ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 12389

Received 9th September 2024,
Accepted 30th September 2024

DOI: 10.1039/d4cc04650a

rsc.li/chemcomm

Photoinduced fluoroalkylation-peroxidation of alkenes enabled by ligand-to-iron charge transfer mediated decarboxylation†

Qiuwei Huang, Chenhao Lou, Leiyang Lv* and Zhiping Li*

We report here a photoinduced iron-catalyzed fluoroalkylation-peroxidation of activated and/or unactivated alkenes with fluoroalkyl carboxylic acids and hydroperoxide. The ligand-to-iron charge transfer strategy effectively overcomes the high redox potential of the fluoroalkyl carboxylic acids, facilitating the difunctionalization reaction to occur smoothly under mild reaction conditions. The late-stage functionalization of drug and natural product derivatives was also demonstrated.

The incorporation of fluoroalkyl motifs into organic frameworks has emerged as a powerful strategy in the development of pharmaceuticals and agrochemicals. This approach can substantially enhance the therapeutic profiles of the parent compounds by improving their bioavailability, lipophilicity and metabolic stability.[1] Among the various fluoroalkyl groups, the introduction of the trifluoromethyl (CF_3) group, which functions as a valuable bioisostere for the methyl group, into aliphatic chains has gained increasing interest in recent years.[2] In this regard, the radical fluoroalkylation of alkenes offers a straightforward approach to accessing a variety of trifluoromethylated products in a single step.[3] To facilitate this transformation, several reagents have been developed, including Togni's reagent, Umemoto's reagent, Langlois' reagent and Ruppert–Prakash reagent, all of which enable the efficient installation of the CF_3 group. Nevertheless, the high cost of these reagents raises concerns regarding their accessibility and application.

Decarboxylative functionalization of carboxylic acids represents research in the field of synthetic chemistry.[4] Among the various candidates, trifluoroacetic acid (TFA) is of particular interest due to its stability and low cost, which makes it an attractive option to achieve trifluoromethylation. Theoretically, TFA can undergo single-electron transfer (SET) oxidation to generate a CF_3 radical, accompanied by the release of CO_2. However, carboxylates bearing strong electron-withdrawing fluoroalkyl substituents display an exceptionally high redox potential for CF_3COO^- [$E_{p/2} > 2.28$ V *vs.* a saturated calomel electrode (SCE)].[5] This elevated redox potential makes the seemingly straightforward decarboxylative pathway quite challenging. Consequently, the direct outer-sphere electron oxidation of TFA necessitates the use of harsh reaction conditions, such as elevated temperatures (>120 °C), and the use of strong oxidants such as XeF_2.[6]

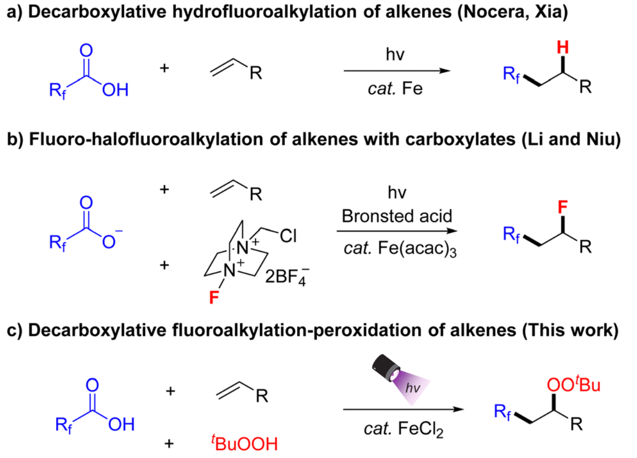
Photocatalysis has emerged as a powerful approach to facilitate challenging organic transformations under mild reaction conditions.[7] Among the various photocatalytic strategies, ligand-to-metal charge transfer (LMCT) processes have been used to generate radical species from inactive substrates. As a representative inner-sphere single electron transfer mechanism, LMCT enables electron transfer to or from a directly coordinated substrate and a metal, irrespective of the redox potentials of the substrates and the photocatalyst.[8] In 2023, West and coworkers reported a state-of-the-art iron-mediated photocatalytic hydrofluoroalkylation of alkenes with diverse fluoroalkyl carboxylic acids *via* LMCT and a thiol-mediated HAT process (Scheme 1a).[9] Based on the Fe-LMCT strategy, Xia and coworkers also achieved a similar transformation shortly thereafter, demonstrating the feasibility of performing hydrofluoroalkylation on a gram-scale in conjunction with continuous flow synthesis.[10] In 2024, Niu, Li and co-workers further developed this strategy by developing a Brønsted acid-mediated Fe-LMCT activation of inert fluoroalkylcarboxylates, which enabled the fluoro-polyfluoroalkylation of alkenes with Selectfluor as the fluorine source (Scheme 1b).[11] Despite these achievements, the incorporation of a CF_3 group and another functional group (*e.g.* difunctionalization) into alkenes using TFA is rather limited.

Organic peroxides play a vital role in a number of fields, particularly in the large-scale production of polymers and in medicinal chemistry.[12] In continuation of our research interests in iron catalysis[13] as well as the synthesis and manipulation of organic

---

Key Laboratory of Advanced Light Conversion Materials and Biophotonics, School of Chemistry and Life Resources, Renmin University of China, Beijing 100872, China. E-mail: lvleiyang2020@ruc.edu.cn, zhipingli@ruc.edu.cn

† Electronic supplementary information (ESI) available: Copies of ^1H NMR and ^{13}C NMR spectra for new compounds. See DOI: **https://doi.org/10.1039/d4cc04650a**

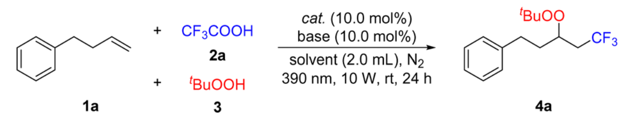

a) Decarboxylative hydrofluoroalkylation of alkenes (Nocera, Xia)

b) Fluoro-halofluoroalkylation of alkenes with carboxylates (Li and Niu)

c) Decarboxylative fluoroalkylation-peroxidation of alkenes (This work)

Scheme 1 Ligand-to-iron charge transfer enabled fluoroalkylation-functionalization of alkenes.

Table 1 Optimization of the reaction conditions[a,b]



Entry	Catalyst	Base	Solvent	Yield of **4a**
1	Fe(acac)$_3$	Na_2CO_3	MeCN	32
2	Fe(OTf)$_2$	Na_2CO_3	MeCN	31
3	$FeCl_3$	Na_2CO_3	MeCN	58
4	$Fe(NO_3)_3\cdot 9H_2O$	Na_2CO_3	MeCN	65
5	Fe(OAc)$_2$	Na_2CO_3	MeCN	71
6	**$FeCl_2$**	**Na_2CO_3**	**MeCN**	**79**
7	$FeCl_2$	Na_2CO_3	EtOAc	36
8	$FeCl_2$	Na_2CO_3	DCM	0
9	$FeCl_2$	Na_2CO_3	DCE	0
10	$FeCl_2$	Na_2CO_3	MTBE	15
11	$FeCl_2$	Na_2CO_3	Benzene	0
12	$FeCl_2$	Na_2CO_3	DMSO	0
13	$FeCl_2$	Li_2CO_3	MeCN	60
14	$FeCl_2$	K_2CO_3	MeCN	45
15	$FeCl_2$	Cs_2CO_3	MeCN	38
16	$FeCl_2$	DIPEA	MeCN	60
17	$FeCl_2$	DABCO	MeCN	58
18[d]	$FeCl_2$	Na_2CO_3	MeCN	40
19	—	Na_2CO_3	MeCN	0
20[c]	$FeCl_2$	Na_2CO_3	MeCN	0

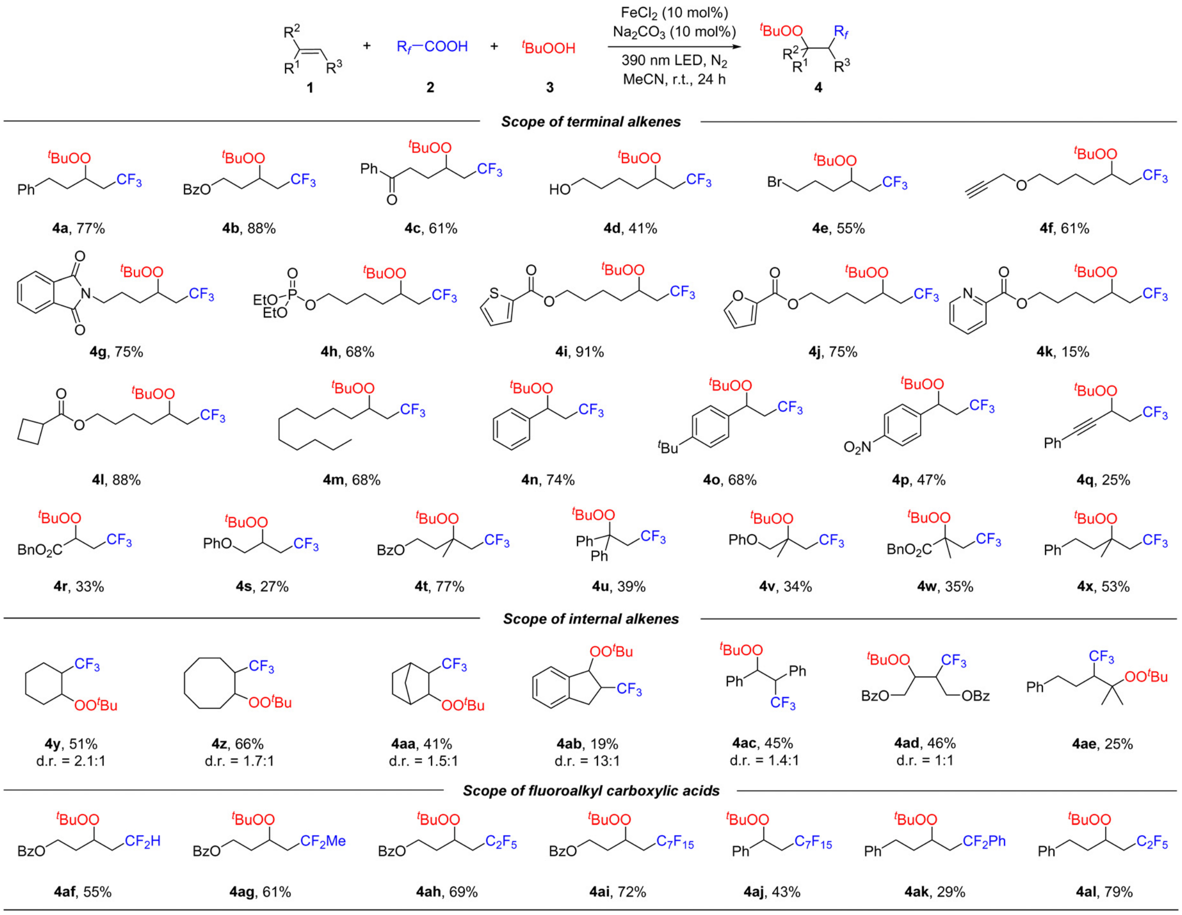
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), ^{t}BuOOH **3** (0.8 mmol, 5–6 M in decane), catalyst (10.0 mol%), base (10.0 mol%), solvent (2.0 mL), 390 nm (10 W), r.t., 24 h in a Schlenk tube under N_2. [b] NMR yields are based on **1a** and determined by ^{1}H NMR using mesitylene as an internal standard. [c] In the dark. [d] ^{t}BuOOH (70% in H_2O).

peroxides,[14] we herein report the photocatalytic fluoroalkylation-peroxidation of alkenes using an iron-LMCT strategy (Scheme 1c). This cooperative catalytic system enables the efficient implementation of the three-component reaction involving fluoroalkyl carboxylic acids, alkenes and *tert*-butyl hydroperoxide, affording a variety of fluoroalkylated organic peroxides in moderate to good yields under mild reaction conditions.

We initiated the investigation with the use of 4-phenylbutene **1a**, TFA **2a** and *tert*-butyl hydroperoxide **3** as the model substrates to test our hypothesis (Table 1). Encouragingly, the desired trifluoromethylation-peroxidation product **4a** was obtained in 32% yield with Fe(acac)$_3$ as the catalyst and a catalytic amount of Na_2CO_3 in MeCN (0.1 M) under 390 nm irradiation at room temperature for 24 h (entry 1). Various iron catalysts, including Fe(OTf)$_2$, $FeCl_3$, $Fe(NO_3)_3\cdot 9H_2O$ and Fe(OAc)$_2$, $FeCl_2$ were tested (entries 2–6). Among these, $FeCl_2$ gives the highest yield of **4a** at 79% (entry 6). Subsequently, we tested different solvents, including ethyl acetate (EtOAc), dichloromethane (DCM), 1,2-dichloroethane (DCE), methyl *tert*-butyl ether (MTBE), benzene and dimethylsulfoxide (DMSO) (entries 7–12), and found that MeCN remained the optimal solvent. The desired product **4a** could also be synthesized in the presence of alternative bases, such as Li_2CO_3, K_2CO_3, Cs_2CO_3, *N*,*N*-diisopropylethylamine (DIPEA) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (entries 13–17). However, the yields were inferior compared to those achieved with Na_2CO_3. The product **4a** was obtained in 40% yield when ^{t}BuOOH (70% in H_2O) was used instead (entry 18). Control experiments confirmed that **4a** was not detected in the absence of a metal catalyst (entry 19) or light (entry 20).

With the optimal reaction conditions established, we set out to investigate the generality of this protocol. As shown in Scheme 2, a variety of fluorinated peroxides were synthesized from unactivated alkenes in moderate to good yields. The functional groups, including ester **1b**, ketone **1c**, alcohol **1d**, bromide **1e**, terminal alkyne **1f**, *N*-phthalimide **1g** and phosphate **1h** were well tolerated, affording the corresponding products **4b–4h** in 41–88% yields. The reaction also proceeded with alkenes containing heterocycles such as thiophene **1i**, furan **1j** and pyridine **1k**, affording the desired products **4i–4k**. Additionally, cyclobutene carboxylic acid derivative **1l** and 1-dodecene **1m** proceeded smoothly, producing the desired products **4l** and **4m** in 88% and 68% yields, respectively. Styrene derivatives **1n–1p**, featuring either electron-donating or electron-withdrawing groups, were successfully converted into the corresponding fluorinated peroxides **4n–4p** in 47–74% yields. Other types of alkenes, including enyne **1r**, acrylate **1q** and allyl ether **1s**, also underwent this iron-mediated photocatalytic trifluoromethylation-peroxidation reaction, although the yields were relatively low (25–33%), probably due to polymerization or other side reactions under 390 nm irradiation. Moreover, 1,1-disubstituted alkenes were suitable substrates as well, affording the corresponding difluorinated peroxides **4t–4x** in 34–77% yields. We also tested a series of internal alkenes under the optimal conditions. Cyclic alkenes, including cyclohexene **1y**, cyclooctene **1z**, norbornene **1aa** and indene **1ab**, provided the corresponding products **4y–4ab** in 19–66% yields. Besides, the peroxides **4ac–4ae** were obtained in 25–46% yields when 1,2-disubstituted or trisubstituted acyclic alkenes were tested accordingly.

In light of our findings regarding the use of trifluoroacetic acid for the trifluoromethylation-peroxidation of alkenes, we proceeded to investigate the potential of other fluoroalkylated carboxylic acids as reaction partners. For example, difluoroacetic acid **2b**, 2,2-difluoropropanoic acid **2c**, perfluorooctanoic acid **2d**, perfluorooctanoic acid **2d** and phenyl difluoroacetic



Scheme 2 Scope of substrates. ^{a} Alkene **1** (0.2 mmol), R_fCOOH **2** (0.6 mmol), ^{t}BuOOH **3** (0.8 mmol, 5.5 M in decane), FeCl$_2$ (10% mol) and Na$_2$CO$_3$ (0.02 mmol) in MeCN (2.0 mL), 390 nm Kessil LED at r.t. for 24 h under N$_2$. d.r. = diastereoselectivity ratio.

acid **2e** were identified as suitable candidates, affording the desired products **4af–4al** in 29–79% yields.

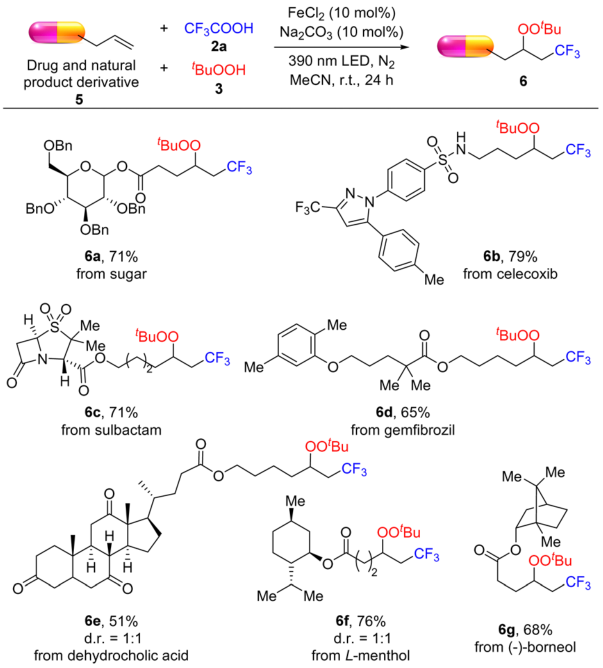
To demonstrate the practical applicability of this protocol, we investigated its potential for late-stage functionalization of drug and natural product derivatives (Scheme 3). The unactivated alkenes derived from various precursors, including sugar, non-steroidal anti-inflammatory and analgesic drugs such as celecoxib, sulbactam, gemfibrozil, as well as steroidal compounds like dehydrocholic acid, were reacted efficiently, providing the corresponding fluorinated peroxides **6a–6e** in 51–79% yields. Moreover, (L)-menthol and the sterically congested (−)-borneol derivatives could also be synthesized efficiently (**6f** and **6g**).

The photoinduced fluoroalkylation-peroxidation reaction was completely inhibited in the presence of radical scavengers, such as TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl). Moreover, the radical clock experiment gave the ring-opening fluorinated peroxide in 48% yield (see the ESI† for details). These findings suggest that a radical pathway was involved in this process.

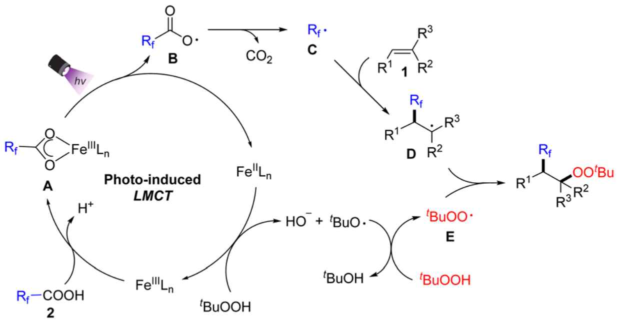
Based on the above results and literature reports,[9–11,14] a plausible reaction mechanism for the fluoroalkylation-peroxidation of alkenes is presented in Scheme 4. Initially, Fe(II) is oxidized by ^{t}BuOOH to give Fe(III) and ^{t}BuO$^\bullet$. The photoactive Fe(III)-carboxylate complex **A** is formed *in situ via* the coordination of fluoroalkyl carboxylic acid **2** with Fe(III). Upon photoexcitation, a LMCT event occurs to generate Fe(II) and an acyloxy radical **B**, which subsequently undergoes decarboxylation to release the fluoroalkyl radical **C**. The electrophilic radical **C** is then trapped by an alkene, leading to the formation of the nucleophilic radical intermediate **D**. Concurrently, ^{t}BuO$^\bullet$ abstracts a hydrogen atom from ^{t}BuOOH, producing the ^{t}BuOO$^\bullet$ **E**. Finally, a polarity-matched radical coupling between radicals **D** and **E** results in the formation of the fluorinated peroxide product **4**.

In conclusion, we have developed a photocatalytic fluoroalkylation-peroxidation of alkenes utilizing an iron-LMCT strategy. The cooperative catalytic system is effective in facilitating a three-component reaction involving fluoroalkyl carboxylic acids, alkenes and *tert*-butyl hydroperoxide. A diverse array of fluoroalkylated organic peroxides were synthesized in moderate to good yields under mild reaction conditions. Furthermore, the late-stage functionalization of drug and natural product derivatives was successfully accomplished.

We gratefully acknowledge the National Natural Science Foundation of China (22071266, 22201300), the Fundamental Research Funds for the Central Universities, and the Research Funds of Renmin University of China (24XNKJ27).



Scheme 3 Modification of drug or natural product derivatives.



Scheme 4 A plausible reaction mechanism.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selected reviews, see: (*a*) W. R. Dolbier, *Chem. Rev.*, 1996, **96**, 1557–1584; (*b*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1–PR43; (*c*) C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441–5454; (*d*) W. Wu, Y. You and Z. Weng, *Chin. Chem. Lett.*, 2022, **33**, 4517–4530.

2 For selected reviews, see: (*a*) X. Yang, T. Wu, R. J. Phipps and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826–870; (*b*) C. Alonso, E. Martinez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935; (*c*) H. Xiao, Z. Zhang, Y. Fang, L. Zhu and C. Li, *Chem. Soc. Rev.*, 2021, **50**, 6308–6319; (*d*) W. C. Fu, P. M. MacQueen and T. F. Jamison, *Chem. Soc. Rev.*, 2021, **50**, 7378–7394.

3 (*a*) H. Xiao, H. Shen, L. Zhu and C. Li, *J. Am. Chem. Soc.*, 2019, **141**, 11440–11445; (*b*) X. Dong, W. Jiang, D. Hua, X. Wang, L. Xu and X. Wu, *Chem. Sci.*, 2021, **12**, 11762–11768; (*c*) N. E. Intermaggio, A. Millet, D. L. Davis and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2022, **144**, 11961–11968; (*d*) S. Fernandez-Garcia, V. O. Chantzakou and F. Julia-Hernandez, *Angew. Chem., Int. Ed.*, 2024, **63**, e202311984; (*e*) B. Wang, Y. Xu, J. Wang, M. Yang, G.-J. Deng and W. Shao, *Chin. Chem. Lett.*, 2024, **35**, 109502; (*f*) X.-Y. Cheng, Y.-F. Zhang, J.-H. Wang, Q.-S. Gu, Z.-L. Li and X.-Y. Liu, *J. Chem. Am. Soc.*, 2022, **144**, 18081–18089; (*g*) Z. Li, L. Jiao, Y. Sun, Z. He, Z. Wei and W.-W. Liao, *Angew. Chem., Int. Ed.*, 2020, **59**, 7266–7270.

4 (*a*) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D. H. Bao, F. L. Wei, T. Zhou, M. D. Eastgate and P. S. Baran, *Nature*, 2017, **545**, 213–218; (*b*) D. M. Kitcatt, S. Nicolle and A. L. Lee, *Chem. Soc. Rev.*, 2022, **51**, 1415–1453; (*c*) P. Xiao, X. Pannecoucke, J. P. Bouillon and S. Couve-Bonnaire, *Chem. Soc. Rev.*, 2021, **50**, 6094–6151.

5 (*a*) C. Depecker, H. Marzouk, S. Trevin and J. Devynck, *New J. Chem.*, 1999, **23**, 739–742; (*b*) D. Nicewicz, H. Roth and N. Romero, *Synlett*, 2015, 714–723.

6 (*a*) M. Chen and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 11628–11631; (*b*) B. Yang, D. Yu, X.-H. Xu and F.-L. Qing, *ACS Catal.*, 2018, **8**, 2839–2843; (*c*) J. Qi, J. Xu, H. T. Ang, B. Wang, N. K. Gupta, S. R. Dubbaka, P. O'Neill, X. Mao, Y. Lum and J. Wu, *J. Am. Chem. Soc.*, 2023, **145**, 24965–24971.

7 (*a*) D. Staveness, I. Bosque and C. R. Stephenson, *Acc. Chem. Res.*, 2016, **49**, 2295–2306; (*b*) F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, *Chem. Soc. Rev.*, 2018, **47**, 7190–7202; (*c*) P. Z. Wang, W. J. Xiao and J. R. Chen, *Nat. Rev. Chem.*, 2023, **7**, 35–50.

8 (*a*) Y. Abderrazak, A. Bhattacharyya and O. Reiser, *Angew. Chem., Int. Ed.*, 2021, **60**, 21100–21115; (*b*) L. Chang, Q. An, L. Duan, K. Feng and Z. Zuo, *Chem. Rev.*, 2022, **122**, 2429–2486; (*c*) A. M. May and J. L. Dempsey, *Chem. Sci.*, 2024, **15**, 6661–6678.

9 K. J. Bian, Y. C. Lu, D. Nemoto, Jr., S. C. Kao, X. Chen and J. G. West, *Nat. Chem.*, 2023, **15**, 1683–1692.

10 (*a*) X.-K. Qi, L.-J. Yao, M.-J. Zheng, L. Zhao, C. Yang, L. Guo and W. Xia, *ACS Catal.*, 2024, **14**, 1300–1310; (*b*) Z. Song, L. Guo, C. Yang and W. Xia, *Org. Chem. Front.*, 2024, **11**, 4436–4441; (*c*) M. Luo, S. Zhu, J. Yin, C. Yang, L. Guo and W. Xia, *Org. Chem. Front.*, 2024, **11**, 4748–4756.

11 X. Jiang, Y. Lan, Y. Hao, K. Jiang, J. He, J. Zhu, S. Jia, J. Song, S. J. Li and L. Niu, *Nat. Commun.*, 2024, **15**, 6115.

12 (*a*) J. K. Cheng and T. P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 42–45; (*b*) B. Schweitzer-Chaput, J. Demaerel, H. Engler and M. Klussmann, *Angew. Chem., Int. Ed.*, 2014, **53**, 8737–8740; (*c*) I. A. Yaremenko, V. A. Vil', D. V. Demchuk and A. O. Terent'ev, *Beilstein J. Org. Chem.*, 2016, **12**, 1647–1748; (*d*) N. Zhu, H. Yao, X. Zhang and H. Bao, *Chem. Soc. Rev.*, 2024, **53**, 2326–2349.

13 (*a*) F. Jia and Z. Li, *Org. Chem. Front.*, 2014, **1**, 194–214; (*b*) L. Lv and Z. Li, *Top. Curr. Chem.*, 2016, **374**, 38.

14 (*a*) W. Liu, Y. Li, K. Liu and Z. Li, *J. Am. Chem. Soc.*, 2011, **133**, 10756–10759; (*b*) L. Lv, B. Shen and Z. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 4164–4167.