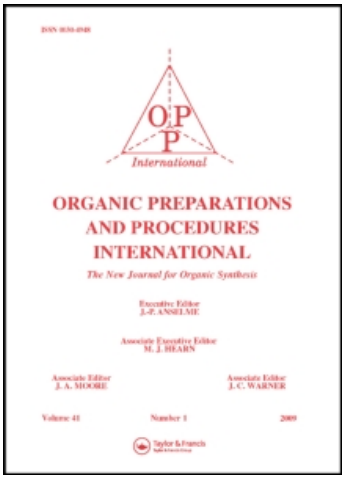

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SYNTHESIS OF α-FLUORO ALDEHYDES AND KETONES. A REVIEW

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SYNTHESIS OF α-FLUORO ALDEHYDES AND KETONES. A REVIEW

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INTRODUCTION

The strategic placement of fluorine into an organic molecule is of considerable current interest because this element exerts unique and often beneficial influences on physical, chemical and biological properties, due to the extreme electronegativity of fluorine which affects the acidity, basicity and overall reactivity of neighboring groups.[1-3] The van der Waal's radius of fluorine (1.47 Å) compared to hydrogen (1.20 Å) and oxygen (1.57 Å) indicates that fluorine is not particularly sterically demanding and is isosteric with oxygen.[4] In addition, the similarities between the carbon-fluorine (1.39 Å) and carbon-oxygen bond lengths (1.43 Å) suggest that fluorine may be an isosteric replacement for the hydroxyl group.[1,4-6] However, the ability of fluorine bonded to carbon to form hydrogen bonds is controversial.[5,6]

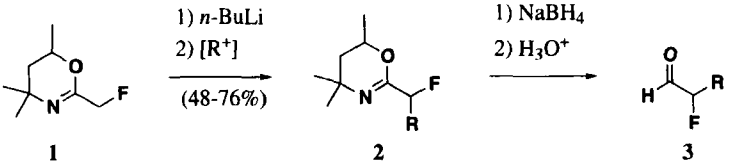
This review focuses on the most recent developments in the synthesis and applications of α-fluoro aldehydes and ketones, with emphasis on their preparation in enantiomerically enriched form. These readily available and easily transformed molecules are potentially valuable building blocks for the construction of more complex organofluoro derivatives. Some overlap with prior reviews on the chemistry of α-fluoro carbonyl compounds is unavoidable.[7,8]

I. SYNTHESIS OF RACEMIC α-FLUORO ALDEHYDES

Several methods for the synthesis of racemic α-fluoro aldehydes, which do not appear to be very stable, have been described and are illustrated in the following sections.

1. Synthesis from 2-Fluoromethyl-4,4,6-trimethyl-1,3-oxazine

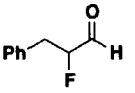
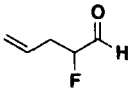
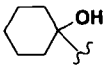
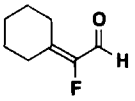
Patrick *et al.* reported the synthesis of α-fluoro aldehydes from 2-fluoromethyl-4,4,6-trimethyl-1,3-oxazine (**1**).[9] This compound is a synthetic equivalent of fluoro acetaldehyde and was prepared in one step from fluoroacetonitrile and 2-methyl-1,3-pentanediol. The anion of **1**, upon alkylation with various carbon electrophiles, afforded the α-alkylated oxazines **2** in moderate to good yields (*Scheme 1*). Reduction, followed by hydrolysis gave the α-fluoro aldehydes **3** which were isolated by flash chromatography (Table 1, entries 1 and 2). When **2** contained β-hydroxy groups, dehydration occurred on hydrolysis giving the α,β-unsaturated α-fluoro aldehydes **3** (Table 1, entry 3).



1 2 3

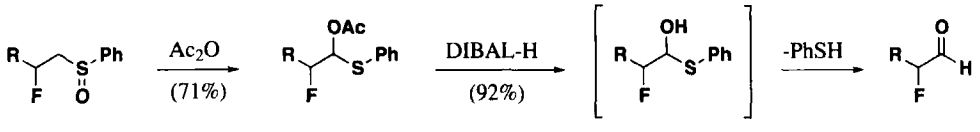
Scheme 1

TABLE 1. Synthesis of α-Fluoro Aldehydes **3** from **2**.[9]

Entry	R =	α-Fluoro Aldehyde **3**	(% yield)
1	$PhCH_2$-		51
2	CH_2=CH-CH_2-		59
3			66
4			68

2. Synthesis from 2-Fluoroalkyl Phenyl Sulfides

Treatment of 2-fluorodecyl phenyl sulfoxide (**4**) with acetic anhydride resulted in a Pummerer rearrangement to 2-fluoro-1-(phenylthio)decyl acetate (**5**) (*Scheme 2*).[10,11] Reduction of the stable ester with DIBAL-H presumably gives hemithioacetal **6** which spontaneously eliminates thiophenol affording 2-fluorodecanal (**7**) in 92% yield (*Scheme 2*). Aldehyde **7** was described as being too labile to be stored at ordinary temperatures.



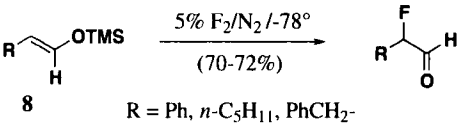
4 5 6 7

R = n-C_8H_{17}

Scheme 2

3. Synthesis from Silyl Enol Ethers

α-Fluoro aldehydes have been generated, in moderate yield, by treatment of silyl enol ethers **8** with molecular fluorine (5% F_2/N_2) (*Scheme 3*).[12] Purrington et al. reported that these aldehydes were unstable, decomposing on standing.



Scheme 3

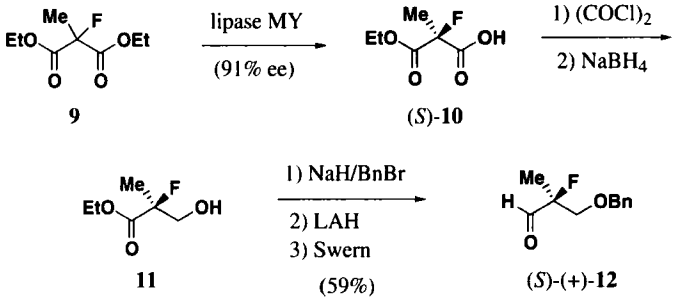
II. SYNTHESIS OF NONRACEMIC α-FLUORO ALDEHYDES

1. Synthesis from β-Fluorohydrins

Oxidation of nonracemic β-fluorohydrins is a useful method for the synthesis of enantiomerically enriched α-fluoro aldehydes.

a. (*S*)-Monoethyl 2-Fluoro-2-methylmalonate

(*S*)-(+)-3-(Benzyloxy)-2-fluoro-2-methylpropanal (**12**) was prepared by Swern oxidation of the corresponding β-fluorohydrin **11** (*Scheme 4*).[13] Fluorohydrin **11** was prepared in a series of steps from (*S*)-monoethyl 2-fluoro-2-methylmalonate (**10**) which was obtained from **9** using enzymes.[13,14] Since the enantiomeric excess (ee) of (*S*)-**10** was 91% it suggests that the fluoro aldehyde has a similar enantiomeric purity; i.e. it is unlikely to have undergone epimerization under the reaction conditions because of its quaternary nature.

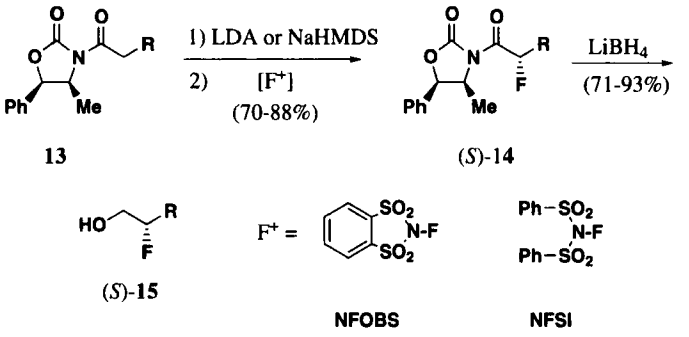


Scheme 4

b. Oxazolidinone α-Fluoro Amides

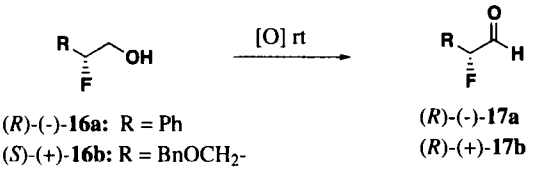
In 1992 Davis and Han introduced the oxazolidinone α-fluoro amide **14** chiral building blocks for the asymmetric synthesis of stereo defined α-fluoro carbonyl compounds (*Scheme 5*).[15] These building blocks were prepared in good to excellent yield by the diastereoselective fluorination of the enolates of *N*-acyloxazolidinones **13** with the stable electrophilic fluorinating reagent *N*-fluoro-*o*-benzenedisulfonimide (**NFOBS**)[15] and more recently with commercially available *N*-fluorobenzenesulfonimide (**NFSI**).[15-17] The diastereoselectivities with **NFSI** (>97%) were excellent and generally better than with **NFOBS** (86-97%). This was attributed to the greater steric bulk of **NFSI** in which the two phenylsulfonyl groups are attached to nitrogen whereas in **NFOBS** they are tied back into a five-membered ring. Importantly the α-fluoro amide **14** is formed with well defined stereochemistry because the fluorinating reagent approaches the enolate from the sterically least hindered *Si*-face affording (*S*)-**14**. The racemization observed on removal of the auxiliary with LiOH or LiOOH was attributed to the enhanced acidity of the α-fluoro proton in **14**.[15] However,

reduction of **14** with $LiBH^4$ gives the β-fluorohydrin (*S*)-**15** without epimerization (*Scheme 5*).[15] Oxazolidinone α-fluoro amide **14** has also been employed in the asymmetric synthesis α-fluoro acids,[15] α-fluoro esters[18] and fluoro sugars.[16]



Scheme 5

The selective oxidation of (*R*)-(-)-2-phenyl-2-fluoroethanol (**16a**) and (*R*)-(+)-3-benzyloxy-2-fluoropropanol (**16b**) to (*R*)-(-)-2-phenyl-2-fluoroethanal (**17a**) and (*R*)-(+)-3-benzyloxy-2-fluoropropanal (**17b**), respectively, is summarized in Table 2 (*Scheme* 6).[17] Only the Dess-Martin periodinane reagent gave the α-fluoro aldehyde **17** without significant racemization and only if the reaction time was carefully controlled. For example, oxidation of **16a** for 10 min. gave **17a** in 90% ee and 90% yield whereas after 30 min. the ee was reduced to 60% (Table 2, compare entries 3 and 4). Swern and PCC oxidation resulted in complete racemization and decomposition, respectively (Table 2, entries 1 and 2). These aldehydes proved to be unstable, decomposing on attempted purification by flash chromatography as well as on storage. The enantiomeric purity was estimated from the ^{19}F NMR spectra of the corresponding diastereomeric imines prepared by treating **17** with (*R*)-(+)-α-methylbenzylamine.[17]



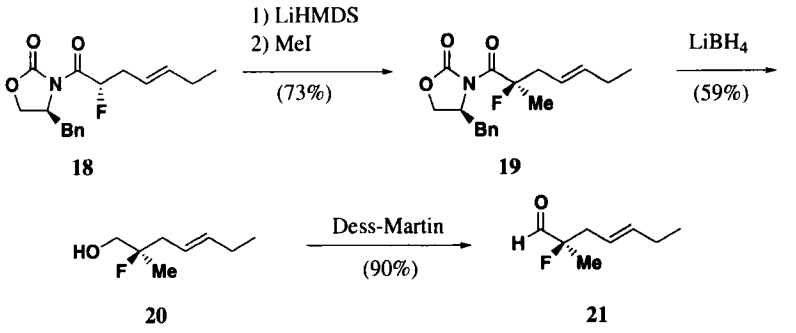
Scheme 6

TABLE 2. Oxidation of β-Fluorohydrins **16** to (*R*)-α-Fluoro Aldehydes **17**[17]

Entry	β-Fluorohydrin	Oxidant/Conditions (Time, min.)	α-Fluoro Aldehyde % Ee[a] (% Yield)[b]
1	(*R*)-**16a** (R = Ph)	Swern (60)	0 (41)
2		PCC	decomposition
3		Dess-Martin (30)	60 (90)
4		Dess-Martin (10)	90 (90)
5	(*R*)- **16b** (R = BnO-CH_2-)	Dess-Martin (10)	94 (95)

a) Determined by $^{19}FNMR$ on the corresponding imines of (*R*)-(+)-α-methylbenzylamine. b) Isolated crude yields.

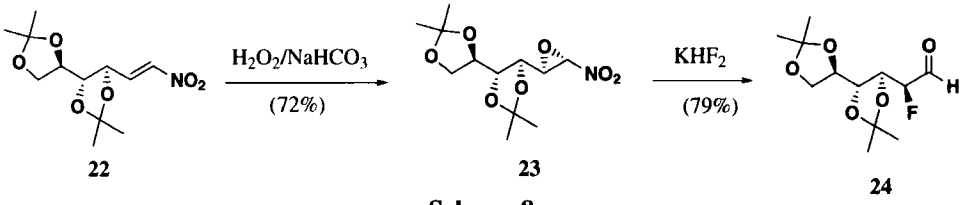
Staunton and co-workers described the asymmetric synthesis of nonepimerizable quaternary α-fluoro aldehyde **21** by Dess-Martin periodinane oxidation of **20** (*Scheme* 7).[19] The fluorohydrin **20** was prepared by reductive removal of the auxiliary with $LiBH_4$ in 59% yield. Alkylation of the α-fluoro enolate of **18** with excess MeI at -25° was completely diastereoselective affording **19** in 73% and >98% de.



Scheme 7

2. Synthesis from Carbohydrates

Epoxidation of 1-deoxy-3,4:5,6-di-*O*-isopropylidene-*C*-nitro-D-mannohexitol (**22**) with alkaline 30% hydrogen peroxide gave 1,2-anhydro-3,4 : 5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (**23**) in 72% yield (*Scheme* 8).[20] With potassium hydrogen fluoride in ethylene glycol **23** gave **24** as a single isomer in 79% yield.



Scheme 8

III. SYNTHESIS OF RACEMIC α-FLUORO KETONES

1. Synthesis by Nucleophilic Displacement

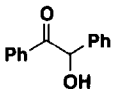
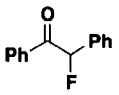
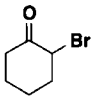
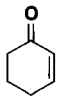
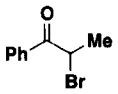
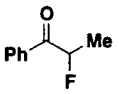
A traditional and widely used method for the synthesis of α-fluoro carbonyl compounds is the reaction of α-substituted carbonyl compounds with a nucleophilic fluoride ion source.[7,8] Some examples are given below.

a. From α-Hydroxy and α-Halo Carbonyl Compounds

Filler and Cantrell described the synthesis of α-fluoro ketones by treatment of α-hydroxy ketones with (diethylamino)sulfur trifluoride (DAST) and α,α-difluoro-alkylamine/α-fluoro enamine (Ishikawa reagent).[21] While acyclic ketones gave good yields of the corresponding α-fluoro derivatives, cyclic examples often failed. For example, benzoin reacts rapidly with the DAST and the Ishikawa reagent to give 2-deoxy-2-fluorobenzoin in 86% and 63% yield, respectively (Table 3, entries 1 and 2). However, under similar conditions 2-hydroxycyclohexanone failed to react. These

same authors further studied the synthesis of cyclic α-fluoro ketones by nucleophilic displacement of α-halo carbonyl compounds with fluoride ion. However, 2-bromocyclohexanone with KF in DMF or in the presence of 18-crown-6 gave 2-cyclohexen-1-one in 71% yield (Table 3, entry 3). Polymer-supported sources of nucleophilic fluoride ion (P^+F^-), prepared from commercially available resins and HF, have also been examined for the synthesis of α-fluoro ketones.[22,23] Thus 2-bromopropiophenone in carbon tetrachloride when heated with the P^+F^- resin gave the α-fluoro ketone in 78% yield (Table, entry 4). Minor products isolated included the corresponding α-chloro and α-hydroxy ketones.

Table 3. Synthesis of α-Fluoro Ketones from α-Hydroxy and α-Halo Ketones

Entry	Substrate	Reagent	α-Fluoro Ketone	% Yield	Ref.
1		DAST		86	21
2		Ishikawa reagen		63	
3		KF/DMF		71	21
4		P^+F^-/CCl_4		78	22

2. Synthesis By Electrophilic Fluorination

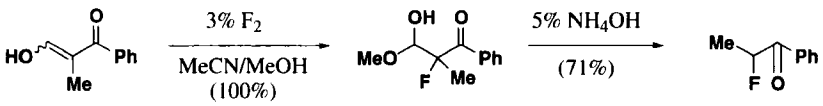
A particularly efficient method for the synthesis of α-fluoro carbonyl compounds is the electrophilic fluorination of enolates and their derivatives. The reagents commonly used for this purpose are dilute F_2 and N-F electrophilic fluorinating reagents, some of which are commercially available.[24]

a. From Silyl Enol Ethers

The fluorination of silyl enol ethers with various electrophilic fluorine sources is given in Table 4. In general, both elemental fluorine (Table 4, entries 1 and 5) and **NFOBS/NFSI** (Table 4, entries 2-4) gave good yields of the corresponding fluoro ketones. The latter reagents are preferable because of their stability and convenience of use.

b. From α-Hydroxymethylene Carbonyl Compounds

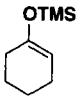
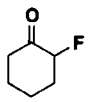
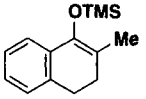
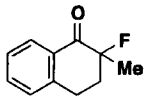
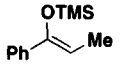
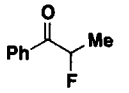
Sato and co-workers found that molecular fluorine (3% F_2/N_2) adds to α-hydroxymethylene compound **25** in the presence of methanol to give the fluorinated hemiacetal **26** in quantitative yield (*Scheme* 9).[26] Deformylation with 5% NH_4OH afforded 2-fluoro propiophenone (**27**) in 71% yield.



25 **26** **27**

Scheme 9

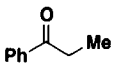
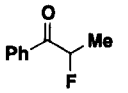
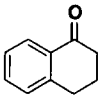
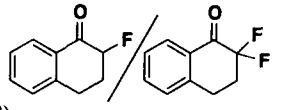
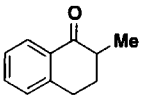
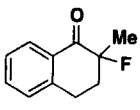
TABLE 4. Electrophilic Fluorination of Silyl Enol Ethers.

Entry	Silyl Enol Ether	Fluorination Reagent/ Conditions	α-Fluoro Ketone (% Yield)		Ref.
1		5% $F_2N_2/CFCl_3$/-78°		(73)	12
2		**NFOBS**/CH_2Cl_2/rt		(79)	24
3		**NFSI**/CH_2Cl_2/rt		(46)	25
4		**NFOBS**/CH_2Cl_2/rt		(86)	24
5		5% $F_2N_2/CFCl_3$/-78°		(59)	12

c. From Ketones

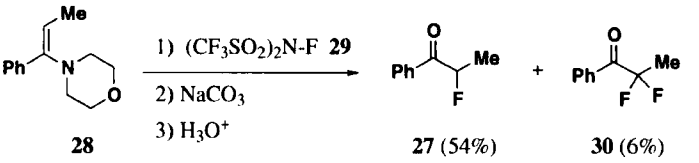
The electrophilic fluorination of metal ketone enolates with **NFOBS** and **NFSI** was studied by the Davis[24] and Differding[25] groups and is summarized in Table 5. In general, the preformed sodium or lithium enolates were treated with a slight excess of the N-F reagent at -78° affording good to excellent yields of the α-fluoro ketone. Higher temperatures and the potassium enolate of 1-tetralone resulted in some difluorination (Table 5, entries 4 and 6).[24]

Table 5. Electrophilic Fluorination of Ketone Enolates with **NFOBS** and **NFSI** at -78°

Entry	Ketone	Base/Reagent	Ketone (% Yield)		Ref.
1		NaHMDS/**NFOBS**		(87)	24
2		LDA/**NFSI**		(85)	25
3		NaHMDS/**NFOBS**		(80/5)	24
4		NaHMDS/**NFOBS** (0°)		(35/12)	
5		LDA/**NFOBS**		(77/5)	
6		KHMDS/**NFOBS**		(51/16)	
7		NaHMDS/**NFOBS**		(95)	24
8		LDA/**NFSI**		(50)	25

d. From Enamines

Enamines also give fluoro ketones on reaction with electrophilic fluorinating reagents. For example, 1-morpholino-1-phenylpropene (**28**) with DesMarteau's *N*-fluoro-*bis*[(trifluoromethyl)-sulfonyl]imide (**29**) reagent gave 2-fluoropropiophenone (**27**) in 54% yield along with some of the difluoro ketone **30** (*Scheme* 10).[27]

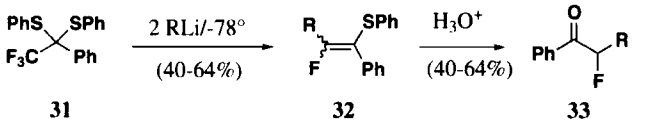


28 **27** (54%) **30** (6%)

Scheme 10

3. Synthesis from β-Fluorovinyl Sulfides

β-Fluorovinyl sulfides **32**, prepared by treating fluoroalkylated dithioketals **31** with alkyl-lithium reagents, gave, on hydrolysis α-fluoro phenyl, alkyl ketones **33** in moderate yield (*Scheme* 11).[28] Interestingly, when R was a phenyl group hydrolysis produced benzil in 54% yield.



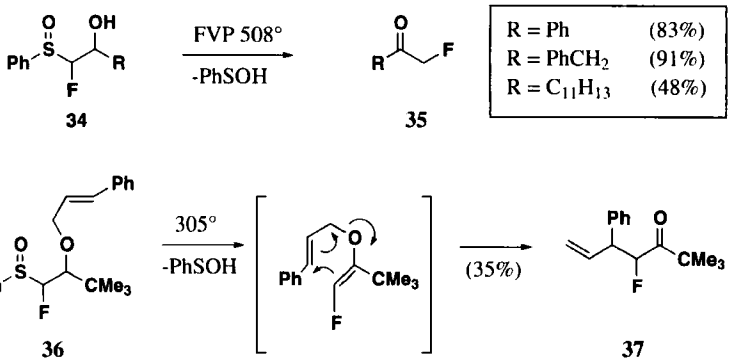
31 **32** **33**

R = Me,*n*-C_4H_9, *s*-C_4H_9, *t*-C_4H_9

Scheme 11

4. Synthesis from α-Fluoro-β-hydroxy Phenylsulfinyl Compounds

Reutrakul et al. found that flash vacuum pyrolysis (FVP) of α-fluoro-β-hydroxy phenyl-sulfinyl compounds **34** at 508° resulted in elimination of benzenesulfenic acid (PhSOH) leading to moderate to good yields of the fluoromethyl ketone **35** (*Scheme* 12).[29] The β-hydroxy sulfoxides **34** were prepared by condensing the anion of α-fluoromethyl phenyl sulfoxide with aldehydes. In a related study FVP of allyl ether **36** at 305° produced **37** in 35% yield *via* a Claisen rearrangement (*Scheme* 12).[30]

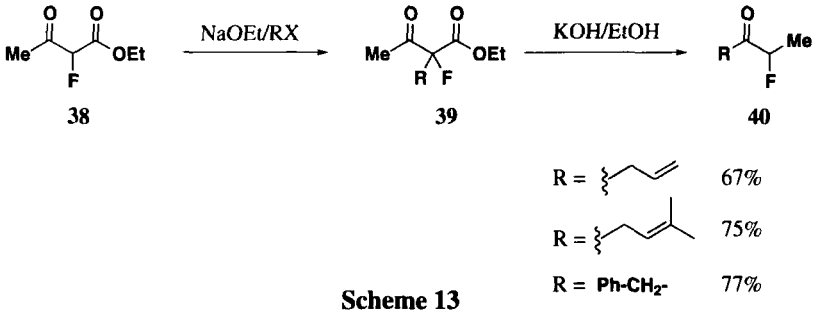


34 **35** **36** **37**

Scheme 12

5. Synthesis from α-Fluoro-α-ketoesters

Ethyl 2-fluoro-3-oxobutanoate (**38**), prepared from ethyl acetoacetate and 10% F_2/N_2, on alkylation and decarboxylation is a useful new route to α-fluoro ketones **40** (*Scheme* 13).[31] Alkylation of **38** to **39** works best with activated halides because steric hindrance to nucleophilic attack by longer chain halides such as *n*-butyl iodide is extremely slow. Decarboxylation occurs readily with potassium hydroxide in ethanol to produce good yields of the fluoro ketone. A "one pot" alkylation/decarboxylation sequence was devised.



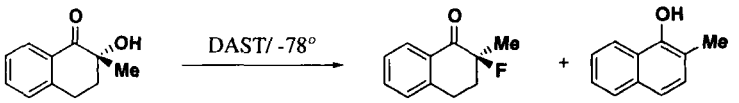
Scheme 13

IV. SYNTHESIS OF NONRACEMIC α-FLUORO KETONES

1. Synthesis by Nucleophilic Displacement

a. From Chiral α-Hydroxy Ketones

Treatment of alcohols with DAST, (diethylamino)sulfur trifluoride, generally affords the corresponding fluoride with inversion of configuration.[32] Thus, treatment of (*R*)-(+)-2-methyl-2-hydroxy-1-tetralone (**41**) with DAST gave (*S*)-(-)-2-methyl-2-fluoro-1-tetralone (**42**) in 20% yield and 70% ee (*Scheme* 14).[33] Unexpectedly, the major product, isolated in 54% yield, was 2-methyl-1-naphthol (**43**).

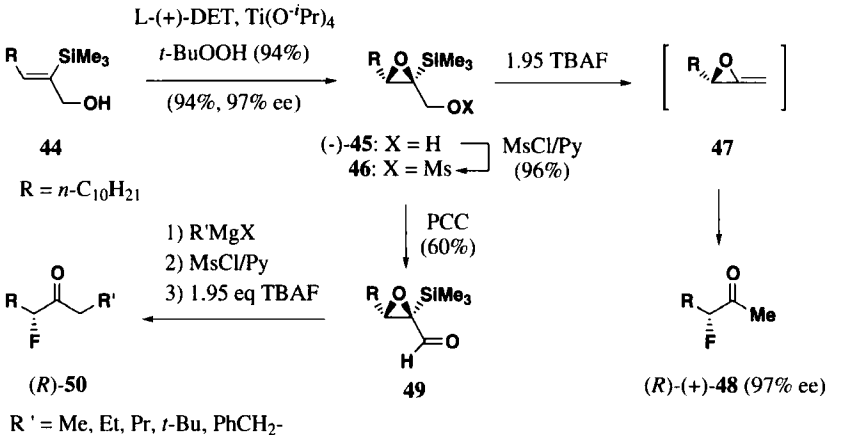


Scheme 14

b. From Chiral Allene Oxides

Kabat introduced useful methodology for the asymmetric synthesis of α-methylene α-fluoro ketones by treating chiral allene oxide intermediates with anhydrous tetrabutylammonium fluoride (TBAF) (*Scheme* 15).[34] In this process, Sharpless asymmetric epoxidation (SAE) of allylic alcohol **44** gave epoxide (*2R,3S*)-**45** in 97% ee which was converted into the mesylate **46**. With 1.95 equiv. of TBAF **46** afforded (*R*)-3-fluorotridecan-2-one (**48**) in 97% ee and 87% yield *via* the fluoride ion promoted ring opening of the intermediate allene oxide **47**. If more than 1.95-2.0 equivalents of TBAF is used racemization occurs. A useful variation of this protocol involves PCC oxidation of alcohol **45** to

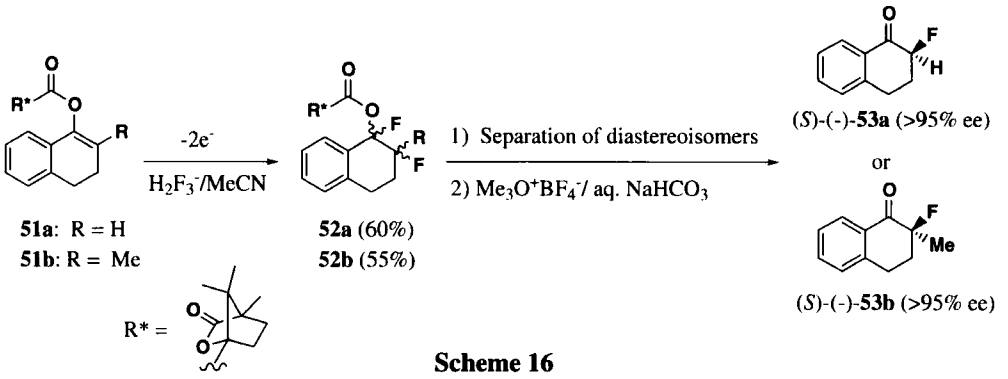
give the aldehyde **49** which is converted in a series of related steps to (*R*)-**50** in 96-97% ee (*Scheme* 15).



Scheme 15

c. From Chiral Enol Esters

Despite the presence of the bulky camphanyl group anodic difuorination of enol ester **51** gave equal amounts of all four diastereomers of **52** which were separated by medium pressure liquid chromatography (*Scheme* 16).[34] To avoid racemization it was necessary to treat the diastereomeric enol esters first with trimethyloxonium tetrafluoroborate and then with aqueous $NaHCO_3$ affording the 2-fluoro-1-tetralones **53** in high enantiomeric purity. The absolute configuration was established by X-ray crystallography.



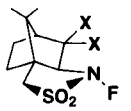
Scheme 16

2. Synthesis by Electrophilic Fluorination

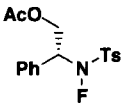
a. From Prochiral Enolates

Only a few nonracemic electrophilic fluorinating reagents have been developed where the asymmetric inducting element resides with the reagent. The *N*-fluoro-2,10-camphorsultams **54** were introduced by the Differding[36] and Davis[33] groups and more recently the *N*-fluorosulfonamides **55** and **56** by Takeuchi, et al. (*Scheme* 17).[37] These reagents were prepared in moderate yields by fluorination

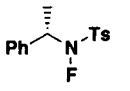
of the corresponding sultams and sulfonamides with 10% F_2/N_2 and $FClO_3$, respectively. As summarized in Table 6 the ee's and yields for the electrophilic fluorination of prochiral metal ketone enolates by these reagents was generally poor. The one exception was the fluorination of the sodium enolate of 2-methyl-1-tetralone with dichloro derivative (+)-**54b** affording (*S*)-2-fluoro-2-methyl-1-tetralone (**53a**) in 76% ee and 53% yield (Table 6, entry 3).[33] The sodium enolate of propiophenone with (+)-**54b** gave racemic material and was attributed to racemization of the product under the reaction conditions (Table 6, entry 10).[33]



(-)-**54a**: X =H
(+)-**54b**: X = Cl
(+)-**54c**: X = OMe



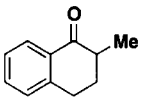
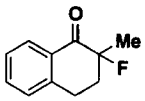
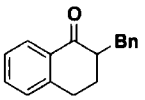
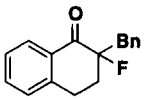
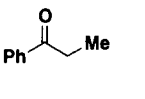
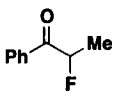
55



(-)-**56**

Scheme 17

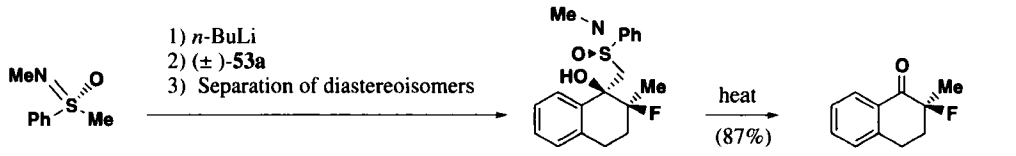
Table 6. Asymmetric Fluorination of Prochiral Ketone Enolates.

Entry	Ketone	Base N-F Reagent		Product % Ee (% Yield)[a]	Ref.
1		NaH	(-)-**54a**	 25 (28)	36
2		LDA		35 (<5)	36
3		NaHMDS	(+)-**54b**	76 (53)[b]	33
4		LDA		10 (10)	33
5		NaHMDS	(+)-**54c**	5 (41)	33
6		LDA	**55**	2 (12)	36
7		LDA	(-)-**56**	46 (16)	36
8		NaHMDS		32 (16)	36
9		LDA	**55**	 9 (6)	36
		LDA	(-)-**56**	54 (26)	36
10		NaHMDS	(+)-**54b**	 0 (41)	33

a) Isolated yields. b) (*S*)-Configuration.

The absolute configuration of (*S*)-2-fluoro-2-methyl-1-tetralone (**53a**) was rigorously established by resolving racemic (±)-**53a** with Johnson's (*R*)-(-)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (**57**)

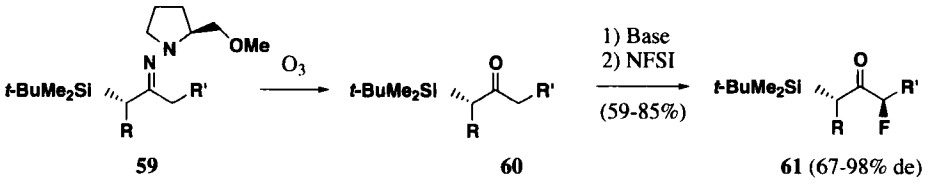
reagent.[33] This involved separation of the resulting diastereoisomers **58**, X-ray crystallographic analysis of one of them and regeneration of the enantiomerically pure α-fluoro ketone (*S*)-(-)-**53a** by heating in 2-butanol (*Scheme* 18).[33]



Scheme 18

b. From Chiral α-Silylketones

Diastereoselective fluorination of enantiopure acyclic and cyclic α-silylketones **60** with *N*-fluorobenzenesulfonimide (**NFSI**) introduces the fluorine atom anti to the bulky silyl group giving the α-fluoro ketones **61** in good to excellent de's (*Scheme* 19).[38] Desilylation to the enantiopure fluoro ketone **62** was readily accomplished by treatment with HF/TBAF. Enders et al. prepared **60** by ozonolysis of the corresponding (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP) α-silyl hydrazone **59**. This methodology is restricted to the synthesis of α-fluoro ketones **62** which lack unsaturated substrates because the α-silyl group is used to direct the asymmetric induction and O_3 is necessary to remove the SAMP auxiliary (*Scheme* 19).

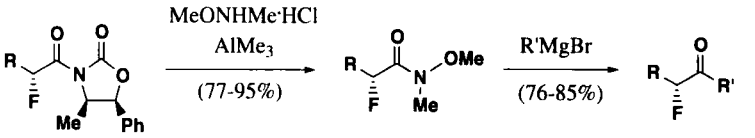


R	R'	% Yield (Config.)
Et	Et	97 (*S*)
Pr	Pr	97 (*S*)
Et	$PhCH_2$	95 (*R*)
$(CH_2)_4$		99 (*R*)

Scheme 19

c. From Oxazolidinone α-Fluoro Amides

Davis and Kasu recently described an enantioselective α-fluoro ketone synthesis which complements the Enders method (*Scheme* 20).[39] In this procedure diastereomerically pure α-fluoro amide (*R*)-**63** were converted into the Weinreb amides, *N*-methoxy-*N*-methylamides **64**, with *N,O* -dimethylhydroxylamine hydrochloride and trimethylaluminum without racemization. With Grignard reagents (*R*)-**64** gives the corresponding α-fluoro ketones (*R*)-**65** in good yield and >96% enantiomeric excess.



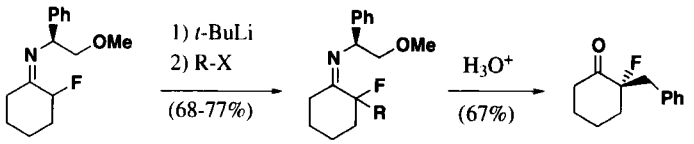
(*R*)-**63** (*R*)-**64** (*R*)-**65** >96% ee

R	R'	% Yield
Ph	Me	77
Me	Ph	80
Ph	Ph	85
Ph	CH_2=CH-	76

Scheme 20

3. Synthesis from Chiral α-Fluoro Ketimines

A potentially important method for the synthesis of enantiomerically enriched α-fluoro ketones is the stereoselective alkylation of fluoro ketimines described by Welch and co-workers (*Scheme* 21).[40] Thus alkylation of the lithium fluoro azaenolate of (*S*)-**66**, derived from 2-fluorocyclohexanone and (*S*)-phenylananinol *O*-methyl ether, afforded the α-alkylated products **67** in modest de's (33-67%). In one case hydrolysis gave (*S*)-2-benzyl-2-fluorocyclohexanone (**68**) in 34% ee which is predicted to have the (*S*)-configuration based on CD studies.



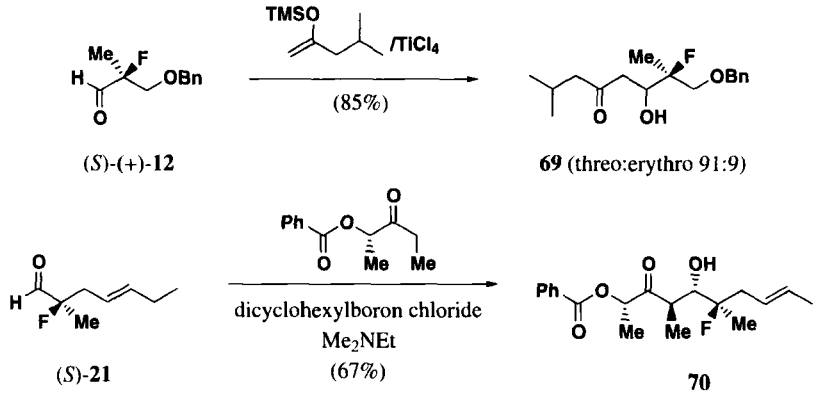
(*S*)-**66** **67** (*S*)-**68**, 34% ee

R	% De
Me-I	67
$PhCH_2$-Br	33
n-Bu-I	58

Scheme 21

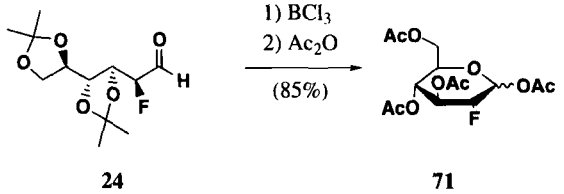
V. APPLICATIONS

Only a few applications of α-fluoro aldehydes have been described. Kitzsume et al. explored the diastereoselective crossed aldol reaction of (*S*)-(+)-3-(benzyloxy)-2-fluoro-2-methylpropanal (**12**) and various metal enolates.[13] For example, the titanium enolate of methyl *iso*-butyl ketone gave **69** in 82% de (*Scheme* 22). They concluded that the α-fluorine substituent had little effect on the diastereoselectivity of the aldol condensation. In another study condensation of the boron enolate of (2*S*)-*O*-benzoyl-3-pentanone with α-fluoro aldehyde **21** gave the *anti*-aldol product **70** exclusively in 67% yield (*Scheme* 22).[19a] This compound is a structural analog of the putative tetraketide biosynthetic precursor of the acyl tetronic acid ionophore tetronasin.



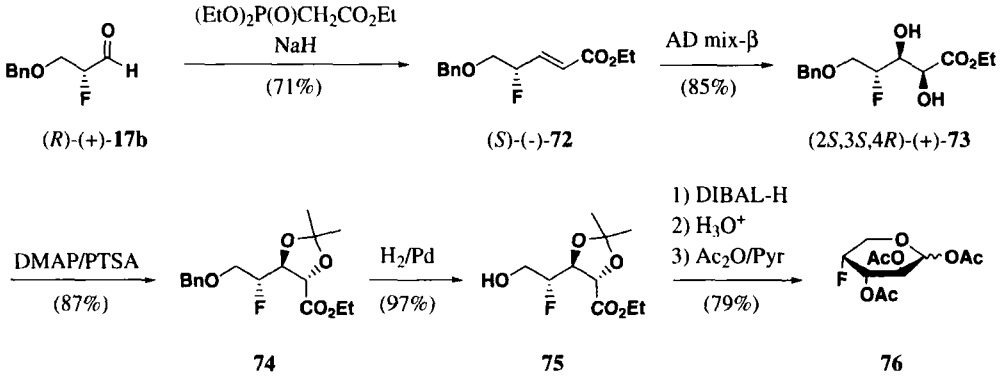
Scheme 22

Two applications of α-fluoro aldehydes to the synthesis of fluoro sugars have been reported. Deprotection of the sugar-derived α-fluoro aldehyde **24** with BCl_3 gave an 85% yield of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose (**71**) (*Scheme* 23).[20]



Scheme 23

A noncarbohydrate synthesis of 1,2,3-tri-*O*-acetyl-4-deoxy-4-fluoro-D-arbinopyranose (**78**) was described by Davis et al. using (*R*)-(+)-3-benzyloxy-2-fluoropropionaldehyde (**17b**), as the precursor (*Scheme* 24).[17] Thus the Horner-Wadsworth-Emmons reaction of (*R*)-**17b** with NaH/triethylphosphonoacetate afforded the allylic fluoride (*S*)-**72** as a separable mixture of *E/Z* isomers. Importantly, racemization of the base sensitive fluoro aldehyde was not detected. Dihydroxylation of *E*-(*S*)-**72** with Sharpless AD-mix β for 2 days resulted in a 97:3 mixture of diastereomers in



Scheme 24

85% yield with the (2*R*,3*S*,4*R*)-**73** isomer predominating. Formation of the acetonide **74** and deprotection afforded alcohol **75** which, following reduction with DIBAL-H and acetylation, produce **76** as a 1:1 mixture of anomers in 79% yield.

VI. CONCLUSIONS

The many methods now available for the synthesis of α-fluoro aldehydes and ketones, particularly enantiomerically pure examples, highlighted in this review make it enviable that these valuable building blocks will be increasingly used in the synthesis and asymmetric synthesis of fluoro organic compounds.

Acknowledgment.- It is a pleasure to acknowledge the important efforts of our co-workers whose names appear in the references. Our own contributions to this review were supported by the National Science Foundation and the National Institutes of Health.

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