ORGANIC LETTERS

2012
Vol. 14, No. 13
3522–3525

Copper-Catalyzed Selective Benzylic C−O Cyclization of *N*-*o*-Tolylbenzamides: Synthesis of 4*H*-3,1-Benzoxazines

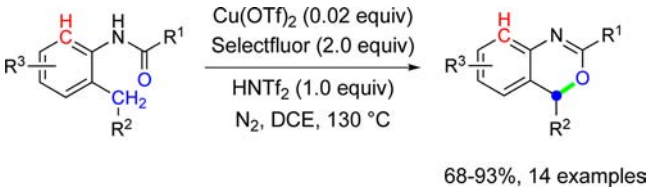
Yan Li,[†,‡] Zhongshu Li,[‡] Tao Xiong,[†] Qian Zhang,[*,†] and Xiangyang Zhang[*,‡]

Department of Chemistry, Northeast Normal University, 130024 Changchun, China, and Laboratory of Organic Chemistry, ETH Zurich, 8093 Zurich, Switzerland

xiangyang.zhang@org.chem.ethz.ch; zhangq651@nenu.edu.cn

Received May 31, 2012

ABSTRACT



A novel Selectfluor-mediated copper-catalyzed highly selective benzylic C−O cyclization for the synthesis 4*H*-3,1-benzoxazines is reported. The predominant selectivity for a benzylic C(sp^3)−H over an aromatic C(sp^2)−H bond in *N*-*o*-tolylbenzamides is achieved.

Selective direct C−H bond functionalization is emerging as a valuable tool in organic synthesis.[1] A particularly appealing aspect of this chemistry is the potential to introduce a new functional group at precise locations, especially in multisite reactive substrates (for example, arenes with multiple aromatic C−H and benzylic C−H bonds). Current paradigms have greatly been achieved in the transition metal catalyzed selective activation of aromatic C−H bonds *ortho*, *meta*, or *para* to the directing group,[2] whereas the proximal benzylic methyl C−H bonds remain inert. Therefore, it is a great challenge to develop transition metal catalyst systems which selectively activate benzylic C−H bonds over the normally "favored" aromatic C−H bonds in the ligand directed C−H functionalization of arenes. Copper catalysts are particularly attractive in transition metal catalyzed direct C−H functionalization reactions because of their low cost and low toxicity.[2b,3−5]

Since Yu et al. first reported copper-catalyzed pyridyl group directed aromatic C−H bond functionalizations,[4] several related reactions have been well explored.[2b,5] And, copper-catalyzed dehydrogenative functionalizations of benzylic C−H bonds with various nucleophiles have also been

[†] Northeast Normal University.
[‡] ETH Zurich.

(1) For selected reviews, see: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70.

(2) For a review on the activation of an aromatic C−H bond *ortho* to the directing group, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. For activation of an aromatic C−H bond *meta* to the directing group, see: (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (c) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. For activation of an aromatic C−H bond *para* to the directing group, see: (d) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694.

(3) For a review on copper-catalyzed aromatic C−H bond functionalizations, see: (a) Zhang, M. *Appl. Organomet. Chem.* **2010**, *24*, 269. For selected examples of copper-catalyzed C−H activation, see: (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (e) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (f) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824. (g) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (h) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (i) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102. (j) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (k) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (l) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (m) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511.

(4) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

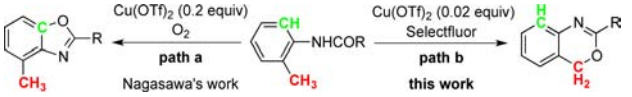
(5) (a) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. *J. Angew. Chem., Int. Ed.* **2011**, *50*, 463. (c) Brashe, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (d) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (e) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272. (f) Xiong, T.; Li, Y.; Bi, X.; Lv, Y; Zhang, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 7140. (g) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415. (h) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078.

10.1021/ol301492d
Published on Web 06/22/2012

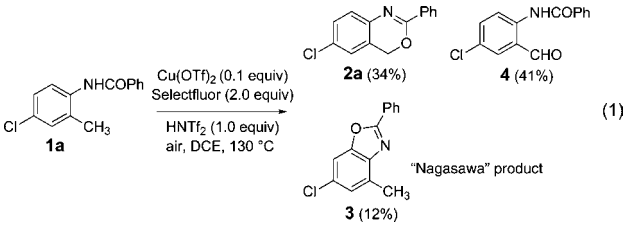
developed in recent years.[6,7] However, to our knowledge, copper-catalyzed directing group assisted C(sp^3)−H bond functionalization is rare, with the only relevant example using imine derivatives to direct benzylic oxidation being reported by Chiba et al.[7]

Recently, Nagasawa et al. reported a copper-catalyzed intramolecular C−O cyclization reaction of benzanilides (Scheme 1, path a).[5d,e] In our previous communication, a copper-catalyzed intermolecular C−H dehydrogenative cross-coupling reaction followed by an intramolecular C−O cyclization reaction was described.[5f] In both of the above reactions, aromatic C−H bonds were efficiently activated, but the benzylic methyl groups *ortho* to the amide group stayed intact. By employing palladium catalysts, Fagnou et al. achieved a selective arylation of the corresponding aromatic C−H and benzylic C−H bonds in azine and diazine *N*-oxide substrates via different activation approaches.[8] Taking the possible copper-mediated single electron trcansfer (SET) mechanism for C−H functionalizaton[9] into account, we postulated that benzylic C−H rather than aromatic C−H bonds could be selectively functionalized when an appropriate copper catalytic system is applied. Herein, we report a straightforward and versatile method to obtain 4*H*-3,1-benzoxazines[10] by copper-catalyzed intramolecular highly selective benzylic C−O bond formation from readily available *ortho*-methyl benzanilides (Scheme 1, path b).

Scheme 1. Copper-Catalyzed Benzylic C−O Cyclization



Initially, *N*-(4-chloro-2-methylphenyl)benzamide (**1a**) was used as a substrate to explore this intramolecular cyclization reaction. The purpose for chloro occupation of the position *para* to the directing group is to avoid any complication due to competitive C−H bonds. In a typical procedure, a mixture of **1a** (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol, 0.1 equiv), Selectfluor (0.8 mmol, 2.0 equiv), and $HNTf_2$ (0.4 mmol, 1.0 equiv) was added to 1,2-dichloroethane (DCE) and heated in a sealed tube under an air atmosphere (eq 1).



When the reaction was performed at 130 °C for 4 h, the desired benzylic C−O cyclization benzoxazine **2a** was obtained in 34% yield, along with benzoxazole **3** (12%) and aldehyde **4** (41%). The "Nagasawa" product **3** and oxidation product **4** clearly showed the influence of oxygen and led us to optimize the benzylic C−O cyclization reaction under a N_2 atmosphere. Expectantly, the reaction became very clean and benzoxazine **2a** was isolated in 71% yield. No aromatic C−H (*ortho* to the directing group) activation product was detected.

To further confirm the inertness of aromatic C−H bonds, the substrate **1b** was used instead. Benzoxazine **2b** was obtained in 81% yield without complication from other aromatic C−H activation products. Therefore, substrate **1b** was used as a model substrate for general optimization (Table 1, entry 1). It should be noted that this is one of the most direct and simplest routes to synthesize benzoxazines **2**.[11] No reaction was observed when the copper catalyst, oxidant, or additive was absent (Table 1, entries 2−4). When the oxidant or additive was reduced by half, the yields also dropped accordingly down to 36% or 41% (Table 1, entries 5 and 6). When other acids such as acetic acid and trifluoroacetic acid were used, only a trace amount of **2b** was detected (Table 1, entries 7 and 8). In the presence of trifluoromethanesulfonic acid, **2b** was obtained in 43% yield (Table 1, entry 9). With *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate or triflate as the oxidant, **2b** was obtained in 72% and 49% yield, respectively (Table 1, entries 10 and 11). However, a widely used oxidant *tert*-butyl hydroperoxide (TBHP) was not effective in the reaction (Table 1, entry 12). Next, we attempted to reduce the loading amount of the copper catalyst (Table 1, entries 13−15). Surprisingly, a decrease

(6) For a review on the general catalytic dehydrogenative cross-coupling−formation of C−C bonds by oxidizing two C−H bonds, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev* **2011**, *111*, 1215. For more specific work on copper-catalyzed dehydrogenative functionalization of a benzylic C−H bond, see: (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (d) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (e) Pelletier, G.; Powell, D. A. *Org. Lett.* **2006**, *8*, 6031. (f) Powell, D. A.; Fan, H. *J. Org. Chem.* **2010**, *75*, 2726. (g) Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008**, *73*, 7822. To our knowledge, there are two examples of platinum- and palladium-catalyzed carboxyl group directed intramolecular benzylic C−O cyclization; see: (h) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375. (i) Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 12236.

(7) To our knowledge, the only example of copper-catalyzed imine assisted benzylic C−H oxygenation can be found in: Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13*, 1622.

(8) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.

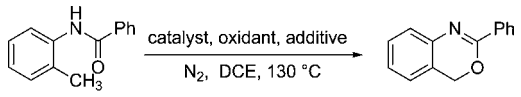
(9) For reviews on C−H oxidation initiated by a single-electron transfer process, see: (a) Part 2 of the review Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062 and references cited therein. (b) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464.

(10) The 4*H*-3,1-benzoxazine ring system displays important biological activities, see: (a) Dias, N.; Goosens, J. F.; Baldeyrou, B.; Lansiaux, A.; Colson, P.; Salvo, D.; Bernal, J.; Turnbull, A.; Mincher, D.; Bailly, C. *Bioconjugate Chem.* **2005**, *16*, 949. (b) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060. (c) Sugiyama, H.; Hosoda, K.; Kumagai,Y.; Takeuchi, M.; Okada, M. U.S. Patent 4.596.801, 1986.

(11) In most cases *ortho*-aminobenzyl alcohols or *ortho*-aminobenzyl halides or acylamino alcohols and also *ortho*-isocyanophenylethanones are used as starting materials for the synthesis of 4*H*-3,1-benzoxazines. These methods require prefunctionalization steps. For selected examples, see: (a) Kobayashi, K.; Okamura, Y.; Konishi, H. *Synthesis* **2009**, *9*, 1494. (b) Besson, T.; Guillaumet, G.; Lamazzi, C.; Rees, C. W. *Synlett* **1997**, 704. (c) Nishio, I.; Kurokawa, Y.; Narasaki, Y.; Tokunaga, K. *Heterocycles* **2006**, *67*, 247.

in the catalyst loading from 0.1 to 0.02 equiv had no influence on the yield of **2b** (Table 1, entries 1, 13, and 14). While decreasing catalyst loading to 0.005 equiv, no reaction was observed (Table 1, entry 15). Other copper salts such as $CuCl_2$, $Cu(OTf)\cdot C_6H_6$, and CuCl were less active and gave **2b** in 69%, 52%, and 61% yield, respectively (Table 1, entries 16–18).

Table 1. Copper-Catalyzed Benzylic C–O Cyclization Reaction of **1b**[a,b]



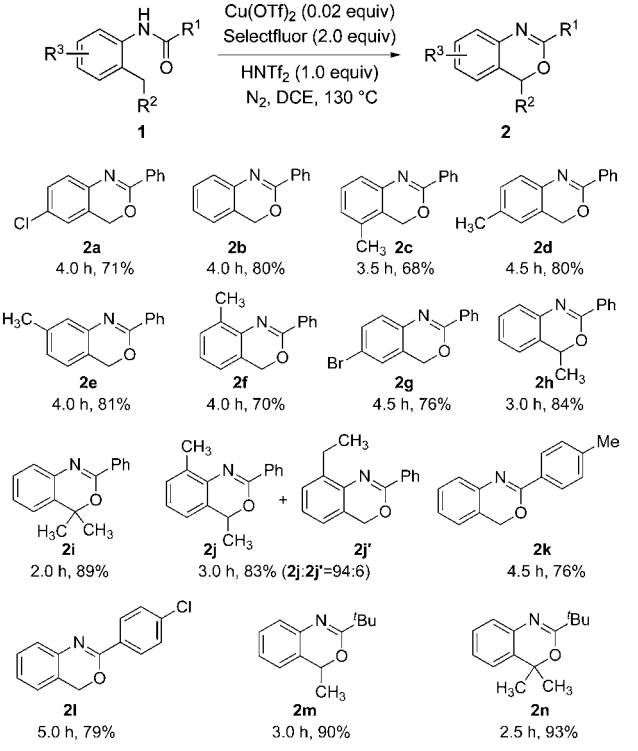
1b **2b**

entry	catalyst	oxidant	additive	**2b** (%)
1	$Cu(OTf)_2$	Selectfluor	$HNTf_2$	81
2	0	Selectfluor	$HNTf_2$	(100)[c]
3	$Cu(OTf)_2$	0	$HNTf_2$	(100)[c]
4	$Cu(OTf)_2$	Selectfluor	0	(100)[c]
5	$Cu(OTf)_2$	Selectfluor[d]	$HNTf_2$	36(40)[c]
6	$Cu(OTf)_2$	Selectfluor	$HNTf_2$[e]	41(38)[c]
7	$Cu(OTf)_2$	Selectfluor	HOAc	Trace
8	$Cu(OTf)_2$	Selectfluor	TFA	Trace
9	$Cu(OTf)_2$	Selectfluor	CF_3SO_3H	43(30)
10	$Cu(OTf)_2$	F[+f]	$HNTf_2$	72(10)[c]
11	$Cu(OTf)_2$	F[+g]	$HNTf_2$	49(30)[c]
12	$Cu(OTf)_2$	TBHP	$HNTf_2$	(100)[c]
13	$Cu(OTf)_2$[h]	Selectfluor	$HNTf_2$	80
14	**$Cu(OTf)_2$**[i]	**Selectfluor**	**$HNTf_2$**	**80**
15	$Cu(OTf)_2$[j]	Selectfluor	$HNTf_2$	(100)[c]
16	$CuCl_2$	Selectfluor	$HNTf_2$	69
17	$Cu(OTf)\cdot C_6H_6$	Selectfluor	$HNTf_2$	52(33)[c]
18	CuCl	Selectfluor	$HNTf_2$	61

[a] Reactions were carried out with **1b** (0.4 mmol), catalyst (0.1 equiv), oxidant (2.0 equiv), and additive (1.0 equiv) in 1,2-dichloroethane (DCE) (1.5 mL) under a nitrogen atmosphere at 130 °C for 4 h, unless otherwise noted. [b] Yield of the isolated product. [c] In the parentheses, recovery of the substrate **1b**. [d] 1.0 equiv of Selectfluor was used. [e] 0.5 equiv of $HNTf_2$ was used. [f] 2.0 equiv of 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate were used. [g] 2.0 equiv of 1-fluoro-2,4,6-trimethylpyridinium triflate were used. [h] 0.05 equiv of $Cu(OTf)_2$ was used. [i] 0.02 equiv of $Cu(OTf)_2$ was used. [j] 0.005 equiv of $Cu(OTf)_2$ was used.

Under the optimized reaction conditions (Table 1, entry 14), various 4*H*-3,1-benzoxazines were synthesized by using this new protocol. As described in Table 2, substrates with electron-donating or -withdrawing groups on the phenyl ring behaved similarly (Table 2, **2a**–**2g**). Reactions of substrates with the second methyl group on the phenyl ring (for example, **1c**, **1d**, and **1e**) provided the exclusively regioselective (only the C–H bond of *ortho*-methyl is activated) intramolecular C–O cyclization product **2c**, **2d**, and **2e**, respectively. Interestingly, no intermolecular C–H dehydrogenative cross-coupling/intramolecular C–O cyclization product was isolated from the substrate **1d**.[5f] Products containing the halogen atom (Table 2, **2a** and **2g**), which offer an opportunity for further cross-coupling, could be obtained in good yields. Replacing the methyl group *ortho* to the directing group by an ethyl or isopropyl group, we found that the reaction time was significantly reduced and the yield was accordingly increased (Table 2, **2b**, **2h**, and **2i**, from 80% to 84% and 89%), with the reactivity order of C(sp^3)–H bonds as follows: tertiary C–H > secondary C–H > primary C–H bond. When **1j** was used as the substrate, a mixture of **2j** and **2j′** with the ratio of **2j** to **2j′** (94:6) was obtained in 83% yield. These results further confirmed that the secondary C(sp^3)–H bond was much more reactive than the primary C(sp^3)–H bond. No obvious electronic effect on the phenyl ring of the directing group was observed (**2b**

Table 2. Copper-Catalyzed Benzylic C–O Cyclization of **1a**–**1n**[a,b]



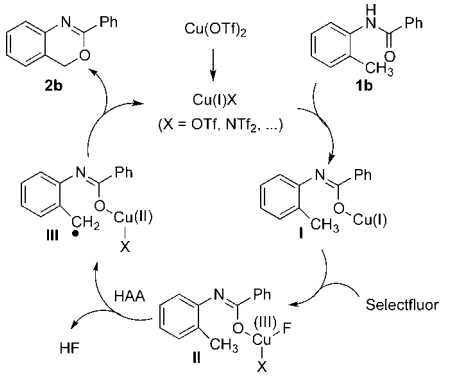
[a] Reactions were carried out with **1** (0.4 mmol), $Cu(OTf)_2$ (0.02 equiv), Selectfluor (2.0 equiv) and $HNTf_2$ (1.0 equiv) in 1,2-dichloroethane (DCE) 1.5 mL under a nitrogen atmosphere at 130 °C. unless specially mentioned. [b] Yield of the isolated product.

(12) (a) Xiong, T.; Li, Y.; Lv, Y.; Zhang, Q. *Chem. Commun.* **2010**, *46*, 6831. (b) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 1244.

(13) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264.

(14) The active Cu(I) species can be initially formed through either the reduction of Cu(II) by the nucleophile or the disproportionation of Cu(II). For reduction, see: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. For disproportionation, see: (c) Ribas, X.; Jackson, D. A; Donnadieu, B.; Mahía, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2991. (d) Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. Commun.* **2009**, 2899. (e) Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gómez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Solà, M.; Llobet, A.; Stack, T. D. P. *J. Am. Chem. Soc.* **2010**, *132*, 12299.

Scheme 2. Proposed Mechanism for the Formation of **2b**



80%, **2k** 76%, and **2l** 79%). **2m**−**n** were obtained in excellent yields (90% and 93%) when the directing group was replaced by the *tert*-butyl group, indicating the *tert*-butyl group is a better promotor.

Combined with our previous work,[5f,12] a radical-involved catalytic cycle was suggested for the transformation from *N*-*o*-tolylbenzamides to 4*H*-3,1-benzoxazines (Scheme 2). A radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT)[13] (2.0 equiv) was added to the reaction under the optimal condition (Table 1, entry 14). As a result, no reaction was observed. This radical-involved mechanism was also confirmed by the fact that the reaction was much slower under an air atmosphere. The diradical-like dioxygen molecule plays a role as a radical scavenger to some extent. The suggested initial step was the formation of the Cu(I) intermediate **I**.[14] Then, the Selectfluor-mediated oxidative addition[15] of Cu(I) provided a Cu(III) species **II**[2b,i,16] in the presence of $HNTf_2$ or CF_3SO_3H. Next, a hydrogen atom abstraction (HAA) of a benzylic methyl group by the Cu(III) center formed a benzyl radical **III** with a Cu(II) center.[12b] Finally, an intramolecular oxidative coupling of intermediate **III** gave the benzeoxazine **2b**, leaving Cu(I) for the next catalytic cycle.

In conclusion, we have developed a copper-catalyzed intramolecular benzylic C−O cyclization of *N*-*o*-tolylbenzamide using Selectfluor as an oxidant for the efficient synthesis of 4*H*-3,1-benzoxazines. The exclusive selectivity for benzylic C−H over aromatic C−H bonds is realized. The detailed mechanistic studies and the application of this methodology for selectively benzylic C−H functionalization are ongoing in our laboratory.

Acknowledgment. Financial support from the ETH Zürich and Swiss National Foundation is gratefully acknowledged. The authors are also thankful for additional financial support by the NCET (08-0756), NNSFC (21172033), and Fundamental Research Funds for the Central Universities (09ZDQD07) from China.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The bystanding oxidant F^+ could effectively oxidize metal but not get involved in the reductive elimination due to the metal−F bond strength. For a review on F^+ oxidant mediated formation of high-valent metal species, see: Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478 and references cited therein.

(16) For discussions of mechanisms involving Cu(III) intermediates, see the following selected examples: (a) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (d) Matsumoto, T.; Ohkubo, K.; Honda, K.; Yazawa, A.; Furutachi, H.; Fujinami, S.; Fukuzumi, S.; Suzuki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9258. In our previous work, the Cu(III) intermediate was detected via the ESI-MS analysis; see ref 5f.

The authors declare no competing financial interest.