ENANTIOSELECTIVE ELECTROPHILIC FLUORINATION

Reported by Christopher M. McGinley February 18, 2002

INTRODUCTION

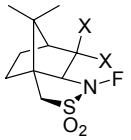
Stereoselective synthesis of organofluorine compounds has attracted considerable attention in recent years owing to the unique properties of the fluoro substituents. Enantiopure organofluoro compounds have important applications in optical materials, liquid crystals, and biological research. β-fluoro α-amino acids[1] have demonstrated a number of biological properties such as antibacterial, antihypertensive, and antitumor activities. Additionally, enantiopure α-fluoro ketones are effective mimics of α-hydroxy ketones, a functionality frequently found in biological research.[2] The strength of the C-F bond also renders these mimics more resistant to enzyme metabolism. Fluoro analogs are useful probes for various biological processes, such as the mechanism of metabolism and biosynthesis of indole.[3]

Many methods for the synthesis of enantioenriched organofluoro compounds have been reported. Fluorodehydration of simple chiral secondary alcohols and propargylic alcohols,[4] and fluorodeamination of chiral α-amino acids with retention of configuration represent a few useful examples. Chemical and biological procedures for resolution of racemic fluoro carboxylic acids have been described, while fluoride addition in chemical and electrochemical reactions can be directed using inherent chirality present in a molecule.[5]

However, these methods require the use of chiral substrates or kinetic resolution to access enantiopure organofluoro compounds. Expansion of the methodology to achiral substrates could greatly expand the synthetic possibilities. This abstract will review efficient methods developed recently for the stereoselective fluorination of achiral substrates. The majority of the progress has been made using an electrophilic fluoro source, and this will be the primary focus.

SULTAMS

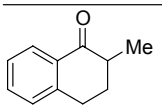
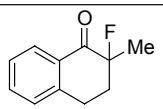
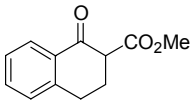
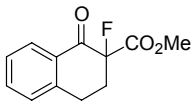
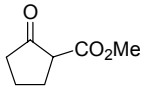
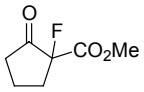
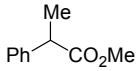
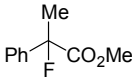
Differding and co-workers reported the first direct enantioselective fluorination in 1988.[6] They achieved selective α-fluorination using chiral *N*-fluorocamphorsultam **1a,** albeit with low enrichments. Although this reagent is not frequently used, the initial discovery was vital to the development of more selective sultam reagents. These results demonstrated the possibility of stereoselective fluorination by reaction with a chiral "F^+" equivalent into a chiral environment. Further development of *N*-fluorosultams was achieved by Davis and co-workers, employing the 3,3-dichlorocamphorsultam **1b**.[7] However, fluorinations with



1a. X = H
1b. X = Cl

these camphorsultams were limited in scope, and good selectivities were achieved with very few substrates. (Table 1) In addition, multi-step synthesis of these fluorinating agents was necessary, and handling of extremely toxic and corrosive fluorine gas was required.

Table 1. N-Fluorocamphorsultams Fluorination with 1a and 1b

N-F Sultam	% ee, [yield]	
	**1a** 35 [<5] **1b** 67 [41]	
	**1a** 14 [8] **1b** 25 [75]	
	**1a** 70 [63] **1b** 34 [59]	
	**1b** 33 [54]	

Nonetheless, *N*-fluoro sultams offer a useful option for electrophilic enantioselective fluorinations. The different chiral environments proximal to the N-F bond in reagents **2-5,** were investigated as mean to improve selectivities (Figure 1). [8-11] A number of these fluorinating agents have demonstrated the ability to fluorinate various aryl ketone enolates enantioselectively. (Table 2). Mechanistic studies conducted by Differding had previously shown the reactions with N-F fluorinating agents likely proceed through an S_N2 type mechanism rather than electron transfer pathway.[12] This conclusion was reached by studies on the fluorination of substrates containing radical traps, and by limited kinetic data. In addition, the solid state conformation of **2** and **3** reveal the fluoro group positioned almost perpendicular to the aromatic ring, thereby limiting the enolate attack to one side of the sultam. Therefore one source of the asymmetric induction is presumably from the directed attack of the enolate and coordination of the metal ion to both the enolate and one sulfonyl oxygen. Overall, these agents show promising yields, selectivity, and substrate compatibility and the limited mechanistic studies should allow further improvements in *N*-fluorosultam fluorinating agents.

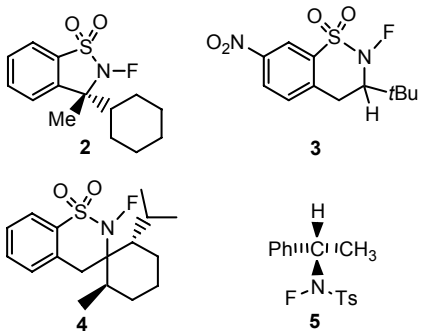
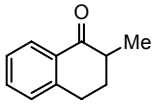
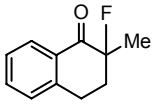
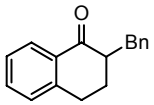
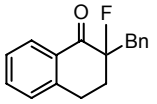
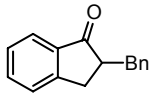
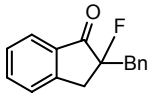
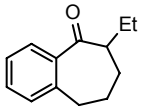
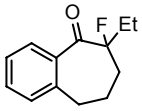


Figure 1. Alternative N-Fluorosultams

Table 2. Asymmetric Fluorination using N-Fluorosultams

N-F Sultam	% ee, [yield]	
	**2** 62 [79] **3** 74 [67] **1** 70 [65]	
	**2** 49 [55] **3** 88 [79]	
	**2** 57 [40] **3** 54 [63] **1** 54 [59]	
	**3** 43 [48]	

SELECTFLUOR™/ALKALOID COMBINATION

A significant step toward the development of an efficient and versatile direct fluorination method was simultaneously reported by Shibata and Cahard.[13,14] *N*-Fluorinations of a cinchona alkaloid with the

commercially available *N*-fluoro quinuclidinium reagent Selectfluor™ generate chiral fluoro reagents capable of selective "F^+" delivery (Figure 2).

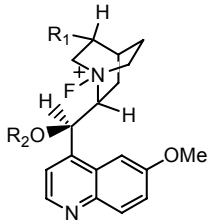


Figure 2. Fluorinated Cinchona Alkaloid

Since initial studies conducted on enol silane **6** (Scheme 1) demonstrated only 40% ee, use of different cinchona alkaloids was investigated. It was found the choice of cinchona alkaloid had a substantial effect on the selectivity observed (Table 3). The most effective cinchona/alkaloid combination was used for fluorination of other aryl enol silanes. These reactions gave α-fluoro ketones in moderate to good enantioselectivities and good yields (Equation 1).[14] Variation in cinchona alkaloid for selectivity optimization was also conducted on cyano esters. This screening revealed an alkaloid combination able to effect fluorination of these acyclic compounds in good yield and enantioselectivities (Equation 2). This result was important for two reasons. First, enantiopure α-fluoro cyano esters are useful chiral derivatizing agents for the absolute configuration determination of secondary alcohols.[15] Second, this represented the first direct electrophilic fluorination of acyclic compounds with moderate enantioselectivity. Enantioselective fluorination of cyclic β-keto esters[16] and oxindoles,[3] afforded useful mechanistic probes for the study of indole metabolism and biosynthesis. The enantioselecitive synthesis of β-fluoro amino acids,[1] having interesting biological properties, was also accomplished using this method. One attractive feature of this fluorination method is the possibility of enantioselectivity optimization, with commercially available alkaloids or their derivatives.

Scheme 1. Fluorination by Selectfluor/Cinchona Alkaloid

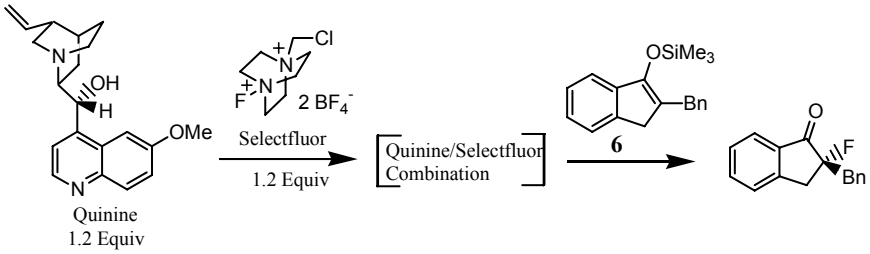
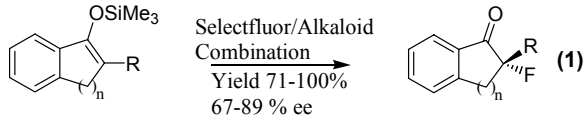
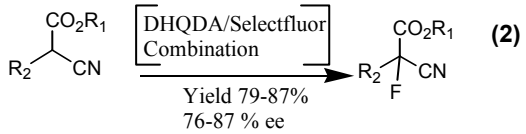


Table 3. Fluorination of 6 with Cinchona Alkaloids

Entry	Alkaloid	Yield	%ee	Config.
1	Quinine	63	44	R
2	Quinidine	84	35	S
3	DHQ	67	54	R
4	DHQB	83	81	S
5	Cinchonine	94	23	R



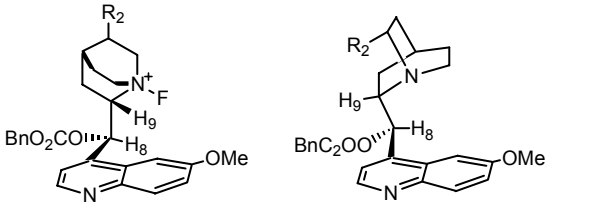
(1)



(2)

Mechanistic studies were conducted to verify that the enantioselectivity originated from generation of a fluorinated cinchona alkaloid. The order of addition was shown to be critical. Enantioselectivity was only observed when the Selectfluor™ and cinchona alkaloid were combined before addition of the enolate. Therefore an alkaloid/enolate complex cannot be responsible for the

selectivity. The formation of a reaction intermediate was further supported by ^{19}F NMR analysis, which demonstrated two important points. First, a decrease in the Selectfluor™ signal was observed as the cinchona alkaloid was added. Second, after equal parts of the cinchona alkaloid/Selectfluor™ had been added, only one fluorine signal could be detected. This demonstrated that a new species was being generated *in situ,* which was likely to be the enantioselective fluoro source. The intermediate was isolated, and an X-ray crystal structure revealed that this intermediate fluorine species is generated by fluorination of the cinchona alkaloid by Selectfluor™ (Figure 3).[17]



Open — NF-DHQB.BF_4: $^3J_{H8,H9}$= 2.6 Hz

Closed — DHQB: $^3J_{H8,H9}$= 7.8 Hz

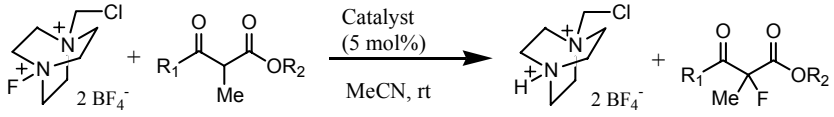
Figure 3. Conformations for Quinine Derivatives

The structure in solid state was shown to be in the open conformation, where the N-F bond is parallel to the bond of the methoxy group. ^1H NMR coupling between H-8 and H-9 in solution state between H-8 and H-9 for the unfluorinated alkaloid indicated a closed conformation, while the smaller coupling for the fluoro intermediate species is consistent with an open conformation (Figure 3).[18] This conformation has been used to propose a mode of asymmetric induction by this fluorinating agent, in which steric interactions between the enolate and the quinuclidinium moiety favor formation of one enantiomer.

CATALYTIC ENANTIOSELECTIVE FLUORINATION

Fluorination by either a Selectfluor™/alkaloid combination or an *N*-fluorosultam require the use of stoichiometric amounts of the valuable chiral fluorinating agent. A more efficient methodology using only a chiral catalyst for asymmetric fluorination would be a significant improvement.

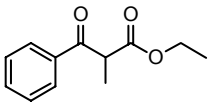
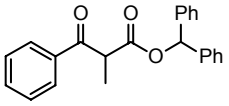
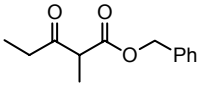
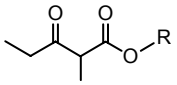
The first catalytic fluorination was recently reported by Togni and co-workers, using catalytic amounts of Ti (IV) complexes **7a** or **7b** (Equation 3).[19] These species have the ability to catalyze enantioselective fluorination of β-keto esters with significantly different substituents. (Table 4). However, only β-keto esters have been demonstrated as effective substrates to date. The reaction presumably proceeds by coordination of titanium to the carbonyl oxygens to catalyze formation of the reactive enolate, therefore not requiring a lithium base. However, the enhanced acidity of β-keto esters is necessary for this catalysis to occur at a viable rate.



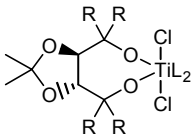
(3)

Exploration of the generality of this method has not been fully completed, nor have extensive mechanistic studies been carried out. However, variation in titanium catalyst does provide some mechanistic insight. The increase in selectivity upon altering the ligand side chain from phenyl, **5a**, to naphthyl, **5b**, indicates at least part of the enantioselective bias is attributable to steric interactions. In addition, computational studies have been conducted to rationalize the mechanistic pathway.

Table 4. Catalytic Enantioselective Fluorination

Substrate	cat = **5a**	cat = **5b**
	28% ee	62% ee
	59% ee	82 % ee
	48% ee	71% ee
 R = D-Arabinitol	d.r. = 60:40	d.r. = 80:20

QM/MM calculations have identified the four most stable conformations of the metal enolate. The most stable conformation has the re-face of the enolate completely shielded by two face-on orientated naphthyl groups (Figure 4). Therefore approach of the fluoro reagent can only occur on the opposite face, leading to the observed absolute configuration for the product. One potential problem with this fluorination method is the similar stability of the other conformers of the metal enolate. The four most stable grounds state conformations differ in energy by only 3 kcal/mol, two leading to one fluorinated product and two to the enantiomer.[20] This small energy difference could potentially allow reactions to occur through two transition state conformations, to lead to both enantiomers and reduction in reaction selectivity.



5a R = Ph, $L_2 = (CH_2OCH_3)_2$
5b R = 1-Nph, $L_2 = 2\ NCCH_3$

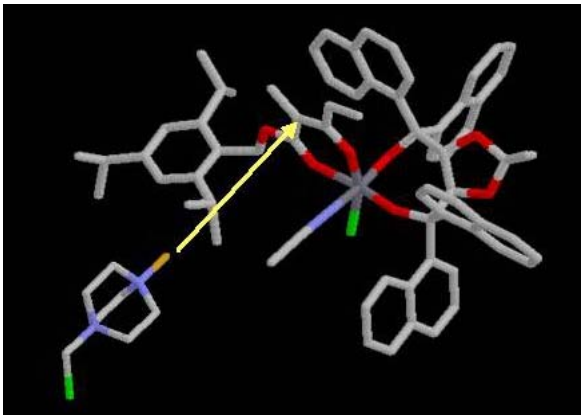


Figure 4. Most Stable Titanium-Enolate Conformation

Computational studies on the fluoro transfer including solvent molecules and solvation indicate approach of the $[N\text{-}F]^+$ species results in electron transfer from the enolate, with almost instantaneous breakage of the N-F bond generating the product.[21] However, calculations conducted without solvent molecules and solvation, indicate that electron transfer leading to a radical species prior to fluoride transfer is likely. These two simulations illustrate the importance of solvent interactions on the mechanistic pathway. Stabilization of the $[N\text{-}F]^+$ cation by the solvent shell allows the fluorinating species to approach closely before single electron transfer (SET) occurs. Therefore, variations in the solvent shell, such as thermal fluctuations, would reduce this cation stabilization and would result in a SET occurring before the fluoride transfer reaction is possible.

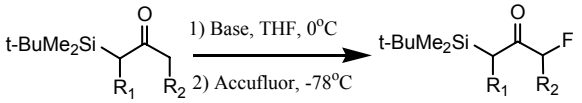
This mechanism explains two interesting experimental observations. First, when the catalyst is the only source of chloride, chlorinated side products are isolated. Second, the amount of chlorinated side product was substantially increased by the addition of NaCl or NH_4Cl. If solvent shell variation does occur, the intermediate [N-F]· radical species could react with the chloride present in solution, and generate the relatively stable Cl· radical responsible for the chlorinated side product formation.

This mechanistic hypothesis was tested by the addition of a radical scavenger. This scavenger should only disrupt the formation of the Cl· radical and side products derived from it, and not the solvent encapsulated SET and fluoride transfer. The fluorination reaction was repeated in the presence of a ferrocene radical scavenger. No chlorination side products were observed, while the fluorination yield and selectivity were unaffected, therefore providing strong support for the computationally proposed pathway.

CHIRAL AUXILIARIES

An alternative method to direct enantioselective fluorinations involves the use of chiral auxiliaries. Covalent bonding of the auxiliary to the substrate, followed by fluorination and subsequent cleavage of the auxiliary, affords the enantio-enriched fluorinated product. Specifically, two chiral directing groups, an α-silyl substituent and Evans' oxazolidinone, have been use for this purpose. Enders and co-workers have focused on α-silyl as directing groups for α'-fluorination of ketones, achieving excellent diastereoselectivies.[22,23] (Table 5) The effectiveness of this auxiliary with a variety of side chains at the α-position is noteworthy. Another benefit is the ability to obtain either fluorinated diastereomer from a single α-silyl enantiomer by use of different lithium bases. LDA is used to generate the *E* enolate, while LHMDS provides the *Z* olefin. Subsequent attack from the sterically less hindered side therefore allows either fluorinated diastereomer to be formed.

Table 5. Fluorination of alpha-Silylketones



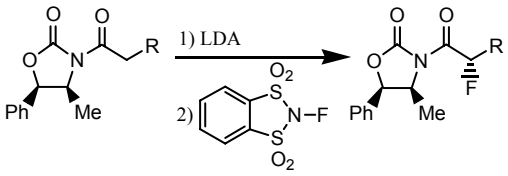
Substrate	Base	R_1	R_2	Yield	% de[a]	Config.
(R)	LDA	Et	Et	79	79 (>98)	(R,S)
(S)	LDA	Me	Bn	74	67 (>98)	(R,S)
(R)	LDA		$(CH_2)_3$	81	>98	(R,R)
(R)	LHMDS	Et	Et	80	89 (>98)	(R,S)
(S)	LHMDS	Me	Bn	77	87 (>98)	(S,S)

[a]In parenthesis, de after flash chromatography

Davis and co-workers have studied oxazolidinones as potential fluorinating chiral auxiliaries. While covalent attachment of the auxiliary to the carbonyl restricts the substrate compatibility, this auxiliary has generated α-fluoro carboximides in excellent diastereomeric excesses and yields (Table 6).[24,25] An important feature of this auxiliary is the ability to convert the fluoro-acyl oxazolidinone product into various functionalities without significant racemization. As shown in scheme 2, these carboximides can be easily reduced to the alcohols with retention of configuration.[24] Alternatively,

conversion to an *N*-methoxy amide followed by Grignard addition provides the ketone. This potential for cleavage of the auxiliary into synthetically useful functionalities has been demonstrated in the synthesis of many bioactive molecules, such as carbohydrates.[25,26]

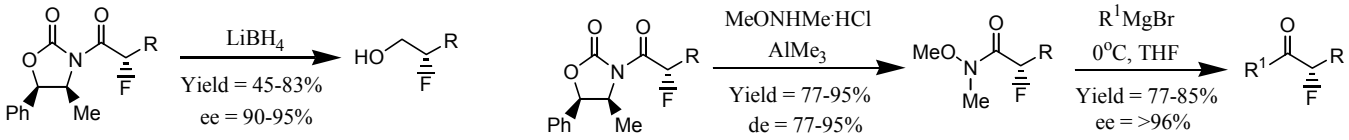
Table 6. Oxazolidinone Directed Fluorinations



R_1	Yield	% de	Config.
n-C_4H_9	88	97	(R,S)
CH_2Ph	84	89	(S,R)
$C(Me)=CH_2$	85	90	(R,S)

A tremendous advantage of chiral auxiliaries is the possibility of separation of the fluorinated diastereomers by chromatography. Subsequent cleavage of the auxiliary could then provide the desired enantiomer in high enantiopurity. Therefore, the enantiopurity possible for α-fluorination of a ketone has very little dependence on the structure of the substrate. However, one disadvantage over direct enantioselective fluorination methods is the additional steps required. While auxiliaries allow for synthesis of a variety of fluoro compounds in high selectivity, the overall yields are often quite poor.

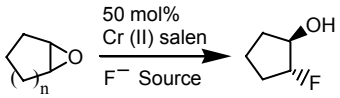
Scheme 2: Derivization of Auxiliary to Alcohol or Ketone



NUCLEOPHILIC FLUORINATION

Not nearly the same degree of progress has been made in enantioselective nucleophilic fluorinations. Until recently, the only example of enantioselective introduction of fluorine occurred in only 16% ee using a (S)-proline-based DAST analogue.[27] Probably the most efficient enantioselective nucleophilic fluorination involves ring opening of epoxides using Cr (salen) complexes.[28] Jacobsen's salen complex has been used for asymmetric ring opening of meso and racemic cyclic epoxides in moderate enantioselectivities (Table 7).[29] Although mechanistic studies have yet to be conducted, it is assumed that the reaction proceeds through Lewis acid activation of the epoxide. While this method provides an efficient synthesis of fluorohydrins, it suffers from slow rates and occasional non-regioselective ring opening in the kinetic resolution of unsymmetric epoxides.

Table 7. Enantioselective Epoxide Ring Opening of Meso Epoxides



n	Fluorinating Agent	Temp (°C)	Time (hrs)	Conversion (%)	Yield [a] (%)	ee (%)
2	KHF_2	60	80	92	64	55
1	AgF	70	50	85	75	44
2	AgF	70	20	100	85	66
3	AgF	60	20	50	82	65

[a]Based on conversion

CONCLUSION

Efficient enantioselective fluorination remains a challenge in organic synthesis. Improved methods would allow access to novel enantiopure fluoro compounds of interest in biochemistry and medicinal chemistry applications. Chiral auxiliaries have the ability to generate a variety of enantiopure fluoro compounds, however, this approach suffers from the numerous synthetic steps involved and poor overall yields. An alternative direct fluorination has been accomplished using a Selectfluor™/cinchona alkaloid combination, while a catalytic fluorination has recently been discovered by Togni and coworkers. Developments in electrophilic enantioselective fluorination are also substantially more advanced than those in enantioselective nucleophilic fluorinations, where epoxide ring opening represent the most efficient method. However, despite the recent improvements in enantioselective fluorinations, research is ongoing to improve the selectivity of these intriguing and important transformations.

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