Chinese Chemical Letters 34 (2023) 107473

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Visible-light-induced direct hydrodifluoromethylation of alkenes with difluoromethyltriphenylphosphonium iodide salt

Xiaojian Ren, Qiang Liu, Zhixiang Wang*, Xiangyu Chen*

School of Chemical Sciences, University of the Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 11 February 2022
Revised 25 April 2022
Accepted 25 April 2022
Available online 30 April 2022

Keywords:
Hydrodifluoromethylation
Difluoromethyltriphenylphosphonium iodide salt
Alkenes
DFT studies
Photoredox

ABSTRACT

Photoredox-catalyzed hydrodifluoromethylation of alkenes has become an effective method to introduce difluoromethyl group into organic molecules. As the reported methods involve either photocatalysts or superstoichiometric amounts of additives, we herein describe a simple alternative without using photocatalyst or additive for the hydrodifluoromethylation of alkenes, through photoactivation of difluoromethyltriphenylphosphonium iodide salt. Mechanistic studies shed light on how the transformation takes place.

The incorporation of difluoromethyl group (CF_2H), a lipophilic hydrogen bond donor, has become a valuable tool in pharmaceutical research and drug development, as the CF_2H can serve as an alternative and complementary bioisostere for alcohols, thiols, amines and hydroxamic acid [1–3]. In the meantime, alkenes are present in a wide range of natural products and bioactive compounds [4]. Thus, the hydrodifluoromethylation of alkenes, which allows installing CF_2H group in a wider scope, has attracted increasing research interest [5–16]. In recent years, an emerging powerful strategy is photoredox-catalyzed hydrodifluoromethylation of alkenes with different CF_2H radical precursors. In this context, Dolbier and co-workers have shown the application of CF_2HSO_2Cl in visible-light-induced hydrodifluoromethylation of activated alkenes in the presence of Ir-based photocatalyst [17]. Qing and co-workers developed several elegant photoredox-catalyzed hydrodifluoromethylation of activated and unactivated alkenes with CF_2Br_2 [18] or difluoromethyltriphenylphosphonium salts [19,20]. An electron donor and acceptor complex strategy was also developed by Xiao and co-workers for the generation of CF_2H radical from difluoromethyltriphenylphosphonium salt [21]. Recently, Gouverneur and co-workers successfully developed an alternative photocatalyst-free protocol by using difluoroacetic acid and superstoichiometric amount of phenyliodine(III) diacetate (Scheme 1A) [22]. Despite these progresses, these methods involve either photocatalysts or superstoichiometric amounts of oxidants and additives. In this regard, the development of a photocatalyst- and additive-free method would benefit the synthetic and biological applications of hydrodifluoromethylation.

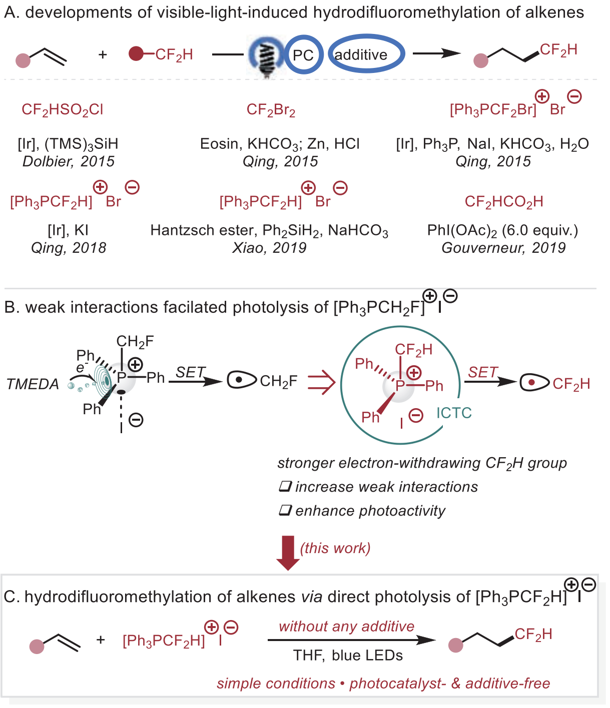
Fluoromethylphosphonium salts are readily available and bench stable and have been used as fluoromethyl source for the synthesis of a variety of fluoro-containing compounds [23,24]. In particular, the photoredox-catalyzed single-electron reduction of difluoromethylphosphoniums to produce CF_2H radical has been extensively investigated since the pioneering study of Qing [25–31]. Very recently, we found that the σ-hole effect could enable the photolysis of monofluoromethyltriphenylphosphonium iodide in the presence of TMEDA as the electron donor [32]. On the basis of these studies, we envisioned that the introduction of a stronger electron-withdrawing CF_2H group can enhance the acidity of α-hydrogen and deepen the σ-hole [33–41], which would facilitate the formation of an intramolecular charge-transfer complex (ICTC) [42–47]. The resultant ICTC can undergo single electron transfer (SET) from I^- to $[PPh_3CF_2H]^+$ to generate CF_2H radical, thus without using additional Lewis base as the electron donor (Schemes 1B and C).

In our previous work, we found that the difluoromethyltriphenylphosphonium iodide salt can react with activated alkenes for the cascade reactions and difluoromethylation reactions [32]. As an ongoing research in weak interaction enabled photoreactions [48,49], we set out to explore the possibility of developing a photocatalyst- and additive-free, visible-light-induced hydrodifluoromethylation of alkenes with difluoromethyltriphenylphosphonium iodide salt. Initially, the model reaction of

---

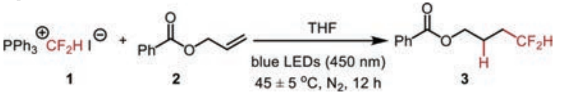
* Corresponding authors.
E-mail addresses: zxwang@ucas.ac.cn (Z. Wang), chenxiangyu20@ucas.ac.cn (X. Chen).

https://doi.org/10.1016/j.cclet.2022.04.071



Scheme 1. Motivation and synthetic strategy.

Table 1
Optimization of the reaction conditions.



Entry	Variations from standard conditions	Yield (%)[a]
1	none	80 (78)
2	DMF	38
3	DMA	56
4	CH_3CN	71
5	Acetone	35
6	Toluene	trace
7	CH_2Cl_2	27
8	Without irradiation (50 °C)	–

[a] Yields were determined by ^{19}F NMR analysis using (trifluoromethyl)benzene as an external standard. The value within parentheses refers to yield of isolated product.

difluoromethyltriphenylphosphonium iodide salt **1** and unactivated alkene **2** was investigated to validate our hypothesis (Table 1). We were pleased to find that the reaction went smoothly with THF as the solvent, giving the desired product **3** in 78% yield, wherein THF serves as the hydrogen atom donor (entry 1). A solvent screening showed that the reaction in DMF, DMA, CH_3CN, acetone, toluene or DCM provided poorer results than in THF (entries 2–7). In addition, no reaction was observed without irradiation (entry 8).

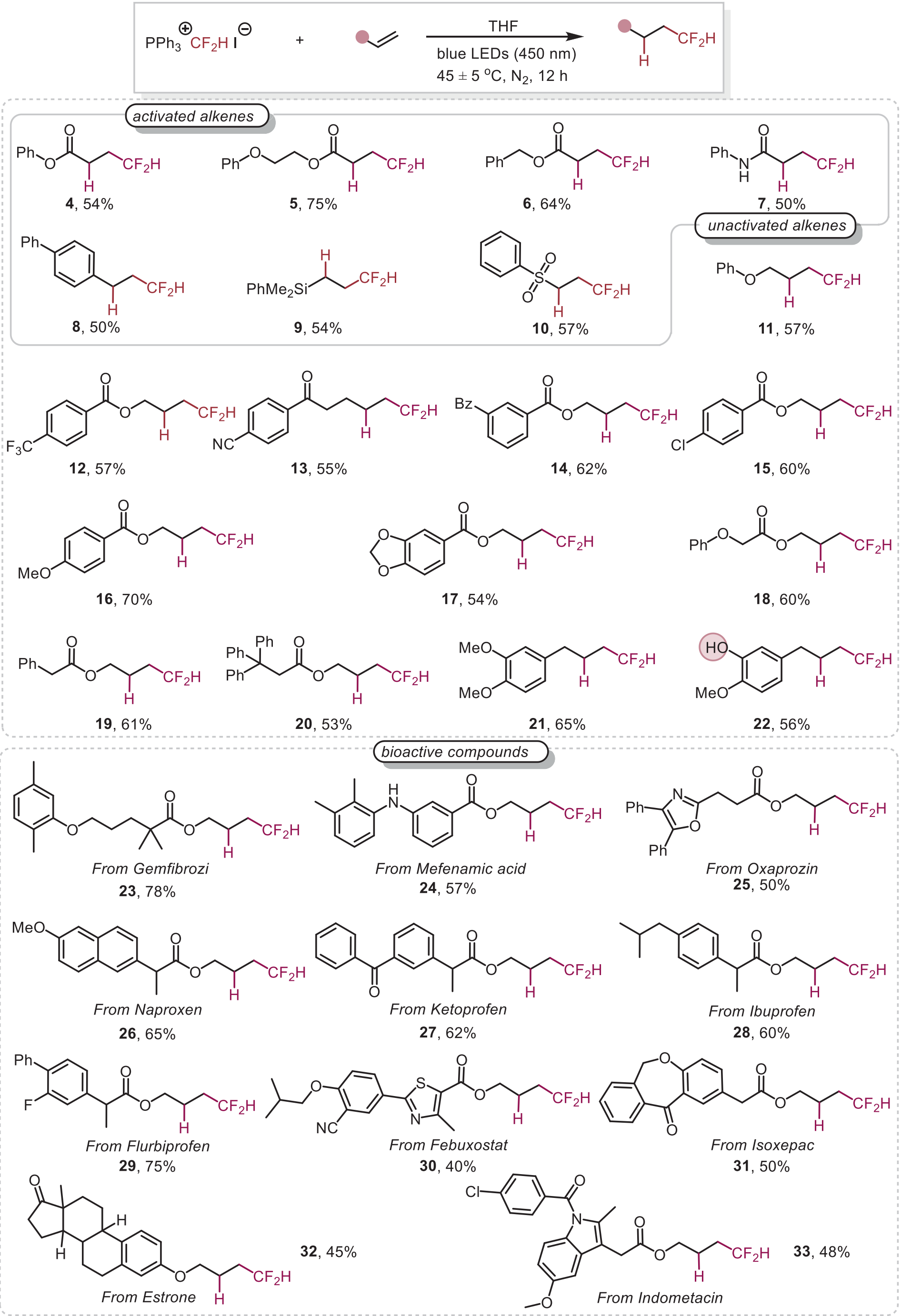
With the optimized conditions in hand, the scope of the alkenes was briefly investigated (Scheme 2). Reactions of a series of α,β-unsaturated esters, amide, 4-vinyl-1,1′-biphenyl, dimethyl(phenyl)(vinyl)silane and (vinylsulfonyl)benzene all reacted well with difluoromethyltriphenylphosphonium iodide salt **1** and gave the desired products **4**–**10** in 50%–75% yields. The use of unactivated alkenes also allowed moderate to good yields. The reaction of (allyloxy)benzene gave the desired product **11** in 57% yield. Both electron-withdrawing (**12**–**15**) and electron-donating (**16** and **17**) groups on the phenyl ring were tolerable. Alkyl substituents (**18**–**20**) worked as well. This was also true for the 4-allyl-1,2-dimethoxybenzene (**21**). A substrate with a free hydroxyl group was also successful and provided the desired product **22** in 56% yield.

To explore the synthetic utility of this simple procedure, a convenient method for the late-stage structural modification of the natural products and drugs containing terminal double bond was developed. The alkenes derived from various scaffolds were all converted into the corresponding products **23**–**33** in moderate to good yields.

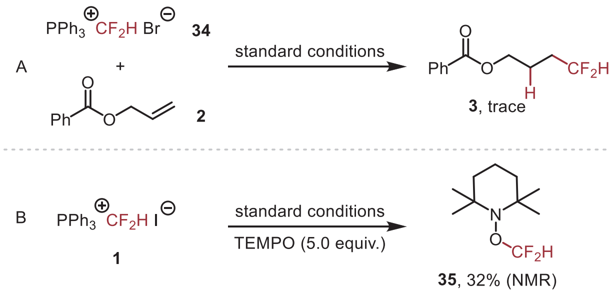
To understand the reaction mechanism, the UV-vis spectrum of difluoromethyltriphenylphosphonium iodide salt was first measured. The tail of the spectrum extends to over 400 nm and overlaps with the emission spectrum of the blue LED employed (Fig. S4 in Supporting information), indicating that the salt could be activated by blue light irradiation. Next, we performed control experiments (Scheme 3). When the difluoromethyltriphenylphosphonium bromide salt **34** was employed as the substrate instead of difluoromethyltriphenylphosphonium iodide salt **1**, only trace amounts of the desired product were observed, indicating the essential role of I^- anion for the formation of ICTC (Scheme 3A). In addition, when we subjected the 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) to difluoromethyltriphenylphosphonium iodide salt **1** and irradiated the mixture, the corresponding trapped radical species **35** was obtained in 32% NMR yield (Scheme 3B). These results suggested that the CF_2H radical was generated by just irradiation of the difluoromethyltriphenylphosphonium iodide salt.

Furthermore, we carried out density functional theory (DFT) and time-dependent DFT (TDDFT) calculations (see Supporting information for computational details) to gain deeper insight into the reaction mechanism, using the model reaction in Table 1. We optimized several structures for difluoromethyltriphenylphosphonium iodide salt **1**. As compared in Fig. 1A, the structure (**IM1**) of the salt with I^- staying at the opposite of CF_2H group is optimal in terms of both stability and absorption wavelength. The structure **IM1a** with hydrogen bonding is slightly more stable than **IM1**, but it has apparently shorter absorption wavelength. The computed UV-vis spectrum of **IM1** and **IM1a** are in reasonable agreement with experimental UV-vis spectrum of the salt (Fig. S4 in Supporting information). The structure **IM1b** featuring halogen bonding has comparable absorption wavelength close to that of **IM1**, but it is 3.0 kcal/mol less stable than **IM1**. The structure **IM1c** involving interaction with a THF molecule is inferior in terms of both stability and photoactivity. These results suggest that the σ-hole effect of phosphorus cation in **IM1** may contribute to its stability and photoactivity. In the following, we use **IM1** to compute the reaction pathway (Fig. 1B).

To start the reaction, **IM1** is vertically excited to its first excited state (^{1}**IM1***) under the blue light irradiation. Examination of the HOMO and LUMO of **IM1** indicates that the excitation results in SET from I^- to $[PPh_3CF_2H]^+$. Then ^{1}**IM1*** relaxes to an equilibrium structure ^{1}**IM1eq*** in the first excited state. Compared to the P–C bond length of 1.89 Å in **IM1**, the bond in ^{1}**IM1eq*** is elongated to 1.94 Å. Thus, the bond tends to break, delivering CF_2H radical (*i.e.*, ^{2}**IM2**). The bond cleavage may take place *via* two possible pathways. Along pathway (a), the P–C bond breaks in the first excited state *via* ^{1}**TS***. Unfortunately, attempts to locate the transition state were unsuccessful. Proceeding along pathway (b), ^{1}**IM1eq*** undergoes inter-system crossing (ISC), reaching triplet ^{3}**IM1eq**, followed by crossing ^{3}**TS1** in which the C–P bond is elongated to 2.35 Å. The resultant CF_2H radical then couples with the terminal carbon of alkene **2** *via* ^{2}**TS2a**, giving alkyl radical ^{2}**IM3**. Because a primary alkyl radical is less stable than a secondary alkyl radical, the $CF_2H^\bullet$ attacks at the internal carbon of **2** *via* ^{2}**TS2b** is less favorable, which accounts for the regioselectivity of the reaction. Finally, the alkyl radical ^{2}**IM3** extracts a hydrogen atom from THF *via* ^{2}**TS3**, affording the product **3**. The resultant THF radical can couple with I radical generated from photoexcitation, giving the by-product **36**.



Scheme 2. Reaction scope. Yields of isolated products are given.



Scheme 3. Control experiments.

Alternative to THF, some substrates featuring benzylic or/and hydroxyl hydrogen (*i.e.*, those of **19**–**21**, **22**) could also serve as hydrogen source. The DFT calculations show that such substrates have somewhat lower barriers than THF to undergo HAT with alkyl radical like ^{2}**IM3**, but deuterium labeling experiments indicate that THF solvent suppressed such substrates to undergo HAT with the alkyl radical, because THF is the solvent and has much higher concentration than the substrates (Fig. S5 in Supporting information for details). Overall, referring to ^{1}**IM1***, the reaction is energetically downhill with a rate-determining barrier of 21.6 kcal/mol for C–C coupling and hydrogen atom abstraction. The results account for the occurrence of the reaction.

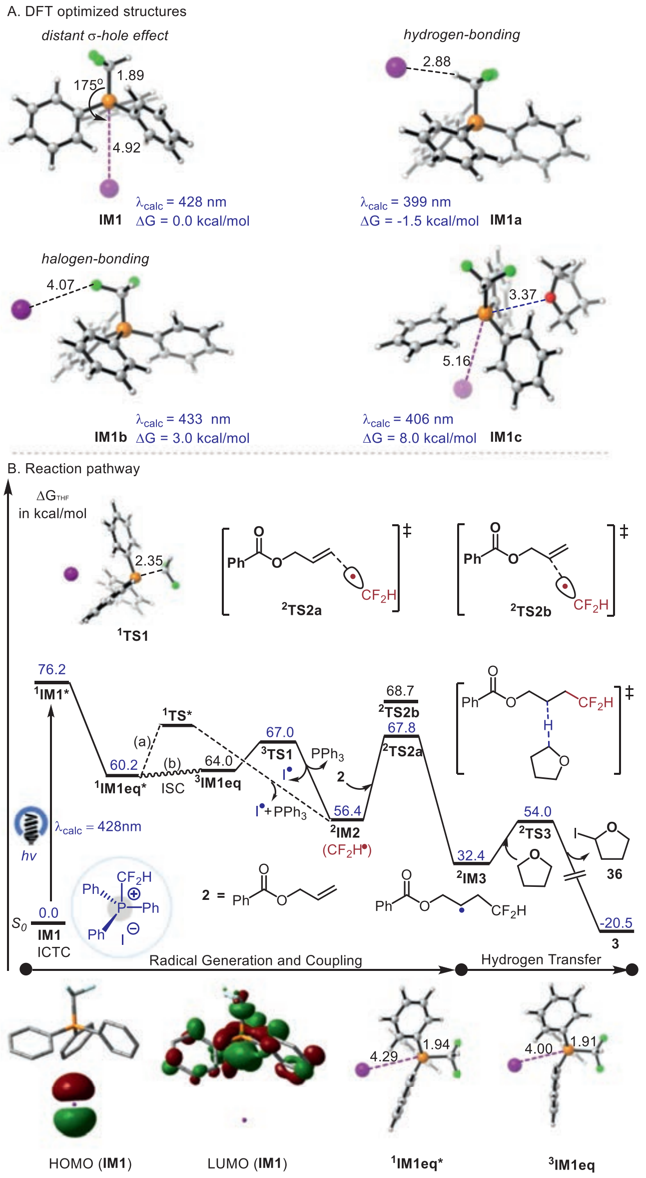


Fig. 1. Computational results. (A) DFT studies of structures of **1**. (B) Free-energy profiles (in kcal/mol) for the reaction of **1** with **2** in THF.

In summary, we have described a photocatalyst- and additive-free method for the hydrodifluoromethylation of alkenes with readily available difluoromethyltriphenylphosphonium iodide salt. Mechanistic studies show that the salt could undergo SET from I^- anion to $[PPh_3CF_2H]^+$ cation under blue light irradiation, giving CF_2H radical. The radical then adds to the alkene to fulfill the hydrodifluoromethylations. The method adds a new choice for the generation of difluoromethyl radical.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We acknowledge financial support from the National Natural Science Foundation of China (Nos. 22001248 and 22173103) and the Fundamental Research Funds for the Central Universities and the University of the Chinese Academy of Sciences.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.04.071.

References

[1] W.K. Hagmann, J. Med. Chem. 51 (2008) 4359–4369.
[2] E.P. Gillis, K.J. Eastman, M.D. Hill, D.J. Donnelly, N.A. Meanwell, J. Med. Chem. 58 (2015) 8315–8359.
[3] Y. Zafrani, D. Yeffet, G. Sod-Moriah, et al., J. Med. Chem. 60 (2017) 797–804.
[4] P. Ertl, T. Schuhmann, J. Nat. Prod. 82 (2019) 1258–1263.
[5] C. Ni, M. Hu, J. Hu, Chem. Rev. 115 (2015) 765–825.
[6] Q. Liu, C. Ni, J. Hu, Natl. Sci. Rev. 4 (2017) 303–325.
[7] J. Rong, C.F. Ni, J.B. Hu, Asian J. Org. Chem. 6 (2017) 139–152.
[8] D.E. Yerien, S.B. Vallejo, A. Postigo, Chem. Eur. J. 23 (2017) 14676–14701.
[9] T. Koike, M. Akita, Org. Biomol. Chem. 17 (2019) 5413–5419.
[10] A. Lemos, C. Lemaire, A. Luxen, Adv. Synth. Catal. 361 (2019) 1500–1537.
[11] N. Levi, D. Amir, E. Gershonov, Y. Zafrani, Synthesis 51 (2019) 4549–4567.
[12] D.Q. Dong, H. Yang, J.L. Shi, et al., Org. Chem. Front. 7 (2020) 2538–2575.
[13] L. Candish, K.D. Collins, G.C. Cook, et al., Chem. Rev. 122 (2022) 2907–2980.
[14] R. Cannalire, S. Pelliccia, L. Sancineto, et al., Chem. Soc. Rev. 50 (2021) 766–897.
[15] P. Xiao, X. Pannecoucke, J.P. Bouillon, S.C. Bonnaire, Chem. Soc. Rev. 50 (2021) 6094–6151.
[16] J.B.I. Sap, C.F. Meyer, N.J.W. Straathof, et al., Chem. Soc. Rev. 50 (2021) 8214–8247.
[17] X.J. Tang, Z.X. Zhang, W.R. Dolbier, Chem. Eur. J. 21 (2015) 18961–18965.
[18] Q.Y. Lin, X.H. Xu, F.L. Qing, Org. Biomol. Chem. 13 (2015) 8740–8749.
[19] Q.Y. Lin, X.H. Xu, K. Zhang, F.L. Qing, Angew. Chem. Int. Ed. 55 (2016) 1479–1483.
[20] W.Q. Hu, X.H. Xu, F.L. Qing, J. Fluorine Chem. 208 (2018) 73–79.
[21] J. Yu, J.H. Lin, Y.C. Cao, J.C. Xiao, Org. Chem. Front. 6 (2019) 3580–3583.
[22] C.F. Meyer, S.M. Hell, A. Misale, A.A. Trabanco, V. Gouverneur, Angew. Chem. Int. Ed. 58 (2019) 8829–8833.
[23] J.H. Lin, J.C. Xiao, Acc. Chem. Res. 53 (2020) 1498–1510.
[24] J.M. Wyatt, J.F. Hooper, Adv. Synth. Catal. 363 (2021) 924–936.
[25] Q.Y. Lin, Y. Ran, X.H. Xu, F.L. Qing, Org. Lett. 18 (2016) 2419–2422.
[26] Y. Ran, Q.Y. Lin, X.H. Xu, F.L. Qing, J. Org. Chem. 81 (2016) 7001–7007.
[27] N.B. Heine, A. Studer, Org. Lett. 19 (2017) 4150–4153.
[28] P. Tian, H. Xiao, L. Wang, Y. Yu, Y. Huang, Tetrahedron Lett. 60 (2019) 1015–1018.
[29] T.H. Zhu, Z.Y. Zhang, J.Y. Tao, K. Zhao, T.P. Loh, Org. Lett. 21 (2019) 6155–6159.
[30] X. Chen, B. Liu, C. Pei, et al., Org. Lett. 23 (2021) 7787–7791.
[31] Z. Feng, B. Zhu, B. Dong, et al., Org. Lett. 23 (2021) 508–513.
[32] Q. Liu, Y. Lu, H. Sheng, et al., Angew. Chem. Int. Ed. 60 (2021) 25477–25484.
[33] S. Scheiner, Acc. Chem. Res. 46 (2013) 280–288.
[34] M.M. Watt, M.S. Collins, D.W. Johnson, Acc. Chem. Res. 46 (2013) 955–966.
[35] J. Schmauck, M. Breugst, Org. Biomol. Chem. 15 (2017) 8037–8045.
[36] M. Breugst, J.J. Koenig, Eur. J. Org. Chem. 2020 (2020) 5473–5487.
[37] K.T. Mahmudov, A.V. Gurbanov, V.A. Aliyeva, G. Resnati, A.J. Pombeiro, Coord. Chem. Rev. 418 (2020) 213381.
[38] S. Benz, A.I. Poblador-Bahamonde, N. Low-Ders, S. Matile, Angew. Chem. Int. Ed. 130 (2018) 5506–5510.
[39] M.X. Yang, D. Tofan, C.H. Chen, K.M. Jack, F.P. Gabbaï, Angew. Chem. Int. Ed. 57 (2018) 13868–13872.
[40] M.X. Yang, M. Hirai, F.P. Gabbaï, Dalton Trans. 48 (2019) 6685–6689.
[41] A. Gini, M.I Paraja, B. Galmés, et al., Chem. Sci. 11 (2020) 7086–7091.
[42] C.G.S. Lima, T.D.M. Lima, M. Duarte, I.D. Jurberg, M.W. Paixão, ACS Catal. 6 (2016) 1389–1407.
[43] A. Postigo, Eur. J. Org. Chem. 2018 (2018) 6391–6404.
[44] Y. Wei, Q.Q. Zhou, F. Tan, L.Q. Lu, W.J. Xiao, Synthesis 51 (2019) 3021–3054.
[45] G.E.M. Crisenza, D. Mazzarella, P. Melchiorre, J. Am. Chem. Soc. 142 (2020) 5461–5476.
[46] Y. Yuan, S. Majumder, M. Yang, S. Guo, Tetrahedron Lett. 61 (2020) 151506.
[47] L.Y. Zheng, L.H. Cai, K.L. Tao, et al., Asian J. Org. Chem. 10 (2021) 711–748.
[48] Y. Lu, Q. Liu, Z.X. Wang, X.Y. Chen, Angew. Chem. Int. Ed. 61 (2022) e202116071.
[49] H. Sheng, Q. Liu, F. Chen, Z.X. Wang, X.Y. Chen, Chin. Chem. Lett. 33 (2022) 4298–4302.