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Highly Efficient Copper-Catalyzed Domino Ring Opening and Goldberg Coupling Cyclization for the Synthesis of 3,4-Dihydro-2*H*-1,4-benzoxazines†

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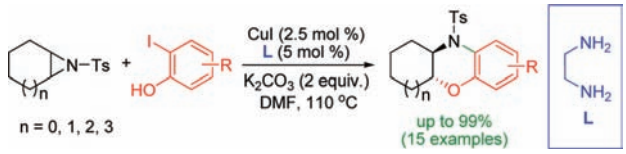
ABSTRACT



***trans*-3,4-Dihydro-2*H*-1,4-benzoxazine moieties can be synthesized by domino aziridine ring opening with *o*-iodophenols followed by the copper-catalyzed Goldberg coupling cyclization (intramolecular C(aryl)−N(amide) bond formation) with good to excellent yields.**

Recently, organic compounds containing 1,4-benzoxazines and phenoxazine moieties have attracted chemists due to their biological activities (Figure 1).[1] Generally, 1,4-benzoxazine compounds are synthesized by multistep synthesis such as cyclocondensation of aminophenols with suitable dihalo derivatives,[2] cyclocondensation of amino phenols with α-halogeno acyl bromides followed by carbonyl reduction with BH_3,[3] and alkylation of *o*-nitrophenol with haloester followed by reductive cyclization.[4] Alternatively, these 1,4-benzoxazine moieties were made by epoxide opening with *o*-halosulfonamides followed by cyclization[5] or epoxide

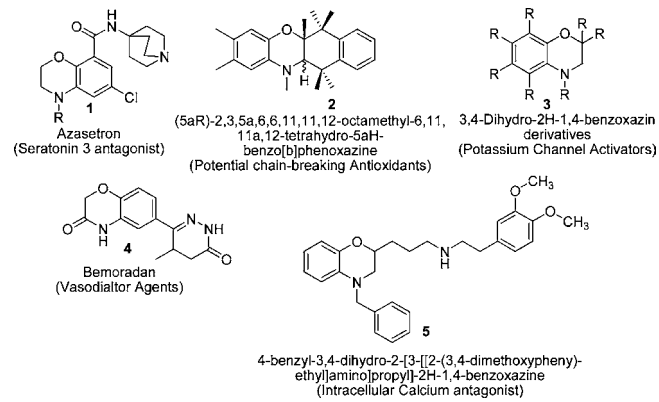


Figure 1. Structures of biologically important compounds containing a 1,4-benzoxazine skeleton.[1]

† Dedicated to Prof. Brian M. Stoltz.

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(2) Kuroita, T.; Sakamori, M.; Kawakita, T. *Chem. Pharm. Bull.* **1996**, *44*, 756.

(3) Butler, R.; Chapleo, C. B.; Myers, P. L.; Welbourn, A. P. *J. Heterocycl. Chem.* **1985**, 177.

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opening with aminophenols followed by cyclocondensation.[6] Adding strength to this field, we have developed a simple, efficient, and alternative method to the conventional multistep process to prepare a 1,4-benzoxazine skeleton in a single process from readily available starting materials.

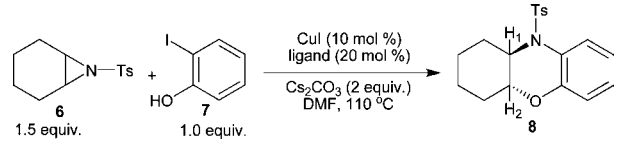
In the past few years, the formation of aryl C−X bonds (X = N, O, S, etc.) via copper-catalyzed Ullmann-type coupling between aryl halides and heteroatom-centered nucleophiles has drawn considerable attention.[7] More recently, the Ullmann coupling was successfully extended to the preparation of many heterocycles via copper-mediated cyclization.[8]

As part of our ongoing research toward copper-catalyzed oxidation chemistry,[9] very recently we reported 1,1′-binaphthyl-2,2′-diamine (BINAM)-Cu as an efficient catalyst for the synthesis of diaryl ethers and aryl alkyl ethers through Ullmann coupling.[10] Herein, for the first time, we report a single process synthesis of the 1,4-benzoxazine skeleton from readily available aziridines and *o*-iodophenols using domino[11] aziridine ring opening[12] followed by intramolecular copper-catalyzed Goldberg-type amidation of aryl iodides.[13] The reaction is very effective, high yielding, and low catalyst loading with the cheapest ligand ethylene diamine.

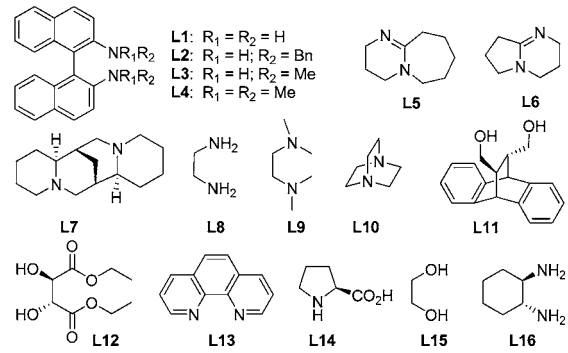
In the initial studies, synthesis of a 1,4-benzoxazine moiety *trans*-**8** was carried out from cyclohexene *N*-tosylaziridine **6** with *o*-iodophenol **7** and Cs_2CO_3 by domino ring opening and Goldberg coupling cyclization in the presence of 10 mol % of CuI and 20 mol % of BINAM **L1** in DMF at 110 °C; the reaction provided 84% of pure **8**.

The *trans* stereochemistry of the product was deduced from the coupling of the methine proton-H[2] (ddd, J = 11.0, 10.5, and 3.2 Hz, 1H) at 3.42 ppm (−C<u>H</u>−O−) in the ^{1}H NMR spectrum. Then we screened the reaction with several oxygen- and nitrogen-based ligands to increase the efficiency of the reaction and to reduce the catalytic load, and the results are summarized in Table 1. Although 1,10-phenanthroline, L-proline, and *trans*-1,2-cyclohexyldiamine provided the product **8** in 92−93% yield, simple ethylene diamine **L8** provided a maximum of 96% of the product in 12 h (entry 8). When the catalytic loading was reduced to 10 mol % or 5 mol % (1:1 catalyst), the yield of the product was reduced to 89% and 79%, respectively. However, usage of 5 mol % of CuI and 10 mol % of **L8** also provided 96% of the product with more or less reaction time (entry 19).

Table 1. Ligand Screening for Domino Aziridine Ring Opening and Goldberg Coupling Cyclization for the Synthesis of **8**



entry	ligand	time (h)	yield (%)[a]
1	**L1**	14	84
2	**L2**	13	66
3	**L3**	14	62
4	**L4**	15	85
5	**L5**	14	63
6	**L6**	13	83
7	**L7**	18	23
8	**L8**	12	96
9	**L9**	16	76
10	**L10**	24	65
11	**L11**	24	55
12	**L12**	18	73
13	**L13**	12	93
14	**L14**	10	93
15	**L15**	15	61
16	**L16**	10	92
17	**L8**	16	89[b]
18	**L8**	18	79[c]
19	**L8**	13	96[d]



[a] Isolated yields. [b] 10 mol % of CuI and 10 mol % of ligand were used. [c] 5 mol % of CuI and 5 mol % of **L8** were used. [d] 5 mol % of CuI and 10 mol % of **L8** were used.

Then the reaction was screened with several copper salts, solvents, and bases to increase the efficiency of the domino reactions, and the results are summarized in Table 2. Although several copper salts catalyzed the reaction, CuI turned out to be the best copper salt of choice in view of yield (entry 1). Similarly, DMF was the best solvent among those examined. K_2CO_3 as base provided comparable results in comparasion with Cs_2CO_3, whereas K_2CO_3 is a cheaper and mild base (entry 14). Then reduction of catalytic loading of the catalyst **L8**−CuI complex from 5 mol % of CuI and

(6) Brown, D. W.; Ninan, A.; Sainsbury, M. *Synthesis* **1997**, 895.

(7) For reviews, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973.

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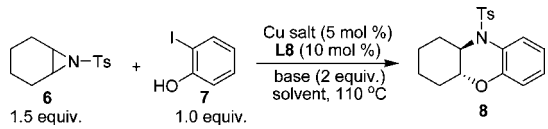
(10) (a) Naidu, A. B.; Raghunath, O. R.; Prasad, D. J. C.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 1057. (b) Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 3147.

(11) A domino reaction is a consecutive series of organic reactions which often proceed via highly reactive intermediates. It allows the organic synthesis of complex multinuclear molecules from a single precursor. The substrate contains many functional groups that take part in chemical transformations one at a time. Often a functional group is generated in situ from the previous chemical transformation. For a recent review, see: Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH, Verlag GmbH & Co: Weinheim, 2006.

(12) (a) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullie, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463. (b) Li, P.; Forbeck, E. M.; Evans, C. D.; Joullie, M. M. *Org. Lett.* **2006**, *8*, 5105.

(13) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.

Table 2. Optimization of Reaction Conditions for the Domino Reaction



entry	Cu salt	solvent	base	time (h)	yield (%)[a]
1	CuI	DMF	Cs_2CO_3	13	96
2	CuBr	DMF	Cs_2CO_3	14	89
3	CuCl	DMF	Cs_2CO_3	14	82
4	$Cu(OTf)_2$	DMF	Cs_2CO_3	12	89
5	$Cu(OAc)_2{\cdot}H_2O$	DMF	Cs_2CO_3	14	91
6	$CuCl_2$	DMF	Cs_2CO_3	12	93
7	CuI	CH_3CN	Cs_2CO_3	36	28
8	CuI	THF	Cs_2CO_3	36	17
9	CuI	DMSO	Cs_2CO_3	12	65
10	CuI	Dioxane	Cs_2CO_3	12	40
11	CuI	Toluene	Cs_2CO_3	24	33
12	CuI	DMF	Cs_2CO_3	12	92
13	CuI	DMF	Na_2CO_3	12	92
14	CuI	DMF	K_2CO_3	12	95
15	CuI	DMF	K_3PO_4	12	87
16	CuI	DMF	K_2CO_3	15	94[b]
17	CuI	DMF	K_2CO_3	15	99[b,c]
18	CuI	DMF	K_2CO_3	24	38[c,d]
19	–	DMF	K_2CO_3	24	00[c,e]

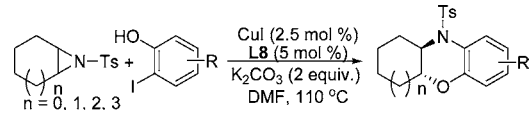
[a] Isolated yield. [b] 2.5 mol % of CuI and 5 mol % of **L8** were used. [c] 1.0 equiv of aziridine was used. [d] 2.5 mol % of CuI and without ligand **L8**. [e] Without CuI and without ligand **L8**.

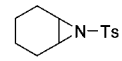
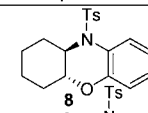
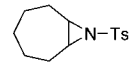
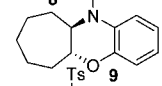
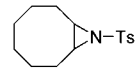
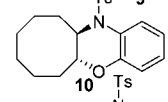
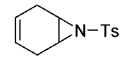
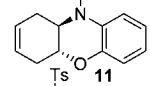
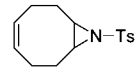
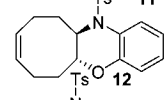
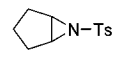
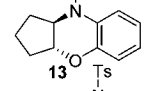
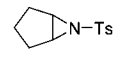
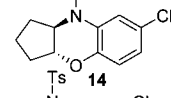
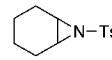
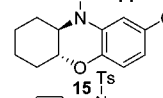
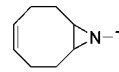
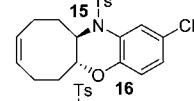
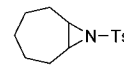
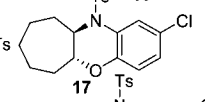
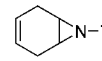
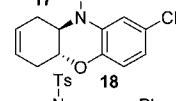
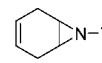
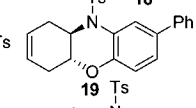
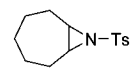
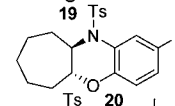
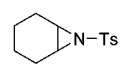
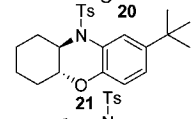
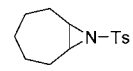
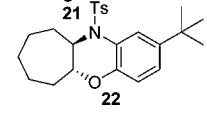
10 mol % of **L8** to 2.5 mol % of CuI and 5 mol % of **L8** reduced the yield slightly (entry 16). Surprisingly, reducing the excess quantity of aziridine from 1.5 equiv to 1 equiv provided a quantitative amount of the product (entry 17). The domino reaction without the **L8**−CuI complex did not give trace amounts of cyclized product **8** (entry 19).

Using the above-mentioned optimized conditions, we initiated our investigation into the scope of the **L8**−CuI complex catalyzed domino aziridine ring opening and Goldberg coupling cyclization for the synthesis of the 1,4-benzoxazine moiety from several aziridines and substituted *o*-iodophenols, and the results are summarized in Table 3. Both saturated and unsaturated aziridines reacted with substituted *o*-iodophenols to give the corresponding 1,4-benzoxazine moiety in excellent yields.

In the case of aziridine, when the aziridine is fused with a six-membered ring, both the electron-withdrawing groups such as the chloro group and the electron-releasing group such as the *tert*-butyl group on *o*-iodophenol slightly decrease the yield for the domino reaction. If the six-membered ring of the aziridine is replaced by a seven- and eight-membered ring, the yield is reduced gradually and provides 80% and 48% (entry 1 vs 2 vs 3). Surprisingly, when the unsaturation was introduced in the eight-membered ring, the isolated yield for the domino reaction increased to 91% (entries 3 vs 5). In general, this methodology works efficiently with a wide range of aziridines and *o*-iodophenols to give the benzoxazine moieties. The *trans*

Table 3. Scope of Domino Ring Opening and Goldberg Coupling Cyclization for the Synthesis of the 1,4-Benzoxazine Moiety



entry	aziridine	product	time (h)	yield (%)[a]
1		 **8**	15	99
2		 **9**	13	80
3		 **10**	26	48
4		 **11**	10	93
5		 **12**	12	91
6		 **13**	20	78
7		 **14**	12	89
8		 **15**	14	94
9		 **16**	13	98
10		 **17**	15	92
11		 **18**	14	88
12		 **19**	16	94
13		 **20**	16	92
14		 **21**	16	85
15		 **22**	16	89

[a] Isolated yield.

stereochemistry of the products was determined by ^{1}H NMR and X-ray crystal structures (Figure 2).

The possible mechanism for the formation of the 1,4-benzoxazine moiety by domino aziridine ring opening and

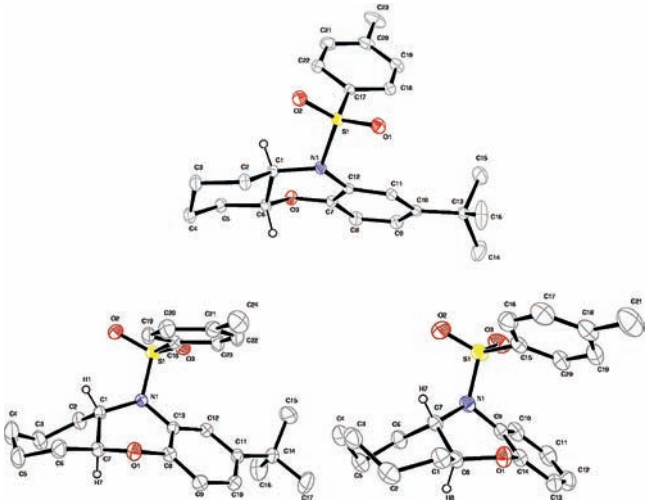
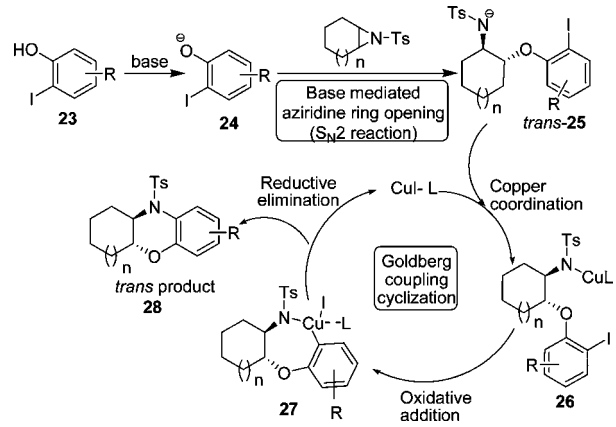


Figure 2. ORTEP drawing of compounds **21**, **22**, and **12**, respectively (CCDC 715059, CCDC 715060, and CCDC 715061). 30% Probability.

Scheme 1. Possible Mechanism for the Formation of the *trans*-1,4-Benzoxazine Moiety by Domino Ring Opening−Goldberg Coupling Cyclization



Goldberg coupling cyclization is shown in Scheme 1. First, the phenol **23** is deprotonated by base to give phenoxide ion **24**. Then **24** opens the aziridine ring through S_N2 reaction to give *trans*-**25**. The coordination of nitrogen with the CuI complex followed by oxidative addition gives compound **27**. Then the reductive elimination releases the product 1,4-benzoxazine moiety *trans*-**28** and regeneration of copper catalyst which involves the catalytic cycle of Goldberg coupling cyclization (Scheme 1).

In conclusion, for the first time we have developed a novel, economical, and practical protocol for the synthesis of the *trans*-1,4-benzoxazine moiety by domino ring opening followed by a Goldberg coupling cyclization using the easily available ethylenediamine−CuI complex as catalyst and K_2CO_3 as base. A variety of *trans*-1,4-benzoxazine moieties were synthesized from corresponding aziridines and *o*-iodophenols in good to excellent isolated yields under relatively mild conditions. Synthesis of other biologically important heterocycles by a copper-catalyzed domino reaction are underway.

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Supporting Information Available: Experimental procedures and characterization data including X-ray diffraction analysis data of compounds **21**, **22**, and **12** and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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