Trifluoromethylthiolative 1,2-difunctionalization of alkenes with diselenides and AgSCF₃†

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An efficient regioselective difunctionalization of alkenes *via* trifluoromethylthiolation has been accomplished employing diaryl diselenide and AgSCF₃ in the presence of BF₃·OEt₂. Various substituted 1,2-dichalcogenated products having the SCF₃ 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 AgSCF₃ 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 –F, –CF₃, –SCF₃, or –SOCF₃.[1] Recently, trifluoromethylthio (–SCF₃) containing organic molecules gained significant attention, due to their unique properties such as high lipophilicity, bioavailability, and metabolic stability. The representative examples of –SCF₃ 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-exchange[3] and direct introduction of –CF₃[4] and –SCF₃[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 (–SCF₃) 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 methods[9] 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 AgSCF₃ in combination with superstiochiometric amounts of persulfate for the difunctionalization of alkenes. Wang and co-workers[10b] utilized a substoichiometric amount of copper acetate and AgSCF₃. On the other hand, the combination of AgSCF₃ and trichloroisocyanuric acid was exploited by Yang and co-workers.[10c] However, to the best of our knowledge, difunctionalization of alkenes with nucleophilic AgSCF₃ 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 AgSCF₃ for the synthesis of 1,2-dichalcogenated compounds, where the potential intermediate ArSeSCF₃ 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 AgSCF₃ was chosen as a model reaction.

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Scheme 1 Trifluoromethylthiolative difunctionalization of alkenes.

Table 1 Difunctionalization of styrene **1a** with diphenyl diselenide **2a** and AgSCF$_3$: optimization[a]

Entry	BF$_3$·OEt$_2$ (equiv.)	Solvent	Yield[b] (%)
1	1.0	CH$_3$CN	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$_3$CN	40
7	0.5	CH$_3$CN	26
8	0.2	CH$_3$CN	24
9[c]	1.0	CH$_3$CN	48
10[d]	1.0	CH$_3$CN	20
11[e]	1.0	CH$_3$CN	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.), BF$_3$·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 BF$_3$·Et$_2$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 BF$_3$·Et$_2$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$_3$CN 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 BF$_3$·OEt$_2$ to 2.0 equivalents doesn't show much improvement in the yield, but decreasing the equivalents of BF$_3$·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 BF$_3$·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 BF$_3$·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
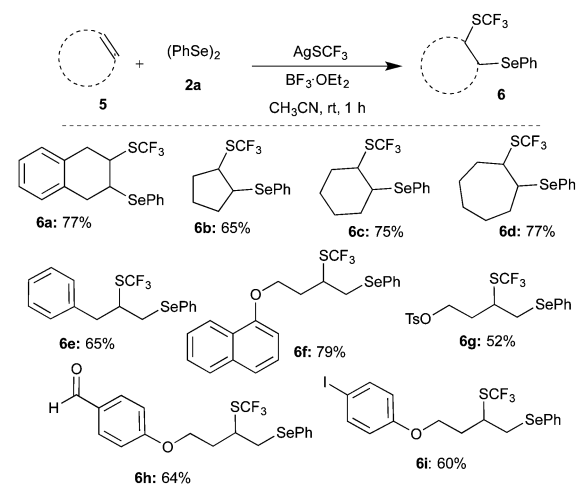

**Scheme 2** Difunctionalization of substituted styrenes.

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 –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)vinylnaphthalene **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.

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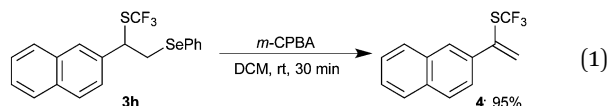
After the successful demonstration of the generality of substituted styrenes, the scope and limitations of other substituted alkenes were examined. Gratifyingly, replacement of styrene with 1,4-dihydronaphthalene under the optimized conditions afforded the difunctionalized product **6a** in 77% yield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

**Scheme 3** Difunctionalization of substituted alkenes.
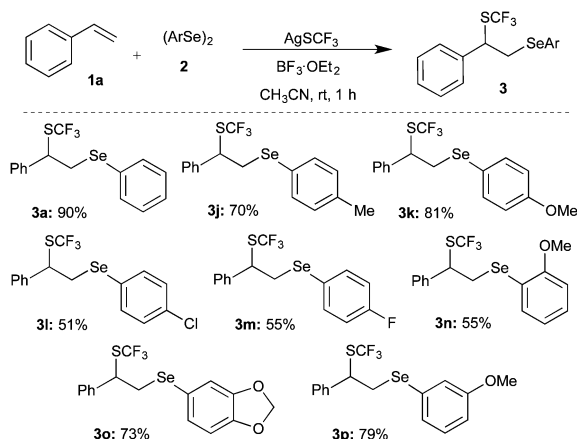
Scheme 4 Difunctionalization of styrene with diaryl diselenide **2** and AgSCF₃.

Scheme 5 Control experiments.

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 allyl-benzene 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, sulfenyl and iodo moieties were well tolerated under the optimized conditions.

Subsequently, various substituted diaryl diselenides[11] 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 BF₃·OEt₂ induced difunctionalization of styrenes and alkenes with diaryl diselenides and AgSCF₃, 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 AgSCF₃ and difunctionalized product **3a**. Subsequently, GCMS analysis revealed the formation of possible intermediate (phenylselanyl)-(trifluoromethyl)sulfane (PhSeSCF₃) from the corresponding diaryl diselenide and AgSCF₃. Consequently, ((4-methoxyphenyl)-selanyl)-(trifluoromethyl)sulfane **7** was synthesized from bis(4-methoxyphenyl)diselenide **2k** and AgSCF₃ 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 BF₃·OEt₂ in CH₃CN 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).
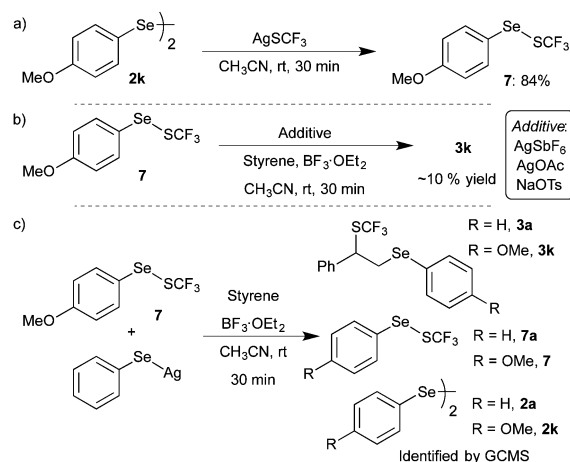
However, the formation of **7**, *via* treatment of diselenide and AgSCF₃ in CH₃CN in the presence of BF₃·OEt₂, followed by the addition of styrene afforded the expected difunctionalized product **3k** in good yield. These studies suggested that ArSeSCF₃ might not be the intermediate of the developed transformation and the formed ArSeSCF₃ might exist in equilibrium with AgSCF₃ and diaryl diselenide. Further, to confirm the reversible formation of ArSeSCF₃ from AgSCF₃ and diselenides, compound **7** was treated with silver phenylselenate and styrene in the presence of BF₃·OEt₂. Interestingly, a mixture of difunctionalized products **3a** and **3k** was observed along with –SCF₃ exchanged products **7** and **7a** and possible diselenides **2a** and **2k** in GCMS and ¹⁹F NMR analysis (Scheme 5c). This –SCF₃ exchange could be explained *via* the initial formation of diselenides followed by reaction with AgSCF₃. All the above observations confirm the possible reversible reaction between diselenides and AgSCF₃.

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 PhTeSCF₃. Thus, based on the observed regioselectivity and mechanistic investigation, in the present strategy diselenide and AgSCF₃ acted as an electrophilic –SeAr source and a nucleophilic –SCF₃ 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 AgSCF₃.

Scheme 7 Plausible mechanism.

Initially, diphenyl diselenide **2a** and AgSCF₃ convert into **7a**, which exists in equilibrium with **2a** and AgSCF₃. The remaining diselenide on reaction with styrene in the presence of BF₃·OEt₂ would afford the episelenonium intermediate **A**. Subsequently, regioselective ring opening of episelenonium ion **A** with AgSCF₃ would furnish the difunctionalized product **3**. Even though the concentration of AgSCF₃ is lower at equilibrium, the overall reaction yield was satisfactory, because of the reversible reaction between AgSCF₃ and diphenyl diselenide.

In conclusion, we have developed an efficient regioselective difunctionalization of alkenes with diaryl diselenide and AgSCF₃ in the presence of BF₃·OEt₂ 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 AgSCF₃ for successful transformation.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, 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.
2 (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.
3 (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. Mulatier and C. Yezeguelian, *J. Fluorine Chem.*, 2007, **128**, 851.
4 (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,

P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.*, 2007, **46**, 754; (d) N. J. W. Straathof, B. J. P. Tegelbeckers, V. Hessel, X. Wang and T. Noel, *Chem. Sci.*, 2014, **5**, 4768; (e) G. Danoun, B. Bayarmagnai, M. F. Gruenberg and L. J. Goossen, *Chem. Sci.*, 2014, **5**, 1312; (f) M. V. Riofski, A. D. Hart and D. A. Colby, *Org. Lett.*, 2013, **15**, 208; (g) J.-J. Ma, W.-B. Yi, G.-P. Lu and C. Cai, *Catal. Sci. Technol.*, 2016, **6**, 417.
5 (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. Bacque 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. Atodiresei 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.
6 (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. Pannecoucke, *Chem. – Eur. J.*, 2014, **20**, 16830; (k) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598.
7 (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.
9 (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, Y. 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. Dagousset, 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.
10 (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.