C–H Amination

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Amination of Benzoxazoles and 1,3,4-Oxadiazoles Using 2,2,6,6-Tetramethylpiperidine-*N*-oxoammonium Tetrafluoroborate as an Organic Oxidant**

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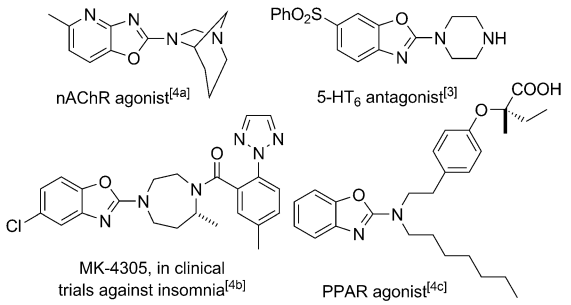
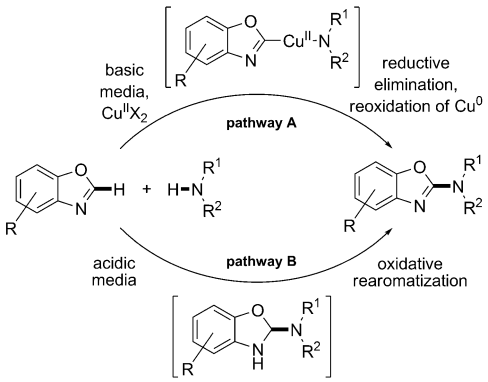
Functionalized azoles occur as substructures in a variety of natural products[1] and show great potential as valuable lead compounds for the development of novel therapeutics.[2] Among them, 2-aminobenzoxazoles display high activity as partial antagonists for 5-HT receptors (5-HT = 5-hydroxytryptamine, seretonine) which are promising targets for the treatment of Alzheimer's disease and schizophrenia.[3] Moreover, numerous other drug targets have been addressed by 2-aminated benzoxazoles (Scheme 1).[4] Therefore, development of efficient methods for their preparation is highly important. 2-Aminophenols are common starting materials, which afford 2-functionalized benzoxazoles in the reaction with aldehydes upon oxidative cyclization.[5] Transition-metal-catalyzed intramolecular oxidative C–O coupling of acylated anilines is an alternative approach.[6] Recently, great efforts have been devoted to the direct C(2)H oxazole functionalization.[7] Along this line, arylation,[8] alkynylation,[9] alkylation,[10] carboxylation,[11] and carbonylation[12] have been achieved. During the last two years, first results on the direct transition-metal-mediated 2-amination of benzoxazoles with nonactivated amines have been published, as recently highlighted in this journal.[13] This straightforward strategy displays higher levels of efficiency and atom economy than the most frequently applied routes towards aminated benzoxazoles, such as the cyclization of 2-aminophenols with isothiocyanates[14] or cyanogen bromide,[15] the conversion of the corresponding thiolated azoles by intermediate chlorination thereof,[4a,16] and the direct use of 2-chlorinated heterocycles.[3]



Scheme 1. Some bioactive 2-aminated benzoxazoles. 5-HT$_6$ = 5-hydroxytryptamine receptor subtype, nAChR = nicotinic acetylcholine receptor, PPAR = peroxisome proliferator-activated receptor.

Mori et al.[17] and Schreiber and Wang[18] independently introduced a method for the direct amination of azoles with amines mediated by copper(II) salts under basic conditions and an oxygen atmosphere. Organocopper species were suggested as intermediates (Scheme 2, pathway A). Other Cu-based protocols for direct C–H amination of oxazoles have been disclosed since.[19]



Scheme 2. Strategies for and key intermediates in the direct amination of benzoxazoles.

In 2009 Chang et al. reported Ag-mediated aminations of benzoxazoles under acidic conditions.[20] Amine/benzoxazole adducts were suggested as intermediates in these reactions (pathway B). Co(OAc)$_2$ and Mn(OAc)$_2$ turned out to be efficient catalysts in combination with *t*BuOOH as oxidant.[21] Moreover, $FeCl_3$ was reported to act as a stoichiometric oxidant for direct 2-amination of benzoxazoles.[22] Herein we disclose the transition-metal-free amination of benzoxazoles[23] using readily prepared 2,2,6,6-tetramethyl piperidine-*N*-oxoammonium tetrafluoroborate (TEMPO$^+$BF$_4^-$) as an organic oxidant following a strategy along the lines of pathway B.

As a model reaction we first investigated the amination of benzoxazole **1** (1 equiv) with piperidine (1.1 equiv) under various conditions (Table 1). The amine and **1** were stirred in the presence of various acids (catalytic amount) in MeCN for 4 h followed by addition of TEMPO$^+$BF$_4^-$[24] and base to

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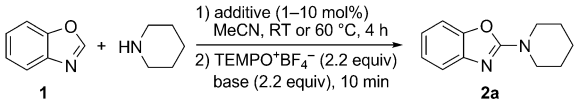
Table 1: Optimization studies: Screening of Brønsted and Lewis acids.



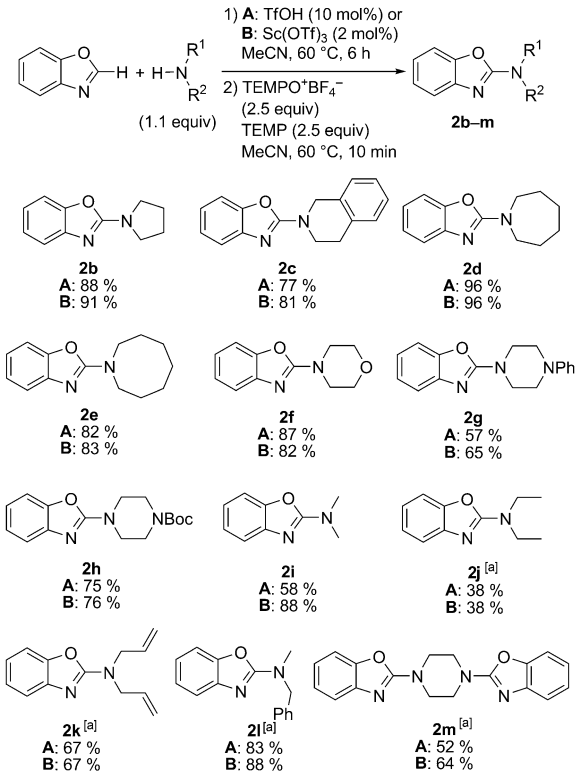
Entry	Additive (mol%)	*T* [°C]	Base	Yield [%][a]
1	–	RT	2,6-lutidine	8
2	$PhCO_2H$ (10)	RT	2,6-lutidine	60
3	$2\text{-}ClC_5H_4CO_2H$ (10)	RT	2,6-lutidine	51
4	$4\text{-}ClC_5H_4CO_2H$ (10)	RT	2,6-lutidine	70
5	$4\text{-}NO_2C_5H_4CO_2H$ (10)	RT	2,6-lutidine	59
6	$2,6\text{-}Cl_2C_5H_3CO_2H$ (10)	RT	2,6-lutidine	72
7	$4\text{-}MeOC_5H_4CO_2H$ (10)	RT	2,6-lutidine	63
8	$2,6\text{-}Cl_2C_5H_3CO_2H$ (10)	RT	TEMP	76
9	$2,6\text{-}Cl_2C_5H_3CO_2H$ (10)[b]	60	TEMP	83
10	TfOH (10)	RT	2,6-lutidine	89
11	TfOH (10)[b]	60	2,6-lutidine	93
12	**TfOH (10)[b]**	**60**	**TEMP**	**93**
13	$BF_3{\cdot}OEt_2$ (5)	RT	2,6-lutidine	40
14	$AlMe_3$ (5)[c]	RT	2,6-lutidine	<2
15	$InBr_3$ (5)	RT	2,6-lutidine	78
16	$Bi(OTf)_3$ (5)	RT	2,6-lutidine	70
17	$Yb(OTf)_3$ (5)	RT	2,6-lutidine	79
18	$Sc(OTf)_3$ (5)	RT	2,6-lutidine	82
19	$Sc(OTf)_3$ (4)[d]	RT	2,6-lutidine	88
20	$Sc(OTf)_3$ (1)	60	2,6-lutidine	78
21	**$Sc(OTf)_3$ (2)[b]**	**60**	**TEMP**	**90**
22	$ScCl_3{\cdot}6H_2O$ (2)[b]	60	TEMP	84

[a] Yield of isolated product. [b] For 6 h. [c] Used as a 2.0 M solution in toluene. [d] For 4 days.

buffer HBF_4 formed as a side product during oxidation. As expected, in the absence of acid additive only a poor yield of the aminated benzoxazole **2a** was obtained (8%; Table 1, entry 1). Repeating reaction in the presence of benzoic acid (10 mol%) using 2,6-lutidine as base for the oxidation step afforded **2a** in 60% yield (Table 1, entry 2). Since amines are readily oxidized with $TEMPO^+BF_4^-$, a sterically hindered base has to be used as buffer. Yields slightly varied when other benzoic acid derivatives were used (51–72%; Table 1, entries 3–7); 2,6-dichlorobenzoic acid, which has the lowest pK_a value among these additives ($pK_a = 1.59$),[25] gave the best results (Table 1, entry 6). The oxidation step turned out to be highly efficient in these reactions and was completed within 10 min. $TEMPO^+BF_4^-$ was cleanly reduced to TEMPO, which did not act as an oxidant in this process (see also the mechanistic studies below). Therefore, two equivalents of $TEMPO^+BF_4^-$ were required for full conversion. With 2,2,6,6-tetramethylpiperidine (TEMP) as base, similar results were achieved (Table 1, entry 8) and the yield was improved when the temperature was increased to 60°C (Table 1, entry 9). The more acidic trifluoromethanesulfonic acid (triflic acid) turned out to be an excellent catalyst: in combination with TEMP or 2,6-lutidine, **2a** was obtained in 93% yield (Table 1, entries 11, 12).

We also investigated the efficiency of some Lewis acids (5 mol%; Table 1, entries 13–22). $BF_3{\cdot}OEt_2$ gave a moderate yield (40%; Table 1, entry 13) and $AlMe_3$ was ineffective (Table 1, entry 14). $InBr_3$ turned out to be best suited among the main-group-based Lewis acids tested (78%; Table 1, entry 15). Bismuth(III) (70%; Table 1, entry 16) and ytterbium(III) triflate (79%; Table 1, entry 17) afforded **2a** in good yields. $Sc(OTf)_3$, known to activate imines in the presence of aldehydes,[26] appeared to be the most efficient in this series and the catalyst loading could be further lowered (Table 1, entries 18–21). Under optimized conditions using 2 mol% of $Sc(OTf)_3$, **2a** was isolated in 90% yield after $TEMPO^+BF_4^-$ oxidation (Table 1, entry 21). To further support our assumption that the scandium(III) salt acts as a Lewis acid for activation of benzoxazole and not possibly liberated triflic acid, we also tested $ScCl_3$ hexahydrate and noted a very good yield (84%; Table 1, entry 22). Since with TfOH a higher catalyst loading was necessary and the $ScCl_3$ also provided excellent results, we suggest that the Sc salt is the catalyst for the first step in these reactions.

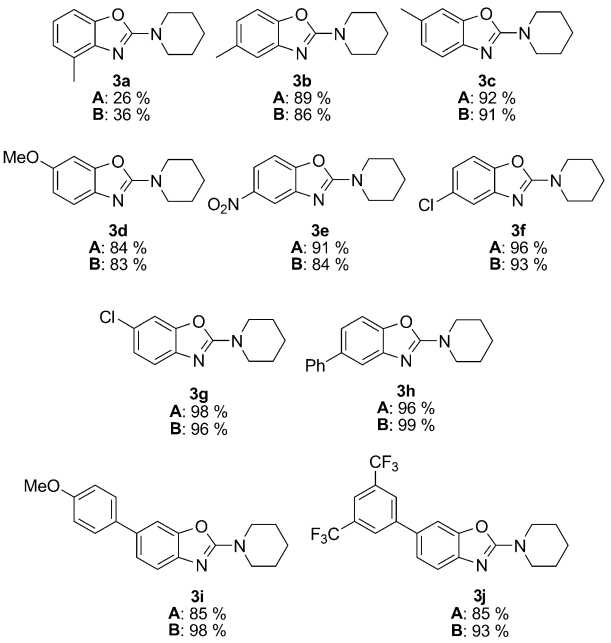
We then focused on testing the substrate scope of our new amination protocol by applying both, TfOH (method A) and $Sc(OTf)_3$ (method B) as catalysts. The results obtained for the direct amination of benzoxazole with various amines are given in Scheme 3. In addition to piperidine, other cyclic secondary amines with varying ring size were oxidatively coupled to benzoxazole with both protocols, and the corresponding aminated heterocycles **2b–e** were isolated in good to excellent yields. In most of the cases the $Sc(OTf)_3$ protocol (method B) delivered slightly higher yields. An additional heteroatom is tolerated, as shown by the successful reaction using morpholine and piperazine derivatives (**2f–h**). With piperazine, a double C–H amination was achieved (**2m**). Moreover, aliphatic noncyclic amines also underwent smooth



Scheme 3. Substrate scope: Variation of the amine. [a] Step (1) for 12 h. Boc = *tert*-butoxycarbonyl.

conversion to the desired products in moderate to good yields as shown for the syntheses of **2i–l**.

We next varied the benzoxazole core and reacted 4-, 5-, and 6-methyl-substituted benzoxazoles with piperidine under optimized conditions (Scheme 4).[27] For the 5- and 6-methyl-substituted derivatives, excellent yields of the amination

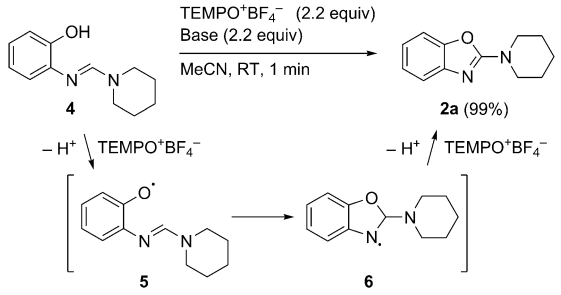


Scheme 4. Substrate scope: Variation of the benzoxazole core.

products **3b** and **3c** were obtained. However, the 4-methyl derivative delivered a significantly lower yield, probably for steric reasons (**3a**). With benzoxazoles bearing electron-donating or -withdrawing substituents amination was very efficient and products **3d–g** were isolated in excellent yields. Arylated benzoxazoles turned out to be very good substrates for direct amination (**3h–j**).

It is important to note that all reactions carried out gave the aminated benzoxazoles in quantitative yield based on recovered starting benzoxazole. No side products were formed and the unreacted heterocycle can be reisolated readily. Even more importantly, the reduced form of the oxidant (the nitroxide) can be recovered in near quantitative yield (see the Supporting Information) and the *N*-oxoammonium salt can readily be regenerated by disproportionation of the nitroxide upon treatment with HBF_4 (see the Supporting Information). The hydroxylamine formed along with the *N*-oxoammonium salt during the disproportionation is readily reoxidized to the nitroxide under basic aerobic atmosphere. Therefore, dioxygen can be considered to be the terminal oxidant in our oxidation protocol.

To shed light onto the reaction mechanism, we performed NMR studies and conducted some preparative control experiments. Stirring **1**, piperidine, and TfOH (10 mol%) in MeCN for 4 h at room temperature followed by basic workup and chromatography provided amidine **4** in 86% yield (see the Supporting Information). We found that **4** was quantitatively oxidized to **2a** upon treatment with $TEMPO^+BF_4^-$ at room temperature within 1 min in the presence of 2,6-lutidine or TEMP. Without added base, the reaction stopped at 50% conversion. These experiments show that amidine **4** is likely an intermediate in our C–H amination. TEMPO and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone[28] did not work as oxidants to convert **4** into **2a**, but 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 1 equiv) was also capable of oxidizing amidine **4** to **2a** (89%; base was not necessary in that case). Moreover, reaction of **1** with piperidine in deuterated MeCN in the presence of 2 mol% $Sc(OTf)_3$ was monitored by ^1H NMR spectroscopy (see the Supporting Information). This experiment revealed clean formation of **4** under the reaction conditions. Along with benzoxazole, no other compound was detected in the reaction mixture. Based on these experiments we suggest the following mechanism. Benzoxazole is first converted to **4**. Single-electron transfer (SET) to $TEMPO^+BF_4^-$ followed by deprotonation generates phenoxyl radical **5** which undergoes 5-*endo* cyclization to give aminyl radical **6**. Renewed SET and deprotonation finally affords product **2a** (Scheme 5).



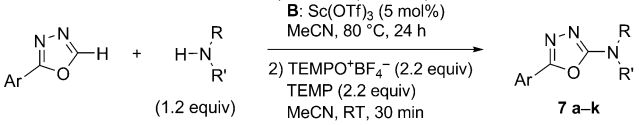
Scheme 5. Mechanistic studies.

To further demonstrate the synthetic potential of our methodology, we used 1,3,4-oxadiazoles as substrates to gain access to the corresponding bioactive 2-aminated heterocycles.[29] To our delight, a variety of substituted 1,3,4-oxadiazoles could be converted to the desired products **7a–k**. In contrast to the benzoxazole amination, higher temperatures, longer reaction times, and increased catalyst loadings were necessary (Table 2). Piperidine as a cyclic amine (Table 2, entries 1, 4, 6, and 9), morpholine as a heteroatom-bearing cyclic amine (Table 2, entries 2, 7, and 10) and the aliphatic *N*-methylbenzylamine (Table 2, entries 3, 5, 8, and 11) were successfully coupled to different arylated 1,3,4-oxadiazoles in moderate to good yields.

Finally, we applied our method to the synthesis of racemic MK-4305 (Scheme 6). Amine **9** was prepared according to a literature procedure,[4b] and the key amination of the commercially available chlorobenzoxazole **8** using the $Sc(OTf)_3$ protocol proceeded with 84% yield. This example demonstrates the great potential of our new method for late-stage benzoxazole amination.

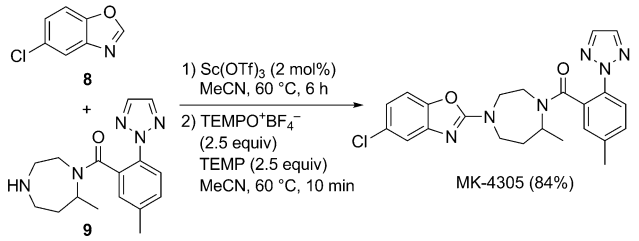
In summary, we have developed a metal-free protocol for the highly efficient direct amination of nonactivated benzoxazoles and 1,3,4-oxadiazoles with secondary amines using

Table 2: 2-Amination of arylated 1,3,4-oxadiazoles.



Entry	Ar	Amine	Product	Yield [%][a]
1	Ph	piperidine	**7a**	A: 75 B: 68
2	Ph	morpholine	**7b**	A: 64 B: 60
3	Ph	CH_3NHBn	**7c**	A: 71 B: 68
4	4-$MeOC_6H_4$	piperidine	**7d**	A: 63
5	4-$MeOC_6H_4$	CH_3NHBn	**7e**	A: 60
6	4-$CF_3C_6H_4$	piperidine	**7f**	A: 78
7	4-$CF_3C_6H_4$	morpholine	**7g**	A: 70
8	4-$CF_3C_6H_4$	CH_3NHBn	**7h**	A: 67
9	2-furanyl	piperidine	**7i**	A: 69
10	2-furanyl	morpholine	**7j**	A: 63
11	2-furanyl	CH_3NHBn	**7k**	A: 60

[a] Yield of isolated product.



Scheme 6. Synthesis of racemic MK-4305.

catalytic amounts of triflic acid and a readily recyclable *N*-oxoammonium salt as an organic oxidant. Generally good to excellent yields were obtained for a broad range of substrates. $Sc(OTf)_3$ is also an efficient catalyst. The stoichiometric oxidant used can be regenerated readily with HBF_4 and O_2. As a first application the method was successfully applied to the synthesis of racemic MK-4305.

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