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Cu-Catalyzed Dehydrogenative C−O Cyclization for the Synthesis of Furan-Fused Thienoacenes

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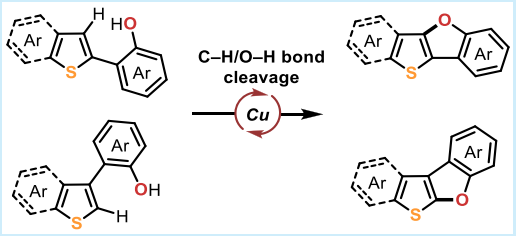
ABSTRACT: The first Cu-catalyzed dehydrogenative C−O cyclization for the synthesis of furan-fused thienoacenes is described. A variety of heteroacenes including a thieno[3,2-*b*]furan or a thieno[2,3-*b*]furan skeleton were synthesized by intramolecular C−H/O−H coupling. The use of a mixed solvent of *N*-methyl-2-pyrrolidone, ethylene glycol monomethyl ether, and toluene was essential for suppressing side reactions and efficiently promoting the reaction. Double C−O cyclization was also conducted to afford highly *π*-expanded furan-fused thienoacenes.

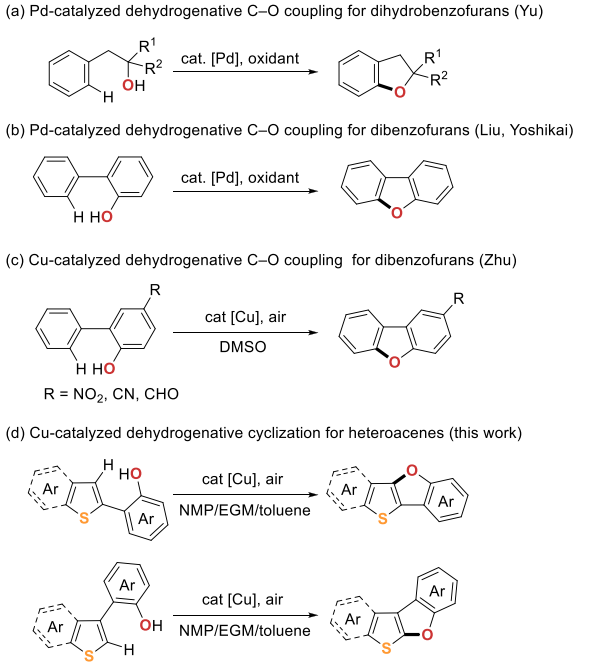


The formation of carbon−oxygen bonds plays a significant role in organic synthesis because C−O bonds are an abundant and ubiquitous moiety in nature,[1] pharmaceuticals,[2] and organic materials.[3] A modern method for constructing C−O bonds is the Buchwald−Hartwig etherification reaction.[4] Recently, transition-metal-catalyzed dehydrogenative coupling reactions have also received considerable attention as a novel and straightforward method for constructing carbon−heteroatom bonds with high atom economy.[5] Whereas there have been many reports on dehydrogenative C−N couplings,[6] there have been few reports on the construction of C−O bonds by dehydrogenative coupling.[7,8]

In 2010, Yu and coworkers reported the first Pd-catalyzed dehydrogenative C−O cyclization to form dihydrobenzofurans under oxidative conditions (Scheme 1a).[7a] The following year, Liu[7b] and Yoshikai[7c] independently reported the Pd-catalyzed dehydrogenative synthesis of dibenzofuran derivatives (Scheme 1b). Zhu and coworkers reported that copper catalysts could also be used for dehydrogenative etherifications (Scheme 1c).[7d] In 2013, Yu,[8a] Wang,[8b] Martin,[8c] and Gevorgyan[8d] reported the C−O cyclization of carboxylic acids to give lactones. To the best of our knowledge, the scope of these reported reactions has been limited to aryl ethers and lactones and there have been no reports on the construction of heteroaromatic ethers.

Meanwhile, heteroacenes, acenes involving heteroaromatic rings, have attracted attention as functional organic materials with excellent atmospheric stability and solubility. In particular, heteroacenes including thiophene,[9] furan,[10] or both[11] have been recognized for their properties as organic field effect transistors (OFETs). We have been interested in the development of novel synthetic methods for heteroacenes.[12] Our attention has recently been focused on dehydrogenative C−O cyclization for the construction of furan-fused thienoacenes. In our preliminary study, Pd-catalyzed dehydro-

Scheme 1. Representative Transition-Metal-Catalyzed Dehydrogenative C−O Coupling Reactions



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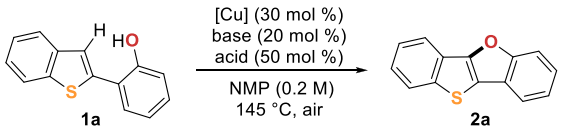
genative C−O cyclization was examined under several conditions, but the desired reaction did not proceed efficiently. We next turned our attention to Cu-catalyzed reactions and found that the designed reaction proceeded under the appropriate conditions (Scheme 1d). Heteroacenes including a thieno[3,2-*b*]furan or thieno[2,3-*b*]furan skeleton could be fabricated by this method. We report here the first copper-catalyzed intramolecular dehydrogenative C−O bond formation for the synthesis of furan-fused thienoacenes.

First, we chose 2-(benzo[*b*]thiophen-2-yl)phenol (**1a**) as a model compound, and Cu-catalyzed dehydrogenative C−O cyclization was examined under several conditions (Table 1).

Table 1. Cu-Catalyzed Dehydrogenative Cyclization of 1a under Several Conditions[a]



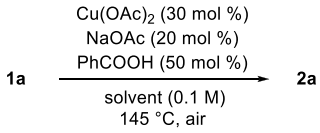
entry	[Cu]	base	acid	yield (%)[b]
1	CuBr	Cs_2CO_3	PivOH	30 (27)[c]
2	CuI	Cs_2CO_3	PivOH	18
3	CuOTf	Cs_2CO_3	PivOH	6
4	$Cu(OAc)_2$	Cs_2CO_3	PivOH	38
5	$Cu(OAc)_2$	K_2CO_3	PivOH	41
6	$Cu(OAc)_2$	K_3PO_4	PivOH	44
7	$Cu(OAc)_2$	KO(*t*-Bu)	PivOH	43
8	$Cu(OAc)_2$	KOAc	PivOH	46
9	$Cu(OAc)_2$	KOAc	AcOH	48
10	$Cu(OAc)_2$	KOAc	CF_3COOH	19
11	$Cu(OAc)_2$	KOAc	PhCOOH	52 (55)[d]
12	$Cu(OAc)_2$	NaOAc	PhCOOH	59[d,e]

[a]Reaction conditions: **1a** (0.20 mmol), [Cu] (30 mol %), base (20 mol %), acid (50 mol %), NMP (0.2 M), 145 °C, air, 24 h. [b]Determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c]Performed with base (50 mol %) and acid (1 equiv) in DMSO. [d]Performed with 0.1 M of **1a**. [e]Performed for 3 h.

First, we carried out the cyclization under conditions similar to those reported by Zhu.[7d] In the presence of CuBr (30 mol %), Cs_2CO_3 (50 mol %), and *t*-BuCO_2H (PivOH; 1 equiv), **1a** in DMSO was heated to 145 °C under air. Although **1a** was completely consumed, product **2a** was obtained in only 27% yield (in parentheses in entry 1). After several attempts at optimization, we found that *N*-methyl-2-pyrrolidone (NMP) was a better solvent than DMSO, and 20 mol % of Cs_2CO_3 and 50 mol % of PivOH were enough to promote the reaction (30% yield, entry 1). We next optimized the copper source (entries 2−4). Among the Cu catalysts we have tried so far, $Cu(OAc)_2$ gave the best results, and the yield of **2a** increased to 38% (entry 4). We next optimized the acids and bases (entries 5−12). The addition of a base and an acid was essential for the reaction and influenced the reaction efficiency. The use of KOAc instead of Cs_2CO_3 slightly increased the yield of **2a** (46%, entry 8). The use of $PhCO_2H$ instead of PivOH also slightly increased the yield of **2a** (52%, entry 11). The concentration of the reaction solution positively affected the reaction. When the solution was diluted to 0.1 M, the yield of **1a** increased to 55%. With NaOAc instead of KOAc, the reaction was finished within 3 h to give **2a** in 59% yield (entry 12).

Whereas several reaction conditions were examined, the efficiency of the reaction was still insufficient. One problem is that complex mixtures were also obtained with **2a**, and thus the suppression of side reactions should significantly promote the reaction progress. To overcome this situation, we tried several ligands, additives, and higher and lower reaction temperatures, but all of these attempts were unsuccessful.[13] Finally, we optimized the solvents for Cu-catalyzed dehydrogenative cyclization using 0.1 M of **1a** (Table 2). Other polar aprotic

Table 2. Effect of Solvents for Cu-Catalyzed Dehydrogenative C−O Cyclization of 1a[a]



entry	solvent	**1a** (%)	**2a** (%)[b]
1	NMP	N.D.[c]	59
2	DMF	N.D.	18
3	DMSO	N.D.	6
4	EGM	60	31
5[d]	EGM	trace	50
6	NMP/EGM (1:1)	N.D.	69
7[e]	NMP/EGM (1:1)	N.D.	74
8[e,f]	NMP/EGM/toluene (1:1:2)	N.D.	78 (73)[g]
9[e,f,g]	NMP/EGM/toluene (1:1:2)	N.D.	62[g]

[a]Reaction conditions: **1a** (0.20 mmol), $Cu(OAc)_2$ (30 mol %), NaOAc (20 mol %), PhCOOH (50 mol %), solvent (0.1 M), 145 °C, air, 3 h. [b]Determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c]Not detected. [d]Performed for 6 h. [e]Performed with 0.05 M of **1a**. [f]Performed for 24 h. [g]Isolated yield. [h]Performed on a 1.0 mmol scale.

solvents such as DMF and DMSO were ineffective (entries 2 and 3). In ethylene glycol monomethyl ether (EGM), **2a** was obtained in 31% yield. Interestingly, the decomposition of **1a** was almost suppressed in EGM, and 60% of **1a** was recovered (entry 4). When the reaction time was extended to 6 h, **1a** was mostly consumed, and the yield of **2a** increased to 50% (entry 5). We considered that EGM would work as a ligand to suppress the side reaction, but its polarity is not enough to efficiently promote the C−O cyclization. To overcome this situation, we next examined the reactions in mixed solvents (entries 6−8). When the reaction was carried out in a mixture of NMP and EGM (1:1), the yield of **2a** increased to 69% (entry 6). We next conducted the reaction with 0.05 M of **1a**, and **2a** was obtained in 74% yield (entry 7). Further tuning revealed that a mixture of NMP, EGM, and toluene (1:1:2) was the best solvent for the reaction (entry 8). Whereas a longer reaction time was required (24 h), **2a** was obtained in the highest yield (78% NMR yield, 73% isolated yield). With a 1.0 mmol scale, **2a** was obtained in 62% yield (entry 9).

To clarify the scope of the reaction, we next examined the Cu-catalyzed dehydrogenative cyclization of several 2-(benzo[*b*]thiophen-2-yl)phenol derivatives **1** under the optimized conditions (Scheme 2). First, p-substituted 2-(benzo[*b*]thiophen-2-yl)phenols **1b−h** were subjected to the reactions. Cu-catalyzed dehydrogenative C−O coupling proceeded smoothly, and the corresponding eight-substituted benzo[4,5]thieno[3,2-*b*]benzofurans **2b−h** were obtained, although the yields of the products were low in some cases (**2c** and **2e**). A

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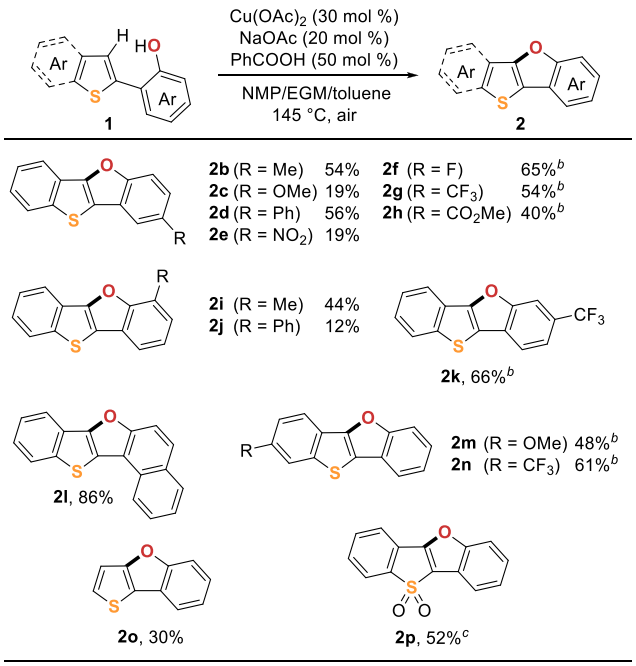
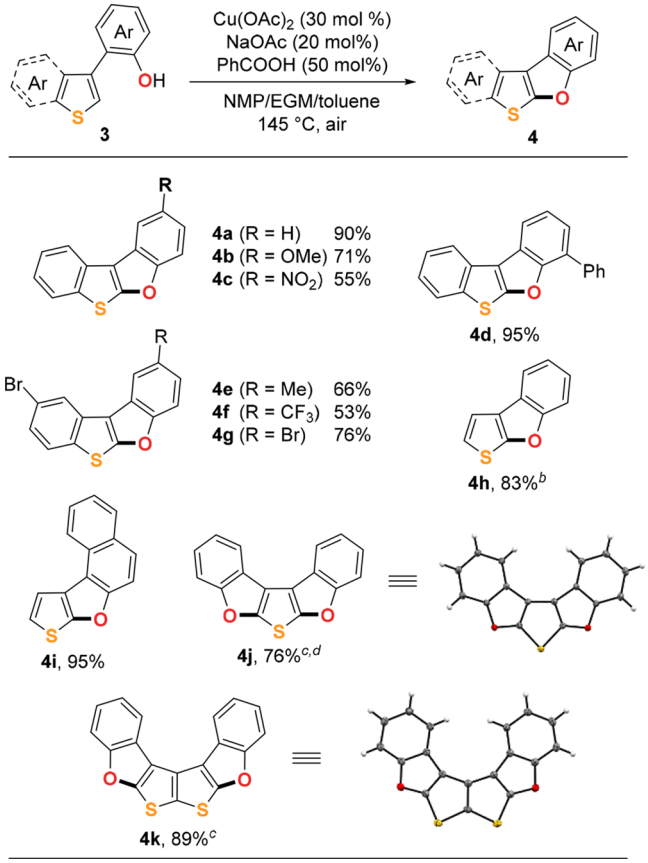
Scheme 2. Cu-Catalyzed Dehydrogenative C−O Cyclization of 1 under the Optimized Conditions[a]



[a]Reaction conditions: **1** (0.20 mmol), $Cu(OAc)_2$ (30 mol %), NaOAc (20 mol %), PhCOOH (50 mol %), NMP/EGM/toluene (1:1:2, 0.05 M), 145 °C, air, 24 h. Isolated yield. [b]Performed at 135 °C. [c]Performed from 2-(2-hydroxyphenyl)benzo[*b*]thiophene 1,1-dioxide (**1p**).

Scheme 3. Cu-Catalyzed Dehydrogenative C−O Cyclization to Form Heteroacenes Involving Thieno[2,3-*b*]furan[a]



[a]Reaction conditions: **3** (0.20 mmol), $Cu(OAc)_2$ (30 mol %), NaOAc (20 mol %), PhCOOH (50 mol %), NMP/EGM/toluene (1:1:2, 0.05 M), 145 °C, air, 24 h. Isolated yield. [b]Performed without NaOAc. [c]Performed with $Cu(OAc)_2$ (0.6 equiv), NaOAc (0.8 equiv), and PhCOOH (2 equiv) in NMP/EGM/toluene (1:1:2, 0.0125 M) under O_2. [d]Performed for 21 h.

variety of substrates with electron-donating or -withdrawing groups could be applied for the reaction. We next used o- or m-substituted 2-(benzo[*b*]thiophen-2-yl)phenols **1i−k**, and the corresponding substituted 2-(benzo[*b*]thiophen-2-yl)-phenols **2i−k** were obtained. From substrate **1l** bearing a 2-naphthol, further π-expanded heteroacene **2l** was obtained in good yield (86% yield). From **1m** or **1n** with substituted benzo[*b*]thiophene moieties, the corresponding substituted products **2m** and **2n** were obtained. Whereas a substrate having a thiophene unit (**1o**) could also be used in the reaction, the yield was insufficient. Interestingly, C−O cyclization also proceeded from **1p** having a benzo[*b*]-thiophene 1,1-dioxide to afford **2p**.

Under the optimized conditions, substrates having 3-thienyl groups **3** were also applicable (Scheme 3). From 2-(benzo-[*b*]thiophen-3-yl)phenol (**3a**), the desired heteroacene **4a** including the thieno[2,3-*b*]furan skeleton was obtained in an excellent yield (90%). Similarly, several mono- and disub-stituted heteroacenes **4b−g** were obtained from the corre-sponding substrates **3b−g**. A bromo group, which can be easily transformed to other groups, was tolerated under the reaction conditions (**3e−g**). With 2-(thiophen-3-yl)phenol (**3h**), C−O cyclization proceeded without a base to give the product **4h** in good yield (83%). From **3i**, a substrate bearing a naphthyl group, naphtho[2,1-*b*]thieno[3,2-*d*]furan (**4i**), was obtained in excellent yield (95%). Notably, C−O cyclization of substrates having two hydroxy groups also proceeded smoothly to afford highly π-expanded heteroacenes such as **4j** and **4k** in good yields (76 and 89% yield, respectively). The structures of **4j** and **4k** were confirmed by X-ray crystallography. Whereas the reactions proceeded in air, the use of oxygen gave better results (Table S9).

To obtain further insight into the reaction, control experiments were carried out (Scheme 4). We first carried out the Cu-catalyzed cyclization of **1q**-*d* (Scheme 4a) to investigate the kinetic isotope effect (KIE) and found that D% of the recovered **1q**-*d* was unexpectedly low (14%D). To clarify the reason for this observation, another D-labeled experiment was conducted with D-labeled **1l**-*d* (Scheme 4b). After heating for 6 h, cyclized product **2l** was obtained in 44% yield, and 47% of **1l**-*d* was recovered (49%D). The drastic decrease in D% of **1l**-*d* strongly suggests that cleavage of the C−H bond would be a reversible process.[14] Finally, the stability of the product **2l** was confirmed under the reaction conditions (Scheme 4c). After the treatment of **2l** for 24 h under the reaction conditions, 95% of **2l** was recovered, meaning that **2l** was stable under these conditions. We next carried out the Cu-catalyzed reaction of **1a** in the presence of TEMPO (Scheme S1). The yield of **2a** decreased to 38%, suggesting that the reaction would not proceed via a radical pathway.

On the basis of the mechanistic studies, a plausible mechanism is illustrated in Figure 1. First, Cu species bearing carboxylates (R = Me or Ph) would react with **1** to form

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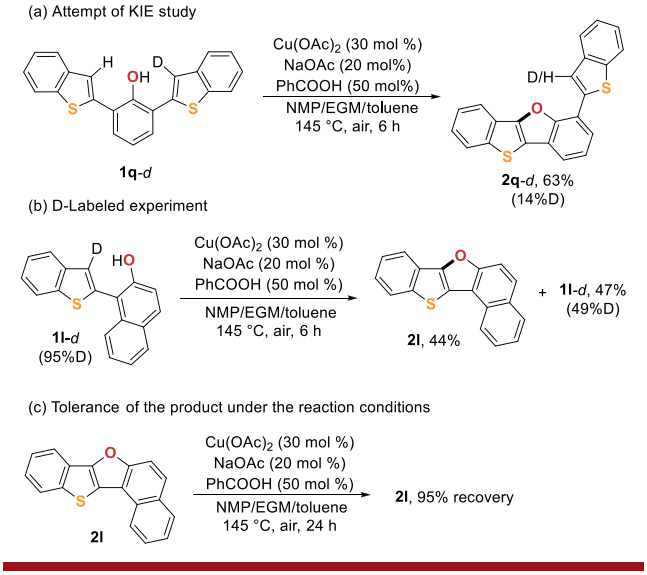
Scheme 4. Control Experiments



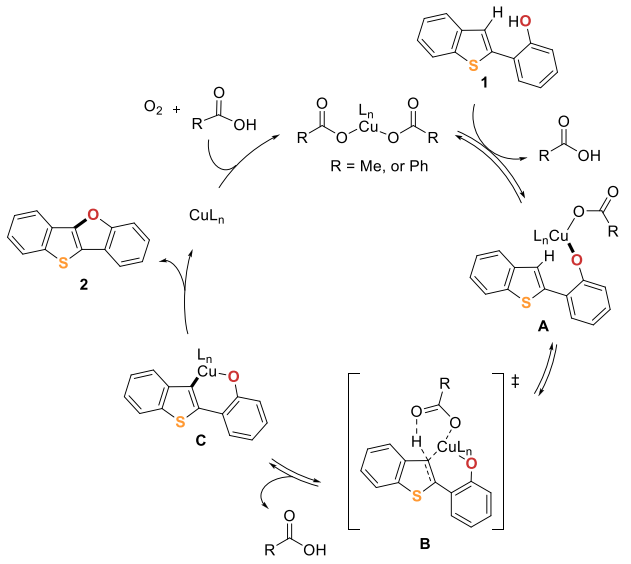


Figure 1. Plausible mechanism for the dehydrogenative C−O cyclization of **1**.

intermediate **A**, which would be converted to metallacycle **C** via transition-state **B** by a concerted metalation deprotonation (CMD) process. The transformations between **1** and **C** should be reversible processes, which is strongly suggested by the D-labeled experiments. Finally, subsequent reductive elimination would proceed irreversibly to afford product **2** with a low valent copper species, which would be oxidized by oxygen to regenerate active copper species. NaOAc would promote the regeneration of the active copper species. Whereas the role of EGM is not yet clear, we assumed that EGM would coordinate with the copper species and prevent its decomposition.

In conclusion, we developed Cu-catalyzed dehydrogenative C−O cyclization to afford furan-fused thienoacenes. Thienoacenes including either thieno[3,2-*b*]furan or thieno[2,3-*b*]furan skeletons were obtained under similar conditions. Double C−O cyclization enabled easy access to highly π-expanded furan-fused thienoacenes. The physical properties of the thus-obtained heteroacenes and further application of this strategy are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01256.

Experimental details and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2040856−2040857 contain 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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(13) For details of the screenings, see the Supporting Information.

(14) This result was highly different from that of Zhu and coworkers, who observed a large KIE in the Cu-catalyzed dehydrogenative cyclization for synthesizing dibenzorfurans; see ref 7d.

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