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Synthesis of Dibenzofurans by Cu-Catalyzed Deborylative Ring Contraction of Dibenzoxaborins

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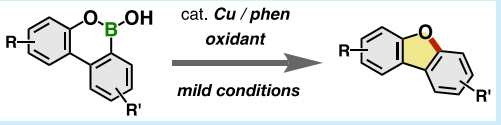
ABSTRACT: An efficient transformation of dibenzoxaborins to dibenzofurans by deborylative ring contraction was achieved under mild conditions using a copper catalyst. The method showed a broad substrate scope enabling the preparation of various dibenzofurans, including those bearing a functional group. The ready availability of various dibenzoxaborins enhances the utility of this method, as demonstrated by the regiodivergent synthesis of dibenzofurans.



Dibenzofuran is a heterocyclic core structure found in various bioactive compounds[1] and organic materials.[2] Dibenzofuran derivatives have been synthesized via numerous methods that can be mainly categorized as intramolecular C−C bond formation[3] and intramolecular C−O bond formation (Figure 1).[1d,2b,4] As many of previous methods require high

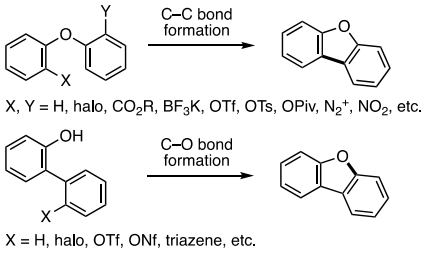


Figure 1. Representative methods for dibenzofuran synthesis.

reaction temperatures (>100 °C) and suffer from substrate scope, a novel method to synthesize a diverse range of dibenzofurans under mild conditions is sought-after.

To achieve the synthesis of dibenzofurans under mild conditions (e.g., weak base, ambient temperature), we focused on the synthesis of dihydrobenzofuran via Cu-catalyzed deborylative ring contraction of dihydrobenzoxaborin previously reported by Sheppard and co-workers (Figure 2A).[5] We anticipated that dibenzofuran could be synthesized under mild conditions by a similar process of Chan−Evans−Lam[6]-type intramolecular C−O bond formation (Figure 2B). In this context, we previously developed a concise synthetic method for 6-hydroxy-6*H*-dibenz[*c*,*e*][1,2]oxaborins, which we referred to as dibenzoxaborins, via boron-selective Suzuki−Miyaura cross-coupling of *o*-borylphenols with aryl halides or triflates bearing an *o*-boryl group protected by 1,8-diaminonaphthalene (dan)[7] group.[8] Herein, we report an efficient synthetic method for diverse dibenzofuran derivatives that was achieved under gentle and aerobic conditions.

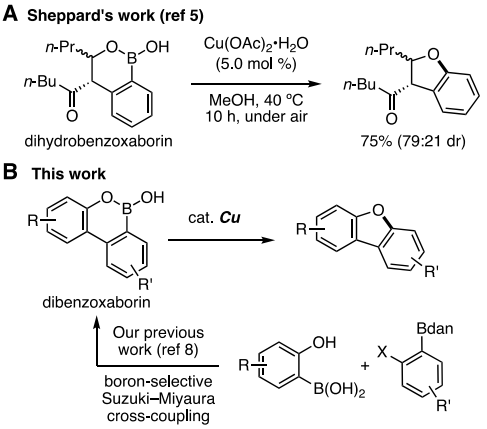


Figure 2. Deborylative ring contraction reactions. (A) Pioneering work reported by Sheppard and co-workers synthesizing dihydrobenzofuran via the Cu-catalyzed deborylative ring contraction of dihydrobenzoxaborin. (B) Concept of the proposed study: synthesis of dibenzofurans via deborylative ring contraction of readily synthesizable dibenzoxaborins.

Initially, we screened the conditions for preparing dibenzofuran (**2a**) from dibenzoxaborin **1a** (Table 1).[9] Under the reported conditions for the synthesis of dihydrobenzofuran from dihydrobenzoxaborin,[5] dibenzofuran (**2a**) was obtained in 20% yield from dibenzoxaborin **1a** (entry 1). However, a significant amount of 2-phenylphenol was also formed as a major product via protodeborylation. This result showed that the C−O bond-forming step, which is apparently the final step of the catalytic cycle, is sluggish compared to that

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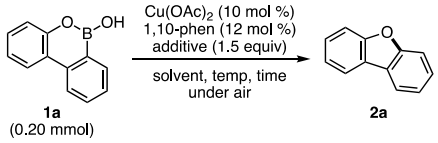
Table 1. Optimization of Reaction Conditions



entry	additive	solvent	temp (°C)	time (h)	yield[a] (%)
1[b]	none	MeOH	40	40	20
2[c]	BzOOBz[d]	1,2-DCE	60	20	32
3[c]	*t*-BuOOBz[d]	1,2-DCE	80	20	77
4	Cs_2CO_3	EtOH	40	19	56
5	Ag_2CO_3	EtOH/H_2O[e]	40	19	quant (95)[f]
6	Ag_2CO_3	EtOH/H_2O[e]	rt	46	quant (96)[f]
7	Ag_2CO_3	dehyd. EtOH	40	16	71
8[g]	Ag_2CO_3	EtOH/H_2O[e]	40	16	89
9	AgOAc	EtOH/H_2O[e]	40	19	21
10	$AgNO_3$	EtOH/H_2O[e]	40	19	4
11	Ag_2O	EtOH/H_2O[e]	40	16	93 (90)[f]
12	Ag_2CO_3[h]	EtOH/H_2O[e]	40	16	51
13	Ag_2CO_3[h]	EtOH/H_2O[e]	40	19	86[i]

[a]Yields were determined by ^{1}H NMR analysis unless otherwise noted. [b]No ligand was added. [c]Under argon. [d]2.5 equiv of additive was used. [e]The ratio of EtOH/H_2O was 20:1. [f]Isolated yields shown in parentheses. [g]The reaction was performed in degassed EtOH and H_2O under argon. [h]0.15 equiv of additive was used. [i]The reaction was performed using 1.0 g (5.1 mmol) of **1a**. 1,10-phen = 1,10-phenanthroline.

of benzoxaborin formation. In an early optimization study, we identified that performing the reaction in 1,2-dichloroethane (1,2-DCE) by using 1,10-phenanthroline as a ligand with the addition of an oxidant such as benzoyl peroxide or benzoyl *tert*-butyl peroxide improved the yield of **2a** (entries 2 and 3). However, this entailed relatively harsh conditions involving the use of a strong oxidant and high reaction temperatures. Since the addition of an organic or inorganic base is often effective for promoting the cross-coupling of phenols with organoboronic acids through activation of the boron center,[10] we further screened for bases and found that the reaction proceeded at 40 °C in ethanol by adding cesium carbonate (entry 4). The addition of silver carbonate gave the best result, affording **2a** almost quantitatively (entry 5). A comparable result was obtained when conducting the reaction over a prolonged period of time at room temperature (entry 6). Performing the reaction in wet ethanol was significant as the yield of **2a** decreased when the reaction was performed in dehydrated ethanol (entry 7). Intriguingly, **2a** was obtained in good yield when the reaction was carried out in degassed ethanol and water under argon (entry 8). This result indicates that silver carbonate works as an oxidant, although its potential as a base cannot be excluded. Among other silver sources examined, silver acetate and silver nitrate were less effective (entries 9 and 10), whereas silver oxide showed comparable activity to silver carbonate (entry 11). When the reaction was performed using 15 mol % of silver carbonate, **2a** was obtained in 51% yield (entry 12), indicating that both the silver(I) species and molecular oxygen (O_2) works as oxidants. Additionally, this transformation was scalable without further optimization, as demonstrated in a reaction using 1.0 g (5.1 mmol) of **1a**, affording **2a** in a reasonable yield (entry 13).

We propose that a catalytic cycle for this reaction could involve a single-electron oxidation step of aryl copper (Figure 3).[11] The proposed catalytic cycle starts from the deborylative transmetalation of dibenzoxaborin with copper(II), which

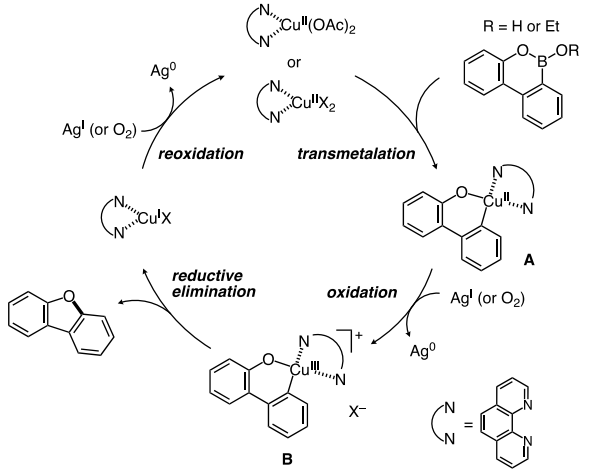


Figure 3. Proposed catalytic cycle.

affords oxa-cupra cycle intermediate **A**. Intermediate **A** is oxidized by either a silver(I) species or oxygen to form trivalent copper intermediate **B** that undergoes facile C−O bond formation to afford dibenzofuran and a copper(I) species. Finally, reoxidation of the copper(I) species with either a silver(I) species or oxygen regenerates the divalent copper(II) species to complete the catalytic cycle.

To assess the validity of the proposed catalytic mechanism, two reactions using stoichiometric amounts of the reagents with and without silver carbonate were conducted (Figure 4).

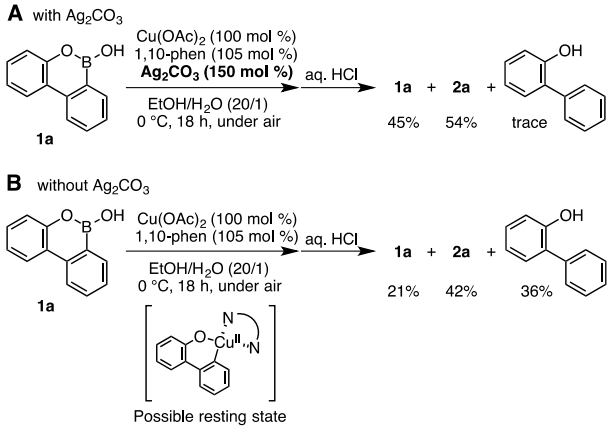


Figure 4. Stoichiometric reactions. Yields were determined by ^{1}H NMR analysis.

After the mixtures were stirred at 0 °C for 18 h, the reactions were quenched by aqueous HCl. Although only trace amounts of the protodeborylated product, 2-phenylphenol, were produced in the reaction performed in the presence of silver carbonate (Figure 4A), significant amounts of 2-phenylphenol were obtained from the silver carbonate-free reaction (Figure 4B). This indicates that the silver reagent dramatically facilitated the oxidation of divalent copper intermediate **A** and the resting state of the catalytic cycle is neither oxa-cupra intermediate **A** nor **B**.

We also investigated the relationship between the product yield and the amount of silver carbonate or the copper catalyst

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(Figure 5). Analyses of the reaction stoichiometry with silver carbonate in the Cu-catalyzed reaction showed no significant

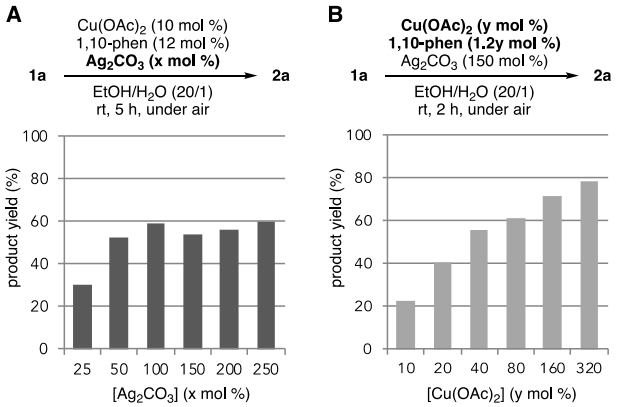


Figure 5. Reaction stoichiometry analyses.

changes in the product yield after 5 h using more than 50 mol % of silver carbonate (Figure 5A). The yield of **2a** was slightly lower when 25 mol % of silver carbonate was employed, which is consistent with the idea that the reaction requires a stoichiometric amount of silver carbonate as an oxidant. Contrastingly, with increased amounts of the copper catalyst, an increase in the product yield was observed (Figure 5B). In addition, the reaction using a stoichiometric amount of $Cu(OAc)_2$ without the ligand under an inert atmosphere afforded only trace amounts of the product, while the reaction partially proceeded in the presence of the ligand,[9] indicating that the optimized catalytic conditions facilitated the transmetalation step. These results suggest that the transmetalation of the starting substrate with copper is likely the turnover-limiting step, although the possibility for the reoxidation step cannot be ruled out.

The optimized reaction conditions were applicable to the deborylative ring contraction of a wide range of dibenzoxaborins that were prepared according to our previously reported method[8] (Figure 6). Substrates bearing electron-donating or -withdrawing groups at different positions of either of their two benzene rings efficiently afforded the corresponding dibenzofurans **2b**−**2j**. The reaction of dibenzoxaborin with substituents at both benzene rings similarly afforded disubstituted dibenzofuran **2k**. The method was also applicable to multisubstituted substrates as demonstrated by the synthesis of trisubstituted **2l**, tetrasubstituted **2m**, and more structurally complicated naphtho[1,2-*b*]benzofuran **2n**. Pyridine-fused benzofuran **2o** was also accessible using this method, although stoichiometric amounts of copper catalyst were needed to promote the reaction. Unfortunately, an attempt to prepare dihydrobenzofuran **2p** from dihydrobenzoxaborin under the conditions was unsuccessful.

The prior functionalization of unsubstituted dibenzoxaborin **1a** followed by the deborylative ring contraction enabled facile synthesis of various functionalized dibenzofurans (Scheme 1). For example, bromination and iodination of **1a** afforded the corresponding 2-halogenated products **1q** and **1r**, respectively, with high regioselectivity. The brominated position of **1q** was confirmed by X-ray crystallography and NMR analyses. The halogenated dibenzoxaborins **1q** and **1r** were further derivatized by Pd-catalyzed cross-coupling reactions to afford the corresponding cross-coupling products such as **1s** and **1t**

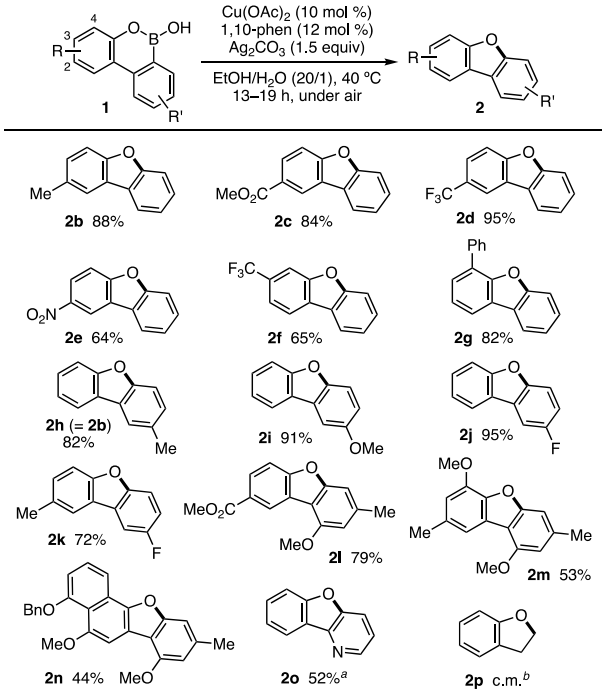
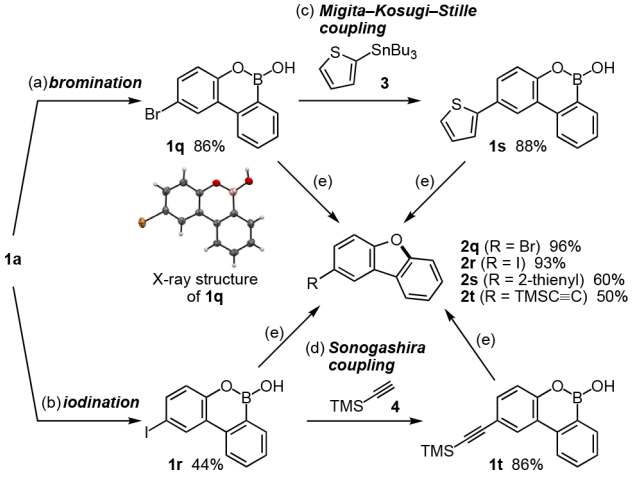


Figure 6. Substrate scope. [a]100 mol % of $Cu(OAc)_2$ and 120 mol % of 1,10-phenanthroline were used. [b]Complex mixture.

Scheme 1. Functionalization of Dibenzoxaborins[a]



[a]Key: (a) NBS (1.1 equiv), CH_2Cl_2, rt, 2 h; (b) I_2 (1.0 equiv), Ag_2SO_4 (0.50 equiv), EtOH, rt, 30 min; (c) $Pd(OAc)_2$ (5.0 mol %), SPhos (10 mol %), **3** (1.1 equiv), $K_3PO_4 \cdot nH_2O$ (1.5 equiv), toluene, 65 °C, 18 h; (d) $PdCl_2(PPh_3)_2$ (5.0 mol %), CuI (10 mol %), **4** (3.0 equiv), toluene/Et_3N (1/1), rt, 3 h; (e) $Cu(OAc)_2$ (10 mol %), 1,10-phenanthroline (12 mol %), Ag_2CO_3 (1.5 equiv), $EtOH/H_2O$ (20/1), 40 °C, 15 h.

while leaving the C−B bonds untouched. All functionalized dibenzoxaborins **1q**−**1t** were efficiently transformed to dibenzofurans **2q**−**2t** by the deborylative ring contraction, evidencing the broad scope of the method.

Using the deborylative ring contraction in combination with the dibenzoxaborin synthesis,[8] regiodivergent synthesis of dibenzofurans was achieved starting from the same *o*-borylated phenol. For example, *o*-borylated estradiol derivative **5**,[12] easily prepared by Ir-catalyzed *o*-borylation of phenols,[13] was converted to dibenzoxaborin **1u** by the boron-selective

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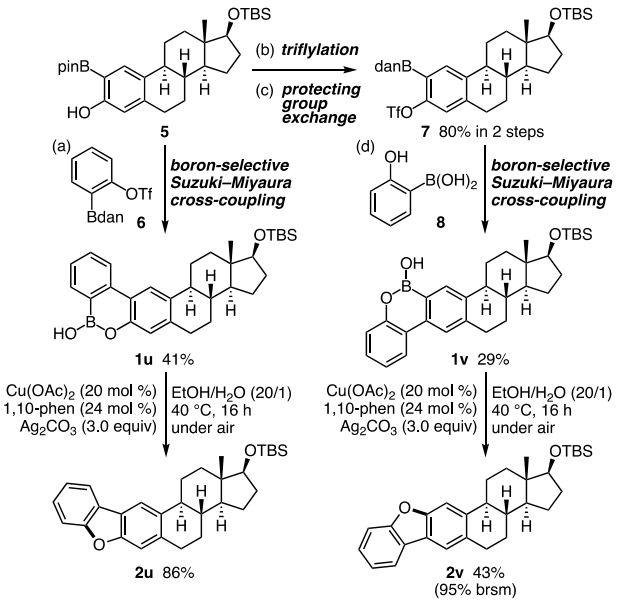
Suzuki−Miyaura coupling with dan-protected *o*-borylphenyl triflate **6** (Scheme 2). On the other hand, *o*-borylated estradiol

Scheme 2. Stereodivergent Synthesis of Dibenzofurans[a]



[a]Key: (a) $Pd(OAc)_2$ (5.0 mol %), CyJohnPhos (10 mol %), **6** (1.0 equiv), $K_3PO_4{\cdot}nH_2O$ (1.0 equiv), dioxane/H_2O (10/1), 90 °C, 1 h; (b) Tf_2O (1.1 equiv), *i*-Pr_2NEt (2.0 equiv), CH_2Cl_2, −78 °C, 30 min; (c) $FeCl_3$ (10 mol %), imidazole (1.5 equiv), H_2dan (1.2 equiv), MeCN/H_2O (4/1), rt, 1 h; (d) $Pd(OAc)_2$ (5.0 mol %), CyJohnPhos (10 mol %), **8** (1.5 equiv), $K_3PO_4{\cdot}nH_2O$ (1.5 equiv), dioxane/H_2O (10/1), 90 °C, 16 h.

derivative **5** was transformed to dan-protected *o*-borylaryl triflate **7** by triflylation and subsequent protecting group exchange.[14] Suzuki−Miyaura cross-coupling of **7** with (2-hydroxyphenyl)boronic acid (**8**) afforded dibenzoxaborin **1v**, which is a regioisomer of **1u**. The deborylative ring contraction of **1u** and **1v** afforded regioisomeric dibenzofurans **2u** and **2v**, respectively.

In summary, we have developed an efficient method for synthesizing dibenzofurans via Cu-catalyzed deborylative ring contraction of dibenzoxaborins. The mild reaction conditions used for the method, coupled with the ready availability of dibenzoxaborins, allows for the synthesis of diverse dibenzofurans including those with functional groups. Further studies regarding the application of this method, including the synthesis of bioactive dibenzofurans, are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02584.

Experimental procedures and characterization for new compounds including copies of NMR spectra and the X-ray crystallographic data for **1q** (PDF)

Accession Codes

CCDC 2003738 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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