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Rapid, General Access to Chiral β-Fluoroamines and β,β-Difluoroamines via Organocatalysis

Olugbeminiyi O. Fadeyi and Craig W. Lindsley*

Departments of Chemistry and Pharmacology, Vanderbilt University, Nashville, Tennessee 37232

craig.lindsley@vanderbilt.edu

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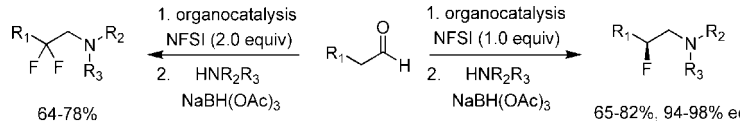
ABSTRACT



A rapid, general route to enantiopure β-fluoroamines and β,β-difluoroamines has been developed employing organocatalysis in both a two-pot and a one-pot procedure. Both chemical yields (64−82%) and enantioselectivity (94−98% ee) were excellent and represent a significant improvement in the art of preparing chemically diverse β-fluoroamines from readily available precursors.

The incorporation of β-fluoroamines into drug candidates has increased dramatically in the past 5 years, with >150 fluorinated drug candidates in phase II and phase III clinical trials.[1] The role of the β-fluorine atom is diverse and has been shown to enhance binding interactions, improve metabolic stability, increase CNS penetration, and eliminate ancillary ion channel activity by attenuating amine basicity (pK_a).[1−5] The inductive effects of a β-fluorine atom are pronounced, lowering the pK_a of a linear aliphatic amine (pK_a ~10.7) to pK_a ~9.0 with a single β-flourine to pK_a ~7.3 with β,β-difluoro substitution. These effects are general and additive, with a β-CF_3 moiety lowering the pK_a to ~5.7.[1−6]

Despite the importance of the β-fluoroamine moiety, there are few synthetic methods in the literature for their preparation.[1−7] Two common methods, the ring opening of aziridines with nucleophilic flouride sources[8] and the hydrofluorination of olefins,[9] deliver β-fluoroamines but lack generality/substrate scope, require starting materials that are not readily available, or in the latter case, do not provide access to enantiopure β-fluoroamines. The route most utilized involves the treatment of ketones or secondary alcohols with DAST, (diethylamino)sulfur trifluoride, to provide β,β-difluoroamine and β-fluoroamines (with inversion of stereochemistry), respectively.[1−10] However, this methodology requires the synthesis of enantiopure secondary alcohols and then suffers from the formation of rearranged and dehydrated products, which in many published cases greatly diminished yields of the desired β-fluoroamines.[10] In this Letter, we describe general and high-yielding protocols to deliver enantiopure β-fluoroamines and β,β-difluoroamines employing organocatalysis and readily available starting materials.

We were attracted to the classical MacMillan work[11] where organocatlysis was employed to deliver enantioselective (91−99% ee) α-fluoroaldehydes **4** by treatment of an

(1) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.
(2) Muller, K.; Mainfisch, P.; Altmann, K. H.; Schlosser, M. *ChemBioChem* **2004**, *5*, 559–572.
(3) Bohm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643.
(4) Kirk, K. L. *Curr. Top. Med. Chem.* **2006**, *6*, 1445–1543.
(5) Kirk, K. L. *Curr. Top. Med. Chem.* **2006**, *6*, 1013–1029.
(6) Morgenthaler, M.; Schweizer, E.; Hoffman-Roder, F.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerili, D.; Schneider, J.; Hiedrich, F.; Kansy, M.; Muller, K. *ChemMedChem* **2007**, *2*, 1100–1115.
(7) Percy, J. M. *Sci. Synth.* **2005**, *34*, 379–416.
(8) Alvenrhe, G. M.; Lacombe, S.; Laurent, A. J. *Tetrahderon Lett.* **1980**, *21*, 289–293.
(9) Thiabaudeau, S.; Martin-Mingot, A.; Jouannetaud, M.-P.; Karam, O.; Zunino, F. *Chem. Commun.* **2007**, 3198–3200.
(10) Hsin, L.-W.; Chang, L-T.; Rothman, R. B.; Dersch, C. M.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2008**, *51*, 2795–2806.
(11) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.

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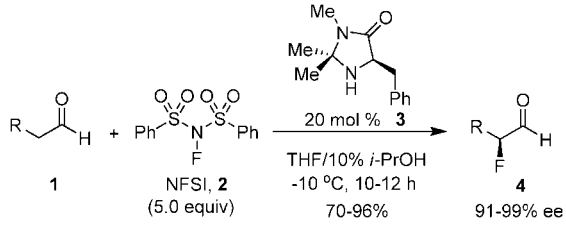
aldehyde **1** with NFSI (*N*-fluorobenzenesulfonamide) **2** and catalytic chiral imidazolidinone ligand **3** (Scheme 1).

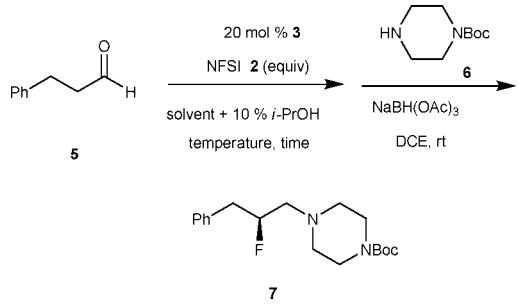
Scheme 1. Organocatalytic α-Fluorination of Aldehydes



If these chiral α-fluoroaldehydes **4** were subjected to a reductive amination protocol, we surmised that chiral β-fluroamines would result, and depending on the chirality of the imidazolidinone ligand, either the (*S*)- or (*R*)-β-fluoroamine would be delivered. Moreover, there are thousands of commercially available amines and aldehydes to employ as reactants, providing improved generality in terms of substrate scope. Surprisingly, this powerful extension of the MacMillan enantioselective α-fluorination of aldehydes has never been described.

We first explored the effect of NFSI equivalents, solvent, and temperature on a prototypical α-fluorination reaction and subsequent reductive amination sequence employing organocatalyst **3** with phenylpropanal **5** and Boc-piperazine **6** to produce chiral β-fluoroamine **7** (Table 1). Our initial attempt (entry 1) employed the conditions prescribed by MacMillan[11]

Table 1. Optimization of Organocatalytic α-Flourination/ Reductive Amination Sequence



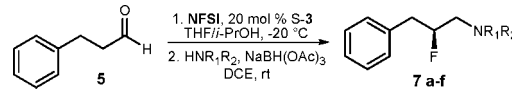
entry[a]	2 (equiv)	solvent	temp (°C)	time (h)	convn (%)[b]	ee (%)[c]
1[d]	5.0	THF	−20	24	99	>98
2[d]	3.0	THF	−20	24	98	>98
3[d]	2.0	THF	−20	24	99	>99
4	1.5	THF	24	3	97	>98
5	1.5	THF	4	12	98	>98
6	1.5	acetone	24	3	91	>96
7	1.5	CH_2Cl_2	24	3	37	84
8	1.5	EtOAc	24	3	89	95
9	1.2	THF	−20	24	99	>99
10	1.0	THF	−20	24	96	>99

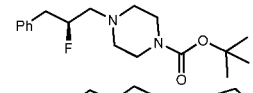
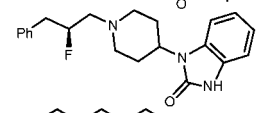
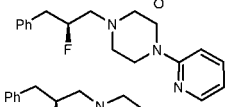
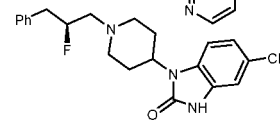
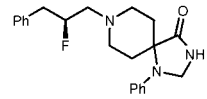
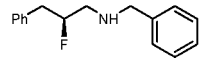
[a] All reactions were performed on a 0.05 mmol scale. [b] Conversion determined by LC/MS and ^{1}H NMR. See Supporting Information for complete details. [c] Enantiomeric excess was determined using chiral stationary phase HPLC. [d] α,α-Difluoro product was observed.

for the α-fluorination, with a quick aqueous workup prior to the reductive amination step. Conversion and enantioselectivity to the desired β-fluoroamine were excellent, but about 20% of the undesired β,β-difluoroamine was observed. To avoid this side product, we decreased the equivalents for NFSI from 5.0 to 3.0 (entry 2), to 2.0 (entry 3), and finally to 1.5 (entry 4). Only in the latter case was the β,β-difluoroamine side product eliminated; moreover, the success of the α-fluorination was not hindered by decreasing the equivalents of costly NFSI, and workup was greatly improved. Other solvent systems were evaluated, with acetone (entry 6) proving to be generally useful, while CH_2Cl_2 (entry 7) suffered diminished yields (37%) and low ee (84%). Ultimately, optimal conditions for the two-step sequence (entry 10) employed 1.0 equiv of NFSI in THF at −20 °C for 24 h, followed by a quick aqueous workup, suspension of the resulting α-fluoroaldehyde in $ClCH_2CH_2Cl$ with **6** and $NaB(OAc)_3H$ at ambient temperature to provide enantiopure (>99% ee) **7** with 96% conversion and 80% isolated yield.

As shown in Tables 2 and 3, this two-pot protocol is general with respect to the amine component, providing

Table 2. Scope of HNR_1R_2 in the Enantioselective Synthesis of (*S*)-β-Fluoroamines

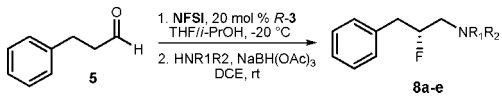


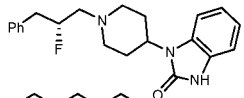
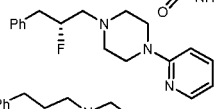
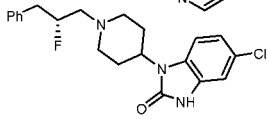
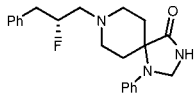
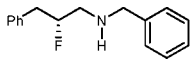
compd[a]	product	yield (%)[b]	ee (%)[c]
7a		80	>99(S)
7b		70	>98(S)
7c		76	>99(S)
7d		69	>98 (S)
7e		65	>96 (S)
7f		82	>95 (S)

[a] All reactions were performed on a 0.5 mmol scale and proceeded to complete conversion. [b] Yield after chromatography. [c] Enantiomeric excess was determined using chiral stationary phase HPLC. See Supporting Information for complete details.

yields from 65−82% employing both primary and secondary amines, which include therapeutically relevant GPCR privileged structures.[12] Importantly, the (*S*)-imidazolidinone catalyst **3** provides the corresponding (*S*)-β-fluoroamines **7a**−**f** in 95−>99% ee (Table 2), whereas the (*R*)-imidazo-

Table 3. Scope of HNR_1R_2 in the Enantioselective Synthesis of (*R*)-β-Fluoroamines



compd[a]	product	yield (%)[b]	ee (%)[c]
8a		70	>98 (R)
8b		80	>87 (R)
8c		76	>98 (R)
8d		69	>94 (R)
8e		65	>96 (R)

[a] All reactions were performed on a 0.05 mmol scale and proceeded to complete conversion. [b] Yield after chromatography. [c] Enantiomeric excess was determined using chiral stationary phase HPLC. See Supporting Information for more details.

lidinone catalyst **3** provides the corresponding (*R*)-β-fluoroamines **8a**−**e** in 87−>95% ee (Table 3).

At this point, we wanted to explore the scope of this new methodology to produce β-fluoroamines employing alternative aldehydes and to determine if this new strategy would allow access to tertiary β-fluoroamines, a moiety inaccessible through DAST and other known chemistries.[8−10] We envisioned that these transformations might require alternative organocatalysts to (*S*)- and (*R*)-**3**, so we assembled a catalyst screening kit composed of compounds **9**−**13** for evaluation (Figure 1).

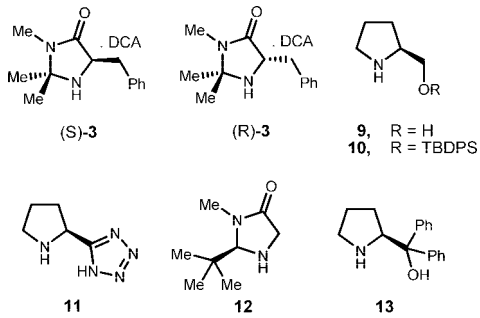
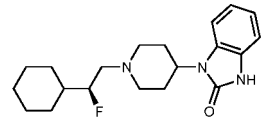
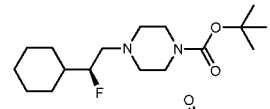
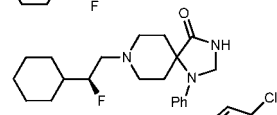
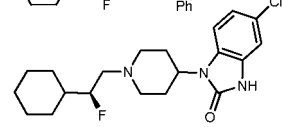
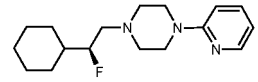
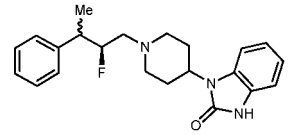
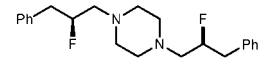
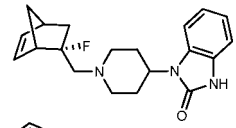
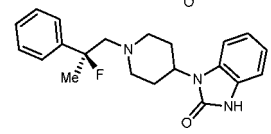


Figure 1. Organocatalysts examined in determining the scope of β-fluoroamine synthesis.

As shown in Table 4, the methdology appears general with respect to both aldehyde and amine component, affording

Table 4. Scope of β-Fluoroamine Synthesis via Organocatalysis

compd[a]	product	cat.	yield (%)[b]	ee (%)[c]
15 a		(*S*)-**3**	87	>99
15b		(*S*)-**3**	92	>98
15c		(*S*)-**3**	90	>96
15d		(*S*)-**3**	84	>99
15e		(*S*)-**3**	88	>99
15f		(*S*)-**3**	75	>95 1.2:1 dr[e]
15g		(*S*)-**3**	58	nd[d]
15h		(*S*)-**3** **9** **10** **11** **12** **13**	93 25 <10 94 83 16	15 13 nd[d] 31 16 12
15i		(*S*)-**3** **11**	74 75	17 40

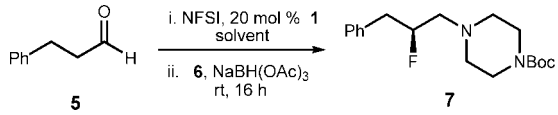
[a] All reactions were performed on a 0.05 mmol scale and proceeded to complete conversion. [b] Yield after chromatography. [c] Enantiomeric excess was determined using chiral stationary phase HPLC. [d] Not determined. [e] Diastereomer ratios were measured by ^{19}F NMR. See Supporting Information for complete details.

chiral β-fluoramines in good isolated yields (58−92%) and with high enantioselectivities (>96%ee). If the aldehyde bears a β-stereogenic center, as in **15f**, the β-fluoroine is still installed with high ee (>95%) but with a 1.2:1 dr. Compounds **15h** and **15i** represent transformations that all known standard β-fluoroamine methodology cannot produce: tertiary β-fluoroamines.[8−10] Standard conditions with (*S*)-**3** provide excellent chemical yield for installation of the tertiary β-fluoroamine but suffer from low enantioselectivity (15% ee). Catalysts **9**, **10**, and **13** provided poor conversion (<25%) and low ee. Like (*S*)-**3**, catalysts **11** and **12** installed the tertiary β-fluoroamine in good chemical yields, but the maximum ee observed was 31% with catalyst **11**. A similar

trend was observed in the synthesis of tertiary β-fluoroamine **15i**. Our standard methodolgy with (*S*)-**3** provided good conversion but only 17% ee. Switching to the tetrazole catalyst **11** provided the desired tertiary β-fluoroamine **15i** in comparable yield but with improved ee (40%). Thus, our new methodology allows access to tertiary β-fluoroamines with modest % ee, as opposed to existing methods that are unable to install tertiary β-fluoroamines.

Our attention now turned to developing a one-pot organocatalytic approach to β-fluoroamines to avoid the aqueous workup step. As shown in Table 5, this was smoothly

Table 5. One-Pot β-Fluoroamine Synthesis via Organocatalysis



5 7

entry[a]	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	THF	24	3	45	>95
2	CH_3CN	24	3	36	>95
3	CH_2Cl_2	24	24	12	nd[d]
4	DCE	24	24	0	nd[d]
5	THF/*i*-PrOH	−20	3	65	>96

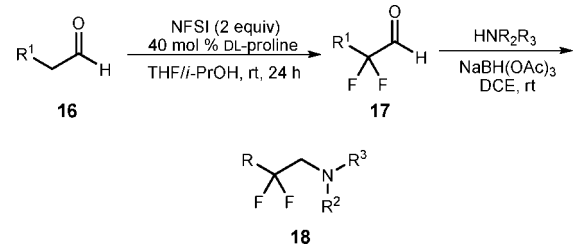
[a] All reactions were performed on a 0.05 mmol scale. [b] Yield after chromatography. [c] Enantiomeric excess was determined using chiral stationary phase HPLC. [d] Not determined.

accomplished by application of 1.0 equiv of NFSI, at −20 °C for 3 h in 10% *i*-PrOH/THF, followed by direct addition of 1.0 equiv of mono-Boc-piperazine **6** and 2.2 equiv of $NaB(OAc)_3H$ for 16 h. The desired β-fluoroamine **7** was delivered in 65% isolated yield and with >96% ee. The Boc protecting groups remained intact, highlighting the mild conditions of this one-pot procedure.

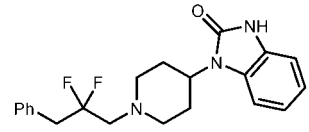
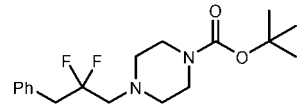
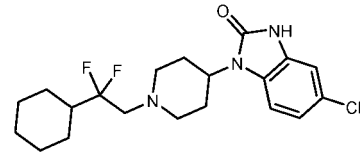
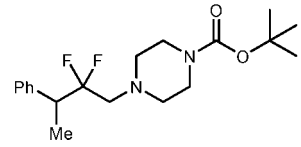
Finally, there are many examples in the literature where a β,β-difluoroamine is required to address a specific liability of a candidate molecule.[1−6] On the basis of an earlier observation of β,β-difluoroamine formation (Table 1) when excess NFSI was employed, we quickly developed a two-pot route to rapidly access this valuable moiety. In this instance (Table 6), aldehydes **16** were treated with 2 equiv of NFSI and 40 mol % DL-proline in 10% *i*-PrOH/THF at room tempertaure for 24 h to provide α,α-difluoroaldehydes **17**. After a quick aqueous workup, the resulting oils were resuspended in DCE, amine and $NaB(OAc)_3H$ were added, and the reaction was allowed to stir at room temperature for 16 h to provide β,β-difluoroamines **18** in isolated yields ranging from 64% to 77%.

In summary, we have developed a powerful extension of the MacMillan enantioselective α-fluorination of aldehydes for the *general* enantioselective synthesis of β-fluoroamines in yields and % ee far exceeding that of any other reported

Table 6. β,β-Difluoroamine Synthesis via Organocatalysis



16 17 18

cmpd[a]	product	yield (%)[b]
18a		64
18b		67
18c		77
18d		68

[a] All reactions were performed on a 0.05 mmol scale and proceeded to complete conversion. [b] Yield after chromatography.

method, and without rearranged and dehydrated side products. Moreover, our new methodology allows for the first synthesis of tertiary β-fluoroamines with enantioselectivities up to 40%. Furthermore, slight modification of our protocol provides rapid, high-yielding access to β,β-difluoroamines. Overall, these novel strategies for the synthesis of β-fluoroamines and β,β-difluoroamines, from readily available precursors, represents a significant improvement in the art to access these therapeutically relevant moieties.

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Supporting Information Available: Experimental procedures, characterization data, chiral LC traces, and ^1H, ^{19}F, and ^{13}C NMR spectra for all new compounds, **7a−f**, **15a−i**, and **18a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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