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Enantioselective Synthesis of β-Fluoroamines from β-Amino Alcohols: Application to the Synthesis of LY503430

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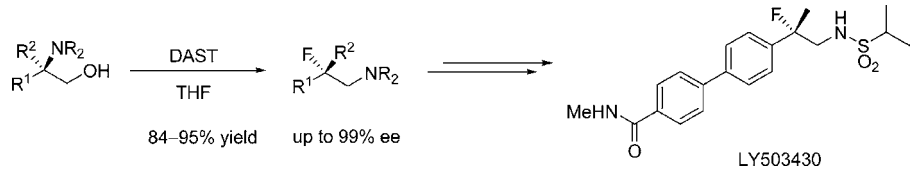
ABSTRACT



***N,N*-Dialkyl-β-amino alcohols were enantiospecifically and regioselectively rearranged by using *N,N*-diethylaminosulfur trifluoride (DAST) to give optically active β-fluoroamines in excellent yields and enantiomeric excesses. This rearrangement was applied to the enantioselective synthesis of LY503430, a potential therapeutic agent for Parkinson's disease.**

The introduction of a fluorine atom in organic molecules can alter their physical, chemical, and biological properties.[1] Because of the great importance of fluorinated compounds as pharmaceuticals and agrochemicals, the development of chiral fluorinating agents and enantioselective methods has been increasing in the last decades.[2,3]

Different fluorinating agents, among them, *N,N*-bis(2-methoxyethyl)aminosulfur trifluoride (deoxo-fluor)[4] and *N,N*-diethylaminosulfur trifluoride (DAST)[5] revealed powerful reagents to transform alcohols to the corresponding monofluorinated products.[6] The fluorination of optically active alcohols by using these reagents proceeds in general with inversion of configuration. Furthermore, these reagents can induce rearrangements such as ring contractions or ring expansions through anchimeric assistance of an electron-rich group present in the vicinity of a hydroxyl group.[7]

Few synthetic methods were developed to prepare linear β-fluoroamines.[8] Recently, organocatalytic fluorination of aldehydes was used to access chiral β-fluoroamines.[8c] However, only secondary β-fluoroamines were obtained with good enantiomeric excesses. Here, we would like to report a general enantioselective rearrangement of optically active linear β-amino alcohols **A** to β-fluoroamines **B** using DAST and its application to the synthesis of LY503430, a potential therapeutic agent for Parkinson's disease[9] (Scheme 1).

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(2) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558–568.
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(6) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561–2578.
(7) (a) Ferret, H.; Déchamps, I.; Gomez Pardo, D.; Van Hijfte, L.; Cossy, J. *ARKIVOC* **2010**, *viii*, 126–159. (b) Ye, C.; Shreeve, J. M. *J. Fluorine Chem.* **2004**, *125*, 1869–1872. (c) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224–4234. (d) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 263–267.
(8) (a) Verniest, G.; Van Hende, E.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2006**, *21*, 4767–4770. (b) Verniest, G.; Colpaert, F.; Van Hende, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 8569–8572. (c) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943–946 and references cited therein.
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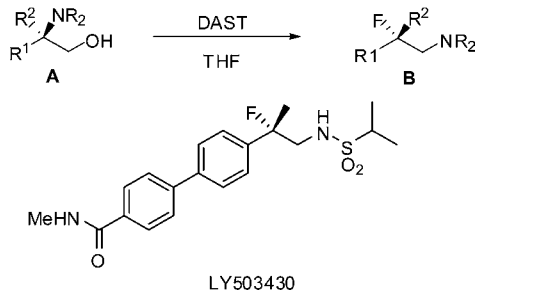
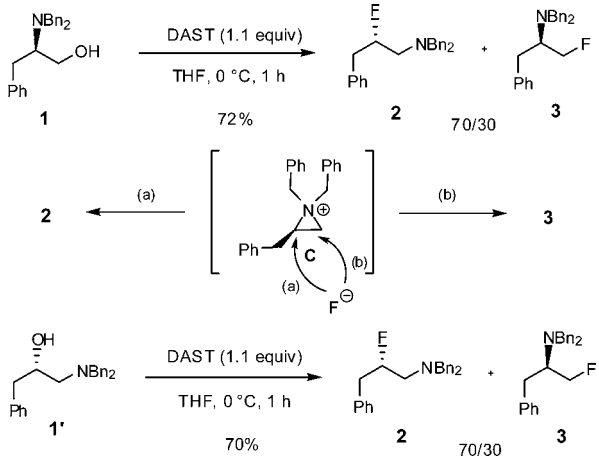
Scheme 1. General Scheme



Our study started with the rearrangement of β-amino alcohol **1**. When this compound was treated with DAST (1.1 equiv) in THF at 0 °C, two fluoroamines **2** and **3** were formed in a ratio 70/30 in 72% yield. To prove that an aziridinium intermediate **C** was involved in the formation of **2** and **3**, amino alcohol **1′** was treated with DAST. After 1 h at 0 °C, compounds **2** and **3** were obtained in a similar ratio (**2**/**3** = 70/30) and in a similar yield (70%). These results suggest that DAST can induce the formation of an aziridinium intermediate **C** (Scheme 2).[10]

Scheme 2. Rearrangement of **1** and **1′**

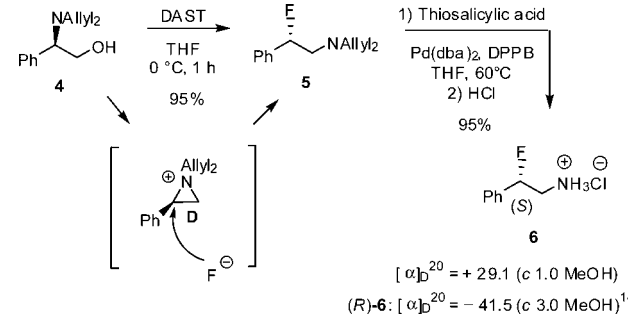


Furthermore, to prove that amines **2** and **3** were not formed under thermodynamic control, β-fluoroamine **2** was treated with DAST (1.1 equiv, 0 °C, 1 h). Under these conditions, compound **2** was recovered quantitatively without any traces of **3**. This result proves that compounds **2** and **3** are not under a thermodynamic equilibrium (via aziridinium **C**). Therefore, this rearrangement is under kinetic control, and the attack of the fluorine atom on aziridinium **C** leads to a mixture of the rearranged β-fluoroamine **2** (attack a) and its regioisomer **3** (attack b) as described for the opening of aziridiniums by fluoride anion.[11]

(10) Metro, T.-X.; Duthion, B.; Gomez Pardo, D.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89–102.

Interestingly, when amino alcohol **4** was treated with DAST (1.1 equiv, THF, 1 h, 0 °C), fluoroamine **5** was formed in 95% yield with no trace of its regioisomer (Scheme 3). This result is certainly due to the presence

Scheme 3. Rearrangement of **4**



of the phenyl group which favored the attack of the fluorine anion on the benzylic carbon of the aziridinium intermediate **D**. This case is closely related to the regioselective rearrangement of benzylic ester of *N*,*N*-dibenzyl-L-serine induced by DAST.[12] The (*S*)-configuration of the tertiary center was determined after transformation of **5** to **6** (thiosalicylic acid, $Pd(dba)_2$, DPPB, THF then HCl, 1 M)[13] and comparison of the α_D of **6** and (*R*)-**6**.[14]

Similarly, when amino alcohol **7**[15] (ee = 93%) was treated with DAST (1.5 equiv, THF, 1 h, 0 °C), fluoroamine **11** was isolated in 84% yield and with an enantiomeric excess of 91%. We have to point out that the regioisomer **11′** was not detected. The configuration of the quaternary center was determined after the transformation of **11** to **16**. After comparison of the α_D of **16** and (*S*)-**16′** described in the literature,[16] the (*R*) configuration was assigned to the quaternary stereogenic center present in **16** (Scheme 4).

This rearrangement is general as amino alcohols **8**−**10** were transformed to **12**−**14** in excellent yields and with good to excellent enantiomeric excesses[17] (Table 1).

This enantioselective rearrangement can be explained by the activation of the hydroxy group of aminoalcohol **A** by DAST to produce intermediate **E** which is transformed to aziridinium **F** by an S_Ni reaction. After selective attack of the fluorine atom on the more substituted carbon of the aziridinium, the fluoroamine **B** is formed (Scheme 5).

(11) (a) D'hooghe, M.; Catak, S.; Stankoviæ, S.; Waroquier, M.; Kim, Y.; Ha, H.-J.; Van Speybroeck, V.; De Kimpe, N. *Eur. J. Org. Chem.* **2010**, 4920–4931 and references cited therein. (b) Alvernhe, G.; Lacombe, S.; Laurent, A. *Tetrahedron Lett.* **1980**, *21*, 289–292.

(12) Somekh, L.; Shanzer, A. *J. Am. Chem. Soc.* **1982**, *104*, 5836–5837.

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(14) Hamman, S. *J. Fluorine Chem.* **1989**, *45*, 377–387.

(15) Smith, N. D.; Wohlrab, A. M.; Goodma, M. *Org. Lett.* **2005**, *7*, 255–258.

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(17) Determined by supercritical fluid chromatography on the chiral phase.

Scheme 4. Rearrangement of **7** and Chemical Correlation

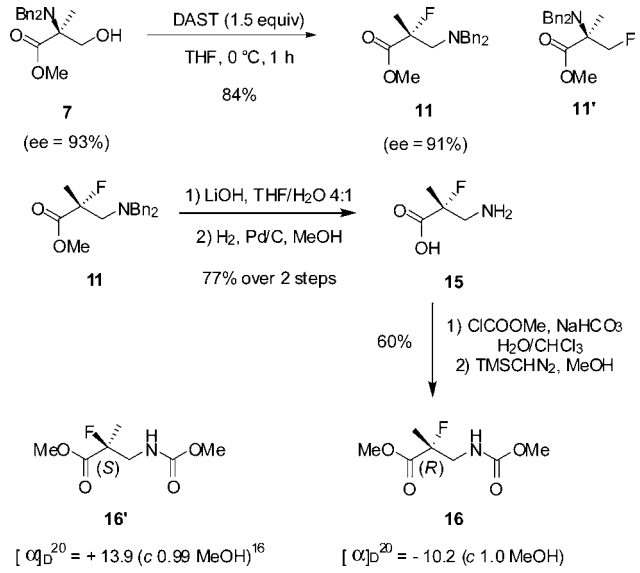
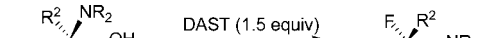


Table 1. Rearrangement of **8**−**10**

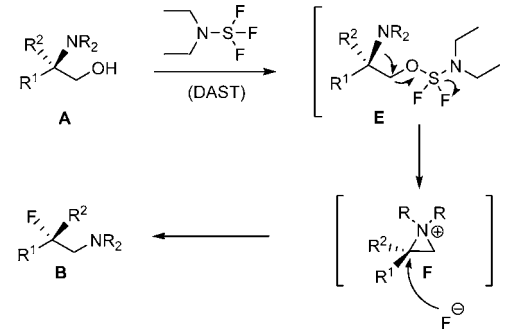


starting material	product (yield; ee[17])
8 (ee > 99%)	**12** (91%; > 99%)
9 (ee > 99%)	**13** (90%; > 99%)
10 (ee = 81%)	**14** (95%; 77%)[a]

[a] 2.2 equiv of DAST was used.

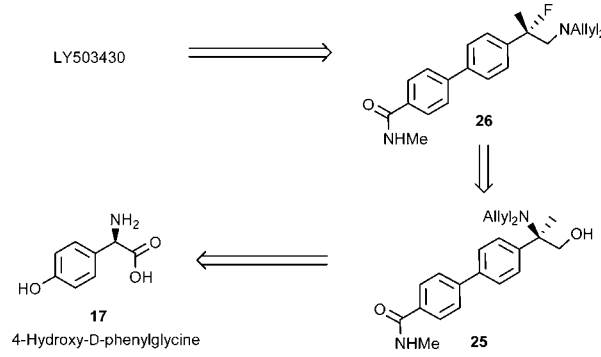
As the rearrangement of amino alcohols **A** induced by DAST is enantioselective and regioselective, its application to the synthesis of LY503430 was envisaged. LY503430 is a potential therapeutic agent for Parkinson's disease[9] which was prepared by Eli Lilly starting from 4-iodoacetophenone and by using a diastereomeric salt resolution to introduce the chirality.[18]

Scheme 5. Mechanism of the Rearrangement



For our part, we have envisaged an enantioselective synthesis of LY503430 from 4-hydroxy-D-phenylglycine **17** utilizing, as the key step, the enantioselective rearrangement of amino alcohol **25** induced by DAST to produce the desired fluoroamine **26** which will be the precursor of LY503430 (Scheme 6).

Scheme 6. Retrosynthesis of LY503430



The synthesis of LY503430 started with 4-hydroxy-D-phenylglycine **17** which was transformed to oxazolidinones **18**/**18′** in a ratio of 5/1 ($ClCO_2Me$/NaOH, then $PhCH(OMe)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, yield = 68%), Scheme 7).[19]

After chromatography, **18** was isolated and converted to the alkylated oxazolidinone **19** (LiHMDS, MeOTf, THF) with a diastereomeric ratio superior to 95/5. After reduction with L-Selectride, oxazolidinone **20** was formed in 74% yield, with an enantiomeric excess of 97%.[17] In order to introduce the biaryl moiety, a Suzuki coupling was envisaged. Thus, **20** was transformed to triflate **21** (Tf_2O, Py, 96%), and this latter was treated with the boronic acid **23** (2.0 equiv) in the presence of palladium(0) [$Pd(OAc)_2$ (5 mol %), X-Phos (12.5 mol %), $K_3PO_4{\cdot}H_2O$ (3.0 equiv), THF, 100 °C, 12 h, MW][20] to produce the desired coupling product **22** (80% yield). Compound **22** was then transformed to

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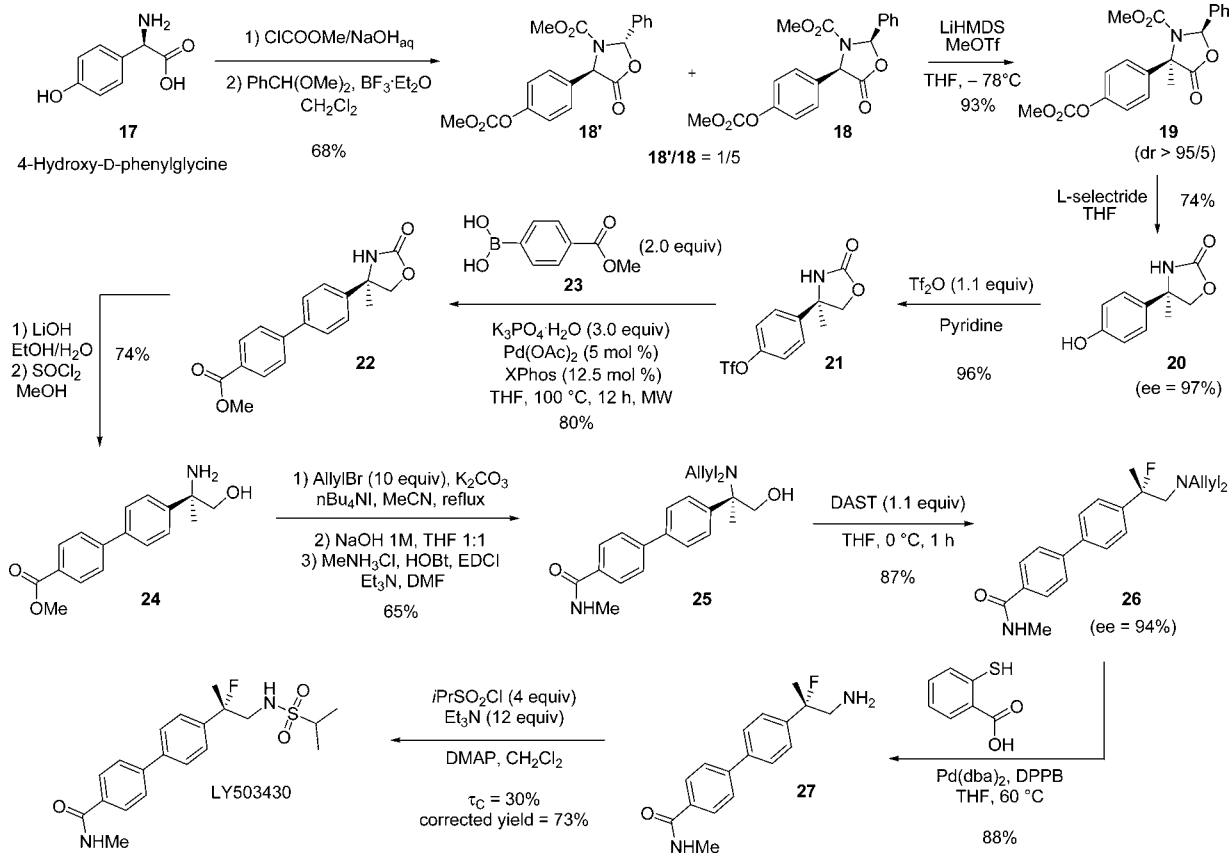
Scheme 7. Synthesis of LY503430



amino alcohol **25** in five steps. The first step was the conversion of **22** into amino alcohol **24** (LiOH, EtOH/H_2O then $SOCl_2$, MeOH, 74%) followed by its *N*,*N*-bis-allylation (AllylBr, K_2CO_3, *n*-Bu_4NI, MeCN, reflux), saponification of the ester group (NaOH, 1 M, THF 1/1), and amidification of the resulting carboxylic acid. Amino alcohol **25** was obtained in 65% overall yield. The key transformation was then realized by treating **25** with DAST (1.1 equiv) in THF (0 °C, 1 h), and under these conditions, the fluoroamine **26** was isolated (87% yield) with an enantiomeric excess of 94%.[17] In order to obtain LY503430, the amino group was deprotected (thiosalicylic acid, $Pd(dba)_2$, DPPB, THF, 88%),[13] and then the sulfonylation of the resulting primary amine **27** was achieved (*i*-$PrSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, τ_C = 30%, corrected yield = 73%). The spectroscopic data as well as the α_D [α_D = +27.7 (*c* 0.1, MeOH)] were in perfect agreement with those previously reported in the literature [α_D = +31.0 (*c* 1.0, MeOH)],[18] demonstrating once again that the rearrangement of β-amino alcohols induced by DAST is highly enantioselective and regioselective whatever the substituents on the quaternary carbon.

In conclusion, we have developed an enantioselective and regioselective rearrangement of linear β-amino alcohols to β-fluoroamines induced by DAST, and this rearrangement can be used to synthesize biologically active compounds such as LY503430.

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Supporting Information Available: General experimental procedure and characterization data of compounds **2**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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