



# Silver-mediated radical aryltrifluoromethylthiolation of activated alkenes by *S*-trifluoromethyl 4-methylbenzenesulfonothioate

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## ABSTRACT

Herein, we describe the preparation of trifluoromethylthiol-substituted oxindoles by silver-mediated aryltrifluoromethylthiolation of activated alkenes, using *S*-trifluoromethyl 4-methylbenzenesulfonothioate as a  $F_3CS$  radical source and showing that the reagent availability, mild conditions, and broad functional group compatibility of this transformation make it a viable alternative strategy of constructing  $C_{sp^3}-SCF_3$  bonds.

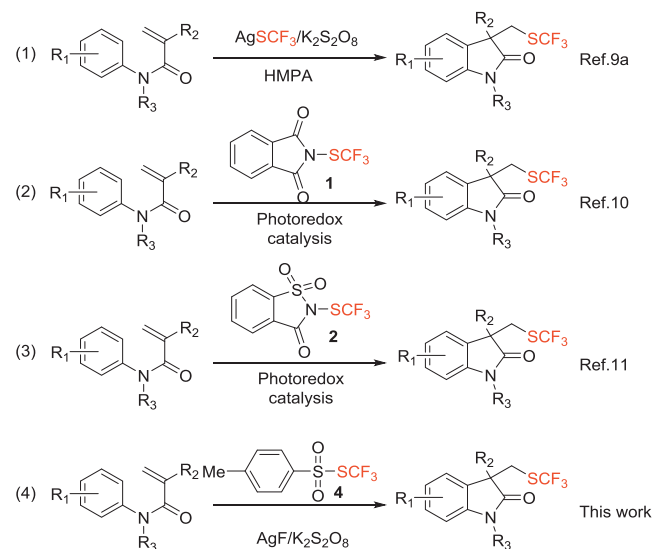
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## Introduction

Trifluoromethylthiolation has recently emerged as a hot organic/medicinal chemistry research field.<sup>1</sup> Since the trifluoromethylthiol ( $CF_3S$ ) group is highly lipophilic (Hansch parameter  $\pi_R = 1.44$ )<sup>2</sup> and electron-withdrawing, its incorporation into bioactive molecules can improve their cell membrane permeation ability<sup>3</sup> and metabolic stability,<sup>4</sup> which makes the development of mild and efficient trifluoromethylthiolation methods a task of high significance.

In addition to nucleophilic trifluoromethylthiolation employing  $AgSCF_3$ ,<sup>5</sup>  $CuSCF_3$ ,<sup>6</sup> or  $Me_4NSCF_3$ <sup>7</sup> as  $SCF_3^-$  sources, great progress has been made in the field of electrophilic trifluoromethylthiolation, with a series of easy-to-handle and shelf-stable trifluoromethylthiolation reagents currently being available.<sup>8</sup> However, although a number of aromatic molecules have been trifluoromethylthiolated by the above nucleophilic/electrophilic reagents, the radical trifluoromethylthiolation of alkenes remains underexplored, mainly due to the limited number of reliable methods of generating the  $F_3CS$  radical. The most common  $F_3CS$  radical source, used in many impressive transformations, is  $AgSCF_3$ , which, however, is expensive and requires *in situ* oxidation by a strong oxidant to generate

the  $SCF_3$  radical (Scheme 1, Eq. 1).<sup>9</sup> In 2016, Hopkinson et al. reported visible-light-promoted radical trifluoromethylthiolation of styrenes by 2-((trifluoromethyl)thio)isoindoline-1,3-dione (**1**) (Scheme 1, Eq. 2).<sup>10</sup> Recently, Dagousset and Magnier reported visible-light-driven radical trifluoromethylthiolation of alkenes



**Scheme 1.** Radical aryltrifluoromethylthiolation of activated alkenes.

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by *N*-trifluoromethylthiosaccharin (**2**) (Shen's reagent) (Scheme 1, Eq. 3).<sup>11</sup> However, the preparation of compounds **1** and **2** requires the use of expensive AgSCF<sub>3</sub> or CuSCF<sub>3</sub>. In 2016, Shen et al. reported an elegant radical-mediated phenylsulfonyl-difluoromethylthio-1,2-difunctionalisation of alkenes by *S*-difluoromethyl benzenesulfonothioate (**3**).<sup>12</sup> Recently, Xu et al. reported a gold and visible-light mediated phenylsulfonyl-trifluoromethylthio-1,2-difunctionalisation of alkenes by *S*-trifluoromethyl 4-methylbenzenesulfonothioate (**4**).<sup>13</sup> Due to being interested in the development of efficient C–S bond construction methods,<sup>14</sup> we herein utilised compound **4**, easily prepared from trimethyl(trifluoromethyl)silane (**5**), *N,N*-diethyl-1,1,1-trifluoro-4-sulfanamine (**6**), aniline (**7**), and sodium 4-methylbenzenesulfinate (**8**) in two steps,<sup>8a,15</sup> as an alternative F<sub>3</sub>CS radical source, successfully achieving silver-mediated oxidative aryltrifluoromethylthiolation of activated alkenes to produce trifluoromethylthiol-substituted oxindoles (Scheme 1, Eq. 4).

## Results and discussion

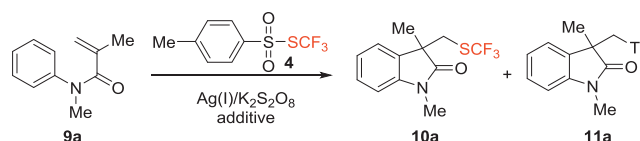
Treatment of *N*-methyl-*N*-phenylmethacrylamide (**9a**) with **4** in the presence of AgNO<sub>3</sub>, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and hexamethylphosphoramide (HMPA) in dimethyl sulfoxide (DMSO) at 40 °C afforded the desired aryltrifluoromethylthiolation product **10a** (24% yield, Table 1, entry 1) and the non-desired arylsulfoxidation product **11a** (40% yield). When the reaction was carried out without HMPA, the yield of **10a** increased to 38%, with only trace amount of **11a** detected (Table 1, entry 2). To optimise the reaction conditions, various oxidants (Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, *t*-BuOOH, and (*t*-BuO)<sub>2</sub> (Table 1, entries 3–6)) were investigated, but none of them was superior to K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, with subsequent screening of silver salts (AgSbF<sub>6</sub>, AgOTf, and AgF) showing that AgF afforded the best yield (Table 1, entries

7–9). Finally, the loading of **4** and AgF, reaction temperature, reactant concentration, and solvent were examined. When the loadings of **4** and AgF were increased from 1.2 to 1.8 equivalents, the yield of **10a** increased from 42 to 58% (Table 1, entries 10 and 11). However, a further loading increase to 2.0 equivalents was counterproductive (Table 1, entry 12). Decreasing the reaction temperature to 20 °C improved the yield to 71% (Table 1, entry 13), whereas increasing the concentration of **9a** from 0.083 to 0.125 M or decreasing it from 0.083 to 0.063 M diminished the yield (Table 1, entries 14 and 15). When other solvents such as acetonitrile (CH<sub>3</sub>CN), toluene, and 1-methylpyrrolidin-2-one (NMP) were used, no desired product was obtained, except for DMF, in which case **10a** was isolated in 34% yield (Table 1, entries 16–19). Thus, the optimised reaction conditions for the aryltrifluoromethylthiolation of **9a** were as follows: **9a** (0.25 mmol), **4** (0.45 mmol), AgF (0.45 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.9 mmol), and DMSO (3 mL) at 20 °C.

With the optimised reaction conditions in hand, the scope of activated alkenes was investigated, with the results presented in Scheme 2. *N*-Methyl-*N*-phenylmethacryl amides **9** with both electron-donating and electron-withdrawing substituents in *ortho*-, *meta*-, and *para*-positions of the aniline ring (**9b–9l**) were smoothly converted into the corresponding oxindoles. Notably, when *N*-methyl-*N*-(pyridin-2-yl)methacrylamide (**9m**) and *N*-methyl-*N*-(*n*-naphthalen-1-yl)methacrylamide (**9n**) were employed as substrates, the desired products **10m** and **10n** were obtained in relatively low yields. Then, other *N*-substituted-*N*-phenylmethacryl amides (**9o–9s**) were tested, affording the desired aryltrifluoromethylthiolation products in moderate yields except for **9r**, which was transformed into **10r** in 34% yield. Finally,  $\alpha$ -substituted acrylamides (**9t–9w**) were examined, and it was found that ethyl, benzyl, and methoxymethyl substituents were tolerated, and the desired products (**10t–10w**) were obtained in moderate to good yields.<sup>16</sup>

**Table 1**

Optimisation of aryltrifluoromethylthiolation of **9a** by **4** in the presence of diverse silver salts and oxidants.<sup>a</sup>



| Entry | <b>4</b> /equiv. | Ag(I)/equiv.            | Oxidant/equiv.   | Temperature (°C) | Solvent            | Yield of <b>10a</b> (%) <sup>b</sup> |
|-------|------------------|-------------------------|--|------------------|--------------------|--------------------------------------|
| 1     | 1.2              | AgNO <sub>3</sub> /1.2  | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 24 <sup>c</sup>                      |
| 2     | 1.2              | AgNO <sub>3</sub> /1.2  | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 38                                   |
| 3     | 1.2              | AgNO <sub>3</sub> /1.2  | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                 | 40               | DMSO               | Trace                                |
| 4     | 1.2              | AgNO <sub>3</sub> /1.2  | (NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6 | 40               | DMSO               | 29                                   |
| 5     | 1.2              | AgNO <sub>3</sub> /1.2  | <i>t</i> -BuOOH/3.6  | 40               | DMSO               | 0                                    |
| 6     | 1.2              | AgNO <sub>3</sub> /1.2  | ( <i>t</i> -BuO) <sub>2</sub> /3.6                                 | 40               | DMSO               | 0                                    |
| 7     | 1.2              | AgSbF <sub>6</sub> /1.2 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 40                                   |
| 8     | 1.2              | AgOTf/1.2               | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 40                                   |
| 9     | 1.2              | AgF/1.2                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 42                                   |
| 10    | 1.5              | AgF/1.5                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 55                                   |
| 11    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 58                                   |
| 12    | 2.0              | AgF/2.0                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 40               | DMSO               | 52                                   |
| 13    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | DMSO               | 71                                   |
| 14    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | DMSO               | 58 <sup>d</sup>                      |
| 15    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | DMSO               | 65 <sup>e</sup>                      |
| 16    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | CH <sub>3</sub> CN | 0                                    |
| 17    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | Toluene            | 0                                    |
| 18    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | NMP                | 0                                    |
| 19    | 1.8              | AgF/1.8                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> /3.6                  | 20               | DMF                | 34                                   |

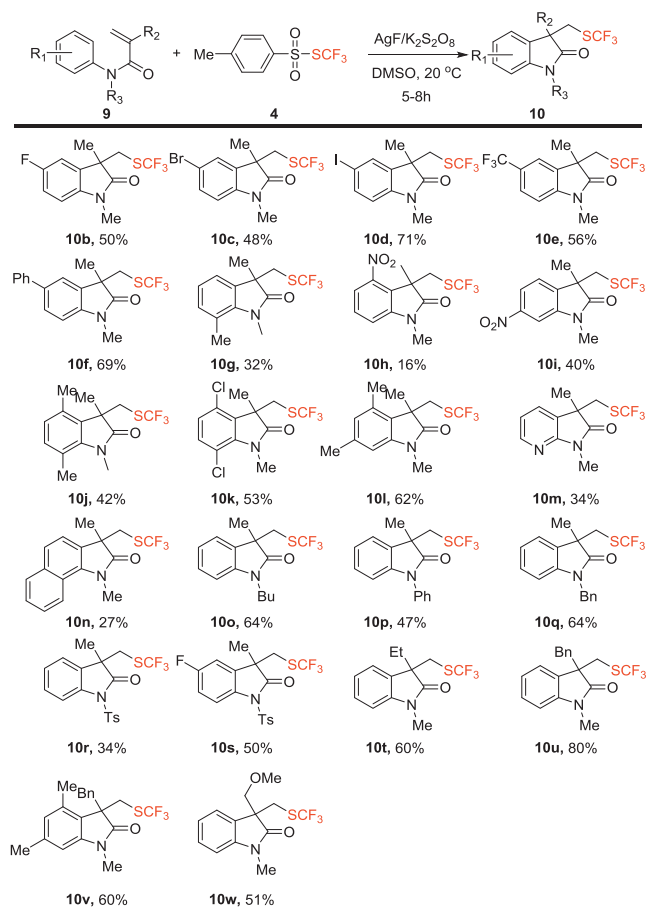
<sup>a</sup> Reaction conditions: **9a** (0.25 mmol), **4** (0.3–0.5 mmol), Ag(I) salt (0.3–0.5 mmol), and oxidant (0.9 mmol) in solvent (3 mL) for 5 h at the indicated temperature.

<sup>b</sup> Yield of isolated product after silica gel chromatography.

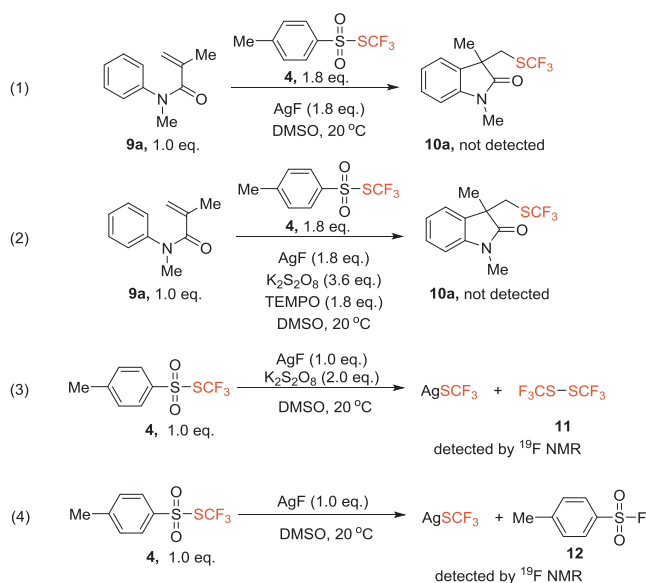
<sup>c</sup> HMPA (0.125 mmol) was used as an additive.

<sup>d</sup> DMSO (2 mL) was used.

<sup>e</sup> DMSO (4 mL) was used.

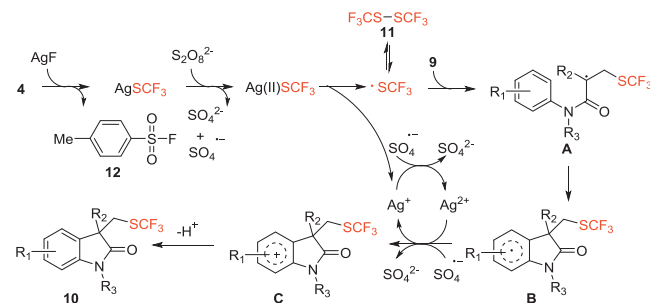


Scheme 2. Substrate scope of activated alkene aryltrifluoromethylthiolation.



Scheme 3. Additional experiments performed to understand the reaction mechanism.

To understand the mechanism of the above transformation, a series of experiments were carried out. In the absence of  $\text{K}_2\text{S}_2\text{O}_8$  or in the presence of 1.8 equivalents of TEMPO as a radical scavenger, no desired product was detected (Scheme 3, Eqs. 1 and 2,



Scheme 4. Proposed aryltrifluoromethylthiolation mechanism.

respectively), which supported the hypothesis that the reaction proceeded via a radical pathway. To gain further insights, **4** was treated with AgF in the presence of  $\text{K}_2\text{S}_2\text{O}_8$  in DMSO at 20 °C, and the reaction was monitored by  $^{19}\text{F}$  NMR for 3 h, with peaks of 1,2-bis(trifluoromethyl)disulfane (**11**) ( $\delta = -46.2$  ppm) and  $\text{AgSCF}_3$  ( $\delta = -20.8$  ppm) observed as a result (Scheme 3, Eq. 3).<sup>17</sup> Notably, when **4** was treated with AgF in DMSO at 20 °C for 12 h in the absence of  $\text{K}_2\text{S}_2\text{O}_8$ , peaks of 4-methylbenzenesulfonyl fluoride **12** ( $\delta = -64.8$  ppm) and  $\text{AgSCF}_3$  were observed (Scheme 3, Eq. 4).<sup>16</sup>

Based on the available literature<sup>9a,18</sup> and the abovementioned results, the investigated aryltrifluoromethylthiolation was thought to proceed as follows (Scheme 4). Initially, **4** reacts with AgF to form  $\text{AgSCF}_3$ , which is oxidised by  $\text{K}_2\text{S}_2\text{O}_8$  to  $\text{Ag(II)SCF}_3$ , with decomposition of the latter species affording Ag (I) and  $\text{F}_3\text{CS}^\cdot$ . Subsequently, the addition of  $\text{F}_3\text{CS}^\cdot$  to **9** affords alkyl radical intermediate **A** that cyclises to afford aryl radical **B**. Finally, oxidation of **B** by  $\text{Ag(II)}$  or  $\text{SO}_4^{\cdot-}$  followed by deprotonation affords the desired product **10**.

## Conclusion

We have successfully developed silver-mediated radical aryltrifluoromethylthiolation of activated alkenes by 4-methylbenzenesulfonylthioate as a  $\text{F}_3\text{CS}^\cdot$  radical source to afford trifluoromethylthiol-substituted oxindoles. The readily accessible reagents, mild reaction conditions, and broad functional group compatibility of the above transformation make it an alternative and practical strategy of constructing  $\text{C}_{\text{sp}^3}-\text{SCF}_3$  bonds, with the extension of this strategy to other substrates currently being investigated in our lab.

## Acknowledgment

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tetlet.2018.03.058>.

## References

- (a) Boiko VN. *Beilstein J Org Chem*. 2010;6:880–921;  
(b) Tlili A, Billard T. *Angew Chem Int Ed*. 2013;52:6818–6819;  
(c) Liu H, Jiang X. *Chem Asian J*. 2013;8:2546–2563;  
(d) Toulgoat F, Alazet S, Billard T. *Eur J Org Chem*. 2014;2415–2428;  
(e) Xu X-H, Matsuzaki K, Shibata N. *Chem Rev*. 2015;115:731–764;  
(f) Shao X, Xu C, Lu L, Shen Q. *Acc Chem Res*. 2015;48:1227–1236.
- Leo A, Hansch C, Elkins D. *Chem Rev*. 1971;71:525–616.
- Leroux F, Jeschke P, Schlosser M. *Chem Rev*. 2005;105:827–856.
- Yagupol'skii LM, Ilchenko AY, Kondratenko NV. *Russ Chem Rev*. 1974;43:32–47.
- (a) For selected examples: Teverovskiy G, Surry DS, Buchwald SL. *Angew Chem Int Ed*. 2011;50:7312–7314;

- (b) Xiao Q, Sheng J, Chen ZY, Wu J. *Chem Commun.* 2013;49:8647–8649;  
(c) Wang KP, Yun SY, Mamidipalli P, Lee D. *Chem Sci.* 2013;4:3205–3211;  
(d) Wang X, Zhou Y, Ji G, et al. *Eur J Org Chem.* 2014;3093–3096;  
(e) Zhu SQ, Xu X-H, Qing FL. *Eur J Org Chem.* 2014;4453–4456;  
(f) Yin W, Wang Z, Huang Y. *Adv Synth Catal.* 2014;356:2998–3006;  
(g) Liu JB, Xu XH, Chen ZH, Qing FL. *Angew Chem Int Ed.* 2015;54:897–900.
6. (a) For selected examples: Adams DJ, Goddard A, Clark JH, Macquarrie DJ. *Chem Commun.* 2000;987–988;  
(b) Lefebvre Q, Fava E, Nikolaenko P, Rueping M. *Chem Commun.* 2014;50:6617–6619;  
(c) Nikolaenko P, Pluta R, Rueping M. *Chem Eur J.* 2014;20:9867–9870;  
(d) Huang Y, He X, Li H, Weng Z. *Eur J Org Chem.* 2014;7324–7328.
7. (a) For selected examples: Orda VV, Yagupolskii LM, Bystrov VF, Stepanyants AU. *J Gen Chem.* 1965;35:1628–1635;  
(b) Clark JH, Jones CW, Kybett AP, McClinton MA. *J Fluorine Chem.* 1990;48:249–253.
8. (a) For selected examples: Ferry A, Billard T, Langlois BR, Bacque E. *J Org Chem.* 2008;73:9362–9365;  
(b) Shao X, Wang X, Yang T, Lu L, Shen Q. *Angew Chem Int Ed.* 2013;52:3457–3460;  
(c) Bootwicha T, Liu X, Pluta R, Atodiresei I, Rueping M. *Angew Chem Int Ed.* 2013;52:12856–12859;  
(d) Yang YD, Azuma A, Tokunaga E, Yamasaki M, Shiro M, Shibata N. *J Am Chem Soc.* 2013;135:8782–8785;  
(e) Vinogradova EV, Muller P, Buchwald SL. *Angew Chem Int Ed.* 2014;53:3125–3128;  
(f) Xu C, Ma B, Shen Q. *Angew Chem Int Ed.* 2014;53:9316–9320;  
(g) Rueping M, Liu X, Bootwicha T, Pluta R, Merckens C. *Chem Commun.* 2014;50:2508–2511;  
(h) Alazet S, Zimmer L, Billard T. *Chem Eur J.* 2014;20:8589–8593;  
(i) Huang Z, Yang YD, Tokunaga E, Shibata N. *Org Lett.* 2015;17:1094–1097;  
(j) Xiao Q, He Q, Li J, Wang J. *Org Lett.* 2015;17:6090–6093;  
(k) Wang Q, Qi Z, Xie F, Li X. *Adv Synth Catal.* 2015;357:355–360;  
(l) Shao X, Xu C, Lu L, Shen Q. *J Org Chem.* 2015;80:3012–3021;  
(m) Zhang P, Li M, Xue X-S, et al. *J Org Chem.* 2016;81:7486–7509;  
(n) Chachignon H, Maeno M, Kondo H, Shibata N, Cahard D. *Org Lett.* 2016;18:2467–2470;  
(o) Jiang L, Yi W, Liu Q. *Adv Synth Catal.* 2016;358:3700–3705;  
(p) Lu K, Deng Z, Li M, Li T, Zhao X. *Org Biomol Chem.* 2017;15:1254–1260;
- (p) Chachignon H, Cahard D. *J Fluorine Chem.* 2017;198:82–88;  
(q) Zhao X, Wei A, Yang B, et al. *J Org Chem.* 2017;82:9175–9181.
9. (a) For selected examples: Yin F, Wang X-S. *Org Lett.* 2014;16:1128–1131;  
(b) Zhang K, Liu J-B, Qing F-L. *Chem Commun.* 2014;50:14157–14160;  
(c) Fuentes N, Kong W, Fernandez-Sanchez L, Merino E, Nevado C. *J Am Chem Soc.* 2015;137:964–973;  
(d) Guo S, Zhang X, Tang P. *Angew Chem Int Ed.* 2015;54:4065–4069;  
(e) Wu H, Xiao Z, Wu J, et al. *Angew Chem Int Ed.* 2015;54:4070–4074;  
(f) Qiu Y-F, Zhu X-Y, Li Y-X, et al. *Org Lett.* 2015;17:3694–3697.
10. Honeker R, Garza-Sanchez RA, Hopkinson MN, Glorius F. *Chem Eur J.* 2016;22:4395–4399.
11. Dagousset G, Simon C, Anselmi E, Tuccio B, Billard T, Magnier E. *Chem Eur J.* 2017;23:4282–4286.
12. Zhu D, Shao X, Hong X, Lu L, Shen Q. *Angew Chem Int Ed.* 2016;55:15807–15811.
13. Li H, Shan C, Tung C, Xu Z. *Chem Sci.* 2017;8:2610–2615.
14. (a) For selected examples Zhao X, Zhang L, Li T, Liu G, Wang H, Lu K. *Chem Commun.* 2014;50:13121–13123;  
(b) Zhao X, Zhang L, Lu X, Li T, Lu K. *J Org Chem.* 2015;80:2918–2924;  
(c) Zhao X, Li T, Zhang L, Lu K. *Org Biomol Chem.* 2016;14:1131–1137;  
(d) Zhao X, Deng Z, Wei A, Li B, Lu K. *Org Biomol Chem.* 2016;14:7304–7312;  
(e) Zhao X, Wei A, Li T, Su Z, Chen J, Lu K. *Org Chem Front.* 2017;4:232–235;  
(f) Lu K, Deng Z, Li M, Li T, Zhao X. *Org Biomol Chem.* 2017;15:1254–1260;  
(g) Zhao X, Wei A, Yang B, et al. *J Org Chem.* 2017;82:9175–9181;  
(h) Zhao X, Li T, Yang B, Qiu D, Lu K. *Tetrahedron.* 2017;73:3112–3117;  
(i) Zhao X, Zheng X, Tian M, Sheng J, Tong Y, Lu K. *Tetrahedron.* 2017;73:7233–7238.
15. Li Y, Qiu G, Wang H, Sheng J. *Tetrahedron Lett.* 2017;58:690–693.
16. General procedure for radical aryltrifluoromethylthiolation of activated alkenes: To a flame-dried Schlenk tube was added activated alkenes **9** (0.25 mmol), AgF (57 mg, 0.45 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (243 mg, 0.9 mmol) and dry DMSO (3 mL). *S*-trifluoromethyl 4-methylbenzenesulfonothioate (**4**) (115 mg, 0.45 mmol) was added to the reaction mixture and the mixture was stirred at 20 °C for 5–8 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography to afford the pure product.
17. See Supporting information for detail.
18. Guo S, Cong F, Guo R, Wang L, Tang P. *Nat Chem.* 2017;9:546–551.