A Metal-Free Oxidative Amination of Benzoxazoles with Primary Amines and Ammonia

Ulrich Kloeckner, Nicole M. Weckenmann, Boris J. Nachtsheim*

Institut für Organische Chemie, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany
Fax +49(7071)295897; E-mail: boris.nachtsheim@uni-tuebingen.de

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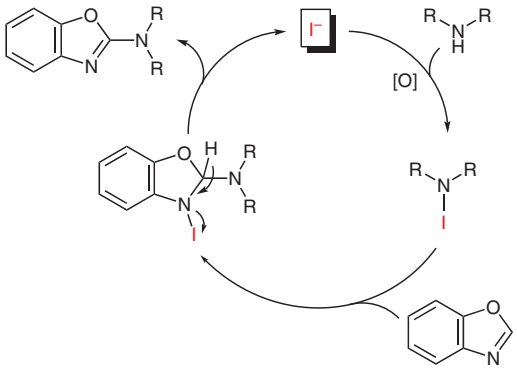
Abstract: An efficient synthesis of 2-aminobenzoxazoles is described by a direct oxidative amination of unfunctionalized benzoxazoles with primary amines. The reaction could be performed in the absence of transition metals by using catalytic amounts of a quaternary ammonium iodide and *tert*-butylhydroperoxide as a cheap and easy-to-handle co-oxidant. In addition to primary amines, aqueous solutions of NH_3 were used to introduce a primary amine group into the heterocyclic core.

Key words: green chemistry, amination, homogeneous catalysis, iodine, oxidation

Aromatic and heteroaromatic amines are widely distributed structural motifs that can be found in important classes of organic molecules such as pharmaceuticals, agrochemicals, organic dyes, and conducting polymers. An efficient way to introduce the crucial C–N functionality is the direct oxidative amination of a (hetero)aryl C–H bond.[1] Meanwhile a variety of transition metals such as Pd,[2] Ag,[3] Cu,[4] Mn, Co,[5] and Fe[6] were described to catalyze this reaction.[7] However, catalytic metal-free oxidative aminations are much less explored.

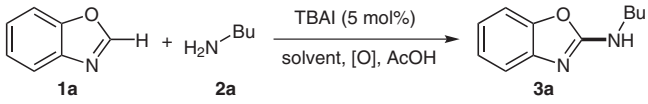


Scheme 1 Iodide-catalyzed oxidative amination of oxazoles

In our attempts to develop novel iodide-catalyzed oxidative C–C and C–X bond-forming reactions we have recently developed a metal-free oxidative direct amination of azoles with secondary amines by using catalytic amounts of tetrabutylammoniumiodide (TBAI) and aqueous solutions of H_2O_2 or *tert*-butylhydroperoxide (TBHP).[8,9] First mechanistic investigations led us to suggest an activation through in situ iodination of the secondary amine and thence an electrophilic amination mechanism (Scheme 1).

Herein we wish to present a first systematic investigation of TBAI-catalyzed aminations of benzoxazoles with much less reactive primary amines. As a starting point we studied the reaction between benzoxazole (**1a**) and *N*-butylamine (**2a**).[10] To find the optimal reaction conditions for this valuable transformation we chose to investigate the reaction between benzoxazole (**1a**) and *N*-butylamine (**2a**) with catalytic amounts of TBAI and acetic acid as acid additive (Table 1). Using 5 mol% of TBAI as catalyst and with H_2O_2 as co-oxidant at ambient temperature the desired 2-aminobenzoxazole **3a** could be isolated in 17% yield (Table 1, entry 2). With TBHP as co-oxidant the yield could be increased significantly to 31% (Table 1, entry 3). Raising the reaction temperature to 80 °C finally gave **3a** in a good isolated yield of 69% (Table 1, entry 6).

Table 1 Optimizing the Reaction Conditions



1a **2a** **3a**

Entry	[O][a]	Solvent	Temp (°C)	Time (h)	Yield (%)[d]
1	–	MeCN	r.t.	24	0
2	H_2O_2[b]	MeCN	r.t.	24	17
3	TBHP[c]	MeCN	r.t.	24	31
4	TBHP	MeCN	40	7	44
5	TBHP	MeCN	60	3.5	63
6	TBHP	MeCN	80	3.5	69
7	TBHP	EtOAc	80	2	19
8	TBHP	DMF	80	2	19
9	TBHP	PhMe	80	2	48
10	TBHP	EtOH	80	2	31
11	TBHP	AcOH	80	2	5

[a] Co-oxidant.
[b] Conditions: 30% aq solution; 3 equiv based on **1a**.
[c] Conditions: 70% aq solution; 1.5 equiv based on **1a** were used for entries 3–11.
[d] Isolated yield after column chromatography.

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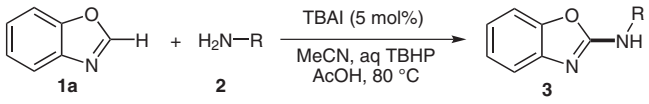
Other polar and nonpolar solvents did not improve the yields (Table 1, entries 7–10). Running the reaction in glacial acetic acid (Table 1, entry 11) gave **3a** in trace amounts only. Furthermore, it is important to note that without the addition of a co-oxidant (Table 1, entry 1) or without addition of an iodide source no reaction was observed.

With our optimized reaction conditions we began to investigate the substrate scope of our oxidative amination reaction. First we examined various primary alkyl amines (Table 2).

Table 2 Reaction Scope with Various Primary Amines[11]



1a **2** **3**

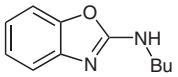
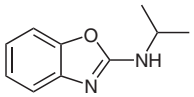
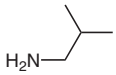
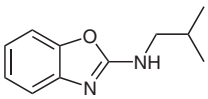
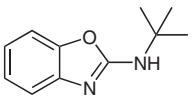
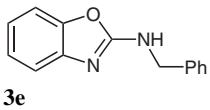
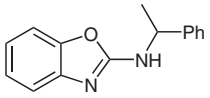
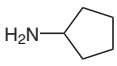
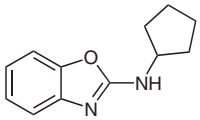
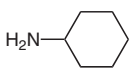
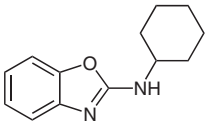
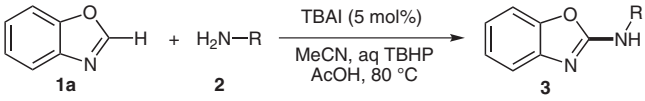
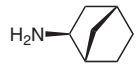
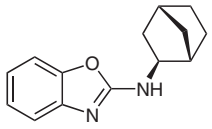
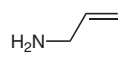
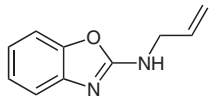
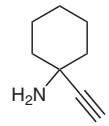
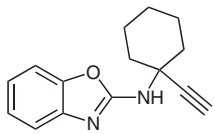
Entry	Amine **2**	Product **3**	Time (h)	Yield (%)
1	 **2a**	 **3a**	3.5	69
2	 **2b**	 **3b**	3.5	72
3	 **2c**	 **3c**	3.5	76
4	 **2d**	 **3d**	2	46
5	 **2e**	 **3e**	1.5	59
6	 **2f**	 **3f**	1.5	81
7	 **2g**	 **3g**	1.5	73
8	 **2h**	 **3h**	1	59

Table 2 Reaction Scope with Various Primary Amines[11] (continued)



1a **2** **3**

Entry	Amine **2**	Product **3**	Time (h)	Yield (%)
9	 **2i**	 **3i**	2	80
10	 **2j**	 **3j**	4	28
11	 **2k**	 **3k**	2	66

Besides the initially chosen *N*-butylamine a variety of other aliphatic primary amines could be used for this reaction such as isopropyl-, isobutyl-, and *tert*-butylamine (Table 2, entries 2–4). The corresponding 2-aminobenzoxazoles **3b–d** were isolated in up to 76% yield.

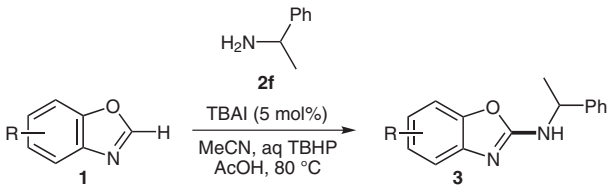
In addition we were able to transform benzylamine (**2e**) and 1-phenylethylamine (**2f**) to the desired products **3e** and **3f** in 59% and 81% yield, respectively. Various cyclic primary amines, such as cyclopentyl- or cyclohexylamine (**2g** and **2h**) as well as *exo*-2-aminonorbornan (**2i**), gave the corresponding 2-aminobenzoxazoles **3g–i** in up to 80% yield (Table 2, entries 7–9).

Allylamine **2j** can be used for this oxidative amination as well, although yielding **3j** only in a moderate yield of 28%. Synthetically highly valuable alkynylamines are also tolerated. As an example 1-ethynylcyclohexanamine (**2k**) gave **3k** in 66% yield. It is worth mentioning that aromatic primary amines such as aniline did not react under our optimized reaction conditions (data not shown).

Subsequently, we varied the benzoxazole motif and reacted diverse substituted azoles with 1-phenylethylamine (Table 3). Benzoxazoles bearing electron-donating alkyl groups (**1b–d**) and a 5-methoxy group (**1e**) showed the highest reactivity (Table 3, entries 1–3). The desired aminated products **3l–o** were isolated in excellent yields of up to 90% after short reaction times (1–2.5 h).

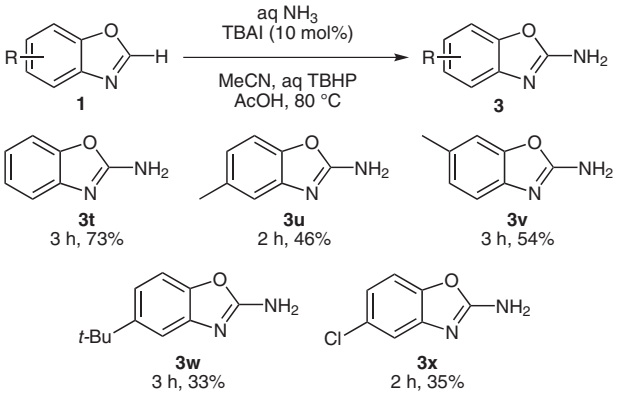
5-Chlorobenzoxazole (**1f**) gave **3p** in a good yield of 71% as well (Table 3, entry 5). However, the more electron-poor 5-fluoro- and 6-nitro-substituted benzoxazoles **1g** and **1h** showed a decreased reactivity yielding **3q** and **3r**, respectively, in only 56% and 18% yield (Table 3, entries 6 and 7). Naphthoxazole **1i** gave the desired product **3s** in 41% yield (Table 3, entry 8).

Table 3 Variation of the Benzoxazole Scaffold[11]



Entry	Benzoxazole **1**	Product **3**	Time (h)	Yield (%)
1	**1b**	**3l**	2.5	86
2	**1c**	**3m**	1	90
3	**1d**	**3n**	1.5	77
4	**1e**	**3o**	2	71
5	**1f**	**3p**	1	71
6	**1g**	**3q**	1.5	56
7	**1h**	**3r**	1	18
8	**1i**	**3s**	5.5	41

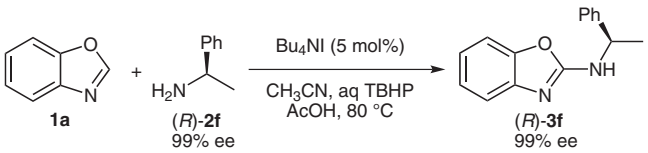
Next we considered whether we could introduce a primary amine group at the 2-position of the benzoxazole scaffold. The easiest way to achieve this goal would be a reaction of the azole with aqueous ammonia. We were pleased to find that benzoxazoles could be easily aminated in the proposed way, under the same reaction conditions that we had used previously, by using ammonia instead of primary amines. However, for this reaction, catalyst loading had to be increased from 5 mol% to 10 mol%.



Scheme 2 Oxidative amination of benzoxazoles with ammonia

Reaction of **1a** with ammonia yielded **3t** in 73% yield (Scheme 2). However, yields dropped significantly for the reaction of other substituted benzoxazoles with ammonia. Alkyl-substituted benzoxazoles gave the desired products **3u–v** in up to 54% yield. The chlorinated benzoxazole **1f** gave the desired 2-amino derivative **3x** in only 35% yield. The reasons for this significant drop in yield by changing the substitution pattern are not clear to us at this point. A detailed side-product analysis is part of ongoing investigations.

Finally, we wanted to investigate whether chiral primary amines keep their stereoinformation in the final reaction product. Thus we decided to react optical pure (*R*)-1-phenylethylamine [(*R*)-**2f**] with **1a** (Scheme 3). Chiral GC analysis indeed showed an optical purity for the reaction product (*R*)-**3f** of 99% ee (see Supporting Information).



Scheme 3 Oxidative amination of benzoxazole with (*R*)-1-phenylethylamine

In summary we have developed an efficient metal-free oxidative amination of benzoxazoles with primary amines and ammonia. With lowest amounts (5–10 mol%) of the quaternary ammonium iodide TBAI the desired 2-aminobenzoxazoles could be obtained in good yields after short reaction times. Chiral primary amines can be used in our oxidative amination reaction without a loss of optical purity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(9) A seminal work describing tetraalkylammonium iodides in oxidative cycloetherifications was described by Ishihara and co-workers: (a) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376. For recently published oxidative transformations catalyzed by quaternary ammonium iodides, see: (b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5331. (c) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085. (d) Rodriguez, A.; Moran, W. J. *Org. Lett.* **2011**, *13*, 2220. (e) Zhu, C.; Wei, Y. *ChemSusChem* **2011**, *4*, 1082.

(10) The reaction between benzo[*d*]oxazole and *N*-butylamine was described in our previous oxidative amination procedure (see ref. 8). However, this was the only example of a primary amine in this article.

(11) **Typical Experimental Procedure**
A reaction vessel was charged with AcOH (0.061 g, 1.010 mmol, 3 equiv) and TBHP (70% solution in H_2O, 0.065 g, 0.504 mmol, 1.5 equiv) in MeCN (0.2 mL). After the addition of TBAI (0.006 g, 0.017 mmol, 5 mol%), 1-phenylethylamine (**2f**, 0.029 g, 0.403 mmol, 1.2 equiv), and benzoxazole (**1a**, 0.040 g, 0.336 mmol, 1 equiv) in MeCN (0.2 mL) were added. The reaction mixture was stirred until TLC showed full conversion of benzoxazole (1.5 h). The reaction was quenched by addition of an aq solution of $Na_2S_2O_5$ (2 mL) and a sat. solution of $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (5 × 5 mL), combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography [silica gel; hexane–EtOAc = 10:1 (v/v)] to yield **3f** (0.061 g, 81%) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 2 H), 7.34–7.31 (m, 2 H), 7.28–7.20 (m, 3 H), 7.12 (t, 1 H, *J* = 7.7 Hz), 6.99 (t, 1 H, *J* = 7.7 Hz), 6.88 (br s, 1 H), 5.11 (q, 1 H, *J* = 6.8 Hz), 1.66 (d, 3 H, *J* = 6.7 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.6, 148.4, 143.4, 142.7, 128.7, 127.4, 125.9, 123.8, 120.6, 116.0, 108.8, 52.8, 23.1. IR (neat): 2970, 1658, 1648, 1580, 1458, 1366, 1217, 698 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{15}N_2O_2$ [M + H]$^+$: 239.1179; found: 239.1178. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.96; H, 5.56; N, 11.88. Detailed spectroscopic data as well as ^{1}H and ^{13}C NMR spectra of all compounds **3a–v** are given in the Supporting Information.

