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An Annulative Electrophilic Amination Approach to 3-Aminobenzoheteroles

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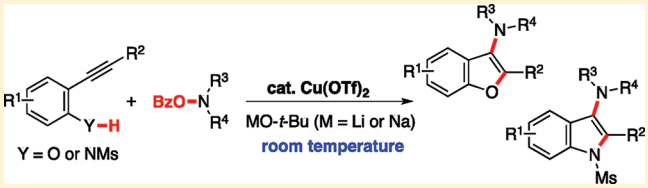
Supporting Information

ABSTRACT: A copper-catalyzed annulative amination approach to 3-aminobenzofurans and -indoles from *o*-alkynylphenols and -anilines has been developed. The Cu-based catalysis is based on an umpolung, electrophilic amination with *O*-benzoyl hydroxylamines and enables the mild and convergent synthesis of various 3-aminobenzoheteroles of biological and pharmaceutical interest. Some mechanistic investigations and an application of this protocol to construction of more complex tricyclic framework are also described.



INTRODUCTION

Heteroarylamines constitute an important class of compounds in organic chemistry as a result of their ubiquity in pharmaceuticals and biologically active compounds. In particular, 3-aminobenzofurans and -indoles have received significant attention as a promising structural candidate for the drug design directed toward a variety of diseases.[1] Such compounds are traditionally prepared by sequential nitration of the parent benzofuran or indole/reduction into amine/alkylation with appropriate electrophiles (Scheme 1, route a).[2] However, the nitration often suffers from harsh conditions and difficulties in controlling the reactivity and regioselectivity. The palladium-catalyzed cross-coupling reaction of the corresponding halides and amines, also known as Buchwald–Hartwig amination, has recently been developed and has largely displaced the above conventional strategy (route b).[3] Despite the advance, high utilities of these amines necessitate further developments of more efficient and versatile synthetic methodologies for their preparation. In this context, we envisioned an annulative amination of *o*-alkynylphenols and -anilines with an electrophilic aminating reagent as the third approach (route c). Our working scenario is illustrated in Scheme 2. An initial activation of the alkyne moiety through coordination to a soft, π-acidic metal (MX_n) triggers an intramolecular attack of a pendant nucleophile, that is *anti*-oxymetalation or -aminometalation (**B**), to generate the benzoheterolyl metal species **C** with concomitant elimination of HX.[4] If an appropriate base suppressed the protonation of resultant organometallics via a proton transfer (**C** to **D**), the subsequent coupling with the electrophilic aminating reagent would occur to afford the desired 3-aminobenzoheteroles **E** along with the regeneration of the starting metal catalyst **A**.[5] The catalysis allows both C–Y and C–N bonds to be formed efficiently in one synthetic operation so as to provide a concise and complementary access to the target motifs. We have now found that a common and bench-stable $Cu(OTf)_2$ salt is the suitable promoter for this type of transformation. The detailed substrate scope and mechanistic investigations are reported herein.[6]

RESULTS AND DISCUSSION

We chose 2-(phenylethynyl)phenol (**1a**) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**)[7] as model substrates and began our studies with a $Cu(acac)_2$/dtbpy (dtbpy = 4,4′-di(*tert*-butyl)-2,2′-bipyridine) catalyst and LiO-*t*-Bu base (Table 1). Initial investigation into solvent systems revealed that polar, aprotic DMSO and amides resulted in a detectable amount of 3-aminobenzofuran **3aa** even at room temperature (entries 1–4), whereas less polar THF and toluene were ineffective (entries 5 and 6). Although the yield was moderate, our postulated catalytic cycle could be indeed operative. With the preliminary but intriguing results, we next evaluated various ligands to support the Cu catalyst. The modification of substituents on the bipyridine ring gave minor effects on yield (entries 7 and 8), while phenanthroline derivatives and phosphorus ligands tested were less efficient or formed no product (entries 9–16). Interestingly, such ancillary ligands were not necessary for the reaction (entry 17). Moreover, copper salts bearing less coordinating counteranions such as hfac (hfac = hexafluoroacetylacetonate), OAc, and OTf showed higher catalytic activity than $Cu(acac)_2$, $CuCl_2$, and CuCN (entries 17–22). These trends are in good agreement with our working hypothesis: the alkynyl moiety would be effectively activated as the metal center become more π-acidic. However, under $Cu(hfac)_2{\cdot}OH_2$ or $Cu(OAc)_2{\cdot}OH_2$ catalysis, the yields varied from 60% to 92% (GC) probably due to presence of water (entries 18 and 19). Thus, $Cu(OTf)_2$ proved to be most reliable and reproducible (entry 20). Some bases other than LiO-*t*-Bu were detrimental. Both more basic Na- and KO-*t*-Bu and less basic Cs_2CO_3 largely diminished the yield (entries 23–25). In the absence of any copper salts, the reaction did not proceed at all (entry 26). On the other hand, the corresponding chloroamine[8] did not act as the nitrogen source under conditions employed for entry 20 (data not shown).

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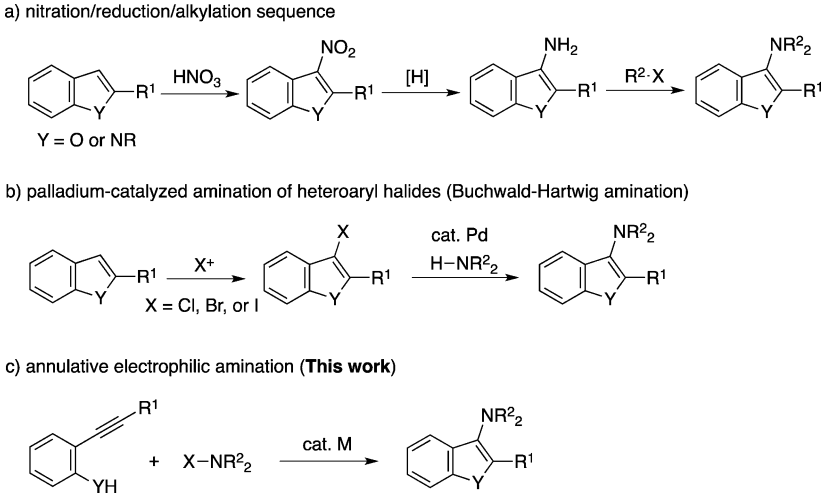
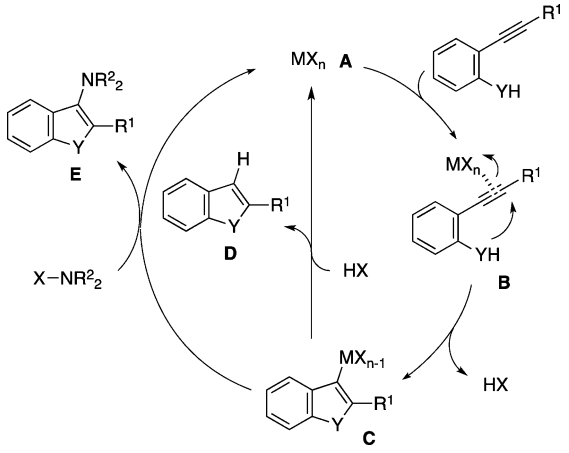
Scheme 1. Approaches to 3-Aminobenzofurans and -indoles

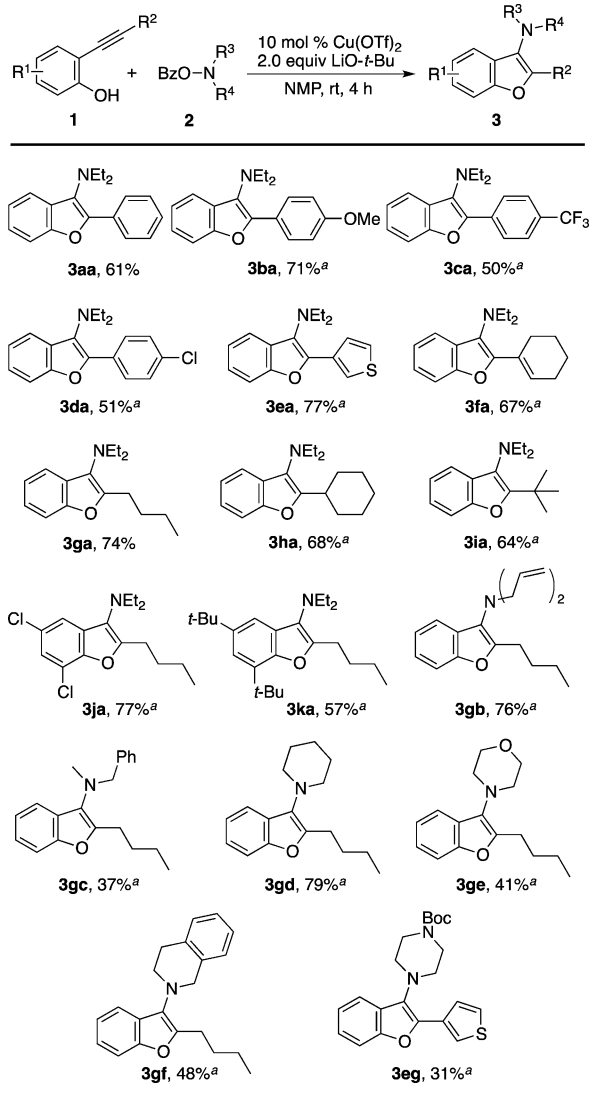


Scheme 2. Working Hypothesis



With the optimized conditions in hand, we investigated the substrate scope of the annulative amination approach to 3-aminobenzofurans (Scheme 3). In many cases, an increase in the amount of hydroxylamines **2** to 2.0 equiv gave a better result. At the alkyne terminus, electron-donating methoxy as well as electron-withdrawing trifluoromethyl and chloro functions were compatible (**3ba**–**3da**). In general, electron-rich compounds tended to show higher reactivity. The benzofuran–thiophene linkage was constructed without any difficulties (**3ea**). The conjugated enyne moiety was transformed into the alkenyl-substituted aminobenzofuran **3fa** with the olefinic moiety left intact. In addition to the above sp^2 carbon substituents, the Cu-based catalysis accommodated the alkyl side chains. The primary, secondary, and tertiary alkyl groups were equally tolerated toward the reaction (**3ga**–**3ia**). The synthesis of multisubstituted benzofuran cores was also successful (**3ja**–**ka**). Especially, Cl substituents that remained unaffected in **3ja** are useful synthetic handles for further structural manipulations via palladium-catalyzed cross-coupling reactions. Not only diethylamine **2a** but also acyclic allyl- and benzylamines could participate in the annulative amination (**3gb**–**gc**). The aminobenzofurans **3gb**–**gc** obtained could enjoy additional and orthogonal functionalizations after the selective deprotection of allylic and benzylic groups.[9] Cyclic frameworks involving piperidine,

Scheme 3. Copper-Catalyzed Annulative Electrophilic Amination of *o*-Alkynylphenols 1 with *O*-Benzoyl Hydroxylamines 2 Leading to 3-Aminobenzofurans 3[a]



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

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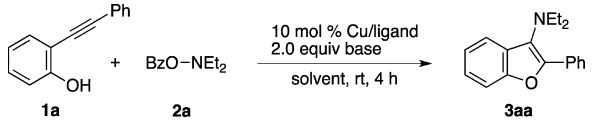
Table 1. Optimization Studies for Annulative Amination of 2-(Phenylethynyl)phenol (1a) and *O*-Benzoyl-*N*,*N*-diethylhydroxylamine (2a)[a]



1a 2a 3aa

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	DMAc	(27)
4	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	NMP	(39)
5	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	THF	trace
6	$Cu(acac)_2$/dtbpy	LiO-*t*-Bu	toluene	trace
7	$Cu(acac)_2$/bpy	LiO-*t*-Bu	NMP	(38)
8	$Cu(acac)_2$/MeO-bpy	LiO-*t*-Bu	NMP	(41)
9	$Cu(acac)_2$/phen	LiO-*t*-Bu	NMP	(20)
10	$Cu(acac)_2$/bathophen	LiO-*t*-Bu	NMP	(14)
11	$Cu(acac)_2/2PPh_3$	LiO-*t*-Bu	NMP	(20)
12	$Cu(acac)_2$/dppbz	LiO-*t*-Bu	NMP	0
13	$Cu(acac)_2$/dppe	LiO-*t*-Bu	NMP	0
14	$Cu(acac)_2$/dppf	LiO-*t*-Bu	NMP	trace
15	$Cu(acac)_2$/DPEphos	LiO-*t*-Bu	NMP	(5)
16	$Cu(acac)_2$/Xantphos	LiO-*t*-Bu	NMP	(2)
17	$Cu(acac)_2$	LiO-*t*-Bu	NMP	(47)
18	$Cu(hfac)_2 \cdot OH_2$	LiO-*t*-Bu	NMP	(65)−(92)
19	$Cu(OAc)_2 \cdot OH_2$	LiO-*t*-Bu	NMP	(60)−(92)
20	$Cu(OTf)_2$	LiO-*t*-Bu	NMP	(92) 61[c]
21	$CuCl_2$	LiO-*t*-Bu	NMP	(9)
22	CuCN	LiO-*t*-Bu	NMP	(11)
23	$Cu(OTf)_2$	NaO-*t*-Bu	NMP	(11)
24	$Cu(OTf)_2$	KO-*t*-Bu	NMP	trace
25	$Cu(OTf)_2$	Cs_2CO_3	NMP	0
26	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 in parentheses determined by GC. [c]The lower isolated yield is due to the partial decomposition of **3aa** during chromatographic purification, while the compound is stable after isolation.

morpholine, tetrahydroisoquinoline, and *N*-Boc-piperazine also could be employed albeit with somewhat lower efficiencies in some cases (**3gd**−**gf** and **3eg**).

On the basis of the above success, we then turned our attention to *o*-alkynylanilines for the synthesis of 3-aminoindoles (Table 2). We were pleased to find that under identical conditions, the annulative amination of *N*-Ms-aniline **4a** with **2a** proceeded to form the desirable 3-aminoindole derivative **5aa** (entry 1). Extensive screening of solvents (entries 2−10) identified DMF to be optimal, and **5aa** was obtained in 93% yield (entry 2). In contrast to phenol derivatives **1**, stronger and milder bases, NaO-*t*-Bu, Cs_2CO_3, K_2CO_3, and K_3PO_4, also promoted the reaction (entries 11−14). The choice of substituents on nitrogen was critical. The free aniline **4a-H** afforded the simply cyclized 2-butylindole (**6**) as the sole detectable product (entry 15). The corresponding acetate **4a-Ac** and benzoate **4a-Bz** were relatively instable under standard conditions and partially deprotected, en route to the same indole **6**, although **4a-Bz** gave **5aa-H** with only 16% yield (entries 16 and 17). The change of base into mild K_3PO_4 suppressed the problematic deprotection, but the yield was not satisfactory (entry 18). On the other hand, an analogous tosylate **4a-Ts** showed comparable reactivity, and the corresponding **5aa-Ts** was obtained in 84% yield (entry 19). The use of *N*,*N*-diethyl-*O*-pivaloylhydroxylamine instead of **2a** resulted in a lower yield of **5aa** probably due to steric reasons (entry 20).

By using conditions employed for entry 2 in Table 2, the reaction with an array of *o*-alkynylanilines was performed (Scheme 4). Compared to **4a**, cyclohexyl- and *tert*-butyl-substituted anilines resulted in lower efficiencies because of their steric reasons (**5ba** and **5ca-H**). The formation of **5ca-H** arose from concomitant deprotection of the corresponding *N*-mesylindole during the reaction course.[10] The annulative amination could be applicable to aromatic systems. The introduction of electron-donating groups increased the reactivity (**5da**−**fa**), whereas that of electron-withdrawing chloro and trifluoromethyl functions dropped the yield (**5ga** and **5ha**). Especially, the conversion of trifluoromethyl-containing substrate was not complete, and about half of the starting material remained unchanged. Similar trends were also observed in the case of phenols **1** (vide supra). The reactivity differences can be explained as follows (Scheme 5). In the *anti*-oxy- or aminometalation step corresponding to the transformation from **B** to **C** in Scheme 2, the productive coordination mode **F** would be preferable with R of electron-neutral or -donating natures. However, the presence of electron-withdrawing R lowers an electron density of alkyne so that the competitive, unproductive *O*- or *N*-bound mode of type **G** would be predominant. Thus, the copper catalyst is poisoned, and its turnover is disturbed.

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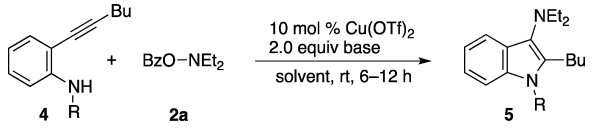
Table 2. Optimization Studies for Annulative Amination of 2-(1-Hexyn-1-yl)anilines 4 and *O*-Benzoyl-*N*,*N*-diethylhydroxylamine (2a)[a]



entry	R, **4**	base	solvent	**5**, yield (%)[b]
1	Ms (**4a**)	LiO-*t*-Bu	NMP	**5aa**, 42
2	**4a**	LiO-*t*-Bu	DMF	**5aa**, 93
3	**4a**	LiO-*t*-Bu	DMAc	**5aa**, (68)
4	**4a**	LiO-*t*-Bu	DMSO	**5aa**, (79)
5	**4a**	LiO-*t*-Bu	THF	**5aa**, (64)
6	**4a**	LiO-*t*-Bu	dioxane	**5aa**, (38)
7	**4a**	LiO-*t*-Bu	DME	**5aa**, (53)
8	**4a**	LiO-*t*-Bu	MeCN	**5aa**, (49)
9	**4a**	LiO-*t*-Bu	CH_2Cl_2	**5aa**, (10)
10	**4a**	LiO-*t*-Bu	toluene	**5aa**, (24)
11	**4a**	NaO-*t*-Bu	DMF	**5aa**, (49)
12	**4a**	Cs_2CO_3	DMF	**5aa**, (34)
13	**4a**	K_2CO_3	DMF	**5aa**, (20)
14	**4a**	K_3PO_4	DMF	**5aa**, (65)
15	H (**4a-H**)	LiO-*t*-Bu	DMF	**5aa-H**, 0[c]
16	Ac (**4a-Ac**)	LiO-*t*-Bu	DMF	**5aa-Ac**, 0[c]
17	Bz (**4a-Bz**)	LiO-*t*-Bu	DMF	**5aa-H**, (16)[c]
18	**4a-Bz**	K_3PO_4	DMF	**5aa-Bz**, (9)
19	Ts (**4a-Ts**)	LiO-*t*-Bu	DMF	**5aa-Ts**, 84
20[d]	**4a**	LiO-*t*-Bu	DMF	**5aa**, (61)

[a]A mixture of Cu salt (0.025 mmol), base (0.50 mmol), **4** (0.25 mmol), and **2a** (0.30 mmol) in solvent (1.5 mL) was stirred at room temperature for 6−24 h under N_2 [b]Yields estimated by ^{1}H NMR in parentheses. [c]In place of **5**, 2-butylindole (**6**) was detected as a major product (ca. 20−30%). [d]With *N*,*N*-diethyl-*O*-pivaloylhydroxylamine instead of **2a**.

On the other hand, 1-naphthyl and heteroaromatic 3-thienyl substitution patterns were suitable (**5ia** and **5ja**). Unfortunately, an introduction of substituents on the benzene ring of aniline generally decreased the reactivity (**5ka−ma**). We then tested some hydroxylamines other than **2a**. For the synthesis of 3-(diallylamino)indole **5eb** and 3-(allylmethyl)indole **5eh,** the use of NaO-*t*-Bu instead of LiO-*t*-Bu gave a better result. The current limitation of the present methodology was found to be lack of generality for cyclic amines: while the piperidine derivative reacted moderately (**5ed**), the annulative aminations with the hydroxylmorpholine and -piperazine were sluggish (**5ee** and **5eg**). In these unsuccessful cases, the simple cyclization predominantly occurred to form the corresponding C3-unsubstituted indole as a major product.[5a]

Although our initial scenario (Scheme 2) can account for some observed reactivity profiles of phenols **1** and anilines **4**, an alternative pathway including a nitrogen-centered radical species might be plausible. Göttlich reported a copper-catalyzed intramolecular oxyamination of alkenes and proposed a formation of aminyl radical intermediate, which was also supported by the fact the reaction was initiated by a catalytic amount of AIBN as well as Cu(I) (Scheme 6).[7c] To determine whether similar radical species are involved in our catalytic cycle, we carried out the reaction of **4a** with **2a** in the presence of radical scavengers TEMPO and galvinoxyl (Scheme 7). However, these additives gave no effect on reaction rate and product yield. Furthermore, AIBN instead of the $Cu(OTf)_2$/LiO-*t*-Bu did not promote the reaction at all. An additional experiment with 4-pentenylhydroxylamine **2i** produced the usual annulative amination product **5ei** exclusively. No pyrrolidine-containing compound arising from the conceivable radical cyclization was detected by GC and GC−MS analyses. These outcomes could exclude the radical process. Another possibility is a copper-catalyzed direct C3-amination of benzofurans and indoles with hydroxylamines,[11] but it is also ruled out by the control experiments illustrated in Scheme 8. Thus, our proposed pathway is considered to be reasonable at this stage, while further efforts are essential for elucidation of the detailed mechanism.

Finally, we applied the annulative amination methodologies to the synthesis of benzofuro[3,2-*b*]azepine core, which is found in potent inhibitors of bone resorption (Scheme 9).[12] Treatment of **1l** with **2h** under identical $Cu(OTf)_2$/LiO-*t*-Bu systems furnished the expected aminobenzofuran **3lh** in 51% yield, leaving the two terminal olefins untouched. The subsequent cycloisomerization catalyzed by a ruthenium hydride[13] constructed the desired tricyclic framework **7** in 77% yield.

CONCLUSION

We have developed a copper-catalyzed annulative amination of *o*-alkynylphenols and -anilines with *O*-acylated hydroxylamines for the synthesis of 3-aminobenzofurans and -indoles. The copper-based catalyses proceed even at room temperature and provide a unique, complementary access to the above heteroarylamines of biological and pharmaceutical interest. Some mechanistic investigations are suggestive of nonradical, electrophilic amination of the heteroarylcopper species in the C−N bond-forming step. Our ongoing work seeks to overcome the current limitation for the coupling of anilines with cyclic amines and to apply the annulative electrophilic amination strategy to construction of other heterocyclic amines.

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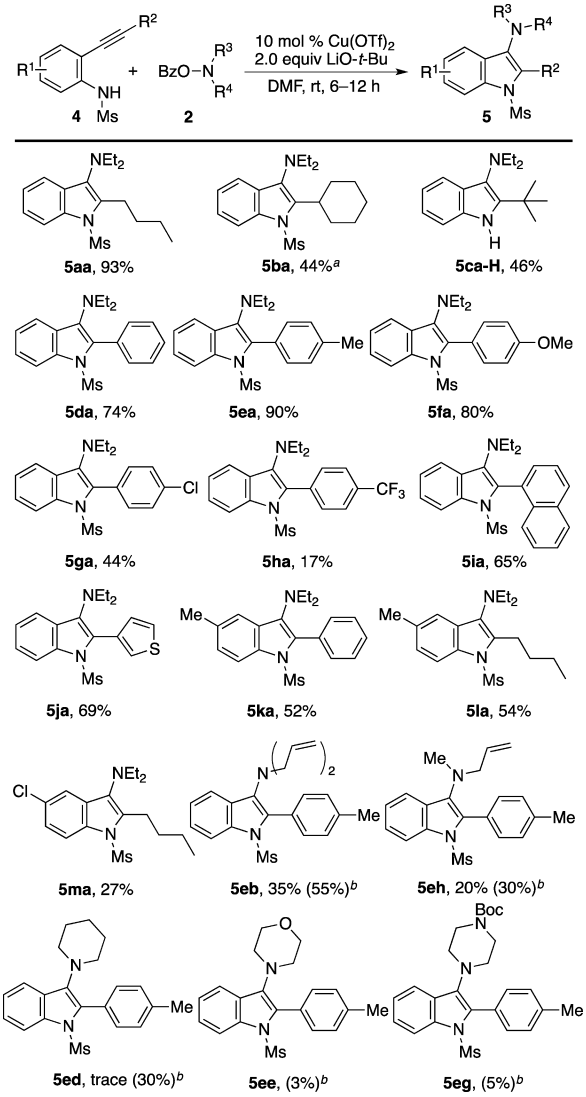
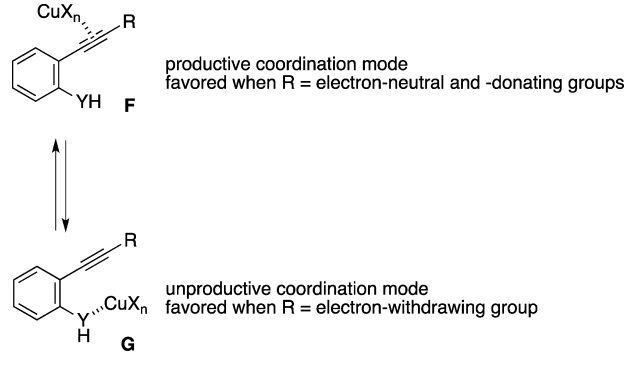
Scheme 4. Copper-Catalyzed Annulative Electrophilic Amination of *o*-Alkynylanilines 4 with *O*-Benzoyl Hydroxylamines 2 Leading to 3-Aminoindoles 5[a]



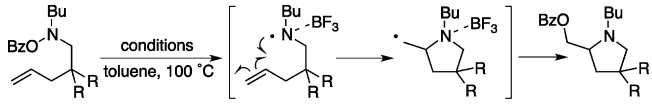
[a]With 20 mol % of $Cu(OTf)_2$.

[b]With NaO-*t*-Bu instead of LiO-*t*-Bu.

Scheme 5. Explanation for Reactivity Differences

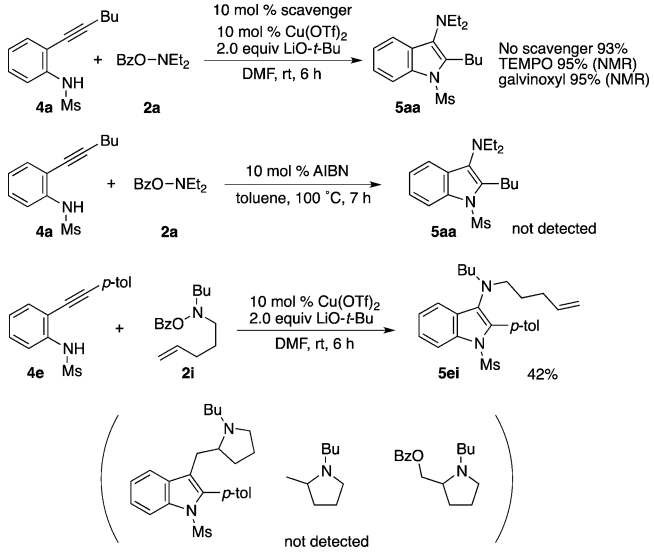


Scheme 6. Radical Intramolecular Oxyamination of Alkenes Reported by Göttlich[7c]

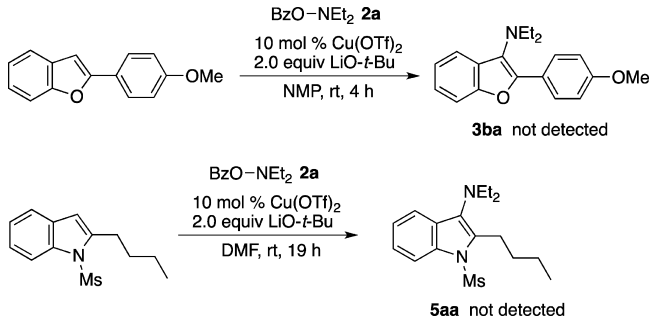


conditions	R	yield of product
cat. $CuPF_6$/stoic. BF_3•OEt_2	Me	79%
cat. $CuPF_6$/stoic. BF_3•OEt_2	H	39%
cat. AIBN/stoic. BF_3	Me	13%

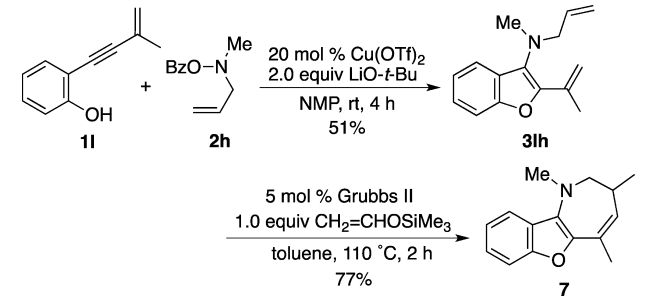
Scheme 7



Scheme 8. Control Experiments



Scheme 9



EXPERIMENTAL SECTION

Typical Procedure for Copper-Catalyzed Annulative Amination of *o*-Alkynylphenols with *O*-Acylated Hydroxylamines. Synthesis of **3aa** (Table 1, entry 20) is representative. $Cu(OTf)_2$ (18 mg, 0.050 mmol) and LiO-*t*-Bu (80 mg, 1.0 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen using the standard Schlenk technique. NMP (1.0 mL) was added, and the suspension was stirred for 10 min at room temperature.

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A solution of 2-(phenylethynyl)phenol (**1a**, 97.1 mg, 0.50 mmol) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**, 116 mg, 0.60 mmol) in NMP (2.0 mL) was then added dropwise. After being stirred for 4 h at the same temperature, the resulting mixture was poured into saturated aq NaCl and extracted with dichloromethane. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Subsequent silica gel column purification with hexane/Et_3N (200/1, v/v) afforded *N*,*N*-diethyl-2-phenylbenzofuran-3-amine (**3aa**, 81 mg, 0.31 mmol) in 61% yield.

***N*,*N*-Diethyl-2-phenylbenzofuran-3-amine (3aa).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.4 Hz, 6H), 3.26 (q, J = 7.4 Hz, 4H), 7.16 (t, J = 7.3 Hz, 1H), 7.26−7.31 (m, 2H), 7.40−7.49 (m, 3H), 7.66 (d, J = 7.8 Hz, 1H), 8.40 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 48.8, 111.7, 121.0, 122.0, 124.0, 125.9, 127.1, 127.7, 127.9, 128.2, 131.1, 149.2, 153.3; HRMS m/z (M^+) calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1466.

***N*,*N*-Diethyl-2-(4-methoxylphenyl)benzofuran-3-amine (3ba).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.4 Hz, 6H), 3.24 (q, J = 7.4 Hz, 4H), 3.85 (s, 3H), 6.95 (dt, J = 8.7, 1.8 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 8.2 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 8.34 (dt, J = 8.7, 2.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 48.8, 55.2, 111.5, 113.6, 120.7, 121.9, 123.5, 124.0, 125.3, 127.4, 128.0, 149.5, 153.1, 159.2; HRMS m/z (M^+) calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1571.

***N*,*N*-Diethyl-2-{(4-trifluoromethyl)phenyl}benzofuran-3-amine (3ca).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 6H), 3.27 (q, J = 7.3 Hz, 4H), 7.19 (t, J = 7.8 Hz, 1H), 7.28−7.32 (m, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 7.8 Hz, 1H), 8.52 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 48.8, 112.0, 121.3, 122.4, 124.2 (q, J = 270.8 Hz), 124.9, 125.1 (q, J = 3.8 Hz), 125.8, 127.6, 129.1 (q, J = 32.4 Hz), 129.2, 134.4, 147.6, 153.5; ^{19}F NMR (373 MHz, $CDCl_3$) δ −62.5; HRMS m/z (M^+) calcd for $C_{19}H_{18}F_3NO$ 333.1340, found 333.1338.

2-(4-Chlorophenyl)-*N*,*N*-diethylbenzofuran-3-amine (3da). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 6H), 3.25 (q, J = 7.3 Hz, 4H), 7.17 (t, J = 7.3 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.38 (dt, J = 8.8, 2.2 Hz, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.3 Hz, 1H), 8.35 (dt, J = 8.8, 2.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 48.8, 111.8, 121.0, 122.2, 124.3, 127.1, 127.5, 127.7, 128.4, 129.6, 133.3, 148.2, 153.3; HRMS m/z (M^+) calcd for $C_{18}H_{18}ClNO$ 299.1077, found 299.1070.

***N*,*N*-Diethyl-2-(3-thienyl)benzofuran-3-amine (3ea).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 6H), 3.24 (q, J = 7.3 Hz, 4H), 7.15 (t, J = 7.3 Hz, 1H), 7.21−7.25 (m, 1H), 7.34 (dd, J = 5.0, 3.2 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 5.0 Hz, 1H), 8.05 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 48.8, 111.7, 120.7, 122.06, 122.07, 123.8, 125.1, 125.4, 126.1, 127.5, 132.0, 147.9, 153.3; HRMS m/z (M^+) calcd for $C_{16}H_{17}NOS$ 271.1031, found 271.1032.

2-(1-Cyclohexen-1-yl)-*N*,*N*-diethylbenzofuran-3-amine (3fa). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 6H), 1.59−1.69 (m, 2H), 1.71−1.77 (m, 2H), 2.2.4−2.27 (m, 2H), 2.64−2.66 (m, 2H), 3.15 (q, J = 7.3 Hz, 4H), 6.67−6.70 (m, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.1, 22.7, 25.6, 25.7, 48.7, 111.3, 120.6, 121.6, 123.3, 125.2, 127.6, 128.0, 128.7, 151.6, 152.8; HRMS m/z (M^+) calcd for $C_{18}H_{23}NO$ 269.1780, found 269.1783.

2-Butyl-*N*,*N*-diethylbenzofuran-3-amine (3ga). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 0.97 (t, J = 7.3 Hz, 6H), 1.38−1.44 (m, 2H), 1.60−1.73 (m, 2H), 2.76 (t, J = 7.3 Hz, 2H), 3.12 (q, J = 7.3 Hz, 4H), 7.11 (td, J = 7.3, 1.4 Hz, 1H), 7.17 (td, J = 7.3, 1.4 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 22.6, 25.4, 30.2, 49.3, 111.3, 119.9, 121.6, 122.7, 124.2, 126.8, 153.5, 155.8; HRMS m/z (M^+) calcd for $C_{16}H_{23}NO$ 245.1780, found 245.1782.

2-Cyclohexyl-*N*,*N*-diethylbenzofuran-3-amine (3ha). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 6H), 1.26−1.44 (m, 4H), 1.65−1.85 (m, 6H), 3.01 (tt, J = 11.4, 3.6 Hz, 1H), 3.12 (q, J = 7.3 Hz, 4H), 7.10 (td, J = 7.3, 0.9 Hz, 1H), 7.17 (td, J = 7.3, 1.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 26.0, 26.4, 31.2, 34.9, 49.4, 111.4, 120.0, 121.5, 122.2, 122.6, 126.6, 153.4, 159.7; HRMS m/z (M^+) calcd for $C_{18}H_{25}NO$ 271.1936, found 271.1935.

2-(*tert*-Butyl)-*N*,*N*-diethylbenzofuran-3-amine (3ia). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 6H), 1.44 (s, 9H), 3.12 (bs, 4H), 7.09 (t, J = 7.3 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 29.6, 34.0, 48.9, 111.3, 120.8, 121.3, 122.7, 124.5, 127.6, 152.6, 160.1; HRMS m/z (M^+) calcd for $C_{16}H_{23}NO$ 245.1780, found 245.1782.

2-Butyl-5,7-dichloro-*N*,*N*-diethylbenzofuran-3-amine (3ja). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 9H), 1.38−1.47 (m, 2H), 1.67−1.74 (m, 2H), 2.77 (t, J = 7.7 Hz, 2H), 3.07 (q, J = 7.3 Hz, 4H), 7.19 (d, J = 2.2 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 22.6, 25.6, 30.0, 49.1, 117.3, 118.1, 122.9, 124.8, 127.5, 129.5, 147.7, 158.6; HRMS m/z (M^+) calcd for $C_{16}H_{21}Cl_2NO$ 313.1000, found 313.1002.

5,7-Di-*tert*-butyl-2-butyl-*N*,*N*-diethylbenzofuran-3-amine (3ka). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 0.99 (t, J = 7.3 Hz, 6H), 1.37 (s, 9H), 1.40−1.44 (m, 2H), 1.50 (s, 9H), 1.66−1.70 (m, 2H), 2.76 (t, J = 7.3 Hz, 2H), 3.13 (q, J = 7.3 Hz, 4H), 7.15 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.3, 22.5, 25.4, 30.0, 30.3, 32.0, 34.3, 34.7, 49.2, 113.9, 117.5, 124.1, 126.8, 133.5, 144.0, 149.8, 154.5; HRMS m/z (M^+) calcd for $C_{24}H_{39}NO$ 357.3032, found 357.3027.

***N*,*N*-Diallyl-2-butylbenzofuran-3-amine (3gb).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.29−1.43 (m, 2H), 1.64−1.72 (m, 2H), 2.76 (t, J = 7.3 Hz, 2H), 3.69 (d, J = 6.6 Hz, 4H), 5.00−5.03 (m, 2H), 5.07−5.13 (m, 2H), 5.83 (ddt, J = 16.5, 10.2, 6.2 Hz, 2H), 7.12−7.18 (m, 2H), 7.34−7.36 (m, 1H), 7.55−7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.5, 25.7, 30.2, 57.3, 111.2, 116.8, 119.7, 121.8, 122.8, 126.1, 127.2, 136.0, 153.2, 154.3; HRMS m/z (M^+) calcd for $C_{18}H_{23}NO$ 269.1780, found 269.1781.

***N*-Benzyl-2-butyl-*N*-methylbenzofuran-3-amine (3gc).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.26−1.38 (m, 2H), 1.51−1.59 (m, 2H), 2.68 (t, J = 7.7 Hz, 2H), 2.83 (s, 3H), 4.21 (s, 2H), 7.14−7.37 (m, 8H), 7.62−7.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.5, 25.8, 30.2, 42.3, 61.3, 111.3, 119.7, 121.7, 122.9, 126.8, 127.0, 128.0, 128.2, 128.8, 139.2, 152.8, 153.2; HRMS m/z (M^+) calcd for $C_{20}H_{23}NO$ 293.1780, found 293.1775.

1-(2-Butylbenzofuran-3-yl)piperidine (3gd). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.35−1.43 (m, 2H), 1.58−1.60 (m, 2H), 1.64−1.70 (m, 6H), 2.79 (t, J = 7.3 Hz, 2H), 3.08−3.11 (m, 4H), 7.11−7.18 (m, 2H), 7.34 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 24.4, 26.0, 26.9, 30.5, 53.7, 111.1, 119.8, 121.6, 122.7, 127.0, 129.3, 151.2, 153.1; HRMS m/z (M^+) calcd for $C_{17}H_{23}NO$ 257.1780, found 257.1777.

4-(2-Butylbenzofuran-3-yl)morpholine (3ge). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.38 (tq, J = 7.3, 7.4 Hz, 2H), 1.65 (tt, J = 7.3, 7.4 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 3.15 (t, J = 4.6 Hz, 4H), 3.85 (t, J = 4.6 Hz, 4H), 7.14−7.21 (m, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 25.7, 30.4, 52.6, 67.8, 111.4, 119.6, 121.9, 123.0, 126.4, 127.9, 152.4, 153.2; HRMS m/z (M^+) calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1573.

2-(2-Butylbenzofuran-3-yl)-1,2,3,4-tetrahydroisoquinoline (3gf). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.34−1.40 (m, 2H), 1.67−1.71 (m, 2H), 2.80 (t, J = 7.3 Hz, 2H), 3.01 (bs, 2H), 3.47 (bs, 2H), 4.34 (s, 2H), 7.04−7.06 (m, 1H), 7.13−7.23 (m, 5H), 7.39 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 25.8, 30.1, 30.4, 50.4, 54.5, 111.3, 119.6, 121.9, 123.0, 125.7, 126.1, 126.3, 126.6, 128.1, 129.1, 134.6, 135.4, 152.5, 153.3; HRMS m/z (M^+) calcd for $C_{21}H_{23}NO$ 305.1780, found 305.1778.

***tert*-Butyl 4-[2-(thiophen-3-yl)benzofuran-3-yl]piperazine-1-carboxylate (3eg).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 3.22 (bs, 4H), 4.32 (bs, 4H), 7.17 (t, J = 7.3 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.38 (dt, J = 5.0, 3.2 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.90−7.91 (m, 1H), 7.98−7.99

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(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 51.6, 79.9, 111.7, 120.7, 122.1, 122.3, 124.0, 125.65, 125.69, 126.6, 127.7, 131.6, 145.2, 153.1, 154.9; HRMS m/z (M^+) calcd for $C_{21}H_{24}N_2O_3S$ 384.1508, found 384.1504.

Typical Procedure for Copper-Catalyzed Annulative Amination of *o*-Alkynylanilines with *O*-Acylated Hydroxylamines. Synthesis of **5aa** is representative (Table 2, entry 2). $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) and LiO-*t*-Bu (40.0 mg, 0.50 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. DMF (0.50 mL) was then added to the flask, and the suspension was stirred for 15 min at ambient temperature. Finally, a solution of 2-hexynylaniline **4a** (63 mg, 0.25 mmol), *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**, 58 mg, 0.30 mmol), and 1-methylnaphthalene (ca. 25 mg, internal standard) in DMF (1.0 mL) was added dropwise. The solution was stirred at ambient temperature for additional 6 h. The resulting mixture was quenched with water. An aqueous solution of 4 M HCl (60 mL) was added to the mixture. The aqueous layer was washed four times with Et_2O, neutralized with 6 M aq NaOH, and then extracted four times with Et_2O. The combined organic layer was dried over sodium sulfate. Concentration in vacuo and subsequent purification by column chromatography on silica gel with hexane/ethyl acetate (5:1, v/v) as an eluent gave 2-butyl-*N*,*N*-diethyl-1-(methanesulfonyl)indol-3-amine (**5aa**, 75 mg, 0.23 mmol) in 93% yield.

2-Butyl-*N*,*N*-diethyl-1-(methanesulfonyl)indol-3-amine (5aa). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 0.99 (t, J = 7.3 Hz, 6H), 1.38−1.48 (m, 2H), 1.58−1.68 (m, 2H), 2.87 (s, 3H), 2.94 (t, J = 7.8 Hz, 2H), 3.17 (q, J = 7.3 Hz, 4H), 7.20−7.28 (m, 2H), 7.60 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 23.25, 25.6, 32.9, 39.4, 49.0, 115.3, 120.0, 123.4, 124.1, 128.9, 130.2, 136.0, 140.0; HRMS m/z (M^+) calcd for $C_{17}H_{26}N_2O_2S$ 322.1715, found 322.1714.

2-Butyl-*N*,*N*-diethyl-1-(*p*-toluenesulfonyl)indol-3-amine (5aa-Ts). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 7.3 Hz, 6H), 0.96 (t, J = 7.3 Hz, 3H), 1.40−1.49 (m, 2H), 1.66−1.74 (m, 2H), 2.26 (s, 3H), 3.01 (t, J = 7.8 Hz, 3H), 3.06 (q, J = 7.3 Hz, 3H), 7.07−7.24 (m, 4H), 7.45−7.49 (m, 3H), 8.20 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.1, 14.2, 21.6, 23.2, 26.1, 33.1, 48.9, 116.3, 119.6, 123.3, 123.8, 126.4, 129.1, 129.6, 130.8, 135.4, 136.6, 140.1, 144.5; HRMS m/z (M^+) calcd for $C_{23}H_{30}N_2O_2S$ 398.2028, found 398.2025.

2-Cyclohexyl-*N*,*N*-diethyl-1-(methanesulfonyl)indol-3-amine (5ba). Mp 98.0−100.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 6H), 1.26−1.43 (m, 4H), 1.72−1.84 (m, 4H), 2.21 (q, J = 12.4 Hz, 2H), 2.93 (s, 3H), 3.18 (q, J = 7.3 Hz, 4H), 3.54 (t, J = 12.4 Hz, 1H), 7.17−7.25 (m, 2H), 7.59 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 26.3, 27.5, 31.6, 37.3, 40.1, 48.9, 115.7, 120.3, 123.2, 124.1, 129.0, 131.9, 136.2, 142.9; HRMS m/z (M^+) calcd for $C_{19}H_{28}N_2O_2S$ 348.1871, found 348.1870.

2-(*tert*-Butyl)-*N*,*N*-diethylindol-3-amine (5ca-H). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, J = 7.3 Hz, 6H), 1.47 (s, 9H), 3.19 (q, J = 7.3 Hz, 4H), 6.98 (t, J = 8.3 Hz, 1H), 7.07 (t, J = 8.3 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.67 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 30.6, 32.9, 49.4, 111.0, 118.6, 120.4, 120.7, 123.6, 126.9, 133.4, 141.5; HRMS m/z (M^+) calcd for $C_{16}H_{24}N_2$ 244.1939, found 244.1940.

***N*,*N*-Diethyl-1-methanesulfonyl-2-phenylindol-3-amine (5da).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 6H), 2.76 (s, 3H), 3.01 (q, J = 7.3 Hz, 4H), 7.29−7.49 (m, 7H), 7.69 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.7, 48.1, 116.1, 120.5, 124.0, 125.2, 127.6, 128.7, 129.7, 131.6, 131.8, 133.0, 134.8, 136.5; HRMS m/z (M^+) calcd for $C_{19}H_{22}N_2O_2S$ 342.1402, found 342.1400.

***N*,*N*-Diethyl-1-methanesulfonyl-2-(4-methylphenyl)indol-3-amine (5ea).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 6H), 2.41 (s, 3H), 2.76 (s, 3H), 3.01 (q, J = 7.3 Hz, 4H), 7.21−7.36 (m, 6H), 7.68 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.7, 39.7, 48.1, 116.1, 120.4, 123.9, 125.1, 128.4, 128.8, 129.8, 131.4, 132.8, 135.0, 136.5, 138.6; HRMS m/z (M^+) calcd for $C_{20}H_{24}N_2O_2S$ 356.1558, found 356.1556.

***N*,*N*-Diethyl-1-methanesulfonyl-2-(4-methoxyphenyl)indol-3-amine (5fa).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 6H), 2.75 (s, 3H), 3.01 (q, J = 7.3 Hz, 4H), 3.85 (s, 3H), 6.95 (d, J = 8.2 Hz, 2H), 7.28−7.35 (m, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.7, 48.0, 55.3, 113.1, 116.1, 120.3, 123.8, 123.9, 125.0, 129.7, 132.7, 132.8, 134.6, 136.4, 159.9; HRMS m/z (M^+) calcd for $C_{20}H_{24}N_2O_3S$ 372.1508, found 372.1505.

2-(4-Chlorophenyl)-*N*,*N*-diethyl-1-(methanesulfonyl)indol-3-amine (5ga). Mp 86.0−87.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 6H), 2.74 (s, 3H), 3.04 (q, J = 7.3 Hz, 4H), 7.30−7.44 (m, 6H), 7.69 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.3, 48.1, 116.3, 120.7, 124.2, 125.5, 127.9, 129.5, 130.2, 132.7, 133.7, 133.9, 134.7, 136.8; HRMS m/z (M^+) calcd for $C_{19}H_{21}ClN_2O_2S$ 376.1012, found 376.1010.

***N*,*N*-Diethyl-1-methanesulfonyl-2-[4-(trifluoromethyl)-phenyl]indol-3-amine (5ha).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 6H), 2.74 (s, 3H), 3.06 (q, J = 7.3 Hz, 4H), 7.34 (t, J = 8.3 Hz, 1H), 7.40 (t, J = 8.3 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.1, 48.3, 116.4, 121.0, 124.37 (q, J = 272.4 Hz), 124.41, 124.5 (q, J = 3.8 Hz), 125.9, 129.4, 130.3 (q, J = 32.7 Hz), 131.7, 133.9, 134.4, 135.5 (q, J = 1.5 Hz), 137.0; HRMS m/z (M^+) calcd for $C_{20}H_{21}F_3N_2O_2S$: 410.1276, found 410.1274.

***N*,*N*-Diethyl-1-methanesulfonyl-2-(1-naphthyl)indol-3-amine (5ia).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 6H), 2.82 (s, 3H), 2.85−2.96 (m, 4H), 7.33−7.56 (m, 6H), 7.69 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 40.2, 47.5, 115.5, 120.5, 123.8, 124.8, 125.2, 126.1, 126.39, 126.42, 128.5, 129.70, 129.72, 129.8, 129.9, 131.4, 133.4, 134.2, 134.4, 136.1; HRMS m/z (M^+) calcd for $C_{23}H_{24}N_2O_2S$ 392.1558, found 392.1561.

***N*,*N*-Diethyl-1-methanesulfonyl-2-(3-thienyl)indol-3-amine (5ja).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 6H), 2.77 (s, 3H), 3.03 (q, J = 7.3 Hz, 4H), 7.24−7.36 (m, 4H), 7.44−7.45 (m, 1H), 7.66 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 39.6, 47.9, 116.1, 120.3, 123.9, 124.2, 125.3, 127.0, 129.4, 129.5, 130.9, 131.2, 133.6, 136.5; HRMS m/z (M^+) calcd for $C_{17}H_{20}N_2O_2S_2$: 348.0966, found 348.0968.

***N*,*N*-Diethyl-1-methanesulfonyl-5-methyl-2-phenylindol-3-amine (5ka).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 6H), 2.47 (s, 3H), 2.73 (s, 3H), 3.01 (q, J = 7.3 Hz, 4H), 7.17 (d, J = 8.2 Hz, 1H), 7.39−7.48 (m, 6H), 8.00 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.6, 39.2, 48.1, 116.0, 120.4, 126.6, 127.5, 128.6, 130.0, 131.5, 131.9, 133.0, 133.8, 134.9, 135.1; HRMS m/z (M^+) calcd for $C_{20}H_{24}N_2O_2S$ 356.1558, found 356.1556.

2-Butyl-*N*,*N*-diethyl-1-methanesulfonyl-5-methylindol-3-amine (5la). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 0.98 (t, J = 7.3 Hz, 6H), 1.38−1.47 (m, 2H), 1.59−1.67 (m, 2H), 2.43 (s, 3H), 2.83 (s, 3H), 2.94 (d, J = 7.6 Hz, 2H), 3.16 (q, J = 7.3 Hz, 4H), 7.07 (d, J = 8.3 Hz, 1H), 7.38 (s, 1H), 7.92 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 21.6, 23.2, 25.6, 32.8, 39.0, 49.0, 115.1, 120.0, 125.4, 129.1, 130.1, 133.1, 134.3, 140.1; HRMS m/z (M^+) calcd for $C_{18}H_{28}N_2O_2S$ 336.1871, found 336.1869.

2-Butyl-5-chloro-*N*,*N*-diethyl-1-(methanesulfonyl)indol-3-amine (5ma). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 0.98 (t, J = 7.3 Hz, 6H), 1.37−1.47 (m, 2H), 1.59−1.67 (m, 2H), 2.88 (s, 3H), 2.95 (t, J = 7.8 Hz, 2H), 3.14 (q, J = 7.3 Hz, 4H), 7.21 (dd, J = 8.3, 2.3 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 23.3, 25.7, 32.8, 39.7, 48.9, 116.3, 119.5, 124.2, 129.3, 129.7, 130.2, 134.3, 141.5; HRMS m/z (M^+) calcd for $C_{17}H_{25}ClN_2O_2S$ 356.1325, found 356.1323.

***N*,*N*-Diallyl-1-methanesulfonyl-2-(4-methyphenyl)indol-3-amine (5eb).** Mp 108.0−111.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.75 (s, 3H), 3.55 (d, J = 6.4 Hz, 4H), 4.99 (dd, J = 9.2, 1.4 Hz, 2H), 5.01 (dd, J = 16.9, 1.4 Hz, 2H), 5.70 (ddt, J = 16.9, 9.2, 6.4 Hz, 2H), 7.22−7.36 (m, 6H), 7.67 (dd, J = 7.1, 2.3 Hz, 1H), 8.11 (dd, J = 7.1, 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 39.7, 56.1, 116.1, 117.0, 120.1, 124.1, 125.2, 128.5, 128.6, 129.6, 131.6, 133.5, 133.8, 135.8, 136.3, 138.8; HRMS m/z (M^+) calcd for $C_{22}H_{24}N_2O_2S$ 380.1558, found 380.1560.

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***N*-Allyl-*N*-methyl-1-methanesulfonyl-2-(4-methylphenyl)-indol-3-amine (5eh).** Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.58 (s, 3H), 2.77 (s, 3H), 3.52 (d, J = 6.4 Hz, 2H), 5.07 (dd, J = 9.2, 1.4 Hz, 1H), 5.11 (dd, J = 16.9, 1.4 Hz, 1H), 5.78 (ddt, J = 16.9, 9.2, 6.4 Hz, 1H), 7.22−7.25 (m, 2H), 7.30−7.37 (m, 4H), 7.65 (dd, J = 6.4, 2.3 Hz, 1H), 8.12 (dd, J = 7.3, 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 39.9, 41.2, 59.0, 116.1, 117.1, 119.9, 124.0, 125.3, 128.5, 128.8, 128.9, 131.3, 131.9, 135.2, 135.8, 136.2, 138.9; HRMS m/z (M^+) calcd for $C_{20}H_{22}N_2O_2S$ 354.1402, found 354.1404.

1-Methanesulfonyl-2-(4-methylphenyl)-3-(1-piperidinyl)-indole (5ed). Mp 163.0−165.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42−1.48 (m, 2H), 1.54−1.59 (m, 4H), 2.42 (s, 3H), 2.76 (s, 3H), 2.82 (t, J = 5.0 Hz, 4H), 7.21 (d, J = 8.3 Hz, 2H), 7.31−7.36 (m, 4H), 7.64 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.4, 27.0, 39.9, 53.3, 116.0, 119.7, 124.0, 125.3, 128.3, 129.0, 129.1, 129.6, 132.1, 136.0, 136.2, 138.8; HRMS m/z (M^+) calcd for $C_{21}H_{24}N_2O_2S$ 368.1558, found 368.1559.

***N*-Butyl-1-methanesulfonyl-2-(4-methylphenyl)-*N*-(4-pent-en-1-yl)indol-3-amine (5ei).** Mp 48.0−49.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3H), 1.12−1.21 (m, 2H), 1.29−1.44 (m, 4H), 1.89 (q, J = 7.3 Hz, 2H), 2.41 (s, 3H), 2.78 (s, 3H), 2.91 (t, J = 7.3 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 4.87 (dd, J = 9.2, 1.4 Hz, 1H), 4.88 (dd, J = 16.9, 1.4 Hz, 1H), 5.68 (ddt, J = 16.9, 9.2, 6.4 Hz, 1H), 7.21−7.23 (m, 2H), 7.25−7.29 (m, 4H), 7.67 (d, J = 7.3 Hz, 1H), 8.13 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.5, 21.7, 28.0, 31.0, 31.4, 39.9, 53.6, 54.3, 114.6, 116.1, 120.3, 123.9, 125.1, 128.4, 128.7, 129.6, 131.5, 133.7, 134.3, 136.4, 138.7, 138.8; HRMS m/z (M^+) calcd for $C_{25}H_{32}N_2O_2S$ 424.2184, found 424.2187.

Synthesis of 7 (Scheme 9). With $Cu(OTf)_2$ (36 mg, 0.10 mmol), under otherwise identical conditions mentioned above, the oxyamination of 2-(3-methylbut-3-en-1-yn-1-yl)phenol (**1l**, 79 mg, 0.50 mmol) with *N*-allyl-*O*-benzoyl-*N*-methylhydroxylamine (**2h**, 191.2 mg, 1.0 mmol) proceeded to furnish *N*-allyl-*N*-methyl-2-(1-propen-2-yl)benzofuran-3-amine (**3lh**, 58 mg, 0.26 mmol) in 51% yield.

***N*-Allyl-*N*-methyl-2-(1-propen-2-yl)benzofuran-3-amine (3lh).** Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.84 (s, 3H), 3.74 (d, J = 6.2 Hz, 2H), 5.09 (dd, J = 10.2, 1.4 Hz, 1H), 5.17−5.20 (m, 1H), 5.20 (s, 1H), 5.81 (s, 1H), 5.88 (ddt, J = 17.0, 10.2, 6.2 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5, 41.5, 59.6, 111.6, 114.9, 117.1, 120.8, 121.9, 124.1, 127.3, 130.0, 134.3, 135.7, 148.6, 152.7; HRMS m/z (M^+) calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1307.

Grubbs second generation catalyst (3.7 mg, 4.4 μmol) was placed in a 5 mL Schlenk tube, which was then filled with nitrogen. Trimethyl(vinyloxy)silane (0.013 mL, 0.087 mmol) and a solution of **3lh** (20 mg, 0.087 mmol) in toluene (1.0 mL) were subsequently added dropwise. The solution was heated at 110 °C for 2 h. The resulting mixture was allowed to cool to room temperature and filtered through a pad of neutral alumina. Concentration under reduced pressure followed by column chromatography on silica gel with hexane/EtOAc/Et_3N (400/20/2.5, v/v/v) produced 1,3,5-trimethyl-2,3-dihydro-1*H*-benzofuro-[3,2-*b*]azepine (7, 15 mg, 0.067 mmol) in 77% yield.

1,3,5-Trimethyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]azepine (7). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 7.4 Hz, 3H), 2.22 (t, J = 1.8 Hz, 3H), 2.38−2.50 (m, 1H), 2.58 (dd, J = 13.3, 7.8 Hz, 1H), 2.99 (s, 3H), 3.12 (dt, J = 13.3, 1.4 Hz, 1H), 5.55−5.56 (m, 1H), 7.17 (td, J = 6.8, 0.9 Hz, 1H), 7.23 (td, J = 7.8, 1.4 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.6, 32.0, 43.6, 59.6, 111.4, 119.6, 121.7, 124.1, 125.9, 130.4, 132.5, 142.0, 152.8 (one sp^2 ^{13}C signal was overlapped by another one); HRMS m/z (M^+) calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1308.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(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., Ed.; Wiley-VCH: Weinheim, 2007. (c) Lehmann, F.; Haile, S.; Axen, E.; Medina, C.; Uppenberg, J.; Svensson, S.; Lundbaeck, T.; Rondahl, L.; Barf, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4445. (d) Bahekar, R. H.; Jain, M. R.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Jadav, P. A.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 3248. (e) Romagnoli, R.; Baraldi, P. G.; Sarkar, T.; Carrion, M. D.; Cara, C. L.; Cruz-Lopez, O.; Preti, D.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Di Christina, A.; Zonta, N.; Balzarini, J.; Brancale, A.; Hseih, H.-P.; Hamel, E. *J. Med. Chem.* **2008**, *51*, 1464.

(2) (a) Stoermer, R.; Richter, O. *Chem. Ber.* **1897**, *30*, 2094. (b) Kaluza, F.; Perold, G. *Chem. Ber.* **1955**, *88*, 597. (c) Berti, G.; Da Settimo, A.; Nannipieri, E. *J. Chem. Soc. C* **1968**, 2145. (d) Pelkey, E. T.; Gribble, G. W. *Synthesis* **1999**, 1117.

(3) 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.

(4) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641. (c) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469.

(5) For synthesis of 2,3-disubstituted benzofurans and indoles from *o*-alkynylphenols and -anilines, respectively: (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **2004**, *69*, 2235. (c) Hu, Y.; Nawoschilk, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235. (d) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (e) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803. (f) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074. (g) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902. (h) Tsuji, H.; Yokoi, Y.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *Chem. Asian J.* **2009**, *4*, 655. (i) Martínez, C.; Álverez, R.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083. (j) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329. (k) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 3412. (l) Álverez, R.; Martínez, C.; Madich, Y.; Denis, J. G.; Aurrecoechea, J. M.; de Lera, Á. R. *Chem.−Eur. J.* **2010**, *16*, 12746. (m) Ye, Y.; Fan, R. *Chem. Commun.* **2011**, *47*, 5626. (n) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 3076. (o) Wang, H.; Han, X.; Lu, X. *Synlett* **2011**, 2590. Relevant Au-mediated processes: (p) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(6) A part of this work was communicated previously: Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395.

(7) For the N−O bond as a useful handle for C−N bond formation, see: (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) Noack, M.; Göttlich, R. *Chem. Commun.* **2002**, 536. (d) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (e) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (f) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (g) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521. (h) Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947. (i) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (j) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (k) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (l) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q.

J. Am. Chem. Soc. **2011**, *133*, 7652. (m) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. Also see: (n) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (o) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (p) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. Alkali-metal-mediated amination of thiadiazoles with NH_2−OH: (q) Rao, V. R.; Srinivasan, V. R. *Indian J. Chem.* **1965**, *3*, 417.

(8) For selected examples of C−N bond formation with chloro-amines or -amides, see: (a) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709. (b) Tsuritani, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 3246. (c) Göttlich, R. *Synthesis* **2000**, 1561. (d) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (e) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (f) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516. (g) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (h) Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 8325. (i) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196.

(9) (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.

(10) The isolated *n*-Bu derivative **5aa** was stable in the presence of a catalytic amount of $Cu(OTf)_2$ and excess of LiO-*t*-Bu and was recovered in 95% yield after 6 h. Thus, we speculate that both steric bulkiness and the electron-donating nature of *t*-Bu may induce the unusual deprotection.

(11) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Rauniyar, V.; Wang, Z. J.; Burks, H. E.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 8486.

(12) (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).

(13) (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.