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Facile and efficient synthesis of polyfunctionalized benzofurans: three-component coupling reactions from an alkynylsilane, an *o*-hydroxybenzaldehyde derivative, and a secondary amine by a Cu(I)–Cu(II) cooperative catalytic system

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Abstract

The combination of 5 mol % $Cu(OTf)_2$ and CuCl in the presence of DMAP effectively catalyzed a three-component coupling reaction involving an alkynylsilane, an *o*-hydroxybenzaldehyde derivative, and a secondary amine. The reaction proceeded via intramolecular 5-*exo*-*dig* cyclization, resulting in direct synthesis of the corresponding benzofuran derivatives in moderate to excellent yields.

Keywords: Copper catalyst; Multi-component reaction; Benzofuran; Alkynylsilane

Multi-component reactions (MCR) are attractive to many organic and pharmaceutical chemists, as these reactions allow construction of basic and important compounds, that serve as molecular skeletons for many naturally occurring products and biologically active substances in a single step.[1] Among the MCR, Mannich or Mannich-type reactions have been widely used as central and practical reactions.[2–4] Petasis and co-workers recently developed an improved Mannich-type reaction, in which a boronic acid, such as aryl/vinyl boronic acid, is used as an effective and easy-to-handle nucleophile.[5] Development of this synthetic protocol permits facile production of a variety of amine derivatives. Alternatively, organosilicon compounds have been employed as convenient partners in Hiyama coupling reactions, due to their availability, relatively low toxicity and high tolerance of functional groups.[6,7] However, use of common organosilicon compounds, such as alkynylsilanes, as the substrate in multi-component coupling reactions, such as the Petasis reaction, has not been extensively examined.[8,9] Thus, based on our previous studies,[10] the focus of our research shifted to the development of a novel three-component coupling reaction using an aldehyde, an amine, and an organosilicon compound, such as an alkynylsilane, to produce a propargylic amine. During ongoing research toward this goal, we found that use of *o*-hydroxybenzaldehyde as the aldehyde leads to the production of a benzofuran derivative via intramolecular 5-*exo*-*dig* cyclization through a propargylamine derivative. The synthesis of polysubstituted benzofurans is of considerable interest to organic and pharmaceutical chemists.[11] In this letter, we report a facile and practical preparation of polyfunctionalized benzofuran derivatives via both a Cu-cocatalyzed three-component coupling reaction from an *o*-hydroxybenzaldehyde derivative, a secondary amine, and an alkynylsilane, and the subsequent intramolecular cyclization.

Initially, we examined the three-component coupling reaction of 1-phenyl-2-(trimethylsilyl)acetylene (**1a**), *o*-hydroxybenzaldehyde (**2a**), and piperidine (**3a**) using a typical copper catalyst. When the reaction mixture

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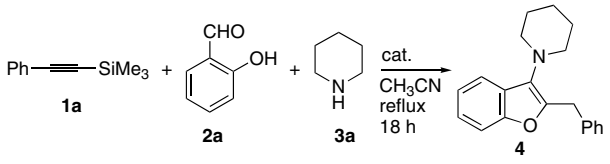
comprising the alkynylsilane (1.5 equiv), the aldehyde (1 equiv), and the secondary amine (1.2 equiv) was treated with 5 mol % $Cu(OTf)_2$ under CH_3CN reflux conditions, the expected cascade reaction, involving both alkynylation and subsequent intramolecular 5-*endo* cyclization, proceeded, producing the desired benzofuran derivative **4** in 35% yield.[12] The structure of benzofuran **4** was determined from spectral data. Thus, to improve the chemical yield, we ran the reaction using both different molar ratios of the substrate and other copper catalysts. The results are summarized in Table 1. When CuCl was used, the chemical yield decreased slightly (run 2). Additionally, a copper catalyst, such as CuOTf and Cu_2O, was ineffective for the reaction (runs 3 and 4). Interestingly, when the reaction was performed using a catalytic system consisting of both $Cu(OTf)_2$ and CuCl, the yield improved to 60% (run 5). Additionally, this result implies that the excess base promotes intramolecular cyclization, enhancing the chemical yield. Thus, we changed the molar ratio of piperidine to other substrates. For example, when the reaction was carried out with 2 equiv of amine to 1 equiv of aldehyde, the yield decreased to 49% (run 6). In contrast, reducing the molar ratio of the base to aldehyde to 0.66 caused the yield to decline dramatically to only 8% (run 7). We found that the product yield was extremely dependent on the molar ratios of the amine. Moreover, increasing the amount of catalyst to 10 mol % did not improve reaction yield, probably due to deactivation of the amine nucleophile by the coordination of the copper catalyst (runs 8 and 9).

Based on the result shown in Table 1, we then investigated several bases as an additive to enhance the cascade reaction. The results are summarized in Table 2. When the reaction was run under standard conditions using a typical tertiary amine, such as Et_3N or *i*-Pr_2NEt, the product was obtained in 41% and 44% yield, respectively. Propargylic amine, which is the reaction precursor of benzofuran **4** (runs 1 and 2), was also produced. DBU was ineffective. However, bases with pyridine skeletons

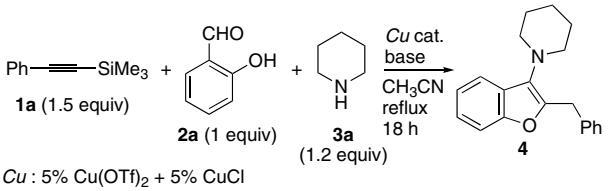
Table 1
Examination of reaction conditions using copper catalysts



Run	Cat. (mol %)	Ratio **1a**:**2a**:**3a**	Yield of **4**[a] (%)
1	$Cu(OTf)_2$ (5)	1.5:1.0:1.2	35
2	CuCl (5)	1.5:1.0:1.2	27
3	CuOTf (5)	1.5:1.0:1.2	21
4	Cu_2O (5)	1.5:1.0:1.2	7
5	$Cu(OTf)_2$ (5) + CuCl (5)	1.5:1.0:1.2	60
6	$Cu(OTf)_2$ (5) + CuCl (5)	1.5:1.0:2.0	49
7	$Cu(OTf)_2$ (5) + CuCl (5)	1.5:1.5:1.0	8
8	$Cu(OTf)_2$ (10) + CuCl (10)	1.5:1.0:1.2	49
9	$Cu(OTf)_2$ (10)	1.5:1.0:1.2	31

[a] NMR yield.

Table 2
Effect of a base



Run	Base (1 equiv)	Yield[a,b] (%)
1	Et_3N	41 (11)
2	*i*-Pr_2NEt	44 (7)
3	DBU	3 (ND)
4	Pyridine	62 (3)
5	2,6-Lutidine	48 (3)
6	DMAP	71 (ND)
7[c]	DMAP	91[d] (ND)

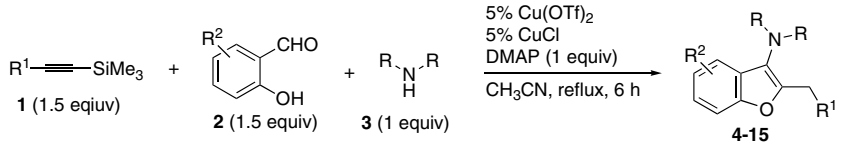
[a] NMR yield.
[b] Yield of the corresponding propargylamine is shown in parentheses.
[c] Alkynylsilane **1a** (1.5 equiv), aldehyde **2a** (1.5 equiv), and amine **3a** (1 equiv).
[d] Isolated yield.

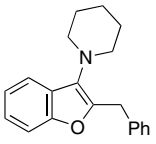
improved heterocycle yield (runs 4–6). Among the pyridine bases, addition of DMAP resulted in the highest cascade-reaction yield. Moreover, when the reaction was run using 1.5 equiv of alkynylsilane **1a**, 1.5 equiv of aldehyde **2a**, and 1 equiv of amine **3a**, in the presence of both these copper catalysts and 1 equiv of DMAP under CH_3CN reflux conditions, the yield of the corresponding benzofuran **4** dramatically improved to nearly quantitative yield (run 7). Thus, the combination of 5 mol % of both $Cu(OTf)_2$ and CuCl in the presence of DMAP gave the best coupling-reaction yield.[13,14]

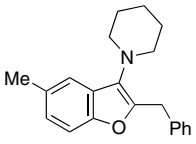
To extend the generality of the reaction, the coupling reaction was carried out under optimized conditions using various alkynylsilanes, *o*-hydroxybenzaldehydes, and secondary amines. The results are displayed in Table 3. The reaction accommodated not only electron-withdrawing groups, such as a nitro group and a halogen, but also electron-donating substituents for the *o*-hydroxyaldehyde derivative. When the reaction was run using a secondary amine, such as morpholine (**3b**), diallylamine (**3c**), or dibenzylamine (**3d**), the corresponding benzofuran derivatives were produced in moderate to excellent yields. When diallylamine was used, the yield decreased drastically to less than 30%. There is no clear explanation for the lower reactivity using this amine. Use of an alkynylsilane was generalized to versatile alkynes with an aliphatic group and a hydrogen atom, such as 1-hexyl-2-(trimethylsilyl)acetylene (**1b**) and trimethylsilylacetylene (**1c**), besides alkyne **1a** having an aromatic group. The alkynylsilane, which is derived from methyl propiolate, did not form the desired benzofuran derivative, but gave the corresponding propargylic amine derivative.

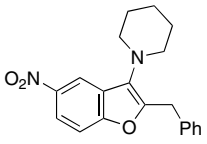
A plausible mechanism for the copper-cocatalyzed coupling reaction that yields the benzofuran derivative is shown in Scheme 1. We assumed that CuCl generates a

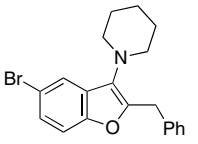
Table 3
Synthesis of various benzofuran derivatives[a]

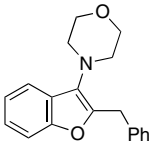


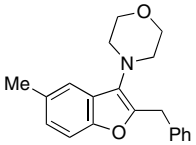

4: 91%

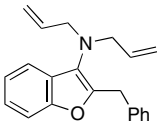

5: 90%

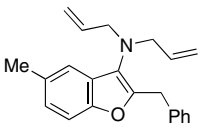

6: 50%

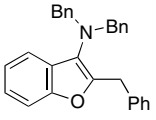

7: 65%

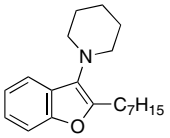

8: 99%

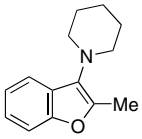

9: 97%

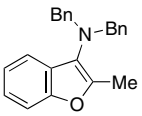

10: 27%


11: 30%

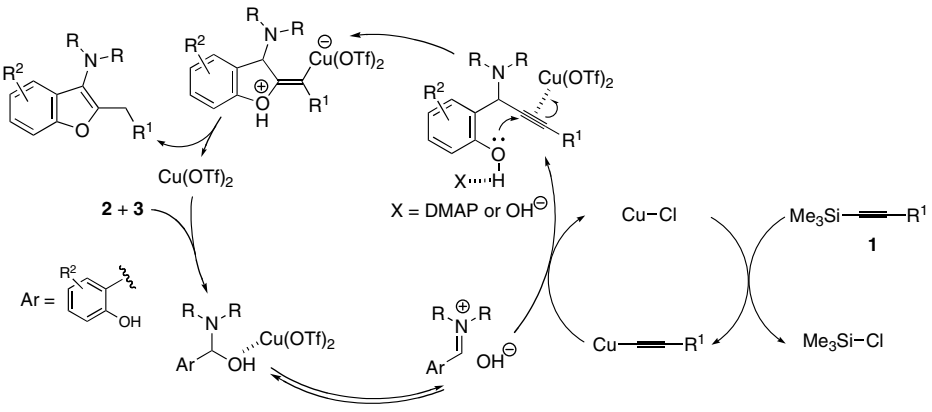

12: 78%


13: 65%


14: 10% (22%)[b]


15: 28%

[a] Isolated yield.
[b] Molar ratio of **1**:**2**:**3** = 1.5:1.0:1.2.



Scheme 1.

copper acetylide intermediate from alkynylsilane **1**,[9e,15] and that $Cu(OTf)_2$ has a dual role: (i) it behaves as a Lewis acid for in situ generation of the iminium intermediate, which forms from the starting materials, aldehyde **2** and amine **3**; and (ii) it activates the alkyne moiety to facilitate intramolecular nucleophilic attack by a hydroxy group via 5-*exo*-*dig* cyclization.

In summary, we have demonstrated that a Cu(I)–Cu(II) cooperative catalytic system effectively catalyzes a three-component coupling reaction of alkynylsilanes, *o*-hydroxybenzaldehyde derivatives, and secondary amines to produce multi-functionalized benzofuran derivatives in moderate to excellent yields. Moreover, we found that addition of a base, such as DMAP, to the reaction system enhances intramolecular 5-*exo*-*dig* cyclization of the in situ generated propargylic amine, thereby improving both the chemical and the practical yields.

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12. *General procedure for the synthesis of 3-aminobenzofuran*: To a CH_3CN solution (300 μL) in a screw-cap vial under N_2 atmosphere, alkynylsilane **1** (0.45 mmol), *o*-hydroxybenzaldehyde **2** (0.45 mmol), secondary amine **3** (0.30 mmol), DMAP (0.3 mmol), $Cu(OTf)_2$ (5.4 mg, 0.015 mmol), and CuCl (1.5 mg, 0.015 mmol) were successively added, and the vial was then sealed with a cap containing a PTFE septum. The reaction mixture was heated at 100 °C for 6 h. After completion of the reaction, the mixture was directly subjected to silica gel without the usual extraction, and was purified by flash column chromatography (hexane–AcOEt) to give the corresponding 3-aminobenzofuran in the yield shown in Table 3. Spectral data for selected novel compounds. *1-(2-Benzyl-1-benzofuran-3-yl)piperidine* (**4**): A pale brown needle (CH_2Cl_2–hexane); mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (quint, 2H, $J = 5.5$ Hz), 1.71 (quint, 4H, $J = 5.5$ Hz), 3.13 (t, 4H, $J = 5.5$ Hz), 4.15 (s, 2H), 7.15 (m, 2H), 7.19 (m, 1H), 7.27 (m, 4H), 7.33 (d, 1H, $J = 7.5$ Hz), 7.64 (d, 1H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 26.8, 32.5, 53.8, 111.5, 120.1, 121.7, 123.2, 126.3, 126.7, 128.4, 128.6, 130.2, 138.6, 148.9, 153.5. MS (EI): *m*/*z* 291 (M^+, 100%); HRMS (FAB): calcd for $C_{20}H_{22}NO$: 292.1701, found: 292.1685.
1-(2-Benzyl-5-methyl-1-benzofuran-3-yl)piperidine (**5**): A yellow needle (CH_2Cl_2–hexane); mp 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (quint, 2H, $J = 5.5$ Hz), 1.70 (quint, 4H, $J = 5.5$ Hz), 2.41 (s, 3H), 3.11 (t, 4H, $J = 5.5$ Hz), 4.13 (s, 2H), 6.97 (d, 1H, $J = 8.0$ Hz), 7.18 (m, 1H), 7.21 (d, 1H, $J = 8.0$ Hz), 7.26 (m, 4H), 7.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 26.8, 32.5, 53.7, 111.0, 120.0, 124.3, 126.2, 126.7, 128.4, 128.5, 130.0, 131.1, 138.6, 149.1, 151.9. MS (EI): *m*/*z* 305 (M^+, 100%); HRMS (EI): calcd for $C_{21}H_{23}NO$: 305.1780, found: 305.1779.
1-(2-Methyl-1-benzofuran-3-yl)piperidine (**14**): Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (quint, 2H, $J = 5.5$ Hz), 1.71 (quint, 4H, $J = 5.5$ Hz), 2.43 (s, 3H), 3.11 (t, 4H, $J = 5.5$ Hz), 7.14 (m, 2H), 7.33 (d, 1H, $J = 7.5$ Hz), 7.59 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 24.4, 26.9, 53.5, 111.0, 119.6,121.7, 122.8, 127.0, 129.5, 146.3, 153.0. MS (EI): *m*/*z* 215 (M^+, 100%); HRMS (FAB): calcd for $C_{14}H_{18}NO$: 216.1388, found: 216.1404.
13. When the reaction using phenylacetylene instead of silylacetylene **1a** was carried out under optimized conditions, the yield of **4** reduced to 75%.
14. When the reaction ran with other solvents under optimal conditions shown in Table 2, the benzofuran **4** was produced in 44% (DMF) and 40% (DMI) yields.
15. Nishihara, Y.; Takemura, M.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *620*, 282.