Letter

Catalytic Hydrodifluoroalkylation of Unactivated Olefins

Wen-Jun Yue, Craig S. Day, Adrian J. Brenes Rucinski, and Ruben Martin*

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ABSTRACT: Herein, we report a modular catalytic technique that streamlines the preparation of *gem*-difluoroalkanes from unactivated sp^3 precursors. The method is characterized by its simplicity, generality, and site selectivity, including the functionalization of advanced intermediates and olefin feedstocks. Our approach is enabled by a cooperative interplay of halogen- and hydrogen-atom transfer, thus offering a new entry point to difluorinated alkyl bioisosteres of interest in drug discovery.
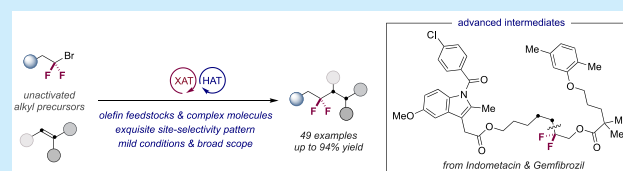
The incorporation of difluoroalkyl groups into hydrocarbon side chains has gained considerable momentum in drug discovery, as these fragments offer different solubility, acidity, molecular shape, and substrate recognition to their parent nonfluorinated sp^3 hybridized analogues (Scheme 1).[1−5]
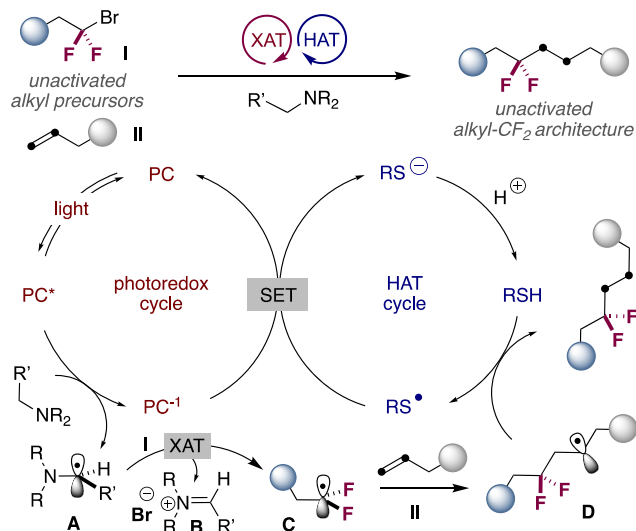
In recent years, a variety of methods have been described for preparing *gem*-difluoroalkanes by using particularly activated precursors adjacent to arenes or carbonyl compounds.[6,7]

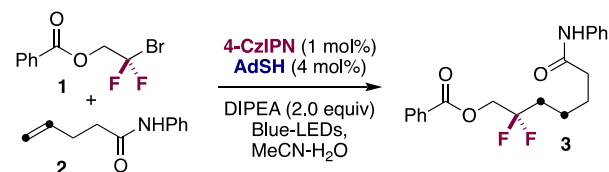## Scheme 1. Catalytic Hydrodifluoroalkylation of Olefins
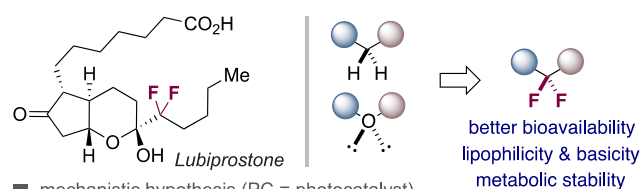
Scheme 2. Optimization of the Reaction Conditions[a]

entry	deviation standard conditions	3 (%)[b]
1	none	92 (89[c])
2	*fac*-Ir(ppy)₃PF₆	78
3	Ir(dFCF₃ppy)₂(dtbbpy)PF₆	85
4	NEt₃ instead of DIPEA	60
5	ⁿBu₃N instead of DIPEA	73
6	PhNMe₂ instead of DIPEA	0
7	HSCH₂CO₂Me instead of AdSH	39
8	HSSiPh₃ instead of AdSH	35
9	PhMe as solvent (Dioxane)	41 (42)
10	No 4CzIPN	12
11	No DIPEA (No light)	0 (0)
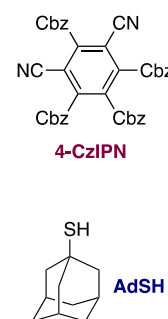
[a]**1** (0.20 mmol), **2** (0.10 mmol), 4-CzIPN (1 mol %), DIPEA (0.20 mmol), AdSH (4 mol %), CH₃CN (1.0 mL) and H₂O (0.1 mL) at 20 °C for 24 h. [b]¹⁹F NMR yields using 3-Nitro-fluorobenzene as internal standard. [c]Isolated yield.

However, the synthesis of *unactivated* $C(sp^3)$−CF_2 architectures is not as commonly practiced as one might initially anticipate.[8] Indeed, these scaffolds are typically obtained (a) via difluorination of carbonyls under harsh conditions with strong acids and/or oxidants or (b) by using stoichiometric

Scheme 3. Catalytic Hydrodifluoroalkylation of Unactivated Olefins with Difluorinated Bromoalkanes[a,b]
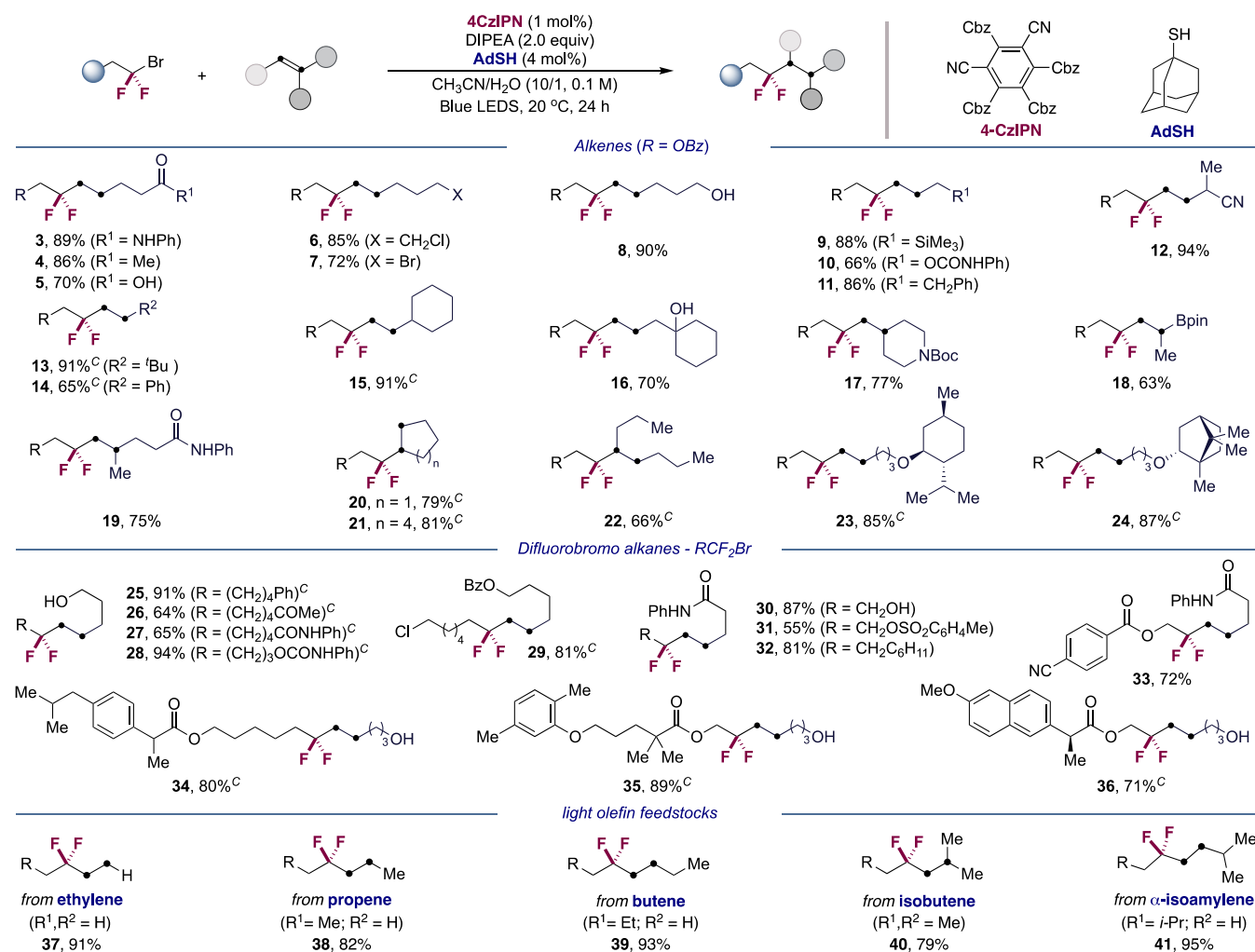
[a]Reaction conditions: as for Scheme 2, entry 1. [b]Isolated yields, average of two independent runs. [c]Olefin (3.0 equiv).

Lewis acids or organometallics.[9−11] In contrast, catalytic hydrodifluoroalkylation of *unactivated* olefins and difluoroalkyl motifs devoiding act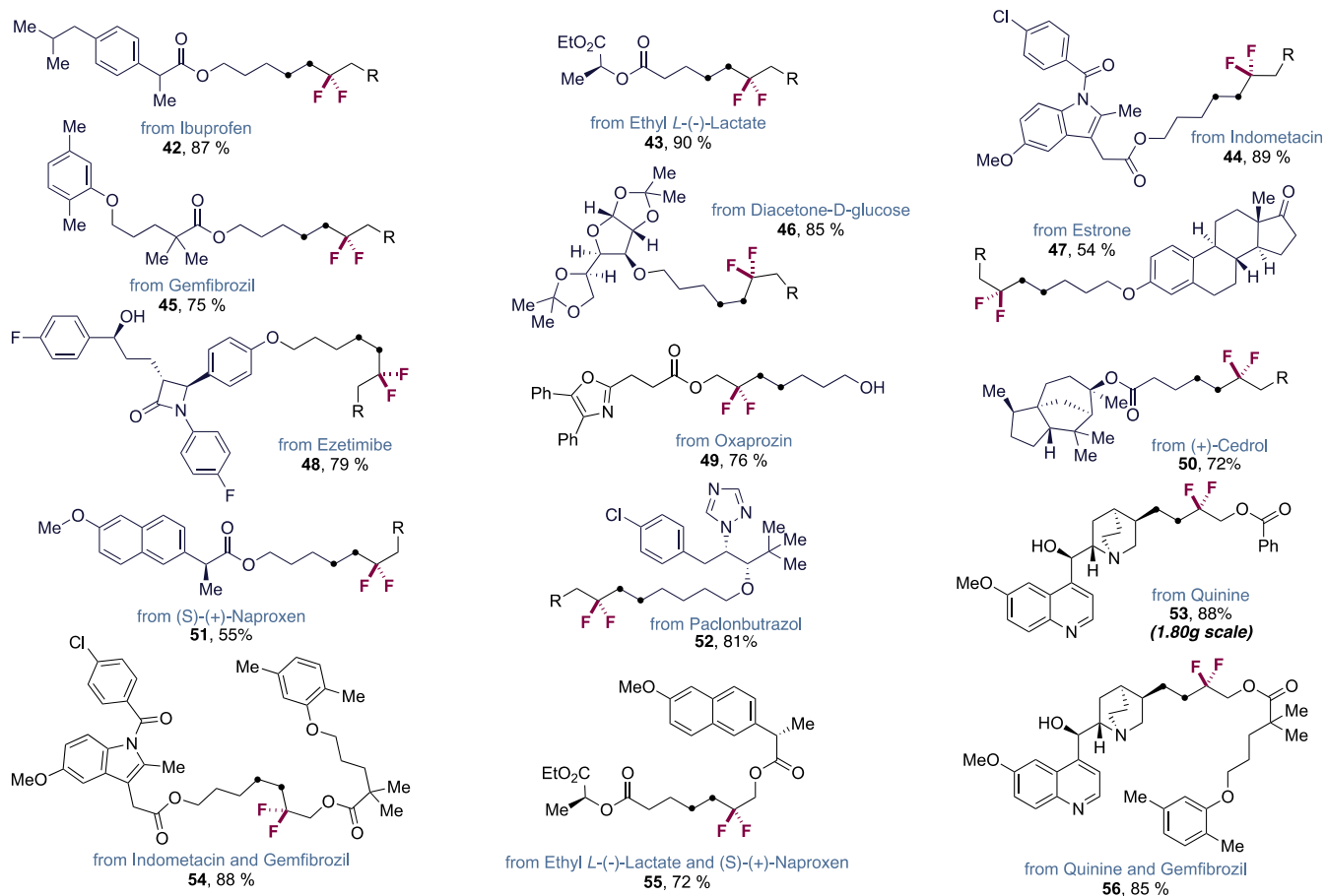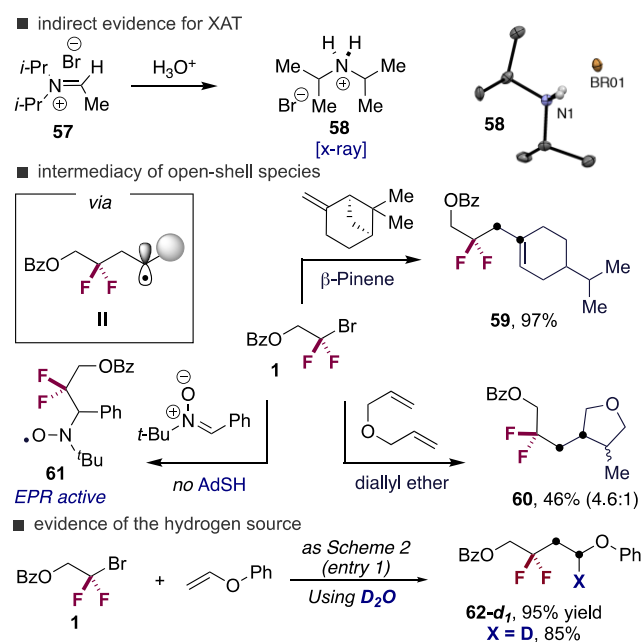ivating neighboring groups, and/or stoichiometric organometallic reagents, still remains a particularly challenging, yet highly rewarding, scenario due to the inherent propensity of alkyl fluorides to undergo β-fluoride elimination and/or competitive defluorination.[12−15] We hypothesized that the merger of halogen-atom transfer (XAT) and hydrogen-atom transfer (HAT) might be suited for our purposes (Scheme 1).[16] Specifically, one-electron photochemical oxidation of a tertiary amine might generate an α-amino radical (**A**) upon deprotonation, setting the scene for an XAT with an accessible, difluoro bromoalkane (RF$_2$C−Br = 69 kcal·mol$^{−1}$) prior to addition to an unactivated olefin. HAT of the resulting open-shell species **D** with an alkyl thiol (C(sp^3) S−H = 87 kcal·mol$^{−1}$) might deliver the targeted difluoroalkyl compound and a thiyl radical. Turnover could be accomplished by a final single-electron transfer (SET) with the reduced form of the photocatalyst followed by protonation of the thiolate with water, thus recovering back the propagating alkyl thiol and photocatalyst. Herein, we report the realization of this goal, culminating in a broadly applicable catalytic hydrodifluoroalkylation of *unactivated* olefins, including the use of light olefin feedstocks and advanced reaction intermediates.

Our study began by evaluating the catalytic hydrodifluoroalkylation of **1** with **2** (Scheme 2). After some experimentation, the best results were found by utilizing a combination of 4-CzIPN (1 mol %), AdSH (4 mol %), DIPEA in MeCN/H$_2$O under blue-LED irradiation, obtaining **3** in 89% isolated yield.[17] Interestingly, significant amounts of **3** were formed regardless of the redox properties of the photocatalysts employed, thus reinforcing the notion that XAT was decoupled from redox events (entries 2−3). Note, however, that the utilization of electron deficient amines failed to provide even traces of **3** (see entry 6). Evaluation of the hydrogen atom donors resulted in changes to the product ratio depending on the steric and electronic properties of the former. Indeed, the utilization of methyl thioglycolate and HSSiPh$_3$ in lieu of AdSH resulted in yields not exceeding 40%, with significant dehalogenation of **1** being observed in the crude mixtures (entry 7 and 8). Control experiments in the presence of other solvents or without photocatalyst or DIPEA resulted in a significant erosion in yield (entries 9−11).

Prompted by these results, we next focused our attention on the preparative potential of our protocol (Scheme 3). As shown, substrates containing alcohols (**8**, **16**, **25**−**28**, **30**, **34**−**36**) or carboxylic acids (**5**), which are sensitive to oxidation or prone to react with low-valent transition metals, were well

Scheme 4. Advanced Synthetic Intermediates (R = OBz)[a,b]

from Ibuprofen
42, 87 %

from Ethyl L-(-)-Lactate
43, 90 %

from Indometacin
44, 89 %

from Gemfibrozil
45, 75 %

from Diacetone-D-glucose
46, 85 %

from Estrone
47, 54 %

from Ezetimibe
48, 79 %

from Oxaprozin
49, 76 %

from (+)-Cedrol
50, 72%

from (S)-(+)-Naproxen
51, 55%

from Paclonbutrazol
52, 81%

from Quinine
53, 88%
(1.80g scale)

from Indometacin and Gemfibrozil
54, 88 %

from Ethyl L-(-)-Lactate and (S)-(+)-Naproxen
55, 72 %

from Quinine and Gemfibrozil
56, 85 %

[a]Reaction conditions: as for Scheme 2, entry 1. [b]Isolated yields, average of two independent runs.

Scheme 5. Preliminary Mechanistic Experiments[a]

■ indirect evidence for XAT

57

58
[x-ray]

58

■ intermediacy of open-shell species

via

II

β-Pinene

59, 97%

61
EPR active

no AdSH

diallyl ether

60, 46% (4.6:1)

■ evidence of the hydrogen source

1

as Scheme 2
(entry 1)
Using D₂O

62-d₁, 95% yield
X = D, 85%

[a]**58**: thermal ellipsoids drawn at 50% probability.

tolerated. In addition, olefins possessing secondary or tertiary sp^3 C−H bonds that are a priori susceptible for HAT with in situ generated **C** (Scheme 1; **15**, **17**, **23**, **24**) or activated olefins posed no problems (**14**). Although olefins containing alkyl halides might compete with **1** for XAT, this was not the case and **6**, **7**, and **29** could be obtained in good yields, providing an additional handle via cross-coupling reactions. As shown, the method displayed a good functional group tolerance in the presence of ketones (**4**, **26**), amides (**3**, **27**, **30**−**33**), carbamates (**10**, **17**, **28**), nitriles (**12**, **33**), sulfonates (**31**), boronic esters (**18**), or esters (**33**−**36**). Even substrates containing benzylic stereocenters were suitable substrates, resulting in **36** without noticeable erosion in stereochemical integrity. Ethylene, the largest-volume organic chemical with an annual production over 150 million tonnes, could be employed as an olefin precursor en route to **37** in 91% yield. Similarly other light olefin feedstocks such as propene, butene, isobutene, or α-isoamylene could be employed as substrates, obtaining the corresponding difluoroalkylated compounds **38**−**41** in excellent yields. The applicability of our protocol is further illustrated in Scheme 4. As shown, a variety of difluorinated architectures derived from Ibuprofen (**42**), ethyl L-(−)-Lactate (**43**), Indomethacin (**44**), Gemfibrozil (**45**), D-Glucose (**46**), Estrone (**47**), Ezetimibe (**48**), Oxaprocin (**49**), Naproxen (**51**), Paclonbutrazol (**52**), or Cedrol (**50**) could be prepared in good yields. The latter is particularly noteworthy given the multiple number of bridged carbon stereocenters

susceptible to ring-opening, racemization, and the presence of tertiary alkyl sp^3 C−H bonds suited for competitive HAT. Likewise, heterocycles did not interfere (**44**, **48**, **49**, **52**, **53**, **54**, **56**). Indeed, Quinine—a priori susceptible to Minisci addition into the pyridine backbone with alkyl radical intermediates—could be coupled in good yield, and on a large scale (**53**). Even the combination of two bioactive molecules possessing an alkene and difluorinated backbone could be within reach, enabling the rapid and reliable formation of **54**−**56**.[18]

Although unravelling the mechanism of our catalytic difluoroalkylation should await further investigations, we decided to conduct experiments that might support the mechanistic interpretation depicted in Scheme 1. Indirect evidence for XAT between **A** and **I** could be gathered by the isolation of **58**—the identity of which was univocally confirmed by X-ray crystallography—that likely arises from hydrolysis of **57** (Scheme 5).[17] The intermediacy of open-shell species of type **II** was indirectly corroborated by radical-clock experiments with both β-pinene and diallyl ether, resulting in **59** and **60** as the only observable products. In line with this notion, EPR spectroscopy revealed the presence of nitroxide-based persistent radicals **61** upon exposure of **1** to spin-trapping *N-tert*-butyl-α-phenylnitrone (PBN). Next, we conducted isotope-labeling studies with D_2O, **1**, and phenyl vinyl ether.[19] Full deuteration of **62** was anticipated for a mechanism consisting of HAT from AdSH whereas an erosion in deuterium content might be expected with DIPEA competing with AdSH as the hydrogen atom donor. This was indeed the case, and 85% deuterium incorporation was found in **62-d_1**.[20,21]

In summary, we report a mild and modular catalytic strategy for accessing difluoroalkanes from simple unactivated olefins. By leveraging the merger of halogen-atom transfer with the appropriate radical philicities and hydrogen-atom donors, a reliable and rapid access to a broad range of alkyl difluoroalkanes can be within reach. The transformation is distinguished by its exquisite chemoselectivity pattern and broad utility across a wide variety of coupling partners, including the application to densely functionalized intermediates and light olefin feedstocks. We anticipate that this technique might find immediate utility for expediting access to valuable sp^3 fluorinated architectures.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01941.

    Experimental procedures, spectral and crystallographic data (PDF)

Accession Codes

CCDC 2122288 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(17) See Supporting Information for details.

(18) The utilization of difluoroalkanes in lieu of difluorobromoalkenes resulted in no conversion to the targeted difluoroalkane products.

(19) Phenyl vinyl ether was chosen as substrate for its convenience due to its simple ^{1}H NMR spectrum.

(20) A bathochromic shift was observed upon exposure of **1** and DIPEA, reinforcing the notion that an electron-donor acceptor complex may assist the fragmentation of **1**. However, it is currently not clear whether or not this has an enhanced effect on quenching the excited state of the photocatalyst

(21) The quantum yield (Φ) was found to be 0.06. For other mechanistic experiments, see ref 17.