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Copper-Catalyzed Annulative Amination of *ortho*-Alkynylphenols with Hydroxylamines: Synthesis of 3-Aminobenzofurans by Umpolung Amination Strategy

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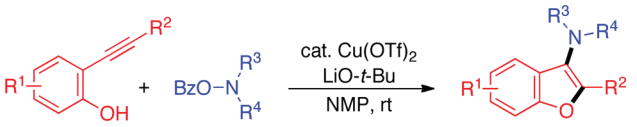
ABSTRACT

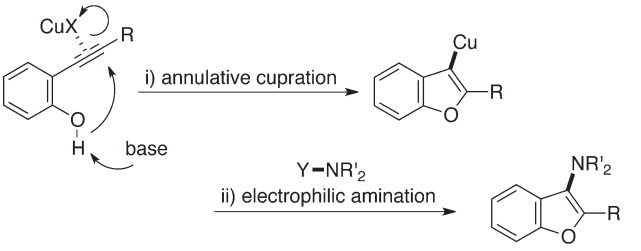


A room temperature copper-catalyzed annulative amination of *ortho*-alkynylphenols with electrophilic amination reagents, *O*-acylated hydroxylamines, proceeds efficiently to provide the corresponding 3-aminobenzofurans of biological and pharmaceutical interest.

Aminobenzofuran and its derivatives may constitute an important class of heteroarylamines, which are of current interest in biological and pharmaceutical sciences.[1] Recent advances in the palladium-catalyzed cross-coupling reaction of aryl halides and amines, that is the Buchwald–Hartwig amination,[2] provide a powerful synthetic tool for the construction of this type of compound.

Meanwhile, we have recently introduced chloroamines as new, effective electrophilic amination reagents for heteroaromatic C–H bonds and succeeded in the copper-catalyzed rapid and concise synthesis of the corresponding heteroarylamines even at room temperature.[3,4] In this context, we may envisage that the electrophilic, umpolung amination strategy could be applicable to the efficient synthesis of 3-aminobenzofuran derivatives. Thus, our blueprint consists of (i) initial annulative cupration of *ortho*-alkynylphenols[5] and (ii) an electrophilic C–N bond forming reaction (Scheme 1). If the process were feasible, it would enable an orthogonal and complementary access to aminobenzofuran structures. Indeed, we have found that the process can be realized by employing *O*-acylated hydroxylamines as the amination reagents, while chloroamines are ineffective.

Scheme 1



(1) (a) Hili, R; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (b) *Amino Group Chemistry, From Synthesis to the Life Sciences*; Ricci, A., Eds.; Wiley-VCH: Weinheim, 2007.

(2) Reviews: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(3) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900.

(4) N–Cl or N–O bond as a useful handle for C–N bond formation: (a) Erdick, E.; Ay, M. *Synth. React. Inorg. Met.-Org. Chem.* **1989**, *19*, 663. (b) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, *26*, 317. (c) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (d) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (e) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (f) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521. (g) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (h) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (i) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (j) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (k) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (l) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (m) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.

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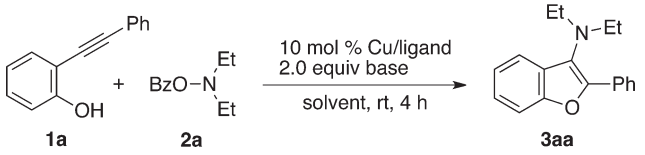
Table 1. Optimization Studies for Annulative Coupling of 2-(Phenylethynyl)phenol (**1a**) with *O*-Benzoyl-*N,N*-diethylhydroxylamine (**2a**)[a]

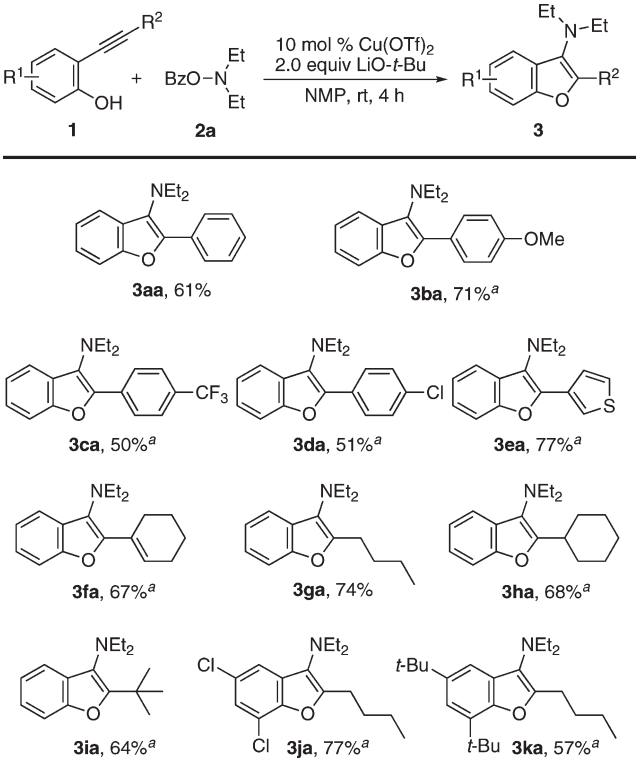


entry	Cu/ligand	base	solvent	**3aa**, yield (%)[b]
1	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	DMSO	14
2	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	DMF	18
3	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	NMP	39
4	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	toluene	0
5	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	THF	0
6	$Cu(acac)_2$/phen	LiO-*t*-Bu	NMP	20
7	$Cu(acac)_2$/bpy	LiO-*t*-Bu	NMP	38
8	$Cu(acac)_2/2PPh_3$	LiO-*t*-Bu	NMP	20
9	$Cu(acac)_2$/dppe	LiO-*t*-Bu	NMP	0
10	$Cu(acac)_2$	LiO-*t*-Bu	NMP	47
11	$CuCl_2$	LiO-*t*-Bu	NMP	9
12	CuCN	LiO-*t*-Bu	NMP	11
13	$Cu(OAc)_2$	LiO-*t*-Bu	NMP	63
14	$Cu(OTf)_2$	LiO-*t*-Bu	NMP	92 (61)[c]
15	$Cu(OTf)_2$	NaO-*t*-Bu	NMP	11
16	$Cu(OTf)_2$	KO-*t*-Bu	NMP	trace
17	$Cu(OTf)_2$	Cs_2CO_3	NMP	0
18	none	LiO-*t*-Bu	NMP	0

[a] A mixture of Cu salt (0.050 mmol), base (1.0 mmol), **1a** (0.50 mmol), and **2a** (0.60 mmol) in solvent (3.0 mL) was stirred at room temperature for 4 h under N_2. [b] Yield determined by GC. Yield of isolated product in parentheses. [c] The lower isolated yield is due to the partial decomposition of **3aa** during chromatographic purification, while the compound is stable after isolation. See Supporting Information for details.

We initially selected 2-(phenylethynyl)phenol (**1a**) and *O*-benzoyl-*N,N*-diethylhydroxylamine (**2a**) as model substrates. In an early examination, treatment of **1a** with **2a** in the presence of $Cu(acac)_2$/dtbpy (dtbpy = 4,4′-di(*tert*-butyl)-2,2′-bipyridine) and LiO-*t*-Bu as catalyst and base, respectively, in DMSO provided 3-(*N,N*-diethylamino)benzofuran (**3aa**) in 14% yield (GC) (Table 1, entry 1).[6] The choice of solvent was critical: aprotic polar solvents were effective, with NMP proving to be optimal, while the formation of **3aa** was not detected in less polar toluene or THF (entries 1−5). Although other nitrogen- and phosphorus-based ligands were investigated, $Cu(acac)_2$ itself afforded a better yield (entries 6−10). Among the various copper salts tested, the best result was obtained with $Cu(OTf)_2$ (entries 10−14). Alternative bases including NaO-*t*-Bu, KO-*t*-Bu, and Cs_2CO_3 were detrimental (entries 15−17). Without any copper catalyst, the reaction did not occur (entry 18). Thus, the reaction proceeded very smoothly in the presence of $Cu(OTf)_2$ and LiO-*t*-Bu in NMP even at room temperature and completed within 4 h (entry 14), the conditions being remarkably milder than those for the precedent similar types of reaction of **1a**.[5]

Scheme 2. Copper-Catalyzed Annulative Coupling of *ortho*-Alkynylphenols **1** with *O*-Benzoyl-*N,N*-diethylhydroxylamine (**2a**)



[a] With 1.0 mmol of **2a**.

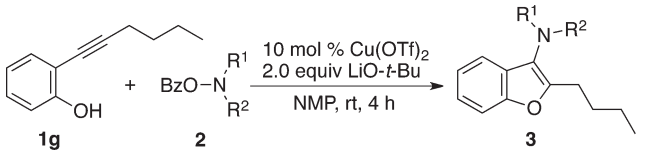
With the optimized conditions in hand, the oxyamination of a variety of *ortho*-alkynylphenols **1** was carried out (Scheme 2). The substrate with an electron-donating methoxy group showed comparable reactivity (**3ba**), while electron-withdrawing trifluoromethyl and chloro substituents resulted in a somewhat lower efficiency (**3ca**−**da**). In addition to the benzene ring, the heteroaryl function, thiophene was tolerant toward the reaction (**3ea**). Moreover, the conjugated enyne system **1f** (R^1 = H, R^2 = 1-cyclohexenyl) could be converted to **3fa** with the olefin moiety left intact. It is noteworthy that the copper catalysis accommodated alkyl substitutions at the alkyne terminus: primary, secondary, and tertiary alkyl-substituted *ortho*-alkynylphenols reacted with **2a** without any difficulties (**3ga**−**ia**). The 4,6-disubstituted pattern on phenol was also available for use (**3ja**−**ka**), and especially, **3ja** could enjoy further manipulation of the remaining C−Cl functions.

We then performed the reaction of **1g** with an array of *O*-benzoylhydroxylamines **2** (Table 2). Acyclic allyl- and benzylamines **2b** and **2c** formed the corresponding

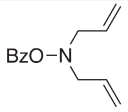
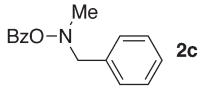
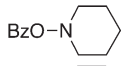
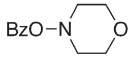
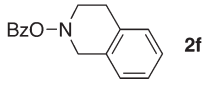
(5) Metal-mediated sequential C−O/C−C bond-forming reactions with *ortho*-alkynylphenols: (a) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **2004**, *69*, 2235. (b) Hu, Y.; Nawoschilk, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235. (c) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (d) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803. (e) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074. (f) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902. (g) Martínez, C.; Álverez, R.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083. (h) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329. (i) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (j) Álverez, R.; Martínez, C.; Madich, Y.; Denis, J. G.; Aurrecoechea, J. M.; de Lera, Á. R. *Chem.—Eur. J.* **2010**, *16*, 12746.

(6) The detectable byproduct was simply cyclized product, 2-phenylbenzofuran.

Table 2. Copper-Catalyzed Annulative Coupling of *ortho*-Alkynylphenol **1g** with *O*-Benzoylhydroxylamines **2**[a]



1g **2** **3**

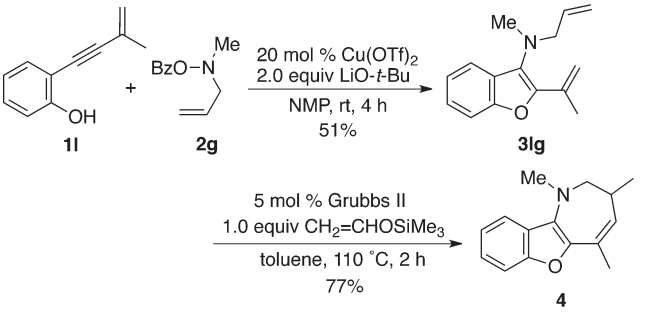
entry	2	3, yield (%)[b]
1	 **2b**	**3gb**, 76
2	 **2c**	**3gc**, 37
3	 **2d**	**3gd**, 79
4	 **2e**	**3ge**, 41
5	 **2f**	**3gf**, 48

[a] A mixture of $Cu(OTf)_2$ (0.050 mmol), LiO-*t*-Bu (1.0 mmol), **1g** (0.50 mmol), and **2** (1.0 mmol) in NMP (3.0 mL) was stirred at room temperature for 4 h under N_2. [b] Yield of isolated product.

3-aminobenzofurans **3gb** and **3gc**, respectively, the additional derivatization of which could be easily operative after the appropriate deprotection (entries 1 and 2).[7] Cyclic systems were also compatible toward the reaction (entries 3−5). Thus, piperidine-, morpholine-, and tetrahydroisoquinoline-substituted benzofurans **3gd**−**gf** were obtained with substantial yields.

To demonstrate the synthetic utility of the present process, a two-step synthesis of the benzofuro[3,2-*b*]azepine core, which is found in potent inhibitors of bone resorption,[8] was carried out (Scheme 3). When *ortho*-(3-methyl-3-buten-1-yn-1-yl)phenol (**1l**) was subjected to our oxyamination with *N*-allyl-*O*-benzoyl-*N*-methylhydroxylamine (**2g**), the

Scheme 3



1l **2g** **3lg** **4**

corresponding 3-aminobenzofuran **3lg** was produced, leaving the two terminal olefin moieties untouched. Subsequent ruthenium-catalyzed cycloisomerization[9] afforded the desired tricyclic framework **4** in 77% yield.

Although the exact mechanism remains unclear at this stage, some observations are to be noted: the control experiment of 2-(4-methoxyphenyl)benzofuran with **2a** under identical conditions resulted in no formation of **3ba** (vs Scheme 2); $Cu(OTf)_2$ of a more π-acidic nature worked much better than $CuCl_2$, $Cu(acac)_2$, and CuCN (Table 1); Lewis basic ligands (to the copper center) such as diamines and phosphines gave negative effects on yield (Table 1). These phenomena support that the reaction would be triggered by the nucleophilic oxymetalation of alkyne activated through the π-coordination to Cu(II),[10] which is consistent with our initial working hypothesis. Further efforts on elucidation of the detailed mechanism involving the C−N bond-forming step[11] are ongoing.[12]

In conclusion, we have developed an effective copper-catalyzed annulative amination of *ortho*-alkynylphenols with *O*-acylated hydroxylamines. The reaction system may compensate for the precedents[13] and provide a new, facile route to the 3-aminobenzofuran skeletons of biological and pharmaceutical interest. Further efforts seek to apply the methodology to alkene analogues and the synthesis of other heteroarylamines.

Acknowledgment. This work was partly supported by Grants-in-Aid from MEXT and JSPS, Japan.

Supporting Information Available. Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(7) Selected examples: (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett*. **1998**, *39*, 1313. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Chem. Commun*. **2005**, 4086. (c) Wang, J.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem*. **2007**, *72*, 2040.

(8) (a) Kawai, Y.; Yamazaki, H.; Kayakiri, N.; Yoshihara, K.; Yatabe, T.; Oku, T. PCT Int. Appl. 1995, WO 9529907, A1 19951109 (CAN 124:202000). Also see: (b) Cho, H.; Wakitani, Y. Jpn. Kokai Tokkyo Koho 1997, JP 09020779, A 19970121 (CAN 126:186116). (c) Cho, H.; Wakitani, Y. PCT Int. Appl. 1997, WO 9717349, A1 19970515 (CAN 127:5023). (d) Kondo, K.; Yamashita, H.; Kitano, K.; Shinohara, Y.; Kan, K.; Ogawa, H.; Mori, T. Jpn. Kokai Tokkyo Koho 1999, JP 11001456, A 19990106 (CAN 130:139333).

(9) Cycloisomerization of *N*-allyl-2-vinylanilines catalyzed by ruthenium hydrides generated in situ from Grubbs' catalysts and vinyl ethers: (a) Terada, Y.; Arisawa, M.; Nishida, A. *Angew. Chem., Int. Ed*. **2004**, *43*, 4063. (b) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem*. **2006**, *71*, 4255. However, this isomerization mode was unprecedented, to the best of our knowledge. This unique reactivity is probably due to the benzofuran system and methyl substitution at the olefinic moiety.

(10) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev*. **2008**, *108*, 3395. (b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem*. **2004**, *69*, 1126.

(11) Mechanistic studies with organozinc reagents: ref 4f.

(12) At this stage, an alternative pathway involving a radical species could not be completely excluded; see: Noack, M.; Göttlich, R. *Chem. Commun*. **2002**, 536.

(13) Alternative accesses: (a) Sakai, N.; Uchida, N.; Konakahara, T. *Tetrahedron Lett*. **2008**, *49*, 3437. (b) Li, H.; Liu, J.; Li, Y. *Tetrahedron Lett*. **2009**, *50*, 2353. (c) Ramazani, A.; Mahyari, A. T.; Rouhani, M.; Rezaei, A. *Tetrahedron Lett*. **2009**, *50*, 5625.