Catalytic enantioselective synthesis of heterocyclic vicinal fluoroamines using asymmetric protonation: A method development and mechanistic study

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ABSTRACT: A catalytic enantioselective synthesis of heterocyclic vicinal fluoroamines is reported. A chiral Bronsted acid promotes aza-Michael addition to fluoroalkenyl heterocycles to give a prochiral enamine intermediate, which undergoes asymmetric protonation upon rearmatization. The reaction accommodates a range of azaheterocycles and nucleophiles, generating the C–F stereocenter in high enantioselectivity, and is also amenable to stereogenic C–C(sp2)F bonds. Extensive DFT calculations have provided insight into the reaction mechanism and the origin of catalyst selectivity. Crystal structure data shows the dominance of non-covalent interactions in the core structure conformation, enabling modulation of the conformational landscape. Ramachandran-type analysis of conformer distribution and protein data bank mining has indicated benzylic fluorination using this approach has potential for improved potency in several marketed drugs.

Introduction

Incorporation of fluorine into organic compounds is prominent in the pharmaceutical, agrochemical, and materials industries.[1] The unique characteristics of the C–F bond enable modulation of physicochemical properties while mitigating steric contributions.[2] A key attribute is the intrinsic polarity of the C–F bond, which can induce conformational changes through electrostatic and dipole interactions with neighboring functional groups. Installation of a chiral C–F bond with a vicinal relationship to a heteroatom or electron-withdrawing group is particularly valuable as exploitation of the gauche effect allows predictable conformational control.[3] For example, fluorinated phenethylamines are especially valuable based on the demonstrable utility of this compound class within bioactive molecules[4] and the topological control afforded by the gauche effect can enable bespoke biological target engagement.[5] Similarly, fluorine is often considered as a minimal change to block metabolism, for example of labile benzylic positions.[6] Given the stereoselective nature of most metabolic processes, substitution of a specific C–H for C–F in a methylene represents a very efficient means of benefiting from this effect, thus the introduction of fluorine in a stereoselective fashion holds significant appeal.

Overcoming the problems with the use of MF3 salts remains a major challenge in this field. There are limited examples of the use of alkali metal fluorides (KF and CsF) for deoxyfluorination.6 Recent seminal studies by Gouverneur demonstrated that KF and CsF can also be used for nucleophilic additions,7a including asymmetric ring opening of thionium and aziridinium ions.7b,7c Here, the poor reactivity of F− is overcome by the use of a chiral H-bonding phase transfer catalyst that facilitates F− transfer. However, the general challenges of MF3 use in deoxyfluorination remain and, despite recent advances with alkali metal fluorides, readily available transition metal fluorides remain overlooked.8 Here we show the development of a simple method for deoxyfluorination with typically unreactive transition metal (TM) fluorides, using CuF2 as an example (Scheme 1b).
lectivity (82% and 96:4 e.r.; entry 1). Several observations relating to optimization were noted (see Supporting Information (SI) for full details and additional experiments). Ethereal solvents (THF, CPME) were particularly effective (entries 1 and 2), with other solvents affording good to excellent conversion but with notably poorer enantioselectivity (entries 3 and 4). Lowering the reaction temperature from −10 °C to −20 °C had little effect on enantioselectivity but impacted reaction efficiency (entry 5). A similar effect was observed by lowering catalyst loading, where 10 mol% was less efficient but maintained selectivity (entry 6). Control experiments supported a catalyst-promoted reaction that lacked background reactivity (entry 7).

Table 1. Reaction development.

| Entry | Deviation from 'standard conditions' | Yield [%] (e.r. (R:S)) [b] |
|-------|-------------------------------------|-----------------------------|
| 1     | None                                | 82 (96:4) [b]               |
| 2     | CPME                                | 89 (95:5) [b]               |
| 3     | PhMe                                | 95 (89:11)                  |
| 4     | CH₂Cl₂                              | 70 (75:25)                  |
| 5     | −20 °C                               | 40 (96:4)                   |
| 6     | 10 mol% 9a, −20 °C                   | 37 (95:5)                   |
| 7     | 0 mol% 9a, −20 °C                    | 0 (---)                     |

[a] Determined by HPLC using an internal standard. [b] Isolated yield.

Based on this hypothesis, a benchmark process was established where 5a was subjected to aniline (8), and Brønsted acid catalyst 9a (Table 1; a range of catalysts were evaluated, vide infra and see ESI). Optimization of reaction parameters delivered a system that afforded the desired product 7a in high conversion and enantioselectivity (82% and 96:4 e.r.; entry 1). Several observations relating

Scheme 2. (a) Our previous work and simplified mechanism indicating asymmetric induction is a function of enamine geometry control. (b) Preliminary DFT conformational analysis suggesting high enamine diastereoselectivity.

However, this was only amenable with the steric control of enamine geometry afforded by aryl substituents at the α-carbon: alkyl substituents led to poor geometry control of the intermediate enamine 3, resulting in lower enantioinduction in product 4. While fluorine has a small steric footprint, we postulated that dipole minimization might provide an alternative selectivity determinant (Scheme 2b). Indeed, preliminary DFT studies highlighted the preferred s-trans geometry for benchmark starting material 5a, which was anticipated to assist geometrical control of the developing fluoroamine 6 and enhancing enantioinduction in 7.

(a) Previous work: Steric control of geometry (simplified mechanism)

(b) Formation of stereogenic C–F bonds: Dipole enforced control of geometry

Scheme 3. Substrate Scope. Isolated yields. Enantiomeric ratios determined by HPLC analysis on a chiral stationary phase. See ESI for details. [a] CPME, −20 °C; 5 d. [b] −20 °C, 5 d. [c] CPME, −10 °C. [d] CPME, rt. [e] 1 equiv. of 9a, CPME, −50 °C.

The scope of the reaction was investigated (Scheme 3). A range of aryl amine nucleophiles was accommodated with variation in functional group (e.g., halides, alkyl groups, BPin, heterocycles) and regiochemical substitution (ortho, meta, para) was typically accommodated while maintaining selectivity (Scheme 3a). Additionally, substitution on the aniline nitrogen was tolerated (7m). It should be noted that the choice of solvent was important for conversion, due to solubility: product precipitation as the reaction progressed became problematic for certain substrates; however,
changing ethereal solvent based on substrate (THF or CPME) resolved this issue.

A range of vinylheterocycles was also generally well accommodated (Scheme 3b). Variation in substitution of the benchmark 2-vinylquinoline was straightforward (7a, 7n-q) and the reaction tolerated quinoxaline (7r), benzothiazole (7s), and pyridine (7t), with the latter a significantly more challenging substrate due to its higher dearomatization barrier, hence requiring a high temperature for the reaction to proceed, which negatively affects enantioinduction. Significantly, the reaction also allows enantioselective formation of stereogenic C-CF bonds (11); however, catalyst loading had to be increased and reaction temperature decreased to overcome a significant non-selective background reaction observed for this substrate (see ESI).

Mechanistic Analysis. Two main mechanistic pathways are possible for the key asymmetric protonation event (Scheme 4). The initial events common to both pathways involve reversible protonation of the substrate (5a) by the catalyst to provide LUMO-lowered intermediate complex 12 and enabling reversibleaza-Michael using PhNH₂ (8) to deliver key intermediate 13. Two mechanistic pathways are then possible from this intermediate: pathway 1 proceeds via direct stereocatalyzed proton transfer from the anilinium via TS1 and delivers the product-catalyst complex 15, which subsequently liberates the product (7a). Alternatively, in pathway 2 proton transfer from the anilinium of 13 to the phosphate (via TS2) delivers 14, which undergoes stereocatalyzed proton transfer via TS3 to deliver 15. In our previous report,[14] computational analysis supported pathway 1, with selectivity arising from good shape and electrostatic complementarity between the catalyst and TS1 leading to the observed enantiomer. These purely quantum mechanical studies did not yield transition states that would have supported pathway 2 (or other alternative mechanisms). A series of kinetic isotope effect experiments were conducted via the use of [15N]-aniline and PhND₂. However, these proved inconclusive, with independent rate experiments (see ESI) resulting in observed [14,15]N KIE of ca. 0.8 and H/D KIE of ca. 1.8, which may be affected by the pre-RDS equilibrium associated with this reaction.

Goodman and others have shown that catalysis by BINOL-derived catalysts, such as 9a, can be studied effectively and efficiently by QM/MM ONIOM calculations where the quantum mechanical aspects are described by B3LYP/6-31G* and the molecular mechanics by UFF.[15] Accordingly, a more exhaustive theoretical exploration was undertaken using this approach (Figure 1 and ESI).

Experimentally, no background reaction was observed, which was consistent with DFT calculations that indicated a prohibitively high barrier for direct reaction of 5a with 8 (see ESI).

Complexation of 5a with 9a to give 12 is moderately favorable, with the preferred dipole-induced s-trans conformation of 5a also retained in 12. This initial complex is held together by a H-bond (OH...N = 1.63 Å) and a weak per CH--O=π interaction (2.40 Å). Complex 12 then undergoes deaeromatizingaza-Michael addition to deliver 13, where the loss of aromaticity is compensated for by the formation of a tightly bound ionic interaction between the anilinium NH and phosphate (P=O--HNHPH = 1.38 Å and P=O--HNquin = 1.71 Å). Rearrangement within this complex by proton transfer from the anilinium to the phosphate involves a low barrier and yields a complex of the enamine (14) that is higher in energy than reactants. All of these steps are therefore strongly reversible and no significant concentration of any of the intermediates subsequent to quinoline complexation would be expected—this was confirmed by parallel NMR experiments (see ESI).

Transition states leading to each low energy conformation of complex 15-(R) and 15-(S) were optimized leading to an array of conformations for each of TS1 and TS3. Consistent with our previous report,[14] pathway 1, via direct proton transfer to the prochiral center was identified (TS1). This process has a significant barrier (+35 kcal mol⁻¹) but is predicted to be highly stereoselective (ΔΔG° = 4.4 kcal mol⁻¹, >99.1 c.r.) in favor of the experimentally observed enantiomer. Although this rationalizes the stereoselectivity of the process, it is not consistent with the experimental rate of reaction.

However, pathway 2 was more consistent with the experimentally observed rate. The key step, in which the stereochemistry is generated, involves protonation of the enamine by the POH in complex 14 via TS3 and exhibits a clear preference for the experimentally observed enantiomer (ΔΔG° = +3.5 kcal mol⁻¹), which arises from geometrical restrictions between the catalyst and enamine in the developing transition state TS3-(R) and TS3-(S) (vide infra). The i-Pr substituents of catalyst 9a are also particularly important for imposing this geometrical restriction (vide infra: Table 2 and Figure 3). This mechanistic overview reveals that the catalyst provides its effect by acting as both acid and base at each stage as required and does so in a way that imposes specific shape requirements on the substrate that interplay with the polar interactions that hold the complex together.

Based on these results, a complete reinvestigation of the computational analysis of our previous process using aryl substituents (Scheme 2a)[14] using the approach delineated above suggests that pathway 2 is a more likely reaction mechanism in this process. The full profile for this reaction is provided in the ESI.

Control substrates 7u-7w provided additional support of the DFT conclusions (Figure 2). Despite moderate yields of product for each, enantioinduction was poor, which arises from features that are not well-tolerated in the lowest energy transition state.
Substrate 7u places the fused phenyl ring in a position that clashes with the i-Pr groups of 9a in TS3. By contrast, 7v prevents the required simultaneous interactions of 5a and 8 with 9a and also lacks the dipole-induced geometry control. Lastly, the essential enamine NH–OP H-bond in TS3 is impaired by the adjacent chlorine in substrate 7w, weakening the association between the substrate and catalyst.

Figure 2. Control substrates. Reaction conditions as per Scheme 3 unless noted. [a] CPME. [b] CPME, rt. [c] CPME, 40 °C.

With regards to the optimal catalyst, a catalyst survey demonstrated the superior level of asymmetric induction using 9a (Table 2; see ESI for full details). To determine the origin of this enhanced selectivity, we analyzed 9a in comparison to the related 3,3’-mesityl (9b) and -phenyl (9c) analogues (Figure 3). As the stereodirecting group on the catalyst is reduced in size from 9a to 9b and 9c, there is a general tendency for the barrier for the catalyzed reaction to increase (from 16.2 to 16.6 and 18.5 kcal mol$^{-1}$, respectively), resulting in the observed diminished conversion. This is accompanied by a sharp erosion in $\Delta \Delta G^\ddagger$ between TS3-(R) and TS3-(S) – the energy associated with TS3-(R) remains similar for all three and this erosion is principally driven by a change in energy of TS3-(S). This is highlighted in the preferred conformation of each of the three structures equivalent to TS3-(S) (Figure 3). The red arrows (Figure 3a) indicate where the bulk of the i-Pr groups of 9a press against both ends of the bound substrate. This causes the break-up of an intramolecular H-bond between the aniline nitrogen and the NH of the nitrogen arising from the quinoline (2.48 Å for 9a, but 2.02 Å and 2.03 Å for 9b and 9c, respectively); this interchanges with an interaction between the aniline NH and a phosphate oxygen (2.01 Å for 9a, but 2.69 Å and 2.67 Å for 9b and 9c, respectively). The combination of the steric clashing and this change in hydrogen bonding pattern clearly disfavors TS3-(S) compared to TS3-(R) for 9a; this difference is significantly reduced for 9b and 9c.

In line with experimental observations, the computational model also confirms a lower rate of catalyzed reaction for 5f, associated with the larger dearomatization barrier (see ESI).
16 display specific low energy conformations biased by the presence of the fluorine and that are likely to be populated in solution.

Table 2. Catalyst structure vs. enantioselectivity.

| Entry | Catalyst | R            |
|-------|----------|--------------|
| 1     | 9a       | 2,4,6-(i-Pr)CH2 |
| 2     | 9b       | 2,4,6-(Me)C6H5 |
| 3     | 9c       | Ph           |

[a] Determined by HPLC using an internal standard.

The observed significant background reaction for 10 was also investigated computationally, confirming the accelerating role of the LUMO-lowering CF3 unit as previously observed for other Michael acceptors.[17]

Implications for Conformational Control. The value of the substructures accessible using the developed protocol was explored by investigating their conformational properties. The crystal structure of 7a shows an anti relationship between C–F and the aniline nitrogen (dihedral angle = 179º), which is likely preferred in comparison to the gauche due to a favorable Nsp2–σ*CF3 interaction (Figure 4). The C–F bond is almost perpendicular to the carbon framework of the quinoline (dihedral angle = 107º), which we believe arises due to a favorable Σ*CF3–πA interaction competing with C–F/Nquin dipole minimization.[18] Hydrogen bonding of the quinoline nitrogen with a hydrogen bond donor would reduce this dipole and is a key feature of this system: the crystal structure has an intermolecular hydrogen bond between the quinoline nitrogen and the HNPh in an adjacent molecule.

To reduce the impact of hydrogen bonding and any Nsp2 interactions, 7a was acetylated to give 16 (Figure 4a). The preference towards the anti conformation is diminished, with the gauche conformation noted in the crystal structure (FCCNamide dihedral angle = 58º). The dihedral angle between the C–F bond and quinoline nitrogen is 174º, explicitly affected by the C–F/NA dipole minimization and no longer modulated by the other effects described.

Ramachandran plots for dihedral angles 1 and 2 of 7a, 16, and the parent 2-pyridylethylamine (not shown) were computed and reveal that the introduction of the benzylc fluoride has a profound effect on the overall conformational landscape (Figure 4 and ESI). 7a and 16 display specific low energy conformations biased by the presence of the fluorine and that are likely to be populated in solution.

Figure 3. Structures equivalent to TS3-(S) for catalysts 9a, 9b, and 9c

(a) Conformational analysis and crystal structure of 7a and 16

(b) Ramachandran plot for 7a

(c) Potential pharmacokinetic enhancement from conformational control

Figure 4. (a) Conformational analysis and crystal structures of 7a and 16.
(b) Ramachandran plot for 7a. (c) Drug-like molecules in PDB that may benefit from conformational control induced by benzylc fluorination.

This presents opportunities for application in drug discovery by improving binding affinity and selectivity by decreasing the population of alternative, less favorable conformations. The protein database was searched for ligands that contain the 2-pyridylethylamine substructure and the conformations that are populated in these crystal structures are mapped onto the Ramachandran plot for 7a (Figure 4b, black dots). Five compounds in particular adopt a conformation that would be enhanced by the introduction of fluorine at the benzylc position (Figure 4b, circled), including inhibitors of HIV reverse transcriptase,[19] cathepsin L,[20] and purine nucleoside phosphorylases (Figure 4c).[21] This highlights the value of this structural change for enhancing potency and selectivity of potential drug molecules.

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