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Practical Methodology for the Asymmetric Synthesis of Organofluorine Compounds

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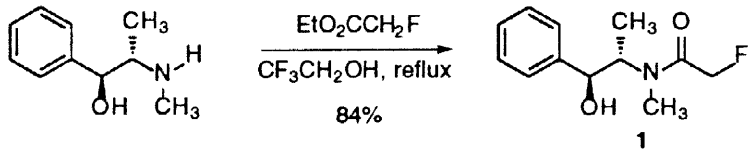
Abstract: Pseudoephedrine α-fluoroacetamide (**1**), a nonvolatile, crystalline solid, is alkylated efficiently and with high diastereoselectivity with reactive alkyl halides. The alkylation products can be hydrolyzed under mild basic conditions to form α-fluoro carboxylates with high enantiomeric enrichment.

One of the most common and powerful strategies for lead development in the pharmaceutical industry involves the selective replacement of C-H bonds with C-F bonds. The large number of organofluorine compounds within FDA-approved pharmaceuticals is testimony to the prevalence of this strategy.[1] It is perhaps surprising, then, how few drugs have been developed that bear C(sp^3)-F bonds where the carbon atom forms a stereogenic center. A major contributing factor in this regard is no doubt the paucity of practical methodology for the asymmetric synthesis of chiral organofluorine compounds, particularly methodology in which a C-C(F) bond is formed.[2] In extension of studies of the use of pseudoephedrine as a chiral auxiliary for asymmetric carbon-carbon bond formation,[3] we describe herein practical methodology for the preparation of highly enantiomerically enriched α-fluoro carboxylic acids by an asymmetric alkylation procedure.

The synthetic method employs pseudoephedrine α-fluoroacetamide (**1**), a crystalline, nonvolatile compound, as the substrate in the initial carbon-carbon bond forming step. This substrate was initially prepared by the acylation of pseudoephedrine with fluoroacetyl chloride,[4] however the inconvenience and hazards associated with the production and use of fluoroacetyl chloride led us to develop an alternative preparation of **1** that uses the readily available reagent ethyl fluoroacetate as the acylating agent, as detailed in the procedure below.



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****CAUTION:** Fluoroacetyl chloride, fluoroacetic acid, and derivatives of fluoroacetic acid are exceedingly toxic, causing convulsions and ventricular fibrillation upon inhalation and should be used only under adequate supervision and in an appropriate fume hood. Although the specific toxicities of **1** and other fluorinated pseudoephedrine amides described herein are unknown, we urge that extreme caution be exercised in their preparation and handling.

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Pseudoephedrine α-Fluoroacetamide (1) A suspension of (1*S*,2*S*)-(+)-pseudoephedrine (5.019 g, 30.37 mmol, 1 equiv) in a mixture of ethyl trifluoroacetate (3.82 mL, 39.5 mmol, 1.3 equiv) and 2,2,2-trifluoroethanol (10.8 mL)[5] was heated at reflux for 2 h. During this time the solids dissolved to form a clear, colorless solution. The reaction mixture was cooled and concentrated, and the residue was partitioned between 1 N aqueous hydrochloric acid solution (50 mL) and ethyl acetate (100 mL, 3 x 50 mL). The combined organic extracts were dried (sodium sulfate) and concentrated. The colorless oily residue was dissolved in toluene (20 mL) and the solution was concentrated to afford a white solid (6.427 g, 94%). Recrystallization of the solid from toluene (12 mL, 0 °C, 2 crops) provided **1** as white crystals (5.757 g, 84%, mp 84-85 °C). Calcd for $C_{12}H_{16}FNO_2$: C, 63.98; H, 7.16; N, 6.22. Found: C, 63.94; H, 7.32; N, 6.12.

In earlier studies, alkylation reactions of a wide range of α-substituted pseudoephedrine acetamides, to include α-chloro, were found to be highly diastereoselective, an outcome which must rely, in part, upon the selective generation of essentially one enolate isomer, presumed to be of *Z*-configuration.[3] The diminished steric requirements of the fluorine atom of **1** make the stereochemical outcome of enolization reactions of this substrate, be they kinetically or thermodynamically controlled, uncertain.[6] Perhaps for this reason, enolization and alkylation of **1** under conditions previously developed for the alkylation of pseudoephedrine amides [2.15 equiv lithium diisopropylamide (LDA), 6.0 equiv LiCl, –78 °C, 1.3 h; 3.0 equiv CH_3I, –78 °C, 2.5 h][3] was found to afford a diastereomeric mixture of alkylation products (64% de, 81% yield). Although the major diastereomer had been formed with the same sense of induction as observed previously with other substrates, the magnitude of the diastereoselectivity was much reduced. By contrast, when the enolization of **1** was conducted with lithium hexamethyldisilazide (LHMDS, 2.15 equiv) as base followed by trapping with methyl iodide (3 equiv, –78 °C, then warming to –50 °C for 30 min) a highly selective alkylation reaction took place (99% crude de, as determined by capillary GC analysis of the corresponding acetate) to provide the diastereomer indicated in the equation below in 97% yield after purification by flash column chromatography (≥99% isolated de, stereochemistry determined by X-ray crystallographic analysis). The basis for the improved selectivity in alkylations conducted with LHMDS versus LDA is not known, however, as suggested above, an immediate consideration is the stereochemistry of enolate formation. In analogy with proposals set forth concerning the enolization and alkylation of other pseudoephedrine amides,[3] it is presumed that the enolization of **1** with LHMDS, be it kinetically or thermodynamically controlled, exhibits a strong preference for the *Z*-configuration (fluorine cis to the oxyanion). Experiments to determine the stereochemistry of the enolate(s) formed from **1** and LHMDS or LDA using low temperature ^{1}H NMR and ^{19}F NMR spectroscopy have thus far been inconclusive.[6]

The efficiency and selectivity of the forgoing transformation appears to be general for alkylations with reactive electrophiles, as illustrated in Table 1 below. The sense of alkylation in entries 1 and 4 was established by X-ray crystallography; other entries were assigned by analogy in a comparative analysis of ^{1}H and ^{13}C NMR spectra. Unlike other pseudoephedrine amide enolates, the enolate derived from the fluoroacetamide **1** exhibits limited thermal stability above ~ –40 °C and, as a consequence, alkylation reactions with less reactive halides such as ethyl iodide (entry 6, Table 1) proceed poorly. The use of ethyl triflate in the reaction (entry 5, Table 1) provides improved results. A representative alkylation procedure follows:

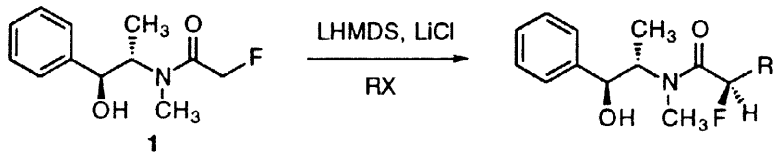

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Table 1. Diastereoselective Alkylation of Pseudoephedrine Fluoroacetamide (**1**).

Entry	RX[a]	Temp (°C)	Time (h)	Crude de (%)	Isolated de (%)	Isolated Yield (%)
1	CH_3I	–50	0.5	99	≥99	97
2	CH_2=$CHCH_2I$	–78	3	≥90	≥96	88
3	CH_2=$C(CH_3)CH_2Br$	–40	4	94	≥95	91
4	$C_6H_5CH_2Br$	–40	5	92	≥99	87
5	$C_2H_5OSO_2CF_3$	–78	3	89	99	54
6	CH_3CH_2I	–55	5	–	93	29

[a]Alkylation reactions employed 3 equiv of electrophile.

[1*S*(*R*),2*S*]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2-fluoropropionamide (Entry 1) Anhydrous lithium chloride (1.27 g, 30.0 mmol, 6.00 equiv) was flame-dried under vacuum to ensure dryness, then was allowed to cool under an atmosphere of dry argon. Bis(trimethylsilyl)amine (2.32 mL, 11.0 mmol, 2.20 equiv) and THF (5.00 mL) were added to the solid lithium chloride after it had cooled, and the resulting suspension was cooled to –78 °C in a dry ice-acetone bath whereupon *n*-butyllithium (2.56 M in hexanes, 4.20 mL, 10.8 mmol, 2.15 equiv) was added. The reaction vessel was briefly transferred to an ice bath (15 min), then was cooled to –78 °C. A solution of pseudoephedrine α-fluoroacetamide (**1**, 1.13 g, 5.00 mmol, 1 equiv) in THF (15 mL) was added via cannula, and the addition was quantitated with a 5-mL portion of THF. After stirring at –78 °C for 1.3 h, the reaction solution was treated with methyl iodide (0.934 mL, 15.0 mmol, 3.00 equiv). The reaction mixture was warmed to –50 °C and was stirred at that temperature for 30 min. Following an aqueous work-up, the product was purified by flash column chromatography (1:1 ethyl acetate-hexanes) to provide 1.16 g (97%) of [1*S*(*R*),2*S*]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2-fluoropropionamide as a viscous oil (de 99%, capillary GC analysis of corresponding acetate) which solidified upon standing. Recrystallization (ethyl acetate:benzene:hexanes 1:3:10, 0 °C) afforded a white crystalline solid (1.10 g, 92%, ≥99% de, mp 76-79 °C). Calcd for $C_{13}H_{18}FNO_2$: C, 65.24; H, 7.59; N, 5.86. Found: C, 65.03; H, 7.36; N, 5.75.

A particular advantage of the alkylation methodology described herein is the facility with which the products are hydrolyzed to the corresponding carboxylic acids (Table 2). Hydrolysis is brought about within a few hours by warming (~75 °C) each substrate in a biphasic solution of 2 N sodium hydroxide in a mixture of water, *t*-butyl alcohol, and methanol (2:1:1, respectively). Importantly, the hydrolysis proceeds with little to no

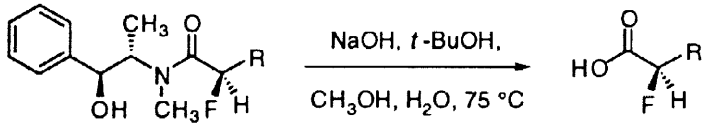

Table 2. Basic Hydrolysis of Pseudoephedrine α-Fluoro Amides.

Entry	Substrate de (%)	R	Isolated Yield (%)	Isolated ee (%)
1	≥99	CH_3	91	98
2	99	C_2H_5	95	96
3	≥96	CH_2CH=CH_2	90	93

racemization of the α-stereocenter in the cases examined thus far. The conditions for hydrolysis of the amide bond are exceedingly mild, a fact that is rationalized as a consequence of inductive activation of the carbonyl group by the adjacent fluorine atom. As we have observed previously in the basic hydrolysis of α-amino pseudoephedrine amides,[3c,d] the α-heteroatom appears to accelerate nucleophilic addition to the carbonyl group to a much greater extent than the enolization reaction that brings about racemization. The α-fluoro carboxylates are readily isolated by a simple extraction procedure and, if desired, the pseudoephedrine auxiliary can be recovered in high yield. The procedure that follows provides experimental detail.

(2*R*)-2-Fluoropropionic Acid A biphasic solution of [1*S*(*R*),2*S*]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2-fluoropropionamide (≥99% de, 0.837 g, 3.50 mmol, 1 equiv) in a mixture of 2 N aqueous sodium hydroxide solution (17.5 mL, 35.0 mmol, 10 equiv), *t*-butyl alcohol (8.75 mL), and methanol (8.75 mL) was heated in an oil bath at 75 °C for 4 h. The hydrolysis mixture was allowed to cool to 23 °C whereupon the pseudoephedrine auxiliary was removed by extraction with ether (3 x 2.5 mL). The aqueous layer was acidified to pH ≤1 by the addition of 3 N aqueous hydrochloric acid solution, then was saturated with sodium chloride. The product was extracted into ether (3 x 5 mL) and, after drying (Na_2SO_4), the ethereal solution was carefully concentrated (bath temperature ≤15 °C). The residue was dissolved in benzene and the resulting solution was passed through a pad of Celite (benzene eluent) to afford, after concentration (bath temperature ≤15 °C) the title compound as a colorless oil (0.295 g, 91%). High field ^{1}H NMR and capillary GC analysis of the corresponding α-methylbenzylamide, formed from the product by reaction with (*R*)-(+)-α-methylbenzylamine [1.5 equiv, 99+% optical purity, HOBT (2.0 equiv), EDC (2.0 equiv), Et_3N (4.0 equiv), in CH_2Cl_2] established an enantiomeric excess (ee) of ≥98% for the carboxylic acid.

In conclusion, the methodology described herein provides a practical route for the synthesis of a wide range of α-fluoro carboxylic acids of high enantiomeric excess.

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