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Efficient synthesis of 2,3-dihydro-1,4-benzoxazines via intramolecular copper-catalyzed O-arylation

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ABSTRACT

A highly efficient synthetic approach to 2,3-dihydro-1,4-benzoxazines is described. The method involves a mild intramolecular copper-catalyzed O-arylation of β aminoalcohol, which works well without N-protection.

2,3-Dihydro-1,4-benzoxazines are an important class of molecules, which are a common heterocyclic scaffold in biologically active and medicinally significant compounds. For example, levofloxacin that exhibits excellent activities against Gram-positive and Gram-negative bacteria, possesses 2,3-dihydro-1,4-benzoxazine moiety. In addition, some benzoxazines are central nervous system depressants, antipsychotic agents, calcium antagonists, and antibacterial agents; moreover, some are potential drugs for neuroprotective, antitumor, antithrombotic, antihypertensive agents, and cardiovascular drugs.[1] Due to the importance of 1,4-benzoxazines, several synthetic methods for 2,3-dihydro-1,4-benzoxazines have been reported over the past few decades.[1a,2] However, these methods suffered some limitations in the generation of molecular diversity.[2] The recent developments of metal-catalyzed intramolecular O-arylation and N-arylation provide efficient methods for benzoxazines synthesis. Buchwald reported benzoxazines synthesis via palladium-catalyzed intramolecular etherification.[3] More recently, synthesis of 2,3-dihydro-1,4-benzoxazines through palladium-catalyzed intramolecular N-arylation has been reported.[4] However; these methods have some limitations with respect to the toxic catalysts and N-protection. Thus, there is clearly a demand for more general and environment friendly entries to this interesting class of substances.

Since the discovery, the copper-mediated Ullmann coupling reaction is the straightforward method to form carbon–heteroatom bonds. However, traditional copper-catalyzed Ullmann coupling reaction[5] was conducted under harsh conditions, including high temperature, stoichiometric amount of copper agent, and extended period of time which limited the scope of the reaction. Since Buchwald's and Taillefer's pioneering work, exhaustive efforts have been made to explore efficient copper/ligand systems and significant progresses have been achieved.[6] The achievements have been widely used in heterocycle synthesis.[7] Moreover, Buchwald reported control of the chemoselectivity of N-arylation versus O-arylation of 1,2-aminoalcohols with different copper/base combinations or other aminoalcohols with copper/ligand/base combinations.[8] Herein, we would like to describe an efficient methodology for the synthesis of 2,3-dihydro-1,4-benzoxazine by CuI/1, 10-phenanthroline system catalyzed intramolecular O-arylation of β-aminoalcohols without N-protection.

As reported, the chemoselectivity of intermolecular O-arylation was low with copper/ligand systems and moderate with ligand-free system when β-aminoalcohol was employed.[8a] However, under the ligand free condition, the intramolecular coupling of **1a** was the minor reaction.[9,10] Then, we performed the intramolecular coupling of **1a** in the presence of CuI/1, 10-phenanthroline with various bases in different solvents (Table 1). The reaction was first carried out in toluene mediated by K_3PO_4; however, no desired coupling product was obtained with starting material quantitatively recovered (entry 1). To our surprise, when a stronger base, NaO*t*-Bu was used, the O-arylation product **2a** was obtained with 75% yield (entry 2). Encouraged by this finding, the optimal cyclization conditions were screened. Several solvents including

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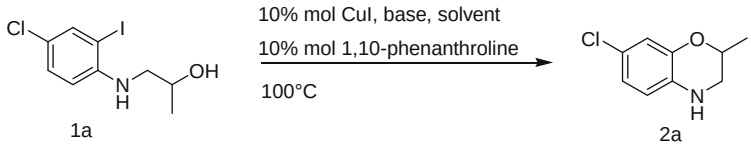
Table 1
Optimization of reaction conditions[a]



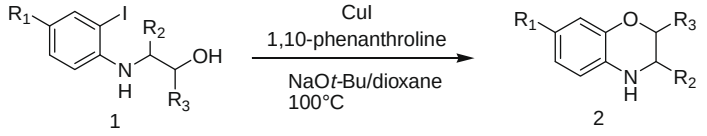
Entry	Base	Solvent	Yield[b] (%)
1	K_3PO_4	Toluene	NR
2	NaO*t*-Bu	Toluene	75
3	NaO*t*-Bu	*o*-Xylene	71
4	NaO*t*-Bu	Dioxane	86
5	NaO*t*-Bu	DMF	Trace
6	NaO*t*-Bu	MeCN	Trace
7	Cs_2CO_3	Dioxane	Trace
8	KO*t*-Bu	Dioxane	Trace

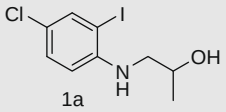
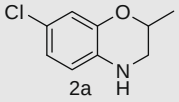
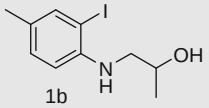
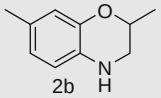
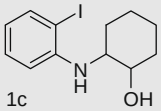
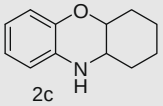
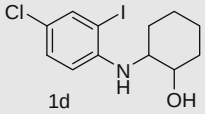
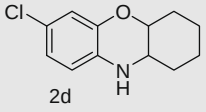
[a] Reaction conditions: **1a** (0.5 mmol); CuI (10 mol %); 1,10-phenanthroline (20 mol %); base (1 mmol); dry solvent (2 ml); reaction time 12–24 h; under N_2 atmosphere.
[b] Isolated yield.

toluene, *o*-xylene, dioxane, DMF, and MeCN were tested (entries 2–6). It turned out that dioxane was superior to the other solvents (entry 4). It was found that NaO*t*-Bu was the most efficient base. When stronger base such as KO*t*-Bu or weaker base such as Cs_2CO_3 was employed, only trace cyclization product was obtained (entries 7 and 8).

Having established the preferred reaction condition, we applied this methodology to synthesize a series of 2,3-dihydro-1,4-benzoxazine derivatives. The representative results are summarized in Table 2.[11] Substituent variations such as chloro- and methyl groups on the iodoaryl moiety of 1 were tolerated and 2 was obtained in excellent yields (entries 1 and 2).[12] It should be noted that the

Table 2
Cu catalyzed intramolecular O-arylation to form 2,3-dihydro-1,4-benzoxazines



Entry	**1**	**2**	Yield of **2**[a] (%)
1			86
2			95
3[b]			92
4			91

(*continued on next page*)

Table 2 (*continued*)

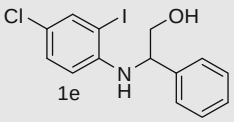
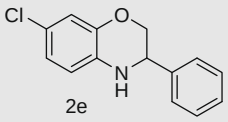
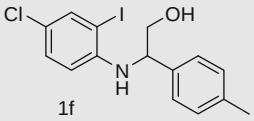
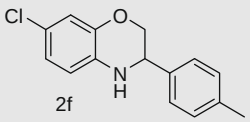
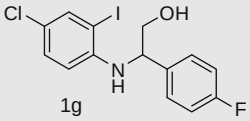
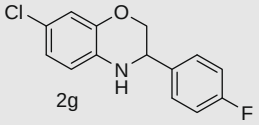
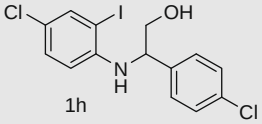
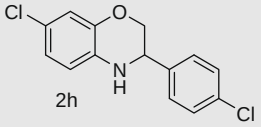
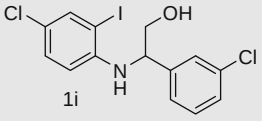
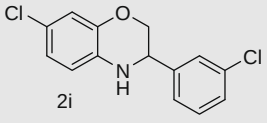
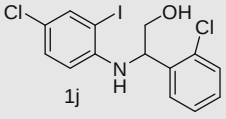
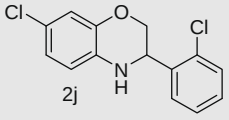
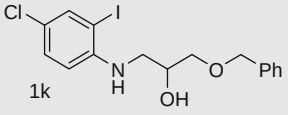
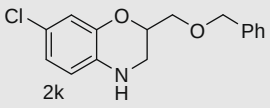
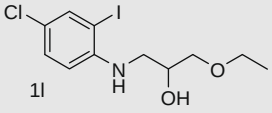
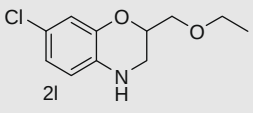
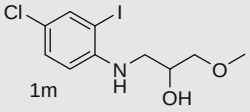
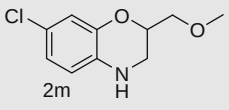
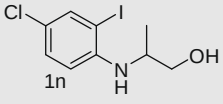
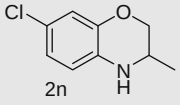
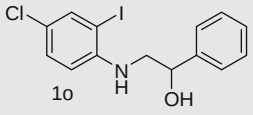
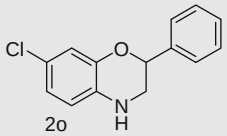
Entry	1	2	Yield of **2**[a] (%)
5	 1e	 2e	84
6	 1f	 2f	85
7	 1g	 2g	86
8	 1h	 2h	87
9	 1i	 2i	81
10	 1j	 2j	82
11	 1k	 2k	91
12	 1l	 2l	94
13	 1m	 2m	89
14	 1n	 2n	87

Table 2 (*continued*)

Entry	1	2	Yield of 2[a] (%)
15	 1o	 2o	82

[a] Isolated yield.
[b] The configuration of **2c** is determined by comparison of the data with the literature (see Ref. 2f).

trans-cyclohexyl amino alcohol moiety was also tolerated well to give corresponding *trans*-benzoxazine with excellent yield (entries 3 and 4).[2f,9] Substrates with aryl substituents on the amino alcohol moiety were examined as well (entries 5–10 and 15). The phenyl ring could be substituted in 2, 3, or 4 positions and the substituents can be electron-withdrawing or electron-donating groups. When 4-methyl, 4-fluoro, and 4-chloro phenyl moiety were employed, good yields of **2** were obtained (entries 6–8). 2-Chloro phenyl moiety and 3-chloro phenyl moiety could cyclize smoothly to give benzoxazine with 82% and 81% yields, respectively (entries 9 and 10). The compound that has bulky substituent on the alcohol moiety could also give cyclization product with good yield (entry 15). Methyl and ether groups on amino alcohol moiety were also well tolerated under these conditions (entries 11–14).

In conclusion, we have developed a general, more sustainable methodology for the copper-catalyzed intramolecular O-arylation to synthesize benzoxazines, which is a valuable framework with interesting therapeutic properties. In addition, the process tolerates variation of both aryl iodide and amino alcohol portions of the substrate. Furthermore, this methodology allows free N–H group which was protected in other benzoxazines synthesis methods.[8]

Acknowledgment

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References and notes

1. (a) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449–2467. and references therein; (b) Rybczynski, P. J.; Zeck, R. E.; Dudash, J.; Combs, D. W.; Burris, T. P.; Yang, M.; Osborne, M. C.; Chen, X.; Demarest, K. T. *J. Med. Chem.* **2004**, *47*, 196–209; (c) Yang, W.; Wang, Y.; Ma, Z.; Golla, R.; Stouch, T.; Seethala, R.; Johnson, S.; Zhou, R.; Güngör, T.; Feyen, J. H. M.; Dickson, J. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2327–2330; (d) Blattes, E.; Lockhart, B.; Lestage, P.; Schwendimann, L.; Gressens, P.; Fleury, M. B.; Largeron, M. *J. Med. Chem.* **2005**, *48*, 1282–1286; (e) La, D. S.; Belzile, J.; Bready, J. V.; Coxon, A.; DeMelfi, T.; Doerr, N.; Estrada, J.; Flynn, J. C.; Flynn, S. R.; Graceffa, R. F.; Harriman, S. P.; Larrow, J. F.; Long, A. M.; Martin, M. W.; Morrison, M. J.; Patel, V. F.; Roveto, P. M.; Wang, L.; Weiss, M. W.; Whittington, D. A.; Teffera, Y.; Zhao, Z. Y.; Polverino, A. J.; Harmang, J. C. *J. Med. Chem.* **2008**, *51*, 1695–1705; (f) Haš, J.; Tomašic, T.; Kikelj, D. *J. Med. Chem.* **2008**, *51*, 2863–2867; (g) Bourlot, A. S.; Sánchez, I.; Dureng, G.; Guillaumet, G.; Massingham, R.; Monteil, A.; Winslow, E.; Pujol, M. D.; Mérour, J. Y. *J. Med. Chem.* **1998**, *41*, 3142–3158; (h) Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M. C.; Renard, P.; Mérour, J. Y. *J. Med. Chem.* **2003**, *46*, 1962–1979; (i) Anderluh, P. Š.; Anderluh, M.; Haš, J.; Mravljak, J.; Dolenc, M. S.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2005**, *48*, 3110–3113; (j) Largeron, M.; Lockhart, B.; Pfeiffer, B.; Fleury, M. B. *J. Med. Chem.* **1999**, *42*, 5043–5052; (k) Haš, J.; Jakopin, Z.; Bonrštnar, T.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2008**, *51*, 5617–5629; (l) Caliendo, G.; Perissutti, E.; Santagada, V.; Fiorino, F.; Severino, B.; Cirillo, D.; d'Emmanuele di Villa Bianca, R.; Lippolis, L.; Pinto, A.; Sorrentino, R. *Eur. J. Med. Chem.* **2004**, *39*, 815; (m) Thomas, A.; Ross, R. A.; Saha, B.; Mahadevan, A.; Razdan, R. K.; Pertwee, R. G. *Eur. J. Pharmacol.* **2004**, *487*, 213–221; (n) Lee, H. J.; Ban, J. Y.; Seong, Y. H. *Life Sci.* **2005**, *78*, 294–300; (o). *J. Neurosci.* **2005**, *25*, 584–593.
2. (a) Ilas, J.; Stefanic, A. P.; Sollner, D. M.; Kikelj, D. M. *Tetrahedron* **2005**, *61*, 7325–7348; (b) Kundu, N. G.; Chaudhuri, G.; Upadhyay, A. *J. Org. Chem.* **2001**, *66*, 20–29; (c) Blattes, E.; Fleury, M. B.; Largeron, M. *J. Org. Chem.* **2004**, *69*, 882–890; (d) Zhou, Y. G.; Peng, Y. Y.; Han, X. W. *J. Org. Chem.* **2005**, *70*, 1679–1683; (e) Blattes, E.; Fleury, M. B.; Largeron, M. *J. Org. Chem.* **2006**, *71*, 6374–6381; (f) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Ind. Eng. Chem. Res.* **2003**, *42*, 680–686; (g) Brown, D. W.; Ninan, A.; Sainsbury, M. *Synthesis* **1997**, 895–898.
3. Kuwabe, S.; Torraca, K. F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206.
4. Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283–3286.
5. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; (b) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097–1107; (c) Fanta, P. E. *Synthesis* **1974**, 9–21; (d) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327–3359; (e) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. and references therein.
6. (a) Taillefer, M. Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. Fr 2833947-WO 0353225 (Pr. Nb. Fr 2001 16547), 2001; Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Ouali, A. Fr 2840303-WO 03101966 (Pr. Nb. Fr 2002 06717), 2002.; (b) Buchwald, S. L.; Klapars, A.; Antilla, J. C.; Job, G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G.; Hennessy, E. J. WO 02/085838 (Priority number US 2001 0286268), 2001.; (c) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096–3099. and references therein; (d) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976; (e) Hosseinzadeh, R.; Tajbakhsh, M.; Mohajerani, M.; Alikarami, M. *Synlett* **2005**, 1101–1104; (f) Zhang, H.; Ma, D.; Cao, W. *Synlett* **2007**, 243–246; (g) Manback, G. F.; Lipman, A. J.; Stockland, R. A., Jr.; Freidl, A. L.; Hasler, A. F.; Stone, J. J.; Guzei, I. A. *J. Org. Chem.* **2005**, *70*, 244–250; (h) Xiao, X. Y.; Li, R.; Hurst, D.; Zhuang, H.; Shi, S.; Czarnik, A. W.; Robichaud, A. J.; Wacker, D. A.; Robertson, D. W. *J. Comb. Chem.* **2002**, *4*, 536–539; (i) Chen, Y. J.; Chen, H. H. *Org. Lett.* **2006**, *8*, 5609–5612; (j) Cristau, H. J.; Pascal, P. C.; Hamada, S.; Francis, J. S.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913–916.
7. (a) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379–9382; (b) Viirre, R. D.; Evindar, G.; Bartey, R. A. *J. Org. Chem.* **2008**, *73*, 3452–3459; (c) Salcedo, A.; Neuville, L.; Zhu, J. P. *J. Org. Chem.* **2008**, *73*, 3600–3603; (d) Li, C. J.; Fang, Y. W. *J. Am. Chem. Soc.* **2007**, *129*, 8092–8093; (e) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821; (f) Evindar, G.; Bartet, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808; (g) Li, C. J.; Fang, Y. W. *J. Org. Chem.* **2006**, *71*, 6427–6431; (h) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452–3459; (i) Carril, M.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, *8*, 1467–1470; (j) Zhao, Q. W.; Li, C. Z. *Org. Lett.* **2008**, *10*, 4037–4040; (k) Vina, D.; Olmo, E. D.; Feliciano, A. S. *Org. Lett.* **2007**, *9*, 525–528; (l) Bao, W. L.; Liu, Y. Y.; Qian, W. X. *Org. Lett.* **2008**, *10*, 3899–3902; (m) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125–128; (n) Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379–3382; (o) Tadd, A. C.; Feilding, M. R.; Willis, M. C. T. *Tetrahedron Lett.* **2007**, *48*, 7578–7581; (p) Hoogenband, A. V.; Lange, J. H.; Hartog, J. J.; Henzen, R.; Terpstra, J. W. T. *Tetrahedron Lett.* **2007**, *48*, 4461–4465.
8. (a) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491; (b) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703–3706.
9. Chakraborti, A.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597–3600.
10. *Typical procedure for the preparation of* **1a**: The reactor was charged with 4-chloro-2-iodobenzenamine (2 mmol), 2-methyloxirane (6 mmol), LiBr (2 mmol), and 3 ml dry THF, and the resultant mixture was stirred at 35 °C for 72 h. Addition of water, extraction with CH_2Cl_2, drying with Na_2SO_4, filtration, and solvent removal in vacuo gave a residue that was purified by column chromatography using ethyl acetate/petroleum ether as eluent to give **1a** (410 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, J = 6 Hz, 3H), 1.90 (br s, 1H), 3.00–3.07 (m, 1H), 3.19–3.25 (m, 1H), 4.01–4.11 (m, 1H), 4.46 (br s, 1H), 6.49 (d, J = 8 Hz, 1H), 7.14–7.18 (m, 1H), 7.62 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 137.8, 129.1, 122.0, 111.0, 85.1, 65.9, 51.5, 20.9.
11. *Typical representative experimental procedure*: NaO*t*-Bu (96 mg, 1 mmol), CuI (9.5 mg, 0.05 mmol), 1,10-phenanthroline (18 mg, 0.1 mmol), and **1a** (155 mg, 0.5 mmol) were taken in a 10 ml round-bottomed flask. The flask was evacuated and back-filled with nitrogen three times. Dry dioxane (2 ml) was added to the mixture at room temperature. The resulting mixture was placed at oil base, and heated for 24 h at 100 °C. after complete disappearance of **1a** (TLC), the reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The mixture was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluent to give white solid **2a** (79 mg, 86%).
12. *Analytical data for* **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, J = 6 Hz, 3H), 3.03–3.10 (m, 1H), 3.30–3.35 (m, 1H), 3.74 (br s, 1H), 4.16–4.23 (m, 1H), 6.49 (d, J = 8 Hz, 1H), 6.69–6.73 (m, 1H), 6.78 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.4, 46.6, 70.4, 115.7, 116.8, 120.8, 122.8, 131.7, 144.4; ESI-MS: m/z calcd for $C_9H_{10}NOCl$: 183.0529; found: 184.0518 [M+H].