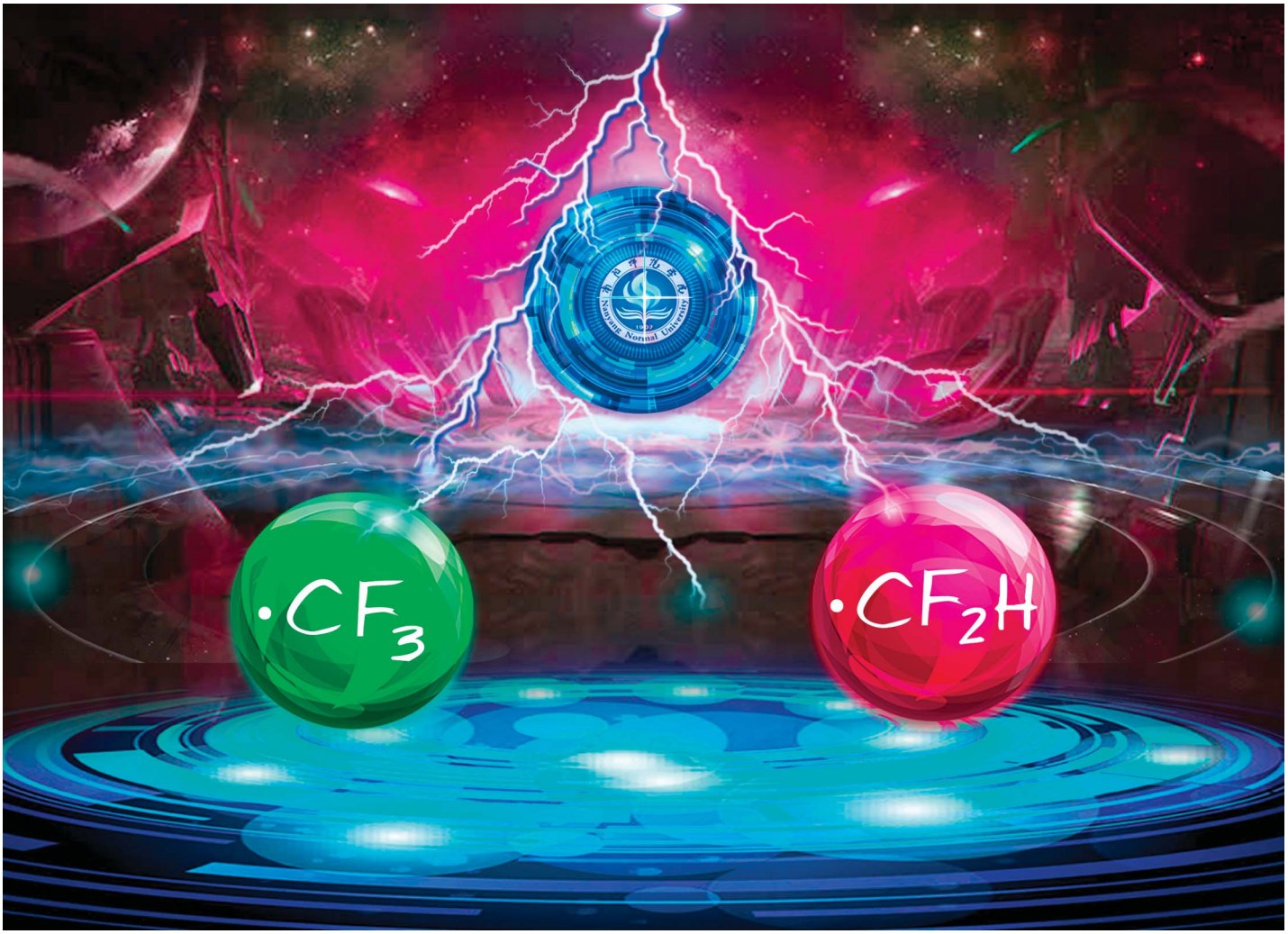

Showcasing research from Zhang and Xu's group, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Henan, China.

Electrochemical fluoromethylation triggered lactonizations of alkenes under semi-aqueous conditions

Electrochemical difluoromethylation triggered lactonization of alkenes was realized under additional supporting electrolyte- and catalyst-free conditions. This method provides a direct route for the construction of unprecedented CF_2H-substituted lactones.

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Electrochemical fluoromethylation triggered lactonizations of alkenes under semi-aqueous conditions†

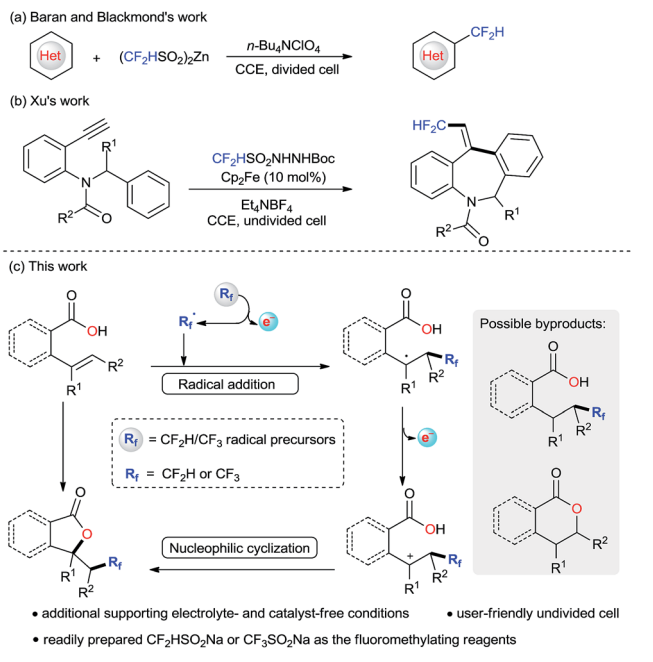
Sheng Zhang,*[a] Lijun Li,[a] Jinjin Zhang,[a] Junqi Zhang,[a] Mengyu Xue[a] and Kun Xu*[ab]

An electrochemical difluoromethylation triggered lactonization of alkenes was developed for the first time. This protocol employs readily prepared CF_2HSO_2Na as the difluoromethylating reagent, affording unprecedented CF_2H-containing lactones in moderate yields. Moreover, with CF_3SO_2Na as the trifluoromethylating reagent, a wide array of CF_3-containing lactones were obtained under additional supporting electrolyte- and catalyst-free conditions.

Introduction

The introduction of fluorine atoms into organic molecules has attracted increasing interest because the incorporation of fluorine-containing groups can significantly modify the properties of bioactive molecules.[1] In contrast to various methods for trifluoromethylation of organic substrates,[2,3] direct difluoromethylation is still underdeveloped,[4] even though the difluoromethyl group (CF_2H) is an intriguing structural motif in drug design.[5] Among the existing methods for direct difluoromethylations, radical processes have played an important role in obtaining CF_2H-containing compounds.[6] It is noteworthy that there are many recent reports of photoinduced difluoromethylations of heterocycles[7] and alkenes.[8] However, expensive Ir- or Ru-based photoredox catalysts and synthetically challenging CF_2H radical precursors are commonly required. Synthetic electrochemistry has the obvious advantage of generating radicals in a controllable way to minimize the possibilities of radical dimerizations, and can realize some transformations in ways that were previously difficult or inaccessible by traditional methods.[9,10] In this context, Baran, Blackmond and co-workers disclosed an electrochemical difluoromethylation of heterocycles in a divided cell with zinc sulfinates as the difluoromethylating reagent and *n*-Bu_4NClO_4 as the supporting electrolyte (Scheme 1a).[11] Recently, a breakthrough in electrochemical difluoromethylation of alkynes with $CF_2HSO_2NHNHBoc$ was reported by Xu and co-workers with Et_4NBF_4 as the supporting electrolyte (Scheme 1b).[12] Given the importance of the CF_2H group in medicinal chemistry and the advantages of synthetic electrochemistry, the development of new electrochemical difluoromethylation reactions in a user-friendly single cell setup in the absence of an additional supporting electrolyte is attractive.

Lactones constitute useful building blocks in many pharmaceutically relevant molecules.[13] In this regard, the construction of unprecedented CF_2H-containing lactones may be



Scheme 1 Electrochemical difluoromethylations.

[a]*Engineering Technology Research Center of Henan Province for Photo- and Electrochemical Catalysis, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, 473061, China. E-mail: shengzhang@nynu.edu.cn; xukun@nynu.edu.cn*

[b]*College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China*

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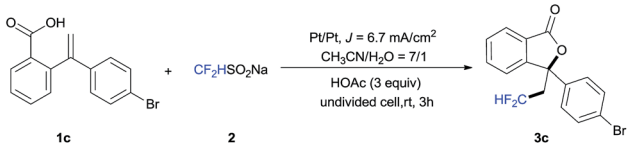
beneficial for medicinal chemistry.[14] We have been interested in electrochemical lactonizations; however, only C–O bonds were constructed for these transformations.[15,16] Considering the powerfulness of radical alkene difunctionalizations for the enhancement of molecular complexity in a single preparative operation,[17] we speculated that it might be possible to construct CF_2H-containing lactones *via* an electrochemical difluoromethylation triggered lactonization of alkenes. The proposed synthetic pathway is shown in Scheme 1c. First, electrochemically generated fluoromethyl radical undergoes alkene addition to give a carbon radical intermediate. Further electrochemical oxidation gives a carbocationic intermediate, which undergoes subsequent nucleophilic cyclization to afford desired fluoromethylated lactones. While the proposed reaction pathway appears quite reasonable, its implementation proved to be challenging. First, the electrochemical oxidation of the carbon radical intermediate should occur quickly before H· abstraction. Second, the oxidation potentials of R_f radical precursors should be much lower than that of alkenes. Otherwise, the undesired single C–O bond formation would be the predominant process instead of desired alkene difunctionalization. In this report, we establish that electrochemical difunctionalization of alkenes can be achieved using semi-aqueous conditions to afford unprecedented CF_2H-containing lactones with CF_2HSO_2Na[18] as the CF_2H radical precursor under catalyst-free conditions. Moreover, this environmentally benign protocol could also be applicable for the access to CF_3-containing lactones in the absence of a metal catalyst, chemical oxidant, and additional supporting electrolyte.

Results and discussion

Initially, we commenced the electrochemical carboxydifluoromethylation reaction by using **1c** and CF_2HSO_2Na (**2**) as the model substrates in an undivided cell equipped with platinum electrodes (Table 1). When HOAc was employed as the additive with a mixture of CH_3CN and H_2O as the solvent, the isolated yield of the corresponding CF_2H-containing lactone **3c** was obtained to be 67% (entry 1). Interestingly, adding supporting electrolytes into this reaction mixture led to a decrease in the yields (entries 2 and 3).[19] Changing the Pt electrodes to graphite failed to maintain the reaction yield (entries 4 and 5). When the reaction was carried out in the absence of HOAc, only a trace amount of the desired product **3c** was detected (entry 6). This result suggested that the cathodic proton reduction may limit the overall reaction rate.[20] Replacing HOAc with HCl only led to a trace amount of the product **3c** (entry 7). Increasing or decreasing the current density failed to improve the yield (entries 8 and 9).

Having established the optimized reaction conditions, we then examined the substrate scope of electrochemical difluoromethylation triggered lactonization of alkenes. As shown in Table 2, the aromatic carboxylic acids were tolerated

Table 1 Optimization of carboxydifluoromethylation of alkenes[a]

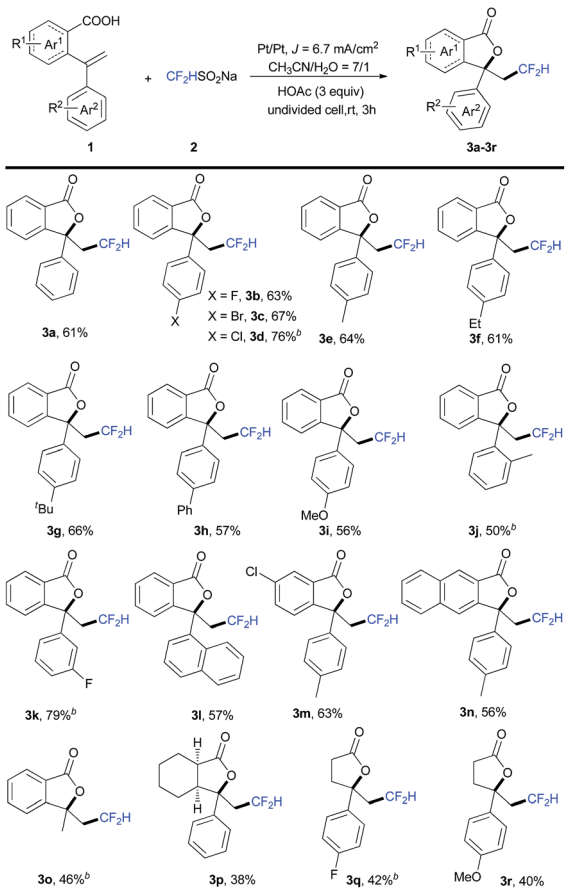


1c 2 3c

Entry	Changes from standard conditions	Yield[b] (%)
1	None	67
2	0.1 M $^nBu_4NPF_6$ was used as the electrolyte	59
3	0.1 M $LiClO_4$ was used as the electrolyte	52
4	Graphite(+) and Pt(−) were used as the electrodes	47
5	Pt(+) and graphite(−) were used as the electrodes	39
6	No HOAc	Trace
7	HCl was used instead of HOAc	Trace
8	$J = 10$ mA cm^{-2}	61
9	$J = 5$ mA cm^{-2}	43

[a] Reaction conditions: undivided cell, Pt plate (1.5 × 1.5 cm^2, $J = 6.7$ mA cm^{-2}), **1c** (0.5 mmol), **2** (1.25 mmol), CH_3CN/H_2O (7/1 mL, v/v), rt, 3 h, and 3.4 F. [b] Isolated yield.

Table 2 The substrate scope of electrochemical carboxydifluoromethylation[a]



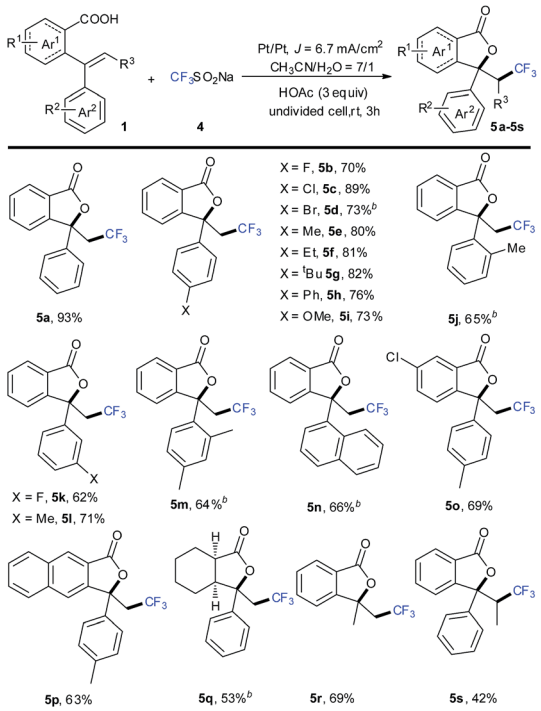
[a] Reaction conditions: undivided cell, Pt plate (1.5 × 1.5 cm^2, $J = 6.7$ mA cm^{-2}), **1** (0.5 mmol), **2** (1.25 mmol), additive HOAc (1.5 mmol), CH_3CN/H_2O (7/1 mL, v/v), 3 h, and 3.4 F. [b] Additive HOAc was replaced with TFA (1.5 mmol).

well to give the corresponding CF_2H-containing lactones in moderate yields (**3a–3o**). For the substituents on the Ar^2 ring, the *para*-substituents had little effect on the chemical yields (**3b–3i**). The *ortho*-substituted substrate **1j** showed decreased reactivity to give the corresponding product **3j** in 50% yield with TFA as the acidic additive instead of HOAc. When the fluoro group was placed at the *meta* position of the Ar^2 ring, the corresponding lactone **3k** was obtained in 79% yield. Replacing the phenyl group with the 1-naphthyl group decreased the yield of **3l** to 57%.

When Ar^2 was replaced with the methyl group, the corresponding lactone **3o** was afforded in 46% yield. It is noteworthy that the challenging substrates of aliphatic carboxylic acids could also be tolerated to give the corresponding lactones **3p–3r** in 38–42% yields.

To make this synthetic methodology more appealing, the electrochemical trifluoromethylation triggered lactonization of alkenes was then examined. As shown in Table 3, moderate to excellent yields of CF_3-containing lactones were obtained regardless of the electronic nature of *para*-substitutions on the Ar^2 ring (**5a–5i**). Changing the substitution on the Ar^2 ring from the *para*-position to the *ortho*- or *meta*-position caused lower yields (**5j–5l**). The substrate containing a disubstituted Ar^2 group was also tolerated well affording the product **5m** in 64% yield. The fused ring substituted substrates also underwent the cyclizations smoothly to give the corresponding lactones **5n** and **5p** in 66% and 63% yields, respectively. Replacing the aromatic Ar^1 or Ar^2 group with aliphatic ones decreased the reaction efficiency, giving the corresponding lactones **5q** and **5r** in 53% and 69% yields, respectively. More importantly, the trisubstituted olefin was demonstrated to be a suitable substrate to give the lactone **5s** in 42% yield.

Table 3 The substrate scope of electrochemical carboxytrifluoromethylation[a]



[a] Reaction conditions: undivided cell, Pt plate (1.5 × 1.5 cm^2, J = 6.7 mA cm^{-2}), **1** (0.5 mmol), **4** (1.25 mmol, purity > 98%), additive HOAc (1.5 mmol), CH_3CN/H_2O (7/1 mL, v/v), 3 h, and 3.4 F. [b] Additive HOAc (1.5 mmol) was replaced with TFA (1.5 mmol).

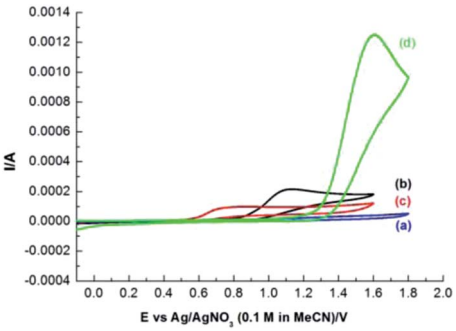


Fig. 1 Cyclic voltammograms of substrates in 0.1 M $LiClO_4/CH_3CN$, using a Pt wire working electrode and glassy carbon and $Ag/AgNO_3$ (0.1 M in CH_3CN) as counter and reference electrodes at a 100 mV s^{-1} scan rate: (a) background (0.1 M $LiClO_4$ in CH_3CN), (b) CF_3SO_2Na (5 mmol L^{-1}), (c) CF_2HSO_2Na (5 mmol L^{-1}), and (d) **1a** (5 mmol L^{-1}).

In order to provide a rationale for the reaction pathway proposed in Scheme 1c, cyclic voltammetric (CV) experiments were carried out. As shown in Fig. 1, CF_2HSO_2Na and CF_3SO_2Na have the oxidation potentials of 0.72 V and 1.06 V, respectively. However, the oxidation potential of alkenes is 1.58 V. These results indicated that CF_2HSO_2Na and CF_3SO_2Na are much easier to be electrochemically oxidized to generate fluoromethyl radicals than the alkene moiety. The CV experiments which were carried out in CH_3CN/HOAc or CH_3CN/H_2O also indicated that CF_2HSO_2Na and CF_3SO_2Na are much easier to be electrochemically oxidized than the alkene moiety (see the ESI† for details). The much lower oxidation potentials of CF_2H and CF_3 radical precursors than that of alkenes are the key to electrochemical carboxyfluoromethylation reactions.

Experimental

An undivided cell was equipped with a magnet stirrer and platinum plate (1.5 × 1.5 cm^2) electrodes. The substrate 2-(1-phenylvinyl)benzoic acid **1a** (112 mg, 0.5 mmol), CF_3SO_2Na **4** (195 mg, 1.25 mmol) and additive HOAc (86 μL, 1.5 mmol) were added to a mixed solvent of CH_3CN/H_2O (7/1 v/v). The resulting mixture was allowed to stir and electrolyze under constant current conditions (J = 6.7 mA cm^{-2}) at room temperature for 3 hours. Then the volatile solvent was removed with a rotary evaporator and then water (10 mL) was added. The resulting mixture was extracted with ethyl acetate (10 × 3 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (ethyl acetate/petroleum ether = 1/15–1/10) on silica gel to afford the desired product **5a** in 93% yield.

Conclusions

We have developed the first example of electrochemical difluoromethylation triggered lactonization of alkenes. Under additional supporting electrolyte- and catalyst-free conditions, a wide array of CF_2H-containing lactones were obtained in moderate yields. Moreover, this environmentally benign method is also applicable to access pharmaceutically important CF_3-containing lactones in the absence of a metal catalyst, chemical oxidant, and additional supporting electrolyte.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity Applications*, Wiley-VCH, Weinheim, 2004; (*b*) T. Yamazaki, T. Taguchi and I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, Great Britain, 2009.

2 For recent reviews on trifluoromethylations, see: (*a*) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (*b*) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (*c*) X. Pan, H. Xia and J. Wu, *Org. Chem. Front.*, 2016, **3**, 1163; (*d*) H.-X. Song, Q.-Y. Han, C.-L. Zhao and C.-P. Zhang, *Green Chem.*, 2018, **20**, 1662; (*e*) S. Barata-Vallejo, M.-V. Cooke and A. Postigo, *ACS Catal.*, 2018, **8**, 7287.

3 For recent examples on trifluoromethylations, see: (*a*) W. Yang, D. Ma, Y. Zhou, X. Dong, Z. Lin and J.-W. Sun, *Angew. Chem., Int. Ed.*, 2018, **57**, 12097; (*b*) E. Valverde, S. Kawamura, D. Sekine and M. Sodeoka, *Chem. Sci.*, 2018, **9**, 7115; (*c*) H. Wang, Q. Xu and S.-Y. Yu, *Org. Chem. Front.*, 2018, **5**, 2224; (*d*) B.-K. Mai, K.-J. Szabó and F. Himo, *ACS Catal.*, 2018, **8**, 4483; (*e*) A.-J. Borah and Z.-Z. Shi, *Chem. Commun.*, 2017, **53**, 3945; (*f*) H.-S. Han, E.-Y. Oh, Y.-S. Jung and S.-B. Han, *Org. Lett.*, 2018, **20**, 1698; (*g*) B. Yang, D. Yu, X.-H. Xu and F.-L. Qing, *ACS Catal.*, 2018, **8**, 2839; (*h*) M. Imiołek, G. Karunanithy, W.-L. Ng, A.-J. Baldwin, V. Gouverneur and B.-G. Davis, *J. Am. Chem. Soc.*, 2018, **140**, 1568.

4 For recent reviews, see: (*a*) J.-B. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465; (*b*) M.-C. Belhomme, T. Besset, T. Poisson and X. Pannecoucke, *Chem.–Eur. J.*, 2015, **21**, 12836; (*c*) D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem.–Eur. J.*, 2017, **23**, 14676; (*d*) A. D. Dilman and V. V. Levin, *Acc. Chem. Res.*, 2018, **51**, 1272. For selected recent works, see: (*e*) P. S. Fier and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 5524; (*f*) 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; (*g*) G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck and G. A. Olah, *Angew. Chem., Int. Ed.*, 2012, **51**, 12090; (*h*) T. Iida, R. Hashimoto, K. Aikawa, S. Ito and K. Mikami, *Angew. Chem., Int. Ed.*, 2012, **51**, 9535; (*i*) P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2015, **54**, 6558; (*j*) N.-B. Heine and A. Studer, *Org. Lett.*, 2017, **19**, 4150; (*k*) T. T. Tung, S. B. Christensen and J. Nielsen, *Chem.–Eur. J.*, 2017, **23**, 18125.

5 (*a*) M. A. Chowdhury, K. R. A. Abdellatif, Y. Dong, D. Das, M. R. Suresh and E. E. Knaus, *J. Med. Chem.*, 2009, **52**, 1525; (*b*) N.-A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529.

6 T. Koike and M. Akita, *Chem*, 2018, **4**, 409 and references cited therein.

7 (*a*) P. Xu, S. Guo, L. Wang and P. Tang, *Synlett*, 2014, **26**, 36; (*b*) R. Sakamoto, H. Kashiwagi and K. Maruoka, *Org. Lett.*, 2017, **19**, 5126; (*c*) S.-Q. Zhu, Y.-L. Liu, H. Li, X.-H. Xu and F.-L. Qing, *J. Am. Chem. Soc.*, 2018, **140**, 11613.

8 (*a*) X.-J. Tang and W. R. Dolbier Jr, *Angew. Chem., Int. Ed.*, 2015, **54**, 4246; (*b*) Y. Xiang, Y. Li, Y. Kuang and J. Wu, *Chem.–Eur. J.*, 2016, **23**, 1032; (*c*) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J.-B. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743; (*d*) Q.-Y. Lin, X.-H. Xu, K. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2016, **55**, 1479; (*e*) J.-S. Lin, F.-L. Wang, X.-Y. Dong, W.-W. He, Y. Yuan, S. Chen and X.-Y. Liu, *Nat. Commun.*, 2017, **8**, 14841; (*f*) N. Noto, T. Koike and M. Akita, *Chem. Sci.*, 2017, **8**, 6375.

9 For recent reviews, see: (*a*) R. Feng, J. A. Smith and K. D. Moeller, *Acc. Chem. Res.*, 2017, **50**, 2346; (*b*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (*c*) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and C. J. Kampf, *Chem. Rev.*, 2018, **118**, 6706; (*d*) C. Ma, P. Fang and T.-S. Mei, *ACS Catal.*, 2018, **8**, 7179; (*e*) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086; (*f*) J.-i. Yoshida, A. Shimizu and R. Hayashi, *Chem. Rev.*, 2018, **118**, 4702; (*g*) Y. Okada and K. Chiba, *Chem. Rev.*, 2018, **118**, 4592; (*h*) Y. Jiang, K. Xu and C.-C. Zeng, *Chem. Rev.*, 2018, **118**, 4485; (*i*) M. D. Kärkäs, *Chem. Soc. Rev.*, 2018, **47**, 5786.

10 For selected recent examples, see: (*a*) Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 7448; (*b*) T. Gieshoff, A. Kehl, D. Schollmeyer, K. D. Moeller and S. R. Waldvogel, *J. Am. Chem. Soc.*, 2017, **139**, 12317; (*c*) N. Fu, G. S. Sauer, A. Saha, A. Loo and S. Lin, *Science*, 2017, **357**, 575; (*d*) Q.-L. Yang, X.-Y. Wang, J.-Y. Lu, L.-P. Zhang, P. Fang and T.-S. Mei, *J. Am. Chem. Soc.*, 2018, **140**, 11487; (*e*) S. Tang, L. Zeng and A. Lei, *J. Am. Chem. Soc.*, 2018, **140**, 13128; (*f*) R. Mei, N. Sauermann, J. C. A. Oliveira and L. Ackermann, *J. Am. Chem. Soc.*, 2018, **140**, 7913; (*g*) S. Zhang, L. Li, M. Xue, R. Zhang, K. Xu and C. Zeng, *Org. Lett.*, 2018, **20**, 3443; (*h*) K.-S. Du and J.-M. Huang, *Org. Lett.*, 2018, **20**, 2911; (*i*) H. Wang, J. Zhang, J. Tan, L. Xin, Y. Li, S. Zhang and K. Xu, *Org. Lett.*, 2018, **20**, 2505; (*j*) Q. Liu, B. Sun,

Z. Liu, Y. Kao, B.-W. Dong, S.-D. Jiang, F. Li, G. Liu, Y. Yang and F.-Y. Mo, *Chem. Sci.*, 2018, **9**, 8731; (*k*) J. Li, W. Huang, J. Chen, L. He, X. Cheng and G. Li, *Angew. Chem., Int. Ed.*, 2018, **57**, 5695; (*l*) M. Rafiee, F. Wang, D. P. Hruszkewycz and S. S. Stahl, *J. Am. Chem. Soc.*, 2018, **140**, 22; (*m*) B. Schille, N. O. Giltzau and R. Francke, *Angew. Chem., Int. Ed.*, 2018, **57**, 422. For some pioneering electrochemical fluorination studies, see: (*n*) A. Konno, K. Nakagawa and T. Fuchigami, *J. Chem. Soc., Chem. Commun.*, 1991, 1027; (*o*) K. Uneyama, *Tetrahedron*, 1991, **47**, 555.

11 A. G. O'Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran and D. G. Blackmond, *Angew. Chem., Int. Ed.*, 2014, **53**, 11868.

12 P. Xiong, H.-H. Xu, J. Song and H.-C. Xu, *J. Am. Chem. Soc.*, 2018, **140**, 2460.

13 (*a*) Y.-J. Zhang, T. Abe, T. Tanaka, C.-R. Yang and I. Kouno, *J. Nat. Prod.*, 2001, **64**, 1527; (*b*) J. J. Beck and S.-C. Chou, *J. Nat. Prod.*, 2007, **70**, 891.

14 The use of α-bromodifluoromethyl substituted esters and amides to stabilize the *in situ* generated $CF_2H\cdot$ to access to CF_2H-containing lactones has been described, see: Y. Da, S. Han, X. Du, S. Liu, L. Liu and J. Li, *Org. Lett.*, 2018, **20**, 5149.

15 (*a*) S. Zhang, F. Lian, M. Xue, T. Qin, L. Li, X. Zhang and K. Xu, *Org. Lett.*, 2017, **19**, 6622; (*b*) S. Zhang, L. Li, H. Wang, Q. Li, W. Liu, K. Xu and C.-C. Zeng, *Org. Lett.*, 2018, **20**, 252.

16 A previous work on the construction of two C–O bonds during lactonization of alkenes was reported by Moeller and co-workers, see: R. J. Perkins, H.-C. Xu, J. M. Campbell and K. D. Moeller, *Beilstein J. Org. Chem.*, 2013, **9**, 1630.

17 For selected recent reviews, see: (*a*) G. Yin, X. Mu and G. Liu, *Acc. Chem. Res.*, 2016, **49**, 2413; (*b*) J. R. Coombs and J. P. Morken, *Angew. Chem., Int. Ed.*, 2016, **55**, 2636. For recent examples of electrochemical alkene difunctionalizations, see: (*c*) Y. Yuan, Y. Gao, Y. Lin, Y. Li, Z. Huang and A. Lei, *ACS Catal.*, 2018, **8**, 10871; (*d*) K.-Y. Ye, G. Pombar, N. Fu, G. S. Sauer, I. Keresztes and S. Lin, *J. Am. Chem. Soc.*, 2018, **140**, 2438; (*e*) Y. Wang, L. Deng, H. Mei, B. Du, J. Han and Y. Pan, *Green Chem.*, 2018, **20**, 3444; (*f*) C.-Y. Cai and H.-C. Xu, *Nat. Commun.*, 2018, **9**, 3551; (*g*) S. Zhang, L. Li, P. Wu, P. Gong, R. Liu and K. Xu, *Adv. Synth. Catal.*, 2019, **361**, 485. For recent example of electrochemical alkyne difunctionalizations, see: (*h*) C. Tian, L. Massignan, T. H. Meyer and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 2383.

18 Z. He, P. Tan, C. Ni and J.-B. Hu, *Org. Lett.*, 2015, **17**, 1838.

19 The addition of additional electrolyte may be favourable for the formation of a more defined double layer, which could slow the bimolecular reactions.

20 The adding of acidic additives also lower the pH of the solvent. The low pH of the solvent is unfavourable for the unexpected Kolbe reactions.