Introduction

The research on polycyclic aromatic hydrocarbons has achieved substantial advances in the past decades, which have led to the development of various materials for organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs) and photovoltaics (OPVs). Ladder-type thiophene derivatives such as benzothieno[3,2-b]benzothiophene (BTBT) have played a key role in the development of high-performance optoelectronic devices such as OFETs and OPVs. 7,8 2,7-Diethyl[1]benzothieno[3,2-b][1]benzothiophene (C8-BTBT) showed an ultra-high maximum hole mobility of 43 cm² V⁻¹ s⁻¹ in thin film transistors, 9 which is among the highest values reported to date for all organic molecules. Inspired by the great success of BTBT derivatives in OFETs, we have recently designed and synthesized benzofuro[3,2-b][1]benzothiophene derivatives and benzofuro[3,2-b][1]benzofuran derivatives with either one or two furan rings substituting for thiophene rings, and investigated their packing mode, photophysical and charge transport properties.

As we all know, an oxygen atom and a sulfur atom have a similar valence electron configuration; the difference is that the oxygen atom has a smaller atomic radius and a larger electronegativity. The smaller atomic radius of the oxygen atom has only one valence state of 2 to construct the furan ring. Thus, developing a new and efficient synthetic method toward BTBFs is paramount for their material applications.

The synthesis of BTBF was firstly realized by Aitken group using flash vacuum pyrolysis of 2-methylthiophenyl substituted phosphorus ylides in 1995 (Scheme 1a). 10,11 By the reaction of benzothieno[3,2-b]furanyl with substituted dienes, Svoboda group synthesized tetrahydro[1]benzo[3,2-b][1]benzofuran derivatives which were transformed into BTBFs by dehydrogenative aromatization (Scheme 1b). 12 A Pd-catalyzed intramolecular oxidative C–H/C–H coupling of 3-aryloxybenzo[b]thiophenes was independently reported by Kuninobu 13 and Miura group 14 in 2015 (Scheme 1c). Then a Cu-catalyzed Ullmann-type intramolecular C–O bond coupling reaction toward BTBFs was developed by our group and coworkers (Scheme 1d). 15 Later on, You group used a similar strategy to synthesize these compounds. 16 Recently, Mitsudo group have reported an electrochemical synthesis of this type of compounds from 2-benzox[b] furan-2-yl]benzenethiol via a dehydrogenative C-H/S-H coupling (Scheme 1e). 17 Most recently, John group have developed a mild metal-free synthetic route toward BTBFs by the annulation of 3-nitrobenzothiophene with phenols (Scheme 1f). 18 However, all these methods required metal catalysts or harsh conditions, and multistep transformations for the synthesis of BTBFs with limited scopes.

The construction of furan-fused π-conjugated molecules through dehydrogenative C–H/O–H coupling has been studied...
in the past decade. Liu\textsuperscript{33} and Yoshikai group\textsuperscript{34} independently reported the Pd-catalyzed synthesis of dibenzofuran derivatives through dehydrogenative C–H/O–H coupling. Zhu group discovered that copper catalysts could also promote dehydrogenative etherification to form dibenzofurans.\textsuperscript{35,36} Hong et al. reported the synthesis of heterocyclic-fused benzofurans via dehydrogenative C–H/O–H coupling of flavones and coumarins.\textsuperscript{37} Shimada and coworkers reported that dual C–H/O–H coupling of binaphthols occurred to furnish peri-xanthanoxanthenes.\textsuperscript{38} To be noted, the products by the methods mentioned above have been limited to aryl ethers and lactones.

Inspired by the results mentioned above, we hypothesized that BTBFs could be constructed via intramolecular dehydrogenative C–H/O–H coupling reaction. Herein, due to our continuing interest in Cu-catalyzed synthesis of furan-fused π-conjugated molecules,\textsuperscript{13–15} we have been motivated to investigate the construction of BTBFs via dehydrogenative C–H/O–H coupling reaction as shown in Scheme 1g. The advantages of this novel approach compared with our previous strategy (Scheme 1d) are as followed: (1) the bromination of β-position of thiophene is unnecessary which simplifies the reaction; (2) the debromination side reaction which was found in our previous strategy could be avoided which helps to improve the reaction yield.

Results and discussion

Our investigations commenced with the synthesis of 2-(benzo[b]thiophen-2-yl)phenol derivatives in Suzuki coupling reaction, and the yields were very high (75–98%, see ESIF). With the above compounds in hand, we started to investigate the construction of BTBFs via intramolecular dehydrogenative C–H/O–H coupling reaction. Initially, intramolecular dehydrogenative C–H/O–H coupling reaction of 2-(benzo[b]thiophen-2-yl)phenol (1a) was selected as the model reaction. We first tried Pd(OAc)\textsubscript{2}, as the catalyst, 1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-imidazole (IPr) as the ligand, Cs\textsubscript{2}CO\textsubscript{3} as the base, toluene as the solvent, and the reaction was performed under air (i.e., air as the oxidant), but no target product BTBF (2a) was observed (see Table 1, entry 1). When the oxidant was replaced by 3 equivalent of Cu(OAc)\textsubscript{2}, the target product was produced in 8% nuclear magnetic resonance (NMR) yield (see Table 1, entry 2). Then the ligand was replaced by pyridine (Table 1, entry 3), the yield of BTBF (2a) increased to 11%; if pyridine was used as the ligand and solvent, the yield was further increased to 21% (Table 1, entry 4). However, if a catalytic amount of Cu(OAc)\textsubscript{2} (0.2 equivalent) was used as the catalyst instead of Pd(OAc)\textsubscript{2}, and the reaction was performed under air, only a trace amount of target compound was observed either with or without ligands (Table 1, entries 5–7). To our delight, when the amount of Cu(OAc)\textsubscript{2} was gradually increased to 0.5, 1 and 3 equivalent, the yield increased to 32%, 47%, 51% respectively (Table 1, entries 8–10). When the reaction was performed under pure oxygen, the yield dropped to 35% (Table 1, entry 11), which is probably due to oxidation of starting material by oxygen. Intriguingly, when 3 equivalent of Cu(OAc)\textsubscript{2} was used, and the reaction was performed under nitrogen, the NMR yield increased to 90% (86% isolated yield) (Table 1, entry 12). Actually, Cu(OAc)\textsubscript{2} was used as a catalyst and oxidant under this condition. Afterward, we screened a variety of copper oxidants (entries 13–20), bases (entries 21–23) and solvents (entries 24–28), the yields were much lower than the above yield (Table 1, entry 12).

To clarify the reaction scope, we next devoted our efforts to test a variety of 2-(benzo[b]thiophen-2-yl)phenol derivatives 1 under the optimized reaction conditions (Scheme 2). Firstly, we selected o-, m- or p-substituted 2-(benzo[b]thiophen-2-yl)phenols as the substrates, and found that all the yields (2b–k, 64–91%) were good to excellent no matter the substituted group is electron-donating or electron-withdrawing. The substrates with weak electron-donating groups such as alkyl chains afforded very high yields (2b–d, 85–91%), however, the substrate with a strong electron-donating group such as methoxy group gave comparably low yield (2e, 64%). For a specific substituent, the substituting position affects the yield: p-fluoro substituted BTBF (2f, 85%) > m-substituted BTBF (2g, 78%) > o-substituted BTBF (2h, 68%), probably due to the different steric hindrance of fluoro substituent in different position.

Next, we tested phenols with substituted benzo[b]thiophene moieties, and also got excellent yields (2l–2m, 81–91%). For more π-extended 3-(benzo[b]thiophen-2-yl)naphthalen-2-ol as the substrate, the yield only slightly dropped, affording benzo [4,5]thieno[3,2-b]naphtho[2,3-d]furan (2n, BTNF, 63%). Although substrates having a thiophene unit (1o) or bithiophene unit (1p) could also be used in this reaction, the yields significantly dropped (2o, 45%; 2p, 40%), probably because the cation intermediate could not be effectively stabilized without the resonance with phenyl group (see proposed mechanism,
vide infra). Thus, not surprisingly, the yield of 2q is even lower (16%) because it is obtained via two subsequent intramolecular dehydrogenative C–H/O–H couplings. Thus, three-to-six fused ring thienofuran compounds could be constructed. Notably, the yields of BTBFs are comparable or even higher than those reported in our previous paper (2c 91% vs. 87%, 2f 85% vs. 90%, 2l 81% vs. 66%, and 2m 91% vs. 81%), indicating advantage of the new synthetic approach.

Subsequently, we investigated the gram-scale synthesis of copper-mediated construction of benzothieno[3,2-b]benzofurans by intramolecular dehydrogenative C–O coupling reaction. 2-(Benzo[b]thiophen-2-yl)phenol derivatives 1a and 1f (6 mmol) reacted under the optimised reaction conditions, affording their corresponding benzothieno[3,2-b]benzofurans 2a and 2f in high yields which are comparable with those obtained on a 0.2 mmol scale (Fig. 1).

| Table 1 | Screening reaction conditions for the synthesis of BTBFs via intramolecular dehydrogenative C–O coupling reaction<sup>a</sup> |
| --- | --- |

| Entry | [Pd]/[Cu] | Ligand | Base | Oxidant | Solvent | Yield<sup>b</sup> (%) |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | Pd(OAc)<sub>2</sub>, 0.2 equiv. | IPr | Cs<sub>2</sub>CO<sub>3</sub> | Air | Toluene | 0 |
| 2 | Pd(OAc)<sub>2</sub>, 0.2 equiv. | IPr | Cs<sub>2</sub>CO<sub>3</sub> | Cu(OAc)<sub>2</sub> | Toluene | 8 |
| 3 | Pd(OAc)<sub>2</sub>, 0.2 equiv. | Pyridine | Cs<sub>2</sub>CO<sub>3</sub> | Cu(OAc)<sub>2</sub> | Toluene | 11 |
| 4 | Pd(OAc)<sub>2</sub>, 0.2 equiv. | Pyridine | Cs<sub>2</sub>CO<sub>3</sub> | Cu(OAc)<sub>2</sub> | Pyridine | 21 |
| 5 | Cu(OAc)<sub>2</sub>, 0.2 equiv. | o-Phen | Cs<sub>2</sub>CO<sub>3</sub> | Air | Pyridine | Trace |
| 6 | Cu(OAc)<sub>2</sub>, 0.2 equiv. | 2,2'-Bipyridine | Cs<sub>2</sub>CO<sub>3</sub> | Air | Pyridine | Trace |
| 7 | Cu(OAc)<sub>2</sub>, 0.2 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | Air | Pyridine | Trace |
| 8 | Cu(OAc)<sub>2</sub>, 0.5 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | Air | Pyridine | 32 |
| 9 | Cu(OAc)<sub>2</sub>, 1 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | Air | Pyridine | 47 |
| 10 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | Air | Pyridine | 51 |
| 11 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | O<sub>2</sub> | Pyridine | 35 |
| 12 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 90 (86)<sup>c</sup> |
| 13 | Cu(OAc)<sub>2</sub>-H<sub>2</sub>O, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 64 |
| 14 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 51 |
| 15 | CuS, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 7 |
| 16 | CuS, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | Trace |
| 17 | CuCl<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 0 |
| 18 | CuCl<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 0 |
| 19 | CuBr<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 0 |
| 20 | CuI, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 0 |
| 21 | CuOAc, 3 equiv. | — | K<sub>2</sub>CO<sub>3</sub> | — | Pyridine | 34 |
| 22 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | NaOAc | — | Pyridine | 59 |
| 23 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | — | — | Pyridine | 20 |
| 24 | Cu(OAc)<sub>2</sub>, 3 equiv. | Pyridine | Cs<sub>2</sub>CO<sub>3</sub> | — | Toluene | 30 |
| 25 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | DMSO | 44 |
| 26 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | DMF | Trace |
| 27 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | t-Butanol | 0 |
| 28 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | Isopropanol | 0 |
| 29 | Cu(OAc)<sub>2</sub>, 3 equiv. | — | Cs<sub>2</sub>CO<sub>3</sub> | — | t-Butanol | 0 |

<sup>a</sup> Reaction conditions: 1a (0.20 mmol), Pd(OAc)<sub>2</sub> or Cu catalyst (0.2–3 equiv., 0.04–0.6 mmol), ligand (0.4 equiv., 0.08 mmol), base (1 equiv., 0.20 mmol), oxidant (for entries 2–4, 3 equiv., 0.60 mmol), solvent (4 mL), 110 °C, the reactions were performed under nitrogen if the oxidant is neither air nor oxygen. <sup>b</sup> Determined by 1H NMR with 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Isolated yields.
Although the detailed mechanism remains to be elucidated, a possible reaction pathway is proposed based on the above observations (Scheme 5). At first, 1a reacts with a base, generating anionic intermediate A. Then phenoxy radical B is produced via single electron transfer with Cu(OAc)$_2$, followed by intramolecular C–O cyclization to generate radical intermediate C. Afterward, cationic intermediate D is formed by oxidation with Cu(OAc)$_2$. Finally, the target product 2a is obtained by the abstraction of a proton with the base.

**Conclusions**

In summary, we have developed an efficient method to synthesize benzothieno[3,2-β]benzofurans via intramolecular dehydrogenative C–H/O–H coupling in up to 91% yield. Notably, three-to-six fused ring thiienofuran compounds could be constructed. The advantages of this novel approach include unnecessary bromination of β-position of thiophene and thus inhibition of the debromination side reaction and high yield. Reaction mechanism study showed that it is a radical pathway initiated by single electron transfer between substrate and copper catalyst.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**

1. J. E. Anthony, *Chem. Rev.*, 2006, **106**, 5028–5048.
2. J. Wu, W. Pisula and K. Mullen, *Chem. Rev.*, 2007, **107**, 718–747.
3. A. Pron, P. Gawrys, M. Zagorska, D. Djurado and R. Demadrille, *Chem. Soc. Rev.*, 2010, **39**, 2577–2632.
4. W. Wu, Y. Liu and D. Zhu, *Chem. Soc. Rev.*, 2010, **39**, 1489–1502.
5. A. Chaskar, H. F. Chen and K. T. Wong, *Adv. Mater.*, 2011, **23**, 3876–3895.
6. J. Jung, N. J. Tremblay, M. L. Yeh and H. E. Katz, *Chem. Mater.*, 2011, **23**, 568–582.
7. C. Wang, H. Dong, W. Hu, Y. Liu and D. Zhu, *Chem. Rev.*, 2012, **112**, 2208–2267.
8. J. Lee, A. J. Kalin, T. Yuan, M. Al. Hashimi and L. Fang, *Chem. Sci.*, 2017, **8**, 2503–2521.
9. H. Tsuji and E. Nakamura, *Acc. Chem. Res.*, 2017, **50**, 396–406.
10. Y. Yan, X. Liu and T. Wang, *Adv. Mater.*, 2017, **29**, 1601074.
11. For recent representative reports, see: (a) A. Y. Amin, A. Khassanov, K. Reuter, T. M. Friedrichsen and M. Halik, *J. Am. Chem. Soc.*, 2012, **134**, 16548–16550; (b) K. Takimiya,
I. Osaka, T. Mori and M. Nakano, Acc. Chem. Res., 2014, 47, 1493–1502.  
(c) G. Schweicher, V. Lemaur, C. Niebel, C. Ruzié, Y. Diao, O. Goto, W. Y. Lee, Y. Kim, J. B. Arlin, J. Karpinska, A. R. Kennedy, S. R. Parkin, Y. Olivier, S. C. B. Mannsfeld, J. Cornil, Y. H. Geerts and Z. Bao, Adv. Mater., 2015, 27, 3066–3072.  
(d) A. L. Capodilupo, E. Fabiano, L. De Marco, G. Ciccarella, G. Gigli, C. Martinelli and A. Cardone, J. Org. Chem., 2016, 81, 3235–3245.  
12 Y. Yuan, G. Giri, A. L. Ayzner, A. P. Zoombelt, S. C. Mannsfeld, J. Chen, D. Nordlund, M. F. Toney, J. Huang and Z. Bao, Nat. Commun., 2014, 5, 3005.  
13 D. Chen, D. Yuan, C. Zhang, H. Wu, J. Zhang, B. Li and X. Zhu, J. Org. Chem., 2017, 82, 10920–10927.  
14 W. Ma, J. Huang, C. Li, Y. Jiang, B. Li, T. Qi and X. Zhu, RSC Adv., 2019, 9, 7123–7127.  
15 D. Chen, J. Li, W. Ma, B. Li, Y. Zhen, X. Zhu, W. Hu, H. Tsuji and E. Nakamura, Asian J. Org. Chem., 2018, 7, 2228–2232.  
16 K. Niimi, H. Mori, E. Miyazaki, I. Osaka, H. Kakizoe, K. Takimiya and C. Adachi, Chem. Commun., 2012, 48, 5892–5894.  
17 B. Li, Chin. J. Org. Chem., 2015, 35, 2487.  
18 C. Mitsui, J. Soeda, K. Miwa, K. Shoyama, Y. Ota, H. Tsuji, J. Takeya and E. Nakamura, Bull. Chem. Soc. Jpn., 2015, 88, 776–783.  
19 C. Mitsui, M. Yamagishi, R. Shikata, H. Ishii, T. Matsushita, K. Nakahara, M. Yano, H. Sato, A. Yamano, J. Takeya and T. Okamoto, Bull. Chem. Soc. Jpn., 2017, 90, 931–938.  
20 Y. Zhao, L. Yan, L. Murtaza, X. Liang, H. Meng and W. Huang, Org. Electron., 2017, 43, 105–111.  
21 X. Zeng, D. Zhang, Y. Zhu, M. Chen, H. Chen, S. Kasai, H. Meng and O. Goto, J. Mater. Chem. C, 2019, 7, 14275–14283.  
22 Y. S. Yang, T. Yasuda and C. Adachi, Bull. Chem. Soc. Jpn., 2012, 85, 1186–1191.  
23 W. Ma, G. Liu, L. Zhou, B. Li and Y. Wang, J. Mater. Chem. C, 2020, 8, 8796–8803.  
24 M. Shi, Y. He, Y. Sun, D. Fang, J. Miao, M. U. Ali, T. Wang, Y. Wang, T. Zhang and H. Meng, Org. Electron., 2020, 84, 105793.  
25 (a) R. A. Aitken, C. K. Bradbury, G. Burns and J. J. Morrison, Synlett, 1995, 53–54; (b) R. A. Aitken, G. Burns and J. J. Morrison, J. Chem. Soc., Perkin Trans. 1, 1998, 3937–3941.  
26 R. A. Aitken and A. N. Garnett, Synthesis, 2017, 49, 4955–4977.  
27 P. Pihera, J. Paleček and J. Svoboda, Collect. Czech. Chem. Commun., 1998, 63, 681.  
28 K. Saito, P. K. Chikkade, M. Kanai and Y. Kuninobu, Chemistry, 2015, 21, 8365–8368.  
29 H. Kaida, T. Satoh, K. Hirano and M. Miura, Chem. Lett., 2015, 44, 1125–1127.  
30 Y. M. Wu, W. Li, L. F. Jiang, L. Q. Zhang, J. B. Lan and J. S. You, Chem. Sci., 2018, 9, 6878–6882.  
31 K. Mitsudo, R. Matsuo, T. Yonezawa, H. Inoue, H. Manai and S. Suga, Angew. Chem., Int. Ed., 2020, 59, 7803–7807.  
32 R. A. Krishnan, S. A. Babu, P. R. Nitha, J. Krishnan and J. John, Org. Lett., 2021, 23, 1814–1819.  
33 B. Xiao, T. J. Gong and L. Liu, J. Am. Chem. Soc., 2011, 133, 9250–9253.  
34 Y. Wei and N. Yoshikai, Org. Lett., 2011, 13, 5504–55047.  
35 Y. W. Jiaji Zhao, Y. He, L. Liu and Q. Zhu, Org. Lett., 2012, 14, 1078–1081.  
36 J. Zhao, Q. Zhang and Q. Zhu, Org. Lett., 2012, 14, 5362–5365.  
37 Y. Moon, Y. Kim, H. Hong and S. Hong, Chem. Commun., 2013, 49, 8323–8325.  
38 T. Kamei, M. Uryu and T. Shimada, Org. Lett., 2017, 19, 2714–2717.  
39 H. J. Zhang, F. Su and T. B. Wen, J. Org. Chem., 2015, 80, 11322–11329.  
40 R. H. Liu, D. Wei, B. Han and W. Yu, ACS Catal., 2016, 6, 6523–6530.  
41 C. Theunissen, J. Wang and G. Evano, Chem. Sci., 2017, 8, 3465–3470.  
42 M. Wang, J. Wei, Q. Fan and X. Jiang, Chem. Commun., 2017, 53, 2918–2921.  
43 A. Cai, W. Yan and W. Liu, J. Am. Chem. Soc., 2021, 143, 9952–9960.