



Cite this: *Chem. Commun.*, 2019, 55, 4639

Received 29th January 2019,
Accepted 22nd March 2019

DOI: 10.1039/c9cc00815b

rsc.li/chemcomm

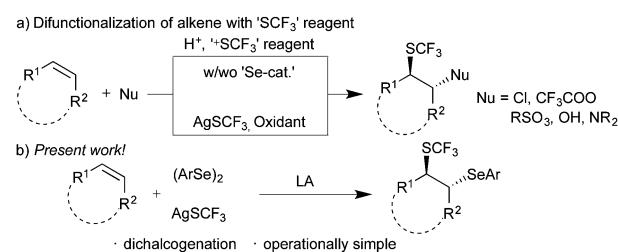
An efficient regioselective difunctionalization of alkenes via trifluoromethylthiolation has been accomplished employing diaryl diselenide and AgSCF_3 in the presence of $\text{BF}_3\text{-OEt}_2$. Various substituted 1,2-dihalogenated products having the SCF_3 moiety were synthesized in good to excellent yields under mild conditions. The preliminary mechanistic investigation revealed the possible reaction pathway and unique combination of diselenide and AgSCF_3 for successful transformation.

Fluorinated molecules have found widespread application in various fields. Notably, a significant number of drugs in pharmaceuticals and agrochemicals contain at least one fluorine atom/group in the form of $-\text{F}$, $-\text{CF}_3$, $-\text{SCF}_3$, or $-\text{SOCF}_3$.¹ Recently, trifluoromethylthio ($-\text{SCF}_3$) containing organic molecules gained significant attention, due to their unique properties such as high lipophilicity, bioavailability, and metabolic stability. The representative examples of $-\text{SCF}_3$ containing drug molecules include toltrazuril, cefazaflur, and fipronil. Thus, the development of an elegant strategy for the construction of trifluoromethylthiolated molecules has been of continuing interest in organic synthesis and other fields.² Consequently, enormous efforts have been dedicated towards the development of various strategies for the construction of trifluoromethylthiolated compounds such as F-exchange³ and direct introduction of $-\text{CF}_3$ ⁴ and $-\text{SCF}_3$ ⁵ groups. Among them, direct trifluoromethylthiolation, using electrophilic or nucleophilic 'SCF₃' reagents, is the most efficient and viable strategy in the synthesis of trifluoromethyl sulfides *via* the direct construction of C-SCF₃ bonds.

On the other hand, difunctionalization of readily accessible substituted alkenes with electrophiles and nucleophiles is an efficient multi-component approach for the synthesis of structurally complex frameworks.⁶ In this context, the incorporation of the trifluoromethylthio ($-\text{SCF}_3$) group along with other functional groups, such as amines, amides, and acids,⁷ is

a useful concept for the synthesis of trifluoromethylthiolated molecules, which could provide the excellent opportunity for medicinal chemists in the drug evolution. Billard and co-workers reported for the first time trifluoromethylthiolative functionalization of alkenes using electrophilic trifluoromethylthiolating reagents.⁸ Subsequently, numerous methods⁹ employing electrophilic trifluoromethylthiolating reagents have been documented (Scheme 1a). However, use of nucleophilic trifluoromethylthiolating reagents is rather limited.¹⁰ For instance, the groups of Wang^{10a} and Qing^{10d} utilized AgSCF_3 in combination with superstoichiometric amounts of persulfate for the difunctionalization of alkenes. Wang and co-workers^{10b} utilized a substoichiometric amount of copper acetate and AgSCF_3 . On the other hand, the combination of AgSCF_3 and trichloroisocyanuric acid was exploited by Yang and co-workers.^{10c} However, to the best of our knowledge, difunctionalization of alkenes with nucleophilic AgSCF_3 in the absence of a metal catalyst or oxidant was not documented in the literature. Thus, we envisioned an arylselenative trifluoromethylthiolation of alkenes with diaryl diselenide and nucleophilic AgSCF_3 for the synthesis of 1,2-dihalogenated compounds, where the potential intermediate ArSeSCF_3 might afford the expected product in the presence of Lewis acids (Scheme 1b). We herein disclose an elegant arylselenative trifluoromethylthiolation of substituted alkenes.

Initially, the difunctionalization of styrene **1a** with diphenyl diselenide **2a** and AgSCF_3 was chosen as a model reaction.



Scheme 1 Trifluoromethylthiolative difunctionalization of alkenes.

Department of Chemistry, Indian Institute of Technology Madras, Chennai-600036, India. E-mail: anbarasan@iitm.ac.in; Web: <https://home.iitm.ac.in/anbarasan/>

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9cc00815b

Table 1 Difunctionalization of styrene **1a** with diphenyl diselenide **2a** and AgSCF_3 : optimization^a

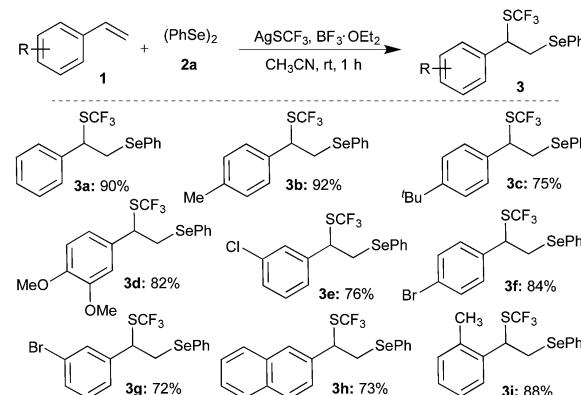
Entry	$\text{BF}_3\text{-OEt}_2$ (equiv.)	Solvent	Yield ^b (%)
1	1.0	CH_3CN	44
2	1.0	DCE	<5
3	1.0	DCM	20
4	1.0	THF	20
5	1.0	DMF	<5
6	2.0	CH_3CN	40
7	0.5	CH_3CN	26
8	0.2	CH_3CN	24
9 ^c	1.0	CH_3CN	48
10 ^d	1.0	CH_3CN	20
11 ^e	1.0	CH_3CN	96

^a Reaction conditions: styrene **1a** (0.24 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.0 equiv.), AgSCF_3 (0.24 mmol, 1.0 equiv.), $\text{BF}_3\text{-OEt}_2$, solvent (0.24 M), rt, 1 h. ^b Isolated yield. ^c At 50 °C. ^d 0.5 equiv. of styrene. ^e 2.0 equiv. of styrene.

Initial screening of Lewis acids suggested that $\text{BF}_3\text{-Et}_2\text{O}$ was the most suitable promoter of the expected difunctionalization (see the ESI†). Thus, the reaction of 1 equiv. of **1a** with 1 equiv. of both **2a** and AgSCF_3 in the presence of 1 equiv. of $\text{BF}_3\text{-Et}_2\text{O}$ in acetonitrile at room temperature afforded the expected product **3a** in 44% yield after 12 h. Having identified the formation of the expected product **3a**, various conditions were examined to improve the yield of **3a**. Thus, different solvents such as DCM, DCE, and CH_3CN were screened at room temperature to enhance the transformation (Table 1, entries 1–5). Among them, only acetonitrile showed a better yield.

Next, increasing the $\text{BF}_3\text{-OEt}_2$ to 2.0 equivalents doesn't show much improvement in the yield, but decreasing the equivalents of $\text{BF}_3\text{-OEt}_2$ shows drastic reduction in the yield (Table 1, entries 6 and 7). Subsequently, the focus was directed to study the effect of temperature. Increasing the reaction temperature to 50 °C with one equivalent of $\text{BF}_3\text{-OEt}_2$ furnished product **3a** in only comparable yield (Table 1, entry 9). On the other hand, altering the equivalents of styrene showed a drastic change in the outcome (Table 1, entries 10 and 11). The best yield of 96% for the formation of **3a** was observed with 2.0 equivalents of styrene in the presence of one equivalent of **2a**, AgSCF_3 and $\text{BF}_3\text{-OEt}_2$ at room temperature after 1 h; the same conditions were used for further studies.

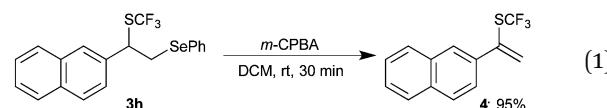
Having achieved the suitable conditions for the tri-component difunctionalization of **1a** for the synthesis of the highly functionalized molecule, the scope and generality of the transformation were investigated. For example, 4-alkyl (methyl/tert-butyl) substituted styrenes gave products **3b** and **3c** in 92% and 75% yield, respectively (Scheme 2). Similarly, electron donating group (3,4-dimethoxy) and halogen (bromo/chloro) substituted styrenes were also well tolerated under the optimized conditions to afford the corresponding difunctionalized products **3d**, **3e**, **3f**, and **3g** in excellent yields. The reaction of 2-vinylnaphthalene also furnished a similar product, **3h**, in 73% yield. Also, sterically hindered



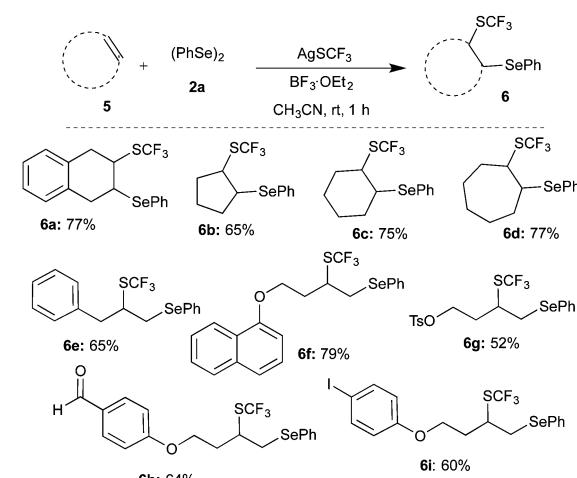
Scheme 2 Difunctionalization of substituted styrenes.

2-methylstyrene underwent smooth reaction to give **3i** in 88% yield. However, actively coordinating cyano and NMe_2 group substituted styrenes do not afford difunctionalized products.

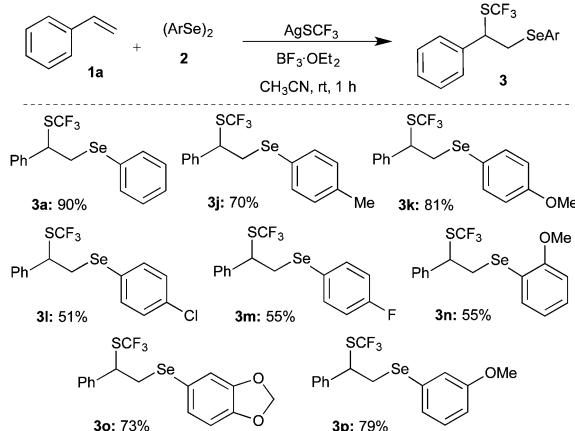
Further, to confirm the regioselectivity of the difunctionalized product, oxidative elimination of $-\text{SePh}$ was envisioned. Thus, the isolated difunctionalized compound **3h** was treated with *m*-CPBA in DCM at room temperature. Interestingly, the formation of α -(trifluoromethylthio)vinyl naphthalene **4** was observed in 95% yield (eqn (1)). The formation of **4** further confirms that SCF_3 and SePh were attached at α -carbon and β -carbon, respectively.



After the successful demonstration of the generality of substituted styrenes, the scope and limitations of other substituted alkenes were examined. Gratifyingly, replacement of styrene with 1,4-dihydronaphthalene under the optimized conditions afforded the difunctionalized product **6a** in 77% yield (Scheme 3). Similarly, other cyclic alkenes such as cyclopentene, cyclohexene, and cycloheptene also underwent smooth



Scheme 3 Difunctionalization of substituted alkenes.



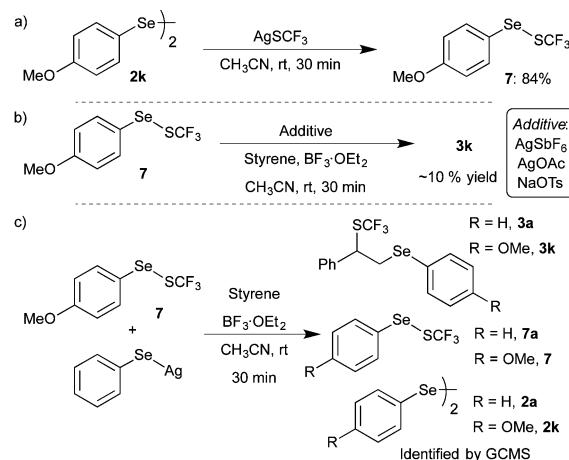
Scheme 4 Difunctionalization of styrene with diaryl diselenide **2** and AgSCF_3 .

reaction to afford the corresponding difunctionalized products **6b**, **6c**, and **6d** in 65, 75 and 77% yield, respectively. Also, difunctionalization of simple terminal alkenes such as allylbenzene was achieved in good yield. Consequently, various substituted homoallylic ethers were tolerated under the optimized conditions to afford difunctionalized products **6f–6i** in good to excellent yields. It is important to note that reactive functional groups such as formyl, sulphenyl and iodo moieties were well tolerated under the optimized conditions.

Subsequently, various substituted diaryl diselenides¹¹ were subjected to the difunctionalization of styrene under the optimized conditions. Methyl, methoxy, and halogen substituted diaryl diselenides gave the corresponding difunctionalized products **3j**, **3k**, **3l**, **3m** and **3p** in 70, 81, 51, 55 and 79% yields, respectively (Scheme 4).

Interestingly, sterically hindered *o*-methoxy substituted diaryl diselenide furnished the corresponding product **3n** in good yield. Acid-sensitive acetal containing difunctionalized product **3o** was synthesized in 73% yield from the corresponding diaryl diselenide.

After the successful demonstration of $\text{BF}_3\text{-OEt}_2$ induced difunctionalization of styrenes and alkenes with diaryl diselenides and AgSCF_3 , the formation of potential intermediates and the plausible reaction mechanism of the developed transformation were investigated. ¹⁹F NMR analysis of the optimized reactions showed an additional singlet at δ –45.3 along with AgSCF_3 and difunctionalized product **3a**. Subsequently, GCMS analysis revealed the formation of possible intermediate (phenylselanyl)-(trifluoromethyl)sulfane (PhSeSCF_3) from the corresponding diaryl diselenide and AgSCF_3 . Consequently, ((4-methoxyphenyl)-selanyl)-(trifluoromethyl)sulfane **7** was synthesized from bis(4-methoxyphenyl)diselenide **2k** and AgSCF_3 in acetonitrile in 84% yield (Scheme 5a).¹² After the successful synthesis of **7**, the reactivity of **7** with styrene was investigated under the optimized conditions. The initial reaction of styrene **1a** with **7** in the presence of $\text{BF}_3\text{-OEt}_2$ in CH_3CN didn't afford the expected product. A detectable amount of difunctionalized product **3k** was observed in ¹⁹F NMR upon addition of an additive such as silver salt or NaOTs (Scheme 5b).

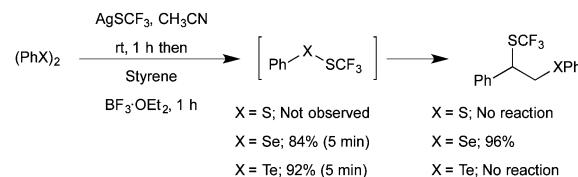


Scheme 5 Control experiments.

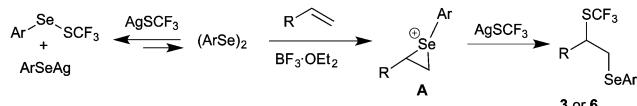
However, the formation of **7**, *via* treatment of diselenide and AgSCF_3 in CH_3CN in the presence of $\text{BF}_3\text{-OEt}_2$, followed by the addition of styrene afforded the expected difunctionalized product **3k** in good yield. These studies suggested that ArSeSCF_3 might not be the intermediate of the developed transformation and the formed ArSeSCF_3 might exist in equilibrium with AgSCF_3 and diaryl diselenides. Further, to confirm the reversible formation of ArSeSCF_3 from AgSCF_3 and diselenides, compound **7** was treated with silver phenylselenate and styrene in the presence of $\text{BF}_3\text{-OEt}_2$. Interestingly, a mixture of difunctionalized products **3a** and **3k** was observed along with $-\text{SCF}_3$ exchanged products **7** and **7a** and possible diselenides **2a** and **2k** in GCMS and ¹⁹F NMR analysis (Scheme 5c). This $-\text{SCF}_3$ exchange could be explained *via* the initial formation of diselenides followed by reaction with AgSCF_3 . All the above observations confirm the possible reversible reaction between diselenides and AgSCF_3 .

Furthermore, difunctionalization was performed with other dichalcogenides in place of diselenides. Unfortunately, both diphenyl disulfide and diphenyl ditelluride did not afford the expected product (Scheme 6). Further analysis of the reaction mixture suggested the possible reasons that the disulfides failed to get activated due to the high bond energy of the S–S bond and no availability of ditelluride due to the rapid, irreversible formation of PhTeSCF_3 . Thus, based on the observed regioselectivity and mechanistic investigation, in the present strategy diselenide and AgSCF_3 acted as an electrophilic $-\text{SeAr}$ source and a nucleophilic $-\text{SCF}_3$ source, respectively.

Based on the mechanistic study, the possible pathway for the difunctionalization of alkenes was proposed as shown in Scheme 7.



Scheme 6 Reaction of styrene with different dichalcogenides and AgSCF_3 .



Scheme 7 Plausible mechanism.

Initially, diphenyl diselenide **2a** and AgSCF_3 convert into **7a**, which exists in equilibrium with **2a** and AgSCF_3 . The remaining diselenide on reaction with styrene in the presence of $\text{BF}_3\cdot\text{OEt}_2$ would afford the episelenonium intermediate **A**. Subsequently, regioselective ring opening of episelenonium ion **A** with AgSCF_3 would furnish the difunctionalized product **3**. Even though the concentration of AgSCF_3 is lower at equilibrium, the overall reaction yield was satisfactory, because of the reversible reaction between AgSCF_3 and diphenyl diselenide.

In conclusion, we have developed an efficient regioselective difunctionalization of alkenes with diaryl diselenide and AgSCF_3 in the presence of $\text{BF}_3\cdot\text{OEt}_2$ as an activator. The developed reaction tolerates various functional groups and allows the synthesis of diverse 1,2-dichalcogenated products having a trifluoromethylthio moiety in good to excellent yield. The preliminary mechanistic investigation revealed the possible reaction pathway and unique combination of diselenide and AgSCF_3 for successful transformation.

We thank the Indian Institute of Technology Madras for financial support. P. S. thanks CSIR, New Delhi, for a fellowship.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fuster, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- (a) F. Toulgoat, S. b. Alazet and T. Billard, *Eur. J. Org. Chem.*, 2014, 2415; (b) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (c) X. Shao, C. Xu, L. Lu and Q. Shen, *Acc. Chem. Res.*, 2015, **48**, 1227; (d) H. Zheng, Y. Huang and Z. Weng, *Tetrahedron Lett.*, 2016, **57**, 1397; (e) S. Barata-Vallejo, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 7150.
- (a) T. Umemoto and S. Ishihara, *J. Fluorine Chem.*, 1998, **92**, 181; (b) B. Gutmann, D. Obermayer, B. Reichart, B. Prekodravac, M. Irfan, J. M. Kremsner and C. O. Kappe, *Chem. - Eur. J.*, 2010, **16**, 12182; (c) E. A. Nodiff, S. Lipschutz, P. N. Craig and M. Gordon, *J. Org. Chem.*, 1960, **25**, 60; (d) B. R. Langlois, T. Billard, J.-C. Matalier and C. Yezeguelian, *J. Fluorine Chem.*, 2007, **128**, 851.
- (a) V. G. Koshechko, L. A. Kiprianova and L. I. Fileleeva, *Tetrahedron Lett.*, 1992, **33**, 6677; (b) A. Harsányi, É. Dorkó, Á. Csapó, T. Bakó, C. Peltz and J. Rábai, *J. Fluorine Chem.*, 2011, **132**, 1241; (c) I. Kieltsch,
- (a) G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164; (b) C. Matheis, V. Wagner and L. J. Goossen, *Chem. - Eur. J.*, 2015, **22**, 79; (c) A. B. Durr, G. Yin, I. Kalvet, F. Napoly and F. Schoenebeck, *Chem. Sci.*, 2016, **7**, 1076; (d) J.-B. Liu, X.-H. Xu, Z.-H. Chen and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2014, **54**, 897; (e) P. Zhu, X. He, X. Chen, Y. You, Y. Yuan and Z. Weng, *Tetrahedron*, 2014, **70**, 672; (f) Y. Huang, X. He, H. Li and Z. Weng, *Eur. J. Org. Chem.*, 2014, 7324; (g) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782; (h) A. Ferry, T. Billard, E. Bacqué and B. R. Langlois, *J. Fluorine Chem.*, 2012, **134**, 160; (i) S. Alazet, L. Zimmer and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 10814; (j) T. Bootwicha, X. Liu, R. Pluta, I. Atodiasei and M. Rueping, *Angew. Chem., Int. Ed.*, 2013, **52**, 12856; (k) X. Wang, T. Yang, X. Cheng and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 12860; (l) S. Alazet, L. Zimmer and T. Billard, *Chem. - Eur. J.*, 2014, **20**, 8589.
- (a) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981; (b) M. R. Heinrich, *Chem. - Eur. J.*, 2009, **15**, 820; (c) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (d) Y. A. Cheng, W. Z. Yu and Y.-Y. Yeung, *Org. Biomol. Chem.*, 2014, **12**, 2333; (e) X.-W. Lan, N.-X. Wang and Y. Xing, *Eur. J. Org. Chem.*, 2017, 5821; (f) Y. Shimizu and M. Kanai, *Tetrahedron Lett.*, 2014, **55**, 3727; (g) K. H. Jensen and M. S. Sigman, *Org. Biomol. Chem.*, 2008, **6**, 4083; (h) J.-S. Zhang, L. Liu, T. Chen and L.-B. Han, *Chem. - Asian J.*, 2018, **13**, 2277; (i) S. R. Chemler, *Org. Biomol. Chem.*, 2009, **7**, 3009; (j) T. Besset, T. Poisson and X. Panneccoucke, *Chem. - Eur. J.*, 2014, **20**, 16830; (k) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598.
- (a) J. Sheng, C. Fan and J. Wu, *Chem. Commun.*, 2014, **50**, 5494; (b) S. Pan, H. Li, Y. Huang, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2017, **19**, 3247.
- 8 A. Ferry, T. Billard, B. R. Langlois and E. Bacqué, *Angew. Chem., Int. Ed.*, 2009, **48**, 8551.
- (a) J. Luo, Z. Zhu, Y. Liu and X. Zhao, *Org. Lett.*, 2015, **17**, 3620; (b) Y. Yang, X. Jiang and F.-L. Qing, *J. Org. Chem.*, 2012, **77**, 7538; (c) C.-C. Xi, Z.-M. Chen, S.-Y. Zhang and Y.-Q. Tu, *Org. Lett.*, 2018, **20**, 4227; (d) L. Jiang, T. Ding, W.-b. Yi, X. Zeng and W. Zhang, *Org. Lett.*, 2018, **20**, 2236; (e) X. Liu, Y. Liang, J. Ji, J. Luo and X. Zhao, *J. Am. Chem. Soc.*, 2018, **140**, 4782; (f) Y. Jia, H. Qin, N. Wang, Z.-X. Jiang and Z. Yang, *J. Org. Chem.*, 2018, **83**, 2808; (g) Z. Zhu, J. Luo and X. Zhao, *Org. Lett.*, 2017, **19**, 4940; (h) J. Luo, Y. Liu and X. Zhao, *Org. Lett.*, 2017, **19**, 3434; (i) P. Zhang, M. Li, X.-S. Xue, C. Xu, Q. Zhao, Y. Liu, H. Wang, Y. Guo, L. Lu and Q. Shen, *J. Org. Chem.*, 2016, **81**, 7486; (j) C. Xu and Q. Shen, *Org. Lett.*, 2015, **17**, 4561; (k) J. Luo, Q. Cao, X. Cao and X. Zhao, *Nat. Commun.*, 2018, **9**, 527; (l) Y. Li, T. Koike and M. Akita, *Asian J. Org. Chem.*, 2016, **6**, 445; (m) G. Dagoussset, C. Simon, E. Anselmi, B. Tuccio, T. Billard and E. Magnier, *Chem. - Eur. J.*, 2017, **23**, 4282; (n) H. Li, C. Shan, C.-H. Tung and Z. Xu, *Chem. Sci.*, 2017, **8**, 2610; (o) X. Liu, R. An, X. Zhang, J. Luo and X. Zhao, *Angew. Chem., Int. Ed.*, 2016, **55**, 5846.
- (a) F. Yin and X.-S. Wang, *Org. Lett.*, 2014, **16**, 1128; (b) L. Zhu, G. Wang, Q. Guo, Z. Xu, D. Zhang and R. Wang, *Org. Lett.*, 2014, **16**, 5390; (c) H. Xiang and C. Yang, *Org. Lett.*, 2014, **16**, 5686; (d) S. Pan, Y. Huang, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2017, **19**, 4624.
- 11 Z. Li, F. Ke, H. Deng, H. Xu, H. Xiang and X. Zhou, *Org. Biomol. Chem.*, 2013, **11**, 2943.
- 12 M. Jereb and D. Dolenc, *RSC Adv.*, 2015, **5**, 58292.