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DIASTEREOSELECTIVE FLUORINATION OF CHIRAL IMIDE ENOLATES USING N-FLUORO-*O*-BENZENEDISULFONIMIDE (NFOBS)

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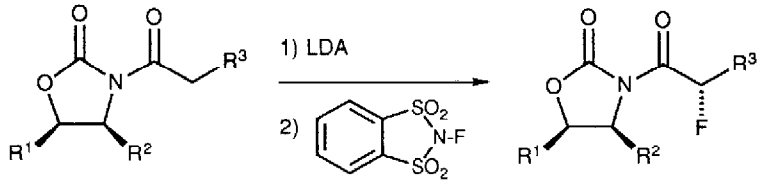
Summary: *α-Fluoro acids (78-90% ee) and β-fluoro alcohols (89->95%ee) of well defined stereochemistry are prepared via the diastereoselective fluorination of chiral imide enolates with NFOBS (**3**).*

Regio- and stereoselective fluorination often profoundly affects the physical, chemical and biochemical properties of the parent molecule.[1] For this reason there is considerable current interest in the development of efficient methodology for the asymmetric synthesis of organofluorine compounds where at least one of the chiral centers bears a fluorine atom.[2] Of particular concern is the asymmetric synthesis of α-fluoro carbonyl compounds because they have found important applications in studies of enzyme mechanisms, as enzyme inhibitors and as synthons for the asymmetric synthesis of chiral organofluorine compounds.[2a,1c,3] Furthermore, this moiety is often found in bioactive compounds.[1] Although the direct diastereoselective fluorination of chiral enolates with electrophilic fluorinating reagents is a potentially attractive route to these materials it has received limited attention. For example, treatment of the lithium enolate of methyl phenylmenthyl methymalonate with 1-fluoro-2,4,6-trimethylpyridinum triflate affords the monofluorinated esters in 58 % de[4] while the mono α-fluoro ketone peptide isostere was obtained as a 1:1 diastereomeric mixture on reaction of the corresponding silyl enol ether with XeF_2.[5] In this context we describe results of a study of the diastereoselective fluorination of chiral imide enolates **1**/**2** to α-fluoro carboximides **4**/**5** in 86->95% de using N-fluoro-*o*-benzenedisulfonimide [NFOBS] (**3**), a stable, easily prepared, fluorinating reagent.[6]



1, R^1=Ph, R^2=Me
2, R^1=H, R^2= *i*-Pr

3

4, R^1=Ph, R^2=Me
5, R^1=H, R^2= *i*-Pr

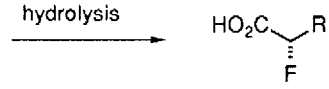
R^3= a) *n*-Bu, b) *tert*-Bu, c) $PhCH_2$, d) Ph,

The chiral auxiliary based enolate and enol diastereoselective synthesis of α-chloro and α-bromo carbonyl compounds have previously been described by Evans[7] and by Oppolzer.[8] In these examples no attempt was made to remove the chiral auxiliary, and the α-halo carbonyl compounds were transformed to α-amino acids by treatment with N_3^-. In our studies, the choice of the Evans oxazolidone chiral auxiliary was dictated by the perception that it could be more easily removed under milder conditions than the sultam auxiliary. Typically, chiral imide enolates were generated at -78 °C in THF by treatment of 0.3 to 3.0 mmoles of **1**/**2** with 1.1 equivalents of lithium diisopropyl amide (LDA) for 20 min.[8] α-Fluorination was accomplished by addition of a THF solution of NFOBS **3**[6] to the enolate, stirring for 2.5 hr. and warming to 0 °C for 20 min. prior to quenching with NH_4Cl. The α-fluoro carboximides **4**/**5** were isolated by flash chromatography (silica gel; 8% ethyl acetate-*n*-pentane) and the de's determined by capillary GC or ^1H NMR. These results are summarized in Table 1.

Good to excellent diastereoselectivities (86 to >97% de) were obtained for the monofluorination of the lithium enolates of carboximides **1** and **2** with **3**. Crystallization of **4d** improved the diastereomeric purity to >95% (entry 6). Isolated yields were good to excellent. Although the sodium enolates of **1**/**2** gave comparable results the yields were lower (68-72%). The one exception was the unsaturated carboximide where the lithium enolate proved to be unreactive (entry 7). Warming to 20 °C prior to quenching resulted in 15-20% racemization of **4**/**5**. This undoubtedly occurs due to the enhanced acidity of the α-fluoro proton in **4**/**5** compared to the starting material. Indeed treatment of *n*-butyl derivative **4a** with 1.0 eq of NaHMDS followed by quenching with NH_4Cl gave a 25:75 mixture of **4a** and its diastereoisomer.[9]

As a consequence of the acidity of the α-fluoro proton in **4**/**5** removal of the oxazolidone auxiliary, as anticipated, proved problematic. Hydrolysis of **4a** and **4d** at 0 °C with 1.3 eq of LiOH gave the corresponding α-fluoro acids **6a** and **6d** in 82-89%, but some racemization occurs. Less racemization was observed with LiOOH. Products were isolated by extracting the aqueous mixture with CH_2Cl_2, to remove the auxiliary, and acidification with 1.0 N HCl gave the acid. The fact that hydrolysis of **4a** and **4b** gave (*S*)-(-)-2-fluorohexanoic acid (**6a**)[10] and (*S*)-(+)-2-fluorophenyl acetic acid (**6d**),[11] of known absolute configuration, confirms approach of NFOBS **3** from the least hindered *Si*-face of the chiral imide enolate as observed for other electrophiles with this enolate system.[7]

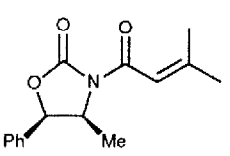
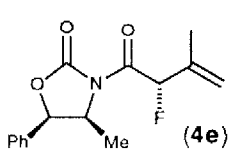
4a, R= *n*-Bu (97% de)
4d, R= Ph (94% de)



	LiOH	LiOOH
(*S*)-(-)-**6a**,	87% ee (89%)	90% ee (86%)
(*S*)-(+)-**6d**,	69% ee (82%)	78% ee (80%)

The most effective method for removal of the auxiliary proved to be reduction with $LiBH_4$. Thus, treatment of α-fluoro carboximides **4a-e** in THF or ether with 1.2 eq of $LiBH_4$ for 1-2 hrs.

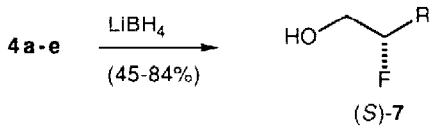
Table 1: Fluorination of the Chiral Lithium Imide Enolates with NFOBS at -78 to 0 °C

entry	Carboximide **1**			α-Fluoro Carboximide **4/5**		
	R^1	R^2	R^3	% De[a]	%Yield	^{19}F NMR δ[b]
1	Ph	Me	*n*-C_4H_9 (**1a**)	97	88	-194.4
2	H	*i*-Pr	*n*-C_4H_9 (**2a**)	96	85	-193.6
3	Ph	Me	*tert*-C_4H_9 (**1b**)	96	86	-196.5
4	H	*i*-Pr	*tert*-C_4H_9 (**2b**)	97	80	-195.6
5	Ph	Me	$PhCH_2$ (**1c**)	89	84	-191.2
6	Ph	Me	Ph (**1d**)	86	86	-186.7
7[c]			 (**4e**)	90	85	-185.5

a) De's were determined by GC or ^1H NMR [entries 5 and 6]. b) $CFCl_3$. reference. c) Sodium enolate prepared using sodium bis(trimethylsilyl)amide (NaHMDS).

and quenching with water gave β-fluoro alcohols **7** in good yields as oils following flash chromatography[12]. The enantiomeric purity of the β-fluoro alcohols **7** was determined to be 89 to >95% ee by conversion to the Mosher esters.[13] Significantly, reduction takes place without racemization. The results are summarized in Table 2.

Table 2: Reduction of α-Fluoro Carboximides **4** to (*S*)-β-Fluoro Alcohols **7**



(*S*)-**7**

(*S*)-β-Fluoro alcohol **7** (R=)	Solvent	% Yield[a]	% ee[b]	$[\alpha]^{20}_D$ ($CHCl_3$)	^{19}F δ[c]
n-C_4H_9 (**7a**)	Et_2O	83	>95	-16.8 (c 3.0)	-190.2
tert-Bu (**7b**)	Et_2O	71	>95	-14.2 (c 2.2)	-196.0
$PhCH_2$ (**7c**)[d]	THF	81	89	-17.6 (c 1.7)	-188.2
Ph (**7d**)[e]	THF	84	94	+52.5 (c 1.1)	-187.4
$C(Me)=CH_2$ (**7e**)	Et_2O	45	90	+12.1 (c 0.9)	-189.2

a) Isolated yields. b) From the Mosher ester. c) $CFCl_3$ reference. d) Ref. 14. e) Ref. 11.

In summary, the diastereoselective fluorination of chiral imide enolates **1/2** with the electrophilic fluorinating reagent NFOBS **3** gives α-fluoro carboximides **4/5** in generally high de's. Although some racemization occurs on removal of the chiral auxiliary under basic conditions, α-fluoro acids **6** with good ee's and well defined stereochemistry are obtained. A highly enantioselective synthesis of β-fluoro alcohols **7** results on reduction of α-fluoro carboximides **4** with $LiBH_4$.

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