A Domino Copper-Catalyzed C–N and C–O Cross-Coupling for the Conversion of Primary Amides into Benzoxazoles

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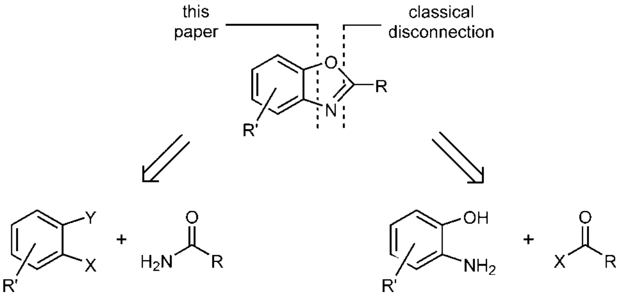
Abstract: Benzoxazoles can be efficiently prepared in a single step and in good yield from primary amides and *o*-dihalobenzenes using Cu catalysis. Starting from substituted *o*-bromochlorobenzenes this unusual domino reaction allows the regioselective formation of benzoxazoles.

Keywords: benzoxazoles; C–N and C–O cross-coupling; copper; cyclization; domino reactions; heterocycles

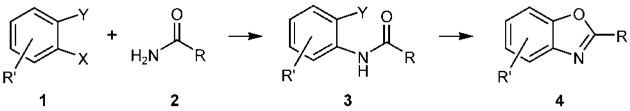
Benzoxazoles are an important subunit of many compounds from different areas of chemistry, like natural products,[1] biologically active compounds,[2] fluorescent probes[3] or heat-resistant polymers.[4] However, whereas many different strategies for the synthesis of related oxazoles exist, the 2-substituted benzoxazole ring system is mostly built up by classical approaches as shown in Scheme 1.[5] In these classical syntheses of benzoxazoles, 2-aminophenols are coupled with aldehydes under oxidative conditions[6] or with carboxylic acid derivatives,[7] either sequentially or in a one-step process.[5] In many cases rather harsh reaction conditions (oxidative, acidic or high temperature) are needed for these transformations. In addition, these approaches are limited by the availability of the properly substituted *o*-aminophenols. Different strategies for the synthesis of the benzoxazole ring system should significantly increase the attractivity of this important entity. Herein, we report an efficient Cu-catalyzed formation of benzoxazoles from *o*-dihaloaromatic compounds and primary amides in a single step (Scheme 1).

The cyclization of *o*-halobenzeneamides **3** to benzoxazoles **4** has been reported several times,[8,9] including two copper-mediated transformations (Scheme 2).[10] However, these methods were hampered by the use of stoichiometric amounts of catalyst, harsh reaction conditions, low yields or limited substrate scope. Because of our interest and experience in Pd- and Cu-catalyzed coupling reactions[11] we felt that cross-coupling chemistry could potentially fill this gap. Our ultimate goal was the formation of benzoxazoles by the domino C–N and C–O bond formation under the same reaction conditions (**1**+**2**→**4**).

The starting point of our investigation was the cyclization of 2-bromobenzene amide **3a** (Y=Br, R=Me, R′=H) to the corresponding benzoxazole **4a**.[12] Despite many Pd catalysts being known to catalyze C–N and C–O bond formations,[13] all palladium catalysts tested failed to produce the desired product.[14] Since the pioneering work of Ullman and Goldberg on Cu-catalyzed cross-coupling reactions, many efficient protocols for otherwise difficult C–N and C–O bond formations have been developed.[15] Fortunately, Cu catalysis under conditions developed by Buchwald for the amidation of aryl halides[16] resulted in the formation of significant amounts of **4a**, although the conversion was not complete. Screening of different conditions led to the identification of an optimal protocol (5 mol % CuI, 10 mol % dmeda, K_2CO_3, toluene, 110 °C) for the complete conversion of **3a**, resulting in the formation of **4a** in 81% yield (Scheme 3). The use of K_3PO_4 instead of K_2CO_3



Scheme 1. Retrosynthetic analysis of benzoxazole formation.



Scheme 2. Sequential C–N and C–O couplings in the formation of benzoxazoles (X, Y=halides).

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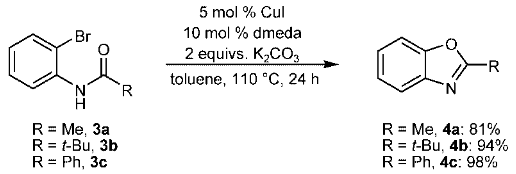


Scheme 3. Cu-catalyzed C–O bond formation of 2-bromobenzene amides **3**; dmeda = *N,N'*-dimethylethylenediamine.

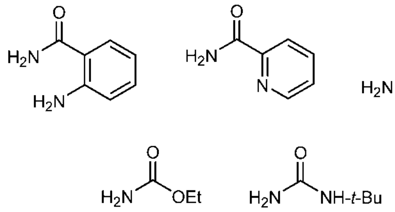


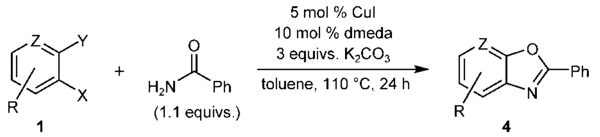
Figure 1. Amide substrates **2** that do not result in benzoxazole formation.

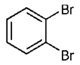
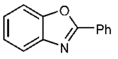
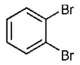
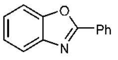
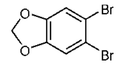
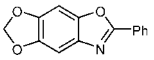
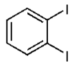
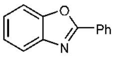
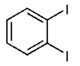
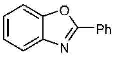
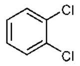
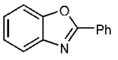
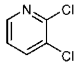
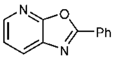
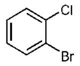
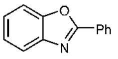
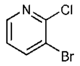
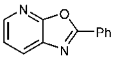
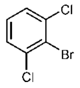
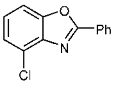
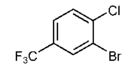
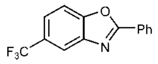
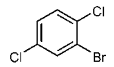
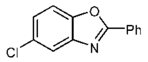
as a base resulted in comparable results. Acetamides **3b** and **3c** were also cyclized in good yields.

Encouraged by these results we decided to investigate the one-step synthesis of benzoxazoles **4** from *o*-dihalobenzene derivatives **1** and primary amides **2** (Scheme 2). The amidation of halobenzenes is a well known reaction and several protocols for this transformation have been developed in recent years.[18] We were pleased to find that under Cu catalysis, benzoxazoles were formed from primary amides and *o*-dihalobenzene derivatives. An extensive screening of the reaction conditions was performed for the reaction of 1,2-dibromobenzene with benzamide.[19] Under optimized conditions (5 mol % CuI, 10 mol % dmeda, 3 equivs. K_2CO_3, toluene, 110 °C) the desired benzoxazole was smoothly formed and isolated in 90% yield (Table 1, entry 1). This reaction can also be run on a 20 mmol scale without any problems (entry 2). Even a sensitive acetal moiety is well tolerated under the reaction conditions (entry 3). Furthermore, the reaction of benzamide with several other *o*-dihaloaromatic substrates was investigated. Whereas standard conditions result in incomplete conversion of 1,2-diiodobenzene, the use of more catalyst (10 mol % CuI and 20 mol % dmeda) results in a high yield (entries 4 and 5). Even though the Cu-catalyzed amidation of aryl chlorides has been reported,[16] no amidation or benzoxazole formation was observed with 1,2-dichlorobenzene under our standard conditions (entry 6). Interestingly, whereas 1,2-dichlorobenzene and 2,3-dichloropyridine result in no product formation (entries 6 and 7), 1-bromo-2-chlorobenzene and 2-chloro-3-bromopyridine smoothly react with benzamide to yield **4c** and **4e** (entries 8 and 9). Moreover, differently substituted benzoxazoles can regioselectively be formed from the corresponding 1-bromo-2-chlorobenzenes (entries 10–12).[20] The other regioisomers were not observed. These high levels of regioselectivity nicely demonstrate the utility of this method by expanding the scope of benzoxazole synthesis. From the outcome of these reactions of 1-bromo-2-chlorobenzenes it is obvious that the amidation occurs selectively at the C–Br position followed by the subsequent cyclization and C–O bond formation with the C–Cl moiety (Scheme 2, X = Br, Y = Cl). Furthermore, whereas iodides or bromides are required as coupling partners for the amidation step (entries 6 and 7), chlorides are sufficiently reactive for the final cyclization step (entries 8–12).

Some primary amides did not react with 1,2-dibromobenzene to give the desired benzoxazoles (Figure 1).

Table 1. Cu-catalyzed formation of 2-phenyl benzoxazoles.[a]



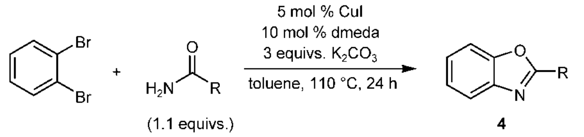
Entry	*o*-Dihalo substrate	Product		Isolated yield [%]
1			**4c**	90
2[b]			**4c**	95
3			**4d**	88
4			**4c**	65
5[c]			**4c**	89
6			**4c**	0
7			**4e**	0
8[c]			**4c**	95
9			**4e**	77
10			**4f**	75
11			**4g**	59
12			**4h**	72

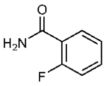
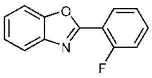
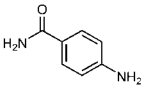
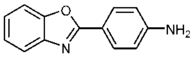
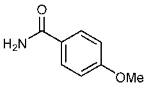
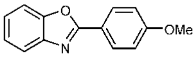
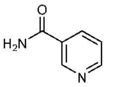
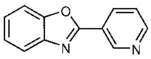
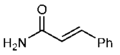
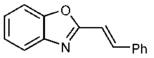
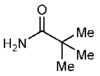
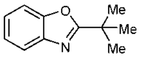
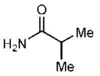
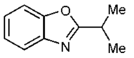
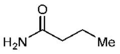
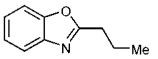
[a] General conditions: *o*-dihaloaromatic substrate (1 mmol), amide (1.1 mmol), CuI (5 mol %), *N,N'*-dimethylethylenediamine (10 mol %), K_2CO_3 (3 mmol), toluene (3 mL), 110 °C, 24 h.

[b] 20 mmol scale.

[c] CuI (10 mol %), *N,N'*-dimethylethylenediamine (20 mol %).

Table 2. Cu-catalyzed formation of differently 2-substituted benzoxazoles.[a]



Entry	Amide substrate	Product		Isolated yield [%]
1			**4i**	86
2			**4j**	67
3			**4k**	72
4			**4l**	78
5			**4m**	77
6			**4b**	92
7[b]			**4n**	68
8[b]			**4o**	68

[a] General conditions: o-dihaloaromatic substrate (1 mmol), amide (1.1 mmol), CuI (5 mol %), N,N′-dimethylethylenediamine (10 mol %), K_2CO_3 (3 mmol), toluene (3 mL), 110 °C, 24 h.

[b] CuI (10 mol %), N,N′-dimethylethylenediamine (20 mol %), K_2CO_3 (4.3 mmol).

However, the broad scope of this synthetic method was showcased by the successful variation of the primary amide coupling partner (Table 2). Several aromatic and aliphatic amides are good substrates, resulting in product formation in yields ranging from 67 to 92%. Even an aniline derivative is tolerated under the reaction conditions (entry 2). It is important to note that small variations can have a profound effect. For example, while 4-aminobenzamide is a good substrate (entry 2), no reaction is seen with 2-aminobenzamide. Furthermore, whereas 3-pyridylamide (nicotinic acid amide) leads to the formation of the desired product (entry 4), the regioisomeric 2-pyridylamide does not. In some cases, astonishing volatility of the product can complicate the efficient purification and may result in a loss in yield (entries 7 and 8). These results demonstrate that the *o*-dihalobenzene derivative as well as the primary amide can be varied over a wide range allowing the formation of numerous differently substituted benzoxazoles.

In conclusion, we have developed an efficient Cu-catalyzed method for the single-step synthesis of benzoxazoles from readily available primary amides and *o*-dihalobenzene derivatives. To the best of our knowledge this is the first benzoxazole synthesis of this type.[21] While some limitations were found the scope of this transformation seems to be rather broad. It is hoped that this non-classical synthetic approach will increase the popularity of the versatile benzoxazole moiety in all areas of chemistry.

Experimental Section

Representative Procedure for the Synthesis of Benzoxazoles (Tables 1 and 2)

1,2-Dibromobenzene (120 μL, 1.0 mmol), benzamide (133 mg, 1.1 mmol), K_2CO_3 (414 mg, 3.0 mmol) and CuI (10 mg, 0.05 mmol) were weighed into a vial under air. The vial was evacuated and filled with argon, followed by the addition of *N,N′*-dimethylethylenediamine (11 μL, 0.1 mmol) and toluene (3 mL). The vial was closed and the reaction mixture stirred at 110 °C for 24 h. After cooling to room temperature the reaction mixture was poured into 25% aqueous NH_4OH, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. Chromatography over silica gel (EtOAc/hexane = 1/10) yielded **4c** as a white powder; yield: 176 mg (90%).

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References and Notes

[1] a) A. D. Rodriguez, C. Ramirez, I. I. Rodriguez, E. Gonzalez, *Org. Lett.* **1999**, *1*, 527–530; b) J. Kobayashi, T. Madono, H. Shigemori, *Tetrahedron Lett.* **1995**, *36*, 5589–5590.

[2] a) H. Razavi, S. K. Palaninathan, E. T. Powers, R. L. Wiseman, H. E. Purkey, N. N. Mohamedmohaideen, S. Deechongkit, K. P. Chiang, M. T. A. Dendle, J. C. Sacchettini, J. W. Kelly, *Angew. Chem. Int. Ed.* **2003**, *42*, 2758–2761; b) K. Devinder, M. R. Jacob, M. B. Reynolds, S. M. Kerwin, *Biorg. Med. Chem.* **2002**, *10*, 3997–4004; c) M. B. Reynolds, M. R. DeLuca, S. M. Kerwin, *Bioorg. Chem.* **1999**, *27*, 326–337; d) Y. Sato, M. Yamada, S. Yoshida, T. Soneda, M. Ishikawa, T. Nizato, K. Suzuki, F. Konno, *J. Med. Chem.* **1998**, *41*, 3015–3021; e) D. B. Olsen, S. S. Carroll, J. C. Culberson, J. A. Shafer, L. C. Kuo, *Nucleic Acids Res.* **1994**, *22*, 1437–1443.

[3] K. Tanaka, T. Kumagai, H. Aoki, M. Deguchi, S. Iwata, *J. Org. Chem.* **2001**, *66*, 7328–7333.

[4] a) C. C. Wu, P. Y. Tsay, H. Y. Cheng, S. J. Bai, *J. Appl. Phys.* **2004**, *95*, 417–423; b) K. Tamargo-Martinez, S. Villar-Rodil, J. I. Paredes, A. Martinez-Alonso, J. M. D. Tascon, *Chem. Mater.* **2003**, *15*, 4052–4059; c) S. Bourbigot, X. Flambard, *Fire Mater.* **2002**, *26*, 155–168.

[5] a) H. Döpp, D. Döpp, in: *Houben-Weyl: Methoden der Organischen Chemie*, Vol. E8a (Ed.: E. Schaumann), Thieme, Stuttgart, **1993**, pp. 1020–1193; b) G. V. Boyd, in: *Science of Synthesis: Houben-Weyl methods of molecular transformations*, Vol. 11 (Ed.: E. Schaumann), Thieme, Stuttgart, **2002**, pp. 481–492; c) G. V. Boyd, in: *Comprehensive Heterocyclic Chemistry*, Vol. 6 (Eds.: A. R. Katritzky, C. W. Rees, K. T. Potts), Pergamon Press, New York, **1984**, pp. 177–223; d) A. R. Katritzky, Z. Wang, C. D. Hall, N. G. Akhmedov, A. A. Shestopalov, P. J. Steel, *J. Org. Chem.* **2003**, *68*, 9093–9099 and references cited therein.

[6] a) Y. Kawashita, N. Nakamichi, H. Kawabata, M. Hayashi, *Org. Lett.* **2003**, *5*, 3713–3715; b) J. Chang, K. Zhao, S. Pan, *Tetrahedron Lett.* **2002**, *43*, 951–954; c) R. S. Varma, D. Kumar, *J. Heterocyclic Chem.* **1998**, *35*, 1539–1540.

[7] a) M. Terashima, M. Ishii, Y. Kanaoka, *Synthesis* **1982**, 484–485; b) K. Bougrin, A. Loupy, M. Soufiaoui, *Tetrahedron* **1998**, *54*, 8055–8064; c) R. S. Pottorf, N. K. Chadha, M. Katkevics, V. Ozola, E. Suna, H. Ghane, T. Regberg, M. R. Player, *Tetrahedron Lett.* **2003**, *44*, 175–178.

[8] a) Ref.[5a] pp 1089–1091; b) Y.-T. Park, M.-G. Song, M.-S. Kim, J.-H. Kwon, *Bull. Korean Chem. Soc.* **2002**, *23*, 1208–1212; c) Y.-T. Park, C.-H. Jung, K.-W. Kim, H. S. Kim, *J. Org. Chem.* **1999**, *64*, 8546–8556; d) R. J. Perry, B. D. Wilson, *J. Org. Chem.* **1992**, *57*, 6351–6354; e) D. R. Reavill, S. K. Richardson, *Synth. Commun.* **1990**, *20*, 1423–1436; f) Y. Inukai, Y. Oono, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 516–520; g) B. F. Hrutford, J. F. Bunnett, *J. Am. Chem. Soc.* **1958**, *80*, 2021–2022; h) R. Adams, J. W. Way, *J. Am. Chem. Soc.* **1954**, *76*, 2763–2767.

[9] For the cyclization of 2-halo-3-amidopyridines, see: a) M. H. Norman, D. J. Douglas, G. E. Martin, *J. Heterocycl. Chem.* **1993**, *30*, 771–780; b) C. Flouzant, G. Guillaumet, *Synthesis* **1990**, 64–66; c) C. Flouzat, G. Guillaumet, *J. Heterocycl. Chem.* **1991**, *28*, 899–906; d) P. Savarino, G. Viscardi, R. Carpignano, E. Barni, *J. Heterocycl. Chem.* **1989**, *26*, 77–80; for a Cu-mediated process, see: e) J.-F. Briere, G. Dupas, G. Queguiner, J. Bourguignon, *Heterocycles* **2000**, *52*, 1371–1384.

[10] a) T. Minami, T. Isonaka, Y. Okada, J. Ichikawa, *J. Org. Chem.* **1993**, *58*, 7009–7015; b) M. Iizuka, M. Yamamoto, J. Matsumura, M. Yoshida (Hodogaya Chemical Co., Ltd.), *US Patent* 3147253, **1964**; *Chem. Abstr.* **1964**, *61*, 16209.

[11] a) F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, 2704–2705; b) F. Glorius, *Tetrahedron Lett.* **2003**, *44*, 5751–5754; c) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed.* **2003**, *42*, 3690–3693; d) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 2850–2852.

[12] For some related transition-metal catalyzed cyclizations, see: a) L. L. Joyce, G. Evindar, R. A. Batey, *Chem. Commun.* **2004**, 446–447; b) G. Evindar, R. A. Batey, Org. Lett. 2003, 5, 133–136; c) C. Benedi, F. Bravo, P. Uriz, E. Fernandez, C. Claver, S. Castillon, *Tetrahedron Lett.* **2003**, *44*, 6073–6077; d) C. T. Brain, J. T. Steer, *J. Org. Chem.* **2003**, *68*, 6814–6816 and references cited therein.

[13] Review on Pd-catalyzed C-N- and C-O-bond formations: A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131–209.

[14] This is in agreement with a recent literature report, see ref.[12c]

[15] Profound reviews on Cu-catalyzed C–N, C–O and C–S couplings: a) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439.

[16] A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

[17] The use of K_3PO_4 instead of K_2CO_3 as a base resulted in comparable results.

[18] For Pd-catalyzed amidations, see: a) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575–5580; b) J. J. Yin, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1101–1104; for Cu-catalyzed amidations, see c) M. Sugahara, T. Ukita, *Chem. Pharm. Bull.* **1997**, *45*, 719–721; d) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729; e) ref.[16]

[19] Parameters varied in the screening experiments: solvents: acetonitrile, cyclohexane, dioxane, DMF, isopropyl alcohol, toluene; bases: NaOAc, K_2CO_3, K_3PO_4, CsOAc, Cs_2CO_3, EtN(*i*-Pr)$_2$, proton sponge; Cu salts: CuI, CuCN, CuOTf, Cu(CN)$_4$PF$_6$; ligands: 1,2-diaminocyclohexane, *N*,*N*′-dimethylethylenediamine, phenanthroline, proline.

[20] Whereas the regiochemistry of the **4e**, **4f** and **4h** was firmly established, the regiochemistry of **4g** was assigned by analogy only.

[21] However, the uncatalyzed coupling and cyclization of activated hexafluorobenzene and benzamide in 32% yield has been reported as a one-step procedure: Y. Inukai, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657–2660.