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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Enantioselective Synthesis of β-Fluoro Amines via β-Amino α-Fluoro Nitroalkanes and a Traceless Activating Group Strategy

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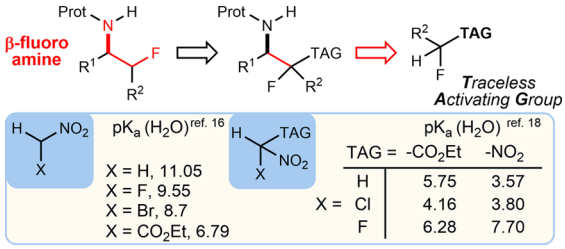
Supporting Information

ABSTRACT: Preparation of a range of enantioenriched β-fluoro amines (α,β-disubstituted) is described in which the nitrogen and fluorine atoms are attached to sp^3-hybridized carbons. The key finding is a chiral bifunctional Brønsted acid/base catalyst that can deliver β-amino-α-fluoro nitroalkanes with high enantio- and diastereoselection. A denitration step renders the nitro group "traceless" and delivers secondary, tertiary, or vinyl alkyl fluorides embedded within a *vicinal* fluoro amine functional group. A synthesis of each possible stereoisomer of a β-fluoro lanicemine illustrates the potential ease with which fluorinated small molecules relevant to neuroscience drug development can be prepared in a stereochemically comprehensive manner.

The introduction of the fluorine atom into small molecules has received increased attention,[1] in recognition of its ability to impart specific and dramatic pharmacological effects in bioactive pharmaceutical and agrochemical small molecules. Replacement of a single hydrogen with fluorine in a small molecule can increase metabolic stability, improve lipophilicity, and improve bioavailability.[2] Such a substitution, however, remains a formidable challenge, especially when the fluorine-bearing carbon is stereogenic.[3] β-Fluoro amines are a class of fluorinated compounds[4] that display remarkable CNS-penetrant properties. Additionally, the β-fluoro amine Sofosbuvir is an RNA polymerase inhibitor that is in part responsible for the recent and unprecedented high cure rates of the hepatitis C virus.[5] β-Fluoro amines exhibit decreased amine basicity and enhanced binding interactions.[6] From a synthetic standpoint, enantioselective methods to prepare chiral fluorocarbons have focused on C−F bond formation using both electrophilic[7] and nucleophilic[8,9] fluorine reagents.[1] Herein we report an approach to saturated β-fluoro amines by carbon−carbon bond formation,[10,11] reliant on a traceless nitroalkane activation strategy. A broad range of stereoenriched β-fluoro amines can be accessed, but of particular note is the convergency with which fluorinated derivatives of 1-phenethyl amines can be prepared,[12] because these are common substructures of neurologically active small molecules. β-Fluoro amines in which both carbons are chiral have few direct preparative solutions.

A convergent approach to the β-fluoro amine substructure involves formation of the central carbon−carbon bond, but requires both relative and absolute stereocontrol. Among possible fluoroalkyl nucleophiles activated by a traceless activating group (TAG,[13] Scheme 1), esters, *gem*-diesters and nitroalkanes can be

Scheme 1. Considerations for use of a Traceless Activating Group Strategy for Enantioselective β-Fluoro Amine Synthesis



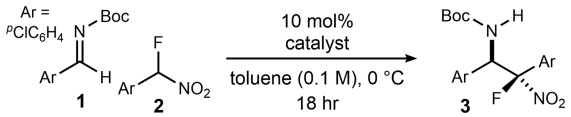
fluorinated, but only substrates bearing an α-fluoro carbonyl have been utilized broadly in enantioselective synthesis.[14] Lu reported enantioselective reactions using α-fluorinated nitroalkanes, but an additional activating group (ester or aryl) at the fluoromethyl carbon was required in the additions to nitro-olefins for a reaction to occur.[15] This highlights fluorine's limited effect on nitroalkane acidity relative to its higher halogen counterparts (Scheme 1).[16,17] Moreover, fluorine can actually deacidify carbon acids (Scheme 1): fluoronitromethane is less acidic than bromonitromethane, and fluoro dinitromethane is less acidic than dinitromethane.[18]

α-Fluoro nitroalkanes were prepared from their hydrocarbon parents by a deprotonation (KOH, aq CH_3CN) and fluorination (Selectfluor) treatment as outlined by Guo.[19] α-Fluoro aryl nitromethane **2** was used to first benchmark reactivity in a reaction with aldimine **1** (Table 1). Brønsted base catalyst HQuin-BAM (**4a**)[20] provided a low level of conversion, and equally low levels of diastereoselection (2.1:1 dr) and enantioselection (25% ee) (Table 1, entry 1). Increasingly Brønsted basic catalysts were examined, leading to good levels of conversion, but with little improvement to selectivity (Table 1, entries 2 and 3).[21] Examination of the reactivity of catalyst **4c** was extended to its acid salt (Table 1, entry 4), for which a corresponding increase in enantioselection, but not diastereoselection, was observed. Diastereoselection could be improved at the sacrifice of enantioselection by adding an additional electron-donating substituent to the catalyst (Table 1, entry 5), but its acid salt was unexpectedly less selective. The behavior was also observed with its 8-alkyl counterpart (Table 1, entry 7). It was not until a further increase in Brønsted basicity of the acid salts was sought that $^{6,7}(MeO)_2$PBAM·$HNTf_2$ (**4g**·$HNTf_2$) emerged as the key to formation of **3** with high yield (97%), diastereoselection (4.8:1), and enantioselection (91/86% ee) (Table 1, c.f. entries 8 and 9).

Received: August 1, 2016
Published: October 17, 2016

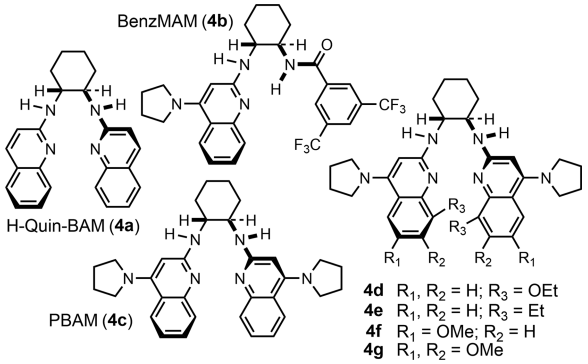
DOI: 10.1021/jacs.6b07731
J. Am. Chem. Soc. 2016, 138, 13794−13797

Table 1. Diastereo- and Enantioselective Synthesis of β-Amino-α-Fluoro Nitroalkanes: Catalyst Discovery and Development



entry	catalyst base	catalyst acid[a]	yield[b]	d.r.[c]	ee (%)[c]
1	HQuinBAM (**4a**)	–	<20	2.1:1	25/24
2	BenzMAM (**4b**)	–	93	4.4:1	25/36
3	PBAM (**4c**)	–	96	1.4:1	41/71
4	**4c**	$HNTf_2$	71	1.9:1	83/81
5	[8](EtO)PBAM (**4d**)	–	97	2.8:1	68/68
6	**4d**	$HNTf_2$	80	1.5:1	40/41
7	[8]EtPBAM (**4e**)	$HNTf_2$	42	1.6:1	70/71
8	[6](MeO)PBAM (**4f**)	$HNTf_2$	96	2.3:1	86/84
9	[6,7]$(MeO)_2$PBAM (**4g**)	$HNTf_2$	97	4.8:1	91/86
10	**4g**	–	84	1.4:1	63/77
11	**4g**	$HNTf_2$	71[d]	5.8:1	94/87
12	**4g**	$HNTf_2$	73[e]	4.1:1	88/77
13	**4g**	$HNTf_2$	62[f]	3.3:1	86/71

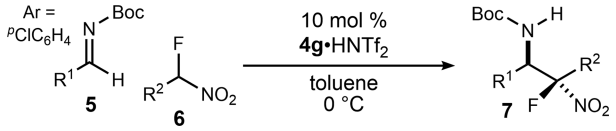
[a]Catalyst prepared as the 1:1 base:acid salt. Reactions are 0.1 M toluene unless otherwise noted. [b]Isolated yield. [c]Diastereomeric ratios determined by ^{1}H NMR, and enantiomeric excess (ee) determined by HPLC using a chiral stationary phase. The major diastereomer/enantiomer of **3** was determined by X-ray crystallographic analysis. [d]Reaction temp was −20 °C and ran for 40 h. [e]5 mol % catalyst employed. [f]2 mol % catalyst employed.

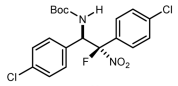
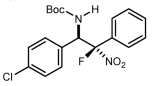
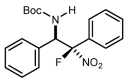
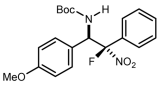
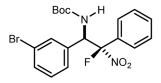
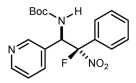
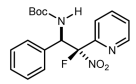
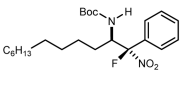
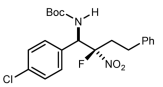
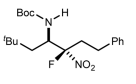
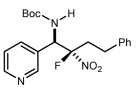


Use of the free base provided inferior results (Table 1, entry 10), in line with similar comparisons outlined, but in contrast to work with aryl nitromethanes that showed equal selectivity when comparing free base to its salt.[22,23] A temperature decrease led to improved selectivity (Table 1, entry 11). Catalyst loading could be decreased at some expense to selectivity (Table 1, entries 12 and 13). Assignment of absolute configuration was made using X-ray analysis of **3**.

An investigation of the level of generality inherent to the reaction and catalyst reagent is summarized in Table 2. The overall objective was to target four general classes of β-fluoro amines, defined by the type of substituent, aryl or alkyl, at the aminomethyl (R^1) and fluoromethyl (R^2) carbons (R^1,$R^2 \neq$ H). For example, the combination of aryl aldimine and aryl fluoronitromethane leads to a permutation with an aryl substituent at the aminomethyl and fluoromethyl carbons (**3**,**7a**–**f**). In this context, an electronically diverse group of aryl aldimines performed well (Table 2) en route to masked-fluoro stilbene amine compounds (*vide infra*). A highlight is the 3-pyridyl imine, resulting in relatively high diastereoselection at 6.9:1 dr and providing a heterocycle-containing product in high ee (Table 2, entry 6). A heterocycle

Table 2. Examination of Various Fluoro Nitroalkanes and Boc-Imines in the Enantioselective Aza-Henry Reaction[a]



entry	product	product	temp	yield[b]	dr[c]	ee (%)[c]
1		**3**	0 °C	97	4.8:1	91
2		**7a**	0 °C	93	5.2:1	95
3		**7b**	0 °C	87	4.5:1	95
4		**7c**	0 °C	86	5.6:1	96
5		**7d**	0 °C	92	4.8:1	92
6		**7e**	0 °C	86	6.9:1	95
7		**7f**	0 °C	81	2.5:1	95
8		**7g**	0 °C	21[e]	6.1:1	84
9			-20 °C	70[d,e]	9.0:1	93
10		**7h**	24 °C	85	5.0:1	93
11		**7i**	24 °C	21[e]	>10:1	84
12		**7j**	24 °C	84	4.4:1	96

[a]Catalyst prepared as the 1:1 acid salt. Reactions were 0.1 M in dry toluene for 18 h, unless otherwise noted. Relative and absolute configuration assigned by analogy to **3** (X-ray). [b]Isolated yield. [c]Diastereomeric ratios determined by ^{1}H NMR, and enantiomeric excess (ee, major enantiomer shown) determined by HPLC using a chiral stationary phase. [d]48 h reaction time. [e]Yield over 2-steps from α-amido sulfone (see Supporting Information).

is also allowable on the nitroalkane component, even when the pyridine nitrogen is in close proximity to the nitro group (Table 2, entry 7). This case was anticipated to be the most challenging from a catalyst selectivity standpoint, as it could serve as a frustrating hydrogen bond acceptor in the transition state. This feature may have contributed to the relatively low diastereoselection at 2.5:1 dr, but both diastereomers were formed with high enantioselection (95/94% ee), and in 81% yield (Table 2, entry 7).

N-Boc aldimines could provide an alkyl substituent at the aminomethyl carbon, but are challenging electrophiles due in part to their sensitivity to tautomerization to unreactive *N*-Boc enamides. Under the standard conditions, α-fluoro phenyl nitromethane engaged the imine to produce the product in moderate yield (53%, two steps from the α-amido sulfone) at 0 °C

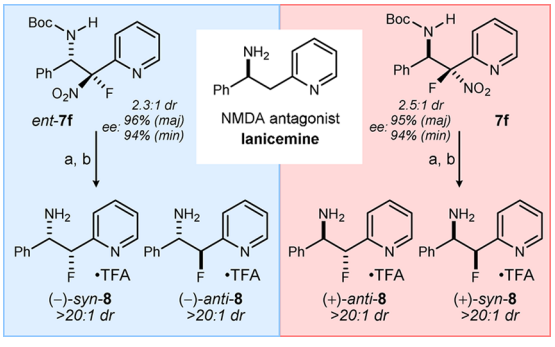
DOI: 10.1021/jacs.6b07731
J. Am. Chem. Soc. 2016, 138, 13794–13797

and serviceable stereoselection (6.1:1 dr, 84% ee) (Table 2, entry 8). Gratifyingly, improved stereocontrol and yield were obtained at −20 °C (9:1 dr, 93% ee, 70% yield over 2 steps: Table 2, entry 9) as a result of decreased imine tautomerization.[24] Alkyl fluoronitroalkanes can be easily prepared (2 steps from various alkyl bromides)[19] and are also suitable here for the first time in enantioselective catalysis, in direct contrast to previously reported attempts[15] (Table 2, entries 10−12). Notably, the alkyl fluoronitroalkanes react only at warmer temperatures (24 °C), allowing for an even more simplified reaction setup. Regardless, high levels of stereocontrol can be readily obtained (**7h**; 5:1 dr, 93% ee, 85% yield) (Table 2, entry 10).[25]

The coupling of two aliphatic partners (Boc-imine and fluoronitroalkane) is the most challenging pair due to the lower reactivity of each (21% yield, 2 steps), yet very useful levels of stereocontrol can be achieved (**7i**; > 10:1 dr, 84% ee) (Table 2, entry 11). In a final example, an alkyl fluoronitroalkane can engage a heteroaromatic pyridyl Boc-imine at room temperature to afford the adduct (**7j**) in good yield (84%) (Table 2, entry 12: 4.4:1 dr, 96% ee). Preliminary work to assess reactivity of α-fluoro nitroalkanes relative to their nonfluorinated counterparts replicated the trend suggested by relative pK_a (Scheme 1).[26] This aligns with the hypothesis that a more Brønsted basic catalyst is necessary for activation, and may explain the lack of prior success.[15]

The addition reactions in Table 2 are the basis for a collective preparation of the four stereoisomers of β-fluoro amines, a need that is particularly pressing in therapeutic development where a small molecule's conformation and protonation state affect its pharmacologic properties.[27] We targeted fluorinated lanicemine (**8**), a stereoisomeric series of compounds unknown in the literature. Lanicemine (AZD-6765) is a potent, low-trapping NMDA receptor antagonist (Scheme 2).[28] Preparation of both

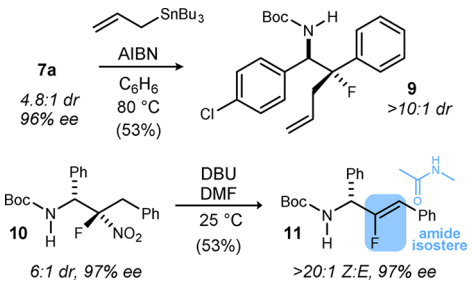
Scheme 2. Lanicemine (AZD6765) and Preparation of All Four Stereoisomers of "β-Fluoro-Lanicemine" (8)[a]



[a]Reaction conditions: (a) Bu_3SnH (4 equiv), AIBN (0.4 equiv), benzene, 80 °C, 180 min (dr ≈ 2:1 *anti*:*syn*, 74%); (b) TFA, CH_2Cl_2, 180 min (98%). In each case, diastereomers **8** were purified by reverse phase preparatory HPLC as their TFA salt adducts (see Supporting Information). Enantiomeric excess (ee) for stereoisomers **8** follow from ee of **7f**/*ent*-**7f**.

fluorine diastereomers would be considered important in exploratory studies for several reasons, including the conformational effects that result from the chiral fluoromethyl group.[29] Using the (*R*,*R*) and (*S*,*S*) antipodes of **4g**·$HNTf_2$ separately, each enantiomer of the addition product **7f** was obtained with high enantioselection (95−96% ee, Scheme 2). Conversions of β-fluoro-β-nitro amines to β-fluoro amines are unprecedented,[30] but were readily performed under reductive conditions using free

Scheme 3. Transformations of Enantioenriched α-Amino Fluoronitroalkanes: Denitrative Functionalizations



radical-mediated denitration.[31] It is this step that establishes the nitro functionality as a TAG.[13] Boc-deprotection produced the desired β-fluoro-lanicemine derivatives **8** in good yield overall.[32]

The potential versatility of the nitro group as a TAG was probed further (Scheme 3). Reductive allylation of **7a** formed the tertiary fluoro-β-amine **9** in >10:1 dr and 53% yield.[33] Under basic conditions, conversion of **10** to vinyl fluoride **11** was accomplished by regio- and stereoselective elimination of the nitro group.[34] This transformation establishes a new enantioselective approach to an amide isostere of phenyl glycine in this case.[13j,35−37]

In summary, a convenient stereocontrolled synthesis of β-fluoro amines has been developed, particularly those involving sp^3-hybridized secondary and tertiary fluoromethyls. The approach required development of the catalyzed addition of α-fluoro nitroalkanes to imines, one that allowed each permutation of aryl and alkyl substituent to be used for each reactant. High diastereoselection and enantioselection is possible when using a more Brønsted basic ligand (**4g**) within the Brønsted acid catalyst (**4g**·$HNTf_2$), which counteracted the acid-weakening effect of fluorine on nitroalkane acidity. A selection of denitrative functionalizations provided entry to several fluorinated pharmacophores.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07731.

Complete experimental details (PDF); NMR and HPLC trace data (PDF); Data for $C_{19}H_{19}Cl_2FN_2O_4$ (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

B.A.V. was supported in part by a Lamar Field Research Award. We are grateful to the National Institute of General Medical Sciences (NIH GM 084333) for financial support, Dr. Maren Pink (Indiana University Molecular Structure Center) for X-ray analysis, and Jade Bing for data collection.

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DOI: 10.1021/jacs.6b07731
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DOI: 10.1021/jacs.6b07731
J. Am. Chem. Soc. 2016, 138, 13794−13797