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Catalytic, Enantioselective 1,2-Difluorination of Cinnamamides

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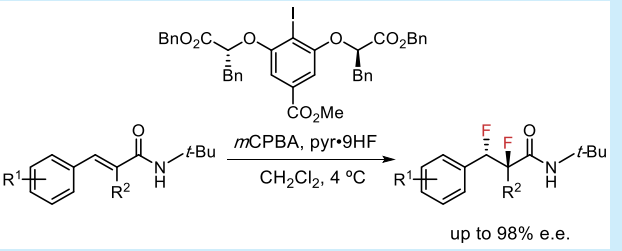
Supporting Information

ABSTRACT: The enantio- and diastereoselective synthesis of 1,2-difluorides via chiral aryl iodide-catalyzed difluorination of cinnamamides is reported. The method uses HF-pyridine as a fluoride source and *m*CPBA as a stoichiometric oxidant to turn over catalyst, and affords compounds containing vicinal, fluoride-bearing stereocenters. Selectivity for 1,2-difluorination versus a rearrangement pathway resulting in 1,1-difluorination is enforced through anchimeric assistance from a *N*-*tert*-butyl amide substituent.



The stereocontrolled introduction of fluorine atoms into organic molecules is a long-standing challenge in synthetic chemistry driven, to a significant extent, by the beneficial properties fluorination can impart to the physical and biological properties of organic molecules.[1] Due to their known preference for adopting gauche conformations, vicinal difluorides represent a particularly interesting subset of organofluorine compounds.[2] The direct, enantioselective 1,2-difluorination of alkenes represents a most appealing approach to this class of compounds, but no general methods have yet been identified for accomplishing such a transformation.[3] Reported examples of enantiocontrolled synthesis of vicinal difluorides most often involve deoxyfluorination of 1,2-fluoroalcohols derived from stereodefined epoxides or diols.[4] However, these reactions are prone to competitive elimination pathways and are often low-yielding.[5] New methods for direct, enantioselective vicinal difluorination could enable a more thorough exploration of the gauche effect on molecular structure and function.

There has been remarkable progress over the past decade in the development of enantioselective alkene difunctionalization reactions using hypervalent iodine reagents and catalysts.[6] In that context, the Gilmour lab and our group recently developed catalytic variants of the alkene 1,2-difluorination first reported by Hara.[3n,6g,h] Our system engaged HF-pyridine as a nucleophilic fluoride source and *meta*-chloroperbenzoic acid (*m*CPBA) as the stoichiometric oxidant,[7] and included a single example of an enantioselective variant in the 1,2-difluorination of trisubstituted cinnamamide **2q** catalyzed by chiral aryl iodide **1a** (Scheme 1).[8] However, in subsequent work, we found that the scope of that reaction was severely limited due to competing rearrangement pathways. Here, we address that selectivity challenge through a systematic study of the factors influencing product distribution, leading to the development of a protocol for the highly chemo- and enantioselective 1,2-difluorination of trisubstituted cinnamamide substrates. These reactions provide versatile synthetic building blocks bearing contiguous secondary and tertiary fluorine-bearing stereocenters. Concurrent with our efforts, Gilmour and co-workers reported a complementary method

Scheme 1. Product Selectivity in Aryl Iodide-Catalyzed Difluorination of Cinnamamides

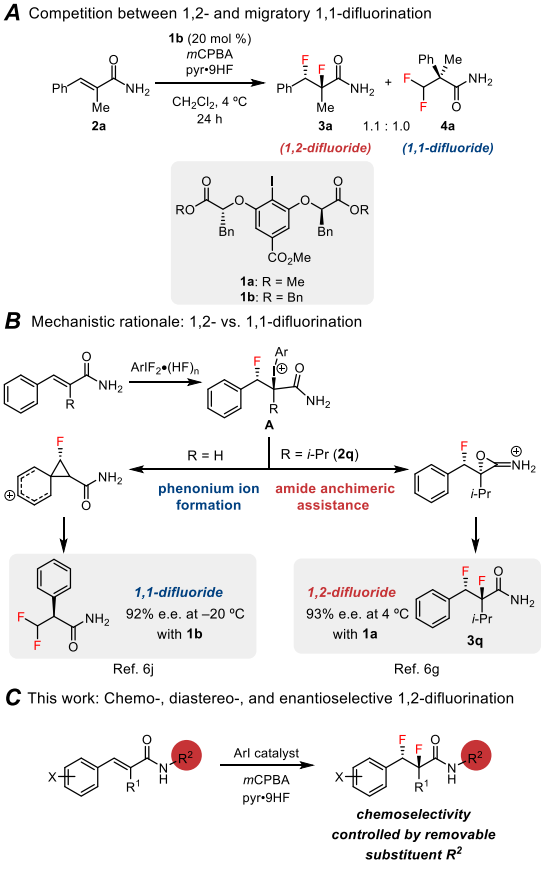


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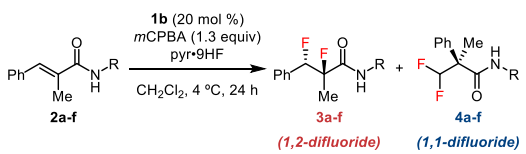
Table 1. Optimization of the 1,2-Difluorination Reaction[a]



entry	substrate	R	pyr•9HF (equiv.)	3 : 4	yield of 3 (%)	e.e. of 3 (%)
1[a]	**2a**	H	11	1.1 : 1.0	17	91
2[a]	**2b**	Me	11	1.1 : 1.0	38	95
3	**2b**	Me	5.6	3.3 : 1.0	51	94
4	**2c**	Et	5.6	4.3 : 1.0	61	95
5	**2d**	*i*-Pr	5.6	4.8 : 1.0	56	95
6	**2e**	*n*-Bu	5.6	6.9 : 1.0	63	94
7	**2f**	*t*-Bu	5.6	39 : 1.0	81	96
8[b]	**2f**	*t*-Bu	11	5.9 : 1.0	65	96

[a]Unless noted otherwise, reactions were conducted on a 1.00 mmol scale and isolated yields of **3** are listed. Reported ratios of 1,2-difluoride to 1,1-difluoride were determined by ^{19}F NMR analysis of crude product mixtures. [b]Reaction conducted on 0.10 mmol scale, with yields of 1,2-difluoride determined by ^{1}H NMR against an internal standard.

for the enantioselective 1,2-difluorination of simple, electron-deficient styrenes.[9]

Styrenyl substrates are susceptible to rearrangement pathways under electrophilic fluorination conditions, thereby affording 1,1-difluorinated products.[10,11] For example, in the attempted difluorination of trisubstituted cinnamamide **2a** catalyzed by aryl iodide **1b**, a mixture of 1,2- and 1,1-difluoride products was obtained unselectively (Scheme 1A). Product partitioning is proposed to arise from the initial fluoroiodination adduct **A**, which can undergo aryl iodide displacement either by the amide carbonyl oxygen or by the aryl group (Scheme 1B).[6g,j] The basis for enantioinduction is likely common to both pathways and was explored computationally in a recent collaborative study.[11e] We hypothesized that the amide anchimeric assistance pathway leading to the 1,2-product might be enhanced through judicious introduction of *N*-substituents, since substitution has been demonstrated to lower the strain energy in small rings in specific cases.[12]

We evaluated a series of *N*-substituted amides as model substrates for the enantioselective 1,2-difluorination reaction with catalyst **1b** (Table 1). While tertiary amide derivatives of **2** displayed poor reactivity, secondary amides underwent reaction more efficiently than the primary amide **2a**. Thus, the difluorination of *N*-methyl amide **2b** (entry 2) proceeded with improved yield and enantioselectivity, although without any change in product ratio. Decreasing the HF-pyridine concentration led to a modest improvement in selectivity for the 1,2-product **3b**, with optimal yields obtained using 5.6 equiv (entry 3). The dependence of product ratio on HF-pyridine loading might be attributable to attenuation of amide nucleophilicity by hydrogen bonding between the amide and HF.[13] Increasing the size of the secondary amide *N*-substituent resulted in increased selectivity for formation of 1,2-difluoride products (entries 3−7), with the *N*-*tert*-butyl amide **2f** affording the desired 1,2-difluoride **3f** almost exclusively (entry 7). Notably, the reaction of **2f** proceeded with significantly diminished chemoselectivity when 11 equiv of HF-pyridine were used (entry 8).[14]

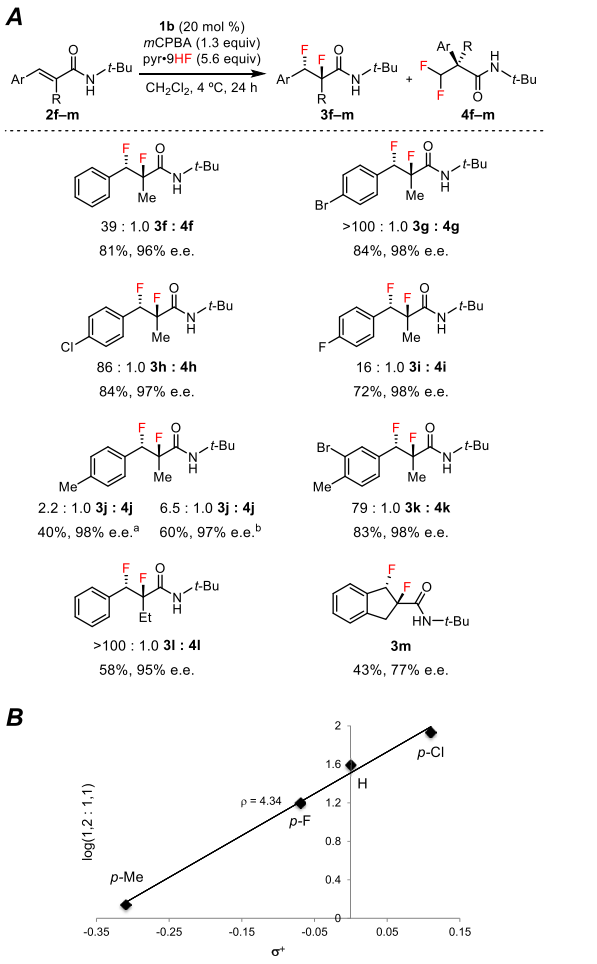


Figure 1. (A) Scope of the enantioselective 1,2-difluorination of *N*-*tert*-butyl cinnamamides. Reactions were conducted on 1.00 mmol scale with 5.6 equiv of HF-pyridine. Ratios of 1,2-difluoride to 1,1-difluoride were determined by ^{19}F NMR analysis of crude product mixtures. Isolated yields of diastereomerically pure 1,2-difluoride are reported unless otherwise noted. The relative and absolute configurations of all 1,2-difluorination products were assigned by analogy to those of **3q** (ref 16). [a] Reaction conducted with 2.8 equiv of HF-pyridine. [b] Reaction conducted on 0.20 mmol scale with 2.8 equiv of HF-pyridine and added pyridine (pyr/HF = 1:4.5). The reported yield was determined by ^{1}H NMR using nitrobenzene as an internal standard. (B) Hammett plot of σ^{+} values of the aryl substituents in **2f** and **2h−j** versus the product ratio (log(1,2:1,1)) obtained for each substrate.

Under the optimized conditions, a variety of *tert*-butyl cinnamamide derivatives were found to undergo highly diastereo- and enantioselective formation of the corresponding 1,2-difluorination products (Figure 1A).[15] Substrates bearing electron-withdrawing and mildly electron-donating substituents (**2g−i**) were particularly effective. The electron-rich cinnamamide **2j** underwent reaction with only modest chemoselectivity to generate a 2.2:1.0 ratio of the desired 1,2-difluoride to the 1,1-difluoride, with the 1,2-difluoride isolated in 40% yield and 98% e.e. This result is nonetheless notable because it overturns the overwhelming selectivity for 1,1-difluoride observed for the analogous primary amide substrate (see Supporting Information). A further increase in chemoselectivity for the 1,2-product was obtained by increasing the ratio of pyridine to HF from 1:9 to 1:4.5. Although we have not performed a systematic investigation of

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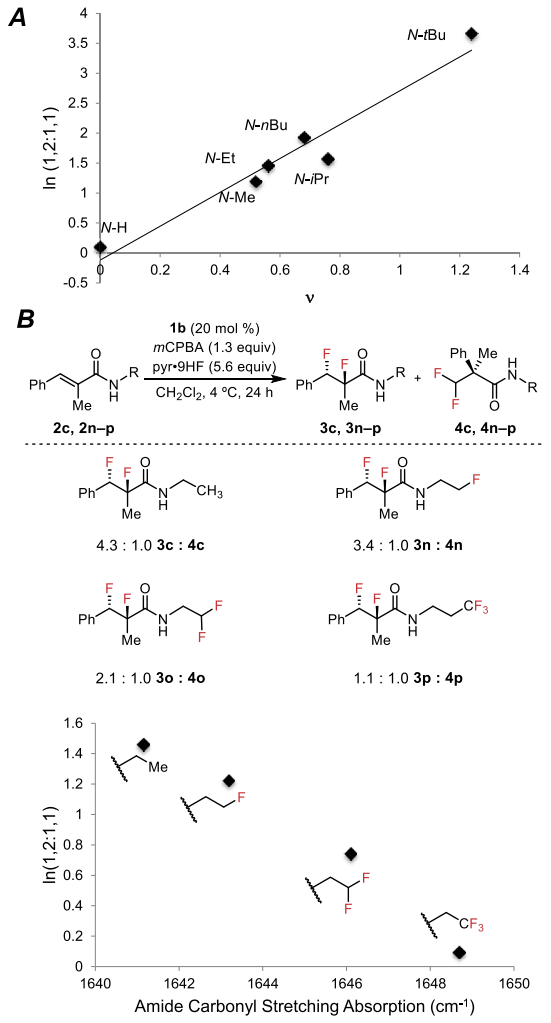
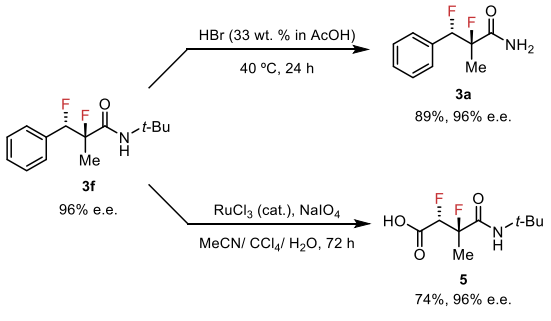


Figure 2. (A) Plot of Charton values (ν) for amide *N*-substituents of **2a–f** versus the product ratio (ln(1,2:1,1)) obtained for each substrate. (B) Plot of amide carbonyl stretching absorptions for **2c** and **2n–p** versus the product ratio (ln(1,2:1,1)) obtained for each substrate. Reactions were conducted on a 1.00 mmol scale. Reported ratios of 1,2-difluoride to 1,1-difluoride were determined by ^{19}F NMR analysis of the crude mixture.

Scheme 2. Product Derivatization



the effect of the reaction medium on product distribution, Gilmour and co-workers have demonstrated clearly that 1,2:1,1 product ratios are dependent on amine concentrations in difluorinations of electron-deficient styrenes.[9] Chemoselectivity for 1,2- vs 1,1-difluorination was observed to be correlated directly to the nucleophilicity of the arene, as evidenced by the positive linear correlation (ρ^+ = 4.34) between the Hammett substituent σ^+ constants and log(**3**:**4**) for substrates **2f** and **2h–j** (Figure 1B). The α-alkyl substituent of the cinnamamide could also be varied (Figure 1A). Substrate **2l**, which bears an ethyl substituent at the α-position of the cinnamamide, undergoes 1,2-difluorination exclusively. Indene **2m**, which is not susceptible to an aryl migration pathway, afforded **3m** in moderate yield and enantioselectivity. Nonstyrenyl unsaturated amides display poor reactivity under the reaction conditions.

We sought to elucidate the basis for the significant impact of the amide *N*-substituent on product ratio. A strong linear free-energy correlation was observed between the 1,2- vs 1,1-product ratios and the Charton values (ν) of the amide *N*-substituents for **2a–f** (Figure 2A), indicating that the effect is primarily steric in nature.[17] Larger substituents thus appear to enhance amide anchimeric assistance relative to aryl migration, thereby favoring the 1,2-difluorination pathway.

The electronic effect of the amide *N*-substituent on the competition between the aryl migration and amide trapping pathways was probed by examining substrates bearing fluorinated *N*-substituents (**2n–p**). Substrates bearing electron-withdrawing *N*-alkyl substituents underwent difluorination with lower product selectivity for the 1,2-difluoride (Figure 2B, top). The experimentally measured infrared stretching frequencies of the amide carbonyls of **2c** and **2n–p** correlate to ln(**3**:**4**) (Figure 2B, bottom). As might be anticipated, decreased nucleophilicity of the amide oxygen disfavors anchimeric assistance relative to phenonium ion formation.

The products of the difluorination reaction can be derivatized to access versatile, enantioenriched vicinal difluoride building blocks (Scheme 2). Treatment of **3f** with a solution of hydrogen bromide in acetic acid resulted in efficient cleavage of the *tert*-butyl group to afford primary amide **3a**. The arene of **3f** can be degraded oxidatively to give carboxylic acid **5**, thereby providing a 1,4-dicarbonyl bearing a second functional handle off the stereodefined difluoride framework.

In conclusion, we have developed a catalytic, enantioselective 1,2-difluorination of cinnamamides. The competing 1,1-difluorination resulting from phenonium rearrangement was suppressed through enhancement of anchimeric assistance by a proximal *tert*-butyl amide. The resulting products and their derivatives may serve as versatile building blocks for the preparation of 1,2-difluoride-containing compounds, enabling further study of this interesting motif. Efforts are underway to extend the scope of this methodology to other enantioselective fluorofunctionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00938.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(13) However, primary amide **2a** did not display the same sensitivity to HF-pyridine loading (see Supporting Information).

(14) The 1,2- to 1,1-selectivity in the difluorination of secondary amides **2b**−**2e** also displayed significant sensitivity to HF-pyridine loading (see Supporting Information).

(15) The reactions of **2j** and **2m** yielded the 1,2-difluorides as 6.1:1.0 and 5.1:1.0 mixtures of diastereomers, respectively (diastereomeric ratios were determined by ^{19}F NMR analysis of the crude reaction mixtures). For all other substrates, difluorination reactions proceeded with greater than 25:1.0 d.r.

(16) The *N-tert*-butyl derivative of cinnamamide **2q** (Scheme 1B) was prepared and subjected to the difluorination reaction conditions to afford the corresponding 1,2-difluoride as the exclusive product in 97% ee. This product was treated with 33 wt % hydrobromic acid in acetic acid to afford the primary amide product **3q** (see Supporting Information for details). The sign of the measured optical rotation of **3q** prepared by this method matched that previously reported for **3q** prepared directly by difluorination of **2q**. The relative and absolute configurations of **3q** have been previously assigned by X-ray diffraction of a single crystal (see ref 6g).

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