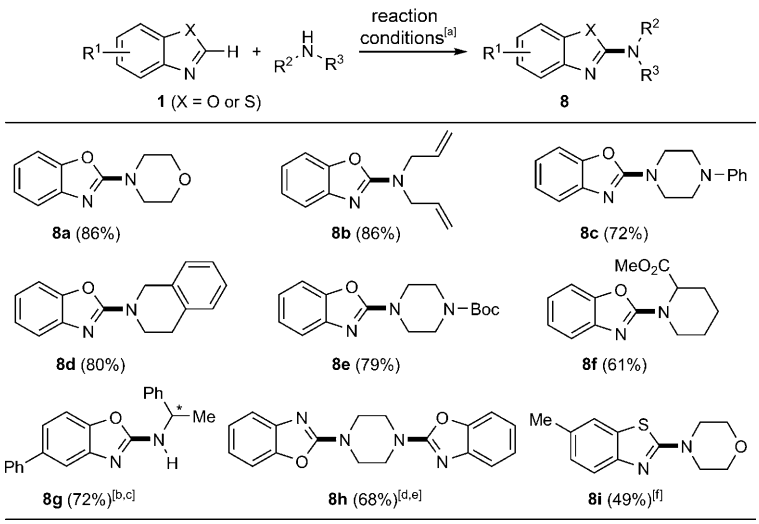
Indeed, we were delighted to find that when amines were treated with benzoxazoles, 2-aminated products were obtained in good yields (Scheme 5).[13] The silver-mediated reaction of benzoxazoles with amines proceeded smoothly under much milder reaction conditions as compared to formamides: temperatures (60 °C for amines versus 130–140 °C for formamides), number of equivalents of the amine sources (0.8–1 equiv for amines versus 40 equiv for formamides), or acid additives (2 equiv for amines versus 5 equiv for formamides). It should also be mentioned that organic solvents could be employed in the reaction with amines to make the direct amination reaction more versatile (i.e., solid substrates can be used).

The fact that the use of carboxylic acid additives was also important in the reaction with amines to achieve high efficiency suggests that protonated benzoxazole **5** (Scheme 4) would be involved as a key species—even in the direct amination reaction discussed in our mechanistic proposal. We observed that the new reaction conditions were compatible with a wide range of functional groups. For instance, benzoxazoles bearing 2-amino groups such as morpholinyl- (**8a**), *N*,*N*-diallyl (**8b**), or piperazinyl (**8c**) moieties could be isolated in high yields. The tetrahydroquinolinyl group was readily introduced at the 2-position of benzoxazole (**8d**) in good yield.

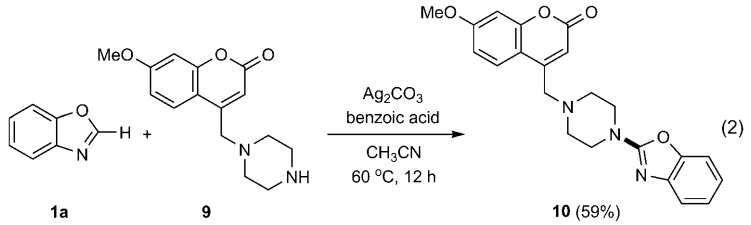
Although no aminated products were obtained from the reaction with formamides containing amido or ester groups (Scheme 3, **4h** and **4i**), the direct use of amines resulted in high yields of the corresponding benzoxazoles (**8e** and **8f**) under mild reaction conditions. An optically active amine was directly introduced at the 2-postion of a benzoxazole derivative without racemization (**8g**). In addition, 2,2′-(1,4-piperazinediyl)bisbenzoxazole (**8h**) was efficiently prepared in one-pot by simply controlling the stoichiometry of reactants, albeit under slightly more demanding conditions. It was intriguing to observe that 6-methylbenzothiazole reacted with an amine and gave the desired product (**8i**) using silver(I) oxide in the presence of a catalytic amount of zinc(II) acetate instead of acid additives.[21]

As an interesting application of the present reaction, the coumarinyl piperazine derivative **9** was treated with benzoxazole (**1a**) under the direct amination conditions. The reaction proceeded smoothly and afforded the corresponding 2-aminobenzoxazole product **10**, which is known to display highly potent anti-HIV and antitumor activities [Eq. (2)].[22]

In summary, we have disclosed the first example of silver-mediated amination of benzoxazoles using formamides or parent amines as an amino group source. Although reactions with formamides proceed at high temperatures, the direct amination with amines takes place under much milder conditions to afford 2-aminobenzoxazoles bearing a wide range of functional groups, thereby opening a new avenue for



Scheme 5. Direct amination using parent amines. [a] Reaction conditions: **1** (1.2 equiv), amine (0.5 mmol), Ag_2CO_3 (1.2 equiv), benzoic acid (2.0 equiv) in CH_3CN at 60 °C for 12 h. Yield of isolated product shown in brackets. [b] Enantiomeric excess (*ee*) of both amine reactant and product was 96%. [c] *p*-Anisic acid (2.0 equiv) was used instead of benzoic acid. [d] The reaction was carried out for 24 h. [e] 3.0 equivalents of **1a**, benzoic acid, and Ag_2CO_3 were used relative to the amine. [f] Reaction conditions: **1** (1.2 equiv), amine (0.5 mmol), Ag_2O (2.0 equiv), $Zn(OAc)_2$ (0.2 equiv) in CH_3CN at 80 °C for 12 h.



the regioselective formation of C–N bonds through direct C(sp^2)–H functionalization of heteroarenes.

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