Radical Hydrodifluoromethylation of Unsaturated C–C Bonds via an Electroreductively Triggered Two-pronged Approach

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Abstract: 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.

Introduction

The replacement of hydrogen atoms with fluorides has now become a quintessential approach for new chemical entities to regulate physicochemical and biological properties such as metabolic stability, lipophilicity, hydrogen bonding ability and bioavailability.[1-7] 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.[8-11]

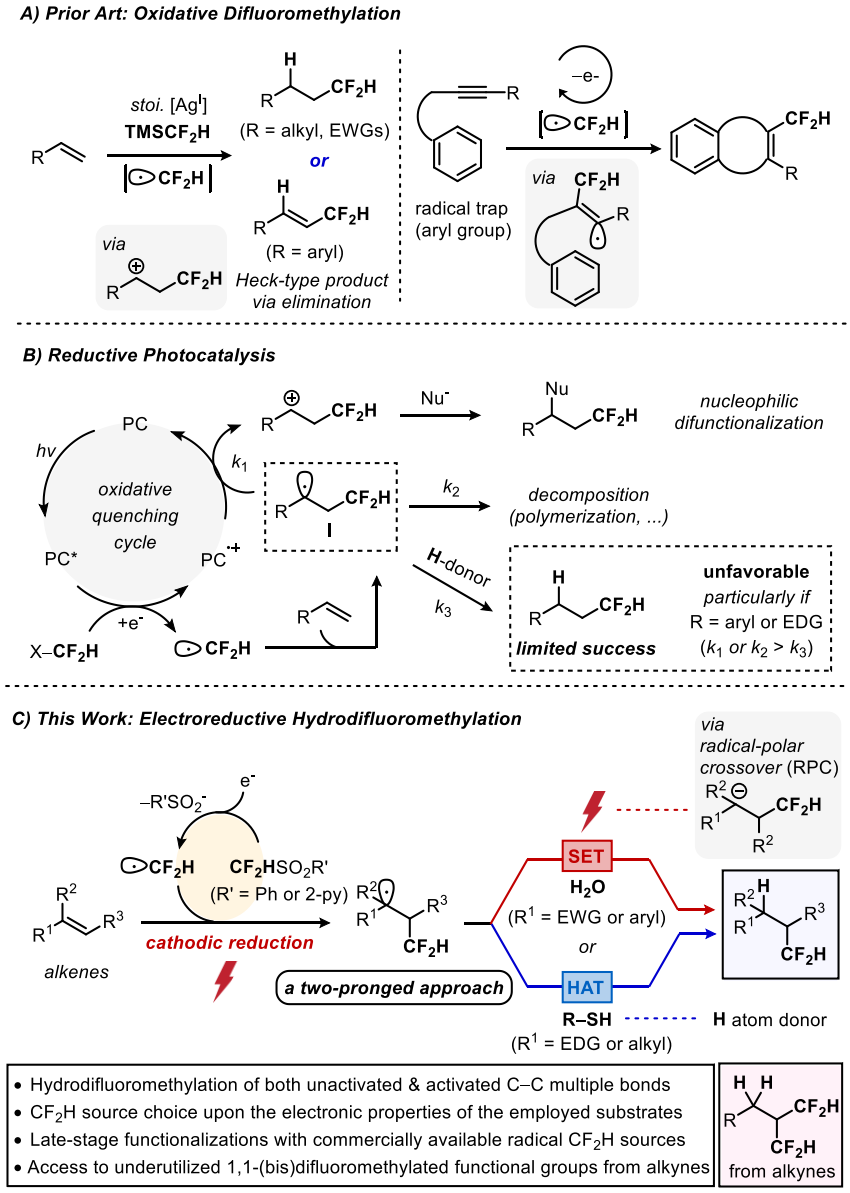


Figure 1. Radical Hydrodifluoromethylation of Unsaturated C–C bonds.

In this context, difluoromethylative functionalization, where a difluoromethyl anion,[12-21] carbene[22-27] or radical precursor[28-42] 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.[43-49] 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.[38,43] Additionally, several groups independently demonstrated oxidative difluoromethylative radical annulation of alkynes in the presence of aryl groups as the radical trap (Fig 1A, right).[39-40]

On the other hand, CF_2H radicals generated by reductive photocatalysis[44-45] or photosensitization[47] 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 carbocation (k_1), eventually leading to the formation of less-desirable difunctionalization products upon nucleophilic trapping.[10] 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).[47] 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 newly developed protocol 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 the first 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 PhSH as the hydrogen sources.

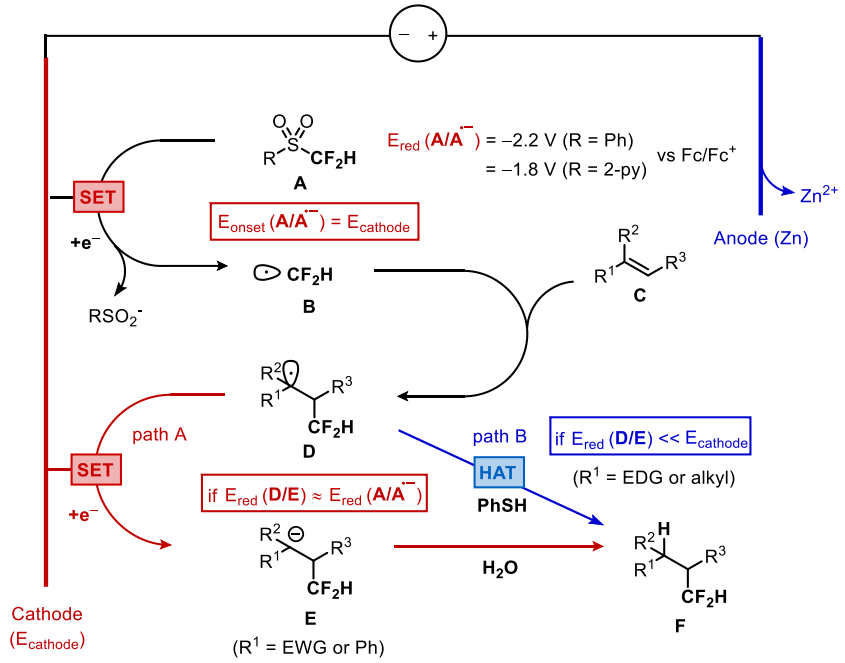
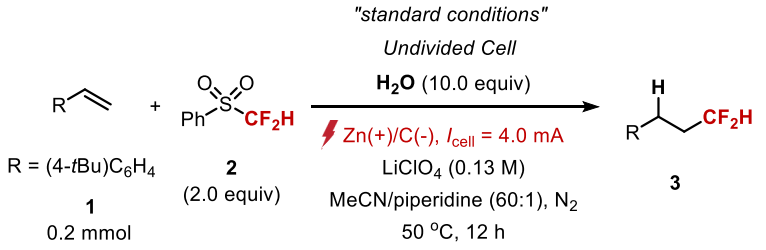


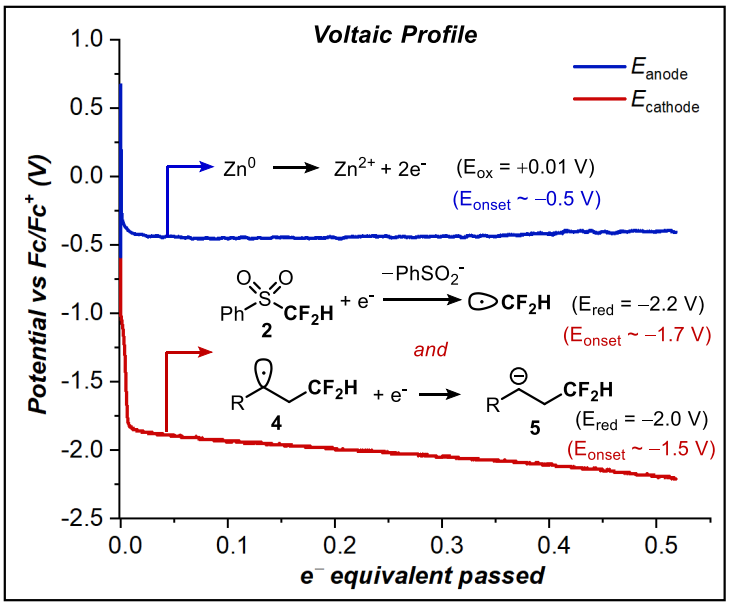
Figure 2. Hypothetic Mechanistic Postulate

Results and Discussion

To invent a less oxidizing hydrodifluoromethylation system, we anticipated an electroreductive reaction conditions using a sacrificial anode (Fig 2).[50-63] A cathodic reduction of **A** would furnish a 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**)] 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[52,64-65] radical-polar crossover

mechanism.[66-69] Alternatively, a carbon-centered radical **D** would directly perform hydrogen-atom transfer (HAT) to form **F** in the presence of H 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).





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

Figure 3. Reaction Parameter Optimization

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 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 $LiClO_4$ 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).[70-71] 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** ≅ −2.0 V)].[72]

As anticipated, a control experiment without applied current revealed that electrolytic conditions is necessary for desired reactivity (entry 2). In the absence of either water or piperidine additive, the reaction was prematurely terminated with a significant decrease in yield (entries 3–4). In both cases, we observed the formation of a zinc bridge between the cathode and anode that short-circuited the electrochemical setup. We assume that these additives would facilitate the formation of an electrochemically more stable Zn^{2+} complex, thereby preventing unproductive reduction of naked Zn^{2+} ion back to Zn^0 on the cathode.[73] Among a variety of amine additives tested, it was found that piperidine was most beneficial to reaction efficiency (entry 5, see Supplementary Information (SI) for full data). Importantly, changing the CF_2H radical precursor from **2** to **2-py** which exhibits more easily reducible potential (E_{red} = −1.9 V)[41] was detrimental to desired reactivity (entry 6). We hypothesized that this low reactivity is attributed to the change of reaction potential upon choice of radical precursor under constant current electrolysis. Indeed, the cathodic voltage shifts to a less reducing potential of −1.6 V in the presence of **2-py**, which is not capable enough to efficiently reduce a radical intermediate **4** (Fig S5, see SI). Similarly, a variety of CF_2H radical sources

that are more readily reducible,[41-42] was totally ineffective for the present hydrodifluoromethylation (Table S1). On the other hand, we note that the reaction current was measured to be very high (>20 mA) and quickly drops when the electrolysis was conducted at constant potential of $E_{cathode}$ = −2.2 V, leading to rapid decomposition of **2** with full recovery of **1** (entry 7, see also Fig S6 for current profile). These results suggest that precise balancing of electron transfer kinetics of the radical precursor and the key reaction intermediate is important to predict the reaction feasibility. The reaction was also proven to be efficient at room temperature albeit in slightly decreased yield (entry 8). It was noteworthy that changing sacrificial anodes that possess different oxidation potentials (e.g. Mg or Al) was not productive (entries 9–10).

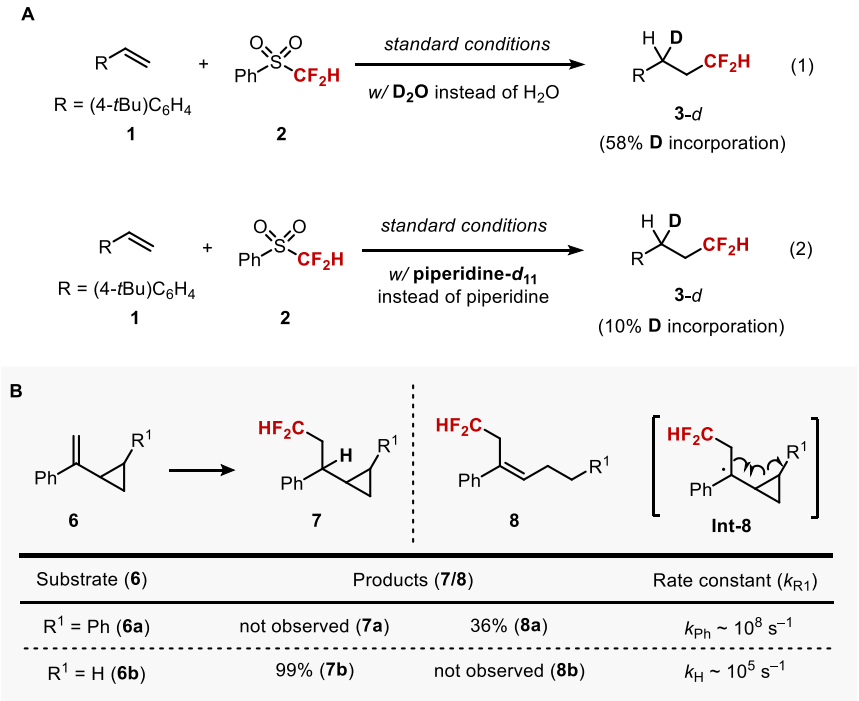


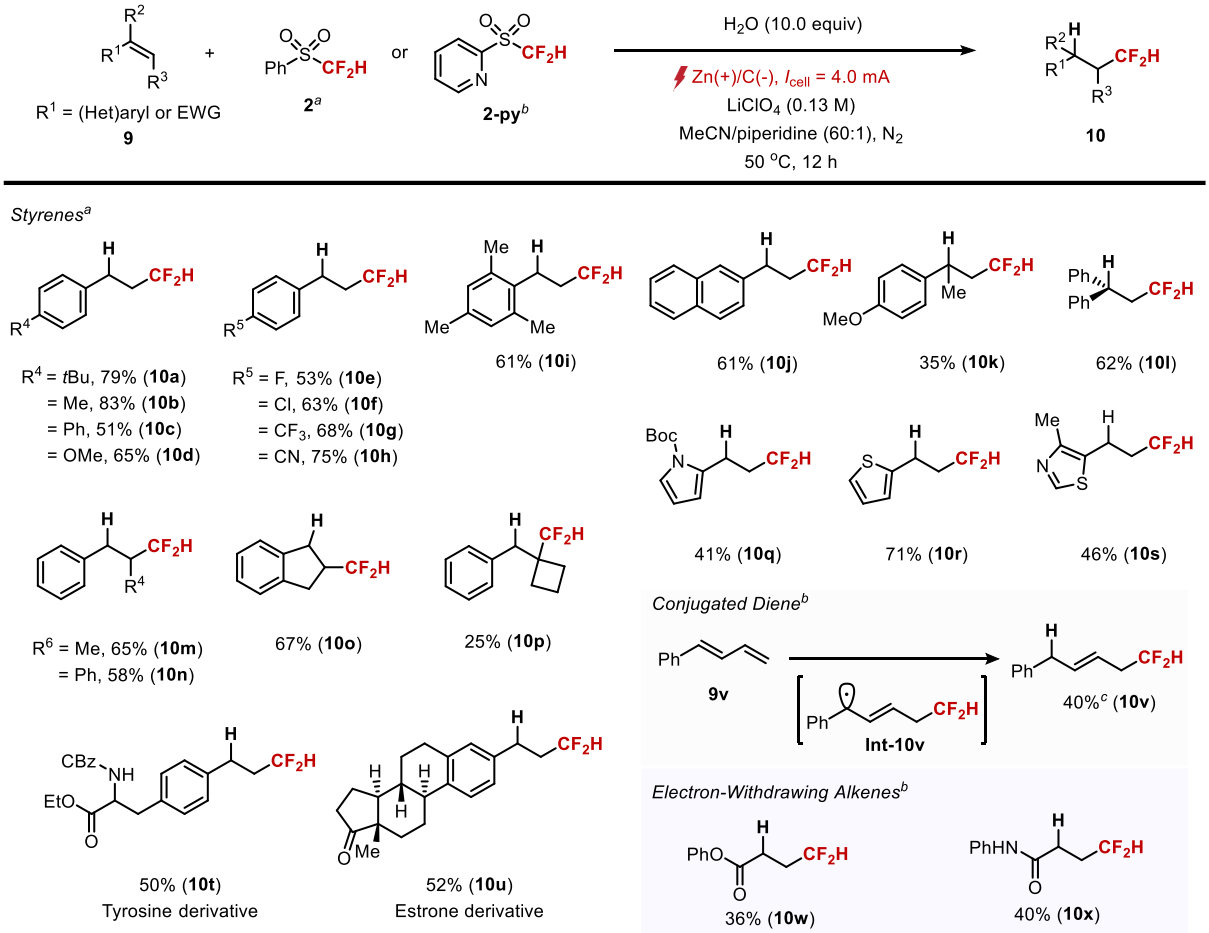
Figure 4. Preliminary Mechanistic Investigation

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 {equation (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 H atom transfer is less conceivable {equation (2)}.[74]

Further experiments using radical probe substrates were conducted (Fig 4B). Interestingly, vinyl cyclopropane **6a** with higher ring opening rate constant (k_{Ph} = ~10^8 s^{-1}) underwent rupture of the three-membered ring (**8a**), while the cyclopropyl ring in **6b** (k_H = ~10^5 s^{-1}) remained intact after electrolysis under standard conditions (**7b**).[72] 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).

Table 1. 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. Isolated yields are reported unless otherwise noted.

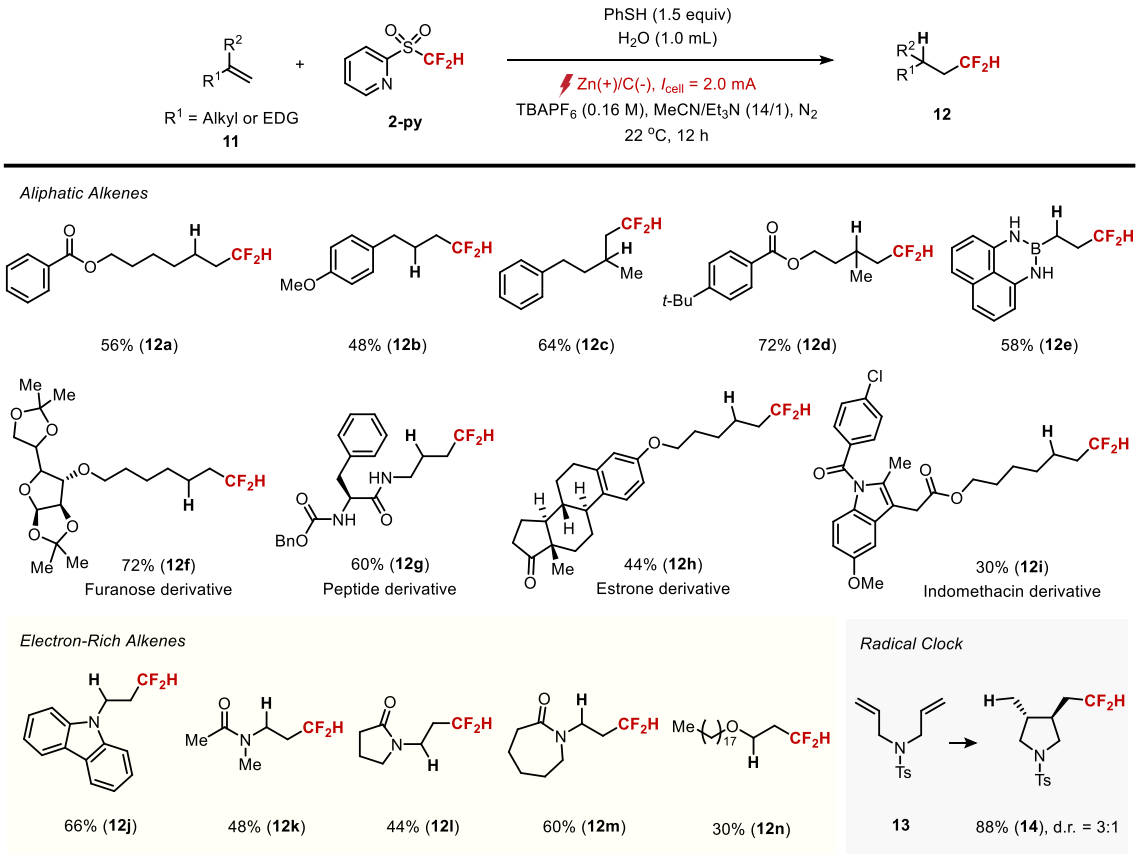
Having identified the optimized reaction parameters, we next explored the substrate scope of conjugated alkenes (Table 1). A wide range of terminal styrenes that possess functional groups such as alkyls (**10a**–**b**), phenyl (**10c**), methoxy (**10d**), halides (**10e**–**f**), trifluoromethyl (**10g**) 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 (**10m**–**p**). It was notable to see that the regioselectivity was consistent even with the trisubstituted styrene **9p**, furnishing corresponding difluoromethylated quaternary carbon center (**10p**). 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, 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 (Table 2). 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 $TBAPF_6$ 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.

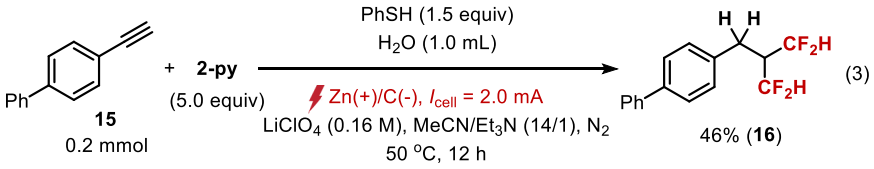
Table 2. Substrate Scope of Aliphatic and Electron-Rich Alkenes[a]



[a]**11** (0.2 mmol), **2-py** (0.6 mmol), $TBAPF_6$ (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.

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 monosubstituted (**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.

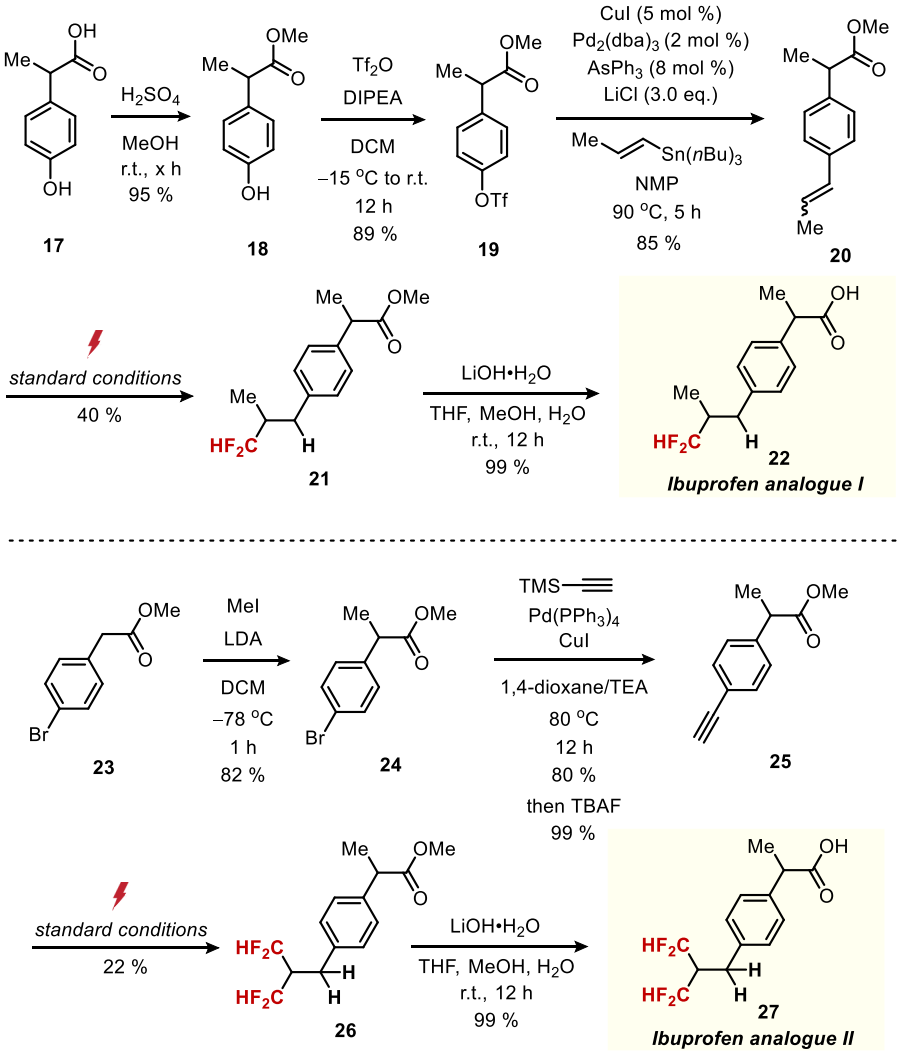


As a logical extension, we envisioned the development of a novel platform for the regioselective consecutive hydrodifluoromethylation of alkynes based on the fact that the hydrocarbons bearing two difluoromethyl groups remain rare but should possess unique properties for drug discovery. Indeed, the ability 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 ^{o}C and $LiClO_4$ as the electrolyte under otherwise identical conditions to the aliphatic alkene hydrodifluoromethylation reaction, successfully generating a geminal bis-difluoromethylation product **16** on terminal position as a single regioisomer {equation (3)}. We assumed that the first hydrodifluoromethylation proceeds via HAT of difluoromethylated vinyl radical intermediate, while the second reaction proceeds presumably via a radical-polar crossover mechanism driven by aryl substituents of the employed alkynes (Fig S7).

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 (Scheme 1).[75-76] 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).



Scheme 1. Synthesis of CF_2H Analogues of Ibuprofen.

Notably, the newly 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.

Methods

Detailed information of experimental procedures as well as analytical data are provided in the Supplementary Information.

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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.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper.

Competing financial interests

The authors declare no competing financial interests.