Communication

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Catalytic Difluorination of Olefins

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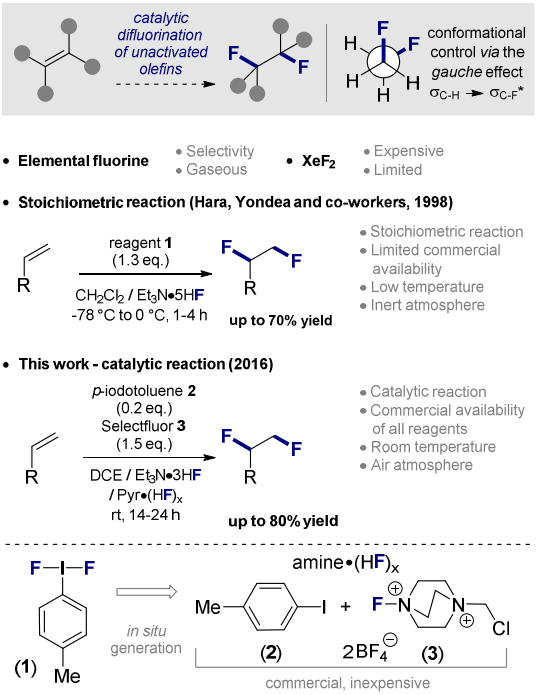
Supporting Information Placeholder

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 1,2-difluoroethylene moiety from simple olefins without a pre-functionalization 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 towards 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 [$H^{\delta+}\rightarrow F^{\delta-}$], whilst unfavourable 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 ($\sigma_{C\text{-}F}$*) can participate in stabilizing hyperconjugative interactions with π-systems, non-bonding 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 1,2-difluoroethylene units, this counterintuitive effect aligns the fluorine atoms in a *syn-clinal* ($\phi_{FCCF} = 60^{\circ}$) conformation, as a consequence of reinforcing hyperconjugative interactions ($\sigma_{C\text{-}H}\rightarrow\sigma_{C\text{-}F}$*).[5] Since the remaining substituents are necessarily positioned in a pre-determined 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 can be 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]

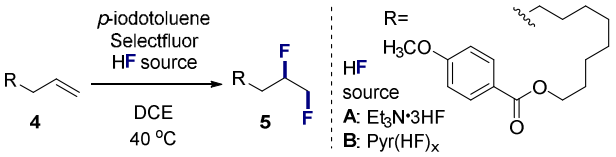
Scheme 1. Development of a catalytic, vicinal difluorination of unactivated olefins.



The general reliance on 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 and co-workers disclosed the vicinal difluorination of monosubstituted olefins, and a single example of a disubstituted, system using stoichiometric *p*-iodotoluene difluoride (**1**) and Et_3N•5HF.[14] In view of this seminal study, and the rapid growth of hypervalent iodine in catalysis, we envisaged the development of a catalytic processes based on the *in situ* generation of **1** from commercially available *p*-iodotoluene (**2**).[15] A study by Shreeve and co-workers has established that hypervalent iodine(III) reagents can be prepared in a facile manner by treatment with Selectfluor® (**3**).[16] This would minimize potential complica-

tions 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•5HF.

Table 1. Identification of an efficient HF source and solvent.[a]

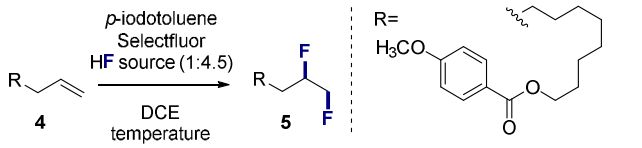


	HF source (amine:HF)[a]	Solvent	Time [h]	Conv. [%][b]	Yield [%][c]
1	-	DCE	14	<5	<1
2	**A** (1:3)	DCE	24	<5	<1
3	**B** (1:9.23)	DCE	14	>95	19
4	**A+B** (1:3.5)	DCE	14	15	11
5	**A+B** (1:4)	DCE	14	72	66(55)
6	**A+B** (1:4)	DCE	24	76	66(53)
7	**A+B** (1:4.5)	DCE	14	>95	89(76)
8	**A+B** (1:5)	DCE	14	>95	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.

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 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•3HF and $Pyr(HF)_x$ were examined as reagent and co-solvent, 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 eq.) as oxidant and *p*-iodotoluene as the organocatalyst (20 mol%). Reactions were performed at 40 °C with the HF source as a co-solvent 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 the Et_3N•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 optimum (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.[20]

Table 2. Optimization of concentration and temperature.[a]

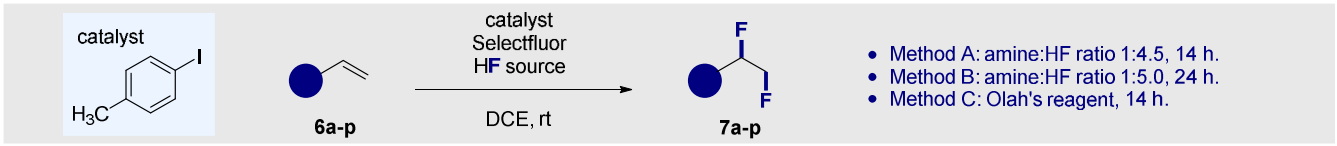


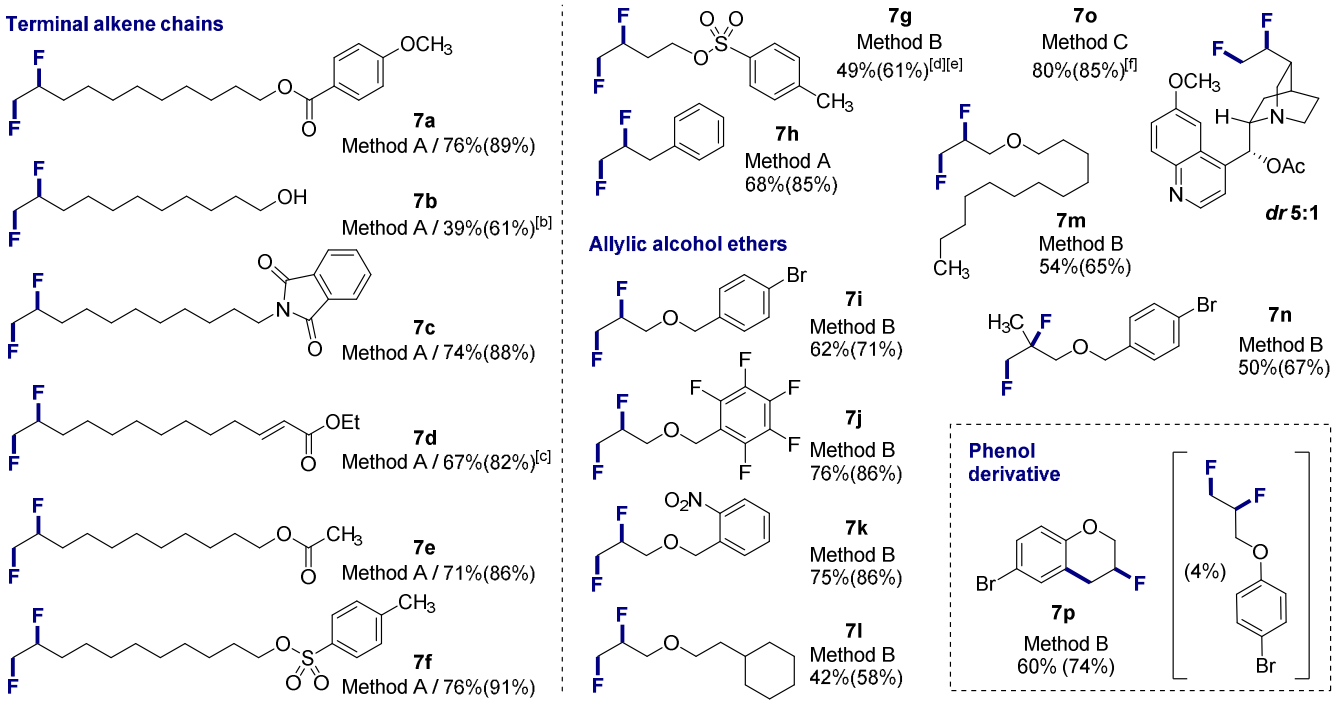
	Solvent:HF source	Conc. [mol/mL]	Temp. [°C]	Conv. [%][b]	Yield [%][c]
1	2:1	0.133	40	>95	89(76)
2	2:1	0.133	rt	75	69(61)
3[d]	2:1	0.133	0	24	22(19)
4[e]	2:1	0.133	rt	75	68(59)
5	1:1	0.1	rt	>95	86(76)
6	1:1	0.2	rt	>95	89(75)
7	1:1	0.4	rt	65	58(50)
8[f]	1:1	0.2	rt	>95	89(76)

[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 ca. 15 mL screw-cap Teflon® reaction vessel.

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 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 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 proved to be extremely well tolerated by an array of functional groups.

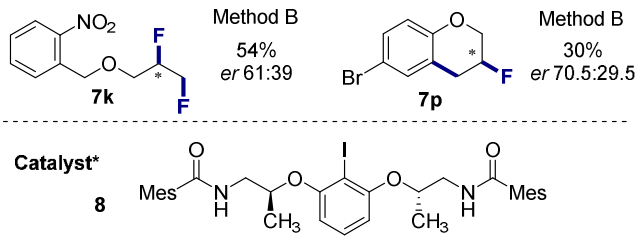
Table 3. Exploring the substrate scope and functional group tolerance of the title reaction.[a]





[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 *ca.* 15 mL screw-cap Teflon® reaction vessel at room temperature for the time indicated. Numbers refer to isolated yield. (^{19}F NMR yield in parentheses determined from the crude reaction mixture using ethyl fluoroacetate as internal standard). [b] Significant amount of homo-coupled 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.

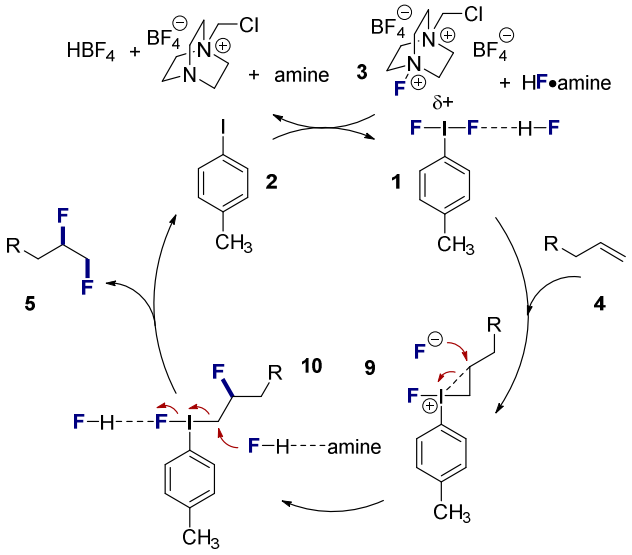
Scheme 2. Towards an enantioselective difluorination.



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 difluoroethylene 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, attemptes to difluorinated 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, non-racemic 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 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** generates a transient cation (**9**). This facilitates an activation - displacement sequence via intermediates **9** and **10** to generate the 1,2-difluoroethylene system **5** with regeneration of **2**, thereby completing the catalytic cycle. The postulated intermediacy of cation **9** 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.

Scheme 3. Tentative mechanistic proposal.



ASSOCIATED CONTENT

Supporting Information

NMR spectra and experimental procedures. Supporting information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

Author Contributions

All authors have given approval to the final version of the manuscript.

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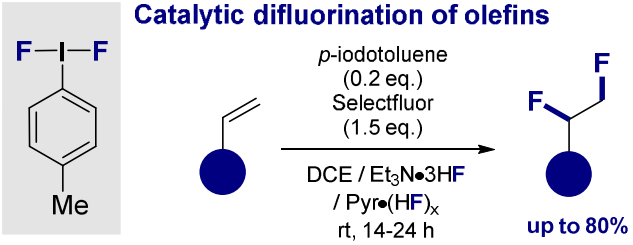
REFERENCES

(1) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197-201.
(2) (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun*. **2007**, 1003-1022; (b) Nair, R. R; Ren, W.; Jalil, R.; Riaz, I. ; Kravets,V. G.; Britnell, l.; Blake, P.; Schedin, F.; Mayorov, A. S.; Yuan, S.; Katsnelson, M. I.; Cheng, H.-M.; Strupinski, W.; Bulusheva, L. G.; Okotrub, A. V.; Grigorieva, I. V.; Grigorenko, A. N.; Novoselov, K. S.; Geim, A. K. *Small* **2010**, *6*, 2877–2884.
(3) (a) Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358–6383; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320-330.
(4) (a) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed*. **2011**, *50*, 11860-11871 (b) Cahard, D.; Bizet, V. *Chem. Soc. Rev*. **2014**, *43*, 135-147.
(5) (a) Wolfe, S. *Acc. Chem. Res*. **1972**, *5*, 102-111. (b) O'Hagan, D. *Chem. Soc. Rev*. **2008**, *37*, 308-319.
(6) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem*. **2015**, *58*, 9041-9060.
(7) For selected examples see (a) O'Hagan, D. *J. Org. Chem.* **2012**, *48*, 5247-4249. (b) Hunter, L.; Kirsch, P.; Slawin, A. M. Z.; O'Hagan, D. *Angew. Chem. Int. Ed*. **2009**, *48*, 5457-5460. (c) Hunter, L; O'Hagan, D. *Org. Biomol. Chem*. **2008**, *6*, 2843-2848. (d) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc*. **2005**, *127*, 482-483.
(8) All-*cis* 1,2,3,4,5,6-hexafluorocyclohexane, is reported to have the largest dipole moment of any organic material Keddie, N.; Slawin, A. M. Z.; Lebl, T.; Philp, D.; O'Hagan, D. *Nat. Chem*. **2015**, *7*, 483-488.
(9) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605-6634.
(10) Sandford, G. *J. Fluorine Chem.* **2007**, *128*, 90-124.
(11) (a) Cook, A.; Sanford, M. S. C-Hal Bond Formation by Arene C-H Activation. In *Catalytic Transformations via C-H Activation, Vol. 2; Science of Synthesis*, Yu, J.-Q., Ed.; Thieme, **2015**, 183–219; (b) McMurtrey, K. B.; Sanford, M. S. C-F Bond-Forming Reactions. In *Cross-Coupling and Heck-Type Reactions from the Science of Synthesis Reference Library. Vol. 2,* John P. Wolfe, Ed., Thieme, **2012**, 551–565*;* (c) Campbell, M.; Ritter, T. *Chem. Rev*. **2015**, *115*, 612–633.
(12) (a) Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. *J. Am. Chem. Soc.* **2014**, *136*, 9780–9791; (b) Bloom, S.; Knippel, J. L.; Lectka, T. *Chem. Sci.* **2014**, *5*, 1175–1178; (c) Pitts, C. R.; Bloom, M. S.; Bume, D. D.; Zhang, Q. A.; Lectka, T. *Chem. Sci.* **2015**, *6*, 5225–5229.
(13) (a) For an excellent review see Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E. *Angew. Chem. Int. Ed*. **2015**, *54*, 15642-15682; (b) Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. *Nat. Chem*. **2015**, *7*, 146-152; (c) For examples of enantioselective vicinal halogenation of allylic alcohols see Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134-8137 (chlorination); Hu, D. X.; Shibuya, G. M.; Burns, N. Z. *J. Am. Chem. Soc*. **2013**, *135*, 12960-12963 (bromination); (d) For I(II)-catalyzed dichlorination and dibromination see Stodulski, M.; Goetzinger, A.; Kohlhepp, S. V.; Gulder, T. *Chem. Commun*. **2014**, *50*, 3435-3438.
(14) Hara, S.; Nakahigashi, J.; Ishi-I, K.; Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *Synlett* **1998**, 495-496. Also see Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *J. Fluorine Chem*. **2000**, *104*, 277-280.
(15) For the discovery of aryliodonium(III) difluorides see Weinland, R. F.; Stille, W. *Chem. Ber*. **1901**, *34,* 2631-2633. Also see Edmunds, J. J.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.,* **1989**, 881-883. For a review on hypervalent iodine chemistry see Wirth, T. *Angew. Chem. Int. Ed*. **2005**, *44*, 3656-3665.
(16) For a facile synthesis of hypervalent iodine(III) reagents using Selectfluor® see Ye, C.; Twamley, B.; Shreeve, J. M. *Org Lett*. **2005**, *7*, 3961-3964.
(17) Selectfluor® can react directly with highly electron rich substrates. See Lal, G. S. J. *Org. Chem*. **1993**, *58*, 271-2796.
(18) For a recent example of the hypervalent iodine mediated fluorination of styrene derivatives to generate 2,2-difluoroethylarenes see Kitamura, T.; Muta, K.; Oyamada, J. *J. Org. Chem*. **2015**, *80*, 10431-10436.
(19) Full experimental details are provided in the SI.
(20) (a) Kitamura, T.; Kuriki, S.; Muta, K.; Morshed, M. H.; Muta, K.; Gondo, K.; Hori, Y.; Miyazaki, M. *Synthesis* **2013**, *45*, 3125-3130. (b) The addition of $PhICl_2$ to olefins is catalysed by TFA by a similar H-bonding effect: Cotter, J. L.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc*. **1962**, *84*, 793-797.
(21) Haubenreisser, S.; Wöste, T. H.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem. Int. Ed*. **2016**, *55*, 413-417.
(22) For recent syntheses of fluorodanicalipin A and bromodanicalipin A see: (a) Fischer, S.; Huwyler, N.; Wolfrum, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 2555–2558; (b) White, A. R.; Duggan, B. M.; Tsai, S.-C.; Vanderwal, C. D. *Org. Lett*. **2016**, *18*, 1124-1127.
(23) Coombs, J. R.; Morken, J. P. *Angew. Chem. Int. Ed*. **2016**, *55*, 2636-2649.


Catalytic difluorination of olefins
F—I—F
Me
p-iodotoluene
(0.2 eq.)
Selectfluor
(1.5 eq.)
DCE / Et3N•3HF
/ Pyr•(HF)x
rt, 14-24 h
F
F
up to 80%