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# Copper-Catalyzed Ring-Opening Silylation of Benzofurans with Disilane

Hayate Saito, Keisuke Nogi, and Hideki Yorimitsu\*

Dedication

**Abstract:** Catalytic ring-opening silylation of benzofurans has been achieved by employing a copper catalyst and 1,2-di-*tert*-butoxy-1,1,2,2-tetramethyldisilane, which could be easily prepared and handled without special care. The reaction afforded (*E*)-o-( $\beta$ -silylvinyl)phenols with complete stereoselectivity. The scope of benzofurans was well explored, and functional groups such as chloro, fluoro, and acetal were compatible with the reaction conditions. DFT calculations figured out the energy profile of the silylation and the origin of the stereoselectivity. The silylated product was proved to be useful as a synthetic intermediate and subsequently underwent transformations such as Pd-catalyzed cross-coupling with iodoarenes.

Heteroaromatic compounds represent an important class of molecules of their wide variety and availability. Despite great progress of organic synthesis, catalytic functionalizations of heteroaromatic compounds are still limited to cleavage of exocyclic bonds. There are few examples of catalytic transformations with breaking their heteroaromatic cores, mainly because cleavage of endocyclic carbon-heteroatom bonds are obstructed by aromatic stabilization and high bond strength. If heteroaromatic cores could be catalytically opened and used as building blocks, such transformations would be novel and useful methodologies for organic synthesis.

As one of the pioneering works, Wenkert achieved ringopening arylation of benzofuran with the aid of a nickel catalyst and an organomagnesium reagent.<sup>[1a]</sup> Although many followers reported a series of catalytic ring-opening transformations of benzofurans, such reactions were limited to C–C bond formations (Scheme 1a).<sup>[1b–g]</sup> Very recently, Studer reported ring-opening silylation of benzofurans and indoles mediated by a silyllithium reagent (Scheme 1b).<sup>[2]</sup> Considering the importance of organosilicon compounds in modern chemistry,<sup>[3]</sup> this silylation is a potentially useful transformation of heteroarenes to expand chemical space. However, it lacks compatibility of functional groups due to the high reactivity of silyllithium species.

Recently our group has been interested in skeletal transformations of heteroarenes by employing transition metal catalysts.<sup>[4][5]</sup> To overcome the shortcomings of Studer's silylation, we envisioned that the combination of a disilane and a transition metal catalyst<sup>[6]</sup> would provide milder conditions to break heteroaromatic cores. We herein report copper-catalyzed ring-opening silylation of benzofurans with the aid of 1,2-di-*tert*-butoxy-

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1,1,2,2-tetramethyldisilane<sup>[7]</sup> (Scheme 1c). This unexplored disilane has proved to be uniquely effective to this end.

(a) C–C bond formations



THF/pyridine

25 °C



Ò*t*Bu

tBuŐ

Optimization of the reaction conditions is described in Table 1 (For more details, see Supporting Information). We carried out the reactions of benzofuran (1a) with disilane 2a in the presence of a base and a copper catalyst at room temperature. As an activator of the disilane, KOtBu was specifically effective for the reaction while other inorganic and organic bases including NaOtBu did not give the product 3a. (entries 1-5). Although NHC and phosphine ligands on copper catalysts accelerated the conversion of 1a, decomposition of 3a was also promoted by those ligands and unidentified byproducts showing broad <sup>1</sup>H NMR signals around the aromatic region were formed. Finally, we found that simple CuCl was the better catalyst for this reaction than any other copper catalysts because decomposition of 3a was reduced (entry 9). The choice of solvent was fatal for this silylation. Only THF and pyridine gave 3a although other solvents including Et<sub>2</sub>O and 1,4-dioxane were totally ineffective (entries 10-14). THF/pyridine co-solvent systems improved the yields, and the best ratio of THF/pyridine was determined to be 3/1 (entry 15).

Table 1. Optimization of reaction conditions.[a]

	-0 + -S # tBuO	i-Si— OfBu	Cu catalyst base	OH OtBu
1a		2a	solvent, 25 °C	3a
entry	Cu catalyst	base	solvent	yield <sup>[b]</sup> /%
1	CuCl(IPr)	CsF	THF	0
2	CuCl(IPr)	Et₃N	THF	0

.OtBu

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3	CuCl(IPr)	KN(SiMe <sub>3</sub> ) <sub>2</sub>	THF	0
4	CuCl(IPr)	NaO <i>t</i> Bu	THF	0
5	CuCl(IPr)	KO <i>t</i> Bu	THF	17
6	CuCl(dppe)	KO <i>t</i> Bu	THF	20
7	CuBr(PPh <sub>3</sub> ) <sub>3</sub>	KO <i>t</i> Bu	THF	25
8	Cul	KO <i>t</i> Bu	THF	17
9	CuCl	KO <i>t</i> Bu	THF	48
10 <sup>[c]</sup>	CuCl	KO <i>t</i> Bu	THF	68
11 <sup>[c]</sup>	CuCl	KO <i>t</i> Bu	Et <sub>2</sub> O	0
12 <sup>[c]</sup>	CuCl	KO <i>t</i> Bu	1,4-dioxane	0
13 <sup>[c]</sup>	CuCl	KO <i>t</i> Bu	DMF	0
14 <sup>[c]</sup>	CuCl	KO <i>t</i> Bu	pyridine	67
15 <sup>[c]</sup>	CuCl	KO <i>t</i> Bu	THF/pyridine (3/1)	84 (80) <sup>[d]</sup>

[a] Conditions: **1a** (0.3 mmol), 2 equiv disilane, 5 mol% catalyst, 3 equiv base, solvent (0.2 mL), 25 °C, 12 h. [b] Determined by <sup>1</sup>H NMR. [c] Conditions: **1a** (0.3 mmol), 3 equiv disilane, 20 mol% catalyst, 4 equiv base, solvent (0.2 mL total), 25 °C, 40 h. [d] Isolated yield.

The silylated product was obtained only as the (E)-isomer, and the (Z)-isomer as well as the cyclic product, an oxasilin derivative, was not observed at all. Although we tested other vinyl ethers such as methyl styryl ether and *tert*-butyldimethylsilyl styryl ether for this silylation, none of them gave the corresponding silylation product.



Scheme 2. Scope of silicon sources 2. Yields were determined by <sup>1</sup>H NMR.

Disilane **2a** could be handled under air and prepared in one step from commercially available 1,2-dichloro-1,1,2,2tetramethyldisilane by Denmark's procedure<sup>[6g]</sup> with some modifications. Disilane **2a** showed uniquely excellent reactivity in this silylation. Other disilanes and a silylborane were also tested as silicon sources (Scheme 2). In the case of 1,2-diethoxy-1,1,2,2-tetramethyldisilane **(2b)**, the corresponding silylated product was not obtained but byproducts giving messy signals in <sup>1</sup>H NMR spectra were observed despite full conversion of **1a**. We assume that the vinylsilane product was decomposed under the reaction conditions due to the small steric hindrance around an ethoxy group. In the case of disilane **2a**, a bulky *tert*-butyl group would prevent the silylation product from degradation during the reaction. Unsymmetrical disilane **2c** gave two silylation products, **3a** and trimethylvinylsilane **3a'**, derived from two different silicon atoms in **2c** with no selectivity. Hexamethyldisilane (**2d**) did not react with **1a** at all and both **1a** and **2d** were recovered quantitively. The reaction with silylborane **2e** which is often used as a silylanion equivalent<sup>[8]</sup> did not afford the corresponding silylation product and a complicated mixture was obtained.



Scheme 3. Scope of substrates. [a] 1.84 g (7.4 mmol) of 3a was obtained. [b] 4 equiv disilane, 5 equiv KO*t*Bu. [c] 30 mol% CuCl, 60 h. [d] NMR yield. [e] 25 equiv Mel was added before workup.

With the optimal conditions in hand, we investigated the scope of benzofurans **1** (Scheme 3). Both chloro and fluoro moieties in **1d** and **1e** were compatible with the reaction conditions since copper complexes are reluctant to undergo oxidative addition. A diethyl acetal unit survived under the conditions and the corresponding product **3g** was obtained in good yield without deprotection. Notably, a pinacolatoboryl group (Bpin) was partly endured under the silylating conditions although the product **3h** was gradually decomposed via transmetalation in the presence of KO*t*Bu and copper species. Unfortunately, carbonyl moieties such as ester and amide were incompatible due to the high nucleophilicity of silylcopper species generated *in situ*.

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Monocyclic heteroaromatic cores such as furan and thiophene in 3i and 3j did not react and the benzofuran skeleton was selectively cleaved. Although a methyl group and a phenyl group at the 7-positions of benzofurans slightly lowered the reactivity, the corresponding products 3k and 3l were obtained in moderate yields. Steric hindrance at the 2- or 3-position retarded the reaction (not shown) probably due to interruption of coordination of the olefinic moiety to the copper catalyst. This silylation could be also applied to  $\pi$ -extended benzofurans, and naphthofuran **1m** was converted into silvlvinylnaphthol 3m in excellent yield. Naphthobifuran 1n did not undergo the expected double silvlation and the monosilylated naphthofuran 3n-Me was obtained after methylation of the phenoxide. The selective monosilylation would be achieved because a negative charge on the phenoxide moiety of the monosilylated product would prevent a copper catalyst from coordination to the remaining furan moiety for second silvlcupration (vide infra).



Scheme 4. A plausible reaction mechanism.

Scheme 5. Energy profile of the silylation with 2a.

G (kcal/mol)

A plausible reaction mechanism is shown in Scheme 4. As the initial step, silylcopper species would be generated from the disilane 2a and CuOtBu,<sup>[9]</sup> which should be formed from CuCl and KOtBu in situ. After coordination of the olefinic moiety of 1a to the copper center, silvlcupration would take place to form the intermediate Cu-1a-Si. Subsequent β-oxygen elimination would result in formation of the silvlated product 3a-K and regeneration of CuOtBu. Catalytic ring-opening processes of benzofurans via 1,2-addition and  $\beta$ -elimination are known as exemplified by rhodium- or iron-catalyzed ring-opening arylations of benzofurans.<sup>[1e,f]</sup> As a reaction of a related copper species with heteroarenes, conjugate addition of borylcopper species to 2alkoxycarbonylindoles without  $\beta$ -elimination was also reported.<sup>[10]</sup>

To support the proposed reaction pathway in Scheme 4, we carried out DFT calculations of the silvlation (Scheme 5). [11-14] Considering the experimental observations that strongly coordinating solvents such as THF and pyridine which would reduce aggregation of copper species were specifically effective for this silvlation, monomeric copper species were employed in this computational study. At the initial step (1a to INT1), pyridinecoordinated neutral silvlcopper undergoes complexiation with 1a while anionic and electron-rich silvlcuprate with an anionic ligand (tBuO- or CI-) shows weaker interaction with 1a.[15] On the other hand, for the  $\beta$ -elimination step (INT3 to INT4), it is important to form the anionic copper center by ligand exchange (INT2 to INT3), which is expected to increase the electron density of the C-Cu bond. In the case of the corresponding pyridine-ligated neutral copper species instead of INT3, the  $\beta$ -elimination requires a larger activation energy than the case of INT3 (Details of the other pathway of  $\beta$ -elimination is described in Scheme S1). As well as the status of the copper center, bidentate coordination of the two oxygen atoms to the potassium cation would accelerate the elimination of the phenoxy moiety by the Lewis acidity of Finally silylcopper species would be potassium cation. regenerated from disilane 2a and CuOtBu unit in INT4 by forming a strong Si-OtBu bond.

The activation barriers of the silylcupration (**INT1** to **TS1**) and the  $\beta$ -elimination (**INT3** to **TS2**) in this model were estimated to be 21.5 kcal mol<sup>-1</sup> and 14.1 kcal mol<sup>-1</sup>, respectively, and the rate-determining step of the silylation would be the silylcupration process. These results agree with the experimental result that 2-silyldihydrobenzofuran derived from **INT2** or **INT3** was not



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detected at all after acidic workup. In addition, the  $\beta$ -elimination proceeds as *syn*-elimination bridged by KO*t*Bu, which would be the origin of the complete *E*-selectivity of the product.

Finally we conducted transformations of silylation product **3a** to prove the synthetic utility of our silylation. Cross-couplings of **3a** with iodoarenes by using SingaCycle-A1<sup>[16]</sup> as a palladium catalyst in the presence of tetrabutylammonium fluoride took place in excellent yields (Scheme 6a). The cross-coupling could employ a substrate with an ester moiety which could not endure under Wenkert's conditions.<sup>[1a]</sup> According to Kishi's procedure,<sup>[17]</sup> Compound **3a** was also converted to the corresponding (*E*)-iodoalkene **5** protected by a silyl group on the phenol moiety (Scheme 6b).

(a) Pd-catalyzed cross-coupling



Scheme 6. Transformations of 3a. IPr = 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene, NIS = *N*-iodosuccinimide.

In conclusion, we have established catalytic ring-opening silylation of benzofurans by employing a combination of a copper catalysis and 1,2-di-*tert*-butoxy-1,1,2,2-tetramethyldisilane (**2a**), which was easily prepared and significantly effective for this silylation. DFT calculations provided insight into the reaction mechanism and stereoselectivity of this silylation. In addition, transformations of the silylated product was demonstrated to prove the products to be nice building blocks in organic synthesis.

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#### **Conflict of interest**

The authors declare no conflict of interest

**Keywords:** Benzofurans • Copper catalyst • DFT calculations • Disilane • Silylation

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- [13] Although optimization of the structure of INT4 was almost completed, the flexibility of the coordinating THF disturbed convergence despite many attempts.
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Copper-catalyzed ring-opening silylation of various benzofurans proceeds with 1,2di-*tert*-butoxy-1,1,2,2-tetramethyldisilane to afford (*E*)-o-hydroxystyrylsilanes of synthetic use. DFT calculations figured out the energy profile of the completely *E*selective silylation that includes rate-determining silylcupration and subsequent  $\beta$ oxygen elimination. H. Saito, K. Nogi, H. Yorimitsu\*

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