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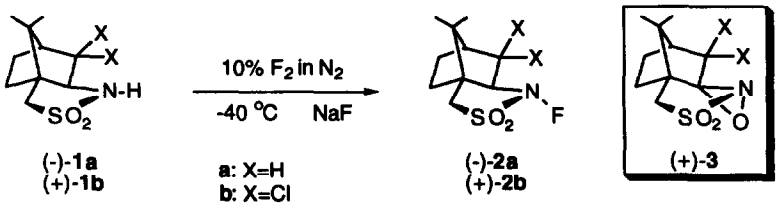
ASYMMETRIC FLUORINATION OF ENOLATES WITH N-FLUORO 2,10-(3,3-DICHLOROCAMPHORSULTAM)

Franklin A. Davis, Ping Zhou and Christopher K. Murphy*
Department of Chemistry, Drexel University, Philadelphia, PA 19104

Summary: *Asymmetric fluorination of enolates with nonracemic N-fluoro dichlorocamphorsultam* ***2b*** *affords α-fluoro carbonyl compounds in good yield and up to 75% ee.*

There is considerable current interest in the development of efficient methodologies for the asymmetric synthesis of organofluorine compounds where one of the chiral centers bears a fluorine atom.[1] This element exerts unique influences upon the physical, chemical and biological properties of the parent molecule.[2] Nonracemic α-fluoro carbonyl compounds are of particular interest because of their utility in studies of enzyme mechanisms, as enzyme inhibitors and synthons for the asymmetric synthesis of chiral organofluorine compounds.[1a,2c,3] Preparations of nonracemic α-fluoro carbonyl compounds include enzyme catalyzed kinetic resolution of α-fluoro esters,[4] fluorodeamination of α-amino acids[5] and treatment of α-hydroxy acids with nucleophilic fluorine sources.[5a,6] The highly diastereoselective (up to 97% de) fluorination of chiral oxazolidone enolates with the electrophilic fluorine source N-fluoro-*o*-benzenedisulfonimide (NFOBS) is another route to these materials recently introduced by us.[7] However, some racemization (~10%) occurs in hydrolytic removal of the chiral auxiliary, although reduction gives the β-fluorohydrin without racemization. The availability of an electrophilic asymmetric fluorinating reagent that affords high ee's and predictable stereochemistry for enolate fluorinations would avoid this problem.

The first asymmetric fluorinating reagent, (-)-N-fluoro camphorsultam (**2a**), was prepared by Differding and Lang in 1988 by treatment of (-)-camphorsultam (**1a**) with F_2.[8] In one example the ee reached 70 % for the fluorination of a β-ketoester enolate, but with other enolates the ee's and yields were much poorer. We describe here details of an investigation of the asymmetric fluorination of enolates using (-)-**2a** and a new reagent (-)-N-fluoro 2,10-(3,3-dichlorocamphor-



(-)-**1a**
(+)-**1b**

a: X=H
b: X=Cl

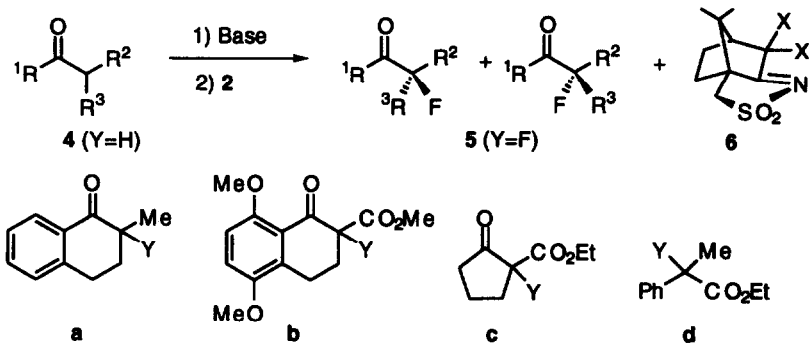
(-)-**2a**
(+)-**2b**

(+)-**3**

sultam) (**2b**). This work is related to our asymmetric enolate hydroxylation studies with camphorsulfonyloxaziridine **3** because the precursor of **3** is the precursor of **2** and the molecular recognition for the two systems may be related.[9]

Camphorsultam (+)-**2b** was prepared by passing 10% F_2/N_2 through a solution of (+)-**1b** in $CHCl_3$ at -40 °C for 1 h in the presence of powdered NaF. N-Fluoro sultam **2b** was isolated in 68% yield by flash chromatography on silica gel.[10] Synthesis of (+)-2,10-(3,3-dichlorocamphorsultam (**1b**) was accomplished in 96% yield by reduction with $NaBH_4$ of the corresponding imine (+)-**6b** (X=Cl).[10,11] The ^{19}F NMR of (+)-**2b** at ca 20 °C appears as a doublet at δ -53.5 ppm (J= 48.4 Hz) relative to $CFCl_3$ whereas in (-)-**2a** the fluorine is a broad singlet at δ -64.9 ppm. This suggests that the nitrogen atom in the latter compound is not configurationally stable under these conditions.

Asymmetric enolate fluorinations were typically carried out by addition of 0.8-1.5 equivalents of **2a-b** to the preformed enolates of **4a-d** prepared at -78 °C by treatment with 1.1-1.3 equivalents of the appropriate base. The reactions were quenched at -78 °C by addition of sat. NH_4Cl solution and the products isolated by preparative TLC. Identification was accomplished by comparison of their spectral properties with authentic samples or they had elemental analysis and spectra consistent with their structures. The enantiomeric purity was assessed by NMR using the chiral shift reagent $Eu(hfc)_3$ (Table).



The results summarized in the Table reveal several trends. First, **2b** generally gave higher yields of **5** than did **2a**. This may be a consequence of its greater reactivity; i.e. fluorinations with **2b** occur at -78° whereas **2a** requires higher temperatures. Higher yields with **2b** may also reflect less H-F elimination giving **6b** at the lower temperatures (see entries 5 and 6). In this regard it is interesting to note that fluorination of the sodium enolate of **4a** with 0.8 equivalents of **2b** gave, in addition to **5a** (41%), an 11% yield of 2-chloro-2-methyl-1-tetralone **5a** (Y=Cl) (entry 3). This unexpected product is formed by chlorination of the enolate of **4a** by the dichloroimine **6b** (X=Cl).[11] Enolate chlorination by **6b** (X=Cl) can be avoided by carrying out the fluorination at -78 °C or using an excess of the reagent (entries 4 and 6). The less basic β-keto ester enolates gave the highest yields of **5** (entries 7-11).

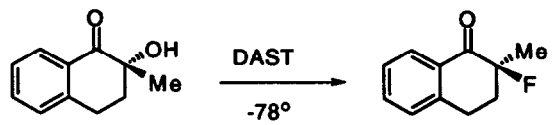
Table: Asymmetric Fluorination of Enolates using N-Fluoro Camphorsultams **2**.

entry	Ketone/ Ester **4**	Sultam[a] **2**	Reaction Conditions Base/Solvent/Temp.%	Products ee[b] (config.) [% Yield][c] $[\alpha]_D^{20}$ (*c*, $CHCl_3$)
1	**4a**	(-)-**2a** (X=H)[d]	LDA/THF/-78°-r.t.	**5a**, 35 [<5]
2		(+)-**2b** (X=Cl)	LDA/THF/-78°	**5a**, 10 (*S*) [49], **6b** [25], -2.9° (1.4)
3		e	NaHMDS/THF/-78-0°,[f]	**5a**, 67 (*S*) [41], **6b** [17], **5a** (Y=Cl) [11]
4		e	NaHMDS/THF/-78°	**5a**, 65 (*S*) [40] **6b** [30] -20.4 (1.8)
5		(-)-**2b** (X=Cl)[g]	NaHMDS/THF/-78-0°	**5a**, 75 (*R*) [40], **6b** [32], +21.8° (1.5)
6			NaHMDS/THF/-78°	**5a**, 65 (*R*) [50], **6b** [20] +20.1° (2.0)
7	**4b**	(-)-**2a** (X=H)	NaH/Et_2O/0°-r.t.[h]	**5b**, 25 [28], **6b** [28], -2.68° (1.6)
8		(-)-**2b** (X=Cl)	NaH/Et_2O/0°-r.t.	**5b**, 46 [>95], +4.93° (1.4)
9			NaHMDS/THF/-78-0°,[d]	**5b**, 26 [57], **6b** [28], +2.83° (2.1)
10	**4c**	(-)-**2a** (X=H)[d]	NaH/Et_2O/0°-r.t.	**5c**, 70 [63], -18.5° (4.8)[h]
11		(+)-**2b** (X=Cl)[e]	NaH/Et_2O/-78-0°	**5c**, 34 [59], **6b** [27], -9.5° (5.24)
12	**4d**	(+)-**2a** (X=H)[d],	LDA/THF/-78°-r.t.	**5d**, 35 [<10],
13		(+)-**2b** (X=Cl)	LDA/THF/-78°	**5d**, 29 [62], **6b**, [21]
14			NaHMDS/THF/-78°	**5d**, 33 [54], **6b**, [24], +0.92° (1.1)

a) 1.5 Equivalents of **2** used unless otherwise noted. b) Ee's determined using $Eu(hfc)_3$. c) Isolated yields. d) Reference 8. e) 0.8 Equivalents of (+)-**2b** used. f) Monochloro imine of **6** isolated.[11] g) Addition of the enolate to **2**. h) This work.

As previously observed for the asymmetric hydroxylation of enolates by the (camphorsulfonyl)oxaziridine **3**[9] the enantioinduction for enolate fluorinations by **2a-b** is highly dependent on the enolate structure, the fluorinating reagent and the reaction conditions. Note that the configuration of **2** controls the absolute stereochemistry of the product (compare entries 3-4 to 5-6). Higher ee's were observed with **2b** for fluorination of tetralone enolate **4a** compared with (-)-**2a**; 75% vs 35% (entries 5 and 1). In only one case did (-)-**2a** give a higher ee; i.e. with β-keto ester **4c** (entry 10).

As mentioned earlier the molecular recognition for hydroxylation and fluorination of enolates by **3** and **2** may be similar.[9] If this hypothesis is correct, fluorination of the enolate of **4a** by (+)-**2b** will give (+)-(*R*)-2-fluoro-2-methyl-1-tetralone (**5a**). However, treatment of (*R*)-2-hydroxy-2-methyl-1-tetralone (**7**)[11] with DAST at -78° in CH_2Cl_2 afforded a 20% yield (70% ee) of (-)-**5a** following



(*R*)-**7** (>95%ee) (20%) (-)-(*S*)-**5a** (70% ee)

isolation by TLC. DAST is known to transform α-hydroxy esters to α-fluoro esters with inversion of configuration and therefore (-)-**5a** has the*S*-configuration.[5a,12] This was further confirmed by comparison of its CD[13] spectra with (*R*)-**7** and application of the CD octet rule.[14] *In this case (+)-2 gave the opposite stereoinduction compared to oxaziridine (+)-3b suggesting that the mechanisms of chiral recognition are different.*

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10. (+)-**1b**: mp 200 °C; $[\alpha]_D^{20}$ +20.2° (*c* 2.6 $CHCl_3$); (+)-**2b**: mp 161-2 °C; $[\alpha]_D^{20}$ +16.5° (*c* 1.5 $CHCl_3$); (-)-**1b**: mp 201 °C; $[\alpha]_D^{20}$ -20.4° (*c* 2.6 $CHCl_3$); (-)-**2b**: mp 161-2 °C; $[\alpha]_D^{20}$ -16.6° (*c* 1.37, $CHCl_3$).
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