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A general, enantioselective synthesis of β- and γ-fluoroamines

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Abstract

In this Letter, we describe a short, high yielding protocol for the enantioselective (87–96% ee) and general synthesis of β-fluoroamines and previously difficult to access γ-fluoroamines from commercial aldehydes via organocatalysis.

Keywords

β-fluoroamine; γ-fluoroamine; Enantioselective; Organocatalysis

Small molecule probes and drug candidates that contain one or more chiral fluorine atoms are commonplace and represent a critical component of the medicinal chemists' toolbox.[1,2] In the context of amine-containing ligands, introduction of a fluorine atom either β- or γ- to the amine often maintains activity at the desired target while providing a 1–2 log reduction in pK_a. That shift in electronic structure often results in diminished ancillary pharmacology at cardiac ion channels, improved metabolic stability, enhanced pharmacokinetics, and increased CNS penetration.[1–3] In some cases, introduction of a chiral β-fluoroamine, due to the almost 2-log impact on pK_a, can diminish activity at the desired target; however, moving the fluorine atom to the γ-position has been shown to maintain the desired bioactivity, while still affording the benefits of the β-fluoroamine congeners.[1–6]

While we and others have made considerable advances in the synthesis of chiral β-fluoroamines,[7–13] the synthesis of γ-congeners still relies on classical DAST approaches which are plagued with rearranged and dehydrated products.[1–6,14] Therefore, new synthetic strategies to access these elusive, chiral γ-fluoroamines were warranted.

Previous work from our lab (Fig. 1) employed a one-pot protocol to access chiral β-fluoroamines via organocatalysis in high yield and % ee (Eq. 1); however, the configurational instability of the incipient α-fluoroaldehyde required its immediate conversion to the β-fluoroamine.[7,8] Later efforts utilized a similar strategy, but employed the analogous α-chloroaldehydes, to access chiral *N*-terminal aziridines[15] and chiral morpholines and piperazines;[16] however, the configurational instability of the α-chloroaldehyde also necessitated immediate, one-pot use. To provide additional flexibility, we developed an approach (Fig. 1, Eq. 2) that improved yields and % ee for the synthesis of

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chiral morpholines and piperazines by reducing the α-chloroaldehyde to an alcohol, converting the hydroxyl to a leaving group, displacing the leaving group with an amino alcohol or diamine followed by base-induced cyclization.[16,17]

These results led us to reflect on the β- and γ-fluoroamine problem, and apply this strategy to their asymmetric construction (Fig. 2). Here, we envisioned standard organocatalytic α-fluorination followed by reduction to the β-fluoroalcohol to provide a bench stable, chiral intermediate. Conversion of the hydroxyl to a leaving group followed by S_N2 displacement with an amine would provide chiral β-fluoroamines **2**, whereas a cyanide displacement, followed by nitrile reduction, would afford rapid access to chiral γ-fluoroamines **3**.

To validate this new approach, we prepared a number of β-fluoroalcohol substrates **4a–g** under standard conditions in good yields (65–77%) and high enantioselectivity (87–96% ee) as expected from literature precedent (Scheme 1).[7,8,18–20] Conversion to the corresponding triflate, and displacement with benzylamine delivered the desired chiral β-fluoroamines **2a–c** (Scheme 2) in high yields (84–96%) and in excellent enantioselectivity (90–94% ee). In essence, this new strategy sets the key stereocenter in a conformationally stabile way, affording the β-fluoroamines with reproducibly high % ee, and higher yields than the first generation chiral β-fluoroamine route.[7]

In some instances, a β,β-difluoroamines have been shown to be an important pharmacophore,[1–7] and we wanted to determine if this new approach would grant access to this moiety as well. Here (Scheme 3), organocatalytic α-fluorination with excess NFSI leads to α,α-difluorination, and reduction affords the β,β-difluoroalcohol. Conversion to the triflate and displacement with benzylamine provides the desired β,β-difluoroamine **5** from the difluoroalcohol in 81% yield, representing another improvement over our first generation methodology.[7]

While the ability to access β-fluoroamines was gratifying, our main objective with this approach was to gain access to chiral γ-fluoroamines, a chemotype that is very challenging to prepare in high enantioselectivity.[1–8,14] We began our attempts with a racemic **4a** congener and surveyed a variety of leaving groups for cyanide displacement en route to γ-fluoroamines. Interestingly, when tosylate **6** was employed, all attempts (independent of cyanide source, stoichiometry, solvent, and temperature) afforded a 1,2-bis-cyano adduct **7** (Scheme 4). As more forcing conditions were required for tosylate displacement, a competing displacement of the fluoride by cyanide occurred. When triflate **8** was used, excess KCN in refluxing DCM provided the desired β-fluoronitrile **9**, but in only 50% conversion accompanied by considerable decomposition. Further surveying of reaction conditions and refinement led to the discovery of optimal conditions (10 equiv KCN in the presence of 20 mol % 18-crown-6 at room temperature in MeCN for 16 h) to fully convert triflate **8** to the desired fluoronitrile **9**, without any evidence of cyanide displacement of the fluoride.

With racemic **9** in hand, we then evaluated a number of reducing agents to provide the γ-fluoroamine. Interestingly, the vast majority of common methods for nitrile reduction ($LiAlH_4$, DIBALH, H_2/Pd, Ni(0)/$NaBH_4$) failed to reduce the β-fluoronitrile without considerable decomposition or defluorination. Ultimately, good results were obtained with the milder conditions of $InCl_3$/$NaBH_4$,[21,22] delivering the γ-fluoroamines in yields up to 90%.

Having developed a route to racemic γ-fluoroamines, attention was now directed at accessing chiral γ-fluoroamines, an elusive and difficult to prepare pharmacophore. Here, the chiral β-fluoroalcohols **4a–g** (Scheme 1) were converted into the corresponding triflates,

which were then displaced under the optimized cyanide displacement conditions to deliver chiral β-fluoronitriles **9a–g** in yields ranging from 71% to 93% (Table 1). Our optimized reduction protocol with $InCl_3/NaBH_4$ smoothly provided the chiral γ-fluoroamines **3a–g** in excellent yields (73–90%) and enantioselectivity (87–96% ee). The overall yields starting from commercial aldehydes **1** range from 40–58%. Of particular utility of this approach is the commercial availability of both enantiomers of the organocatalyst, enabling either enantiomer of the chiral γ-fluoroamine to be prepared. We were now able to access chiral β-fluoro- and γ-fluoroamines, as well as β,β-difluoroamines, providing a range of finely tuned amine basicity (with pK_as of 10.7 (parent amine) to 9.0 (β-fluoro), to 7.3 (β,β-difluoro) to 9.7 (γ-fluoro)). Attempts to prepare a γ,γ-difluoro congener, to provide an amine substrate with a pK_a of ~8.7 failed, as we were unable to displace the β,β-difluorotriflate with cyanide in yield greater than 10%, despite surveying a broad spectrum of reaction conditions (cyanide source, temperature, solvent, additives).[23]

By synthesizing β-fluoronitriles, we envisioned them not only as precursors to γ-fluoroamines, but also as intermediates poised to access a variety of fluorinated scaffolds using the nitrile as a handle. To illustrate this idea, we performed common reactions to exemplify the β-fluoronitrile as a lynchpin providing access to other, difficult to prepare, fluorinated moieties. As seen in Scheme 5, the β-fluoronitrile **10** was used in a [3+2] cycloaddition with sodium azide to provide β-fluorotetrazole **11**, a common carboxylic acid bioisostere.[24] Additionally, hydrolysis of the nitrile with hydroxylamine provided amide oxime **12**, a precursor for oxadiazole synthesis.[25] Overall, the chiral β-fluoronitrile linchpin offers rapid entry to a wide range of valuable fluorinated functional groups with subtle perturbations of pK_a and electronic properties.

In summary, we have developed a powerful extension of our one-pot, chiral β-fluoroamine work, that overcomes issues related to variable % ee due to configurationally unstable α-fluoroaldehydes, by a two-pot protocol that affords β-fluoroamines in high yields and reproducibly high enantioselectivity (90–94% ee). A further extension allows access to highly elusive and previously difficult to prepare chiral γ-fluoroamines using a three-pot protocol in good overall yields (40–58%) and excellent enantioselectivities (87–96%) from commercial aldehydes. Importantly, outside of classical DAST chemistry, this work represents the only other approach for the enantioselective synthesis of γ-fluoroamines, an important pharmacophore in drug discovery and development. Moreover, the chiral β-fluoronitrile linchpin offers rapid access to a wide range of valuable fluorinated functional groups with subtle perturbations of pK_a and electronic properties. Additional refinements are under development and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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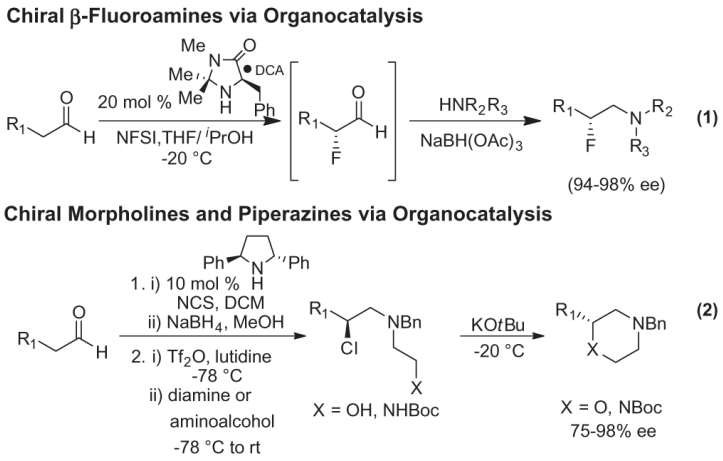


Figure 1.
First generation organocatalytic approach to chiral β-fluoroamines and refined approach to chiral morpholines and piperazines.

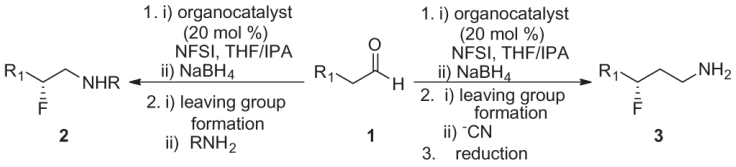
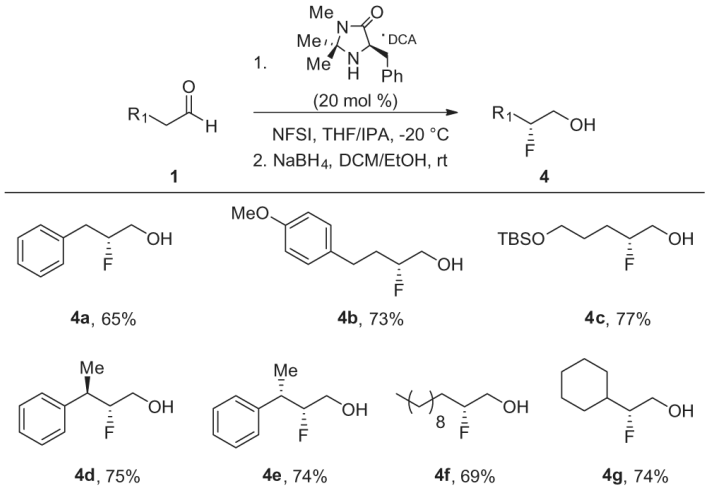
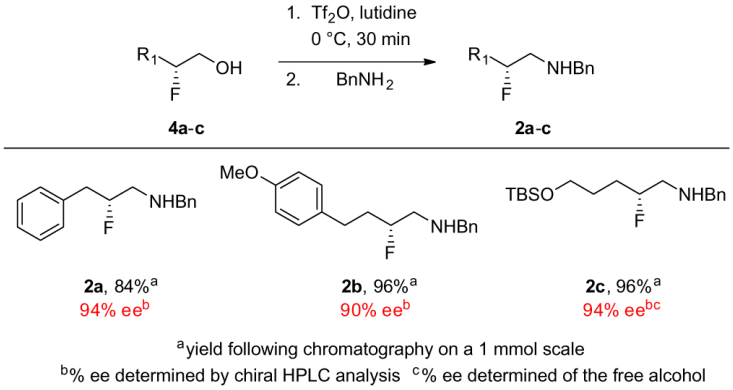


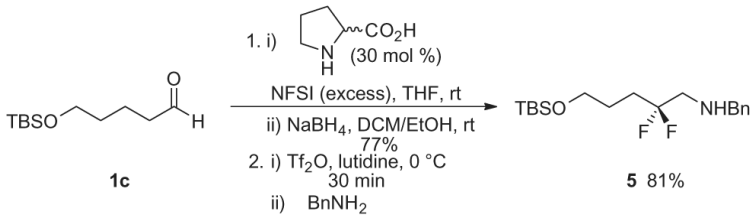
Figure 2.
Envisioned route to access both chiral β- and γ-fluoroamines via organocatalysis.



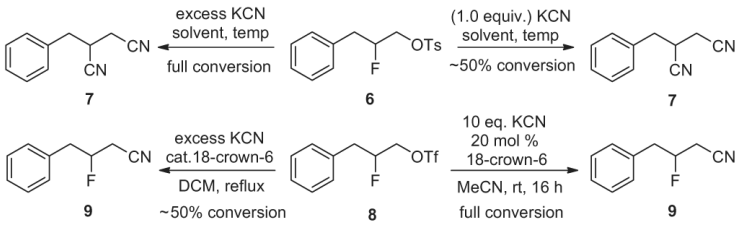
Scheme 1.
Organocatalytic, enantioselective synthesis of β-fluoroalcohols **4a–g**.



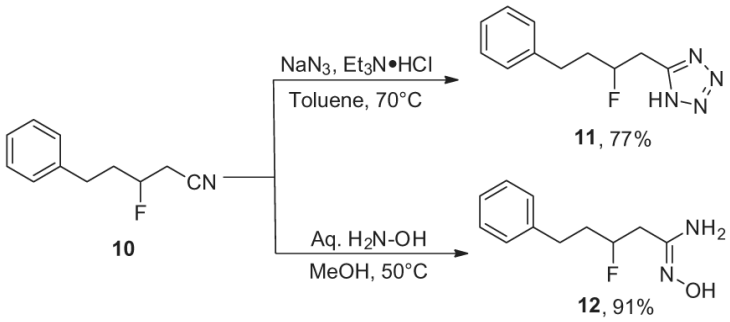
Scheme 2.
Synthesis of chiral β-fluoroamines **2a–c**.



Scheme 3.
Synthesis of a β,β-difluoroamine **5**.



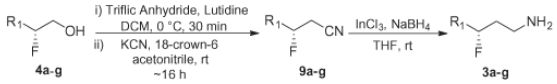
Scheme 4.
Optimization of β-fluoronitrile **8** synthesis.



Scheme 5.
Synthesis of a β-fluoro tetrazole and a β-fluoro amide oxime.

Table 1

Chrial γ-fluoroamines **10a–g** via organocatalysis



Starting material	Yield of 9a–g[a]	Yield of 3a–g[b]	% ee[c]
4a	**9a**, 71%	**3a**, 87%	94%
4b	**9b**, 92%	**3b**, 84%	87%
4c	**9c**, 73%	**3c**, 86%	92%
4d	**9d**, 93%	**3d**, 83%	96%
4e	**9e**, 77%	**3e**, 90%	96%
4f	**9f**, 82%	**3f**, 89%	95%
4g	**9g**, 84%	**3g**, 73%	96%

[a] All reactions were performed on a 1.0 mmol scale.

[b] All reactions were performed on a 0.5 mmol scale.

[C] Enantiomeric excess determined by ^{19}F NMR using the (*R*)-Mosher amide of the final amine.