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Highly diastereoselective synthesis of enantioenriched anti-α-allyl-β-fluoroamines

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Abstract

A highly diastereoselective synthesis ofanti-a-allyl-b-fluoroamineshas been developed involving enantioselectivea-fluorination ofaldehydes followed by a diastereoselective Petasis allyl borono-Mannich reaction. The products are obtained generally in goodoverall yields for the two steps and with drs of 97 : 3-99 : 1 and eesof 86-92%. Selected products were converted to 3-, 5- and6-membered ring heterocycles, the latter two types incorporatingan exo-cyclic fluorine.

Keywords

enantioenriched, synthesis, diastereoselective, highly, anti-α-allyl-β-fluoroamines

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COMMUNICATION

Highly diastereoselective synthesis of enantioenriched *anti*-α-allyl-β-fluoroamines

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A highly diastereoselective synthesis of *anti*-α-allyl-β-fluoroamines has been developed involving enantioselective α-fluorination of aldehydes followed by a diastereoselective Petasis allyl borono-Mannich reaction. The products are obtained generally in good overall yields for the two steps and with drs of 97:3–99:1 and ees of 86-92%. Selected products were converted to 3-, 5- and 6-membered ring heterocycles, the latter two types incorporating an exo-cyclic fluorine.

Fluorine plays an important role in the development of pharmaceutical drugs, chiral ligands and organocatalysts[1] as it can modulate the electronic and conformational properties of molecules without imposing severe steric effects. The inductive effect of fluorine results in reduced basicity of neighbouring amines, which often leads to more desirable pharmacokinetic (PK) properties in amine based drugs, including increased bioavailability, enhanced metabolic stability, and desirable drug lipophilicity. In the case of PF-06459988 (Fig. 1 (a)), an irreversible and selective inhibitor of oncogenic EGFR mutants, the inductive effect of the fluoro substituent is essential for the enhanced reactivity of the acrylamide "warhead" moiety.[2] The neuroprotective agent P7C3-A20 (X = F) was significantly more potent than its hydroxy (X = OH) analogue (Fig. 1 (a)), with the F-substituent leading to reduced toxicity and better PK properties.[3] A recent survey of clinical candidates published in the *Journal of Medicinal Chemistry* (2016-2017) indicated that 43 out of 65 had at least one heterocyclic nitrogen while 20 had at least one fluorine atom.[4] Thus new methods to prepare cyclic and acyclic fluoro-substituted amines, are of significant importance in pharmaceutical drug development, including β-fluoroamines, as exemplified in the drug structures in Fig. 1 (a).

Several methods have been developed to prepare these compounds in enantioenriched form using chiral substrates or catalysts and nucleophilic[5] and electrophilic[6] fluorine regents, the Mannich[7] and aza-Henry reactions,[8] the hydrogenation of β-fluoro-enamines and enamides,[9] and the aminofluorination of alkenes.[10]

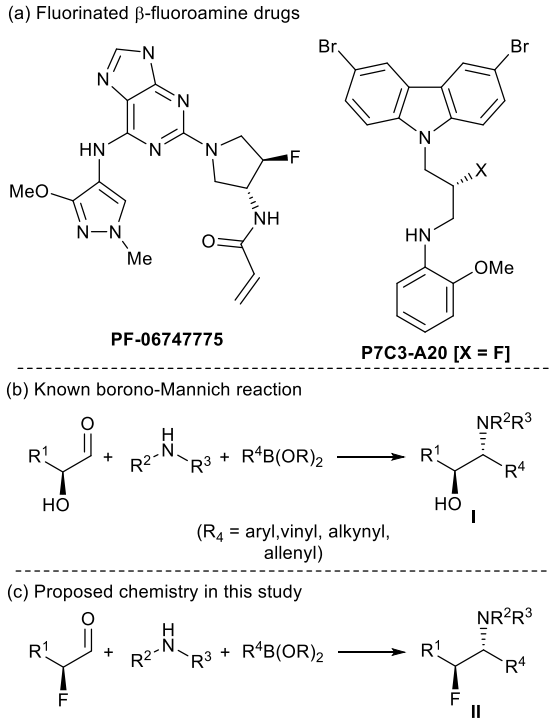

Fig. 1 (a) Structures of β-fluoroamine drugs. (b) Known borono-Mannich reaction. (c) Proposed chemistry in this study.

We report here a straightforward method of preparing α-allyl-β-fluoroamines (**II**, R^4 = allyl) with excellent *anti*-diastereoselectivities (dr 97:3–99:1) and high enantiomeric purities (ee 84–92%) using the three component Petasis borono-Mannich reaction (BMR) of chiral α-fluoroaldehydes, primary amines and pinacol allylboronate (Fig. 1 (b) and (c)). The

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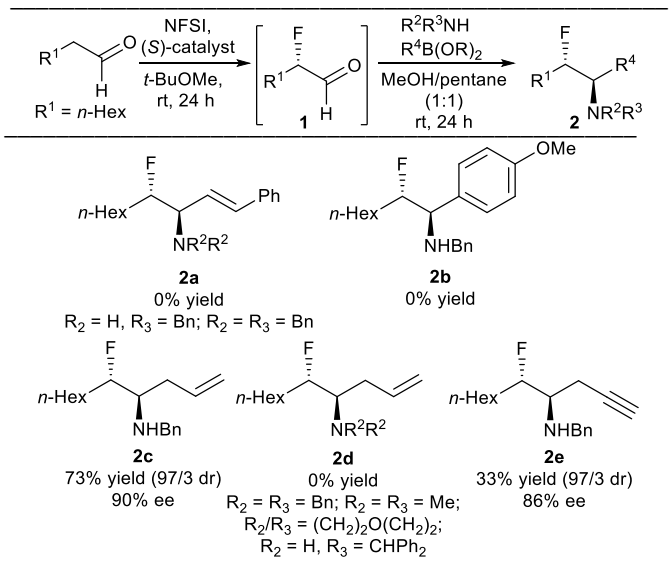
† Electronic Supplementary Information (ESI) available: [Experimental procedures, copies of NMR spectra and ORTEP plots for **3** (CCDC 1904599) and **5** (CCDC 1904600)]. See DOI: 10.1039/x0xx00000x

products have been converted to novel, 3-, 5- and 6-membered ring heterocycles.

Table 1 Scope of the boronate and amine components[a]



[a] Reaction conditions; Step 1: octanal (1.5 equiv), NFSI (1.0 equiv), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (0.001 equiv). Step 2: amine (2 equiv), organoboron reagent (2 equiv).

The BMR works most efficiently on substrates having a proximal hydroxy group (e.g. α-hydroxyaldehydes) which can activate the boron component by coordination.[11] Based on the strong inductive effect of fluorine we reasoned that α-fluoroaldehydes should also be productive components in the BMR. The report by Lindsley[6(a)] on the reductive amination of chiral α-fluoroaldehydes to give β-substituted-β-fluoroamines in high enantiomeric purities provide strong evidence for the stereochemical integrity and stability of the intermediate β-fluoroimines which would be a requirement for their successful BMRs to give enantioenriched α,β-disubstituted-β-fluoroamines (**II**) .

In this study we used the method of Jørgensen[12] to prepare (*S*)-α-fluorooctanal **1** (R = *n*-Hex) using (S)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether as the chiral organocatalyst, and *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating agent. We initially encountered isolation problems because of the volatility of this fluorinated product. To circumvent this, the reaction mixtures were diluted with pentane to precipitate unwanted by products and the solution was filtered then diluted with methanol (1:1) and treated directly with a primary or secondary amine (2.0 equiv, based on the amount of NFSI used) and a boronic acid, boronate ester or potassium trifluoroborateboronate (2.0 equiv) at ambient temperature. Those reactions using benzylamine and β-styrenylboronic acid, pinacol β-styrenylboronate or potassium β-styrenyl trifluoroborateboronate were unsuccessful and none of the desired BMR product **2a** (R^2 =H, R^3 = Bn) could be isolated (Table 1). The combination of dibenzylamine and β-styrenyl boronic acid was also ineffective at producing **2a** (R^2 =Bn, R^3 = Bn). The combination of 4-methoxyphenylboronic acid and benzylamine failed to produce the desired product **2b**. Other solvents (dichloromethane, or acetonitrile) were examined however these proved to be unsuccessful. The more reactive pinacol allylboronate[13] however, smoothly provided the desired β-fluoroamine **2c** in 73% yield as a 97:3 mixture of *anti* and *syn* diastereomers, respectively from ^{19}F NMR analysis (SI) (Table 1, entry 1).[14] Surprisingly, the BMR of **1** (R = *n*-Hex), pinacol allylboronate and secondary amines (Bn_2NH, Me_2NH and morpholine) or the hindered primary amine Ph_2CHNH_2 were unsuccessful in producing their respective products **2d**. An almost identical yield and dr of **2c** was obtained using potassium allyltrifluoroborateboronate. Lesser amounts (1.0 or 1.5 equiv) of either the amine or organoboron reagent or both resulted in reduced yields of product **2c**. The reaction involving pinacol allenylboronate[15] and benzylamine produced the propargyl product **2e** in modest yield (33%) but with high regiochemistry and diastereoselectivity (dr = 97:3). The enantiomeric purities of the *anti*-products of **2c** and **2e** were determined as 90% and 86%, respectively from ^{1}H and ^{19}F NMR analysis of their corresponding (1*S*)-camphorsulfonamide derivatives (SI).[16] This analysis method was validated for **2c**, and the latter compounds **2h**, **2i**, **2k**, **2l**, **2m** and **2o**, from the synthesis and NMR analysis of their corresponding enantiomeric compounds (e.g. *ent*-**2c**, Table 3) and their diastereomeric (1*S*)-camphorsulfonamide derivatives. The ee values of *anti*-**2c** and **2e** were slightly less than the reported 96% ee of (*S*)-α-fluorooctanal,[12] determined on its more stable alcohol derivative, indicating some erosion of the stereochemical integrity of **1** (R = *n*-Hex) had occurred. The major diastereomer of the (1*S*)-camphorsulfonamide derivative **3** of **2e** provided suitable crystals for X-ray structure determination which identified its absolute configuration and the *anti*-stereochemical relationship of the vicinal heteroatoms (Fig. 2).[17]

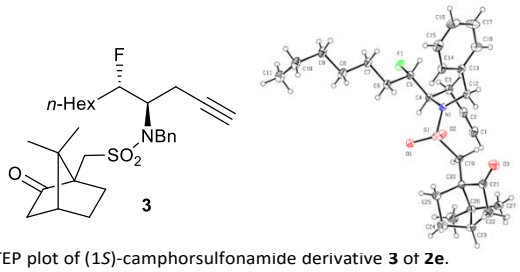
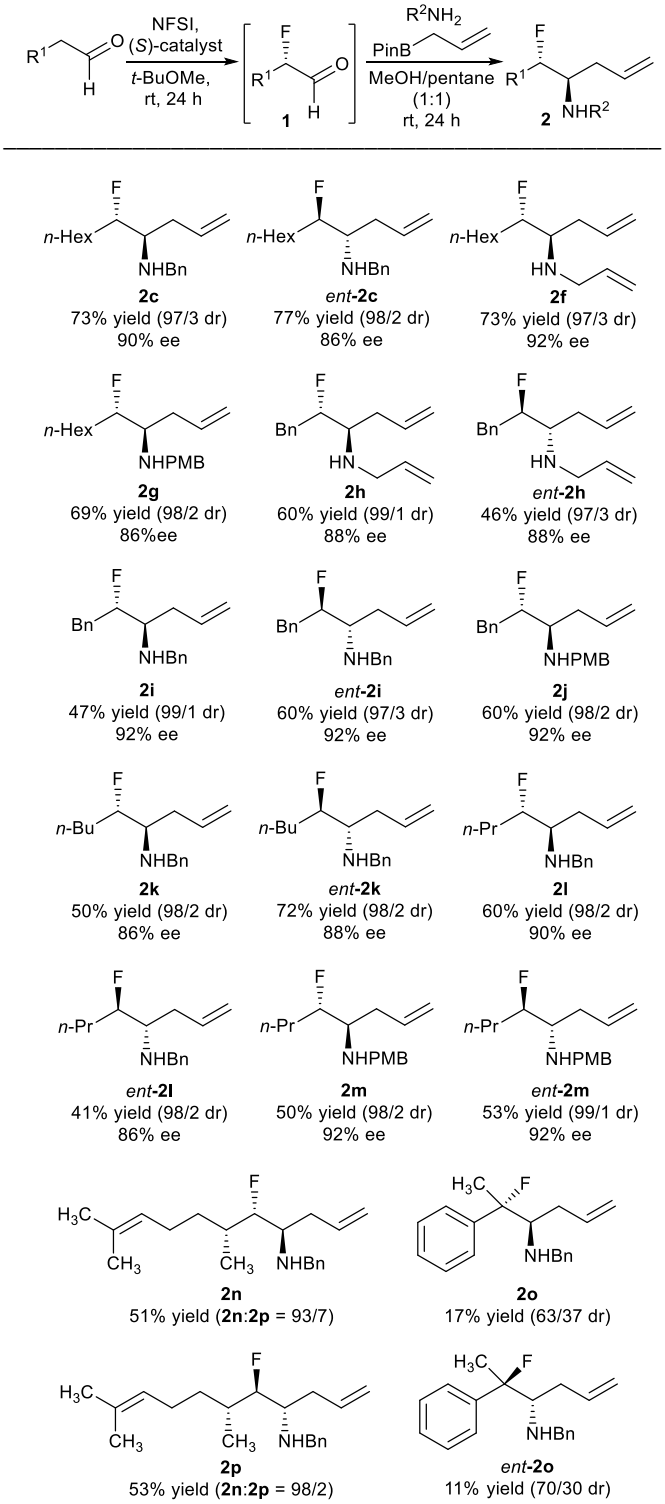


Fig. 2 ORTEP plot of (1*S*)-camphorsulfonamide derivative **3** of **2e**.

The generality of this diastereoselective allylation reaction with pinacol allylboronate, non-hindered primary amines and other (*S*)- (**1**) and (*R*)-α-aldehydes (*ent*-**1**) was further examined and the results are presented in Tables 2 and 3, respectively. Similar yields and diastereomeric ratios to **2c** were obtained for the products **2f**-**2m** starting with straight chain aldehydes and using benzylamine, allylamine or *p*-methoxybenzylamine (Table 2). Diastereomeric ratios were generally high (dr 97:3–99:1).[14] The enantiomeric purities (ee 86–92%) of the products derived from these aldehydes were similar, but slightly lower than those reported for the parent (*S*)-α-fluoroaldehydes (ee 91-96%).[12]

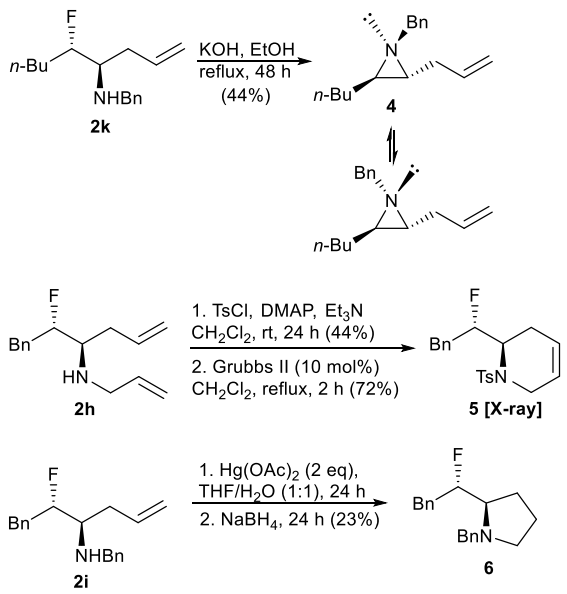
Table 2 Synthesis of (4*R*,5*S*) β-fluoroamines **2** and their (4*S*, 5*R*)-enantiomers (*ent*-**2**)[a]



[a]See Table 1 for general conditions. Yields based on NFSI as the limiting reagent. *Ent*-**2** compounds were prepared using the (*R*)-organocatalyst.

These reactions were also successful for the more hindered aldehydes, (*S*)-(-)-citronellal and racemic 2-phenylpropanal. The former aldehyde gave **2n** in a lower diastereoselectivity (**2n**:**2p** = 93:7) than obtained for its diastereomer **2p** (**2p**:**2n** = 98:2, Table 3) using the enantiomeric (*R*)-organocatalyst, likely reflecting a minor mismatching of catalyst and substrate in the asymmetric fluorination step in the former case. The latter, more hindered substrate, gave a relatively low yield of **2o** as a 63:37 mixture of diastereomers. An enantiomeric series of α-allyl-β-fluoroamines (*ent*-**2**) could be formed from (*R*)-α-fluoroaldehydes *ent*-**1** which, as expected, were formed in similar yields with comparable drs and ees (Table 2).

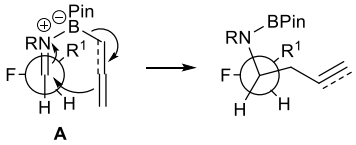
To demonstrate the potential utility of these *anti*-α-allyl-β-fluoroamine products, compound **2k** was treated with KOH in EtOH/H_2O under refluxing conditions.[18] This gave the expected *trans*-aziridine **4** as a 1:1 mixture of *N*-invertomers.[19] A ring-closing metathesis reaction of the *N*-tosyl derivative of **2h** gave the unsaturated piperidine **5** bearing a fluorinated side chain at C-2. The structure of this compound was secured by a single-crystal X-ray diffraction analysis (SI).[17] While cyclization of **2i** using $Hg(OAc)_2$[20] gave the analogous pyrrolidine derivative **6** in an unoptimized yield of 23%.



Scheme 1. Synthesis of 3-, 5- and 6-membered heterocycles

The success of only pinacol allylboronate and allenylboronate and primary amines, and the *anti*-diastereoselective outcomes in these BMRs can be readily rationalized by invoking the reactive imine intermediate **A**, involving B-N coordination (Scheme 2). Such coordination and activation of allenyl boronic acid and pinacol allenyl boronate has been suggested previously to explain the formation of propargyl products from their BMR reactions with α-hydroxyaldehydes and primary amines.[15] Intermediate **A** (R^1 = *n*-Hex) can reactive to give the allylic or propargylic products **2c** or **2d** via a favourable six-membered ring transition state involving a polar Felkin-Ahn model.[21] Clearly, an analogous intermediate for the unsuccessful β-styrenyl organoboron reagents and 4-methoxyphenylboronic acid (Table 1) would require a highly unfavourable four-membered ring transition

state. Interestingly, this stereochemical outcome is opposite to that found in the BMR of an α-hydroxy aldehyde with pinacol allylboronate which resulted in exclusive formation of the *syn* 1,2-amino alcohol product,[13] and not the expected *anti* one when aryl,- allenyl- or aryl-organoboron reagents are used.[11,15]



Scheme 2. Possible reactive intermediate **A**

In contrast, the analogous α-chloroaldehyde to **1** (R^1 = *n*-Bu, see SI for Scheme), gave, under similar BMR conditions using benzylamine, followed by treatment with KOH/EtOH/H_2O, a separable mixture of **4** (32%) and its *cis*-aziridine isomer (10%), thus indicating significantly poorer diatereoselectivity in the BMR than its fluoro counterpart.

In conclusion, we have developed a direct method for preparing *anti*-α-allyl-β-fluoroamines in two easily manipulated steps from aldehydes with excellent diastereoselectives (dr = 97:3–99:1) and high enantiomeric purities (ee 86-92%). These compounds would be difficult to prepare using many of the existing methods due to incompatibly of the allyl substituent to hydrogenation,[9] or electrophilic fluorine reagents,[6] or regioselectivity issues when using ring-opening of 2-allyl-3-alkyl aziridines with nucleophilic fluorine,[18] or would otherwise require a more lengthy synthesis. Thus, this work offers a complementary and practical method towards these important compounds.

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Conflicts of interest

There are no conflicts to declare.

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16 The ee values of the *anti*-β-fluoroamines **2** and *ent*-**2** were calculated from the dr of their resulting (1*S*)-camphorsulfonamide derivatives which were determined by ^1H and ^{19}F NMR analysis. Typically, the diastereotopic methylene protons next to the SO_2 group showed well resolved ^1H NMR doublet resonances unique to each diastereomer. For NBn and NPMB derivatives the diastereotopic benzylic methylene resonances could also be used to calculate dr values. In each case, the ratios calculated from ^1H and ^{19}F NMR analysis were identical within experimental error. In contrast, the resonances for the (1*S*)-camphorsulfonamide derivatives of the minor *syn*-isomers were relatively minor; with the minor diastereomer usually not detected.

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