Catalytic, asymmetric difluorination of alkenes to generate difluoromethylated stereocenters

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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-chloroperbenzoic acid and hydrogen fluoride pyridine) and is carried out readily on a 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 effect of fluoroalkyl groups on the physical and biological properties of molecules (1–4) has inspired substantial research effort aimed toward identifying general methods for the controlled introduction of these motifs into organic compounds (5–7). 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). 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) (10–13). Deoxyfluorination of aldehydes (14–16) is a conceptually straightforward approach to constructing CHF₂ groups, but α-branched chiral tertiary aldehydes are prone to epimerization and other decomposition pathways (15, 17, 18), whereas α-quaternary aldehydes are susceptible to rearrangement reactions (14, 19–21) (Fig. 1C). Other established methods for gem-difluorination, such as fluoroiodomethylation of dithianes or dithiolanes, have not been widely applied to the synthesis of compounds bearing CHF₂ groups bound to defined stereogenic centers (22, 23). Although moderate progress has been achieved in the development of enantioselective methods targeting Cₛ–CHF₂ bond construction, these approaches generally require the use of a CHF₂ equivalent that must be unmasked in a separate process.

Fig. 1. Previous and current approaches to difluoromethylation. (A) The difluoromethyl group is a bioisostere for alcohols and other protic functionality. (B to 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.
operation (Fig. 1D) (24–26). 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 nonobvious, 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 (28–31) alkyl-substituted styrenes through the intermediacy of phenonium ion intermediates (e.g., III) (Fig. 1E), and Kitamura and co-workers 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 because 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 diastereoselective 1,2-difluorination with H₂Fpy (pyridine) and m-chloroperbenzoic acid (mCPBA) in the presence of chiral aryl iodide catalyst 1a (33, 34). However, if aryl migration via a phenonium ion intermediate (III) is favorable to enantioselective 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 by-products accounted for the mass balance of the reactions, and no products resulting from direct oxidation with mCPBA were identified.

Resorcinol-based frameworks related to 1a have been used extensively as effective templates in a range of hypervalent iodine-mediated asymmetric alkenec difunctionalization reactions (35–39). 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 that the polarizable aromatic groups enhance stereodifferentiation through specific attractive noncovalent 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 enantiomeric excess (e.e.) (see Table S1). Under optimized conditions, the conversion of cinnamamide 2a to 3a could be accomplished on a 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 higher levels of by-product formation were observed with the tertiary amides. Cinnamate esters were also oxidized successfully to the difluoromethyl-containing rearrangement products (3k to 3n), albeit with slightly diminished yields and enantioselectivities compared with the corresponding primary cinnamamides. Simple styrene and stilbene derivatives lacking conjugation to carbonyl groups also underwent oxidative rearrangement successfully, although the resulting noncrystalline products 3o to 3r were obtained with more modest (64 to 77%) enantioselectivities.

Engagement of β,β-disubstituted styrene substrates in the rearrangement reaction would allow construction of quaternary difluoromethylated

FIG. 2. Substrate scope with β-monosubstituted styrenes. Reactions were conducted on a 1.04-mmol scale with 1.1 to 1.3 equivalents of mCPBA and 1.1 equivalents of pyr·9HF (pyr is 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 −40°C; ‡, reaction conducted with (Z)-methyl cinnamate; §, reaction conducted at −50°C.
Fig. 3. Substrate scope with trisubstituted cinnamate ester derivatives and product elaboration. (A) Reactions were conducted on a 1.04-mmol scale with 1.3 equivalents of mCPBA and 1.1 equivalents of pyr+9HF; 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. SmI₂ in tetrahydrofuran (THF) for 5 min followed by Et₃N and H₂O at room temperature. b. BH₃-dimethyl sulfoxide in THF at 65°C for 16 hours, then HCl. c. tert-butyl nitrite in MeCN and H₂O at 80°C for 48 hours. d. [bis(trifluoroacetoxy)iodo]benzene (PIFA) in MeCN and H₂O for 36 hours at room temperature; then HCl. e. i. NaOH in H₂O, THF, and MeOH for 12 hours at room temperature; ii. (COCl)₂, N,N-dimethylformamide (DMF, catalyst) in CH₂Cl₂ for 6 hours at 0°C; iii. 4-bromoaniline, N,N-dimethylamino- pyridine (DMAP) in CH₂Cl₂ for 24 hours at room temperature; f. i. RuCl₃ (catalyst), NaIO₄ in MeCN and H₂O for 24 hours at room temperature; ii. 4-bromoaniline, (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), and disopropylaluminum hydride (DIBAL) in THF for 72 hours at room temperature. g. disobutylaluminum hydride (DIBAL) in THF for 1.5 hours at 0°C.

Fig. 4. Catalyst substituent effects on enantioselectivity. (A) Catalyst comparison revealing that the enantioselectivity in the conversion of 4a to 5a is correlated with the x-donor properties of the catalyst substituents. (B) Eyring analysis. The differential activation parameters were calculated using the following relationship: ln(e.r.) = −ΔH°/RT + ΔS°/R [where R = 1.986 cal/(mol·K), T is temperature in Kelvin, and e.r. is enantiomeric ratio].
stereocenters. However, trisubstituted cinna- namamide derivatives undergo selective an- chimeric assistance by the amide group en route to 1,2-difluoroamin products (i.e., 2s) (33). According to the mechanism outlined in Fig. 1E, decomposition of intermediate 1f via the phenonium ion rearrangement should be favored by the use of cinnamate derivatives bearing less nucleophilic carbonyl groups. Indeed, trisubstituted methyl cinnamate res- idues 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 amines such as phenols are incompati- ble with the oxidative hypervalent iodine conditions due to dearmatization pathways (40), suitably protected derivatives such as the acetate 4g were found to undergo the desired diflu- oriuration to produce 5g in high enantioselectivity and yield. The α-alkyl substituent of the cinna- mate ester could also be varied without deter- rimental effect on reaction outcome (5j to 5l), further underlining the utility of this rearrange- ment approach for the synthesis of sterically congested stereocenters. Low reactivity was observed in the difluoriniative rearrangement of 3-chloropropyl-substituted 4m, suggesting that relatively long-range inductive effects can influence the susceptibility of the alkene to the oxida- tion reaction. This deactivating effect is offset, however, by introduction of a donor-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 enantio- meric integrity (Fig. 3B). Cinnamamide-derived 3a was reduced in high yield to alcohol 6 or primary amine 7. Although erosion of stereo- chemical purity was observed in the hydrolysis of 3a under acidic conditions, diazotization with tert-butyl nitrite and hydrolysis under neutral conditions provided 8 with retention of c.e. Hoffman degradation of 3a provided 9 in excel- lent 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 arenne and subsequent amide bond for- mation provided 11 with preservation of stereo- chemical purity. This reaction sequence allows for the synthesis of synthetically versatile, chiral malonate derivatives bearing difluoromethylated quaternary stereocenters.

As noted above, pronounced enhancement in enantioselectivity is observed in difluorini- tative rearrangements using catalysts bearing benzylly (i.e., 1a and 1b) versus aliphatic substi- tuents (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 struc- tures in the hypervalent iodine-catalyzed reac- tion, 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 cata- lyst was not a viable approach because these groups are incompatible with the strongly ox- idizing reaction medium. However, the more electron-deficient 3,4,5-trifluorophenethyl analog 1d (Fig. 4B) could be evaluated and was found to be markedly less enantioselective than 1b, as expected if cation-π interactions play a produc- tive 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 enthalpical- ly controlled, with a relatively small entropic compensation. The significant difference in the differential enthalpy of activation (ΔH‡) 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 ΔH‡ value more similar to that of 1c. This analysis is consistent with a more electron- donating π surface contributing to the high enantioselectivity in the 1,1-difluorination reac- tion, and it raises the intriguing possibility that cation-π interactions might be used to modulate enantioselectivity in other hypervalent iodine-mediated alkene oxidations.

REFERENCES AND NOTES

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