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Catalytic, Asymmetric Difluorination of Alkenes to Generate Difluoromethylated Stereocenters

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Abstract

Difluoromethyl groups possess specific steric and electronic properties that invite their use as chemically inert surrogates of alcohols, thiols, and other polar functional groups important in a wide assortment of molecular recognition processes. We report here a method for the catalytic, asymmetric, migratory geminal difluorination of β -substituted styrenes to access a variety of products bearing difluoromethylated tertiary or quaternary stereocenters. The reaction uses commercially available reagents (*m*CPBA and HF•pyridine) and a simple chiral aryl iodide catalyst, and is carried out readily on gram scale. Substituent effects and temperature-dependent variations in enantioselectivity suggest that cation- π interactions play an important role in stereodifferentiation by the catalyst.

The impact of fluoroalkyl groups on the physical and biological properties of molecules (1, 2, 3, 4) has inspired substantial research effort aimed toward identifying general methods for the controlled introduction of these motifs into organic compounds (5, 6, 7). Particular focus on the geminal or 1,1-difluoro group, motivated by its facile synthesis from simple carbonyl compounds, has showcased its useful properties as a chemically inert isostere of a variety of polar functional groups (8). The difluoromethyl group (CHF₂) has the additional feature of bearing a slightly acidic C-H bond, allowing it to act as a lipophilic hydrogen bond donor (9) and, by extension, as a bioisostere for alcohols and thiols (Fig. 1A) (8). Difluoromethyl group incorporation into molecules can therefore confer the advantageous effects of fluorination, such as modulated bioavailability, metabolic stability, and lipophilicity, while also introducing or retaining a key recognition element for biologic targets.

Stereochemically defined hydrogen-bond donors are often critical contributors to specific interactions of bioactive small molecules with chiral receptors (*e.g.* enzymes and proteins).

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Complete experimental and characterization data are provided as Supporting Information.

SUPPLEMENTARY MATERIAL

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In order for difluoromethylated compounds to be fully exploited as bioisosteres of protic functional groups, practical methods for their stereocontrolled preparation are needed. However, no broadly effective strategy for the construction of enantioenriched tertiary and quaternary centers bearing CHF₂ groups has emerged. To date, elaboration of prochiral electrophiles bearing pre-installed CHF₂ groups has been the most widely studied strategy for generating enantioenriched CHF₂-containing small molecules (Fig. 1B) (10, 11, 12, 13). Deoxyfluorination of aldehydes (14, 15, 16) is a conceptually straightforward approach to constructing CHF₂ groups, but α -branched chiral aldehydes are prone to epimerization and other decomposition pathways (15, 17, 18), whereas α -quaternary aldehydes are susceptible to rearrangement reactions (14, 19, 20, 21) (Fig. 1C). Other established methods for *gem*-difluorination, such as fluorodesulfurization of dithianes or dithiolanes, have not been widely applied to the synthesis of compounds bearing CHF₂ groups bound to defined stereogenic centers (22, 23). While moderate progress has been achieved in the development of enantioselective methods targeting C_{sp}³-C_{CHF₂} bond construction, these approaches generally require the use of a CHF₂ equivalent that must be unmasked in a separate operation (Fig. 1D) (24, 25, 26). A straightforward and general approach to enantioenriched difluoromethyl group-bearing building blocks from simple starting materials would facilitate the preparation of a wide array of molecular architectures containing the CHF₂ bioisostere. We report here the direct, catalytic, and highly enantioselective conversion of styrenes to versatile chiral building blocks containing difluoromethyl groups.

Direct difluorination of alkenes provides a non-obvious, but potentially powerful, approach to the stereoselective synthesis of difluoromethylated compounds. In particular, hypervalent iodoarenes have been demonstrated to mediate the 1,1-difluorinative rearrangement of both cyclic (27) and acyclic (28, 29, 30, 31) alkyl-substituted styrenes through the intermediacy of phenonium ion intermediates (e.g., **III**, Fig. 1E), and Kitamura and coworkers have reported a catalytic protocol for the conversion of unfunctionalized, terminal styrenes to achiral difluorinated products (32). We considered that invention of an enantioselective catalytic difluorinative rearrangement reaction could provide an attractive means to access useful chiral building blocks bearing difluoromethyl groups, particularly if it could be extended to styrene derivatives possessing useful functional handles (Fig. 1E).

We chose to examine cinnamic acid derivatives as candidate substrates, as their difluorinative rearrangement would generate synthetically versatile, chiral aryl propionic acid derivatives as products. In this manner, we discovered that two distinct pathways are available in the difluorination of cinnamamides catalyzed by aryl iodides. We have reported recently that the trisubstituted cinnamamide derivative **2s** undergoes enantioselective and diastereospecific 1,2-difluorination with HF•pyridine and *m*CPBA in the presence of chiral aryl iodide catalyst **1a** (33, 34). However, if aryl migration via a phenonium ion intermediate (**III**) is favorable relative to anchimeric assistance by the neighboring amide group, then the rearrangement pathway dominates and the 1,1-difluorination product is obtained. The latter reactivity is observed in the reaction of the disubstituted cinnamamide **2a**, which undergoes the desired rearrangement reaction in the presence of catalyst **1a** to afford difluoromethylated phenyl propionamide **3a** (Fig. 1E). Remarkably, no 1,2-product was observed in the difluorination of **2a**, nor was 1,1-product detected in the difluorination of **2s**;

recovered starting material and unidentified byproducts accounted for the mass balance of the reactions, and no products resulting from direct oxidation with *m*CPBA were identified.

Resorcinol-based frameworks related to **1a** have been used extensively as effective templates in a range of hypervalent iodine-mediated asymmetric alkene difunctionalization reactions (35, 36, 37, 38, 39). In the difluorination of cinnamamide derivatives (Fig. 1E), we observed that the presence of benzylic substituents at the catalyst stereogenic centers as in **1a** is essential for obtaining high enantioselectivity. As discussed below, we propose the polarizable aromatic groups enhance stereodifferentiation through specific attractive non-covalent interactions. Introduction of benzylic groups at the ester position as in **1b** did not have an analogous beneficial effect on enantioselectivity, but led to an increase in reactivity, allowing reactions to be conducted at reduced temperatures with concomitant improvements in e.e. (see table S1). Under optimized conditions, the conversion of cinnamamide **2a** to **3a** could be accomplished on gram scale with high (>90%) enantioselectivity.

In an examination of the scope of the difluorinative rearrangement reaction catalyzed by **1b**, high enantioselectivities and good yields were obtained with a variety of cinnamamide derivatives (Fig. 2). The low temperatures required to attain optimal e.e.'s (−20 to −50 °C, depending on the substrate) were maintained conveniently using commercial circulatory baths. Primary, secondary, and tertiary cinnamamides all underwent highly enantioselective reactions, although lower yields and significant levels of byproduct formation were observed with the tertiary amides. Cinnamate esters were also oxidized successfully to the difluoromethyl-containing rearrangement products (**3k–3n**) albeit with slightly diminished yields and enantioselectivities compared to the corresponding primary cinnamamides. Simple styrene and stilbene derivatives lacking conjugation to carbonyl groups also underwent oxidative rearrangement successfully, although the resulting non-crystalline products **3o–r** were obtained with more modest (64–77%) enantioselectivities.

Engagement of β,β -disubstituted styrene substrates in the rearrangement reaction would allow construction of quaternary difluoromethylated stereocenters. However, trisubstituted cinnamamide derivatives undergo selective anchimeric assistance by the amide group *en route* to 1,2-difluorination products (i.e. **2s**) (33). According to the mechanism outlined in Fig. 1E, decomposition of intermediate **II** via the phenonium ion rearrangement should be favored by the use of cinnamate derivatives bearing less nucleophilic carbonyl groups. Indeed, trisubstituted methyl cinnamate derivatives were found to be excellent substrates for enantioselective oxidative rearrangement catalyzed by **1b** (Fig. 3). As illustrated with **4a**, comparable results were obtained on both 1-mmol and gram scale in good yields. Although electron-rich arenes such as phenols are incompatible with the oxidative hypervalent iodine conditions due to dearomatization pathways (40), suitably protected derivatives such as the acetate **4g** were found to undergo the desired difluorination to produce **5g** in high enantioselectivity and yield. The α -alkyl substituent of the cinnamate ester could also be varied without detrimental effect on reaction outcome (**5j–5l**), further underlining the utility of this rearrangement approach for the synthesis of sterically congested stereocenters. Low reactivity was observed in the difluorinative rearrangement of 3-chloropropyl-substituted **4m**, suggesting that relatively long-range inductive effects can influence the susceptibility of

the alkene to the oxidation reaction. This deactivating effect is offset, however, by introduction of an electron-donating group on the aromatic ring of the substrate as in **4n**.

The products of this asymmetric reaction can be elaborated through a variety of synthetic manipulations without compromise of enantiomeric integrity (Fig. 3B). Cinnamamide-derived **3a** was reduced in high yield to alcohol **6** or primary amine **7**. Although erosion of stereochemical purity was observed in the hydrolysis of **3a** under acidic conditions, diazotization with *tert*-butylnitrite and hydrolysis under neutral conditions provided **8** with retention of e.e.. Hoffman degradation of **3a** provided **9** in excellent yield and complete preservation of optical purity. Quaternary difluoromethyl-containing building block **5a** lacks an acidic α -proton and is therefore not prone to epimerization under saponification conditions. The resulting carboxylic acid was converted easily to amide **10** via the acid chloride. Ruthenium-catalyzed oxidation of the arene and subsequent amide bond formation provided **11** with preservation of stereochemical purity. This reaction sequence allows for the synthesis of synthetically versatile, chiral malonate derivatives bearing difluoromethylated quaternary stereocenters.

As noted above, significant enhancement in enantioselectivity is observed in difluorinative rearrangements using catalysts bearing benzylic (i.e. **1a–b**) vs. aliphatic substituents (see table S1). We hypothesized that attractive cation– π interactions might play a role in the selective stabilization of high-energy cationic intermediates and/or transition structures in the hypervalent iodine-catalyzed reaction, and we sought to evaluate this possibility by tuning the π -donating ability of the catalysts. The incorporation of more electron-rich or polarizable aromatic substituents into the catalyst was not a viable approach, as these groups are incompatible with the strongly oxidizing reaction medium. However, the more electron-deficient 3,4,5-trifluorophenyl analog **1d** (Fig. 4B) could be evaluated and was found to be significantly less enantioselective than **1b**, as expected if cation– π interactions play a productive role in modulating stereocontrol (41). Eyring analysis in the 23 to –45 °C temperature range of catalysts **1b**, **1c**, and **1d** for reaction of substrate **4a** was performed in order to glean additional insight into the basis for enantioinduction (Fig. 4B). For each catalyst, enantioselectivity was found to be enthalpically controlled, with a relatively small entropic compensation. The significant difference in the differential enthalpy of activation

$H^\ddagger$ between **1b** and **1c** is difficult to ascribe to steric effects alone, and it suggests instead a selective stabilizing interaction with **1b** in the transition state leading to the major enantiomer (42). To the extent that it exists, this stabilization is lost with weaker π -donating catalyst **1d**, as reflected in a $H^\ddagger$ value more similar to that of **1b**. This analysis is consistent with a more electron-donating π surface contributing to the high enantioselectivity in the 1,1-difluorination reaction and it raises the intriguing possibility that cation– π interactions might be used to modulate enantioselectivity in other hypervalent iodine-mediated alkene oxidations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Prior and current approaches to difluoromethylation

(A) The difluoromethyl group is a bioisostere for alcohols and other protic functionality. (B–D) Reported strategies for the preparation of enantioenriched difluoromethylated products. (E) Aryl iodide-catalyzed enantioselective difluorination of cinnamate derivatives. 1,2-Difluorination occurs via anchimeric assistance by the carbonyl group, whereas 1,1-difluorination is achieved through skeletal rearrangement via a phenonium ion intermediate.

Figure 2. Substrate scope with β -monosubstituted styrenes

Reactions were conducted on 1.04 mmol scale with 1.1 to 1.3 equivalents of *m*-chloroperbenzoic acid (*m*CPBA) and 11.1 equivalents of pyr•9HF (pyr = pyridine); isolated yields are reported. The absolute configuration of **3h** was assigned by X-ray crystallography (structure shown), and the configuration of all other products was assigned by analogy. *Reaction conducted at -20°C ; †reaction conducted at -20°C ; ‡reaction conducted with (*Z*)-methyl cinnamate, §reaction conducted at -50°C .

Figure 3. Substrate scope with trisubstituted cinnamate ester derivatives and product elaboration

(A) Reactions were conducted on 1.04 mmol scale with 1.3 equivalents of *m*CPBA and 11.1 equivalents of pyr•9HF (pyr = pyridine); isolated yields are reported; *reaction conducted for 168 hours; †reaction conducted at -50°C ; ‡reaction conducted on 0.68 mmol scale. (B) Diversification of difluoromethyl-containing products. Conditions: **a**, SmI_2 in tetrahydrofuran (THF) for 5 minutes followed by Et_3N and H_2O at room temperature; **b**, $\text{BH}_3\cdot\text{dimethyl sulfide}$ in THF at 65°C for 16 hours, then HCl.; **c**, *t*-butyl nitrite in MeCN and H_2O at 80°C for 48 hours; **d**, [bis(trifluoroacetoxy)iodo]benzene (PIFA) in MeCN and H_2O for 36 hours, then HCl; **e**, i. NaOH in H_2O , THF, and MeOH for 12 hours at room temperature ii. $(\text{COCl})_2$, *N,N*-dimethylformamide (DMF, cat.) in CH_2Cl_2 for 6 hours at 0°C iii. 4-bromoaniline, *N,N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 for 24 hours at room temperature; **f**, i. RuCl_3 (cat.), NaIO_4 in MeCN and H_2O for 24 hours at room temperature ii. 4-bromoaniline, (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), and diisopropylethylamine (DIPEA) in DMF for 72 hours at room temperature; **g**, Diisobutylaluminum hydride (DIBAL) in THF for 1.5 hours at 0°C .

Figure 4. Catalyst substituent effects on enantioselectivity

(A) Catalyst comparison revealing that the enantioselectivity in the conversion of **4a** to **5a** is correlated with the π -donor properties of the catalyst substituents. (B) Eyring analysis. The differential activation parameters were calculated using the following relationship: $\ln(\text{e.r.}) = -H^\ddagger/RT + S^\ddagger/R$ (where $R = 1.986$ cal/(mol•K)).