communications chemistry

ARTICLE

https://doi.org/10.1038/s42004-022-00697-1 OPEN

Radical hydrodifluoromethylation of unsaturated C—C bonds via an electroreductively triggered two-pronged approach

Seonyoung Kim[1,5], Keon Ha Hwang[2,3,5], Hyeong Gyu Park[2,3], Jaesung Kwak[2✉], Hyuk Lee[2✉] & Hyunwoo Kim[4✉]

Due to its superior ability in controlling pharmaceutical activity, the installation of difluoromethyl (CF_2H) functionality into organic molecules has been an area of intensive research. In this context, difluoromethylation of C—C π bonds mediated by a CF_2H radical have been pursued as a central strategy to grant access to difluoromethylated hydrocarbons. However, early precedents necessitate the generation of oxidative chemical species that can limit the generality and utility of the reaction. We report here the successful implementation of radical hydrodifluoromethylation of unsaturated C—C bonds via an electroreductively triggered two-pronged approach. Preliminary mechanistic investigations suggest that the key distinction of the present strategy originates from the reconciliation of multiple redox processes under highly reducing electrochemical conditions. The reaction conditions can be chosen based on the electronic properties of the alkenes of interest, highlighting the hydrodifluoromethylation of both unactivated and activated alkenes. Notably, the reaction delivers geminal (bis) difluoromethylated products from alkynes in a single step by consecutive hydrodifluoromethylation, granting access to an underutilized 1,1,3,3-tetrafluoropropan-2-yl functional group. The late-stage hydrodifluoromethylation of densely functionalized pharmaceutical agents is also presented.

[1] Department of Chemistry and Nanoscience, Ewha Womans University, Seoul 03760, Republic of Korea. [2] Infectious Diseases Therapeutic Research Center, Korea Research Institute of Chemical Technology (KRICT), Daejeon 34114, Republic of Korea. [3] Graduate School of New Drug Discovery and Development, Chungnam University, Daejeon 34134, Republic of Korea. [4] Department of Chemistry, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea. [5] These authors contributed equally: Seonyoung Kim, Keon Ha Hwang. ✉email: jkwak@krict.re.kr; leeh@krict.re.kr; khw7373@postech.ac.kr

The replacement of hydrogen atoms with fluorine has become a quintessential approach for new chemical entities to regulate physicochemical and biological properties such as metabolic stability, lipophilicity, hydrogen bonding ability and bioavailability[1–8]. Particularly, the installation of difluoromethyl (CF_2H) functionality instead of CH_3 or CF_3 groups in bio-relevant chemical structures has been an area of intensive research in drug development due to the highly polarized C−H bond of CF_2H that serves as a bioisostere of hydrogen bonding donors such as hydroxyl, thiol, and amine groups[9–14]. Furthermore, the installation of difluoromethylene group to liquid crystals has also been considered to be important in controlling their physical properties[15,16].

In this context, difluoromethylative functionalization, where a difluoromethyl anion[17–26], carbene[27–32] or radical precursor[33–50] is engaged in the direct transfer of the CF_2H unit, has been vigorously pursued as a strategy with great promise in organic synthesis. Particularly, radical hydrodifluoromethylation in which $CF_2H^{\bullet}$ and $H^{\bullet}$ equivalents add across to unsaturated C−C π bonds has become a central strategy to access a relatively limited class of aliphatic hydrocarbons that contain difluoromethyl group[51–57]. This includes the use of redox-active CF_2H radical precursors with the alkene of interest (Fig. 1A, left). For example, CF_2H radicals generated under oxidative conditions have frequently been utilized in hydrodifluoromethylation as well as difluoromethylative Heck-type coupling[43,51]. Additionally, several groups independently demonstrated oxidative difluoromethylative radical annulation of alkynes in the presence of aryl groups as the radical trap (Fig. 1A, right)[44,45].

On the other hand, CF_2H radicals generated by reductive photocatalysis[52,53] or photosensitization[55] have also enabled hydrodifluoromethylation of aliphatic or electron-deficient alkenes (Fig. 1B). While highly enabling, existing methods often require or involve oxidative chemical species that can presumably hamper the desired reactivity, thus limiting generality of the reaction. For example, a carbon-centered radical intermediate I, which is formed upon addition of CF_2H radical into C=C bond can readily be sacrificially oxidized by the quenching cycle of photocatalysis to afford corresponding

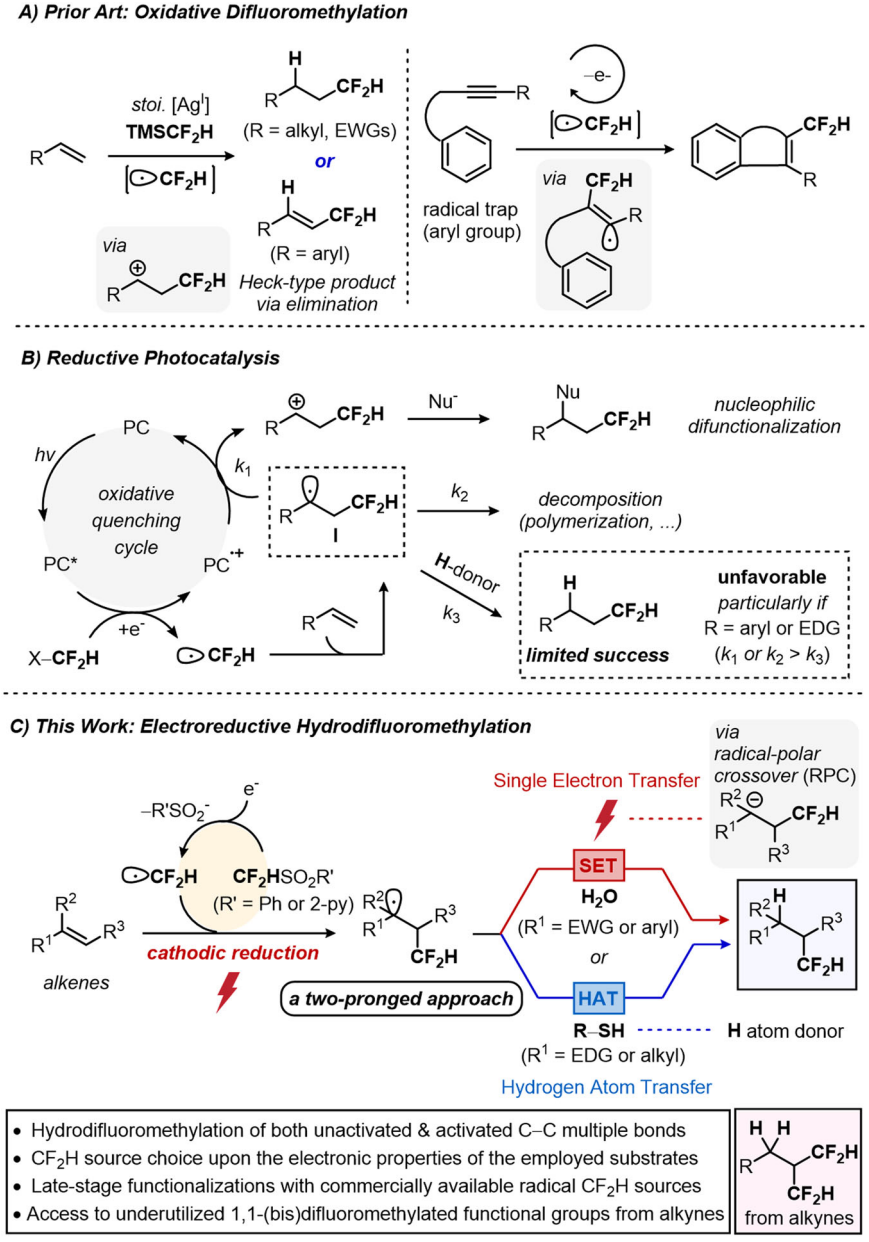


Fig. 1 Radical hydrodifluoromethylation of unsaturated C–C bonds. A Precedent examples of difluoromethylation under oxidizing conditions. **B** Reductive photocatalysis for radical difluoromethylation. **C** A two-pronged electroreductive hydrodifluoromethylation.

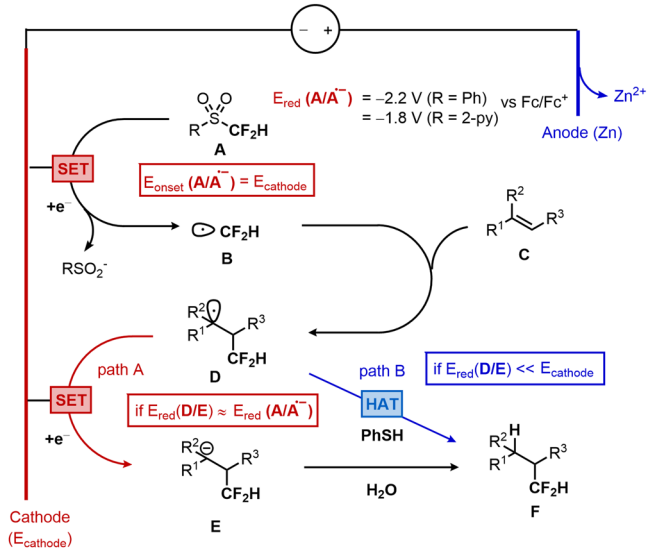


Fig. 2 Proposed mechanism. A cathodic reduction of (**A**) would furnish a CF_2H radical (**B**), which would afford carbon-centered radical (**D**) upon addition into alkene substrate (**C**). The radical (**D**) would be reduced into corresponding carbanion (**E**) when the reduction potential of (**D**) is on par with (**A**) (path A). A subsequent protonation with water would furnish hydrodifluoromethylation product (**F**). Alternatively, a carbon-centered radical (**D**) would directly perform hydrogen-atom transfer (HAT) to form (**F**) in the presence of a hydrogen atom donor, when E_{red}(**D**/**E**) is too negative to be reduced on the cathode (path B).

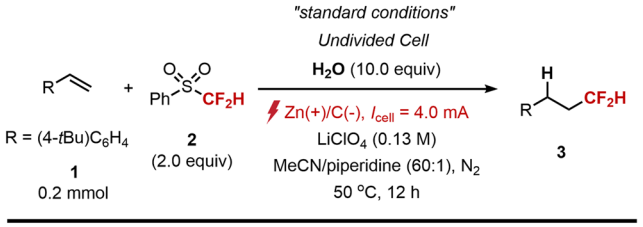
carbocation (k_1), eventually leading to the formation of less-desirable difunctionalization products upon nucleophilic trapping[11]. Indeed, in early examples, tethered nucleophiles were requisite for the intramolecular trapping of resultant carbocation intermediate[58,59].

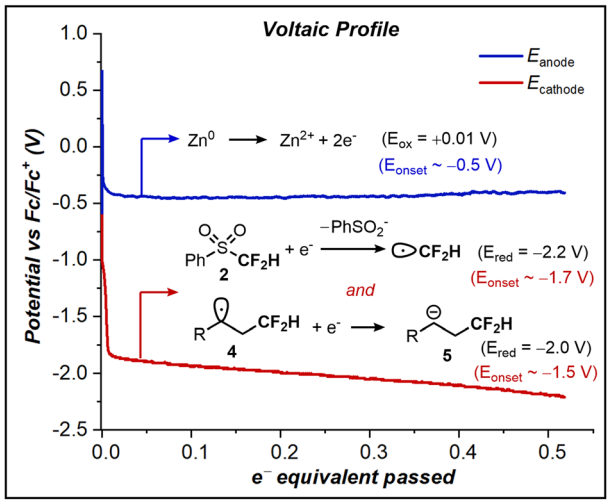
In addition, inherent transiency of these radicals often led to the decomposition of the reaction intermediates particularly if R groups are aromatic or electron-donating substituents (k_2)[55]. Furthermore, super-stoichiometric amounts of CF_2H radical sources with high molecular weight has been often employed that can significantly limit potential utility of these early precedents. To address these intrinsic limitations in terms of modularity and structural diversity, the development of a mechanistically distinct and more generally valid hydrodifluoromethylation approach remains a key challenge.

Herein, we describe the successful implementation of radical hydrodifluoromethylation with a wide range of unsaturated C−C bonds via an electroreductively triggered two-pronged approach (Fig. 1C). The reaction conditions can be chosen based on electronic properties of the alkenes of interest, highlighting a hydrodifluoromethylation of both unactivated and activated alkenes. Notably, the developed protocol herein showcases unique reactivity towards alkynes, granting access to underutilized 1,1,3,3-tetrafluoropropan-2-yl functional group by a regioselective double hydrodifluoromethylation. To the best of our knowledge, this reactivity represents unique example of multiple difluoromethylation of alkynes. Furthermore, this electrochemical approach is applicable to late-stage functionalization and drug modification with use of commercially available CF_2H sources and inexpensive H_2O or thiophenol (PhSH) as the hydrogen sources.

Results and discussion

Inspired by previous reports on the electrochemical or photoelectrochemical activations of strong bonds[60–73], we anticipated electroreductive reaction conditions using a sacrificial anode[74,75] would allow access to deeply reductive potentials and cleavage of strong bonds (Fig. 2). Thereby, a cathodic reduction of A would furnish a





Entry	Variation from "standard conditions"	Yield of **3** (%)
1	none	87 (80)
2	w/o applied voltage	n.r.
3	w/o H_2O	2
4	w/o piperidine	6
5	Et_3N instead of piperidine	36
6	2-pySO_2CF_2H (**2-py**) instead of **2**	<5%
7	under constant voltage ($E_{cathode}$ = −2.2 V)	<5%
8	at room temperature (22 °C)	77
9	Mg as a sacrificial anode	7
10	Al as a sacrificial anode	9

Fig. 3 Reaction parameter optimization. Yields determined by ^{1}H NMR using CH_2Br_2 as an internal standard (isolated yields in parenthesis). The voltaic profile of each electrode during electrolysis of entry 1 is shown (inset box). The sacrificial Zn anode operates at the anticipated onset potential for Zn oxidation (blue line, E_{onset} = ca. −0.5 V vs Fc/Fc^+). The initial cathodic potential ($E_{cathode}$ = −1.8 V) is in accordance with the onset potential for reduction of 2 (red line). Under the given cathodic potential, a simultaneous reduction of benzylic radical intermediate 4 into corresponding carbanion 5 is also conceivable.

CF_2H radical (B), which would afford carbon-centered radical D upon addition into alkene substrate. Two mechanistic scenarios are envisioned based upon electronic properties of the employed alkenes. This radical D would be reduced into corresponding carbanion E when the reduction potential of D [E_{red}(D/E) = −2.0 V vs Fc/Fc^+][76] is on par with E_{red}(A/A$^{\bullet-}$) (path A, if R^1 = EWG or Aryl). A subsequent protonation with water would furnish hydrodifluoromethylation product F, constituting an ECEC-type[62,77,78] radical-polar crossover mechanism[69,70,79–82]. Alternatively, a carbon-centered radical D would directly perform hydrogen-atom transfer (HAT) to form F in the presence of a hydrogen atom donor such as thiol, when E_{red}(D/E) is too negative to be reduced on the cathode (path B, if R^1 = EDG or Alkyl).

To put this hypothetic system in context, we initially commenced our investigation by choosing conjugated alkene 1 as a model substrate for path A, with 2 as CF_2H radical precursor (Fig. 3). After optimization, we observed that the application of a

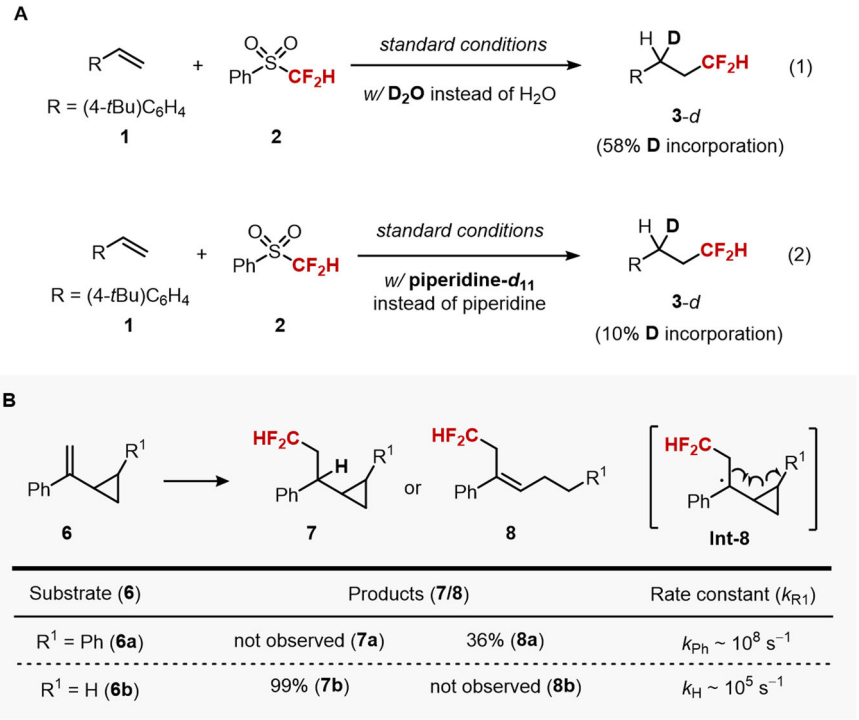


Fig. 4 Preliminary mechanistic investigation. A A significant amount of deuterium incorporation was observed upon employment of D_2O in under optimized reaction conditions (Eq. 1). The reaction with piperidine-d_{11} result in low deuterium incorporation (Eq. 2). **B** Vinyl cyclopropane 6a with higher ring opening rate constant ($k_{Ph} = \sim 10^8\ s^{-1}$) underwent rupture of the three-membered ring (8a), while the cyclopropyl ring in 6b ($k_H = \sim 10^5\ s^{-1}$) remained intact after electrolysis.

constant current of 4 mA in the presence of stoichiometric amounts of water enabled the formation of the desired hydrodifluoromethylation product 3 in 80% yield. The optimal conditions employed lithium perchlorate ($LiClO_4$) as the electrolyte, carbon felt and zinc plate as the cathode and the sacrificial anode respectively, acetonitrile and piperidine as the co-solvent under 50 °C. To verify our initial mechanistic hypothesis, we monitored the voltaic profile of each electrode during electrolysis of entry 1 (Fig. 2, inset box). The sacrificial Zn anode operates at the anticipated onset potential for Zn oxidation (E_{onset} = ca.−0.5 V vs Fc/Fc^+, typically 0.5 V below the thermodynamic potential)[83,84]. Likewise, the initial cathodic potential ($E_{cathode} = -1.8$ V) is in accordance with the onset potential for reduction of 2. Under the given cathodic potential, a simultaneous reduction of benzylic radical intermediate 4 into corresponding carbanion 5 is conceivable presumably via a radical-polar crossover mechanism [path A in Fig. 2, $E_{red}(4/5 \cong -2.0\ V)$][76].

Subsequently, a set of control experiments using deuterated reaction components were conducted to verify our mechanistic hypothesis (Fig. 4A). A significant amount of deuterium incorporation was observed upon employment of D_2O in lieu of H_2O under optimized reaction conditions, as we envisioned at the outset (Eq. 1). On the contrast, we found that the reaction with piperidine-d_{11} result in low deuterium incorporation, suggesting that an alternative mechanism where an α C−H bond of amine additive is engaged in hydrogen atom transfer is less conceivable (Eq. 2)[85,86].

Further experiments using radical probe substrates were conducted (Fig. 4B). Interestingly, vinyl cyclopropane 6a with higher ring opening rate constant due to the generation of more stable benzyl radical ($k_{Ph} = \sim 10^8\ s^{-1}$) underwent rupture of the three-membered ring (8a), while the cyclopropyl ring in 6b ($k_H = \sim 10^5\ s^{-1}$) remained intact after electrolysis under standard conditions (7b)[76]. These results imply that the reduction of the benzylic radical intermediate (Int-8) is sufficiently fast to prevent undesired side reactions, constituting radical-polar crossover mechanism (Fig. 2, path A).

Having identified the optimized reaction parameters, we next explored the substrate scope of conjugated alkenes (Fig. 5). A wide range of terminal styrenes that possess functional groups such as alkyls (10a−b), phenyl (10c), methoxy (10d), halides (10e−f), trifluoromethyl (10g) and cyano (10h) were well tolerated. The methyl groups in vinylmesitylene that are potentially oxidizable remained intact after electrolysis to deliver the product 10i. We found that 2-vinylnaphthalene also afforded the desired hydrodifluoromethylation product 10j in good yield. Additionally, 1,1-disubstituted styrenes such as 9k and 9l were successfully converted into the desired products in good yields. Besides terminal styrenes, more challenging internal styrenes were proved to be compatible with the current electrolytic system with exclusive regioselectivity, due to inherent stability of benzylic radicals over secondary radicals (10m−p). It was notable to see that the regioselectivity was consistent even with tertiary radicals, furnishing corresponding difluoromethylated quaternary carbon center from the trisubstituted styrene 9p. Importantly, vinyl heteroarenes such as pyrrole, thiophene and thiazole were all suitable substrates, transforming into the desired products in satisfactory yields (10q−s). Moreover, the reactivity toward biorelevant structures such as tyrosine (10t) and estrone (10u) was successfully illustrated.

We note that the choice of the radical precursor was important when highly conjugated or electron-withdrawing alkenes were subjected to the reaction. For example, 1-phenyl-1,3-butadiene (9v) was efficiently converted to 1,4-hydrodifluorodifluoromethylated product 10v in the presence of more readily reducible 2-py as a radical precursor. We assumed that less negative reaction potential modulated by the use of 2-py was key to the desired polar crossover of highly conjugated radical intermediate Int-10v. Similarly,

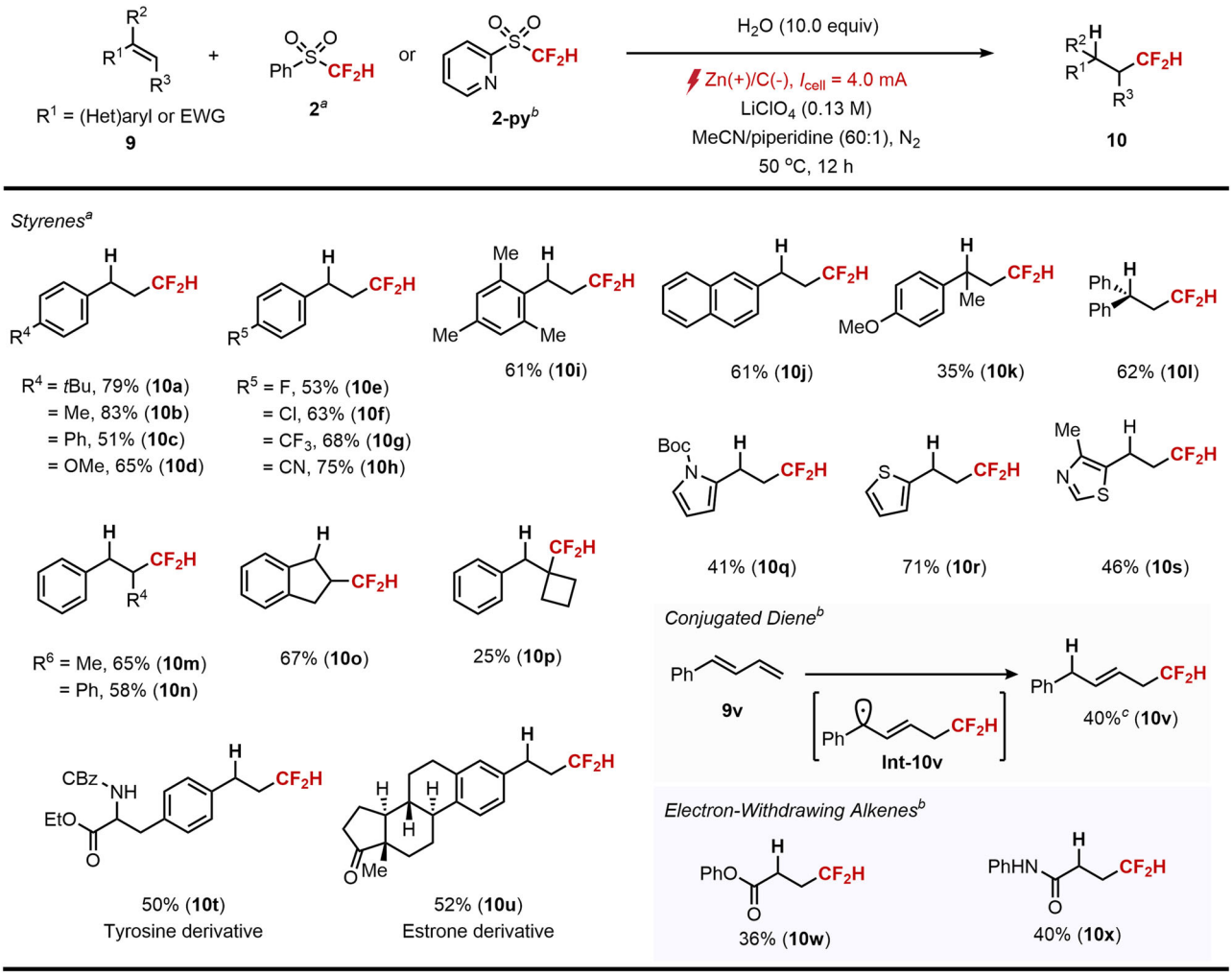


Fig. 5 Substrate scope of conjugated alkenes[a]. [a]9 (0.2 mmol), 2 (0.4 mmol), H_2O (2.0 mmol), $LiClO_4$ (0.8 mmol) in MeCN/piperidine (6.0 mL, 40:1) at 50 °C. [b]9 (0.2 mmol), 2-py (0.6 mmol), $LiClO_4$ (0.8 mmol) and H_2O (1.0 mL) in MeCN/Et_3N (14/1, 4.0 mL) at 22 °C. [c]Yield was measured by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. Isolated yields are reported unless otherwise noted.

electron-deficient alkenes were smoothly participated in the reaction to give corresponding hydrodifluoromethylation products (10w−x) under room temperature.

We further expanded the scope of the current hydrodifluoromethylation reaction with respect to the aliphatic and electron-rich alkenes on the basis of initial mechanistic hypothesis in Fig. 2, path B (Fig. 6). The plausibility of this hypothesis was verified by choosing thiophenol as a hydrogen atom donor in the presence of 2-py as a CF_2H radical source. After optimization of the reaction parameters, we found that the desired reaction can be achieved using TBA·PF_6 as the electrolyte with the application of a constant current of 2 mA in MeCN at room temperature. In addition, the slightly increased amounts of amine (Et_3N) and water additives were found to be optimal in preventing a short-circuit caused by a zinc precipitation.

We have found that a wide range of terminal aliphatic alkenes was compatible with the reaction conditions (12a−i). The hydrodifluoromethylated products derived from both mono-substituted (12a−b) and 1,1-disubstituted alkenes (12c−d) gave good yields. Importantly, a difluoromethylated alkylboron product 12e could readily be obtained from a masked vinylboronic acid 11e, which can serve as a useful synthon in difluoroalkylative functionalization via cross-coupling. Moreover, the synthetic utility of the current protocol was successfully illustrated by applying it to the derivatization of biorelevant structures (12f−h) and a pharmacophore (Indomethacin derivative, 12i). More importantly, electron rich alkenes that have been previously unexplored in photocatalytic hydrodifluoromethylation such as *N*-vinylcarbazole (11j), enamide (11k), *N*-vinyllactams (11l−m) and vinyl ether (11n) underwent smooth conversion to the corresponding products in good to moderate yields under identical reaction conditions. Finally, radical clock substrate 13 afforded cyclized product 14 under standard reaction conditions. This result again highlights the radical intermediacy of the reaction.

As a logical extension, we envisioned the development of an innovative platform for the regioselective consecutive hydrodifluoromethylation of alkynes based on the fact that the hydrocarbons bearing two difluoromethyl groups remain rare but should possess unique properties for drug discovery. Indeed, the ability to introduce multiple difluoromethyl groups into unsaturated C−C bonds presents a difficult proposition even with modern organic chemistry.

As envisioned, we found that a multiple hydrodifluoromethylation of arylalkyne 15 can be achieved with increased amount of 2-py at 50 °C and $LiClO_4$ as the electrolyte under otherwise identical conditions to the aliphatic alkene hydrodifluoromethylation reaction, successfully generating a geminal bis-difluoromethylation products in good to moderate yields as single regioisomers (Fig. 7, 16a−g). We assumed that the first hydrodifluoromethylation proceeds via HAT of difluoromethylated vinyl radical intermediate,

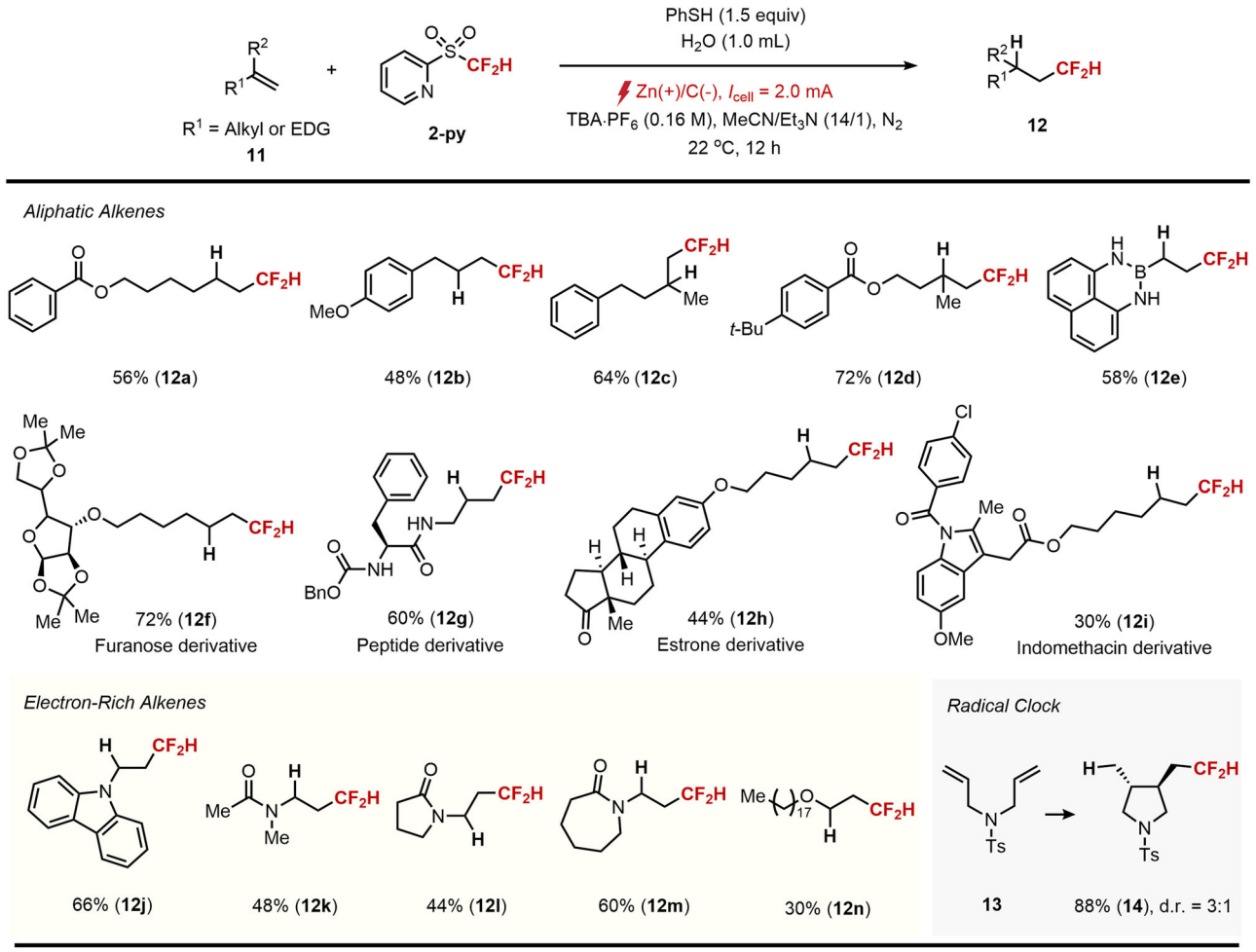


Fig. 6 Substrate scope of aliphatic and electron-rich alkenes[a]. [a]11 (0.2 mmol), 2-py (0.6 mmol), TBA·PF_6 (0.8 mmol) and H_2O (1.0 mL) in MeCN/Et_3N (14/1, 4.0 mL) at 22 °C. Isolated yields are reported unless otherwise noted.

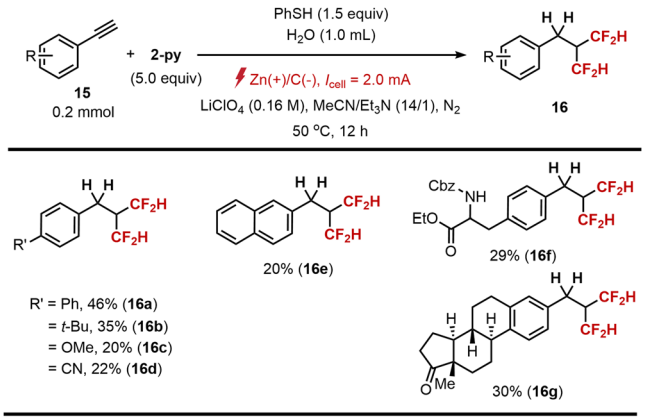


Fig. 7 Double hydrodifluoromethylation of alkynes[a]. [a]15 (0.2 mmol), 2-py (0.6 mmol), $LiClO_4$ (0.8 mmol) and H_2O (1.0 mL) in MeCN/Et_3N (14/1, 4.0 mL) at 50 °C. Isolated yields are reported unless otherwise noted.

while the second reaction proceeds presumably via a radical-polar crossover mechanism driven by aryl substituents of the employed alkynes (Supplementary Fig. 7).

Finally, we showcased our methodology in late-stage drug modification of Ibuprofen, a popular analgesic and antipyretic in which its ameliorative derivatization has attracted constant attention in the pharmaceutical chemistry (Fig. 8)[87,88]. The requisite starting material 20 was prepared with good efficiency in three steps from commercially available 2-(4-hydroxyphenyl) propanoic acid (17). As anticipated, the desired hydrodifluoromethylation was smoothly proceeded under the standard conditions (21). Hydrolysis of 21 was facile under basic conditions, leading to the formation of difluoromethyl analogue of Ibuprofen (22) in 28% overall yield (5 steps).

Notably, the developed double hydrodifluoromethylation protocol allowed conversion of alkyne 25 into corresponding geminal bis-difluoromethylation product 26. Upon treatment of 26 with base under aqueous conditions, a bis-difluoromethyl analogue of Ibuprofen (27) could readily be obtained, demonstrating an operationally simple two-track derivatization of a pharmaceutical agent from commercially available starting materials.

Conclusion

In conclusion, we developed a general electroreductive protocol to achieve hydrodifluoromethylation of a wide range of unsaturated C−C bonds by means of a two-pronged strategy based upon electronic properties of the employed substrates. A key distinction of the present strategy originates from the reconciliation of multiple redox processes under highly reducing electrochemical conditions. We anticipate that this mechanistically distinct and modular protocol will enhance accessibility of a diverse suite of difluoromethylated hydrocarbons which possess high potential utility in pharmaceutical applications.

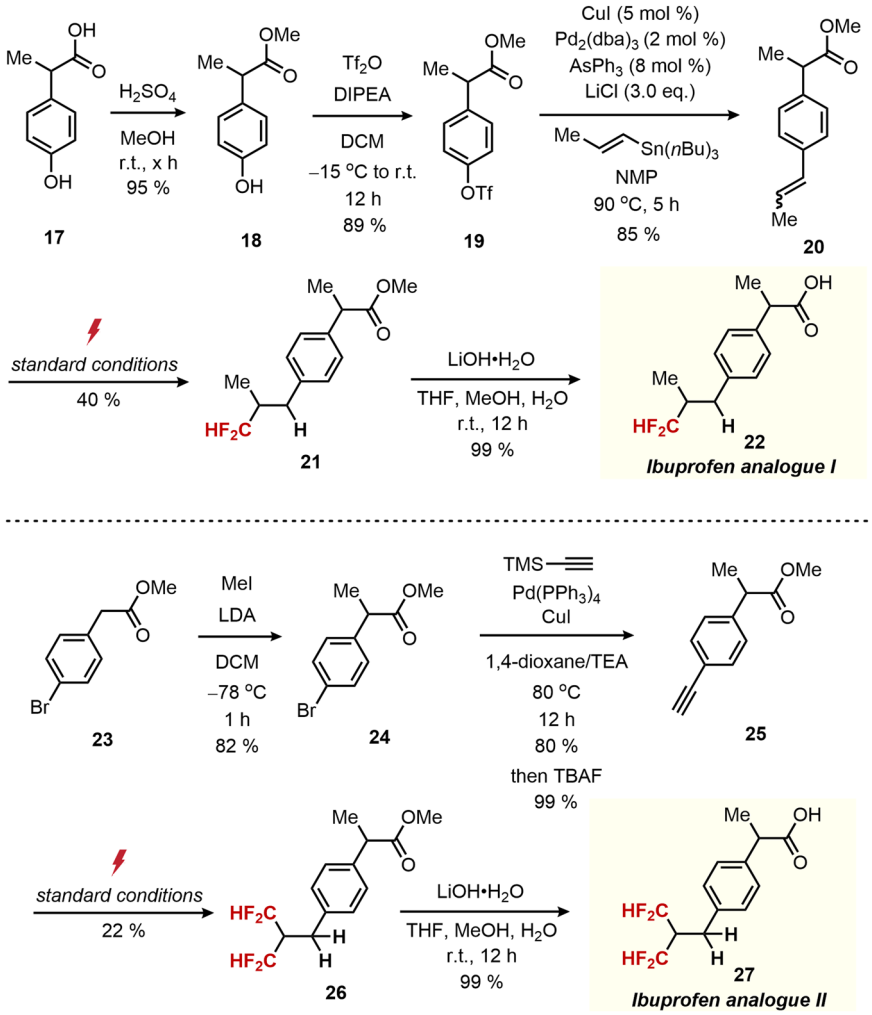


Fig. 8 Synthesis of CF_2H analogues of ibuprofen. The requisite starting material 20 was prepared in three steps from 2-(4-hydroxyphenyl)propanoic acid (17). The desired hydrodifluoromethylation was proceeded under the standard conditions (21). Hydrolysis of 21 led to the formation of difluoromethyl analogue of Ibuprofen (22) in 28% overall yield (5 steps). The developed double hydrodifluoromethylation protocol allowed conversion of alkyne 25 into corresponding geminal bis-difluoromethylation product 26. Upon treatment of 26 with base under aqueous conditions, a bis-difluoromethyl analogue of Ibuprofen (27) was obtained.

Methods

General procedure for electroreductive hydrodifluoromethylation of vinylarenes. An oven-dried, 10 mL two-neck glass tube was equipped with a magnetic stir bar, a rubber septum, a threaded Teflon cap fitted with electrical feed-throughs, a carbon felt anode (1.0×0.5 cm^2) (connected to the electrical feedthrough via a 9 cm in length, 2 mm in diameter graphite rod), and a zinc plate anode ($1 \times 0.5 \times 0.02$ cm^3). To this reaction vessel, $LiClO_4$ (85.1 mg, 0.8 mmol) was added. The cell was sealed and backfilled with nitrogen gas for 3 times, followed by the sequential addition via syringe of MeCN (6.0 mL), water (2.0 mmol, 36.0 µL), **2** (0.4 mmol, 57.0 µL), piperidine (1.0 mmol, 99 µL) and olefin substrate (0.2 mmol, 1.0 equiv). A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. Electrolysis was initiated at a constant current of 4.0 mA at 50 °C for 12 h. The mixture was then diluted with ethyl acetate (30 mL) and then washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield the desired product.

General procedure for electroreductive hydrodifluoromethylation of electron-deficient alkenes. An oven-dried, 10 mL two-neck glass tube was equipped with a magnetic stir bar, a rubber septum, a threaded Teflon cap fitted with electrical feed-throughs, a carbon felt anode (1.0×0.5 cm^2) (connected to the electrical feed-through via a 9 cm in length, 2 mm in diameter graphite rod), and a zinc plate anode ($1 \times 0.5 \times 0.02$ cm^3). To this reaction vessel, $LiClO_4$ (85.1 mg, 0.8 mmol) and 2-py (0.6 mmol, 115.9 mg) were added. The cell was sealed and backfilled with nitrogen gas for 3 times, followed by the sequential addition via syringe of MeCN (4.0 mL), water (1.0 mL) triethylamine (2.0 mmol, 280 µL) and olefin substrate (0.2 mmol, 1.0equiv). A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. Electrolysis was initiated at a constant current of 2.0 mA at 50 °C for 12 h. The mixture was then diluted with ethyl acetate (30 mL) and then washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield the desired product.

General procedure for electroreductive hydrodifluoromethylation of unactivated alkenes. An oven-dried, 10 mL two-neck glass tube was equipped with a magnetic stir bar, a rubber septum, a threaded Teflon cap fitted with electrical feed-throughs, a carbon felt anode (1.0×0.5 cm^2) (connected to the electrical feed-through via a 9 cm in length, 2 mm in diameter graphite rod), and a zinc plate anode ($1 \times 0.5 \times 0.02$ cm^3). To this reaction vessel, TBA·PF_6 (309.9 mg, 0.8 mmol) and 2-py (0.6 mmol, 115.9 mg) were added. The cell was sealed and backfilled with nitrogen gas for 3 times, followed by the sequential addition via syringe of MeCN (4.0 mL), water (1.0 mL), thiophenol (0.3 mmol. 31 µL) triethylamine (2.0 mmol, 280 µL) and olefin substrate (0.2 mmol, 1.0equiv). A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. Electrolysis was initiated at a constant current of 2.0 mA at 22 °C for 12 h. The mixture was then diluted with ethyl acetate (30 mL) and then washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield the desired product.

General procedure for electroreductive double hydrodifluoromethylation of alkynes. An oven-dried, 10 mL two-neck glass tube was equipped with a magnetic stir bar, a rubber septum, a threaded Teflon cap fitted with electrical feed-throughs,

a carbon felt anode ($1.0 \times 0.5\ cm^2$) (connected to the electrical feedthrough via a 9 cm in length, 2 mm in diameter graphite rod), and a zinc plate anode ($1 \times 0.5 \times 0.02\ cm^3$). To this reaction vessel, $LiClO_4$ (85.0 mg, 0.8 mmol) and 2-py (1.0 mmol, 193.2 mg) were added. The cell was sealed and backfilled with nitrogen gas for 3 times, followed by the sequential addition via syringe of MeCN (4.0 mL), water (1.0 mL), thiophenol (0.3 mmol. 31 μL) triethylamine (2.0 mmol, 280 μL) and alkyne substrate (0.2 mmol, 1.0equiv). A nitrogen-filled balloon was adapted through the septum to sustain a nitrogen atmosphere. Electrolysis was initiated at a constant current of 2.0 mA at 50 °C for 18 h. The mixture was then diluted with ethyl acetate (30 mL) and then washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield the desired product.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information. For experimental details and compound characterization data see Supplementary Notes 1–4. For ^1H NMR, ^{11}B NMR, ^{13}C NMR, and ^{19}F NMR spectra see Supplementary Note 5, pages. 31–123.

Received: 17 February 2022; Accepted: 27 June 2022;
Published online: 11 August 2022

References

1. Tseng, C.-C. et al. The trifluoromethyl group as a bioisosteric replacement of the aliphatic nitro group in CB1 receptor positive allosteric modulators. *J. Med. Chem.* **62**, 5049–5062 (2019).
2. Gillis, E. P., Eastman, K. J., Hill, M. D., Donnelly, D. J. & Meanwell, N. A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **58**, 8315–8359 (2015).
3. Xing, L. et al. Fluorine in drug design: a case study with fluoroanisoles. *ChemMedChem* **10**, 715–726 (2015).
4. Purser, S., Moore, P. R., Swallow, S. & Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **37**, 320–330 (2008).
5. Wang, J. et al. Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev.* **114**, 2432–2506 (2014).
6. Meanwell, N. A. Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design. *J. Med. Chem.* **61**, 5822–5880 (2018).
7. Kirk, K. L. Fluorination in medicinal chemistry: methods, strategies, and recent developments. *Org. Process Res. Dev.* **12**, 305–321 (2008).
8. Han, J. et al. Next generation organofluorine containing blockbuster drugs. *J. Fluor. Chem.* **239**,109639 (2020).
9. Zafrani, Y. et al. CF_2H, a Functional group-dependent hydrogen-bond donor: is it a more or less lipophilic bioisostere of OH, SH, and CH_3? *J. Med. Chem.* **62**, 5628–5637 (2019).
10. Levi, N., Amir, D., Gershonov, E. & Zafrani, Y. Recent progress on the synthesis of CF_2H-containing derivatives. *Synthesis* **51**, 4549–4567 (2019).
11. Koike, T. & Akita, M. New horizons of photocatalytic fluoromethylative difunctionalization of alkenes. *Chem.* **4**, 409–437 (2018).
12. Sap, J. B. I. et al. Late-stage difluoromethylation: concepts, developments and perspective. *Chem. Soc. Rev.* **50**, 8214–8247 (2021).
13. Furuya, T., Kamlet, A. S. & Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **473**, 470–477 (2011).
14. Yakubov, S. & Barham, J. P. Photosensitized direct C-H fluorination and trifluoromethylation in organic synthesis. *Beilstein J. Org. Chem.* **16**, 2151–2192 (2020).
15. Kirsch, P. & Bremer, M. Understanding fluorine effects in liquid crystals. *ChemPhysChem* **11**, 357–360 (2010).
16. Kirsch, P. et al. Super-fluorinated liquid crystals: Towards the limits of polarity. *Eur. J. Org. Chem.* 3479–3487 (2008).
17. Fier, P. S. & Hartwig, J. F. Copper-mediated difluoromethylation of aryl and vinyl iodides. *J. Am. Chem. Soc.* **134**, 5524–5527 (2012).
18. Xu, L. & Vicic, D. A. Direct difluoromethylation of aryl halides via base metal catalysis at room temperature. *J. Am. Chem. Soc.* **138**, 2536–2539 (2016).
19. Bour, J. R., Kariofillis, S. K. & Sanford, M. S. Synthesis, reactivity, and catalytic applications of isolable (NHC)Cu(CHF_2) complexes. *Organometallics* **36**, 1220–1223 (2017).
20. Zhu, S.-Q., Liu, Y.-L., Li, H., Xu, X.-H. & Qing, F.-L. Direct and regioselective C–H oxidative difluoromethylation of heteroarenes. *J. Am. Chem. Soc.* **140**, 11613–11617 (2018).
21. Zeng, X. et al. Copper-catalyzed decarboxylative difluoromethylation. *J. Am. Chem. Soc.* **141**, 11398–11403 (2019).
22. Zeng, X. et al. Copper-catalyzed, chloroamide-directed benzylic C–H difluoromethylation. *J. Am. Chem. Soc.* **141**, 19941–19949 (2019).
23. Lalloo, N., Malapit, C. A., Taimoory, S. M., Brigham, C. E. & Sanford, M. S. Decarbonylative fluoroalkylation at palladium(II): from fundamental organometallic studies to catalysis. *J. Am. Chem. Soc.* **143**, 18617–18625 (2021).
24. Cai, A., Yan, W. & Liu, W. Aryl Radical activation of C–O bonds: copper-catalyzed deoxygenative difluoromethylation of alcohols. *J. Am. Chem. Soc.* **143**, 9952–9960 (2021).
25. Cai, A. et al. Copper-catalyzed carbo-difluoromethylation of alkenes via radical relay. *Nat. Commun.* **12**, 3272 (2021).
26. Chen, D. et al. Bis(difluoromethyl)trimethylsilicate anion: a key intermediate in nucleophilic difluoromethylation of enolizable ketones with Me3SiCF2H. *Angew. Chem. Int. Ed.* **55**, 12632–12636 (2016).
27. Shen, X., Zhang, W., Ni, C., Gu, Y. & Hu, J. tuning the reactivity of difluoromethyl sulfoximines from electrophilic to nucleophilic: stereoselective nucleophilic difluoromethylation of aryl ketones. *J. Am. Chem. Soc.* **134**, 16999–17002 (2012).
28. Feng, Z., Min, Q.-Q., Fu, X.-P., An, L. & Zhang, X. Chlorodifluoromethane-triggered formation of difluoromethylated arenes catalysed by palladium. *Nat. Chem.* **9**, 918–923 (2017).
29. Fu, X.-P. et al. Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes. *Nat. Chem.* **11**, 948–956 (2019).
30. Xie, Q., Zhu, Z., Li, L., Ni, C. & Hu, J. A General protocol for C−H difluoromethylation of carbon acids with $TMSCF_2Br$. *Angew. Chem. Int. Ed.* **58**, 6405–6410 (2019).
31. Peng, L., Wang, H. & Guo, C. Copper-catalyzed enantioselective difluoromethylation of amino acids via difluorocarbene. *J. Am. Chem. Soc.* **143**, 6376–6381 (2021).
32. Sheng, H., Su, J., Li, X., Li, X. & Song, Q. Double capture of difluorocarbene by 2-aminostyrenes enables the construction of 3-(2,2-difluoroethyl)-2-fluoroindoles. *Org. Lett.* **23**, 7781–7786 (2021).
33. Fujiwara, Y. et al. A New reagent for direct difluoromethylation. *J. Am. Chem. Soc.* **134**, 1494–1497 (2012).
34. Miao, W. et al. Iron-catalyzed difluoromethylation of arylzincs with difluoromethyl 2-pyridyl sulfone. *J. Am. Chem. Soc.* **140**, 880–883 (2018).
35. Wu, Q.-Y., Ao, G.-Z. & Liu, F. Redox-neutral tri-/difluoromethylation of *para*-quinone methides with sodium sulfinates. *Org. Chem. Front.* **5**, 2061–2064 (2018).
36. Sap, J. B. I. et al. Organophotoredox hydrodefluorination of trifluoromethylarenes with translational applicability to drug discovery. *J. Am. Chem. Soc.* **142**, 9181–9187 (2020).
37. Box, J. R., Atkins, A. P. & Lennox, A. J. J. Direct electrochemical hydrodefluorination of trifluoromethylketones enabled by non-protic conditions. *Chem. Sci.* **12**, 10252–10258 (2021).
38. Zhang, W. et al. Direct C–H difluoromethylation of heterocycles via organic photoredox catalysis. *Nat. Commun.* **11**, 638 (2020).
39. Cheng, X. et al. Organozinc pivalates for cobalt-catalyzed difluoroalkylarylation of alkenes. *Nat. Commun.* **12**, 4366 (2021).
40. Campbell, M. W. et al. Photochemical C–F activation enables defluorinative alkylation of trifluoroacetates and -acetamides. *J. Am. Chem. Soc.* **143**, 19648–19654 (2021).
41. Zou, Z. et al. Electrochemical-promoted nickel-catalyzed oxidative fluoroalkylation of aryl iodides. *Org. Lett.* **23**, 8252–8256 (2021).
42. Yu, J., Wu, Z. & Zhu, C. Efficient docking–migration strategy for selective radical difluoromethylation of alkenes. *Angew. Chem. Int. Ed.* **57**, 17156–17160 (2018).
43. Xu, H.-H., Song, J. & Xu, H.-C. Electrochemical difluoromethylation of electron-deficient alkenes. *ChemSusChem* **12**, 3060–3063 (2019).
44. Xiong, P., Xu, H.-H., Song, J. & Xu, H.-C. Electrochemical difluoromethylarylation of alkynes. *J. Am. Chem. Soc.* **140**, 2460–2464 (2018).
45. Zhang, Y. et al. Electrooxidative dearomatization of biaryls: synthesis of tri- and difluoromethylated spiro[5.5]trienones. *Chem. Sci.* **12**, 10092–10096 (2021).
46. Rong, J. et al. Radical fluoroalkylation of isocyanides with fluorinated sulfones by visible-light photoredox catalysis. *Angew. Chem. Int. Ed.* **55**, 2743–2747 (2016).
47. Arai, Y., Tomita, R., Ando, G., Koike, T. & Akita, M. oxydifluoromethylation of alkenes by photoredox catalysis: simple synthesis of CF_2H-containing alcohols. *Chem. – Eur. J.* **22**, 1262–1265 (2016).
48. Zhang, L., Zhang, X. & Lu, G. Predictions of moiré excitons in twisted two-dimensional organic-inorganic halide perovskites. *Chem. Sci.* **12**, 6073–6080 (2021).
49. Yuan, X. et al. Electrochemical Tri- and Difluoromethylation-Triggered Cyclization Accompanied by the Oxidative Cleavage of Indole Derivatives. *Chem. Eur. J.* **27**, 6522–6528 (2021).
50. Arai, K., Watts, K. & Wirth, T. Difluoro- and trifluoromethylation of electron-deficient alkenes in an electrochemical microreactor. *ChemistryOpen* **3**, 23–28 (2014).
51. Yang, J., Zhu, S., Wang, F., Qing, F.-L. & Chu, L. Silver-enabled general radical difluoromethylation reaction with $TMSCF_2H$. *Angew. Chem. Int. Ed.* **60**, 4300–4306 (2021).

52. Tang, X.-J., Zhang, Z. & Dolbier, W. R. Jr. Direct photoredox-catalyzed reductive difluoromethylation of electron-deficient alkenes. *Chem. – A Eur. J.* **21**, 18961–18965 (2015).
53. Lin, Q.-Y., Xu, X.-H., Zhang, K. & Qing, F.-L. Visible-light-induced hydrodifluoromethylation of alkenes with a bromodifluoromethylphosphonium bromide. *Angew. Chem. Int. Ed.* **55**, 1479–1483 (2016).
54. Yu, J., Lin, J.-H., Cao, Y.-C. & Xiao, J.-C. Visible-light-induced radical hydrodifluoromethylation of alkenes. *Org. Chem. Front.* **6**, 3580–3583 (2019).
55. Meyer, C. F., Hell, S. M., Misale, A., Trabanco, A. A. & Gouverneur, V. Hydrodifluoromethylation of alkenes with difluoroacetic acid. *Angew. Chem. Int. Ed.* **58**, 8829–8833 (2019).
56. Alemán, J., Rodriguez, R. I. & Sicignano, M. Fluorinated sulfinates as source of alkyl radicals in the photo-enantiocontrolled β-functionalization of enals. *Angew. Chem. Int. Ed.* (2022).
57. Zhou, X., Ni, C., Deng, L. & Hu, J. Electrochemical reduction of fluoroalkyl sulfones for radical fluoroalkylation of alkenes. *Chem. Commun.* **57**, 8750–8753 (2021).
58. Zou, G. & Wang, X. Visible-light induced di- and trifluoromethylation of: N -benzamides with fluorinated sulfones for the synthesis of CF2H/CF3-containing isoquinolinediones. *Org. Biomol. Chem.* **15**, 8748–8754 (2017).
59. Zhu, M. et al. Visible-Light-Induced Radical Di- and Trifluoromethylation of β, γ-Unsaturated Oximes: Synthesis of Di- and Trifluoromethylated Isoxazolines. *Eur. J. Org. Chem.* **2019**, 1614–1619 (2019).
60. Peters, B. K. et al. Scalable and safe synthetic organic electroreduction inspired by Li-ion battery chemistry. *Science* **363**, 838–845 (2019).
61. Hu, P. et al. Electroreductive olefin–ketone coupling. *J. Am. Chem. Soc.* **142**, 20979–20986 (2020).
62. Zhang, W. & Lin, S. Electroreductive carbofunctionalization of alkenes with alkyl bromides via a radical-polar crossover mechanism. *J. Am. Chem. Soc.* **142**, 20661–20670 (2020).
63. Lu, L., Siu, J. C., Lai, Y. & Lin, S. An electroreductive approach to radical silylation via the activation of strong Si–Cl bond. *J. Am. Chem. Soc.* **142**, 21272–21278 (2020).
64. Perkins, R. J., Pedro, D. J. & Hansen, E. C. Electrochemical nickel catalysis for sp^2-sp^3 cross-electrophile coupling reactions of unactivated alkyl halides. *Org. Lett.* **19**, 3755–3758 (2017).
65. DeLano, T. J. & Reisman, S. E. Enantioselective electroreductive coupling of alkenyl and benzyl halides via nickel catalysis. *ACS Catal.* **9**, 6751–6754 (2019).
66. Truesdell, B. L., Hamby, T. B. & Sevov, C. S. General C(sp^2)–C(sp^3) cross-electrophile coupling reactions enabled by overcharge protection of homogeneous electrocatalysts. *J. Am. Chem. Soc.* **142**, 5884–5893 (2020).
67. Kim, H., Kim, H., Lambert, T. H. & Lin, S. Reductive electrophotocatalysis: merging electricity and light to achieve extreme reduction potentials. *J. Am. Chem. Soc.* **142**, 2087–2092 (2020).
68. Barham, J. P. & König, B. Synthetic photoelectrochemistry. *Angew. Chem. Int. Ed.* **59**, 11732–11747 (2020).
69. Wu, S., Kaur, J., Karl, T. A., Tian, X. & Barham, J. P. Synthetic molecular photoelectrochemistry: new frontiers in synthetic applications, mechanistic insights and scalability. *Angew. Chem. Int. Ed.* https://doi.org/10.1002/anie.202107811 (2021).
70. Tian, X. et al. Electro-mediated photoredox catalysis for selective C(sp^3)–O cleavages of phosphinated alcohols to carbanions. *Angew. Chem. Int. Ed.* **60**, 20817–20825 (2021).
71. Pollok, D., Gleede, B., Stenglein, A. & Waldvogel, S. R. Preparative batch-type electrosynthesis: a tutorial. *Aldrichimica Acta.* **54**, 3–15 (2021).
72. Park, S. H. et al. Reductive electrosynthesis: a new dawn. *Aldrichimica Acta.* **54**, 17–27 (2021).
73. Meyer, T. H. & Ackermann, L. Chemistry with potential: present challenges and emerging trends in organic electrocatalysis. *Aldrichimica Acta.* **54**, 29–31 (2021).
74. Heard, D. M. & Lennox, A. J. J. Electrode Materials in Modern Organic Electrochemistry. *Angew. Chem. Int. Ed.* **59**, 18866–18884 (2020).
75. Couper, A. M., Pletcher, D. & Walsh, F. C. Electrode materials for electrosynthesis. *Chem. Rev.* **90**, 837–865 (1990).
76. Magri, D. C. & Workentin, M. S. Redox properties of radicals. In *Encyclopedia of Radicals in Chemistry, Biology and Materials* (John Wiley & Sons, New York, 2012).
77. Costentin, C., Nocera, D. G. & Brodsky, C. N. Multielectron, multisubstrate molecular catalysis of electrochemical reactions: formal kinetic analysis in the total catalysis regime. *Proc. Natl Acad. Sci.* **114**, 11303–11308 (2017).
78. Nematollahi, D. & Forooghi, Z. ECEC and ECE-Type mechanisms in electrochemical oxidation of 4-substituted catechols in the presence of 4-hydroxy-6-methyl-2-pyrone. *Electroanalysis* **15**, 1639–1644 (2003).
79. Pitzer, L., Schwarz, J. L. & Glorius, F. Reductive radical-polar crossover: traditional electrophiles in modern radical reactions. *Chem. Sci.* **10**, 8285–8291 (2019).
80. Liu, Y. et al. Merging radical-polar crossover/cycloisomerization processes: access to polyfunctional furans enabled by metallaphotoredox catalysis. *Org. Chem. Front.* **8**, 1732–1738 (2021).
81. Yi, H. et al. Photocatalytic dehydrogenative cross-coupling of alkenes with alcohols or azoles without external oxidant. *Angew. Chem. Int. Ed.* **56**, 1120–1124 (2017).
82. Peng, P. et al. Electrochemical C−C bond cleavage of cyclopropanes towards the synthesis of 1,3-difunctionalized molecules. *Nat. Commun.* **12**, 3075 (2021).
83. Francke, R. & Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **43**, 2492–2521 (2014).
84. Steckhan, E. Indirect electroorganic syntheses—a modern chapter of organic electrochemistry [new synthetic methods (59)]. *Angew. Chem. Int. Ed. Engl.* **25**, 683–701 (1986).
85. Kurtova, O. Y., Kravtsov, V. I. & Tsventarnyi, E. G. Kinetics and mechanism of electroreduction of ethylenediamine and hydroxyethylenediamine complexes of zinc(II) on a dropping-mercury electrode. *Russ. J. Electrochem.* **41**, 346–354 (2005).
86. Luo, J., Hu, B., Sam, A. & Liu, T. L. Metal-free electrocatalytic aerobic hydroxylation of arylboronic acids. *Org. Lett.* **20**, 361–364 (2018).
87. Rainsford, K. D. *Ibuprofen: Discovery, Development and Therapeutics* (Wiley-Blackwell, NJ, 2015)
88. Kleemiss, F. et al. Sila-Ibuprofen. *J. Med. Chem.* **63**, 12614–12622 (2020).

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) [NRF-2021R1C1C1004605 and NRF-2021R1A4A3022415]. This work was also supported by the R&D program of the Institutional Research Program of the KRICT (KK2232-10). This study made use of the NMR facility supported by Korea Basic Science Institute (National Research Facilities and Equipment Center) grant funded by the Ministry of Education (NRF-2020R1A6C101B194). Dedicated to Professor Sukbok Chang on the occasion of his 60th birthday.

Author contributions

J. K., H. L., and H. K. conceived and designed the project. S. K., K. H. H. and H. G. P. carried out the experiments. H. K. organized the research and wrote the manuscript. All authors analyzed the data, discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s42004-022-00697-1.

Correspondence and requests for materials should be addressed to Jaesung Kwak, Hyuk Lee or Hyunwoo Kim.

Peer review information *Communications Chemistry* thanks Miriam O'Duill and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022