# The first enantioselective syntheses of vicinal difluoropyrrolidines and the first catalytic asymmetric synthesis mediated by the $C_2$ symmetry of a –CHFCHF– unit

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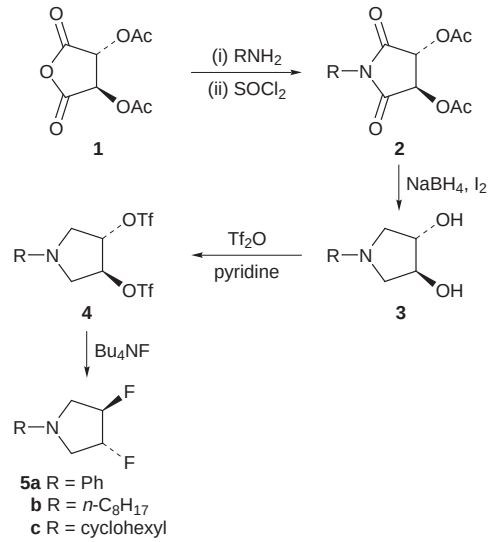
**The first enantiopure vicinal difluorides of $C_2$ symmetry have been prepared by the introduction of fluorine at both centres in a single operation; the first asymmetric synthesis using a catalyst whose chirality depends on organofluorine asymmetry is described.**

The stereoselective synthesis of organofluorine compounds[1,2] is of major importance in many fields, including pharmaceuticals,[1–3] nucleoside and carbohydrate chemistry,[1b] biochemistry,[4,5] liquid crystals[6] and polymers.[7] Many fluorinated α-amino acids are potent antitumour and antiviral agents.[1a,4a] The importance of monofluoro analogues as antimetabolites is illustrated by (2*R*,3*R*)-fluorocitric acid, an aconitase inhibitor that blocks the citric acid cycle.[2,5] Additionally, organofluoro ligands can be more powerful than oxygen ligands in coordinating metals.[8]

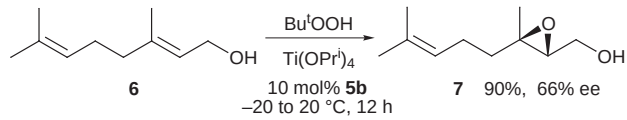
Whereas enantiocontrolled syntheses of monofluoroorganic compounds are well established, synthesis of an enantiopure vicinal difluoro compound, especially of $C_2$ symmetry, has not to the best of our knowledge been reported prior to this communication.[9,10] Generally, molecular fluorine adds to alkenes with *syn*-stereoselection, thereby precluding the formation of $C_2$ symmetric difluorides;[11] where *trans*-addition is observed yields are usually low.[12] For example diethylaminosulfur trifluoride (DAST),[13] one of the most commonly used reagents for the conversion of alcohols into fluorides, gives merely a trace of 1,2-difluorocyclohexanes, and with loss of stereointegrity compared with the initial cyclohexane-1,2-diol.[14] $SF_4$ acts on (+)- or (−)-tartaric acid, exchanging both hydroxy groups for fluorine, but with complete loss of optical activity, by formation of only the *meso*-difluoroacid.[15a] With tartrate esters, $XeF_2$ was similarly unsuccessful.[10c] Despite those previous accounts, we here report the enantiocontrolled introduction of fluorine at two adjacent carbon stereocentres in a single operation, and describe syntheses of enantiopure vicinal difluorides **5**, and an asymmetric process using some of those difluorides as catalysts.

In view of reports[15] that double vicinal displacements of tartaric acid derivatives by fluoride do not proceed with enantiocontrol, displacements on cyclic systems were investigated. (3*R*,4*R*)-Diacetoxysuccinic anhydride **1**[16] was reacted with a primary amine (1 equiv., 12 h, 20 °C), and the intermediate amido acid treated directly with $SOCl_2$ (2 equiv., 24 h, 20 °C) to give the diacetoxypyrrolidin-2,5-dione **2** (**2a**, R = Ph; **2b**, R = *n*-$C_8H_{17}$; **2c**, R = cyclohexyl) (Scheme 1). The pyrrolidin-2,5-diones **2** were reduced with $NaBH_4$–$I_2$ in THF (12 h) and the diols **3** liberated by a two-stage work-up involving stirring with 1:1 AcOH–HCl (10 M) for 10 h, followed by washing with methanolic KOH (2 M). Reaction of the diols **3** with $Tf_2O$ (2 equiv., 4 h, −80 °C) in the presence of pyridine (2 equiv.) afforded the bis(trifluoromethanesulfonates) **4**. These were isolable in the cases of **4a** (R = Ph) and **4b** (R = *n*-octyl) but **4c** (R = cyclohexyl) decomposed rapidly during column chromatography. The bis(trifluoromethanesulfonates) **4** were reacted with $Bu_4NF$ (3 equiv., 16 h, −80 to 20 °C) in THF, resulting in stereoselective introduction of fluorine with clean inversion at both centres to give the difluoropyrrolidines **5a**–**c**, in respective yields of 76, 83 and 40%.‡ To the best of our knowledge, 3,4-difluoropyrrolidines have not been previously prepared, either in racemic or enantiopure form.




**Scheme 1**

Catalysis of the epoxidation of allylic alcohols by difluorides **5** was investigated; reactions were conducted in $CH_2Cl_2$ using 15 mol% of $Ti(OPr^i)_4$ and 10 mol% of catalyst (Scheme 2, Table 1, entries 2–7). In the absence of a catalyst, racemic **7** was obtained in 81% yield. Diol **3a** afforded 2,3-epoxygeraniol **7** (97%) in 25% ee in favour of the (2*S*,3*S*)-enantiomer (entry 2).




**Scheme 2**

**Table 1** Asymmetric epoxidation of geraniol (1.6 mmol) with *tert*-butyl hydroperoxide, titanium tetraisopropoxide (15 mol%) and the difluorinated catalyst **5b** (10 mol%)

| Entry | Catalyst | *T*/°C | *t*/h | Yield (%) | Ee (%) | Configuration |
|---|---|---|---|---|---|---|
| 1 | — | −20 to 20 | 12 | 81 | — | racemic |
| 2 | **3a** | −20 to −10 | 0.67 | 97 | 25 | (*S*,*S*) |
| 3 | **5b** | −20 to 20 | 1 | 68 | 50 | (*R*,*R*) |
| 4 | **5b** | 0 | 1 | 74 | 51 | (*R*,*R*) |
| **5** | **5b** | **−20 to 20** | **12** | **90** | **66** | (***R*,*R***) |
| 6 | **5b** | −80 | 3 | 23 | 27 | (*R*,*R*) |
| 7 | **5c** | −20 to 20 | 12 | 87 | 10 | (*R*,*R*) |

The use of **5c** (−20 to 20 °C over 12 h) afforded 2,3-epoxygeraniol (87%) in 10% ee in favour of the (2*R*,3*R*)-enantiomer (entry 7). However, **5b** afforded a 90% yield of 2,3-epoxygeraniol **7** in 66% ee in favour of the (2*R*,3*R*)-enantiomer (entry 5). Entries 3–5 suggest that fluoro groups may provide greater enantioselection than hydroxy groups (entry 2), at least in the case of a $C_2$ vicinal unit which is part of a heterocyclic ring. The reversal of the major enantiomer of 2,3-epoxygeraniol when using catalyst **3** compared with catalyst **5** would be expected if the modes of binding of the hydroxy and fluoro catalysts had important features in common. Samples of alcohol **7** were converted into the acetate (1 equiv. $Ac_2O$, 1 equiv. pyridine, 10 mol% DMAP in $CH_2Cl_2$ at 0 to 20 °C over 2 h), and the ee determined by observation of $^1$H NMR peak of the acetate methyl group upon treatment with Eu(hfc)$_3$;[17] the acetate (10 mg in 0.5 ml of $C_6D_6$) was treated with consecutive portions of 10–20 ml of a filtered solution of 35 mg of Eu(hfc)$_3$ in 0.5 ml of $C_6D_6$.

The presence of fluorine ligands in organic reactions mediated by catalysis is an emerging area of importance.[18] To date, however, the chirality has not been a consequence of the spatial arrangement of the fluorine atoms, but of the asymmetry of an unrelated organic ligand (*e.g.* BINOL).[18] Consequently, the present examples are, to the best of our knowledge, the first examples of asymmetric synthesis catalyzed by a compound whose chirality depends upon organofluorine asymmetry.

In the catalytic asymmetric Sharpless epoxidation,[19] free hydroxy groups on the catalyst (dialkyl tartrate) are a prerequisite for enantioselectivity. In marked contrast to such Sharpless catalysts, the difluorides **5** lack hydroxy groups and are incapable of deprotonation that could lead to ligand exchange, and yet **5a–c** are viable catalysts for asymmetric epoxidation.

Compounds **5a** and **5c** are particularly suitable substructures for liquid crystal applications, and difluoropyrrolidines **5** and their derivatives are currently being evaluated for use as liquid crystals and other new materials; additional catalytic processes are also under investigation.

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## Notes and References

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‡ All compounds gave satisfactory spectral data (NMR, IR, MS), and all new compounds gave satisfactory elemental analyses or HRMS. *Selected data* for **4a**: prisms, mp 126.5–127 °C (hexane), $[\alpha]_D$ +46.2 (*c* 1, $CHCl_3$); $\delta_H$(250 MHz, $CDCl_3$) 7.30 (m, 2 H), 6.88 (t, *J* 9.0, 1 H), 6.60 (d, *J* 9.0 2 H), 5.52 (t, *J* 2.5, 2 H) 3.95 (dd, *J* 11.0, 5.0, 2 H), 3.65 (dd, *J* 11.0, 3.0, 2 H); $\delta_C$ (62.2 MHz, $CDCl_3$) 145.5 (d), 129.7 (d), 118.9 (s), 118.5 (q), 112.6 (d), 85.4 (d), 51.3 (t). For **5a**: needles, mp 89.5 °C (hexane), $[\alpha]_D$ −40.6 (*c* 3.5, $CHCl_3$); $\delta_H$(600 MHz, $CDCl_3$) 7.30 (m, 2 H), 6.76 (t, *J* 7.0, 1 H), 6.60 (d, *J* 7.0, 2 H), 5.30 (dm, $^2J_{HF}$ 49.3, $^3J_{HF}$ 12.6, 2 H), 3.70 (m, 4 H); $\delta_C$(150.9 MHz, $CDCl_3$) 146.6 (s), 129.4 (d), 117.1 (d), 112.0 (d), 92.8 (ddd, $^1J_{CF}$ 180, $^2J_{CF}$ 33), 51.6 (m); $\delta_F$(564.8 MHz, $CDCl_3$, internal $CFCl_3$) −190.3 (m).


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