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A Metal-Free Amination of Benzoxazoles — The First Example of an Iodide-Catalyzed Oxidative Amination of Heteroarenes

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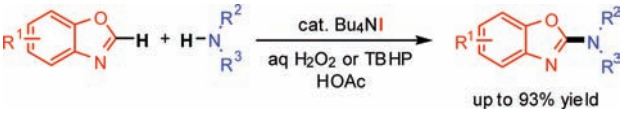
ABSTRACT

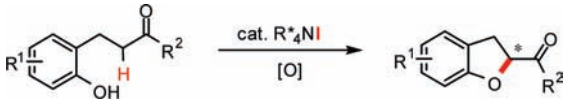


An efficient transition-metal-free amination of benzoxazoles has been developed. With catalytic amounts of tetrabutylammoniumiodide (TBAI), aqueous solutions of H_2O_2 or TBHP as co-oxidant and under mild reaction conditions, highly desirable 2-aminobenzoxazoles were isolated in excellent yields of up to 93%. First mechanistic experiments indicate the in situ iodination of the secondary amine as the putative mode of activation.

Hypervalent iodine compounds have gained much attention as mild oxidation reagents in organic synthesis. In particular aryl-λ^3-iodanes (iodine in the oxidation state +III) have been established as cheap and nontoxic alternatives to transition metals in oxidative C−H bond activations.[1,2] Elegant catalytic methods based on the in situ generation of the reactive iodine(III) species from an iodoarene precursor in combination with stoichiometric amounts of a cheap and easy to handle co-oxidant such as *m*CPBA were developed by Kita and Wirth.[3]

Very recently, a novel class of iodine-based oxidation catalysts was introduced by Ishihara and co-workers. In a seminal work enantiopure tetraalkylammoniumiodides (TAAIs) could be used in a highly enantioselective oxidative cycloetherification of ketophenols (Scheme 1).

Scheme 1. TAAI-Catalyzed Oxidative Cycloetherification[4]



In combination with H_2O_2 or *tert*-butyl hydroperoxide (TBHP) as co-oxidant [O], in situ generated tetraalkylammonium(hypo)iodites were proposed as catalytically active species. Typical aryl-λ^3-iodanes showed only poor reactivity in the same reaction.[4]

Inspired by this novel metal-free oxidative C−H activation approach we now want to present the first direct amination of heteroaromatic C−H bonds catalyzed by

(1) For reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229. (d) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (e) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (f) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524. (g) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517.

(2) Recent examples for hypervalent iodine compounds in oxidative cross-coupling reactions: (a) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301. (b) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668. (c) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3334. (d) Schäfer, S.; Wirth, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 2786.

(3) For reviews, see: (a) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (b) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073.

(4) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376. During the preparation of this manuscript other TBAI-catalyzed C−H activations have been published: (a) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (b) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085. (c) Rodrıguez, A.; Moran, W. J. *Org. Lett.* **2011**, *13*, 2220.

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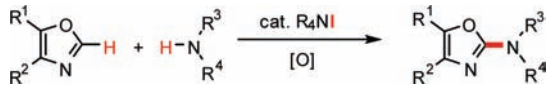
Scheme 2. TAAI-Catalyzed Oxidative Amination of Heteroarenes

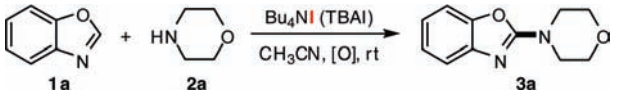


quaternary ammonium iodides under oxidative conditions (Scheme 2).

As heteroaromatic model substrates we chose benzoxazoles since 2-aminooxazoles and 2-aminothiooxazoles are frequently found structural motifs in numerous pharmacological active compounds.[5] Transition-metal-catalyzed direct aminations of azoles have been described recently. In particular Ag(I),[6] Co(II), Mn(II),[7] Fe(III),[8] and Cu(II)[9] were found to catalyze this transformation. However harsh reaction conditions or activated amine derivatives (e.g., *N*-chloroamines or *N*-formamides) were required. A metal-free version of this transformation has not been described so far.

In first experiments we examined the reaction between benzoxazole **1a** and morpholine **2a** (Table 1). With catalytic amounts of simple tetrabutylammoniumiodide (TBAI) as the precatalyst and an aqueous solution of H_2O_2 as the oxidizing reagent at room temperature we were pleased to isolate the desired 2-morpholinobenzoxazole **3a** in 29% yield (Table 1, entry 1). With an aqueous solution of TBHP only traces of **3a** could be detected at room temperature (Table 1, entry 2). Tetrabutylammoniumbromide and -chloride showed no catalytic activity at all. Addition of a base such as K_2CO_3 or NEt_3 (Table 1, entries 3 and 4) resulted in a complete loss of reactivity. Surprisingly, when carboxylic acids, in particular acetic acid or benzoic acid, were added to the reaction mixture, the yields of **3a** increased significantly to 68% and 70% respectively. With further optimization of the reaction conditions, the yields of **3a** finally could be increased to 80%. The necessary high excess of H_2O_2 (5 equiv) is most likely the result of an undesired Bray–Liebhafsky reaction.[10] Since this iodate-catalyzed oscillating decomposition of H_2O_2 is not known for other peroxides, we thought to test the reaction between **1a** and **2a** again with TBHP, now under our optimized conditions. To our delight we found that with only 1.5 equiv of TBHP at 80 °C and with acetic acid as an additive, **3a** can be isolated in a comparable yield

Table 1. Optimizing the Reaction Conditions



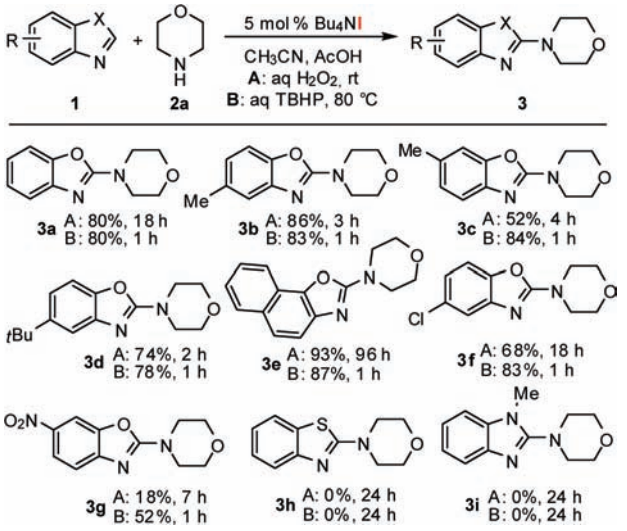
entry[a]	mol % TBAI	[O] (equiv)[b]	additive (equiv)[c]	*t* [h]	yield [%][d]
1	20	H_2O_2 (2)	–	72	29
2	20	TBHP (2)	–	72	traces
3	20	H_2O_2 (2)	K_2CO_3 (2)	12	0
4	20	H_2O_2 (2)	NEt_3 (2)	12	0
5	10	H_2O_2 (2)	HOAc (2)	3	70
6	10	H_2O_2 (2)	Ph–CO_2H (2)	4	68
7	5	H_2O_2 (2)	HOAc (2)	3	70
8	2	H_2O_2 (2)	HOAc (2)	4	18
9	**5**	**H_2O_2 (5)**	**HOAc (5)**	**18**	**80**
10[e]	**5**	**TBHP (1.5)**	**HOAc (3)**	**1**	**80**

[a] General reaction conditions: 0.336 mmol **1a** and 0.672 (2 equiv) **2a** in 1 mL of acetonitrile at rt. [b] All experiments were performed with aqueous solutions of H_2O_2 (30%) or TBHP (70%). The given equivalents are related to **1a**. No reaction was observed without the addition of a co-oxidant. [c] The given equivalents are related to **1a**. [d] Isolated yield after column chromatography. [e] Reaction was performed at 80 °C.

of 80%. Thus we tested both co-oxidants (H_2O_2 and TBHP) simultaneously in the following discussion of our substrate scope.

With our optimized reaction conditions in hand we first investigated the reaction between various benzoxazoles **1** and morpholine **2a** (Scheme 3).

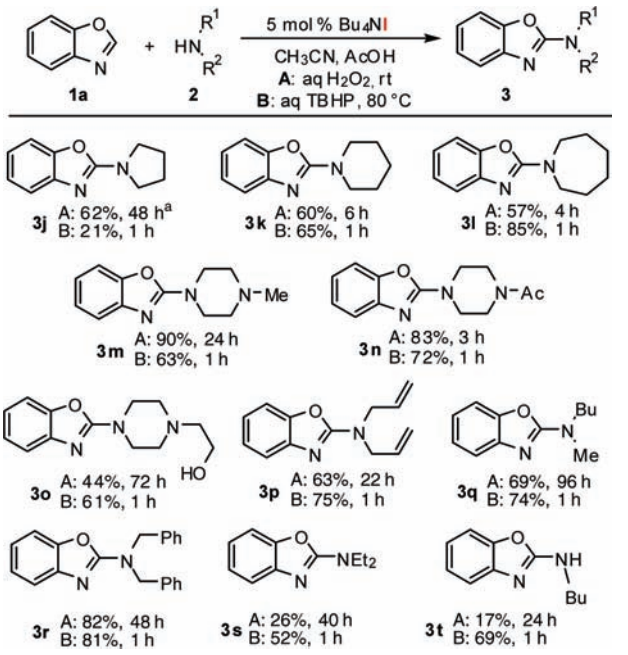
Scheme 3. Amination of Various Benzoxazoles with Morpholine[a]



[a] General reaction conditions: **Method A**: 0.336 mmol of **1**, 0.672 mmol of **2a**, 5 equiv of H_2O_2 (30% aq solution), 5 equiv of HOAc, in 1 mL of acetonitrile. **Method B**: 0.336 mmol of **1**, 0.403 mmol of **2a**, 1.5 equiv of TBHP (70% aq solution), 3 equiv of AcOH in 1 mL of acetonitrile at 80 °C.

(5) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282.
(6) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.
(7) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899.
(8) Wang, J.; Hou, J.-T.; Wen, J.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2011**, *47*, 3652.
(9) (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (b) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (c) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301. (d) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522.
(10) (a) Bray, W. C. *J. Am. Chem. Soc.* **1921**, *43*, 1262. (b) Schmitz, G. *Phys. Chem. Chem. Phys.* **2010**, *12*, 6605.

Scheme 4. Amination of Benzoxazole with Various Amines[a]



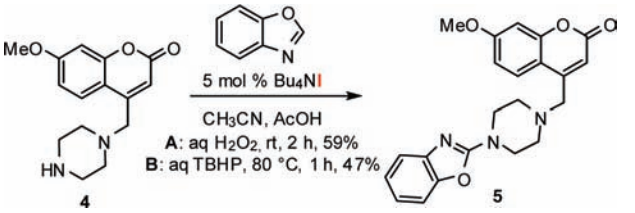
[a] General reaction conditions: **Method A**: 0.336 mmol of **1a**, 0.672 mmol of **2**, 5 equiv of H_2O_2 (30% aq solution), 5 equiv of HOAc in 1 mL of acetonitrile. **Method B**: 0.336 of mmol **1a**, 0.403 mmol of **2**, 1.5 equiv of TBHP (70% aq solution), 3 equiv of AcOH in 1 mL of acetonitrile at 80 °C.

Alkyl- and halogen-substituted benzoxazoles could be aminated in perfect regioselectivity to yield the desired 2-(morpholino)benzoxazoles **3a**–**3f** in up to 86% yield. Reaction of naphtho[1,2-*d*]oxazole with morpholine yielded 2-aminonaphthooxazole **3e** in an excellent yield of 93%. Even the electron-poor 6-nitrobenzoxazole could be derivatized to **3g**, however with decreased yields. Here a significant difference in yields (18% and 52%) was recognized between the two oxidation reagents. Even though yields were comparable when using H_2O_2 or TBHP as co-oxidants, in the latter case a full conversion was observed after 1 h for all substrates.

Next we discovered the reaction between various linear and cyclic secondary amines and benzoxazole **1a** (Scheme 4). In addition to morpholine we could efficiently use pyrrolidine, piperidine, and azepane for our oxidative amination procedure. The desired products **3j**–**3l** were obtained in 57–62% yield. Furthermore we could synthesize 2-piperazylbenzoxazoles **3m** and **3n** in excellent yields starting from *N*-methyl and *N*-acylpiperazine. 2-(*N*-alkylpiperazyl)benzoxazoles of this type were already described as potent 5-HT_3-receptor agonists.[11] To our surprise an unprotected hydroxyl group attached to the *N*-alkyl residue of piperazine is tolerated as well (**3o**), despite the oxidizing reaction conditions. In addition to cyclic amines, secondary aliphatic amines can be used in this transformation (**3p**–**3s**). In addition to simple dialkylamines, synthetically more useful diallylamine and dibenzylamine are tolerated. Undesired oxidations or halogenations of the double bonds, the aromatic ring, or the methylene units have not been observed. Furthermore we were pleased to find that with TBHP even a primary amine such as butyl amine could be used in our amination procedure to yield **3t** in a good yield of 69%.

These promising results prompted us to investigate our novel method toward the synthesis of the coumarin derivative **5**. **5** is known for its potent anti-HIV and antitumor activity, and an efficient late stage arylation of the piperazyl moiety of the potential precursor **4** would give an easy access to various *N*-aryl derivatives.[12] To our delight our standard reaction protocol using aq H_2O_2 yielded **5** in a good yield of 59% under mild reaction conditions (Scheme 5).

Scheme 5. TAAI-Mediated Synthesis of the Anti-HIV Reagent **5**[a]



[a] Reaction conditions: **Method A**: 0.336 mmol of **1a**, 2 equiv of **4**, 5 equiv of H_2O_2 (30% aq solution), 5 equiv of HOAc, 1 mL of acetonitrile. **Method B**: 0.336 mmol of **1a**, 0.336 mmol (1.0 equiv) of **4**, 1.5 equiv of TBHP (70% aq solution) in 1 mL of acetonitrile at 80 °C.

After we examined a satisfying substrate scope we performed several synthetic experiments to unravel the underlying reaction mechanism. Addition of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) had only a slight impact on the yield of **3a** (58%). Furthermore no TEMPO-bound intermediate could be observed. Thus a radical mechanism can be ruled out. Since catalytic amounts of I_2 (without co-oxidant) did not yield **3a**, the in situ generation of I_2 and its subsequent function as a mild Lewis acid is also excluded.

Next we tried to examine the reactivity of iodine in the oxidation state +1 (Scheme 6). Stoichiometric amounts of ICl, a potent source for iodonium ions (IR_2^+), yielded **3a** in 65% yield. Thus a mechanism that passes through I^+ seems plausible. Subsequently we wanted to verify whether in

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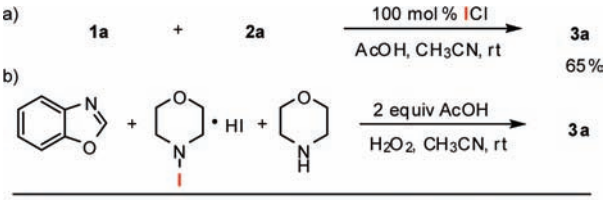
(12) Al-Soud, Y. A.; Al-Sa'doni, H. H.; Amajaour, H. A. S.; Salih, K. S. M.; Mubarak, M. S.; Al-Masoudi, N. A.; Jaber, I. H. *Z. Naturforsch.* **2008**, *63b*, 83.

(13) The potential in situ generation of ammonium(hypo)iodites (IO^-/IO_2^-) as catalytically active species cannot be ruled out at this point and is part of further investigations.

(14) Urbansky, E. T.; Cooper, B. T.; Margerum, D. W. *Inorg. Chem.* **1997**, *36*, 1338.

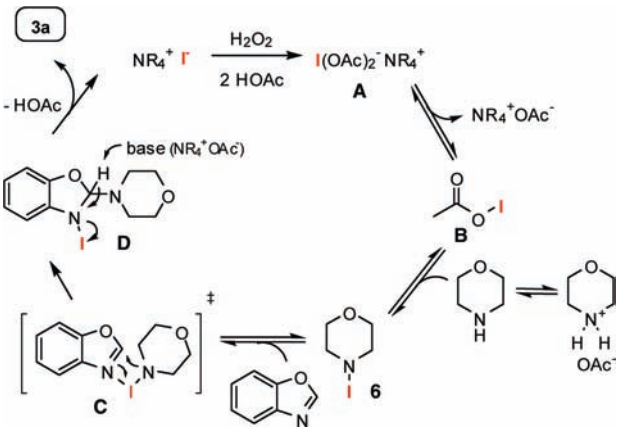
Scheme 6. Reactivity of *N*-Iodomorpholine Hydroiodide **6·HI**[a]



1a	6	2a	equiv H_2O_2	*t* [h]	yield
1	1	0	0	24	33%
1 :	2 :	0 :	0	24	28%
1	0.1	2	5	3	92%

[a] Reaction conditions are given in the Supporting Information.

Scheme 7. A Putative Reaction Mechanism



situ generation of an activated *N*-iodamine is likely. Thus *N*-iodomorpholine hydroiodide (**6·HI**) was synthesized and further investigated. The reaction of **6·HI** with benzoxazole gave **3a** in 33% yield (Scheme 6b). A 2-fold excess of **6·HI** did not increase the yield. However, when catalytic amounts of **6·HI** (10 mol %) were used, **3a** was isolated in 92% yield. As a consequence the activation of the amine via in situ formation of a highly reactive N–I bond from TBAI and the co-oxidant seems plausible.[13] This result in addition to the fact that carboxylic acids, in particular acetic acid, have a positive influence made us think about a first mechanistic proposal for our newly found oxidative amination procedure (Scheme 7). In the presence of an excess of acetic acid, TBAI is oxidized to iodoniumdiacetate **A** and subsequently liberates acetylhypoiodite **B**. **B** is a highly potent I^+ source which generates **6** from morpholine in the next step.[14]

Caused by the slightly acidic reaction conditions, only small amounts of the secondary amine remain in a neutral and reactive state and thus concentrations of **6** can be kept low. This prevents an undesired comproportionation reaction between $R_2N–I$ and I^- to form I_2 that might cause the low yields observed when using stoichiometric amounts of **6** (Scheme 6b). In the next step addition of **6** to benzoxazole yields 2-aminobenzoxazolidine **D** through transition state **C**. After base-induced elimination of iodide the desired reaction product **3a** can be observed.

In conclusion we described the first TBAI-catalyzed direct amination of heteroarenes. This is the first example of a metal-free synthesis of highly desirable 2-aminobenzoxazoles starting from unfunctionalized amines and benzoxazoles. The mild reaction conditions, lowest amounts of cheap and nontoxic TBAI as catalyst, and easy to handle co-oxidants such as H_2O_2 and TBHP make this novel amination protocol highly viable for future applications. In the near future we would like to establish TAAIs in oxidative C–N bond forming reactions as cheap and nontoxic alternatives for noble metals. Furthermore more experiments are needed for a deeper mechanistic understanding of TAAI-catalyzed amination reactions.

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Supporting Information Available. Experimental procedures, analytical data, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.