RSC Advances

PAPER

View Article Online
View Journal | View Issue

Open Access Article. Published on 29 November 2019. Downloaded on 11/26/2025 10:29:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Check for updates

Cite this: *RSC Adv.*, 2019, **9**, 39119

Sequential cycloaddition and ring expansion reaction of arynes and methylenebenzothiopheneones: synthesis of a benzo-fused eight-membered ring *via* sulfonium ylides†

Peng Xiao,[a] Shikuan Su,[a] Wei Wang,[a] Weiguo Cao,[a] Jie Chen,[a] Jian Li *[a] and Yali Chen *[ab]

Received 19th October 2019
Accepted 18th November 2019

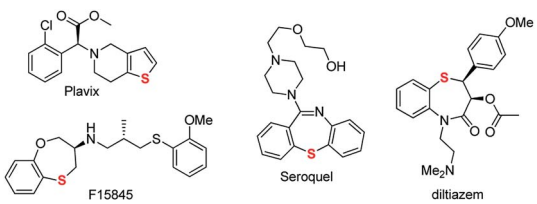
DOI: 10.1039/c9ra09332j

rsc.li/rsc-advances

A sequential cycloaddition and ring expansion of arynes and methylenebenzothiopheneones has been disclosed. This strategy proceeds through a sulfonium ylides intermediate and allows for the efficient synthesis of a sulfur-containing benzo-fused eight-membered ring.

As leading biologically relevant structural components, organosulfur compounds are widely present in many pharmaceuticals and bioactive compounds.[1] Accordingly, sulfur-containing compounds have found their medical applications including as antibacterials, anti-inflammatories, dermatologics, and cancer treatments. A survey of the structures of compounds among the top 200 brand name drugs by U.S. retail sales (RS) in 2011 revealed that 24.8% of the drugs contain sulfur. The list included the famous Plavix (blood thinner, no. 2) and Seroquel (antipsychotic drug, no. 6).[2] In addition, the benzothiazepine-containing drug diltiazem (calcium channel blocker) is used in the treatment of hypertension and angina (Scheme 1).[3] On the other hand, Et743 as a sulfur-containing marine natural product was also used as an effective drug for the treatment of advanced soft tissue sarcoma.[4] As a consequence, many efforts have been devoted to the synthesis of such skeletons.

Arynes are recognized as one of the most reactive intermediates in organic synthesis. The past years have witnessed a great progress with respect to the carbon–carbon and carbon-heteroatom bond-forming reactions involving arynes.[5,6] A careful literature screening revealed that reactions involving the insertion of aryne into C–C, C–N, C–O, C–S, and other bonds have been well documented.[7–9] Furthermore, the aryne-based Diels–Alder reaction, [2 + 5], nucleophilic addition and annulation reactions.[8,9] Among [2 + 8] and many other pericyclic reactions have been intensively investigated for the construction of various benzo-fused frameworks.[10] Remarkably, the reactions between arynes and organosulfur compounds have been widely investigated. As such, arynes can react with a variety of organosulfur compounds including S(II), S(IV), and S(IV) valence state, thus allows for the diversity-oriented synthesis of aromatic organosulfurs that are difficult to access by conventional methods.[11,12] Among them, we are particularly interested in those reactions involves sulfonium ylides, a neutral 1,2-dipolar species consisting of electron-rich carbon atom and an adjacent electro-positive sulfur atom. For example, nucleophilic attack of alkyl thioether towards aryne followed by intramolecular 1,4-proton shift contribute an elegant strategy for the formation of sulfonium ylides (Scheme 2a), which can be further applied to various conversions.[13] Remarkably, this strategy has been established from various modes of trapping of HDDA-generated benzynes with sulfides by Hoye and co-workers.[14] Recently, Studer and co-workers have disclosed that vinyl thioethers lacking α-CH protons reacted with benzyne through direct [3 + 2] cycloaddition to give cyclic sulfonium ylides. This methods eventually enables the preparation of



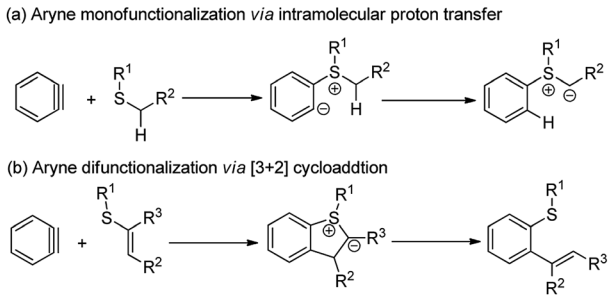
Scheme 1 Representative natural products and bioactive molecules with sulfur-containing ring.

[a]Department of Chemistry, Innovative Drug Research Center, College of Sciences & Institute for Sustainable Energy, Shanghai University, 99 Shangda Road, Shanghai 200444, P. R. China. E-mail: ylchen@staff.shu.edu.cn; lijian@shu.edu.cn

[b]Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200444, P. R. China

† Electronic supplementary information (ESI) available: NMR, HRMS (ESI) and X-ray crystal structure data (CIF) for compound **5j**, **5n**. CCDC 1915323 for compound **5j**; 1915320 for compound **5n**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra09332j

Open Access Article. Published on 29 November 2019. Downloaded on 11/26/2025 10:29:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



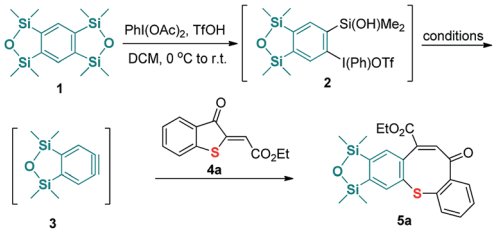
Scheme 2 Representative examples involving sulfonium ylide.

corresponding tetrasubstituted alkenes with high stereoselectivity (Scheme 2b).[15] In the past years, we have paid much attention to the aryne chemistry and the heterocycle synthesis.[16,17] As a continuation, herein we report that the unprecedented reaction of arynes and methylenebenzothiopheneones enables the synthesis of structurally unusual benzo-fused eight-membered ring.

We commenced our investigation using benzyne precursor **1** and 2-methylenebenzothiophene-3-ones **4a** as the model substrates. As shown in Table 1, heating the mixture of **1** and **4a** in CH_3CN with excessive CsF as fluorine source essentially afforded a new product **5a** in 48% yield (Table 1, Entry 1). After that, reactions with other solvents including THF, toluene, 1,4-dioxane and DCM were also performed to enhance the yield of **5a**. Pleasingly, the experimental outcome revealed that the employment of DCM as the solvent significantly increased the yield of **5a** (Table 1, entries 2–5). Encouraged by these results, we then examined the present reactions with different reaction temperature, equivalence ratios and fluorine sources. The best performance was obtained when reaction was conducted under reflux and 1.5 equiv. of **1** (Table 1, entries 5–9). Of the fluorine sources tested, KF/18-C-6 and TBAF could not bring further improvement (Table 1, entries 10–12).

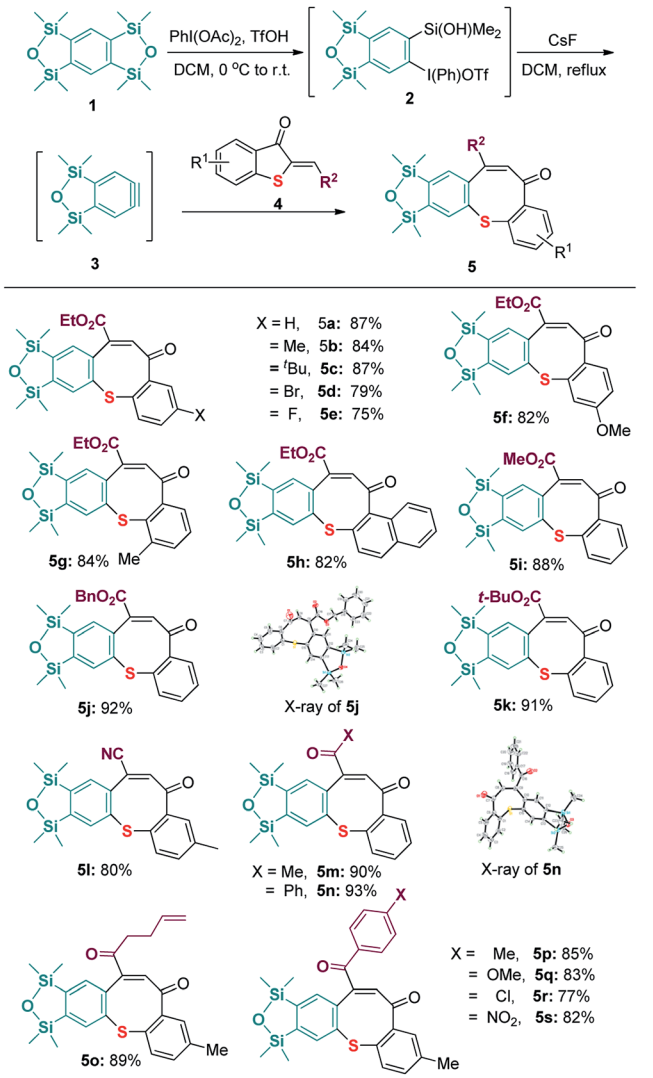
After the best conditions were obtained in hand, the feasibility of substituted 2-methylenebenzothiophene-3-ones **4** was next evaluated. As shown in Scheme 3, a variety of 2-methylenebenzothiophene-3-ones **4** having substituents including methyl, *tert*-butyl, halo, and methoxyl groups at the position 7, 6, 5 of the aromatic ring were used to react with benzyne precursor **1**. All reactions worked well to produce the desired products (**5a–5h**). Additionally, when the ester moiety in substrate **4** was changed from OEt to OMe, OBn, or O^{t}Bu, the corresponding products **5i–5k** were afforded in high

Table 1 Reaction optimization[a]



Entry	F source	Equiv. of 1	Solvent	Temp. (°C)	Yield[b] (%)
1	CsF	1.5	CH_3CN	40	48
2	CsF	1.5	THF	40	63
3	CsF	1.5	Toluene	40	62
4	CsF	1.5	Dioxane	40	59
5	CsF	1.5	DCM	Reflux[c]	87
6	CsF	1.5	DCM	rt	65
7	CsF	1.5	DCM	60[d]	79
8	CsF	2.0	DCM	Reflux	82
9	CsF	1.0	DCM	Reflux	75
10	TBAF	1.5	DCM	Reflux	47
11	KF/18-c-6	1.5	DCM	Reflux	67
12	KF/18-c-6	1.5	THF	Reflux	71

[a] Unless otherwise noted, all reactions were carried out with 1.0 mmol 2-methylenebenzothiophene-3-one **4a**, fluorine source, in 3 mL solvent. [b] Isolated yield. [c] Bp of DCM: 39.8 °C. [d] Sealing reaction temperature.



Scheme 3 Substrate scope of the reaction with respect to the methylenebenzothiopheneone. Reaction condition: 1.5 mmol benzyne precursor **1**, 1.0 mmol 2-methylenebenzothiophene-3-one **4**, CsF (3.0 mmol), in 3 mL DCM. Isolated yields are reported.

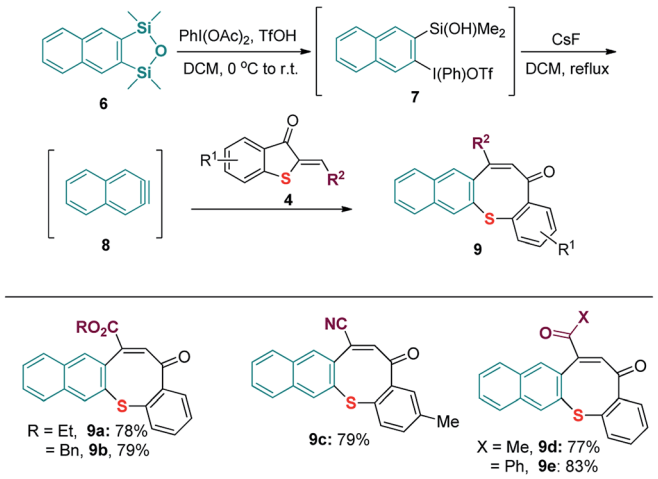
Open Access Article. Published on 29 November 2019. Downloaded on 11/26/2025 10:29:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

performance. It was also worthy to note that when the electron-withdrawing groups such as cyano, and substituted carbonyl groups were employed instead of ester unit, the corresponding products **5l–5s** were isolated in satisfactory yields. Furthermore, the structure of compounds **5j** and **5n** was unambiguously characterized by single-crystal X-ray analysis.[18]

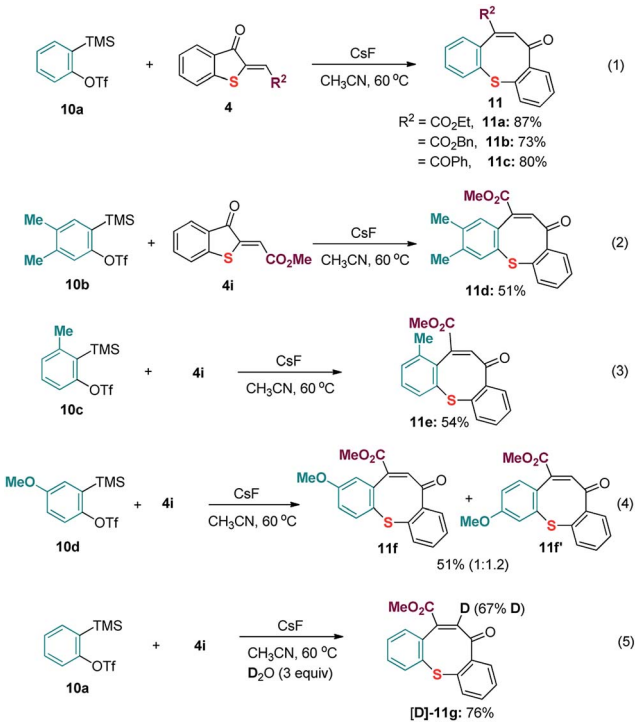
After a broad substrate scope with benzyne precursor was established, reactions of naphthyne precursor **6** and substituted 2-methylenebenzothiophene-3-ones were subsequently tested. As shown in Scheme 4, reactions with 2-methylenebenzothiophene-3-ones **4** bearing different electron-withdrawing groups proceeded smoothly to produce products **9a–9e** in satisfactory yield.

To gain more insight into the present reaction, several control experiments and preliminary mechanistic experiments were next conducted. As shown in Scheme 5, benzyne precursor *ortho*-(trimethylsilyl)aryltriflate **10a** and **10b** were proven to be compatible reaction partners to react with 2-methylenebenzothiophene-3-ones **4** (Scheme 5, eqn (1) and (2)). After that, reactions with unsymmetrical benzyne precursor **10c** and **10d** were also examined (Scheme 5, eqn (3) and (4)). Pleasingly, only one isomer was detected when 3-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **10c** was used. The isotope-labelling experiment with **10a** and **4i** also revealed that deuterium was incorporated in the product to produce [**D**]-**11e** (Scheme 5, eqn (5)). This result suggested that water was also involved in present transformation.

Based on the aforementioned results and previous reports, a plausible reaction mechanism is described in Scheme 6. Firstly, the [3 + 2] cycloaddition between 2-methylenebenzothiophene-3-ones **4** and aryne yields a sulfonium ylide intermediate **B**. In the presence of water, **B** is further protonated to deliver sulfonium salt **C**. After that, the *in situ* generated hydroxide ion serves as a base to facilitate the following intramolecular β-elimination, thus providing a quick access to the product.



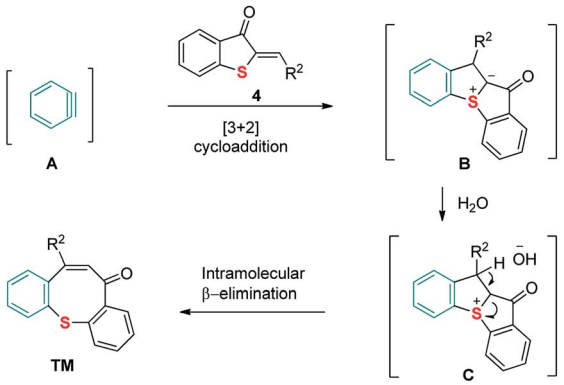
Scheme 4 Reaction conditions: 1.5 mmol naphthyne precursor **6**, 1.0 mmol 2-methylenebenzothiophene-3-one **4**, CsF (3.0 mmol), in 3 mL DCM. Isolated yields are reported.



Scheme 5 Control experiments and preliminary mechanistic studies.

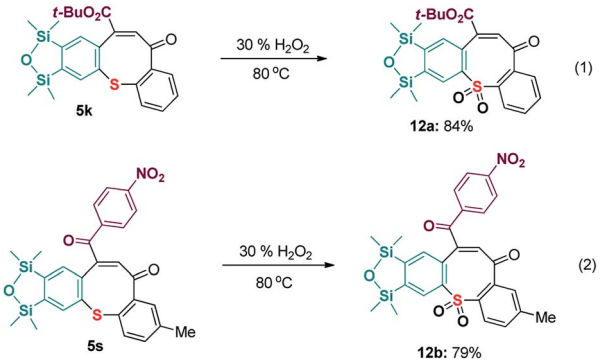
To further explore the application of present reaction, an oxidation reaction of the products was also attempted. In the presence of H_2O_2,[19] the resultant sulfide products **5k** and **5s** experienced oxidation to corresponding functionalized sulfones **12a** and **12b** in an efficient and environmentally friendly manner (Scheme 7, eqn (1) and (2)).

In conclusion, we have described an unprecedented reaction from *in situ* generated aryne and 2-methylenebenzothiophene-3-ones. This strategy allows for a new approach to benzo-fused eight-membered ring containing sulfur, which was difficult to be synthesized by traditional methods. Mechanistically, this reaction proceeds through cycloaddition, proton shift, intramolecular β-elimination, and the formation of sulfonium ylide. Further study and application of the present reaction



Scheme 6 Possible mechanism.

Open Access Article. Published on 29 November 2019. Downloaded on 11/26/2025 10:29:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 7 Further application of the products.

including the biological detection are still underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21272146) and the State Key Laboratory of Applied Organic Chemistry, Lanzhou University for financial support. This work is also sponsored by Natural Science Foundation of Shanghai (18ZR1413900).

Notes and references

1 (*a*) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832; (*b*) *Sulfur Compounds: Advances in Research and Application*, ed. A. Q. Acton, Scholarly Editions, Atlanta, GA, 2012.

2 Please find the data reflecting the top 200 rankings from http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011, 2012.

3 (*a*) K. Asano and S. Matsubara, *ACS Catal.*, 2018, **8**, 6273; (*b*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.*, 1970, **18**, 2284.

4 (*a*) W. He, Z. Zhang and D. Ma, *Angew. Chem., Int. Ed.*, 2019, **58**, 3972; (*b*) J. Chen, X. Chen, M. Bois-Choussy and J. Zhu, *J. Am. Chem. Soc.*, 2006, **128**, 87.

5 For selected reviews on aryne chemistry, see: (*a*) H. Takikawa, A. Nishii, T. Sakai and K. Suzuki, *Chem. Soc. Rev.*, 2018, **47**, 8030; (*b*) T. Roy and A. T. Biju, *Chem. Commun.*, 2018, **54**, 2580; (*c*) J. Shi, Y. Li and Y. Li, *Chem. Soc. Rev.*, 2017, **46**, 1707; (*d*) S. Yoshida and T. Hosoya, *Chem. Lett.*, 2015, **44**, 1450; (*e*) D. Pérez, D. Peña and E. Guitián, *Eur. J. Org. Chem.*, 2013, 5981; (*f*) C. M. Gampe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3766; (*g*) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550; (*h*) A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.*, 2012, **41**, 3140.

6 For selected examples, see: (*a*) Y. Nakamura, Y. Miyata, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2019, **21**, 5252; (*b*) S. Bhattacharjee, A. Guin, R. N. Gaykar and A. T. Biju, *Org. Lett.*, 2019, **21**, 4383; (*c*) J. Zhao, H. Li, P. Li and L. Wang, *J. Org. Chem.*, 2019, **84**, 9007; (*d*) H. Xu, J. He, J. Shi, L. Tan, D. Qiu, X. Luo and Y. Li, *J. Am. Chem. Soc.*, 2018, **140**, 3555; (*e*) S. Yoshida, T. Yano, Y. Misawa, Y. Sugimura, K. Igawa, S. Shimizu, K. Tomooka and T. Hosoya, *J. Am. Chem. Soc.*, 2015, **137**, 14071; (*f*) Y. Nagashima, R. Takita, K. Yoshida, K. Hirano and M. Uchiyama, *J. Am. Chem. Soc.*, 2013, **135**, 18730; (*g*) T. Kitamura, Z. Meng and Y. Fujiwara, *Tetrahedron*, 2000, **41**, 6611.

7 (*a*) U. K. Tambar and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5340; (*b*) U. K. Tambar, D. C. Ebner and B. M. Stoltz, *J. Am. Chem. Soc.*, 2006, **128**, 11752; (*c*) R. Samineni, C. R. C. Bandi, P. Srihari and G. Mehta, *Org. Lett.*, 2016, **18**, 6184; (*d*) P. Gouthami, R. Chegondi and S. Chandrasekhar, *Org. Lett.*, 2016, **18**, 2044.

8 (*a*) J. Schwan, M. Kleoff, B. Hartmayer, P. Heretsch and M. Christmann, *Org. Lett.*, 2018, **20**, 7661; (*b*) A. C. Wright, C. K. Haley, G. Lapointe and B. M. Stoltz, *Org. Lett.*, 2016, **18**, 2793; (*c*) Z. Liu and R. C. Larock, *J. Am. Chem. Soc.*, 2005, **127**, 13112; (*d*) H. Yoshida, E. Shirakawa, Y. Honda and T. Hiyama, *Angew. Chem., Int. Ed.*, 2002, **41**, 3247; (*e*) N. Saito, K. Nakamura, S. Shibano, S. Ide, M. Minami and Y. Sato, *Org. Lett.*, 2013, **15**, 386.

9 (*a*) R. N. Gaykar, S. Bhattacharjee and A. T. Biju, *Org. Lett.*, 2019, **21**, 737; (*b*) S. J. Li, Y. Wang, J. K. Xu, D. Xie, S. K. Tian and Z. X. Yu, *Org. Lett.*, 2018, **20**, 4545; (*c*) J. A. García-López, M. Çetin and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2015, **54**, 2156; (*d*) T. Matsuzawa, K. Uchida, S. Yoshida and T. Hosoya, *Org. Lett.*, 2017, **19**, 5521; (*e*) S. Yoshida, Y. Nakamura, K. Uchida, Y. Hazama and T. Hosoya, *Org. Lett.*, 2016, **18**, 6212; (*f*) H. Yoshida, J. Ikadai, M. Shudo, J. Ohshita and A. Kunai, *J. Am. Chem. Soc.*, 2013, **125**, 6638; (*g*) K. Z. Łączkowski, D. García, D. Peña, A. Cobas, D. Pérez and E. Guitián, *Org. Lett.*, 2011, **13**, 960.

10 (*a*) S. S. Bhojgude, A. Bhunia and A. T. Biju, *Acc. Chem. Res.*, 2016, **49**, 1658; (*b*) V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191; (*c*) Z. Wang, Y. Addepalli and Y. He, *Org. Lett.*, 2018, **20**, 644; (*d*) D. Xu, Y. Zhao, D. Song, Z. Zhong, S. Feng, X. Xie, X. Wang and X. She, *Org. Lett.*, 2017, **19**, 3600.

11 For a recent review on aryne reactions with organosulfurcompounds, see: T. Matsuzawa, S. Yoshida and T. Hosoya, *Tetrahedron Lett.*, 2018, **59**, 4197.

12 For selected examples, see: (*a*) P. Garg and A. Singh, *Org. Lett.*, 2018, **20**, 1320; (*b*) T. Zheng, J. Tan, R. Fan, S. Su, B. Liu, C. Tan and K. Xu, *Chem. Commun.*, 2018, **54**, 1303; (*c*) J. Shi, D. Qiu, J. Wang, H. Xu and Y. Li, *J. Am. Chem. Soc.*, 2015, **137**, 5670; (*d*) S. Yoshida, K. Uchida, K. Igawa, T. Tomooka and T. Hosoya, *Chem. Commun.*, 2014, **50**, 15059; (*e*) F. L. Liu, J. R. Chen, Y. Q. Zou, Q. Wei and W. J. Xiao, *Org. Lett.*, 2014, **16**, 3768; (*f*) S. K. Aithagani, S. Dara, G. Munagala, H. Aruri, M. Yadav, S. Sharma,

Open Access Article. Published on 29 November 2019. Downloaded on 11/26/2025 10:29:15 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

R. A. Vishwakarma and P. P. Singh, *Org. Lett.*, 2015, **17**, 5547; (*g*) J. Nakayama, T. Fujita and M. Hoshino, *Chem. Lett.*, 1983, 249.

13 H. D. Xu, M. Q. Cai, W. J. He, W. H. Hu and M. H. Shen, *RSC Adv.*, 2014, **4**, 7623.

14 J. Chen, V. Palani and T. R. Hoye, *J. Am. Chem. Soc.*, 2016, **138**, 4318.

15 Y. Li, C. Mgck-Lichtenfeld and A. Studer, *Angew. Chem., Int. Ed.*, 2016, **55**, 14435.

16 (*a*) S. Su, J. Li, M. Sun, H. Zhao, Y. Chen and J. Li, *Chem. Commun.*, 2018, **54**, 9611; (*b*) K. Kong, J. Zhang, P. Zhao, H. Lu, Z. Chen, W. Cao, J. Chen and Y. Chen, *Tetrahedron*, 2017, **73**, 6742; (*c*) J. Li, N. Wang, C. Li and X. Jia, *Org. Lett.*, 2012, **14**, 4994; (*d*) Y. Chen, C. Hau, H. Wang, H. He, M. Wong and A. Lee, *J. Org. Chem.*, 2006, **71**, 3512; (*e*) Y. Chen, J. Sun, X. Wei, W. Wong and A. Lee, *J. Org. Chem.*, 2004, **69**, 7190.

17 (*a*) B. Xue, S. Su, Y. Cui, Y. Fei, X. Jia, J. Li and J. Fang, *Chem. Commun.*, 2019, **55**, 12180; (*b*) J. Hu, Y. Fei, H. Zhao, Z. Wang, C. Li and J. Li, *Chem. Commun.*, 2019, **55**, 8394; (*c*) H. Yuan, C. Tang, S. Su, L. Cui, X. Jia, C. Li and J. Li, *Chem. Commun.*, 2019, **55**, 7231; (*d*) T. Jin, Z. Tang, J. Hu, H. Yuan, Y. Chen, C. Li, X. Jia and J. Li, *Org. Lett.*, 2018, **20**, 413.

18 CCDC 1915323, 1915320 for compound **5j**, **5n** contain the supplementary crystallographic data for this paper.

19 M. Jereb, *Green Chem.*, 2012, **14**, 3047.