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Visible-light-induced radical hydrodifluoromethylation of alkenes†

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Described here is the radical-mediated hydrodifluoromethylation of alkenes that occurs under transition-metal-free conditions by using the phosphonium salt $[\text{Ph}_3\text{P}^+\text{CF}_2\text{H}]\text{Br}^-$ under the irradiation of 26 W household compact fluorescent light. The reaction lends itself to a convenient protocol for the installation of a C–CF₂H bond while maintaining good functional group tolerance.

The difluoromethyl group (HCF₂) has received increasing attention in drug design, because it is a lipophilic hydrogen-bond donor and can act as a bioisostere of an OH or SH unit.¹ The past few decades have seen the emergence of many HCF₂-containing pharmaceuticals and agrochemicals, such as eflornithine, deracoxib, sedaxane, isopyrazam, bixafen, and thiazopir.² The high demand for HCF₂-substituted biologically active compounds has prompted the development of efficient methods for the incorporation of a HCF₂ group into organic molecules.

The straightforward strategies for HCF₂ incorporation include the insertion of difluorocarbene into X–H bonds³ (X = C, N, O, S, *etc.*) and direct difluoromethylation with a HCF₂ reagent.^{2,4} Difluorocarbene insertion is highly effective for the installation of an XCF₂H moiety (X = N, O, or S), but for the formation of a C–CF₂H group by this strategy, a reactive substrate or a strong base has to be used.⁵ Over the last few years, a large number of direct difluoromethylation approaches have been developed, such as nucleophilic,⁶ radical,⁷ electrophilic⁸ and transition-metal-promoted reactions,⁹ enabling convenient construction of C–CF₂H bonds. However, the reported methods usually suffer from the use of a transition metal that may limit their biomedical applications, or difluoromethylation reagents that are volatile or difficult to prepare. In addition, a further tedious procedure may be required to remove the undesired auxiliary group X from XCF₂ moieties to form HCF₂-products. It is therefore highly desirable to develop

mild protocols for direct difluoromethylation under transition-metal-free conditions by using an easy-to-handle reagent.

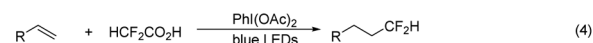
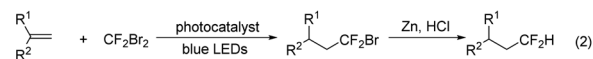
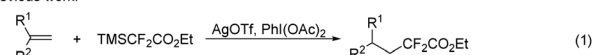
Hydrodifluoromethylation of alkenes is an attractive approach for the installation of a Csp³–CF₂H bond. In 2014, Hao described a hydrodifluoromethylation of terminal alkenes with TMSCF₂CO₂Et, a process in which an excess of silver source is essential (Scheme 1, eqn (1)).¹⁰ In 2015, Qing disclosed a two-step sequence involving visible-light-induced hydrobromodifluoro-methylation with ozone-depleting CF₂Br₂ and the subsequent reductive debromination to convert the BrCF₂ to HCF₂ groups (Scheme 1, eqn (2)).¹¹ Shortly after, they further reported the hydrodifluoromethylation using phosphonium reagents, $[\text{Ph}_3\text{P}^+\text{CF}_2\text{Br}]\text{Br}^-$ ¹² and $[\text{Ph}_3\text{P}^+\text{CF}_2\text{H}]\text{Br}^-$,¹³ under photocatalytic conditions (eqn (3)). Dolbier *et al.* found that the photocatalyzed hydrodifluoromethylation with HCF₂SO₂Cl could also occur well (eqn (3)).¹⁴ Gouverneur reported a visible-light-promoted hydrodifluoromethylation of alkenes with HCF₂CO₂H (eqn (4)).¹⁵ This operationally simple reaction did not require a photocatalyst, affording the hydrodifluoromethylation products in good yields. Although the above approaches are quite efficient, their synthetic utility

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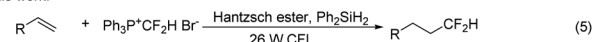
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Previous work:



This work:

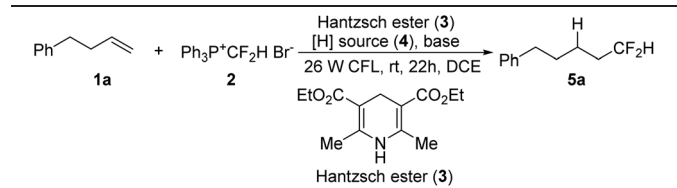


Scheme 1 Hydrodifluoromethylation of alkenes.

may be compromised by the disadvantages such as the need for an additional step to remove an auxiliary group,^{10,11} or the use of an expensive photocatalyst^{12–14} or a strong oxidant.¹⁵ In continuation of our studies on fluoroalkylation,^{6d,16} we investigated the feasibility of performing direct hydrodifluoromethylation of alkenes under radical mediated conditions. Herein, we report the visible light induced hydrodifluoromethylation of alkenes using the phosphonium salt $[\text{Ph}_3\text{P}^+\text{CF}_2\text{H}]\text{Br}^-$ under the irradiation of with 26 W household compact fluorescent light (CFL) (eqn (5)).

We have previously shown that the phosphonium salt, $[\text{Ph}_3\text{P}^+\text{CF}_2\text{H}]\text{Br}^-$ (**2**),^{6d} could be easily prepared from the phosphobetaine $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$, a reagent developed by us,¹⁷ via a convenient decarboxylative protonation. Since salt **2** could be reduced to generate a difluoromethyl radical,¹⁸ various reducing agents were examined in our initial attempts at the hydrodifluoromethylation of alkene **1a** with **2** (Table 1, entries 1–4). However, almost no desired product was detected by using metals as reducing agents (entries 1–3). We then probed Hantzsch ester **3**, as it was known to act as an efficient reducing agent when irradiated with visible light.¹⁹ To our delight,

Table 1 Optimization of the reaction conditions^a

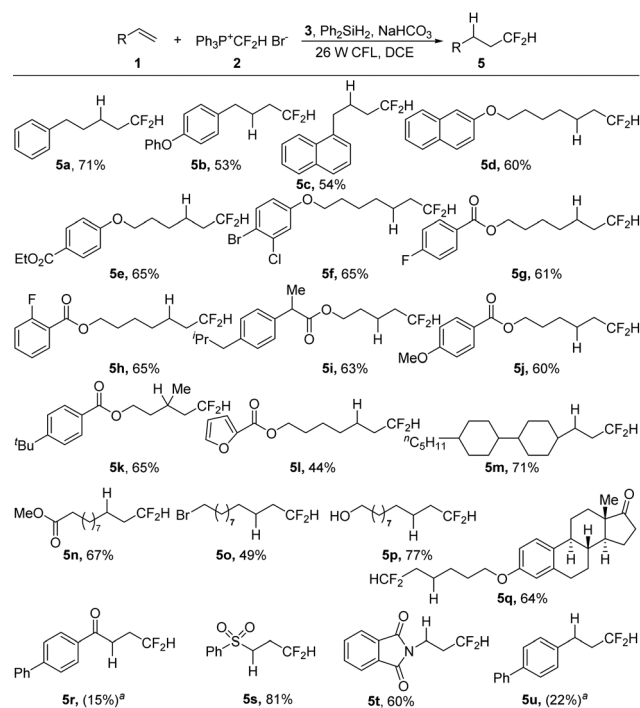


Entry	[H] source	Base	Ratio ^b	Yield ^c (%)
1 ^{d,e}	—	—	1 : 3 : 3 : 0 : 0	ND
2 ^{d,f}	—	—	1 : 3 : 3 : 0 : 0	Trace
3 ^{d,g}	—	—	1 : 3 : 3 : 0 : 0	ND
4 ^d	—	—	1 : 3 : 3 : 0 : 0	16
5 ^h	—	—	1 : 2 : 2 : 0 : 0	4
6 ⁱ	—	—	1 : 2 : 2 : 0 : 0	25
7	—	—	1 : 2 : 2 : 0 : 0	28
8	—	NaHCO_3	1 : 2 : 2 : 0 : 4	41
9	—	KH_2PO_4	1 : 2 : 2 : 0 : 4	17
10	—	CH_3COOK	1 : 2 : 2 : 0 : 4	28
11	—	$\text{Na}_2\text{C}_2\text{O}_4$	1 : 2 : 2 : 0 : 4	16
12	—	Cs_2CO_3	1 : 2 : 2 : 0 : 4	28
13	$(\text{TMS})_3\text{SiH}$	NaHCO_3	1 : 2 : 2 : 4 : 4	15
14	Ph_2SiH_2	NaHCO_3	1 : 2 : 2 : 4 : 4	50
15	Et_3SiH	NaHCO_3	1 : 2 : 2 : 4 : 4	45
16	Bu_3SnH	NaHCO_3	1 : 2 : 2 : 4 : 4	6
17	Ph_2SiH_2	NaHCO_3	1 : 2 : 2 : 4 : 2	31
18	Ph_2SiH_2	NaHCO_3	1 : 3 : 2 : 4 : 4	57
19	Ph_2SiH_2	NaHCO_3	1 : 4 : 2 : 4 : 4	70
20	Ph_2SiH_2	NaHCO_3	1 : 4 : 2 : 2 : 4	71

^a Reaction conditions: **1a** (0.2 mmol), **2**, **3**, **4** and base in 1,2-dichloroethane (3.5 mL) under the irradiation of household 26 W CFL at room temperature for 22 h. ^b Molar ratio of **1a**:**2**:**3**:**4**:base. ^c The yields were determined by ¹⁹F NMR; ND = not detected. ^d CH_3CN was used as the reaction solvent. ^e Mg was used as the reductant instead of a Hantzsch ester. ^f Zn was used as the reductant instead of a Hantzsch ester. ^g Fe was used as the reductant instead of a Hantzsch ester. ^h DMF was used as the reaction solvent. ⁱ DCM was used as the reaction solvent.

16% yield was obtained by irradiating the reaction with household 26 W CFL in the presence of a Hantzsch ester (entry 4). A brief survey of the reaction solvents (entries 4–7) revealed that 1,2-dichloroethane (DCE) was a superior choice (entry 7). The yield was increased in the presence of NaHCO_3 (entry 8 vs. 7), but other bases seemed ineffective (entries 9–12 vs. 7). Apparently, a hydrogen source was needed in this hydrodifluoromethylation reaction. The 41% yield (entry 8) indicated that one of the reagents used also served as a hydrogen source. Since it was difficult to increase the yield further, a second hydrogen source was then added (entries 13–16). The use of Ph_2SiH_2 increased the yield to 50% (entry 14). The molar ratios of the reagents were screened (entries 17–20). An increase in the yield was observed by increasing the loading of phosphonium salt **2** (entry 20).

With the optimized reaction conditions in hand (Table 1, entry 20), we then investigated the substrate scope of the visible-light-induced hydrodifluoromethylation of alkenes (Scheme 2). The process could be applied to a wide range of alkenes, and various functional groups could be tolerated, including ester, carbonyl, halides, heterocycles, hydroxyl, sulfonyl, and imide groups. Besides monosubstituted alkenes, disubstituted terminal alkenes could also be converted smoothly into the desired products (**5k**). However, in the case of trisubstituted alkenes, low regioselectivity was observed, and complex mixtures were obtained. For substrates with electron-

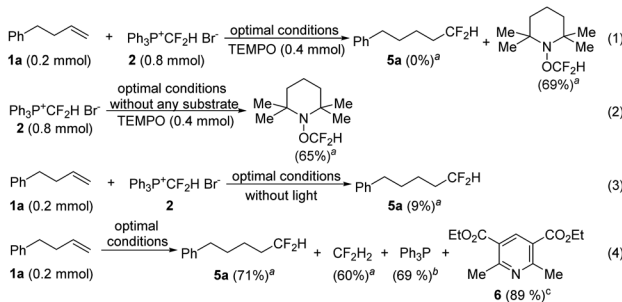


Scheme 2 Hydrodifluoromethylation of alkenes. Isolated yields. Reaction conditions: Substrate **1** (0.5 mmol), salt **2** (4 equiv.), Hantzsch ester (**3**, 2 equiv.), Ph_2SiH_2 (2 equiv.), and NaHCO_3 (4 equiv.) in DCE (9 mL) under the irradiation of 26 W household CFL at room temperature for 22 h. ^a The yields of **5r** and **5u** were determined by ¹⁹F NMR spectroscopy.

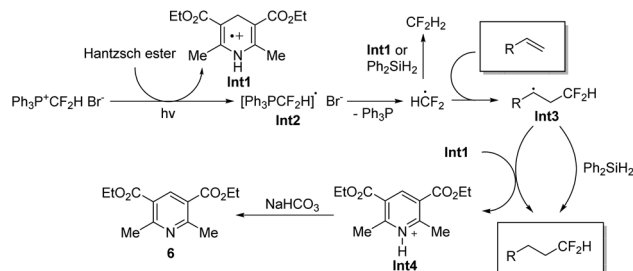
withdrawing carbonyl and sulfonyl groups, although the carbonyl-substituted alkene showed a low reactivity (**5r**), the sulfonyl alkene was transformed into the desired product in a good yield (**5s**). While the reaction of an enamine derivative gave the product in a good yield (**5t**), the hydrodifluoromethylation of an aryl alkene under the present reaction conditions led to a low conversion (**5u**).

More experimental evidence was collected to gain insight into the mechanism of this hydrodifluoromethylation reaction. The addition of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), completely suppressed the formation of the desired product, and the TEMPO-CF₂H byproduct was produced in 69% yield (Scheme 3, eqn (1)). The TEMPO-CF₂H adduct was also detected from the reaction run in the absence of a substrate (eqn (2)), indicating that a radical mechanism is operative. The desired product was generated in a very low yield when the reaction was conducted in the dark (eqn (3)), suggesting that light is essential for this process. After the reaction was complete, CF₂H₂, Ph₃P and pyridine **6** were produced as the byproducts (eqn (4)). In particular, Ph₃P and **6**, formed from [Ph₃P⁺CF₂H]Br⁻ and the Hantzsch ester, respectively, were isolated in high yields, indicating that [Ph₃P⁺CF₂H]Br⁻ was reduced while the Hantzsch ester was oxidized in the reaction. The Stern–Volmer luminescence quenching experiments revealed that the phosphonium salt [Ph₃P⁺CF₂H]Br⁻ could quench the excited Hantzsch ester (see the ESI† for experimental details), suggesting that electron transfer between these two reagents might have occurred.

On the basis of the above results, we proposed the reaction mechanism as shown in Scheme 4. Under the irradiation of light, a single electron transfer from the Hantzsch ester to the phosphonium salt [Ph₃P⁺CF₂H]Br⁻ generates radical cation **Int1** and [Ph₃PCF₂H][•] radical. The release of Ph₃P from [Ph₃PCF₂H][•] radical provides HCF₂[•], which is easily trapped by an alkene to form intermediate **Int3**. The HCF₂[•] radical may also be quenched by **Int1** or Ph₂SiH₂ to give CF₂H₂. Radical **Int3** would abstract a hydrogen atom from Ph₂SiH₂ or radical cation **Int1** to deliver the desired product **5**. The reaction of **Int3** with **Int1** leads to the formation of pyridinium cation **Int4**, which is neutralized by NaHCO₃ to afford compound **6**.



Scheme 3 Mechanistic investigations. ^a The yields were determined by ¹⁹F NMR spectroscopy based on **1a** (0.2 mmol); ^b isolated yield based on [Ph₃P⁺CF₂H]Br⁻; ^c isolated yield based on the Hantzsch ester.



Scheme 4 The proposed mechanism.

Conclusions

In summary, we developed an efficient radical-mediated hydrodifluoromethylation of alkenes using easily available phosphonium salt [Ph₃P⁺CF₂H]Br⁻ with the irradiation of 26 W household CFL under transition-metal-free conditions. This operationally simple reaction offers a convenient protocol for the installation of a C sp³-CF₂H bond. With good functional group tolerance, this approach may find applications in the synthesis of biologically active HCF₂-containing molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) J. A. Erickson and J. I. McLoughlin, *J. Org. Chem.*, 1995, **60**, 1626–1631; (b) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591; (c) C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang and S. J. Lippard, *J. Am. Chem. Soc.*, 2017, **139**, 9325–9332.
- D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem. – Eur. J.*, 2017, **23**, 14676–14701.
- C. Ni and J. Hu, *Synthesis*, 2014, **46**, 842–863.
- (a) Y. Lu, C. Liu and Q. Y. Chen, *Curr. Org. Chem.*, 2015, **19**, 1638–1650; (b) J. Rong, C. Ni and J. Hu, *Asian J. Org. Chem.*, 2017, **6**, 139–152; (c) T. Koike and M. Akita, *Org. Biomol. Chem.*, 2019, **17**, 5413–5419; (d) A. Lemos, C. Lemaire and A. Luxen, *Adv. Synth. Catal.*, 2019, **361**, 1500–1537.
- (a) S.-L. Lu, X. Li, W.-B. Qin, J.-J. Liu, Y.-Y. Huang, H. N. C. Wong and G.-K. Liu, *Org. Lett.*, 2018, **20**, 6925–6929; (b) J. Wang, E. Tokunaga and N. Shibata, *Chem.*

- Commun.*, 2018, **54**, 8881–8884; (c) Q. Xie, Z. Zhu, L. Li, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2019, **58**, 6405–6410.
- 6 (a) Y. Zhao, W. Huang, J. Zheng and J. Hu, *Org. Lett.*, 2011, **13**, 5342–5345; (b) X. Shen, Q. Liu, T. Luo and J. Hu, *Chem. – Eur. J.*, 2014, **20**, 6795–6800; (c) D. Chen, C. Ni, Y. Zhao, X. Cai, X. Li, P. Xiao and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 12632–12636; (d) Z. Deng, J.-H. Lin, J. Cai and J.-C. Xiao, *Org. Lett.*, 2016, **18**, 3206–3209; (e) A. L. Trifonov, A. A. Zemtsov, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2016, **18**, 3458–3461.
- 7 (a) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494–1497; (b) Y. Ran, Q.-Y. Lin, X.-H. Xu and F.-L. Qing, *J. Org. Chem.*, 2016, **81**, 7001–7007; (c) W. Fu, X. Han, M. Zhu, C. Xu, Z. Wang, B. Ji, X.-Q. Hao and M.-P. Song, *Chem. Commun.*, 2016, **52**, 13413–13416; (d) X. Xu and F. Liu, *Org. Chem. Front.*, 2017, **4**, 2306–2310; (e) M. Zhu, W. Fu, Z. Wang, C. Xu and B. Ji, *Org. Biomol. Chem.*, 2017, **15**, 9057–9060; (f) P. Dai, X. Yu, P. Teng, W.-H. Zhang and C. Deng, *Org. Lett.*, 2018, **20**, 6901–6905; (g) J. Yu, Z. Wu and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 17156–17160; (h) M. Zhu, W. Fun, W. Guo, Y. Tian, Z. Wang, C. Xu and B. Ji, *Eur. J. Org. Chem.*, 2019, 1614–1619.
- 8 (a) X. Wang, G. Liu, X.-H. Xu, N. Shibata, E. Tokunaga and N. Shibata, *Angew. Chem., Int. Ed.*, 2014, **53**, 1827–1831; (b) J. Zhu, Y. Liu and Q. Shen, *Angew. Chem., Int. Ed.*, 2016, **55**, 9050–9054.
- 9 (a) Y. Gu, X. Leng and Q. Shen, *Nat. Commun.*, 2014, **5**, 5405; (b) L. Xu and D. A. Vicic, *J. Am. Chem. Soc.*, 2016, **138**, 2536–2539; (c) Z. Feng, Q. Q. Min, X. P. Fu, L. An and X. Zhang, *Nat. Chem.*, 2017, **9**, 918–923; (d) V. Bacauanu, S. b. Cardinal, M. Yamauchi, M. Kondo, D. F. Fernandez, R. Remy and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2018, **57**, 12543–12548; (e) F. Pan, G. B. Boursalian and T. Ritter, *Angew. Chem., Int. Ed.*, 2018, **57**, 16871–16876; (f) G. Tu, C. Yuan, Y. Li, J. Zhang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2018, **57**, 15597–15601; (g) C. Yuan, L. Zhu, R. Zeng, Y. Lan and Y. Zhao, *Angew. Chem., Int. Ed.*, 2018, **57**, 1277–1281; (h) W. Miao, Y. Zhao, C. Ni, B. Gao, W. Zhang and J. Hu, *J. Am. Chem. Soc.*, 2018, **140**, 880–883; (i) S.-Q. Zhu, Y.-L. Liu, H. Li, X.-H. Xu and F.-L. Qing, *J. Am. Chem. Soc.*, 2018, **140**, 11613–11617; (j) X. Zeng, W. Yan, S. B. Zacate, T.-H. Chao, X. Sun, Z. Cao, K. G. E. Bradford, M. Paeth, S. B. Tyndall, K. Yang, T.-C. Kuo, M.-J. Cheng and W. Liu, *J. Am. Chem. Soc.*, 2019, **141**, 11398–11403; (k) K. Hori, H. Motohashi, D. Saito and K. Mikami, *ACS Catal.*, 2019, **9**, 417–421.
- 10 G. Ma, W. Wan, J. Li, Q. Hu, H. Jiang, S. Zhu, J. Wang and J. Hao, *Chem. Commun.*, 2014, **50**, 9749–9752.
- 11 Q.-Y. Lin, X.-H. Xu and F.-L. Qing, *Org. Biomol. Chem.*, 2015, **13**, 8740–8749.
- 12 Q.-Y. Lin, X.-H. Xu, K. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2016, **55**, 1479–1483.
- 13 W.-Q. Hu, X.-H. Xu and F.-L. Qing, *J. Fluorine Chem.*, 2018, **208**, 73–79.
- 14 X.-J. Tang, Z. Zhang and W. R. Dolbier, Jr., *Chem. – Eur. J.*, 2015, **21**, 18961–18965.
- 15 C. F. Meyer, S. M. Hell, A. Misale, A. A. Trabanco and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2019, **58**, 8829–8833.
- 16 (a) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 1896–1900; (b) J. Zheng, J.-H. Lin, X.-Y. Deng and J.-C. Xiao, *Org. Lett.*, 2015, **17**, 532–535; (c) Y.-L. Ji, J.-J. Luo, J.-H. Lin, J.-C. Xiao and Y. C. Gu, *Org. Lett.*, 2016, **18**, 1000–1003; (d) Z. Deng, C. Liu, X.-L. Zeng, J.-H. Lin and J.-C. Xiao, *J. Org. Chem.*, 2016, **81**, 12084–12090; (e) X.-Y. Deng, J.-H. Lin and J.-C. Xiao, *Org. Lett.*, 2016, **18**, 4384–4387; (f) X.-Y. Pan, Y. Zhao, H.-A. Qu, J.-H. Lin, X.-C. Hang and J.-C. Xiao, *Org. Chem. Front.*, 2018, **5**, 1452–1456.
- 17 (a) J. Zheng, J. Cai, J.-H. Lin, Y. Guo and J.-C. Xiao, *Chem. Commun.*, 2013, **49**, 7513–7515; (b) J. Zheng, L. Wang, J.-H. Lin, J.-C. Xiao and S. H. Liang, *Angew. Chem., Int. Ed.*, 2015, **54**, 13236–13240; (c) J. Zheng, R. Cheng, J.-H. Lin, D. H. Yu, L. Ma, L. Jia, L. Zhang, L. Wang, J.-C. Xiao and S. H. Liang, *Angew. Chem., Int. Ed.*, 2017, **56**, 3196–3200; (d) J. Yu, J.-H. Lin and J.-C. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 16669–16673.
- 18 (a) N. B. Heine and A. Studer, *Org. Lett.*, 2017, **19**, 4150–4153; (b) Q.-Y. Lin, Y. Ran, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2016, **18**, 2419–2422.
- 19 (a) S. Azizi, G. Ulrich, M. Guglielmino, S. le Calvé, J. P. Hagon, A. Harriman and R. Ziessel, *J. Phys. Chem. A*, 2015, **119**, 39–49; (b) L. I. Panferova, A. V. Tsymbal, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2016, **18**, 996–999.