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Catalytic Difluorination of Olefins

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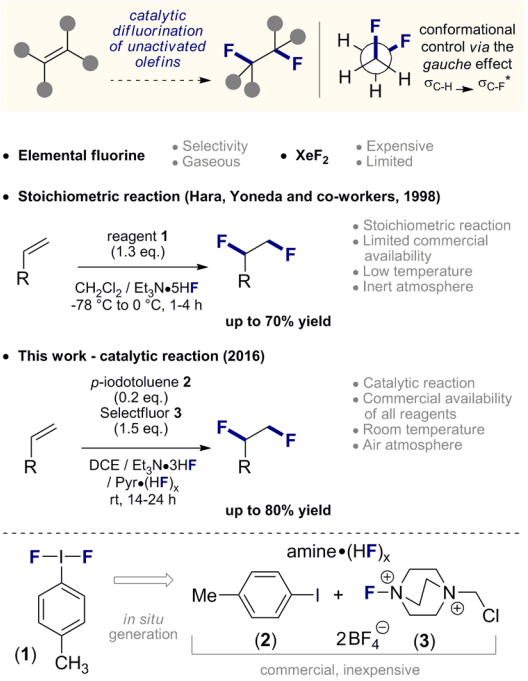
Supporting Information

ABSTRACT: Molecular editing with fluorine is a validated strategy for modulating the structure and function of organic systems. In the current arsenal of catalytic dihalogenation technologies, the direct generation of the vicinal difluoride moiety from simple olefins without a prefunctionalization step remains conspicuously absent. Herein we report a catalytic, vicinal difluorination of olefins displaying broad functional group tolerance, using inexpensive *p*-iodotoluene as the catalyst. Preliminary efforts toward the development of an enantioselective variant are also disclosed.

Of the plethora of strategies employed to synthesize and modulate function at the molecular level, structural editing by fluorine insertion has emerged as one of the most expansive.[1] Routinely exploited in the design of novel materials,[2] chemical biology tools,[3] and catalysts,[4] the strength of fluorination lies in the ability to induce localized polarity inversion [$H^{\delta+} \rightarrow F^{\delta-}$], while unfavorable steric interactions are mitigated. This unique balance of low van der Waals radius and high electronegativity renders fluorinated organic materials inimitable in their structural behavior. In the absence of overriding steric factors, the low-lying antibonding orbital of the C−F bond (σ_{C-F}^*) can participate in stabilizing hyperconjugative interactions with π-systems, nonbonding electron pairs, or vicinal, electron-rich sigma bonds; this latter scenario is exemplified by the stereoelectronic gauche effect (Scheme 1, upper).[4a,5] Inherent to vicinal difluoride units, this counterintuitive effect aligns the fluorine atoms in a syn-clinal (φ_{FCCF} = 60°) conformation, as a consequence of reinforcing hyperconjugative interactions ($\sigma_{C-H} \rightarrow \sigma_{C-F}^*$).[5] Since the remaining substituents are necessarily positioned in a predetermined spacial arrangement, this effect has found application in molecular design.[5b] Moreover, the relative orientation of the C−F bond vectors themselves can be employed to modulate the physicochemical properties of small molecules, as a recent comparison of vicinal versus geminal difluorination has demonstrated.[6] The influence of fluorination pattern on physical properties is even more pronounced in the multivicinal fluoroalkanes $(CHF)_n$.[7] By telescoping the 1,2-difluoroethylene substructure, linear hydrocarbon-Teflon hybrids are generated where the overall conformation can be encoded by the relative stereochemical relationship. These well-defined diastereomers differ from the parent hydrocarbon only in polarity and conformation. Evaluating the, often unprecedented, physical properties of these and related materials[8] is complicated by challenging synthesis campaigns, often requiring multiple deoxofluorination steps. This reliance on deoxofluorination chemistry, coupled with the risk of competing elimination processes render the syntheses challenging, despite being preparatively more attractive than strategies utilizing XeF_2[9] or elemental fluorine (Scheme 1, center).[10]

Scheme 1. Development of a Catalytic, Vicinal Difluorination of Unactivated Olefins



The importance of fluorine incorporation as an editing strategy, together with the emergent interest in more densely fluorinated systems for fundamental research, has led to explosive growth in catalytic fluorination technologies. In particular, aryl $C(sp^2)$−F bond formation has matured at an astonishing pace,[11] and elegant processes to permit direct $C(sp^3)$−H fluorination have been disclosed.[12] However, to the best of our knowledge, the direct generation of vicinal difluoroalkanes in a catalytic paradigm remains conspicuously absent. We therefore questioned the feasibility of developing a vicinal difluorination of olefins under catalyst control (Scheme 1, lower) to complement the existing protocols for dichlorination and dibromination.[13] In 1998, a communication by Hara, Yoneda, et al. disclosed the vicinal difluorination of monosubstituted olefins and a single example of a disubstituted, system using stoichiometric *p*-iodotoluene difluoride (**1**) and $Et_3N{\cdot}5HF$.[14] In view of this

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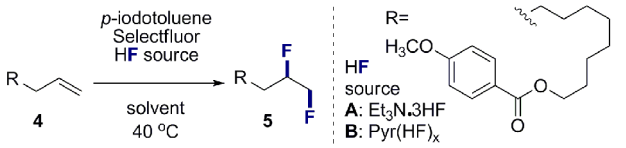
seminal study, and the rapid growth of hypervalent iodine in catalysis, we envisaged the development of a catalytic process based on the *in situ* generation of **1** from commercially available *p*-iodotoluene (**2**).[15] A study by Shreeve et al. has established that hypervalent iodine(III) reagents can be prepared in a facile manner by treatment with Selectfluor (**3**).[16] This would minimize potential complications resulting from direct reaction of the oxidant with the olefinic substrate. Finally, several complications observed in the stoichiometric transformation would have to be circumvented. The reaction is described as being highly capricious, requiring an inert atmosphere and low temperature. Moreover, the HF composition was also reported to be critical; a fact that was further complicated by the limited commercial availability of $Et_3N{\cdot}5HF$.

Cognizant that the success of this investigation hinged on the identification of a suitable HF source, the difluorination of a model olefin bearing a pendant ester moiety was chosen as a benchmark transformation (**4** → **5**, Table 1). Since highly

Table 1. Identification of an Efficient HF Source and Solvent[a]



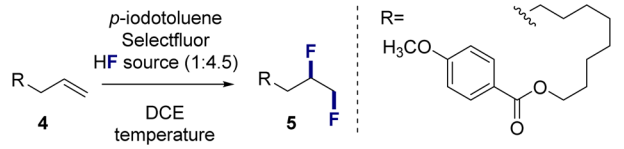
	HF source (amine:HF)[a]	solvent	time (h)	conv. (%)[b]	yield (%)[c]
1	–	DCE	14	<5	<1
2	**A** (1:3)	DCE	24	<5	<1
3	**B** (1:9.23)	DCE	14	>95	19
4	**A**+**B** (1:3.5)	DCE	14	15	11
5	**A**+**B** (1:4)	DCE	14	72	66(55)
6	**A**+**B** (1:4)	DCE	24	76	66(53)
7	**A**+**B** (1:4.5)	DCE	14	>95	89(76)
8	**A**+**B** (1:5)	DCE	14	>95	87(75)
11[d]	**A**+**B** (1:4.5)	DCE (dry)	14	>95	87(72)
12	**A**+**B** (1:4.5)	DCM	14	>95	84(73)
13	**A**+**B** (1:4.5)	MeCN	14	80	17
14	**A**+**B** (1:4.5)	THF	14	<5	<1

[a]General reaction conditions: alkene (0.20 mmol), *p*-iodotoluene (0.04 mmol), solvent (1.0 mL), HF source (0.5 mL), and Selectfluor (0.30 mmol) in a 50 mL screw-cap PP vial at 40 °C for the indicated time. A: Triethylamine trihydrofluoride and B: Olah's reagent (calculated amine to HF ratio in parentheses). [b]Determined by ^{1}H NMR from the crude reaction mixture using ethyl fluoroacetate as internal standard. [c]^{19}F NMR yield determined from the crude reaction mixture using ethyl fluoroacetate as internal standard (isolated yield in parentheses). [d]Performed with anhydrous DCE and under an argon atmosphere.

electron-rich olefins are known to undergo direct reaction with Selectfluor,[17] and I(III)-mediated fluorination often elicits rearrangements in such systems,[18] this investigation focused on unactivated, terminal olefin feedstocks. Commercially available $Et_3N{\cdot}3HF$ and $Pyr(HF)_x$ were examined as reagent and cosolvent and are referred to as sources A and B, respectively, in Table 1. Mixtures of these reagents are described in terms of the combined amine:HF ratio (amine = Et_3N + pyridine).[19] Initially, dichloroethane (DCE) was used as the solvent with Selectfluor (1.5 equiv) as oxidant and *p*-iodotoluene as the organocatalyst (20 mol %). Reactions were performed at 40 °C with the HF source as a cosolvent for the time indicated and monitored by ^{19}F NMR spectroscopy. The control study, in which the reaction was attempted in the absence of the HF source, led to <5% conversion after 14 h (entry 1). This finding was again observed when using only $Et_3N{\cdot}3HF$ (A) (entry 2). Switching to Olah's reagent $Pyr(HF)_X$ (B, 70% w/w) resulted in almost quantitative consumption of the olefin as determined by ^{1}H NMR spectroscopy with an internal standard (entry 3). However, ^{19}F NMR analysis with ethyl fluoroacetate as the internal standard indicated that the desired product was present in only 19% yield. Varying the mixture of reagents A and B proved to have a remarkable effect on the reaction efficiency, as indicated in entries 4−14. Systematically increasing the ratio of HF relative to the amine revealed 1:4.5 to be optimal (entry 7). Using additional HF did little to improve the transformation, and applying this protocol, it was possible to isolate the desired difluoride in 76% yield (89% by ^{19}F NMR). This subtle balance between HF content and yield is fully in line with the observations by Hara et al. regarding the role of HF as a Brønsted acid activator.[14,20]

Having identified suitable conditions to effect this transformation, the influence of modifying reaction parameters was studied (**4** → **5**, Table 2). Of particular importance was the need

Table 2. Optimization of Concentration and Temperature[a]



	solvent:HF source	conc. (mmol/mL)	temp. (°C)	conv. (%)[b]	yield (%)[c]
1	2:1	0.133	40	>95	89(76)
2	2:1	0.133	rt	75	69(61)
3[d]	2:1	0.133	0	24	22(19)
4[e]	2:1	0.133	rt	75	68(59)
5	1:1	0.1	rt	>95	86(76)
6	1:1	0.2	rt	>95	89(75)
7	1:1	0.4	rt	65	58(50)
8[f]	1:1	0.2	rt	>95	89(76)

[a]General reaction conditions: alkene (0.20 mmol), *p*-iodotoluene (0.04 mmol), DCE (0.5 mL), HF source (0.5 mL, amine:HF ratio =1:4.5), and Selectfluor (0.30 mmol) in a 50 mL screw-cap PP vial at the indicated temperature for 14 h. [b]Determined by ^{1}H NMR from the crude reaction mixture using ethyl fluoroacetate as internal standard. [c]^{19}F NMR yield determined from the crude reaction mixture using ethyl fluoroacetate as internal standard (isolated yield in parentheses). [d]Reaction time: 24 h. [e]30 mol % catalyst applied. [f]In a ∼15 mL screw-cap Teflon reaction vessel.

to identify conditions in which the reaction would proceed at ambient temperature. Initially, the concentration was fixed at 0.133 M, and the effects of temperature variations were studied (entries 1−4). Immediately evident was the erosion of reaction efficiency at lower temperatures, and that increasing the catalyst loading was ineffective (cf. entries 2 and 4). However, by fixing the solvent to HF ratio at 1:1, it was possible to obtain the desired product in good yield, irrespective of concentration (up to 76% isolated yield). With an optimized system for catalytic difluorination based on I(I)/I(III) catalysis in hand, efforts were invested in exploring the scope and limitations of the transformation. To expedite isolation and structural analysis of the product difluorides, alkyl spacers were initially employed to

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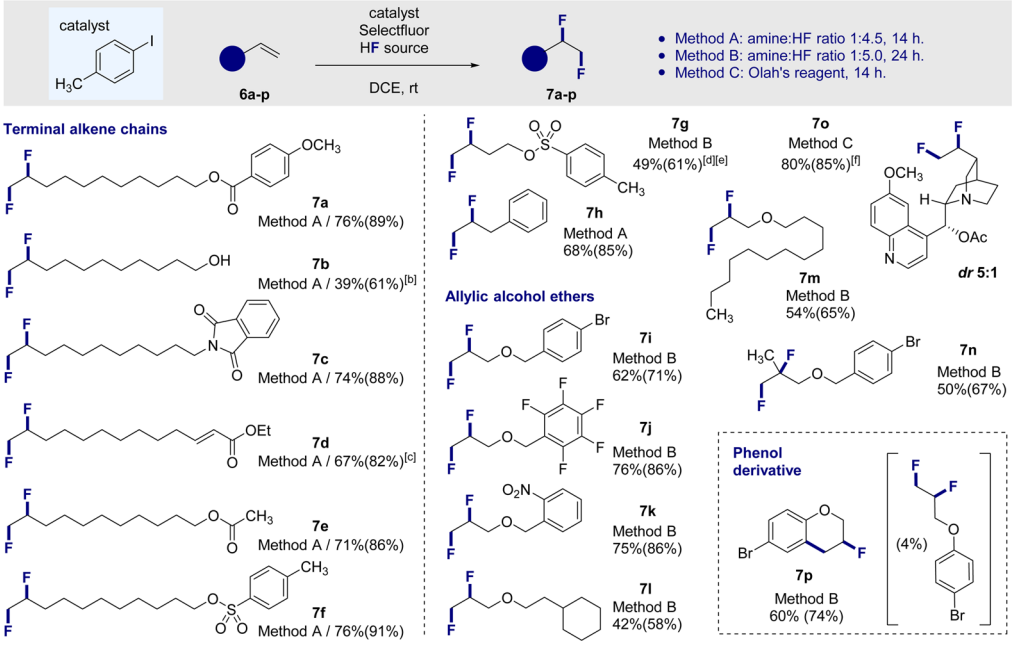
Table 3. Exploring the Substrate Scope and Functional Group Tolerance of the Title Reaction[a]

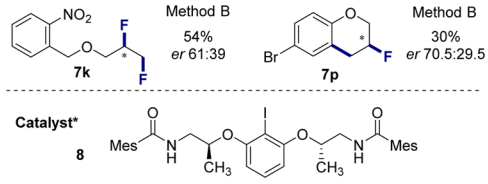


[a]General reaction conditions: The alkene (0.20 mmol), catalyst (0.04 mmol), DCE (0.5 mL), HF source (0.5 mL, ratios above), and Selectfluor (0.30 mmol) were stirred in a ~15 mL screw-cap Teflon reaction vessel at room temperature for the time indicated. Numbers refer to isolated yields. ^{19}F NMR yield in parentheses determined from the crude reaction mixture using ethyl fluoroacetate as internal standard. [b]Significant amount of homocoupled side product observed; full details in the SI. [c]Conversion 93% via ^{1}H NMR using ethyl fluoroacetate as internal standard. [d]Tosyl-migrated regioisomer isolated as major side product; full details in the SI. [e]Conversion 85% via ^{1}H NMR using ethyl fluoroacetate as internal standard. [f]Reaction performed on a 0.18 mmol scale.

separate the terminal olefin from the functional group of interest. The results are summarized in Table 3, where both isolated yields and NMR yields based on ^{19}F NMR spectroscopy (in parentheses) are provided. In contrast to existing state-of-the-art technologies for direct fluorination of olefins, these conditions were extremely well tolerated by an array of functional groups.

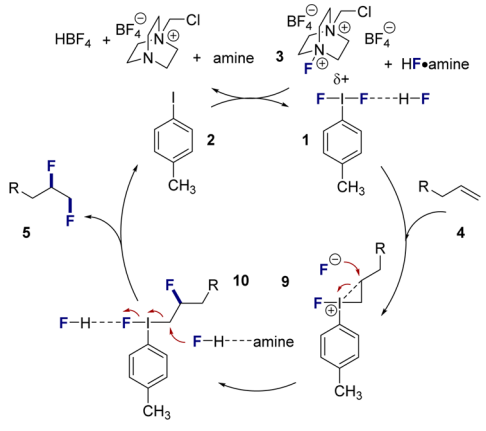
Terminal olefins proved to be viable substrates, and in addition to esters (**7a**, 76% isolated yield), it was possible to directly difluorinate in the presence of unprotected alcohols (**7b**, 39%), phthalimides (**7c**, 74% yield), α,β-unsaturated esters (**7d**, 67%), acetates (**7e**, 71%), tosylates (**7f,g**, up to 76%), and also the allylbenzene scaffold (**7h**, 68%) (Table 3). Allylic alcohol ethers could also be smoothly processed to the corresponding vicinal difluoride analogs (**7i**–**7m**) in up to 76% isolated yield (Table 3, center). It was also possible to extend this operationally simple method to include the 1,1-disubstituted ether derived from 2-methyl-2-propen-1-ol (**7n**, 50%) and acetylated quinine under forcing conditions (**7o**, *dr* 5:1, 80%). Intriguingly, attempts to difluorinate a phenol derivative generated the fluorochromane scaffold **7p** in 60% yield. In an attempt to induce enantioselectivity, the standard difluorination conditions B were repeated using the chiral, nonracemic aryl iodide derivative **8** (Scheme 2).[21] It proved difficult to drive the reaction to completion, and modest enantioselectivity was observed (**7k**, 54%, er 61:39). Albeit encouraging, this proof of concept reiterates Denmark's observation that routes to "enantioenriched vicinal dihalide products remain comparatively underdeveloped" and thus constitute an ongoing challenge in contemporary asymmetric catalysis.[13] It is interesting to note that catalyst **8** proved to be more effective in the enantioselective chromane cyclization (**7p**, er 70.5:29.5). Consistent with previous

Scheme 2. Towards an Enantioselective Difluorination



mechanistic hypotheses pertaining to the stoichiometric variant, it seems reasonable that product formation (**4** → **5**) is the result of two discrete C(sp^3)–F bond-forming processes (Scheme 3).[13a,14] *In situ* generation of the aryliodonium difluoride **1** and engagement of the olefin substrate **4** generate a transient cation (**9**). This facilitates an activation–displacement sequence via

Scheme 3. Tentative Mechanistic Proposal



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intermediates **9** and **10** to generate the vicinal difluoride system **5** with regeneration of **2**, thereby completing the catalytic cycle. The postulated intermediacy of cation **10** is further supported by the intramolecular cyclization to generate the fluorinated chromane **7p**.

In summary, an operationally simple catalytic vicinal difluorination of simple olefins is reported using inexpensive, commercially available reagents. It is envisaged that this expansion of the catalyst-based dihalogenation arsenal to include 1,2-difluorination will accelerate interrogation of more stereochemically complex organofluorine systems[22] and inspire the design of enantioselective variants.[23] Efforts to expand the substrate scope are ongoing and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01183.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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