

RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2019, **6**, 447

Received 3rd November 2018,
Accepted 16th December 2018

DOI: 10.1039/c8qo01192c

rsc.li/frontiers-organic

Intermolecular oxidative radical fluoroalkylfluorosulfonylation of unactivated alkenes with (fluoroalkyl)trimethylsilane, silver fluoride, sulfur dioxide and *N*-fluorobenzenesulfonimide†

Qiongzen Lin,^{‡a,b} Yongan Liu,^{‡b} Zhiwei Xiao,^b Liping Zheng,^c Xiumiao Zhou,^c Yong Guo,^{‡b} Qing-Yun Chen,^b Changge Zheng^{*a} and Chao Liu^{‡b}

An intermolecular oxidative radical fluoroalkylfluorosulfonylation reaction of unactivated alkenes with convenient and commercially available (fluoroalkyl)trimethylsilane, silver fluoride, sulfur dioxide and *N*-fluorobenzenesulfonimide (NFSI) is described. This transformation efficiently affords various fluoroalkyl-containing alkyl sulfonyl fluorides with good functional group tolerance under mild conditions. Silver fluoroalkyl complexes as the fluoroalkyl radical source generated from (fluoroalkyl)trimethylsilane and silver fluoride may be the key intermediate.

The fluoroalkyl group is one of the most important fluorine-containing groups with unique physical and chemical properties. Its selective introduction into diverse classes of organic molecules commonly has beneficial and profound effects on the properties of parent organic molecules.¹ Although impressive progress has been made in direct fluoroalkylation reactions in recent years,² there is still a high demand for rapid and efficient installation of a range of fluoroalkyl groups to target molecules using convenient and commercial available fluoroalkylation reagents. Additionally, due to the unusual stability of the S^{VI}–F bond, fluorosulfonyl (FSO₂) groups have unique reactivity–stability patterns and have broad applications in the field of chemical biology, organic synthesis and materials.³ Notably, although most sulfonyl fluorides studied or utilized in the literature are aromatic sulfonyl fluorides,⁴ the corresponding aliphatic derivatives have also shown promising results as tool compounds in chemical biology^{3a,5} and as better alternatives to sulfonyl

chlorides in sulfonylation reactions, especially for parallel synthesis.⁶ The underestimation of aliphatic sulfonyl fluorides in the literature is probably due to the lack of direct and efficient synthetic approaches to them. To address these issues, an efficient and promising method is to concomitantly introduce a fluoroalkyl group and a fluorosulfonyl group into valuable synthetic targets in one step, and the fluoroalkylfluorosulfonylation of alkenes *via* a radical pathway should be a desirable entry to fulfil the task since the intermolecular radical 1,2-difunctionalization type fluoroalkylation of alkenes has emerged as a powerful tool for the introduction of versatile fluoroalkyl groups into target molecules.⁷

Recently, we developed a novel intermolecular oxidative radical trifluoromethylfluorosulfonylation reaction of unactivated alkenes with readily available Ag(O₂CCF₂SO₂F) and *N*-fluorobenzenesulfonimide (NFSI) (Scheme 1a).⁸ Although the reaction efficiently resulted in CF₃-containing alkyl sulfonyl fluorides, only the CF₃ group can be incorporated. Preliminary mechanistic experiments showed that AgCF₃

^aSchool of Chemical Engineering, Xinjiang Agricultural University, Urumqi, Xinjiang Uygur Autonomous Region 830052, China.

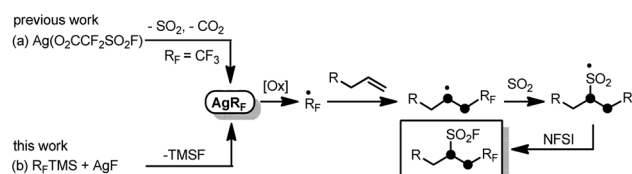
E-mail: cgzheng@jiangnan.edu.cn

^bKey Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: chaoliu@sioac.ac.cn

^cSchool of Chemical Engineering and Food Science, Zhengzhou Institute of Technology, 18 Yingcai Street, Zhengzhou 450044, China

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8qo01192c

‡These authors contributed equally.



Scheme 1 Intermolecular oxidative radical fluoroalkylfluorosulfonylation of unactivated alkenes.

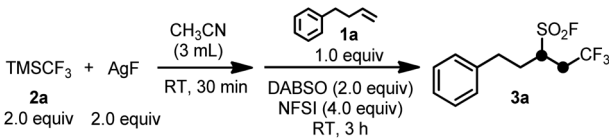
species may be involved in the reaction mechanism as the key intermediate. Also inspired by the recent advance in radical insertion reactions of sulfur dioxide,⁹ we then envision that if the key silver fluoroalkyl complexes (AgR_F)¹⁰ generated from convenient and commercially available reagents TMSR_F and AgF can be utilized in similar reactions in combination with sulfur dioxide, introduction of various fluoroalkyl groups and fluorosulfonyl groups into unactivated alkenes may be expected (Scheme 1b). As a continuation of our research interest in radical fluoroalkylation and sulfur dioxide utilization,^{8,11} we herein present the results.

Initial studies were carried out using (trifluoromethyl)trimethylsilane (Me_3SiCF_3 or TMSCF_3 , commonly known as the Ruppert–Prakash reagent, widely-used and a commercially available nucleophilic trifluoromethylating agent)¹² and silver fluoride to generate the key AgCF_3 species,¹⁰ 4-phenyl-1-butene (**1a**) as the model alkene substrate, 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct (DABSO)¹³ as a convenient and commercially available solid source of SO_2 , and NFSI as an electrophilic fluorination reagent. In our optimization studies of the reaction conditions, it was found that 2.0 equiv. of TMSCF_3 , 2.0 equiv. of AgF , 1.0 equiv. of **1a**, 2.0 equiv. of DABSO, and 4.0 equiv. of NFSI in 3 mL of CH_3CN at room temperature were the suitable conditions to afford the desired product **3a** in excellent yield (86%, Table 1, entry 1). Replacement of CH_3CN with other common reaction solvents,

such as DMF, DMSO NMP or THF resulted in lower yields of **3a** (Table 1, entries 2–4). Notably, water was found to be harmful for the desired reaction since using small amounts of water as the co-solvent resulted in no formation of **3a** (Table 1, entry 5). An attempt at increasing the yield of the desired product by utilizing some additives met with failure (Table 1, entries 6–13). While increased reaction temperatures had a deleterious effect on the desired reaction, room temperature or 0 °C led to an excellent yield of the target product **3a** (Table 1, entries 1, 14 and 15). Finally, the increased concentration of TMSCF_3 and AgF did not have a significant effect on the reaction (Table 1, entry 16).

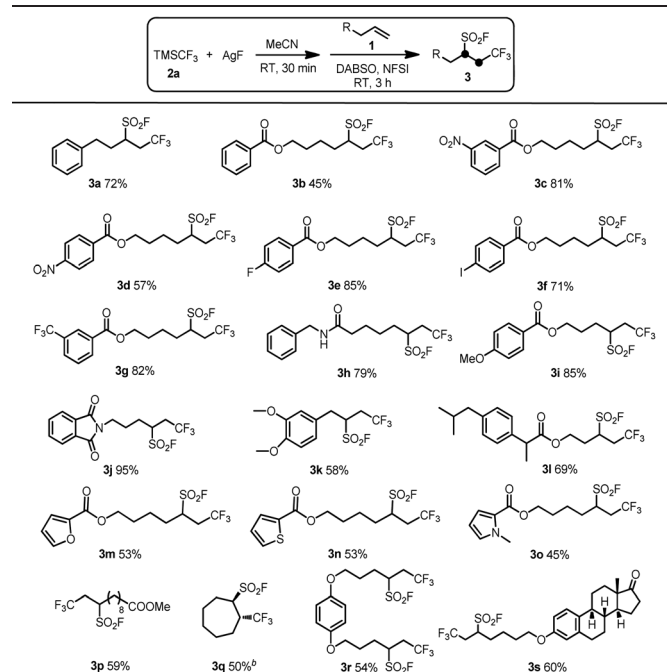
With the optimal reaction conditions established, the substrate scope of the intermolecular oxidative radical fluoroalkyl-fluorosulfonylation reactions with respect to unactivated alkenes was explored. As shown in Table 2, a range of unactivated alkenes participated in our protocol, providing good yields of the desired products **3**. Various functional groups including nitro (**3c**, **3d**), halogen (**3e**, **3f**), amide (**3h**), phthalimide (**3j**), ether (**3i**, **3k**, **3r**, **3s**), ester (**3b–i**, **3l–p**), and heterocyclic (**3m–o**) were well tolerated under the reaction conditions providing the corresponding target products in good yields. In particular, the iodo group in substrate **1f** can survive the standard reaction conditions, affording the desired product **3f** in good yield. Substrate **1r** with two terminal alkenyl groups was

Table 1 Optimization of the reaction conditions^a

|  | | |
|-------------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------|
| Entry | Deviation from the standard conditions | Yield of 3a ^b (%) |
| 1 | None | 86 |
| 2 | DMF instead of CH_3CN | 42 |
| 3 | DMSO instead of CH_3CN | 49 |
| 4 | NMP or THF instead of CH_3CN | 0 |
| 5 | 0.1 mL of H_2O as a co-solvent | 0 |
| 6 | 1.0 equiv. of pyridine as an additive | 19 |
| 7 | 1.0 equiv. of 2,6-dimethylpyridine as an additive | 63 |
| 8 | 1.0 equiv. of 2,2'-bipyridine as an additive | 11 |
| 9 | 1.0 equiv. of o-phenanthroline as an additive | 10 |
| 10 | 1.0 equiv. of 2,6-di- <i>tert</i> -butylpyridine as an additive | 72 |
| 11 | 1.0 equiv. of PPh_3 as an additive | 65 |
| 12 | 1.0 equiv. of Et_3N as an additive | 73 |
| 13 | 1.0 equiv. of 2,4,6-collidine as an additive | 75 |
| 14 | 0 °C | 86 |
| 15 | 50 °C | 76 |
| 16 | 4.0 equiv. of TMSCF_3 and 4.0 equiv. of AgF | 87 |

^a General reaction conditions: TMSCF_3 (0.4 mmol) and AgF (0.4 mmol) in CH_3CN (3 mL) were stirred at room temperature under an Ar atmosphere for 30 min, and then 4-phenyl-1-butene (**1a**, 0.2 mmol), DABSO (0.4 mmol) and NFSI (0.8 mmol) were added in turn and stirred for 3 h. ^b Yields were determined by ^{19}F NMR spectroscopy using 1-methoxy-4-(trifluoromethoxy)benzene as an internal standard.

Table 2 Substrate scope with respect to unactivated alkenes^a

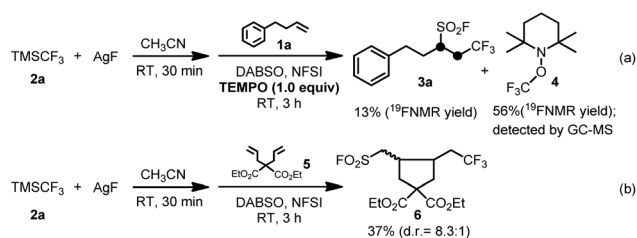


^a Reaction conditions: TMSCF_3 (0.6 mmol) and AgF (0.6 mmol) in CH_3CN (4.5 mL) were stirred at room temperature under an Ar atmosphere for 30 min, and then the alkene **1** (0.3 mmol), DABSO (0.6 mmol) and NFSI (1.2 mmol) were added in turn and stirred for 3 h. Yields refer to chromatographically pure material unless otherwise noted. ^b Yields were determined by ^{19}F NMR spectroscopy with 1-methoxy-4-(trifluoromethoxy)benzene as an internal standard.

smoothly applied to the fluoroalkylfluorosulfonylation reaction to result in the desired product **3r** in an acceptable yield. Moreover, an estrone derivative with an alkenyl group was also a suitable partner for this transformation to successfully produce the desired product **3s**.

To further explore the application of this protocol, various (fluoroalkyl)trimethylsilanes (TMSR_F) were employed under the optimized reaction conditions (Table 3). As expected, replacement of CF₃ in TMSCF₃ with other perfluoroalkyl groups like the C₂F₅ group resulted in the desired pentafluoroethylfluorosulfonylation products in good yields under similar reaction conditions (**3t–y**). However, the use of TMSCF₂H instead of TMSCF₃ under the standard or modified reaction conditions resulted in no formation of the desired product **3z**, probably due to the relative unstability of the key intermediate AgCF₂H and the decreased electrophilic ability of the CF₂H radical compared with the perfluoroalkyl radical such as the CF₃ or C₂F₅ radical. To our surprise, the use of TMSCF₂COOEt as the reactant does not appear to be effective under the standard reaction conditions and led to lower yields of the target products **3aa** and **3bb**. Notably, good yields of the desired products **3aa** and **3bb** were achieved when the formation of the key intermediate AgCF₂COOEt was performed at 0 °C in 15 min, which might be ascribed to the increased stability of AgCF₂COOEt at lower reaction temperatures. All these experimental results showed that the intermolecular oxidative radical fluoroalkylfluorosulfonylation reaction of unactivated alkenes is sensitive to the stability of the key intermediate AgR_F and the electronic properties of the corresponding fluoroalkyl radical generated from TMSR_F and AgF.

Two sets of control experiments were carried out to shed light on the reaction mechanism. In the first experiment, 2,2,6,6-tetramethyl-1-piperidyl-oxyl (TEMPO) as a radical scavenger

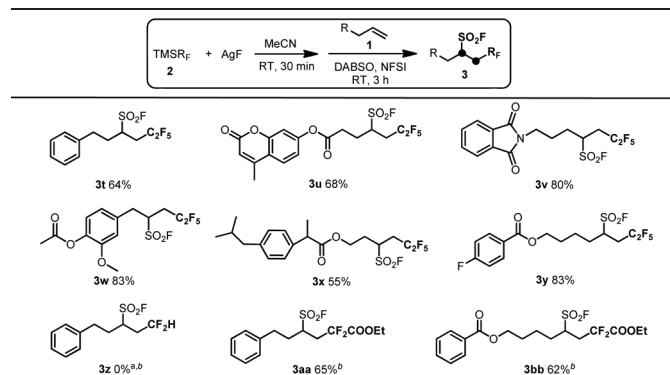


Scheme 2 Control experiments.

was used to trap the possible radical intermediates generated in the reaction system. The corresponding TEMPO-trapped complex **4** was obtained in 56% yield on the basis of ¹⁹F NMR spectroscopic analysis along with only 13% yield of the desired product **3a** (Scheme 2a). In the second experiment, alkene **5** was subjected to the standard reaction conditions to generate the ring-closed product **6** in 37% isolated yield (Scheme 2b). We reasoned that the alkyl radical generated *in situ* from the addition of the CF₃ radical to alkene **5** undergoes an irreversible intramolecular cyclization at a much faster rate than that of the consequent radical insertion of sulfur dioxide and a rapid fluorination process. The above experiments strongly suggested that a radical reaction pathway may be involved in the fluoroalkylfluorosulfonylation reaction of unactivated alkenes, and the corresponding silver fluoroalkyl species as the key intermediate can produce a fluoroalkyl radical to initiate the desired reaction, and the resulting alkyl-sulfonyl radical derived from the radical insertion of sulfur dioxide is rapidly fluorinated by NFSI to give the final desired product (Scheme 1).

In conclusion, we have reported an intermolecular oxidative radical fluoroalkylfluorosulfonylation reaction of unactivated alkenes with convenient and commercially available (fluoroalkyl)trimethylsilane, silver fluoride, sulfur dioxide and *N*-fluorobenzenesulfonimide. This transformation efficiently affords various fluoroalkyl-containing alkyl sulfonyl fluorides with good functional group tolerance under mild conditions. Silver fluoroalkyl complexes generated from (fluoroalkyl)trimethylsilane and silver fluoride may be the key intermediate as the fluoroalkyl radical source, and the alkyl radical produced from the addition of a fluoroalkyl radical to an alkene undergoes radical insertion with sulfur dioxide and the consequent rapid fluorination with NFSI to afford the final product.

Table 3 Substrate scope with respect to (fluoroalkyl)trimethylsilane^a



^a Reaction conditions: TMSR_F (0.6 mmol) and AgF (0.6 mmol) in CH₃CN (4.5 mL) were stirred at room temperature under an Ar atmosphere for 30 min, and then the alkene **1** (0.3 mmol), DABSO (0.6 mmol) and NFSI (1.2 mmol) were added in turn and stirred for 3 h. Yields of isolated products were reported. ^b Reaction conditions: TMSR_F (0.6 mmol) and AgF (0.6 mmol) in CH₃CN (4.5 mL) were stirred at 0 °C under an Ar atmosphere for 15 min, and then the alkene **1** (0.3 mmol), DABSO (0.6 mmol) and NFSI (1.2 mmol) were added in turn and stirred for 3 h. Yields of isolated products were reported.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21421002, 21302207, 21871283), the Science and Technology

Commission of Shanghai Municipality (No. 17ZR1437000), the Foundation of Science and Technology on Sanming Institute of Fluorochemical Industry (FCIT201701BR), and the Henan Province Science and Technology Open Cooperation Program (18210600017).

Notes and references

- For selected reviews, see: (a) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (c) M. Cametti, B. Crousse, P. Metrangolo, R. Milani and G. Resnati, *Chem. Soc. Rev.*, 2012, **41**, 31.
- For selected reviews on fluoroalkylation reactions, see: (a) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (b) Y. Lu, C. Liu and Q.-Y. Chen, *Curr. Org. Chem.*, 2015, **19**, 1638; (c) L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513; (d) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors and F. R. Leroux, *Beilstein J. Org. Chem.*, 2013, **9**, 2476; (e) B. Lantaño, M. R. Torviso, S. M. Bonesi, S. Barata-Vallejo and A. Postigo, *Coord. Chem. Rev.*, 2015, **285**, 76; (f) C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765; (g) Q. Liu, C. Ni and J. Hu, *Natl. Sci. Rev.*, 2017, **4**, 303; (h) H.-X. Song, Q.-Y. Han, C.-L. Zhao and C.-P. Zhang, *Green Chem.*, 2018, **20**, 1662; (i) S. Barata-Vallejo, M. V. Cooke and A. Postigo, *ACS Catal.*, 2018, **8**, 7287.
- (a) J. Dong, L. Krasnova, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2014, **53**, 9430; (b) B. Gao, L. Zhang, Q. Zheng, F. Zhou, L. M. Klivansky, J. Lu, Y. Liu, J. Dong, P. Wu and K. B. Sharpless, *Nat. Chem.*, 2017, **9**, 1083; (c) Z. Liu, J. Li, S. Li, G. Li, K. B. Sharpless and P. Wu, *J. Am. Chem. Soc.*, 2018, **140**, 2919; (d) T. J. Guo, G. Y. Meng, X. J. Zhan, Q. Yang, T. C. Ma, L. Xu, K. B. Sharpless and J. Dong, *Angew. Chem., Int. Ed.*, 2018, **57**, 2605.
- For selected recent examples, see: (a) L. Tang, Y. Yang, L. Wen, X. Yang and Z. Wang, *Green Chem.*, 2016, **18**, 1224; (b) A. T. Davies, J. M. Curto, S. W. Bagley and M. C. Willis, *Chem. Sci.*, 2017, **8**, 1233; (c) Y. Chen and M. C. Willis, *Chem. Sci.*, 2017, **8**, 3249; (d) A. L. Tribby, I. Rodríguez, S. Shariffudin and N. D. Ball, *J. Org. Chem.*, 2017, **82**, 2294.
- (a) S. O. Alapafuja, S. P. Nikas, I. T. Bharathan, V. G. Shukla, M. L. Nasr, A. L. Bowman, N. Zvonok, J. Li, X. Shi, J. R. Engen and A. Makriyannis, *J. Med. Chem.*, 2012, **55**, 10074; (b) A. Narayanan and L. H. Jones, *Chem. Sci.*, 2015, **6**, 2650.
- A. V. Bogolubsky, Y. S. Moroz, P. K. Mykhailiuk, S. E. Pipko, A. I. Konovets, I. V. Sadkova and A. Tolmachev, *ACS Comb. Sci.*, 2014, **16**, 192.
- For selective reviews on radical 1,2-difunctionalization type fluoroalkylation, see: (a) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (b) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (c) T. Koike and M. Akita, *Acc. Chem. Res.*, 2016, **49**, 1937; (d) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284; (e) X.-W. Lan, N.-X. Wang and Y. Xing, *Eur. J. Org. Chem.*, 2017, 5821; (f) X. Wu, S. Wu and C. Zhu, *Tetrahedron Lett.*, 2018, **59**, 1328. For selected examples on radical 1,2-difunctionalization type fluoroalkylation, see: (g) X. Wu, L. Chu and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2013, **52**, 2198; (h) Y.-F. Wang, G. H. Lonca and S. Chiba, *Angew. Chem., Int. Ed.*, 2014, **53**, 1067; (i) G. Ma, W. Wan, J. Li, Q. Hu, H. Jiang, S. Zhu, J. Wang and J. Hao, *Chem. Commun.*, 2014, **50**, 9749; (j) W. Yu, X.-H. Xu and F.-L. Qing, *Adv. Synth. Catal.*, 2015, **357**, 2039; (k) Y.-B. Wu, G.-P. Lu, T. Yuan, Z.-B. Xu, L. Wan and C. Cai, *Chem. Commun.*, 2016, **52**, 13668; (l) Z. Wu, D. Wang, Y. Liu, L. Huan and C. Zhu, *J. Am. Chem. Soc.*, 2017, **139**, 1388; (m) Y.-F. Cheng, X.-Y. Dong, Q.-S. Gu, Z.-L. Yu and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 8883; (n) Q. Zhao, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2017, **56**, 11575; (o) J. Yu, Z. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 17156; (p) X.-T. Li, Q.-S. Gu, X.-Y. Dong, X. Meng and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2018, **57**, 7668.
- Y. Liu, H. Wu, Y. Guo, J.-C. Xiao, Q.-Y. Chen and C. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 15432.
- For recent reviews on sulfur dioxide radical insertion reactions: (a) D. Zheng and J. Wu, *Sulfur Dioxide Insertion Reactions for Organic Chemistry*, Springer, Singapore, 2017; (b) G. Qiu, K. Zhou, L. Gao and J. Wu, *Org. Chem. Front.*, 2018, **5**, 691; (c) K. Hofman, N.-W. Liu and G. Manolikes, *Chem. – Eur. J.*, 2018, **24**, 11852.
- (a) W. Tyrre and D. Naumann, *J. Fluorine Chem.*, 2004, **125**, 823; (b) Y. Zeng, L. Zhang, Y. Zhao, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 2955; (c) Y. Ye, S. H. Lee and M. S. Sanford, *Org. Lett.*, 2011, **13**, 5464.
- (a) H. Wu, Z. Xiao, J. Wu, Y. Guo, J.-C. Xiao, C. Liu and Q.-Y. Chen, *Angew. Chem., Int. Ed.*, 2015, **54**, 4070; (b) B. He, Z. Xiao, H. Wu, Y. Guo, Q.-Y. Chen and C. Liu, *RSC Adv.*, 2017, **7**, 880; (c) Z. Xiao, Y. Liu, L. Zheng, C. Liu, Y. Guo and Q.-Y. Chen, *J. Org. Chem.*, 2018, **83**, 5836; (d) Z. Xiao, Y. Liu, L. Zheng, X. Zhou, Y. Xie, C. Liu, Y. Guo and Q.-Y. Chen, *Tetrahedron*, 2018, **74**, 6213; (e) Y. Liu, Q. Lin, Z. Xiao, C.-G. Zheng, Y. Guo, Q.-Y. Chen and C. Liu, *Chem. – Eur. J.*, 2019, **25**, DOI: 10.1002/chem.201805526.
- (a) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (b) G. K. S. Prakash, R. Krishnamurti and G. A. Olah, *J. Am. Chem. Soc.*, 1989, **111**, 393; (c) I. Ruppert, K. Schlich and W. Volbach, *Tetrahedron Lett.*, 1984, **25**, 2195; (d) S. Krishnamoorthy and G. K. S. Prakash, *Synthesis*, 2017, **49**, 3394.
- (a) P. S. Santos and M. T. S. Mello, *J. Mol. Struct.*, 1988, **178**, 121; (b) B. Nguyen, E. J. Emmett and M. C. Willis, *J. Am. Chem. Soc.*, 2010, **132**, 16372; (c) H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson and M. C. Willis, *Org. Lett.*, 2011, **13**, 4876; (d) E. J. Emmett and M. C. Willis, *Asian J. Org. Chem.*, 2015, **4**, 602.