Catalytic Hydrodifluoroalkylation of Unactivated Olefins

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

ABSTRACT: Herein, we report a modular catalytic technique that streamlines the preparation of gem-difluoroalkanes from unactivated \( \text{sp}^3 \) 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 \( \text{sp}^3 \) hybridized analogues (Scheme 1).

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. However, the synthesis of unactivated C(\( \text{sp}^3 \))−CF\(_2\) architectures is not as commonly practiced as one might initially anticipate. 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...
Lewis acids or organometallics. In contrast, catalytic hydrodifluoroalkylation of unactivated olefins and difluoroalkyl motifs devoiding activating 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. We hypothesized that the merger of halogen-atom transfer (XAT) and hydrogen-atom transfer (HAT) might be suited for our purposes (Scheme 1).

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 (RF₂Br = 69 kcal·mol⁻¹) prior to addition to an unactivated olefin. HAT of the resulting open-shell species D with an alkyl thiol (C(sp³)S⁻H = 87 kcal·mol⁻¹) might deliver the targeted difluoroalkyl compound and a thiy 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/H₂O under blue-LED irradiation, obtaining 3 in 89% isolated yield. 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 HSSiPh₃ 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 3. Catalytic Hydrodifluoroalkylation of Unactivated Olefins with Difluorinated Bromoalkanes

| Reaction conditions: as for Scheme 2, entry 1. | Isolated yields, average of two independent runs. |
|-----------------------------------------------|-----------------------------------------------|
| **Olefin (3.0 equiv).**                      |                                               |

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tolerated. In addition, olefins possessing secondary or tertiary sp³ 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), Oxpreno (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

Scheme 4. Advanced Synthetic Intermediates (R = OBz)α,b

Scheme 5. Preliminary Mechanistic Experimentsα

α58: thermal ellipsoids drawn at 50% probability.
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.

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 S8—the identity of which was univocally confirmed by X-ray crystallography—that likely arises from hydrolysis of S7 (Scheme 5). The intermediacy of open-shell species of type II was indirectly corroborated by radical-clock experiments with both \( \beta \)-pinene and diallyl ether, resulting in S9 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-\( \alpha \)-phenyl nitronitrone (PBN). Next, we conducted isotope-labeling studies with D\(_2\)O, 1, and phenyl vinyl ether. 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\(_4\)).

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 may 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 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.

AUTHOR INFORMATION

Corresponding Author

Ruben Martin − Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; ICREA, 08010 Barcelona, Spain; orcid.org/0000-0002-2543-0221; Email: rmartinromo@iciq.es

Authors

Wen-Jun Yue − Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Universitat Rovira i Virgili, Departament de Química Analítica i Química Orgànica, 43007 Tarragona, Spain

Craig S. Day − Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Universitat Rovira i Virgili, Departament de Química Analítica i Química Orgànica, 43007 Tarragona, Spain

Adrian J. Brenes Rucinski − Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Universitat Rovira i Virgili, Departament de Química Analítica i Química Orgànica, 43007 Tarragona, Spain

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acs.orglett.2c01941

Notes

The authors declare no competing financial interest.

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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 ($\Phi$) was found to be 0.06. For other mechanistic experiments, see ref 17.