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Catalytic, Diastereoselective 1,2-Difluorination of Alkenes

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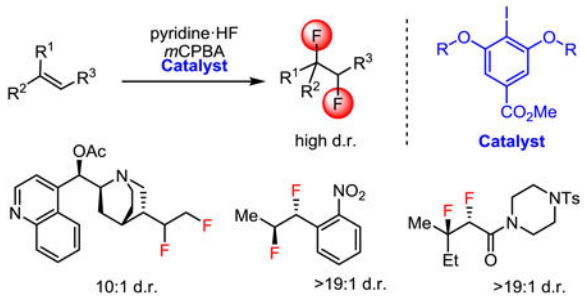
Abstract

We describe a direct, catalytic approach to the 1,2-difluorination of alkenes. The method utilizes a nucleophilic fluoride source and an oxidant in conjunction with an aryl iodide catalyst and is applicable to alkenes with all types of substitution patterns. In general, the vicinal difluoride products are produced with high diastereoselectivities. The observed sense of stereoinduction implicates anchimeric assistance pathways in reactions of alkenes bearing neighboring Lewis basic functionality.

Graphical abstract



In contrast to alkene dichlorination and dibromination, which are among the most general and well-developed reactions in organic chemistry,[1,2] analogous 1,2-difluorination reactions present challenges both fundamental and practical. Direct difluorination of alkenes[3] may be accomplished with stoichiometric amounts of highly reactive and oxidizing F_2,[4] XeF_2,[5] or a combination of reagents such as Selectfluor® or *p*-iodotoluene difluoride with HF.[6,7] Stereocontrol can be difficult to achieve in difluorination reactions utilizing these reagents[4b] due to the participation of open *β*-fluorocarbenium intermediates (Scheme 1A)[6,8–10] although F_2 diluted with N_2 has been demonstrated to effect alkene difluorination diastereoselectively at low temperatures.[11]

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Supporting Information. Experimental procedures and characterization data for new compounds are available free of charge via the Internet at http://pubs.acs.org.

Fluorine incorporation is well-known to modulate a number of important properties of organic molecules, including lipophilicity, bioavailability, and metabolic stability.[12] Vicinal difluorides possess the additional interesting characteristic of adopting preferred gauche conformations.[13–15] We hypothesized that the extent to which the gauche effect may serve as a useful principle in the design of functional molecules might be increased through improved, direct synthetic access to 1,2-difluoride motifs.[16] We report here a new catalytic method for diastereoselective alkene 1,2-difluorination that is applicable to a broad range of alkene substrates.[17]

Alkene 1,2-difluorination has been demonstrated by Hara and coworkers using stoichiometric *p*-iodotoluene difluoride with Et_3N•5HF as the fluorine source and predominantly isolated terminal alkenes as substrates.[7] Based on this seminal report, we envisioned a catalytic method based on a single, readily available nucleophilic fluorination reagent. In this context, aryl iodide catalysis has emerged as a metal-free approach to alkene difunctionalization through the intermediacy of aryliodonium (III) species.[18,19] In the proposed catalytic pathway, an aryl iodide (**I**) could undergo transformation to a reactive iodoarene difluoride (**III**) through stepwise oxidation to the iodosylarene (**II**) and subsequent deoxyfluorination with an appropriate HF source.[20] Vicinal alkene difluorination can then proceed in a stereospecific manner through the intermediacy of discrete intermediates **IV** and **V**.[21,22]

This approach to the catalytic 1,2-difluorination of alkenes was examined using terminal alkenes **2a** and **2b** as model substrates (Scheme 2). A systematic evaluation of fluoride sources and oxidants led to the identification of HF–pyridine (pyr•9HF) and *m*-chloroperbenzoic acid (*m*CPBA) as the most effective reagent combination.[23] Thus, allyl benzene derivative **2a** underwent 1,2-difluorination with **1a** as catalyst, although a large excess of the HF source (20–100 equiv.) was required to achieve good yields.[24] Despite this practical limitation, the reaction mixtures could be worked up safely and in a straightforward manner using basic alumina or aqueous sodium hydroxide to quench excess HF. In the case of isolated alkene **2b** (Scheme 2, Reaction 2), added pyridine afforded significant improvements in product yield, most likely by reducing the acidity of the medium and thereby generating a more nucleophilic source of fluoride. The resorcinol derivative **1b** proved to be measurably more effective than **1a** in catalyzing the 1,2-difluorination of **2b**. On the basis of its performance in these and other model reactions (*vide infra*), as well as the ease of accessing chiral variants for investigation of enantioselectivity (*vide infra*), catalyst **1b** was selected for subsequent studies on the scope of the alkene difluorination reaction.

In general, terminal alkenes were found to undergo 1,2-difluorination in moderate-to-good yield (Figure 1). Reactions proceeded to full conversion, with the only identifiable byproducts resulting from competitive epoxidation/ring-opening or from *m*-chlorobenzoic acid addition to alkyl iodonium intermediates. The difluoride products were readily isolated in pure form by column chromatography. A variety of substituted allylbenzene derivatives were found to display comparable reactivity (**2a, 2c–d**) and afforded good yields of difluoride products using catalyst **1b** and slow addition of alkene on preparative scale. However, phenols and methoxy-substituted arenes were not compatible with the reaction conditions, as expected given the known arene oxidation chemistry of hypervalent iodine

species (**3l**).[25] Amine-containing terminal alkenes were protected from oxidation in situ through protonation, allowing for difluorination of substrates **2f–i** in good yields. Difluorination of 1,1-disubstituted alkene **2j** occurred selectively on the *endo* face to generate 1,2-difluoride **3j** as the major diastereomer.[26] Functional group tolerance was further demonstrated with successful difluorination of *O*-acetylcinchonidine in 63% yield ((–)-**3k**) and high diastereoselectivity (10:1 d.r.).

In efforts to extend the catalytic 1,2-difluorination protocol to internal alkenes as substrates, we found that symmetrical 1,2-disubstituted alkenes such as *E*-5-decene and cyclohexene did not provide the desired products; mixtures of unidentified fluorinated and oligomeric products were obtained instead. However, conjugated trisubstituted alkenes such as *β,β*-dimethylstyrene derivatives **4a–h** underwent reaction to afford the corresponding 1,2-difluorides in good yields (Figure 2).[27] Subjection of trisubstituted indene **4i** to the catalytic reaction conditions provided **5i** in 60% yield and 5:1 d.r. favoring the syn diastereomer, as established by ^{19}F NMR and X-ray diffraction analysis of a crystalline derivative.[26] Although *β*-monosubstituted styrenes are susceptible to rearrangement via phenonium intermediates in hypervalent iodine-promoted reactions,[28] highly electron-deficient **4j** afforded the *syn*-difluorination product in 19:1 d.r. In contrast, *o*-nitrostyrene derivatives **4k–m** underwent difluorination to give the corresponding *anti*-addition products with high diastereoselectivity.[26] The basis for this intriguing stereochemical reversal is discussed below and in Scheme 3A.

Alkenes bearing nitrogen-containing heterocyclic substituents (**4n–q)** were also suitable substrates for the difluorination reactions. The electron-deficient nature of the protonated heterocycles led to diminished reactivity relative to simple styrenes. However, the 1,2-difluoride products (**5n–q**) could be obtained if the reactions were carried out in neat pyr•9HF consistent with the known activating effect of Brønsted acids on aryl iodide intermediates.[29] Amine-containing internal alkene substrates were also compatible with the catalytic reaction conditions. Thus, amitriptyline (**4r**) underwent difluorination to **5r**, and aliphatic internal alkene **4s** afforded difluoride **5s** with a 10:1 d.r. favoring the *endo*-diastereomer, albeit in low yield.[26, 30]

Because of their electron-deficient nature, α, β-unsaturated carbonyl compounds are particularly challenging substrates for electrophilic oxidation reactions. Nonetheless, consistently high product yields and diastereoselectivities (>19:1 d.r.) were obtained in the 1,2-difluorination of a variety of sterically and electronically differentiated acrylamides (Figure 3). In particular, cinnamamides **6a–c** and *β,β*-disubstituted acrylamides **6d–f** proved to be effective substrates, and the difluorination of tetrasubstituted alkene **6d** was executed on gram scale to afford **7d**. Stereoisomers **6e** and **6f** underwent stereospecific 1,2-difluorination to give diastereomeric difluorides **7e** and **7f**, respectively. Acrylamides lacking carbocation-stabilizing groups at the *β*-position (**6g–k**) were found to be poorly reactive with catalyst **1b**. However, modified conditions using catalyst **1c** in neat pyr•9HF gave rise to synthetically useful yields (**7g–k**).

In general, diastereoselectivity in the 1,2-difluorination reactions was found to be high, but the identity of the major adduct was highly dependent on substrate structure. Alkenes

lacking proximal Lewis basic groups (e.g. **4i–j**) underwent addition to give *syn*-difluorination products. This outcome is consistent with the mechanistic hypothesis outlined in Scheme 1C in which intermediate **V** undergoes invertive attack by fluoride at the $C_{sp}3$–iodine(III) bond. Competitive ionization of either a benzylic or tertiary alkyl iodine(III) intermediate could account for formation of the minor diastereomer.[31] However, crystallographic characterization of structures of **7a,c,f–g,k** revealed that difluorination occurred with anti diastereospecificity,[26] in a manner analogous with *o*-nitrostyrene derivatives as noted above. This stereochemical outcome suggests that reactions of alkenes bearing weakly Lewis basic groups adjacent to the reaction site are subject to anchimeric assistance pathways. We propose that complexes $\mathbf{I_{4k–m}}$ and $\mathbf{I_6}$ undergo nucleophilic fluorination at the carbon bearing greater positive charge to generate fluoroalkyl iodonium(III) intermediates $\mathbf{II_{4k–m}}$[32] and $\mathbf{II_6}$ (Scheme 3A and B). Subsequent intramolecular invertive displacement by the nitro group in $\mathbf{II_{4k–m}}$[33a] and by the carbonyl in $\mathbf{II_6}$, affords onium ions $\mathbf{III_{4k–m}}$ and oxiraniminium ion $\mathbf{III_6}$,[33b] respectively. These reactive intermediates are proposed to then undergo invertive attack by a fluoride ion to afford *anti*-difluorinated products **5k–m** and **7**. The observation of these anchimeric assistance pathways[34] highlight the highly electrophilic nature of the aryliodonium(III) species in the catalytic difluorination reactions, and suggest that there may be a rich chemistry associated with trapping the fluorinated intermediates by internal or exogenous nucleophiles.

In a preliminary effort to identify asymmetric variants of the difluorination reaction, chiral aryl iodide **1d** was prepared and examined in the reaction of cinnamamide **6c** (Scheme 4). Reduced reactivity was observed relative to achiral catalyst **1b**, but moderate product yields and excellent enantioselectivity were obtained after 72 hours at 4 °C. This result establishes a strong proof-of-concept for the enantioselective catalytic difluorination of alkenes and also confirms the direct participation of hypervalent iodide species in the C–F bond-forming steps of the catalytic reaction.

This work introduces a new method for catalytic alkene difluorination. Extension of the reactivity principles outlined herein to new alkene 1,2-difunctionalization reactions are under investigation and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. Computational modeling (M062X/6-31+G(d,p)/SDD for I/CPCM(DCM)) of proposed intermediate **IV** (Scheme 1) predicts highly unsymmetrical coordination of the alkene to the

iodonium fluoride, with the more substituted carbon of the alkene bearing more positive charge. For details, see the supporting information.

23. No product was obtained using Et_3N•3HF, and reactions with HF (aq.) were impractically slow. Oxidants examined include: ^tBuOOH, AcOOH, SelectFluor, iodic acid, DDQ, DCC/UHP, sodium peroxydisulfate, $Cu(OTf)_2$, 3,3-dimethyl-2-((4-nitrophenyl)sulfonyl)-1,2-oxaziridine, and oxone.
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27. With substrates **4a–4i**, slow addition of alkene was crucial for reducing competitive epoxidation by *m*CPBA and hydrofluorination. Negligible conversion (<2%) to difluoride products was observed in the absence of catalyst **1b**.
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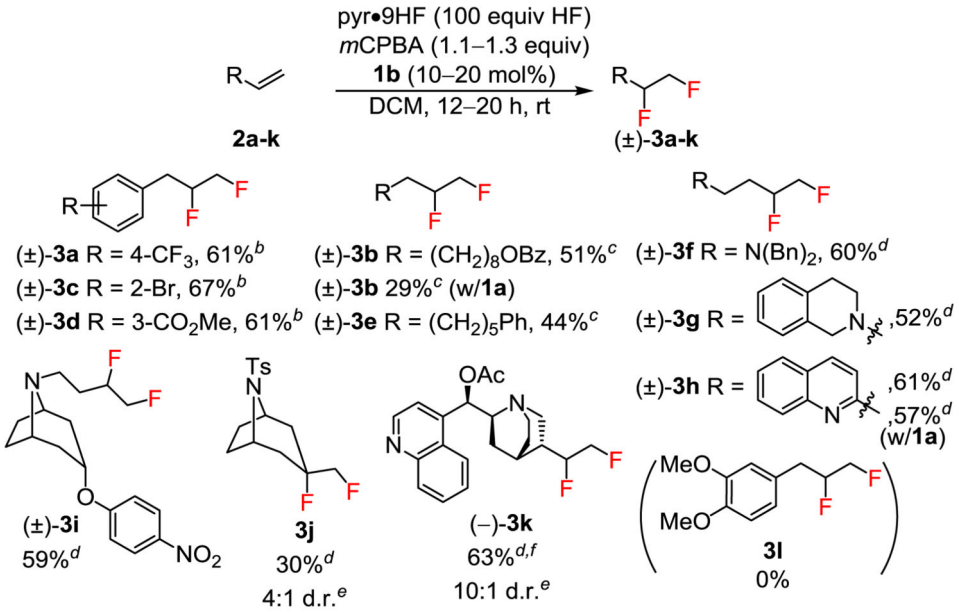


Figure 1. Terminal Alkene Substrate Scope

[a]Reactions were conducted on 1.04 mmol scale, with yields of diastereomerically product isolated after chromatographic purification unless noted otherwise. [b]Reactions conducted with 20 mol% catalyst, with slow addition of substrate over 2 hours. [c]Reactions conducted with 10 mol% catalyst and 6 equivalents of pyridine. [d]Reactions conducted with 20 mol% catalyst. [e]Determined by ^{19}F NMR of the crude reaction mixture. [f]Isolated as a mixture of diastereomers.

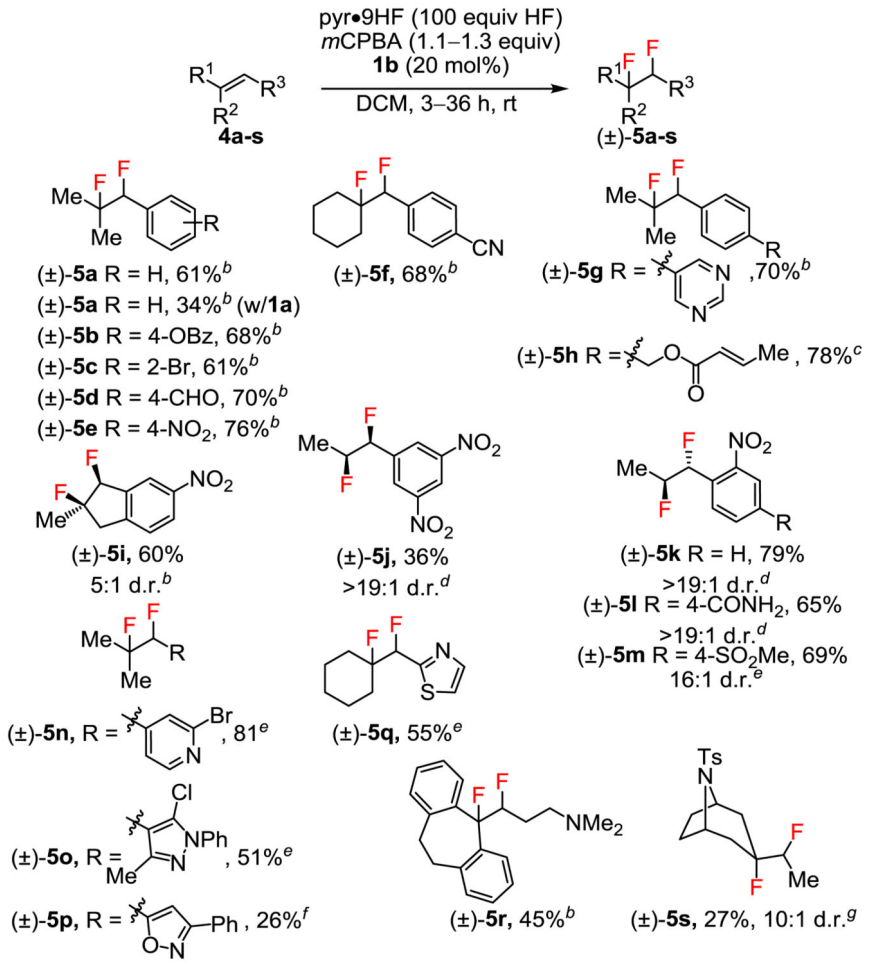


Figure 2. Internal Alkene Substrate Scope

[a]Reactions were conducted on 0.62–1.94 mmol scale, with yields of diastereomerically pure product isolated after chromatographic purification unless noted otherwise. Diastereomeric ratios (d.r. values) were determined by ^{19}F NMR of crude reaction mixtures. [b]Reactions were conducted with slow addition of substrate over 2 hours and were allowed to progress with stirring for an additional 1 hour. [c]Reaction was conducted at 0 °C with slow addition of substrate over 1 hour and stirring for an additional 1 hour. [d]Reactions were conducted with slow addition of substrate over 2 hours and stirring for an additional 10 hours. [e]Reaction was conducted in neat pyr•9HF for 12 hours. Isolated as a mixture of diastereomers. [f]Reaction was conducted in neat pyr•9HF for 36 hours with a second addition of *m*CPBA (0.65 equiv) after 24 hours. [g]Reaction was conducted with 20 equiv of HF for 24 hours. Isolated as a mixture of a diastereomers.

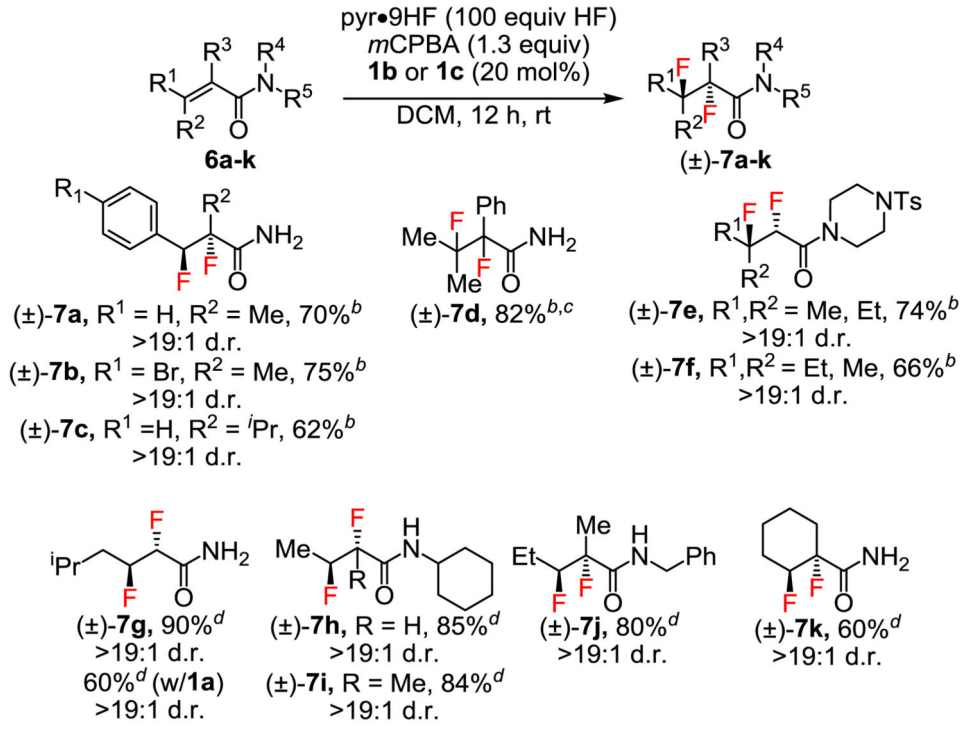
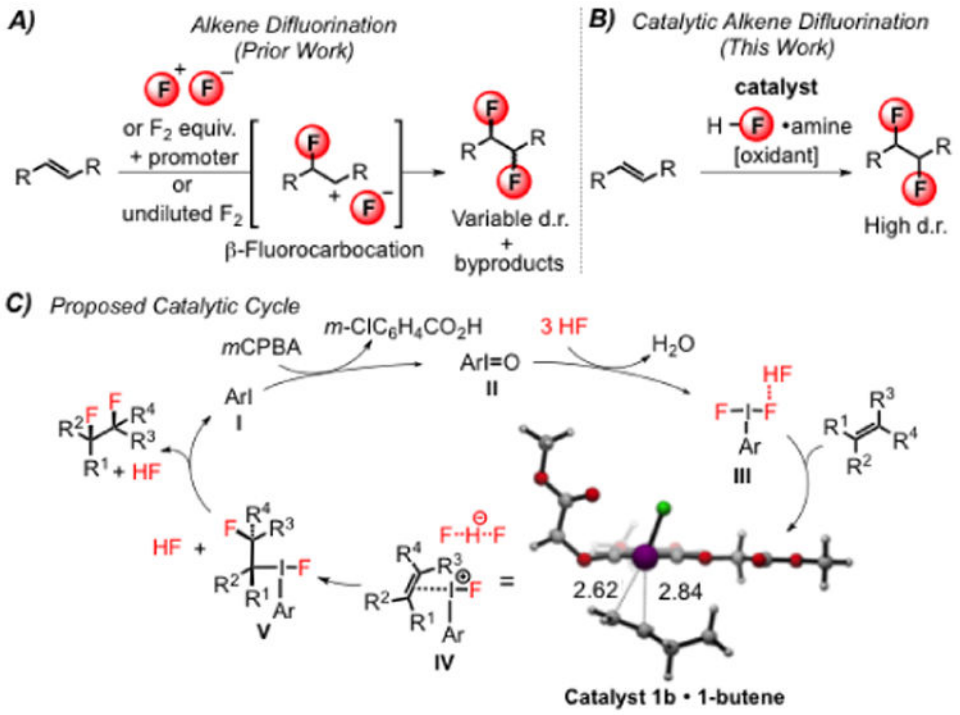
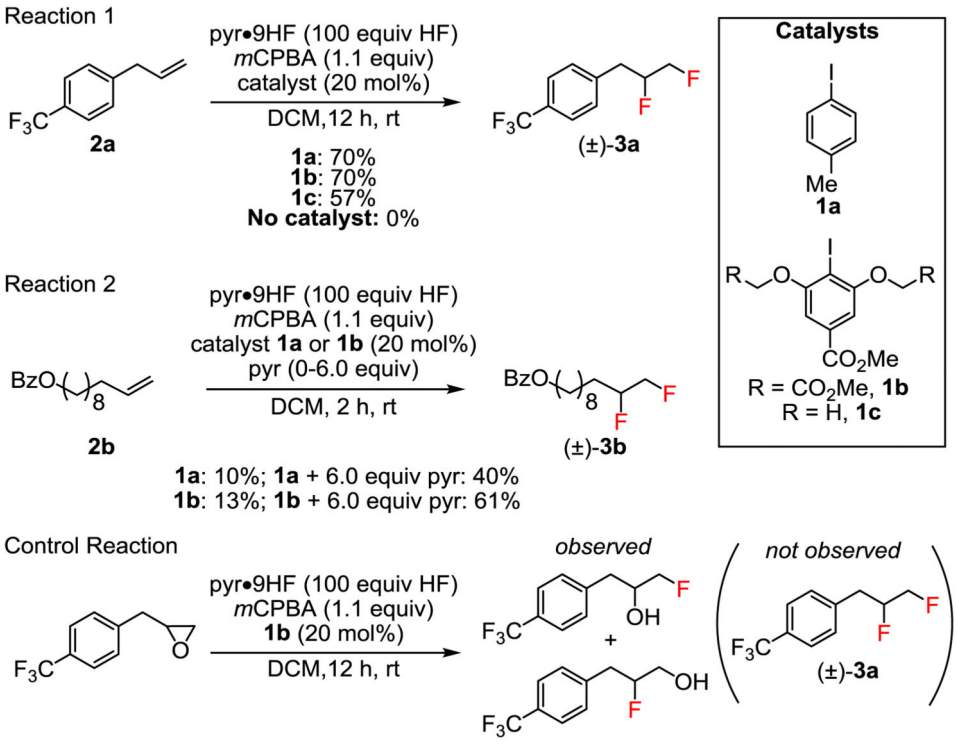


Figure 3. Acrylamide Substrate Scope

[a]Reactions were conducted on 0.55–5.71 mmol scale, with yields of diastereomerically pure product isolated after chromatographic purification. Diastereomeric ratios (d.r. values) were determined by ^{19}F NMR of crude reaction mixtures. [b]Reactions were conducted using catalyst **1b**. [c]Reaction was conducted on 1 gram scale. [d]Reactions were conducted in neat pyr•9HF using catalyst **1c**.

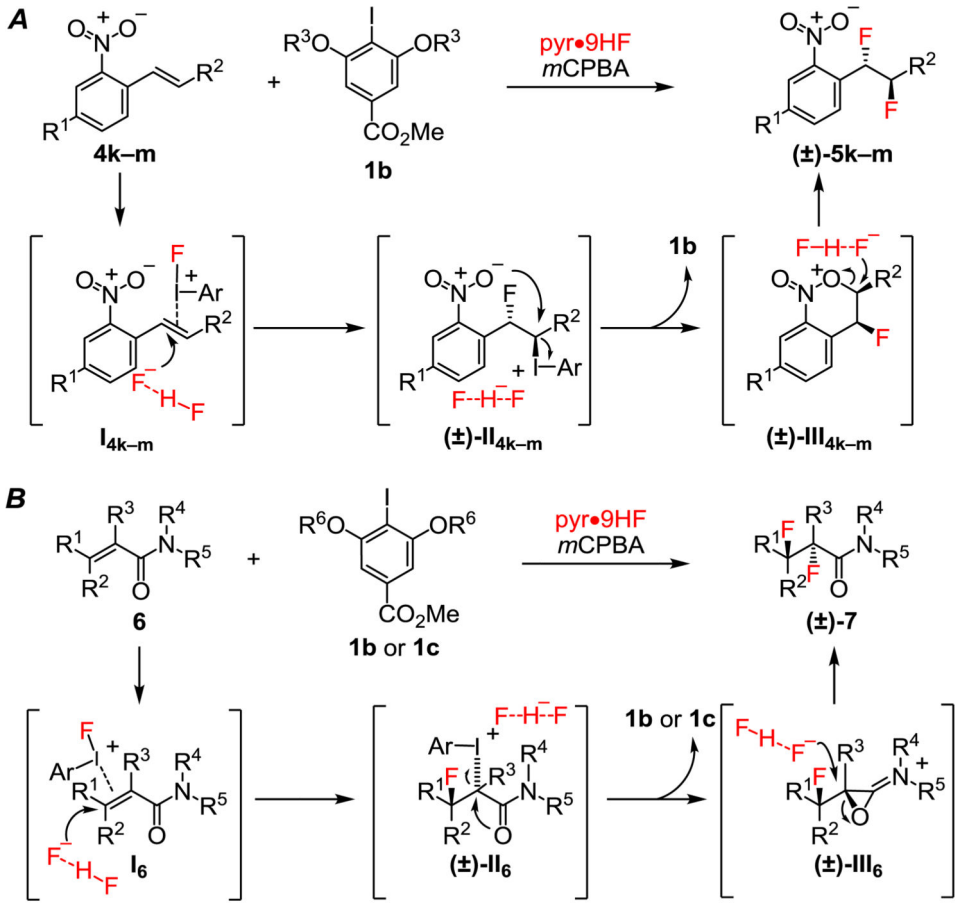


Scheme 1. 1,2-Difluorination of Alkenes

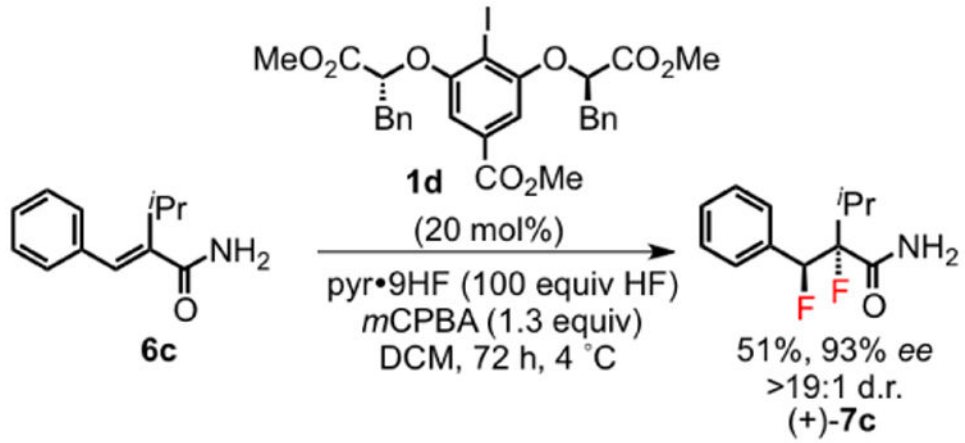


Scheme 2. Catalyst Identification

[a]Yields determined by GC with dodecane as an internal standard.



Scheme 3. Anti Difluorination via Proposed Anchimeric Assistance



Scheme 4. Highly Enantioselective 1,2-Difluorination