

Cite this: *Chem. Sci.*, 2020, **11**, 9691

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 13th August 2020
Accepted 26th August 2020

DOI: 10.1039/d0sc04450d
rsc.li/chemical-science

Introduction

Benzothiophenes are a promising class of organosulfur compounds.^{1–3} In particular, multisubstituted benzothiophenes such as sertaconazole, raloxifene, and DNTT have served in a broad range of research fields including pharmaceutical sciences and materials chemistry (Fig. 1). In spite of their significance, although a number of benzothiophene syntheses such as transition-metal catalyzed reactions have been developed, the synthesis of multisubstituted benzothiophenes remains still difficult in terms of the applicable functional groups and substitution patterns due to the limited methods constructing the benzothiophene skeleton and introducing substituents.^{4,5} We herein present a novel approach to form benzothiophene scaffold from easily available alkynyl sulfides and aryne precursors.

Reactions of aryne intermediates with a variety of sulfides are attractive methods for preparing a wide range of organosulfur compounds (Fig. 2).^{6–9} In the 1980s, a pioneering study on the reaction between sulfides and benzene intermediate (**I**) generated from benzenediazonium-2-carboxylate was reported by Nakayama and coworkers (Fig. 2A).^{9a,b} Recently, an elegant difunctionalization of aryne intermediates was achieved by Studer and coworkers, in which C–S and C–C formations and C–S cleavage simultaneously took place (Fig. 2B).^{9b} Benzothiophene synthesis from *o*-silylaryl triflates and acyl-substituted ketene dithioacetals was developed by Singh and coworkers in 2016 through the formation of benzothiophene skeleton *via* aryne intermediates, and further addition with aryne intermediates (Fig. 2C).^{9c} On the basis of our recent studies of synthetic aryne chemistry,¹⁰ we envisioned that benzothiophenes can be synthesized from aryne precursors and alkynyl sulfides,^{11,12}

starting from the nucleophilic attack of the sulfur or carbon of alkynyl sulfides to electrophilic aryne intermediates followed by ring-closure (Fig. 2D).

Results and discussion

First, a reaction between 2-chloro-6-(trimethylsilyl)phenyl triflate (**1a**) and ethyl *p*-tolylethynyl sulfide (**2a**) was examined (Fig. 3A and B). As a result, we found that treatment of a mixture

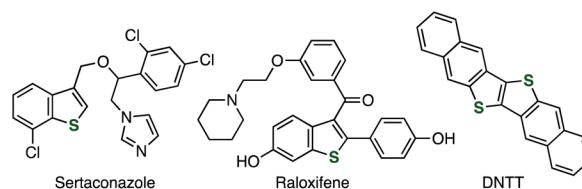


Fig. 1 Various benzothiophene derivatives.

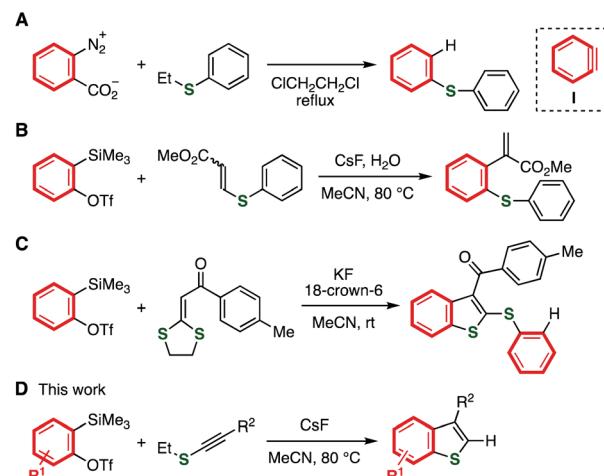


Fig. 2 Aryne reactions with organosulfur compounds. (A) Nakayama's study. (B) Studer's work. (C) Singh's work. (D) This work.

Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan. E-mail: s-yoshida.cb@tmd.ac.jp

† Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: [10.1039/d0sc04450d](https://doi.org/10.1039/d0sc04450d)



between aryne precursor **1a** and alkynyl sulfide **2a** with cesium fluoride in hot acetonitrile provided 3-(4-tolyl)-4-chlorobenzothiophene (**3a**) in high yield. The construction of benzothiophene scaffold was accomplished by C-S bond formation selectively at C1 of 3-chlorobenzyne (**II**), C-C bond formation, protonation, and deethylation, where the regioisomer was not detected. When the reaction was conducted on a larger scale

using 2 mmol of alkynyl sulfide **2a**, the yield of benzothiophene **3a** was slightly decreased. Increasing concentration from 0.05 M to 0.2 or 0.5 M slightly reduced the yield of **3a** (64% or 52%, respectively).¹³ Benzothiophene **3a** was also obtained in moderate to good yields even when the amount of aryne precursor **1a** was decreased from 3.0 equiv. to 2.0, 1.5, and 1.2 equiv.¹³ These results show good practicality of the benzothiophene synthesis from *o*-silylaryl triflates **1** and alkynyl sulfides **2**. The reaction of aryne precursor **1a** with methyl, isopropyl, or benzyl *p*-tolylethynyl sulfides instead of **2a** also afforded benzothiophene **3a**, although **3a** was not detected in the case of *p*-tolyl *p*-tolylethynyl sulfide.¹³

A broad range of 3-aryl- and 3-alkyl-substituted benzothiophene were prepared from aryne precursor **1a** and various alkynyl sulfides **2** (Fig. 3A and B). For example, electron-donating methoxy- and electron-withdrawing chloro- and methoxycarbonyl-substituted arylethynyl ethyl sulfides smoothly reacted with aryne intermediates to afford benzothiophene **3b–d** without damaging these functional groups. Bulky 2-bromophenylethynyl ethyl sulfide also participated in the reaction providing **3e** in good yield. Furthermore, benzothiophenes **3f** and **3g** having π -extended aromatics and **3h** possessing heteroaromatic thiophene ring were synthesized efficiently from the corresponding alkynyl sulfides. The reaction of primary and secondary alkylethynyl ethyl sulfides with aryne intermediates also proceeded under the same conditions to afford **3i** and **3j** in high yields. Moreover, we succeeded in the synthesis of benzothiophene **3k** from alkynyl sulfide **2k** prepared from an ethynylestradiol derivative. Since a wide variety of alkynyl sulfides were easily available from the corresponding terminal alkynes and thiosulfonates catalyzed by copper as we recently reported,^{12e} this method enables the synthesis of diverse 3-substituted benzothiophenes.

Diverse aryne precursors were applicable to the one-step benzothiophene synthesis enabling to prepare a variety of benzothiophenes **3l–v** (Fig. 3A and C). Not only simple benzene but also 3-fluoro-, 3-bromo-, 3-methoxy-, and 3-aminobenzene intermediates reacted with alkynyl sulfide **2a** to furnish **3l–p** in moderate to good yields leaving these functional groups untouched, in which regioisomers were not detected. Especially, selective C-S bond formation proceeded in the reaction of aryne intermediates bearing functional groups at 3-position, showing that the benzothiophene formation triggered by the nucleophilic attack of the sulfur atom onto C1 of the 3-substituted aryne intermediates due to the inductive effect of fluorine, bromine, oxygen, and nitrogen.¹⁴ Reactions of 4-methoxy- and 4-methylbenzyne with alkynyl sulfide **2a** furnished ca. 1 : 1 mixtures of regioisomers of benzothiophenes **3q** and **3r** in moderate to high yields. Trisubstituted benzothiophenes **3s** and **3t** were also synthesized from the corresponding *o*-silylaryl triflates. It is worthy to note that the synthesis of π -conjugated benzothiophenes **3u** and **3v** was accomplished from the corresponding benzothiophene- and phenanthrene-type *o*-silylaryl triflates.^{10c} The broad scope of the synthesizable benzothiophenes clearly demonstrated a benefit of this method by virtue of the recent remarkable advancement of the accessibility

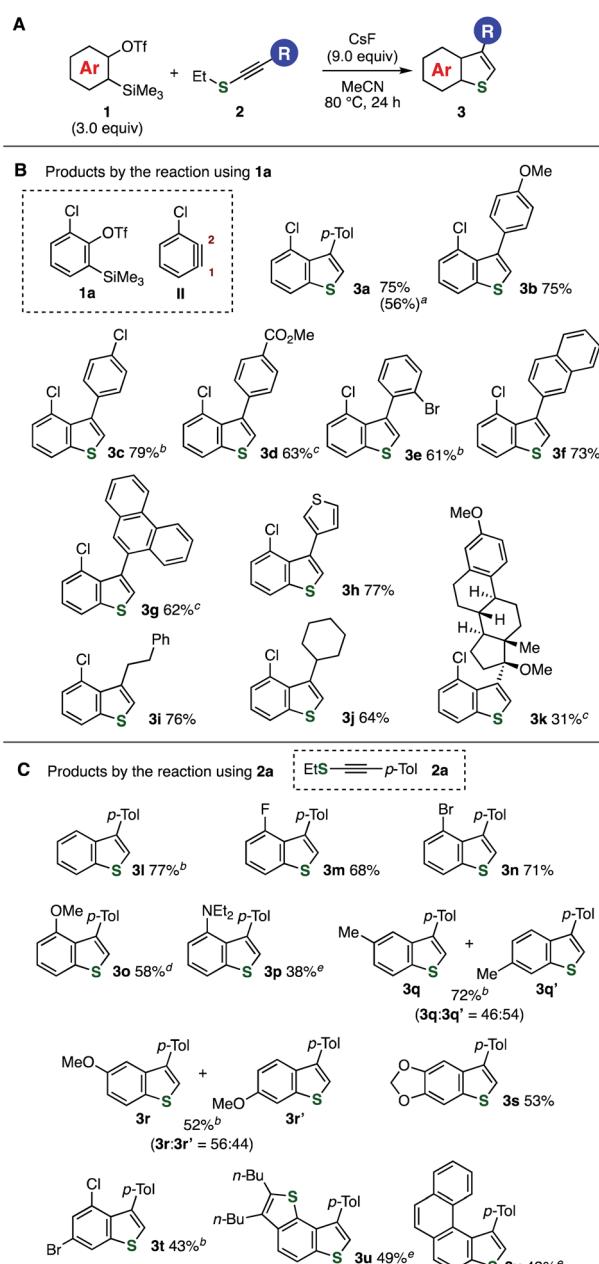


Fig. 3 Synthesis of benzothiophenes **3** from *o*-silylaryl triflates **1** and alkynyl sulfides **2**. See, the ESI† for the structures of **1** and **2**. (A) General scheme. (B) Reactions of various alkynyl sulfides **2** with **1a**. (C) Reactions of various *o*-silylaryl triflates **1** with **2a**. ^a Isolated yield using 2.0 mmol of **2a** in parentheses. ^b The reactions were performed in 1,4-dioxane at 110 °C. ^c The reactions were performed using 5.0 equiv. of **1** and 15 equiv. of CsF. ^d The reaction was performed at rt. ^e The reactions were performed using 5.0 equiv. of **1** and 15 equiv. of CsF in 1,4-dioxane at 110 °C.



of *o*-silylaryl triflates and predictable reactivity of aryne intermediates by the aryne distortion model.¹⁴

A plausible reaction mechanism is shown in Fig. 4A. First, the nucleophilic addition of the sulfur atom of alkynyl sulfides onto arynes and following cyclization to the alkyne carbon construct the benzothiophene skeleton. Then, protonation of the resulting zwitterionic intermediate **IV** leads to benzothiophene **3a**. To examine the proton source, we then performed control experiments using deuterated compounds (Fig. 4B–D). Treatment of *o*-silylaryl triflate **1a** and alkynyl sulfide **2a** dissolved in CD₃CN with cesium fluoride provided benzothiophene **3a** with partial incorporation of deuterium through sulfonium intermediate **V–d** (Fig. 4B).^{9b,15} The reaction using deuterium-labeled ethyl *p*-tolylethynyl sulfide **2a–d** in acetonitrile also resulted in partial deuterium incorporation, suggesting intramolecular deuteration of zwitterionic intermediate **IV**.

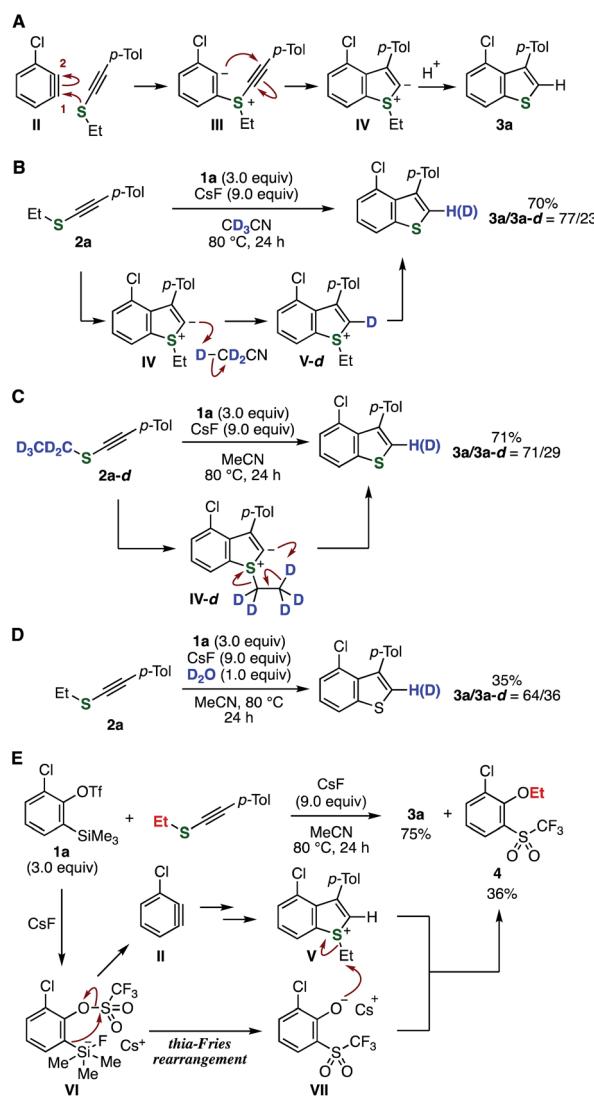


Fig. 4 Mechanistic studies. (A) Plausible reaction pathway. (B) Deuteration experiment using CD₃CN. (C) Deuteration experiment using **2a–d**. (D) Deuteration experiment in the presence of D₂O. (E) Mechanistic insights from side-product **4**.

d with liberating ethylene (Fig. 4C).^{9m} An alternative proton source would be water in the reagents used, since deuterium was incorporated when the reaction was performed in the presence of deuterium oxide (Fig. 4D). Moreover, 2-chloro-6-(trifluoromethanesulfonyl)phenyl ethyl ether (**4**) was detected as a side-product in the synthesis of **3a**, clearly showing that 2-chloro-6-(trifluoromethanesulfonyl)phenolate intermediate **VII** was generated from **1a** via the thia-Fries rearrangement of silicate intermediate **VI**,¹⁶ and cesium phenolate **VII** was involved in the deethylation process of sulfonium intermediate **V** (Fig. 4E). Thus, possible protonation and deethylation mechanisms from zwitterionic intermediate **IV** were supported by these results.

Various C2-functionalizations of benzothiophene **3a** allowed for the preparation of a wide range of 2,3,4-trisubstituted benzothiophenes (Fig. 5).¹⁷ For example, selective deprotonation of **3a** with lithium diisopropylamide (LDA) proceeded efficiently (Fig. 5A). Sulfanylation, iodination, and ethoxycarbonylation of the resulting 2-benzothiophenyllithium **VIII** provided benzothiophenes **5a–c** in good yields. Furthermore, *S*-oxidation followed by the Pummerer-type C2-arylation with phenol through [3,3]-sigmatropic rearrangement selectively afforded benzothiophene **7** (Fig. 5B).^{17h} Additionally, treatment of *o*-silylaryl triflate **1a** and alkynyl sulfide **2a** with cesium fluoride under carbon dioxide furnished benzothiophene **5c** having an ester moiety albeit in low yield, where C–C bond formation of zwitterionic intermediate **IV** and subsequent migration of the ethyl group occurred (Fig. 5C).

We succeeded in the preparation of C3-functionalized benzothiophene **10** from alkyne **8** and aryne precursor **1a** through C–C cleavage of carboxylic acid **9** by virtue of the good accessibility of alkynyl sulfides and broad substrate scope of the aryne

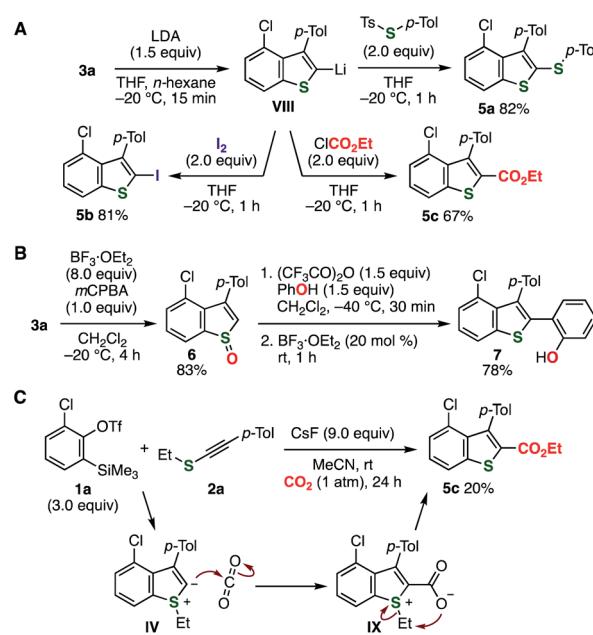


Fig. 5 C2-functionalizations of benzothiophene **3a**. (A) Transformations through C2-deprotonation. (B) Arylation via Pummerer-type activation. (C) Direct ester formation.

reaction (Fig. 6A). Indeed, latently transformable alkynyl sulfide **2l** was synthesized from terminal alkyne **8** and *S*-ethyl *p*-toluenethiosulfonate catalyzed by CuI/xantphos under mild conditions.^{12e} Following aryne reaction between **2l** and *o*-silylaryl triflate **1a** and subsequent removal of the tetrahydropyranyl (THP) group successfully afforded benzothiophene **3w** having chloro and hydroxymethyl groups. Then, carboxylic acid **9** was prepared by oxidation with *tert*-butyl hydroperoxide catalyzed by copper(II) bromide.¹⁸ Considering that recent remarkable achievements for transformations of the carboxy group into a range of functional groups such as halogens, phosphorus moieties, and aryl groups through C–C cleavage,¹⁹ diverse C3-functionalized benzothiophenes will be synthesized from

benzothiophene **9**. For example, decarboxylative iodination of **9** took place smoothly to provide 4-chloro-3-iodobenzothiophene (**10**) in high yield.^{19b} Thus, a wide variety of benzothiophenes can be synthesized through the aryne reaction between alkynyl sulfide **2l** and *o*-silylaryl triflates and decarboxylative transformations.

We achieved the synthesis of benzothiophene **12** bearing four different aryl groups by virtue of the halogen-tolerated benzothiophene synthesis and the versatility of C2-position (Fig. 6B). Indeed, direct C–H arylation of benzothiophene **3t** with 4-iodoanisole proceeded smoothly to provide **11** in moderate yield keeping bromo and chloro groups intact.¹⁷ⁱ Then, a sequential Suzuki–Miyaura cross-coupling of **11** with 4-(trifluoromethyl)phenylboronic acid and phenylboronic acid at the bromo and chloro group, respectively, successfully furnished 2,3,4,6-tetraarylbenzothiophene **12**. This modular synthetic route would enable the preparation of diverse multi-arylated benzothiophenes using various alkynyl sulfides, aryl iodides, and arylboronic acids.²⁰

The good accessibility of *o*-silylaryl triflates and alkynyl sulfides realized the synthesis of polycyclic aromatic compound **14** (Fig. 6C). Firstly, the treatment of 6,7-thienobenzyne precursor **1k** and alkynyl sulfide **2e** with cesium fluoride afforded dithienobenzene **3x** in moderate yield. Then, C2-iodination was realized by deprotonation with LDA followed by the addition of iodine. Finally, palladium-catalyzed amination at C2 of benzothiophene with *p*-toluidine and subsequent cyclization proceeded efficiently to afford pentahelicene analog **14**. This result clearly demonstrated an advantage of the benzothiophene synthesis by the aryne reaction with alkynyl sulfides enabling to prepare π -extended benzothiophenes having functional groups such as halogens. The benzothiophene synthesis will serve in the synthesis of various polycyclic analogs containing benzothiophene skeleton.²¹

Conclusions

In summary, we have developed a facile one-step synthetic method of benzothiophenes from *o*-silylaryl triflates and alkynyl sulfides. The wide scope of the benzothiophene synthesis and the versatile C2-functionalizations enabled the synthesis of a variety of multisubstituted benzothiophenes, which is difficult by the conventional methods. Further studies to clarify the reaction mechanism and to expand synthesizable multi-substituted benzothiophenes involving three-component couplings, and applications to synthesize analogs of bioactive compounds are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Dr Yuki Sakata at Tokyo Medical and Dental University for HRMS analyses. This work was supported by JSPS KAKENHI Grant Numbers JP19K05451 (C; S. Y.), JP18H02104 (B;

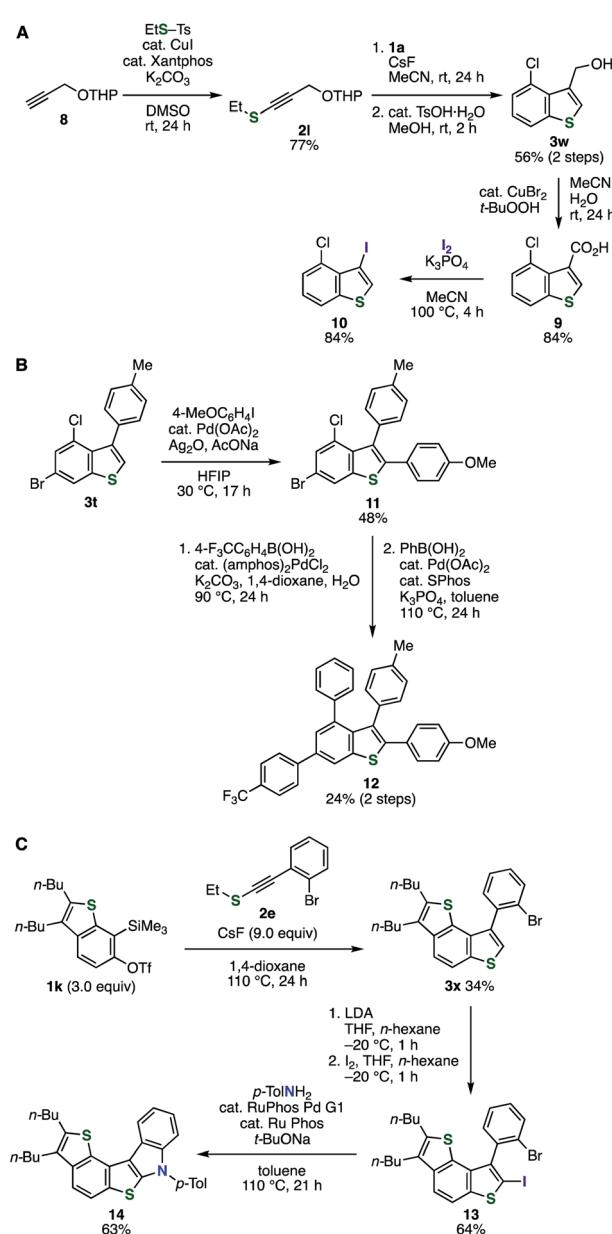


Fig. 6 Applications of the benzothiophene synthesis. (A) Benzothiophene synthesis through C3-functionalizations. (B) Synthesis of tetraarylbenzothiophene **12**. (C) Synthesis of pentacyclic compound **14**.

T. H.), JP18H04386 (Middle Molecular Strategy; T. H.), and 19J14128 (JSPS Research Fellow; T. M.); the Naito Foundation (S. Y.); the Japan Agency for Medical Research and Development (AMED) under Grant Numbers JP20am0101098 (Platform Project for Supporting Drug Discovery and Life Science Research, BINDS) and JP20gm0910007 (CREST); and the Cooperative Research Project of Research Center for Biomedical Engineering.

Notes and references

- (a) J. D. Croxtall and G. L. Plosker, *Drugs*, 2009, **69**, 339; (b) S. Dadiboyena, *Eur. J. Med. Chem.*, 2012, **51**, 17; (c) R. Romagnoli, P. G. Baraldi, C. Lopez-Cara, D. Preti, M. A. Tabrizi, J. Balzarini, M. Bassetto, A. Brancale, X.-H. Fu, Y. Gao, J. Li, S.-Z. Zhang, E. Hamel, R. Bortolozzi, G. Basso and G. Viola, *J. Med. Chem.*, 2013, **56**, 9296; (d) R. S. Keri, K. Chand, S. Budagumpi, S. B. Somappa, S. A. Patil and B. M. Nagaraja, *Eur. J. Med. Chem.*, 2017, **138**, 1002; (e) Y. Lu, L. M. Gutgesell, R. Xiong, J. Zhao, Y. Li, C. I. Rosales, M. Hollas, Z. Shen, J. Gordon-Blake, K. Dye, Y. Wang, S. Lee, H. Chen, D. He, O. Dubrovskiy, H. Zhao, F. Huang, A. W. Lasek, D. A. Tonetti and G. R. J. Thatcher, *J. Med. Chem.*, 2019, **62**, 11301.
- For our study on bioactive benzo[b]thiophenes, see: S. Shimizu, T. Hosoya, M. Murohashi and S. Yoshida, WO2013/118842, 2013.
- (a) T. Yamamoto and K. Takimiya, *J. Am. Chem. Soc.*, 2007, **129**, 2224; (b) H. Takenaka, T. Ogaki, C. Wang, K. Kawabata and K. Takimiya, *Chem. Mater.*, 2019, **31**, 6696.
- For a review on benzothiophene synthesis, see: B. Wu and N. Yoshikai, *Org. Biomol. Chem.*, 2016, **14**, 5402.
- For examples of benzothiophene synthesis, see: (a) R. C. Larock and D. Yue, *Tetrahedron Lett.*, 2001, **42**, 6011; (b) S. Yoshida, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2007, **9**, 5573; (c) C. S. Bryan, J. A. Braunger and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 7064; (d) L.-L. Sun, C.-L. Deng, R.-Y. Tang and X.-G. Zhang, *J. Org. Chem.*, 2011, **76**, 7546; (e) T. Kunz and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 1958; (f) D. P. Hari, T. Hering and B. König, *Org. Lett.*, 2012, **14**, 5334; (g) K. Liu, F. Jia, H. Xi, Y. Li, X. Zheng, Q. Guo, B. Shen and Z. Li, *Org. Lett.*, 2013, **15**, 2026; (h) B. Wu and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 10496; (i) A. Acharya, S. V. Kumar and H. Ila, *Chem.-Eur. J.*, 2015, **21**, 17116; (j) Y. Masuya, M. Tobisu and N. Chatani, *Org. Lett.*, 2016, **18**, 4312; (k) A. J. Eberhart, H. Shrives, Y. Zhang, A. Carrér, A. V. S. Parry, D. J. Tate, M. L. Turner and D. J. Procter, *Chem. Sci.*, 2016, **7**, 1281; (l) L. Gao, B. Chang, W. Qiu, L. Wang, X. Fu and R. Yuan, *Adv. Synth. Catal.*, 2016, **358**, 1202; (m) L. Meng, T. Fujikawa, M. Kuwayama, Y. Segawa and K. Itami, *J. Am. Chem. Soc.*, 2016, **138**, 10351; (n) S. Yugandar, S. Konda and H. Ila, *Org. Lett.*, 2017, **19**, 1512; (o) Z. Zheng, L. Chen, C. Qian, X. Zhu, Y. Yang, J. Liu, Y. Yang and Y. Liang, *Org. Biomol. Chem.*, 2018, **16**, 8020; (p) S. Mikami, H. Tanaka, H. Kishi, S. Yoshida and K. Toyota, *Heterocycles*, 2018, **96**, 1529; (q) R. Zhu, Z. Liu, J. Chen, X. Xiong, Y. Wang, L. Huang, J. Bai, Y. Dang and J. Huang, *Org. Lett.*, 2018, **20**, 3161; (r) J. Yan, A. P. Pulis, G. J. P. Perry and D. J. Procter, *Angew. Chem., Int. Ed.*, 2019, **58**, 15675; (s) A. Mizukami, M. Tsugita, M. Shimura, S. Tanaka, N. Hayama, T. Kimachi and K. Inamoto, *Chem. Lett.*, 2019, **48**, 468; (t) S. Uchida, H. Kinoshita and K. Miura, *Org. Lett.*, 2020, **22**, 3123; (u) S. Moon, M. Kato, Y. Nishii and M. Miura, *Adv. Synth. Catal.*, 2020, **362**, 1669.
- For selected recent reviews on arynes, see: (a) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550; (b) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191; (c) S. Yoshida and T. Hosoya, *Chem. Lett.*, 2015, **44**, 1450; (d) J.-A. García-López and M. F. Greaney, *Chem. Soc. Rev.*, 2016, **45**, 6766; (e) J. Shi, Y. Li and Y. Li, *Chem. Soc. Rev.*, 2017, **46**, 1707; (f) F. I. M. Idiris and C. R. Jones, *Org. Biomol. Chem.*, 2017, **15**, 9044; (g) T. Roy and A. T. Biju, *Chem. Commun.*, 2018, **54**, 2580; (h) S. Yoshida, *Bull. Chem. Soc. Jpn.*, 2018, **91**, 1293; (i) H. Takikawa, A. Nishii, T. Sakai and K. Suzuki, *Chem. Soc. Rev.*, 2018, **47**, 8030; (j) Y. Nakamura, S. Yoshida and T. Hosoya, *Heterocycles*, 2019, **98**, 1623.
- For selected aryne chemistries, see: (a) U. N. Rao and E. Biehl, *J. Org. Chem.*, 2002, **67**, 3409; (b) Y. Chen and M. C. Willis, *Org. Lett.*, 2015, **17**, 4786; (c) J. Shi, D. Qiu, J. Wang, H. Xu and Y. Li, *J. Am. Chem. Soc.*, 2015, **137**, 5670; (d) W. Ding, A. Yu, L. Zhang and X. Meng, *Org. Lett.*, 2019, **21**, 9014; (e) M. Mesgar, J. Nguyen-Le and O. Daugulis, *J. Am. Chem. Soc.*, 2018, **140**, 13703; (f) R. N. Gaykar, A. Guin, S. Bhattacharjee and A. T. Biju, *Org. Lett.*, 2019, **21**, 9613; (g) J. He, Z. Jia, H. Tan, X. Luo, D. Qiu, J. Shi, H. Xu and Y. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 18513; (h) H. Takikawa, A. Nishii and K. Suzuki, *Chem. Sci.*, 2019, **10**, 3840; (i) E. Yen-Pon, P. A. Champagne, L. Plougastel, S. Gabillet, P. Thuéry, M. Johnson, G. Muller, G. Pieters, F. Taran, K. N. Houk and D. Audisio, *J. Am. Chem. Soc.*, 2019, **141**, 1435; (j) X. Xiao and T. R. Hoye, *J. Am. Chem. Soc.*, 2019, **141**, 9813; (k) S. K. Thompson and T. R. Hoye, *J. Am. Chem. Soc.*, 2019, **141**, 19575; (l) T. Hosokawa, T. Asada and K. Kamikawa, *J. Phys. Chem. A*, 2020, **124**, 652; (m) T. Ikawa, S. Masuda and S. Akai, *Chem.-Eur. J.*, 2020, **26**, 4320; (n) W. Cao, S.-L. Niu, L. Shuai and Q. Xiao, *Chem. Commun.*, 2020, **56**, 972; (o) H. Hazarika and P. Gogoi, *Org. Biomol. Chem.*, 2020, **18**, 2727; (p) S. Ghorai, Y. Lin, Y. Xia, D. J. Wink and D. Lee, *Org. Lett.*, 2020, **22**, 626; (q) S. Cho and Q. Wang, *Org. Lett.*, 2020, **22**, 1670; (r) H. Fujimoto, M. Kusano, T. Kodama and M. Tobisu, *Org. Lett.*, 2020, **22**, 2293; (s) H. Takikawa, A. Nishii, H. Takiguchi, H. Yagishita, M. Tanaka, K. Hirano, M. Uchiyama, K. Ohmori and K. Suzuki, *Angew. Chem., Int. Ed.*, 2020, **59**, 12440.
- For reviews on reactions between arynes and organosulfur compounds, see: (a) J. Nakayama and K. Akimoto, *Sulfur Rep.*, 1994, **16**, 61; (b) T. Matsuzawa, S. Yoshida and T. Hosoya, *Tetrahedron Lett.*, 2018, **59**, 4197.
- (a) J. Nakayama, T. Fujita and M. Hoshino, *Chem. Lett.*, 1982, **11**, 1777; (b) J. Nakayama, T. Fujita and M. Hoshino, *Chem. Lett.*, 1983, **12**, 249; (c) S. Yoshida, K. Uchida, K. Igawa, K. Tomooka and T. Hosoya, *Chem. Commun.*, 2014, **50**, 15059;





(d) H.-D. Xu, M.-Q. Cai, W.-J. He, W.-H. Hu and M.-H. Shen, *RSC Adv.*, 2014, **4**, 7623; (e) M. Pawliczek, L. K. B. Garve and D. B. Werz, *Chem. Commun.*, 2015, **51**, 9165; (f) J. Chen, V. Palani and T. R. Hoye, *J. Am. Chem. Soc.*, 2016, **138**, 4318; (g) L.-R. Wen, N.-N. Man, W.-K. Yuan and M. Li, *J. Org. Chem.*, 2016, **81**, 5942; (h) Y. Li, C. Mück-Lichtenfeld and A. Studer, *Angew. Chem., Int. Ed.*, 2016, **55**, 14435; (i) M. Thangaraj, R. N. Gaykar, T. Roy and A. T. Biju, *J. Org. Chem.*, 2017, **82**, 4470; (j) M. M. Ahire, R. Khan and S. B. Mhaske, *Org. Lett.*, 2017, **19**, 2134; (k) X.-B. Xu, Z.-H. Lin, Y. Liu, J. Guo and Y. He, *Org. Biomol. Chem.*, 2017, **15**, 2716; (l) J. Tan, T. Zheng, K. Xu and C. Liu, *Org. Biomol. Chem.*, 2017, **15**, 4946; (m) L. Zhang, X. Li, Y. Sun, W. Zhao, F. Luo, X. Huang, L. Lin, Y. Yang and B. Peng, *Org. Biomol. Chem.*, 2017, **15**, 7181; (n) H. Jian, Q. Wang, W.-H. Wang, Z.-J. Li, C.-Z. Gu, B. Dai and L. He, *Tetrahedron*, 2018, **74**, 2876; (o) P. Garg and A. Singh, *Org. Lett.*, 2018, **20**, 1320; (p) T. Zheng, J. Tan, R. Fan, S. Su, B. Liu, C. Tan and K. Xu, *Chem. Commun.*, 2018, **54**, 1303; (q) R. Fan, B. Liu, T. Zheng, K. Xu, C. Tan, T. Zeng, S. Su and J. Tan, *Chem. Commun.*, 2018, **54**, 7081; (r) Y. Nakamura, Y. Miyata, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 5252; (s) P. Singh, A. G. Cairns, D. E. Adolfsson, J. Ådén, U. H. Sauer and F. Almqvist, *Org. Lett.*, 2019, **21**, 6946; (t) P. Xiao, S. Su, W. Wang, W. Cao, J. Chen, J. Li and Y. Chen, *RSC Adv.*, 2019, **9**, 39119.

10 For selected recent studies of our aryne chemistries, see: (a) T. Matsuzawa, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2017, **19**, 5521; (b) T. Matsuzawa, K. Uchida, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2018, **47**, 825; (c) S. Yoshida, T. Kuribara, T. Morita, T. Matsuzawa, K. Morimoto, T. Kobayashi and T. Hosoya, *RSC Adv.*, 2018, **8**, 21754; (d) Y. Nishiyama, S. Kamada, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2018, **47**, 1216; (e) T. Meguro, S. Chen, K. Kanemoto, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2019, **48**, 582; (f) S. Yoshida, Y. Hazama, K. Kanemoto, Y. Nakamura and T. Hosoya, *Chem. Lett.*, 2019, **48**, 742; (g) Y. Nakamura, S. Ozawa, S. Yoshida and T. Hosoya, *Chem. Lett.*, 2019, **48**, 1296; (h) K. Uchida, Y. Minami, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 9019; (i) T. Kobayashi, T. Hosoya and S. Yoshida, *J. Org. Chem.*, 2020, **85**, 4448; (j) K. Kanemoto, Y. Sakata, T. Hosoya and S. Yoshida, *Chem. Lett.*, 2020, **49**, 593.

11 For selected transformations of alkynyl sulfides, see: (a) I. D. Gridnev, N. Miyaura and A. Suzuki, *J. Org. Chem.*, 1993, **58**, 5351; (b) C. Savarin, J. Srogl and L. S. Liebeskind, *Org. Lett.*, 2001, **3**, 91; (c) L. Aurelio, R. Volpe, R. Halim, P. J. Scammells and B. L. Flynn, *Adv. Synth. Catal.*, 2014, **356**, 1974; (d) L.-G. Xie, S. Shaaban, X. Chen and N. Maulide, *Angew. Chem., Int. Ed.*, 2016, **55**, 12864; (e) R. J. Reddy, M. P. Ball-Jones and P. W. Davies, *Angew. Chem., Int. Ed.*, 2017, **56**, 13310; (f) P. Sharma, R. R. Singh, S. S. Giri, L.-Y. Chen, M.-J. Cheng and R.-S. Liu, *Org. Lett.*, 2019, **21**, 5475; (g) H.-Z. Bu, H.-H. Li, W.-F. Luo, C. Luo, P.-C. Qian and L.-W. Ye, *Org. Lett.*, 2020, **22**, 648; (h) M. B. Reddy and R. Anandhan, *Chem. Commun.*, 2020, **56**, 3781.

12 (a) G. R. Ziegler, C. A. Welch, C. E. Orzech, S. Kikkawa and S. I. Miller, *J. Am. Chem. Soc.*, 1963, **85**, 1648; (b) M. Arisawa, K. Fujimoto, S. Morinaka and M. Yamaguchi, *J. Am. Chem. Soc.*, 2005, **127**, 12226; (c) R. Frei and J. Waser, *J. Am. Chem. Soc.*, 2013, **135**, 9620; (d) W. Wang, X. Peng, F. Wei, C.-H. Tung and Z. Xu, *Angew. Chem., Int. Ed.*, 2016, **55**, 649; (e) K. Kanemoto, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 3172; (f) W.-C. Gao, Y.-Z. Shang, H.-H. Chang, X. Li, W.-L. Wei, X.-Z. Yu and R. Zhou, *Org. Lett.*, 2019, **21**, 6021.

13 See the ESI† for the details.

14 (a) J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 15798; (b) E. Picazo, K. N. Houk and N. K. Garg, *Tetrahedron Lett.*, 2015, **56**, 3511; (c) S. Yoshida, Y. Nakamura, K. Uchida, Y. Hazama and T. Hosoya, *Org. Lett.*, 2016, **18**, 6212.

15 Ethyl triflate was not detected in the ¹H NMR analysis of the reaction mixture in CD₃CN before quenching.

16 C. Hall, J. L. Henderson, G. Ernouf and M. F. Greaney, *Chem. Commun.*, 2013, **49**, 7602.

17 For selected examples of functionalizations of benzothiophenes, see: (a) A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 2958; (b) H. A. Chiong and O. Daugulis, *Org. Lett.*, 2007, **9**, 1449; (c) J.-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama and F. Mongin, *J. Org. Chem.*, 2008, **73**, 177; (d) B. Liégault, D. Lapointe, L. Caron, A. Vlassova and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 1826; (e) T. Liu, X. Shao, Y. Wu and Q. Shen, *Angew. Chem., Int. Ed.*, 2012, **51**, 540; (f) T. Iitsuka, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2015, **80**, 2804; (g) J. M. Hammann, D. Haas and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 4478; (h) Z. He, H. J. Shrvies, J. A. Fernández-Salas, A. Abengózar, J. Neufeld, K. Yang, A. P. Pulis and D. J. Procter, *Angew. Chem., Int. Ed.*, 2018, **57**, 5759; (i) C. Colletto, A. Panigrahi, J. Fernández-Casado and I. Larrosa, *J. Am. Chem. Soc.*, 2018, **140**, 9638; (j) M. Shigeno, K. Hanasaki, K. Sasaki, K. Nozawa-Kumada and Y. Kondo, *Chem.-Eur. J.*, 2019, **25**, 3235; (k) Z.-K. Wen, Z.-K. Zhao, N.-J. Wang, Z.-L. Chen, J.-B. Chao and L.-H. Feng, *Org. Lett.*, 2019, **21**, 9545; (l) J. H. Jang, S. Ahn, S. E. Park, S. Kim, H. R. Byon and J. M. Joo, *Org. Lett.*, 2020, **22**, 1280.

18 R. Das and D. Chakraborty, *Appl. Organomet. Chem.*, 2011, **25**, 437.

19 (a) Y. Zhang, H. Zhao, M. Zhang and W. Su, *Angew. Chem., Int. Ed.*, 2015, **54**, 3817; (b) G. J. P. Perry, J. M. Quibell, A. Panigrahi and I. Larrosa, *J. Am. Chem. Soc.*, 2017, **139**, 11527; (c) J. M. Quibell, G. J. P. Perry, D. M. Cannas and I. Larrosa, *Chem. Sci.*, 2018, **9**, 3860; (d) J.-S. Zhang, T. Chen and L.-B. Han, *Eur. J. Org. Chem.*, 2020, 1148; (e) Y. Wang, B. Li and B. Wang, *Org. Lett.*, 2020, **22**, 83.

20 S. Suzuki and J. Yamaguchi, *Chem. Commun.*, 2017, **53**, 1568.

21 (a) Y. Liao, Y. Peng, H. Qi, G.-J. Deng, H. Gongac and C.-J. Li, *Chem. Commun.*, 2015, **51**, 1031; (b) H. Qi, Y. Zhang, Q. Tao, J. Chen, Z. Li, X. Xu, H. Tan, Q. Peng and W. Zhu, *Tetrahedron*, 2016, **72**, 7430; (c) H. Qi, X. Xu, Q. Tao, Y. Zhang, M. Zhu, L. Shao, W. Zhu, Q. Peng and Y. Liao, *Dyes Pigm.*, 2017, **142**, 406.