




 Cite this: *RSC Adv.*, 2023, 13, 839

 Received 9th December 2022
 Accepted 19th December 2022

DOI: 10.1039/d2ra07856b

rsc.li/rsc-advances

Synthesis of benzo[*b*]furans from alkynyl sulfoxides and phenols by the interrupted Pummerer reaction†

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The interrupted Pummerer reaction of alkynyl sulfoxides with phenols is disclosed. A wide range of benzo[*b*]furans were efficiently synthesized through unexplored electrophilic activation of the electron-deficient alkynyl sulfanyl group. Based on the good availability of alkynyl sulfoxides, we successfully prepared various functionalized benzo[*b*]furans from readily available alkynes, thiosulfonates, and phenols.

Introduction

Benzo[*b*]furan scaffolds are of great importance in a wide range of research fields including pharmaceutical sciences, natural product chemistry, and materials chemistry (Fig. 1A).¹ Various methods to synthesize benzofurans have been developed so far. For example, *O*-alkylation of salicylaldehyde derivatives with chloroacetic acid and subsequent cyclization affords a range of benzofurans.² Despite the significance of benzofurans, the synthesis of highly functionalized benzofurans is not easy by conventional methods due to limitations in the benzofuran skeleton construction. We herein describe a new method to prepare multisubstituted benzofurans from alkynyl sulfoxides and phenols *via* the interrupted Pummerer reaction.

The interrupted Pummerer reactions are emerging methods to synthesize highly functionalized organosulfur compounds from sulfoxides by the electrophilic activation of S=O bonds (Fig. 1B).³ Recently, several unique transformations of a range of alkenyl and aryl sulfoxides with various nucleophiles have been achieved through the electrophilic activation of the sulfoxide moieties followed by smooth charge-accelerated [3,3]-sigmatropic rearrangement.^{4,5} In contrast, interrupted Pummerer reactions of alkynyl sulfoxides have not been developed to the best of our knowledge, which may be due to the electron-deficient nature of the sulfoxide moiety by the electron-withdrawing sp-hybridized carbon. We conceived that the

interrupted Pummerer reaction of alkynyl sulfoxides with phenols with the appropriate activators will allow us to synthesize a wide variety of functionalized benzofurans owing to the good availability of alkynyl sulfoxides and phenols (Fig. 1C).

Before examining the benzofuran synthesis, we evaluated the stability of alkynyl sulfurane intermediate **1c** compared to alkenyl and alkyl sulfuranes **1a** and **1b** by the DFT calculation (Fig. 1D). The calculated energy differences between sulfoxides with trifluoroacetic anhydride (TFAA) and sulfuranes **1a–1c** showed that the electron-deficient alkynyl sulfurane **1c** is unstable in comparison with alkyl and alkenyl sulfuranes **1a** and **1b**. These results clearly show that stability of sulfurane **1c** was decreased by the significant electron-deficiency of alkynyl carbons. Comparing LUMO energies of **1a–1c** suggests higher electrophilicity of alkynyl sulfurane **1c** than that of alkyl and alkenyl sulfuranes **1a** and **1b**.

Results and discussion

After screening the reaction conditions, we established the synthetic method of benzofuran **3a** from phenol (**1a**) and alkynyl sulfoxide **2a** through electrophilic sulfoxide activation (Table 1). While benzofuran **3a** was not obtained when acetic anhydride was used as an activator (entry 1), we found that treating a mixture of phenol (**1a**) and alkynyl sulfoxide **2a** with triflic anhydride (Tf₂O) afforded 3-butyl-2-(ethylthio)benzo[*b*]furan (**3a**) in moderate yield (entry 2). The yield was improved by the addition of 2,6-di(*tert*-butyl)pyridine as a base (entry 3).⁶ We accomplished the synthesis of benzofuran **3a** from **1a** and **2a** in dichloromethane with TFAA in excellent yield (entry 4).⁷ Benzofuran **3a** was also prepared in 1 mmol scale without decreasing the yield, showing the good scalability of the protocol (entry 5). Although we failed the synthesis of benzofuran **3a** when using 2,6-di(*tert*-butyl)pyridine or triethylamine as an additive (entries 6 and 7), benzofuran **3a** was also obtained

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: <https://doi.org/10.1039/d2ra07856b>



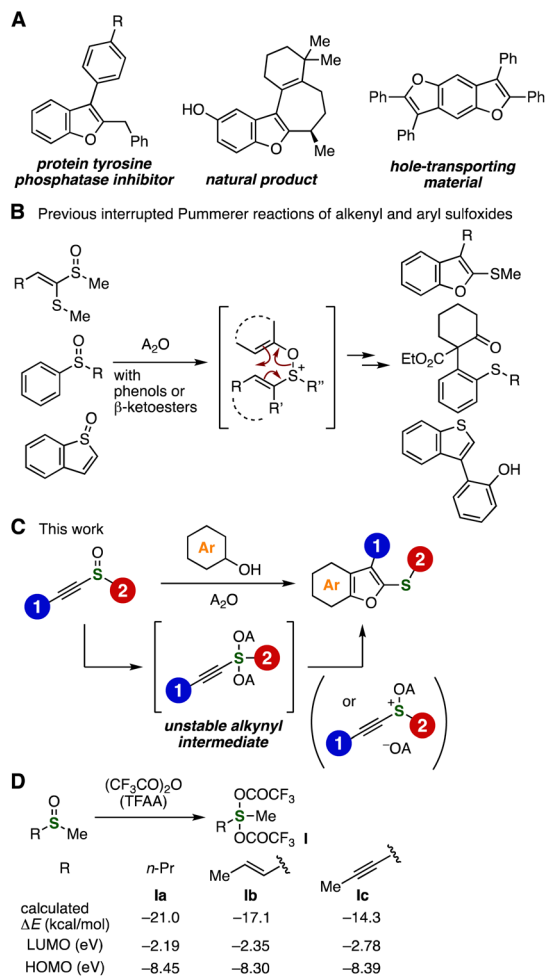


Fig. 1 Backgrounds and an abstract of this study. (A) Significant benzofurans. (B) Interrupted Pummerer reactions. (C) This work. (D) DFT calculations of sulfoxanes **1a**–**1c**. $\Delta E = E(\text{sulfoxanes}) - E(\text{sulfoxides}) - E(\text{TFAA})$. See ESI† for details.

in the presence of sodium carbonate (entry 8). Among solvents examined (entries 4 and 9–12), dichloromethane, toluene, and α, α, α -trifluorotoluene were effective for benzofuran synthesis (entries 4, 11, and 12). Trifluoroacetic acid did not activate sulfoxide **2a** (entry 13).

With optimized conditions in hand, a wide range of 2-sulfanylbenzofurans **3** were synthesized from phenol (**1a**) and various alkyne sulfoxides **2** (Fig. 2). For example, phenethyl-substituted benzofuran **3b** was synthesized in good yield. It is worthy to note that an ester moiety was tolerated under the conditions, providing benzofuran **3c** in high yield. We succeeded in the synthesis of ether-tethered benzofuran **3d** by electrophilic activation with TiF_4 in the presence of 2,6-di(*tert*-butyl)pyridine in good yield, where decomposition took place when the reaction was conducted with TFAA. Benzofurans **3e** and **3f** having aryl groups at 3-position were prepared efficiently without damaging 4-tolyl and 4-chlorophenyl groups. Also, alkyne aryl sulfoxides participated to the benzofuran synthesis affording **3g** and **3h** bearing 4-tolylthio and 4-bromophenylthio groups in high yields. Since a wide variety of alkyne sulfoxides

Table 1 Screening of the reaction conditions

Entry	Activator	Additive	Solv.	Yield ^a (%)
1	Ac ₂ O	None	CH ₂ Cl ₂	0
2	Tf ₂ O	None	CH ₂ Cl ₂	45
3	Tf ₂ O	2,6-(<i>t</i> -Bu) ₂ pyridine	CH ₂ Cl ₂	81
4	TFAA	None	CH ₂ Cl ₂	97 (94) ^b
5	TFAA	None	CH ₂ Cl ₂	95 ^c
6	TFAA	2,6-(<i>t</i> -Bu) ₂ pyridine	CH ₂ Cl ₂	0
7	TFAA	NEt ₃	CH ₂ Cl ₂	0
8	TFAA	Na ₂ CO ₃	CH ₂ Cl ₂	89
9	TFAA	None	MeCN	67
10	TFAA	None	THF	0
11	TFAA	None	Toluene	85
12	TFAA	None	PhCF ₃	91
13	CF ₃ CO ₂ H	None	CH ₂ Cl ₂	0

^a ¹H NMR yield. ^b Isolated yield (0.1 mmol scale). ^c Isolated yield (1 mmol scale).

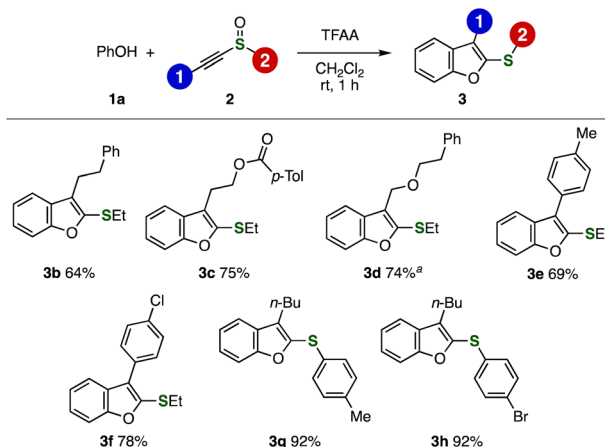


Fig. 2 Syntheses of benzofurans **3** using various alkyne sulfoxides **2**. See the ESI† for details. ^aThe reaction was performed with TiF_4 and 2,6-di(*tert*-butyl)pyridine.

were easily available from terminal alkynes or alkyne silanes,⁸ the broad scope of the benzofuran synthesis is a great advantage over previous reports.⁴

Diverse functionalized benzofurans were successfully synthesized from alkyne sulfoxide **2a** and a broad variety of phenols (Fig. 3). Indeed, phenols having methyl, methoxy, bromo, chloro, and methoxycarbonyl groups served in the benzofuran synthesis with alkyne sulfoxide **2a** in moderate to high yields keeping the functional groups unreacted. Furthermore, the reaction of 2-trimethylsilyl-3-triflyloxyphenol (**1h**) with alkyne sulfoxide **2a** efficiently proceeded to furnish benzofuran **3o** leaving butyl, ethylthio, trimethylsilyl, and



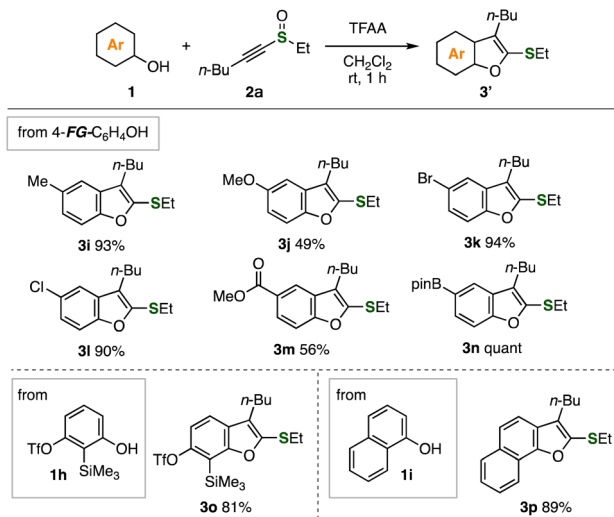


Fig. 3 Syntheses of benzofurans **3** using various phenols. See the ESI† for details.

triflyloxy groups untouched. In addition, naphthofuran **3p** was synthesized from 1-naphthol (**1i**) in good yield.

We then examined the regioselectivity in the benzofuran synthesis (Fig. 4). When the benzofuran synthesis was performed using *m*-cresol, 6-methyl-substituted benzofuran **4a** was majorly obtained along with 4-methylbenzofuran **5a** with moderate regioselectivity, clearly showing that the C–C bond formation at the unhindered site was favorable. Benzofuran **4b** was also synthesized as a major product with good regioselectivity when using 5-hydroxyindane (**1k**). Of note, we succeeded in the preparation of benzofuran **4c** as a sole product, in which the C–C bond formation at the vacant position took place selectively and regioisomer **5c** was not observed. In contrast, naphthols **1m** and **1n** reacted with alkynyl sulfoxide **2a** at the hindered site affording naphthofurans **5d** and **5e** selectively without forming regioisomers **4d** and **4e**, where cyclization took place at more electron-rich carbons.⁹ Moreover, we achieved the synthesis of benzofuran-fused benzofurans **4f** and **5f** in good yields, in which C–C bond formation at 4-position occurred primarily in moderate selectivity.

To clarify the reaction mechanism of the benzofuran formation, we conducted control experiments (Fig. 5A). In order to examine the stability of intermediates generated *in situ* by the electrophilic activation of sulfoxides, we performed the addition of aqueous sodium bicarbonate or phenol (**1a**) after the prior activation of alkynyl sulfoxide **2a** with TFAA in dichloromethane for 1 h at room temperature (Fig. 5A). As a result, sulfoxide **2a** or benzofuran **3a** was respectively obtained through the hydrolysis or the reaction with phenol (**1a**) in slightly decreased yields, suggesting that side reactions such as the Pummerer rearrangement did not take place smoothly even in the absence of phenols.¹⁰

A plausible reaction mechanism is shown in Fig. 5B. First, the formation of sulfurane intermediates **I'** from alkynyl sulfoxides **2** by the electrophilic activation with TFAA followed by the nucleophilic substitution with **1a** would afford intermediates **II**.³ Because side-products by the C–C bond formation of

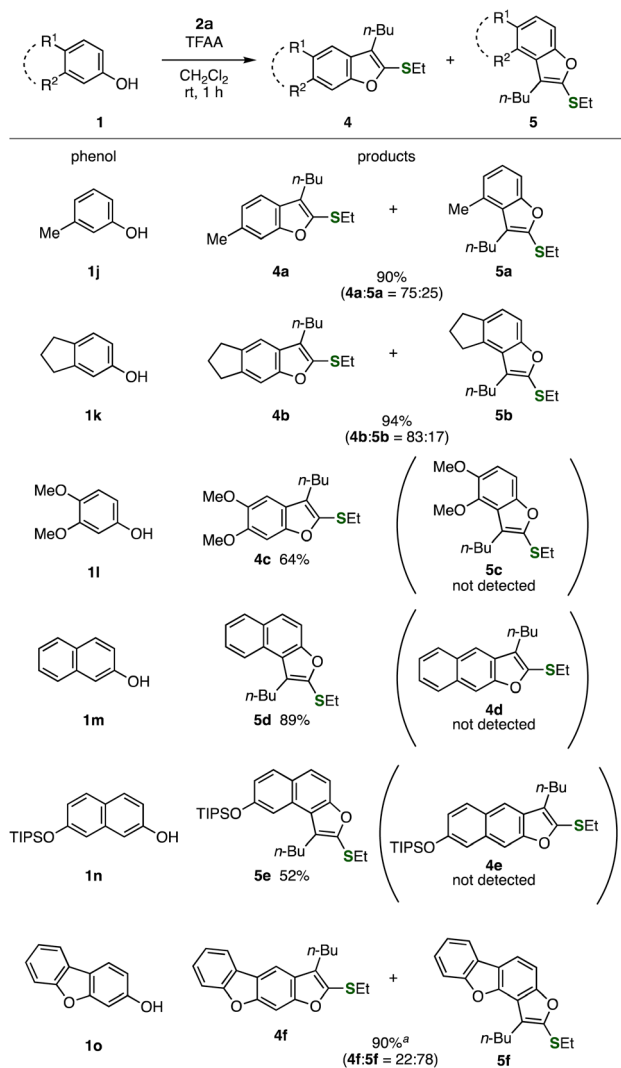


Fig. 4 Syntheses of benzofurans **4** and **5** using various phenols. See the ESI† for details. ^a ¹H NMR yield. Authentic samples (**4f** 7%; **5f** 65%) were isolated respectively.

activated alkynyl sulfoxides **I'** with **1a** at *para*-position were not observed,¹¹ smooth S–O bond formation providing intermediates **II** would take place as previously reported interrupted Pummerer reactions.⁴ Then, the sigmatropic rearrangement of alkynyl sulfuranes **II** and subsequent deprotonation lead to benzofurans **3**.¹²

Then, we showcased the benefits of the benzofuran synthesis from alkynyl sulfoxides and phenols (Fig. 6). A variety of benzofurans **3q–3s** were efficiently synthesized from alkyl halides **6a–6c**, sodium thiosulfonate, 1-hexyne, and phenol since sodium thiosulfonate worked as an “+S[−]” equivalent (Fig. 6A). Indeed, the preparation of alkynyl sulfides by *S*-alkylation and *S*-alkynylation followed by *S*-oxidation and the benzofuran formation allowed us to access easily functionalized benzofurans by the four-step four-component coupling protocols in a modular synthetic manner.

The good transformability of the sulfanyl group served in synthesizing a wide range of benzofurans (Fig. 6B). For example,



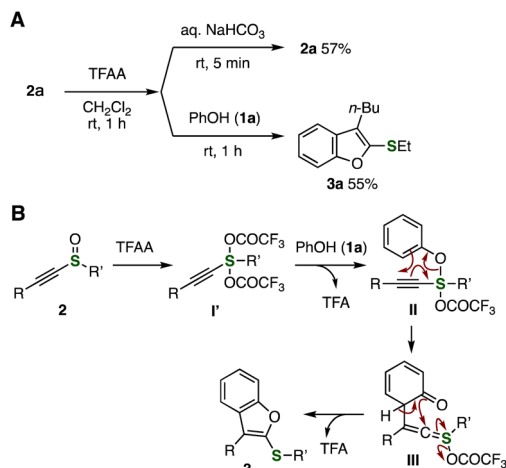


Fig. 5 Control experiments and reaction mechanism. (A) The reaction of alkyne sulfide **2a** with TFAA. (B) Plausible reaction mechanism. See the ESI† for details.

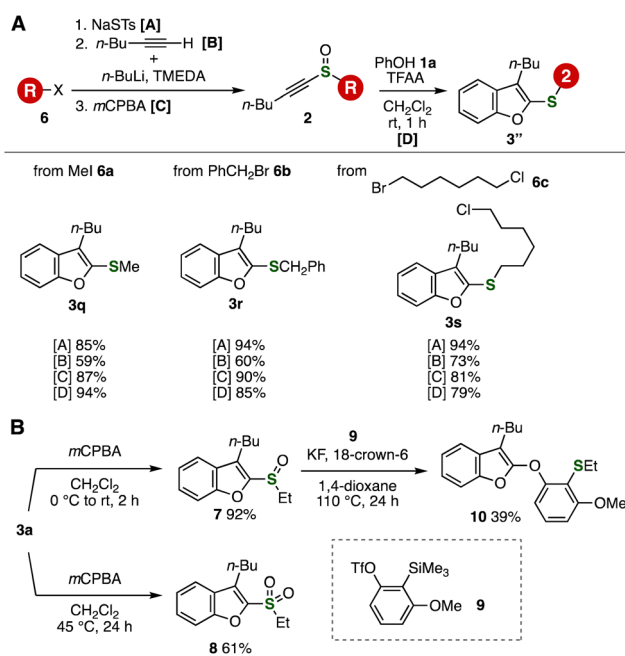


Fig. 6 (A) Benzofuran synthesis from alkyl halides. (B) Synthesis of organosulfur compounds from **3a**.

we succeeded in the preparation of sulfoxide **7** and sulfone **8** by *S*-oxidation of **3a**. Since a variety of transformations of the sulfinyl groups can be accomplished, the benzofuran formation and following *S*-oxidation and subsequent transformations such as aryne reactions^{13,14} realize the synthesis of highly functionalized benzofurans. Indeed, the migratory oxythiolation of 3-methoxybenzynes from *o*-silylaryl triflate **9** and sulfoxide **7** with potassium fluoride and 18-crown-6 in 1,4-dioxane at 110 °C took place smoothly to provide highly functionalized benzofuran **10** via the C–S and two C–O bond formations, in which the migration of the 3-butylbenzofuran-2-yl group selectively proceeded in the C–O bond formation.¹⁴

Conclusions

In conclusion, we found a new method to synthesize benzo[*b*]furans from alkyne sulfoxides and phenols by the electrophilic activation of the electron-deficient alkyne sulfinyl moiety. Owing to the ready availability of alkyne sulfoxides, the efficient synthetic method enabled us to prepare a wide range of functionalized benzofurans having sulfanyl groups. Since organo-sulfur substituents are easily transformed into various functional groups, the benzofuran synthesis will serve in developing diverse bioactive molecules. Further studies such as theoretical calculations are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Central Glass Co., Ltd for providing Tf₂O. This work was supported by JSPS KAKENHI Grant Number JP22H02086 (S. Y.), Uehara Foundation (S. Y.), and JST SPRING Grant Number JPMJSP2120 (A. K.).

Notes and references

- For selected examples, see: (a) A. D. Patil, A. J. Freyer, L. Killmer, P. Offen, B. Carte, A. J. Jurewicz and R. K. Johnson, *Tetrahedron*, 1997, **53**, 5047; (b) M. S. Malamas, J. Sredy, C. Moxham, A. Katz, W. Xu, R. McDevitt, F. O. Adebayo, D. R. Sawicki, L. Seestaller, D. Sullivan and J. R. Taylor, *J. Med. Chem.*, 2000, **43**, 1293; (c) H. Tsuji, C. Mitsui, L. Ilies, Y. Sato and E. Nakamura, *J. Am. Chem. Soc.*, 2007, **129**, 11902.
- A. W. Burgstahler and L. R. Worden, *Org. Synth.*, 1966, **46**, 28.
- For reviews, see: (a) S. K. Bur and A. Padwa, *Chem. Rev.*, 2004, **104**, 2401; (b) L. H. S. Smith, S. C. Coote, H. F. Sneddon and D. J. Procter, *Angew. Chem., Int. Ed.*, 2010, **49**, 5832; (c) H. Yorimitsu, *Chem. Rec.*, 2017, **17**, 1156; (d) D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, 2019, **119**, 8701.
- For selected examples, see: (a) T. Kobatake, D. Fujino, S. Yoshida, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2010, **132**, 11838; (b) X. Huang and N. Maulide, *J. Am. Chem. Soc.*, 2011, **133**, 8510; (c) Y. Ookubo, A. Wakamiya, H. Yorimitsu and A. Osuka, *Chem. Eur. J.*, 2012, **18**, 12690; (d) K. Murakami, H. Yorimitsu and A. Osuka, *Angew. Chem., Int. Ed.*, 2014, **53**, 7510; (e) H. J. Shriver, J. A. Fernández-Salas, C. Hedtke, A. P. Pulis and D. J. Procter, *Nat. Commun.*, 2017, **8**, 14801; (f) K. Okamoto, M. Hori, T. Yanagi, K. Murakami, K. Nogi and H. Yorimitsu, *Angew. Chem., Int. Ed.*, 2018, **57**, 14230; (g) K. Yang, A. P. Pulis, G. J. P. Perry and D. J. Procter, *Org. Lett.*, 2018, **20**, 7498; (h) M. Hori, T. Yanagi, K. Murakami, K. Nogi and H. Yorimitsu, *Bull. Chem. Soc. Jpn.*, 2019, **92**, 302; (i) T. Yanagi, K. Nogi and H. Yorimitsu, *Synlett*, 2020, **31**, 153.



- 5 For recent examples, see: (a) X. Meng, D. Chen, X. Cao, J. Luo, F. Wang and S. Huang, *Chem. Commun.*, 2019, **55**, 12495; (b) J. Li, Y. Chen, R. Zhong, Y. Zhang, J. Yang, H. Ding and Z. Wang, *Org. Lett.*, 2020, **22**, 1164; (c) K. Okamoto, K. Nogi and H. Yorimitsu, *Org. Lett.*, 2020, **22**, 5540; (d) M. Leypold, K. A. D'Angelo and M. Movassaghi, *Org. Lett.*, 2020, **22**, 8802; (e) D. Wang, C. G. Carlton, M. Tayu, J. J. W. McDouall, G. J. P. Perry and D. J. Procter, *Angew. Chem., Int. Ed.*, 2020, **59**, 15918; (f) U. Todorović, I. Klose and N. Maulide, *Org. Lett.*, 2021, **23**, 2510; (g) M. Hu, Y. Liu, Y. Liang, T. Dong, L. Kong, M. Bao, Z.-X. Wang and B. Peng, *Nat. Commun.*, 2022, **13**, 4719.
- 6 S. Yoshida, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2009, **11**, 2185.
- 7 When decreasing the amount of TFAA to 1.0 or 1.1 equivalents, the yield was decreased to 74 or 83%, respectively.
- 8 (a) K. Kanemoto, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 3172; (b) E. Godin, J. Santandrea, A. Caron and S. K. Collins, *Org. Lett.*, 2020, **22**, 5905; (c) A. Kobayashi, T. Matsuzawa, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 5429; (d) Q. Liu, X.-B. Li, M. Jiang, Z.-J. Liu and J.-T. Liu, *Tetrahedron*, 2021, **83**, 131994.
- 9 Treatment of a mixture between 2,6-naphthalenediol and alkynyl sulfide **2a** with TFAA afforded a complex mixture of product.
- 10 A. Padwa, D. E. Gunn and M. H. Osterhout, *Synthesis*, **1997**, 1353.
- 11 S. Yoshida, H. Yorimitsu and K. Oshima, *Chem. Lett.*, 2008, **37**, 786.
- 12 V. S. P. R. Lingam, R. Vinodkumar, K. Mukkanti, A. Thomas and B. Gopalan, *Tetrahedron Lett.*, 2008, **49**, 4260.
- 13 For selected reviews, see: (a) T. Matsuzawa, S. Yoshida and T. Hosoya, *Tetrahedron Lett.*, 2018, **59**, 4197; (b) R. Zhang, X. Peng and J. Tan, *Synthesis*, 2022, **54**, 5064.
- 14 T. Matsuzawa, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2017, **19**, 5521.

