Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions

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1. Introduction

Very few fields in chemistry have shown such a considerable interest as fluoroorganic chemistry. Fluorine is perhaps the element that has experienced the greatest recent interest as pointed out by the exceptionally high number of publications and the high percentage of fluorinated new molecules over recent decades.[1] Today, the significant expansion in the use of fluorinated chemicals has attracted the attention of organic, agricultural, medicinal, and material chemists.[2−10] The replacement of hydrogen by fluorine, the most electronegative element, alters sterically and electronically the properties of the molecules, affecting the basicity or acidity of neighboring groups, dipole moment, and overall reactivity and stability. Fluorine is often regarded as an isostere of hydrogen despite the fact that their van der Waals radii are different (1.47 versus 1.20 Å).[11] The carbon−fluorine bond length (1.39 Å) is similar to the carbon−oxygen one (1.43 Å), suggesting an isosteric behavior. The high carbon−fluorine bond energy (485.7 kJ/mol)[12] confers relative stability against metabolic transformations. In addition, fluorine can participate in hydrogen bonding interactions with H−C even if hydrogen bonds to C−F are definitely much weaker than those observed to oxygen or nitrogen.[13,14] Nevertheless, the controversy remains on the existence of hydrogen bonds between the C−F group and −OH or −NH donors.[15−17] With regard to the CF_3 group, its size (van der Waals volume) is relatively large, between those of the *i*-Pr and the *t*-Bu groups.[18] The CF_3 group has an electronegativity similar to that of oxygen[19] and a large hydrophobic parameter.[20] The trifluoromethyl group appears in many biologically active pharmaceutical and agrochemical compounds. The increased lipophilicity, and a superior metabolic stability compared to that of the trimethyl analogues, often accounts for an improved activity profile. Higher fluoroalkyl groups, which are the perfluoroalkyl groups, are introduced mainly to increase the lipophilicity, and also in the context of fluorous chemistry.[21]

One of the most fascinating aspects of organofluorine chemistry is the asymmetric synthesis of fluorinated molecules.[22−27] It is a very challenging topic with great potential in numerous areas. Several examples of asymmetric reactions have been successfully applied to fluorinated substrates although new problems have been raised due to the unpredictable chemistry of fluorinated molecules.[28] Asymmetric synthesis is now a mature area of organic chemistry; however, asymmetric fluorination and perfluoroalkylation are developing relatively slowly. Nevertheless, we are witnessing, since the beginning of the new century, a remarkable renewal of interest principally for enantioselective fluorination. Asymmetric perfluoroalkylation, taking in trifluoromethylation, is still a timid area, although promising new reagents and methodologies are now available to accomplish such reactions. For the purpose of this review, only asymmetric syntheses, in which the formation of a C−F, C−CF_3, or C−R_f bond is concomitant to the stereocontrolled creation of a new stereogenic center, have been considered. Stereospecific transformations (for example, fluorodehydroxylations with DAST, or replacements of tertiary deactivated hydrogen in

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Dominique Cahard was born in 1968 in Fécamp (Normandy, France). He received his Ph.D. degree at the University of Rouen (under the direction of Pierre Duhamel). He then spent 19 months as a Postdoctoral Research Associate with Professor Chris McGuigan at Southampton University (U.K.) and then at the Welsh School of Pharmacy in Cardiff (Wales). He also worked for a short period of time with Professor Tadashi Nakata at RIKEN, Tokyo (Japan). In 1996 he joined the CNRS at the University of Rouen where he completed his Habilitation in 2001. He has authored 56 publications and 5 patent applications. His current interests are mainly in the field of enantioselective synthesis with emphasis on electrophilic fluorination and phase-transfer catalysis.

steroids) and classical resolutions, which are not asymmetric syntheses, will not be considered, with the exception of kinetic resolutions, which will be mentioned. The electrophilic fluorination−nucleophilic addition reaction upon glycals and other ethylenic systems was intentionally not covered.[29,30] Reactions involving fluorinated chiral building blocks are beyond the scope of this review. Four generations of asymmetric synthesis exist. In the first generation, the stereoselectivity is directed intramolecularly by an enantiomerically pure substrate, almost exclusively of natural origin, which remains incorporated in the product. The second generation is similar to the first one with an intramolecular control of the stereoselectivity, but requires a chiral enantiomerically pure auxiliary that is first covalently linked to the substrate for the diastereoselective reaction, and then removed for potential recycling. In the third and fourth generations, an achiral substrate is transformed into a chiral product with concomitant creation of a stereogenic center with the aid of a chiral stoichiometric reagent (third generation) or a chiral catalyst (fourth generation). Reactions reported in this review belong to all four generations of asymmetric synthesis. The review is organized by fluorine group introduction: F, CF_3, and R_f, with each section dealing with electrophilic, nucleophilic, and radical reactions as well as diastereo- and enantioselective approaches. The literature in this review is comprehensively covered through the end of June 2004.

2. Asymmetric Fluorination Reactions

2.1. Electrophilic Fluorination Reactions

A wide variety of electrophilic fluorinating agents have been developed over the past few decades.[31,32] For the majority of them, they must be prepared from molecular fluorine. Molecular fluorine itself is a versatile reagent able to perform many selective reactions;[33] however, it is quite indiscriminate as a reagent in asymmetric synthesis. Cationic fluorine, F^+, has only been observed spectroscopically in the gas phase; consequently, the ability of electrophilic fluorinating agents to deliver positive fluorine is the subject of some controversy. There is no evidence supporting the existence of the fluoronium ion in solution, while an S_N2 pathway for electrophilic *N*-fluoro reagents was demonstrated.[34,35] Some reviews covering specific electrophilic fluorinating reagents and recent advances in electrophilic fluorination have been published.[36,37]

2.1.1. Diastereoselective Fluorination

This section principally reviews diastereoselective synthetic routes to compounds possessing an α-fluorocarbonyl moiety. A partial coverage of diastereoselective electrophilic fluorinations may be found in previous reviews.[38,39] Compounds having an α-fluorocarbonyl moiety present interesting biological activities; in particular, they are effective mimics of α-hydroxy ketones, they are useful probes for various biological processes, and they can act as enzyme inhibitors. In addition, these compounds are valuable synthons for the construction of active compounds.

2.1.1.1. α-Fluoro Ketones. In all the examples, the stereoselectivity is the result of an intramolecular control from an enantiomerically pure substrate. The chirality remains present in the product, but can be cleaved off as in the case of Enders' α-silyl ketones (vide infra). The following examples illustrate the concept of fluoro analogues of bioactive compounds (steroids, vitamins, β-lactams, cephalosporins, amino acids).

A wide range of electrophilic fluorinating agents (F_2/N_2, XeF_2, O−F, N−F) have been used for the synthesis of fluorosteroids, and the literature is abundant on this subject. Recent work preferably utilized the N−F class of fluorinating agents, which

are easier to handle and safer, for the fluorination at activated positions of steroids. Stavber and co-workers described a direct α-fluorination of two keto steroids (5α-cholestan-3-one and 3β-hydroxy-5α-androstan-17-one) with Accufluor NFTh [1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)], providing the corresponding α-fluoro steroids **1** and **2**, respectively, as single diastereomers by selective α-face fluorination (Figure 1).[40]

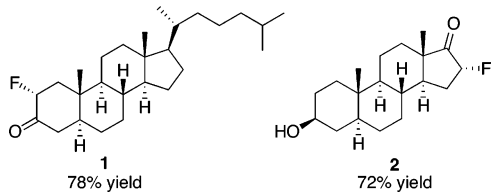
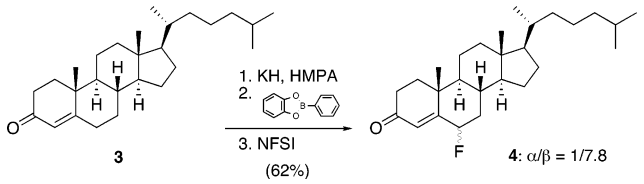


Figure 1. Examples of fluoro steroids.

This direct fluorination was generally superior in terms of diastereoselectivity compared to the methods which require the preparation of enol derivatives used as substrates in the fluorination reaction, such as enol ethers,[41−44] enol acetates,[42,45−50] enamides,[51] or enamines.[52,53]

Using conjugated enol ethers raised the problem of regioselectivity. Selective γ-fluorination of various steroids was realized by Poss and co-workers as exemplified on 4-cholesten-3-one (**3**), leading to an α/β-isomer ratio of 1/7.8 (Scheme 1).[54] The potassium

Scheme 1



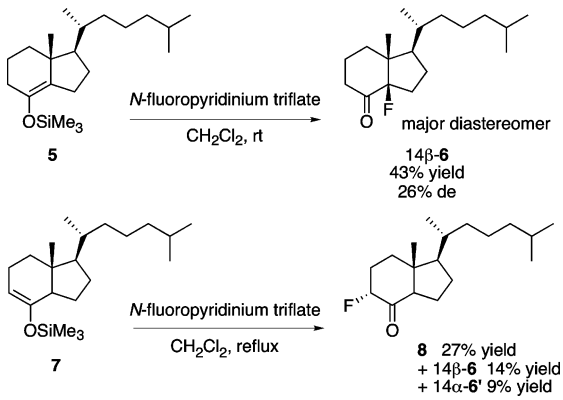
dienoxyboronate generated in situ was reacted with NFSI (*N*-fluorobenzenesulfonimide) to produce the 6-fluoro steroid derivative **4**, preferentially giving the β-isomer. Here again, direct fluorination of conjugated ketones did not require the preparation of intermediate species such as dienamines, dienol ethers, or acetates.[45,47,55−62]

In comparison to the high number of fluorinations of enol ether and ester steroid derivatives, fluorinations of steroidal metal enolates are seldom seen, probably due to undesirable formation of side products.[63,64]

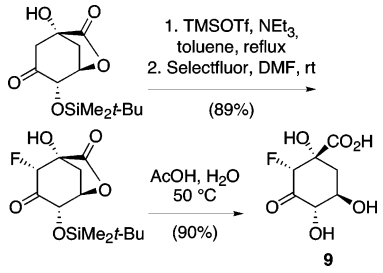
Dauben and Greenfield reported fluoro C/D ring ketones as fluorinated chirons for vitamin D_3 syntheses.[65] Kinetic and thermodynamic silyl enol ethers **5** and **7** reacted with *N*-fluoropyridinium triflate to afford mixtures of fluorinated products, in poor yields and diastereoselectivities, and nonfluorinated side products (Scheme 2).

The synthesis of 2-(*R*)-fluorodehydroquinic acid (**9**) has been achieved from quinic acid including an electrophilic fluorination step by means of Selectfluor [(1-chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate)] (Scheme 3). After recrystallization, a single diastereomer was obtained in 89% yield.[66]

Scheme 2

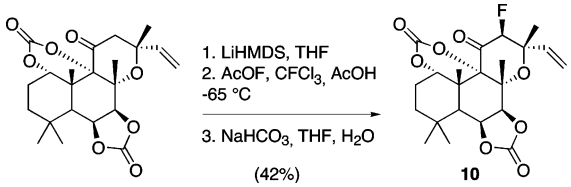


Scheme 3



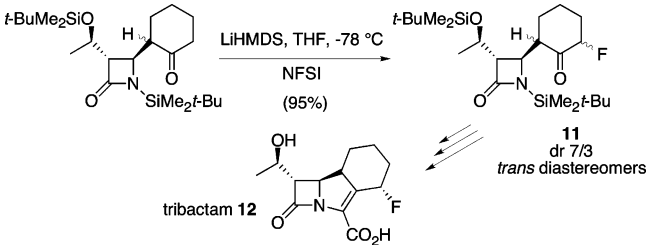
In the synthesis of 12-fluoroforskolin, the fluoro intermediate **10** was obtained by reaction of the lithium enolate with acetyl hypofluorite; a single diastereomer was obtained in 42% yield (Scheme 4).[67]

Scheme 4



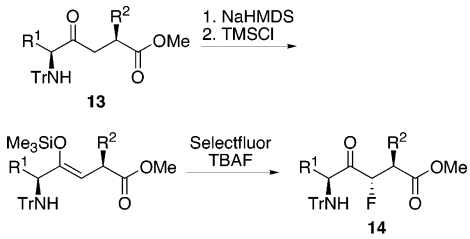
A fluorinated member of a new family of β-lactam antibiotics, tribactam **12**, was prepared utilizing fluorination of a lithium enolate by NFSI in the key step. A mixture of two diastereomers of **11** (ratio 7/3) was obtained in 95% yield, with both isomers having the cyclohexanone *trans* disubstituted (Scheme 5).[68,69]

Scheme 5



Monofluoro ketone peptide isosteres possess therapeutic potential as enzyme inhibitors. The first synthesis of such fluoro peptides utilized fluorination of a silyl enol ether with the aid of XeF_2 in a mixture acetonitrile/1,1,2-trichlorotrifluoroethane, leading to the desired product in 71% yield without any diastereoselectivity.[70] The incorporation of fluorine into dipeptides was further developed by Hoffman and co-

Scheme 6



R^1	R^2	yield, %	de, %
i-Bu	Me	76	>95
i-Bu	$CH_2C_6H_{11}$	73	>95
$(CH_2)_2SCH_3$	Bn	65	>95
Me	*i*-Bu	75	>95
Bn	*n*-Pr	68	>95
"Proline"	*n*-Pr	15	>95
i-Pr	Me (*S*)	71	10
CH_2OBn	*i*-Bu (*S*)	74	20

workers. (2*R*,5*S*)-*N*-tritylated ketone dipeptides **13** were converted to their trimethylsilyl enol ethers and fluorinated with Selectfluor in the presence of TBAF

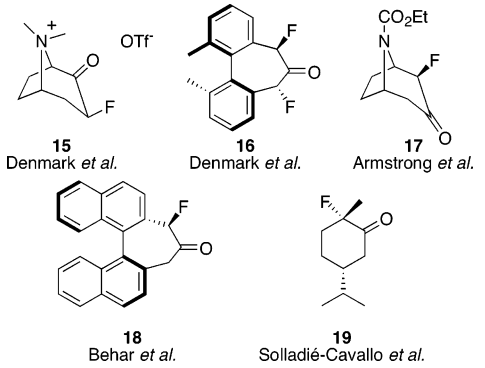


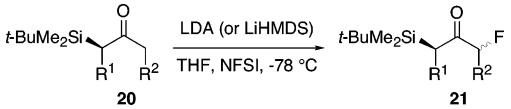
Figure 2. α-Fluoro ketones used in asymmetric epoxidation.

(tetrabutylammonium fluoride). The cooperative stereocontrol between the *N*-tritylamine group and the alkyl group at C-2 allowed high diastereoselectivities, and good yields, 65−76%, of **14** (Scheme 6), to be reached.[71−73]

The asymmetric epoxidation of unfunctionalized alkenes by dioxiranes derived from chiral α-fluoro ketones is an active area of research. Several groups have embarked on the design and the synthesis of new chiral α-fluoro ketones (Figure 2). Denmark and Matsuhashi developed the tropinone-based ketone **15**, which required the fluorination of the sodium enolate of the corresponding β-keto ester by Selectfluor in DMF (26−39%) followed by decarboxylation. An enantiomer resolution was performed to provide optically pure **15**.[74] The same group also reported the quite lengthy synthesis of the biphenyl-based ketone **16** requiring two fluorination steps by Selectfluor and epimerization in triethylamine to afford a single diastereomer.[74] Armstrong and co-workers have synthesized 2-fluoro-*N*-carbethoxytropinone (**17**) via a silyl enol ether and 2 equiv of Selectfluor in 63% yield. The fluorination occurred exclusively on the less hindered exo face of the silyl enol ether.[75] An enantioselective version of the synthesis of **17** was reported by the same group; see section 2.1.2.5. Behar and Stearman prepared chiral binaphthyl α-fluoro ketones by a sequential deprotonation of the corresponding ketone by potassium hydride and fluorination with NFSI at −78 °C to produce the monofluorinated ketone **18** in 77% yield (other distributions of fluorine atoms were also reported).[76] Solladié-Cavallo and co-workers synthesized the α-fluoro ketone **19** by fluorination of the silyl enol ether with Selectfluor, providing a mixture of two diastereomers (54/46) which were separated by column chromatography.[77,78] Other structurally similar α-fluoro ketones were evaluated by the same group in asymmetric oxidation of silyl enol ethers.[79]

Enantiopure α-silyl ketones **20** were prepared by diastereoselective silylation of the (*S*)- or (*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP) hydrazone and used as substrates in diastereoselective electrophilic fluorinations in which the silyl group acts as a traceless directing group.[80,81] Lithium enolates of **20** generated by LDA were fluorinated with

Table 1. Second-Generation Asymmetric Electrophilic Fluorination of α-Silyl Ketones



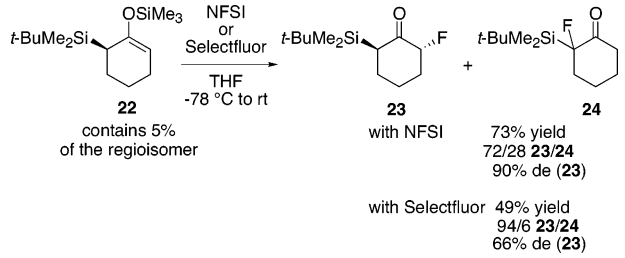
substrate configuration	R^1	R^2	product configuration[a]	yield,[b] %	de,[b] %
R	Me	Me	(2*R*,4*S*) [(2*R*,4*R*)]	53 (65)	55 (76)
R	Et	Et	(3*R*,5*S*) [(3*R*,5*R*)]	79 (80)	79 (89)
R	*n*-Pr	*n*-Pr	(4*R*,6*S*) [(4*R*,6*R*)]	81 (75)	65 (82)
R	$-(CH_2)_3-$		(2*R*,6*R*) [(2*R*,6*R*)]	81 (70)	>98 (76)
R	$-(CH_2)_4-$		(2*R*,7*R*) [(2*R*,7*S*)]	85 (46)	>98 (37)
R	$-CH_2N(Bn)CH_2-$		(3*R*,5*R*) [(3*R*,5*R*)]	69 (84)	>98 (87)
S	Me	*n*-Pr	(2*S*,4*R*) [(2*S*,4*S*)]	57 (68)	65 (63)
S	Me	*i*-Pr	(2*S*,4*R*) [(2*S*,4*S*)]	50 (79)	86 (38)
S	Me	*i*-Bu	(2*S*,4*R*) [(2*S*,4*S*)]	77 (85)	68 (44)
S	Me	Bn	(2*R*,4*S*) [(2*S*,4*S*)]	74 (77)	67 (87)
S	Et	Bn	(2*R*,4*S*) [(2*S*,4*S*)]	59 (70)	67 (78)
S	Bn	*n*-Pr	(2*S*,4*R*) [(2*S*,4*S*)]	66 (90)	37 (54)

[a] Absolute configuration observed for reactions employing LDA and, in brackets, for reactions employing LiHMDS. [b] Yield (or de) for reactions with LDA-generated enolates and, in parentheses, for reactions with LiHMDS-generated enolates.

NFSI in good yields and with high diastereomeric excesses (37% → 98% de) (Table 1). Interestingly, LiHMDS allowed reverse diastereoselectivity to be obtained, whereas the impact on the de's was inconclusive. The diastereoselectivity was found to reflect the ratio of enolate stereomers, with NFSI reacting only from the less sterically hindered enolate face.

This concept was also applied to silyl enol ether **22**; however, the fluorination gave rise to a significant amount of regioisomers **23** and **24** (Scheme 7).[81] The

Scheme 7



unpredictable formation in various amounts (up to 100%) of the regioisomer bearing the fluorine atom on the side of the silyl group is obviously a disadvantage of the method. Desilylation of the enantiopure fluoro ketones was readily accomplished by treatment with HF/TBAF without epimerization.

2.1.1.2. α-Fluoro Esters and Amides. The following examples belong to the first generation of asymmetric synthesis (Figure 3). 2-Fluoropodophyl-

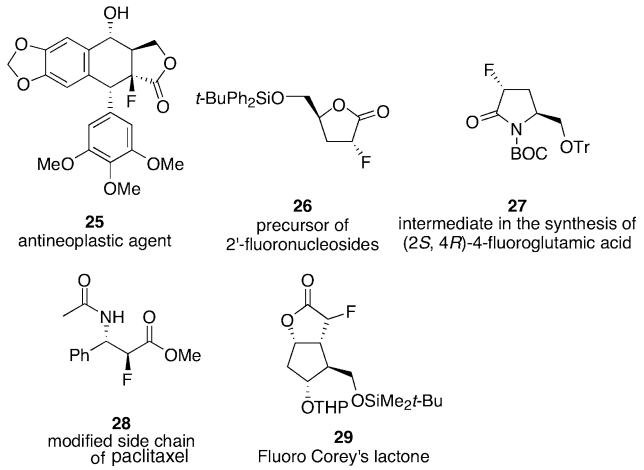


Figure 3. Examples of α-fluoro esters and amides.

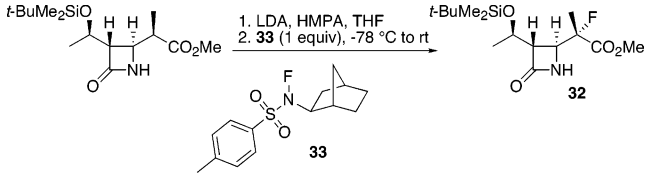
lotoxin (**25**), a potent antitumor agent, was obtained by a completely diastereoselective fluorination of the sodium enolate with NFSI in 99% yield; the stereochemistry at the ring junction was *trans*.[82,83] Liotta and co-workers have also reported a completely diastereoselective electrophilic fluorination of a chiral nonracemic lactone which was further transformed into 2′-fluoronucleosides. Indeed, fluorolactone **26** could be obtained in 50−70% yield with 100% de.[84] Enantiomerically pure 2-pyrrolidinone derived from L-glutamic acid was fluorinated to give **27** in 57% yield and 100% de by reaction with LDA, followed by NFSI in THF at −78 °C. **27** was further converted to the desired (2*S*,4*R*)-4-fluoroglutamic acid as a single stereomer.[85] Fluoro analogues of the side chain of the antitumor agent paclitaxel were synthesized by Davis and Reddy starting from chiral β-amino esters. Treatment of the dianion, generated from LDA (2.2 equiv), with NFSI at −78 °C gave the fluorinated target **28** in 65% yield and a moderate 62% de.[86] The α-fluoro analogue of Corey's lactone (**29**), an important intermediate in the synthesis of prostaglandins, was synthesized by generation of the ketene silyl acetal followed by fluorination with the aid of 2,6-bis(methoxymethyl)pyridinium triflate in 65% overall yield. The configuration of the fluorinated carbon center was not determined.[56] The fluorolactone **29** could also be obtained using NFSI, but was immediately converted to the desired difluorolactone for the synthesis of difluoroprostacyclins.[87]

Elaboration of fluorinated antibiotics was conducted via electrophilic fluorination of functionalized azetidinone **30** by means of NFSI. Attack of the fluorine atom by the less hindered face of the stabilized sodium enolate gave predominantly **31** having the fluorine atom *trans* to the ester moiety (Scheme 8).[88]

Scheme 8

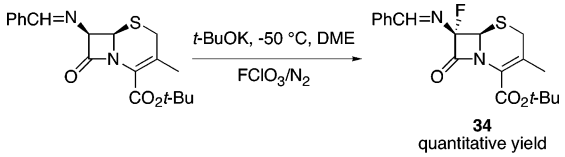
In the chemistry of carbapenems, Wildonger and co-workers prepared 1-fluoro-1-methylcarbapenem **32** by fluorination of the corresponding enolate using *N*-fluoro-*N*-(*exo*-2-norbornyl)-*p*-toluenesulfonamide (**33**).[89] The desired diastereoisomer was purified and isolated pure in 35% yield; however the diastereoselectivity was not reported (Scheme 9).[90]

Scheme 9



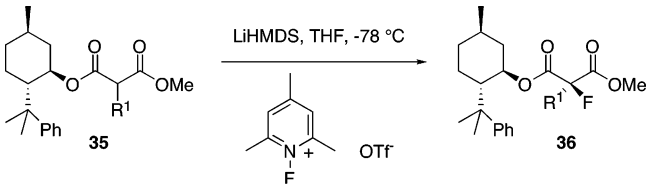
An early example of diastereoselective fluorination with perchloryl fluoride was the preparation of 7α-fluorocephalosporin Schiff base **34** (Scheme 10).[91]

Scheme 10



Examples of second-generation asymmetric fluorination are more frequent in the literature. Fukumoto and co-workers published a series of papers on diastereoselective fluorination of malonates **35** bearing a chiral phenylmenthyl auxiliary for the construction of quaternary fluorinated stereogenic centers (Scheme 11).[92−94]

Scheme 11

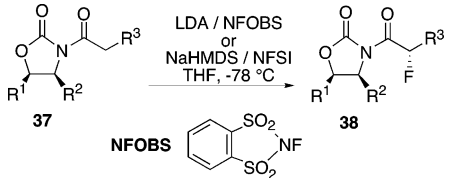


R^1	yield, %	dr
Me	87	79/21
Et	96	67/33
Pr	96	67/33
Bn	88	62/38

A similar strategy was applied for the synthesis of menthyl-2-fluoro-1-tetralone-2-carboxylate from the corresponding chiral β-keto ester by fluorination of the sodium enolate with Selectfluor in 94% yield; the diastereoselectivity was not provided, and the diastereomers were separated by column chromatography.[95]

Davis and co-workers greatly contributed to diastereoselective electrophilic fluorinations. They selected Evans' oxazolidinones as chiral auxiliaries and *N*-fluoro-*O*-benzenedisulfonimide (NFOBS) or NFSI as the fluorinating agent.[96−98] Good to excellent diastereoselectivities were obtained by selective approach of the fluorinating agent from the less hindered *si* face of the chiral imide enolate (Table 2).

Table 2. Diastereoselective Fluorination of Chiral Imide Enolates



using LDA/NFOBS					using NaHMDS/NFSI				
R^1	R^2	R^3	yield, %	de, %	R^1	R^2	R^3	yield, %	de, %
Ph	Me	*n*-Bu	88	97	Ph	Me	Ph	85	>97
H	*i*-Pr	*n*-Bu	85	96	Ph	Me	Me	77	86
Ph	Me	*t*-Bu	86	96	Ph	Me	$CH{=}CH_2$	69	84
H	*i*-Pr	*t*-Bu	80	97	Ph[a]	Me[a]	CH_2OBn	78	94
Ph	Me	Bn	84	89					
Ph	Me	Ph	86	86					

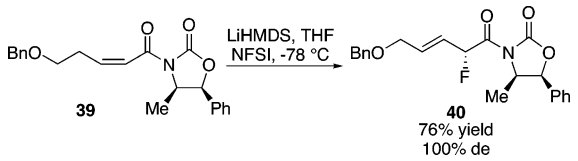
[a] (4*R*,5*S*)-Oxazolidinone was used in this example.

The authors suggested that the fluorination occurred by an S_N2-type mechanism for transfer of fluorine to enolate species.[99] Some racemization occurred on removal of the auxiliary with LiOH or LiOOH due to the enhanced acidity of the α-fluoro proton. However, the reduction of **38** with $LiBH_4$ took place without epimerization leading to the β-fluorohydrins.

Interestingly, conversion into the *N*-methoxy-*N*-methylamides (Weinreb amides) followed by addition of Grignard reagents provided the corresponding α-fluoro ketones without racemization.[97] This synthetic route complements Enders' method (vide supra).

Diastereoselective fluorination of α,β-unsaturated chiral oxazolidinone **39** was conducted by reaction of LiHMDS followed by addition of NFSI to produce a single diastereomer in 76% yield (Scheme 12).

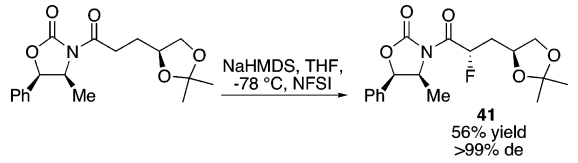
Scheme 12



The complete diastereoselectivity reached with NFSI, compared to 82% de with NFOBS, was attributed to the greater steric bulk of NFSI. The reaction provided a nice example of deconjugative electrophilic fluorination. The acyclic fluoro compound **40** was employed in the synthesis of fluoro carbohydrates.[100,101]

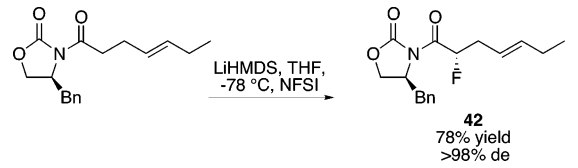
The success of the method stimulated significant efforts to improve the scope of the process. Marquez and co-workers synthesized the key fluorinated intermediate **41** for the preparation of active anti-HIV compounds FddA and FddC. The fluorination proceeded with complete diastereoselectivity (Scheme 13).[102]

Scheme 13



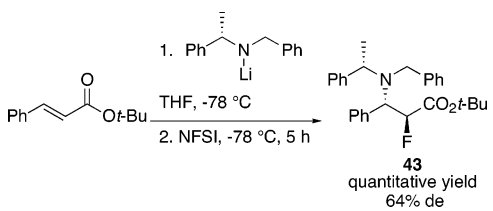
A chiral oxazolidinone auxiliary was also used by Stauton and co-workers to direct the addition of a fluorine atom in the preparation of fluoro analogue **42** as a biosynthetic precursor of the ionophore antibiotic tetronasin (Scheme 14).[103]

Scheme 14



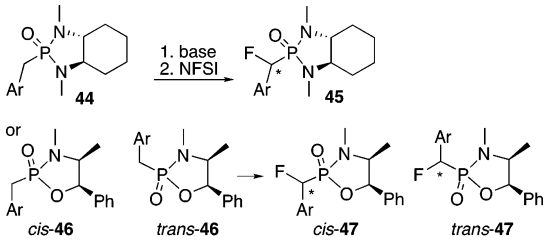
Recently, in 2004, Duggan and co-workers described an elegant tandem conjugate addition of a chiral lithium amide on *tert*-butyl cinnamate followed by a diastereoselective electrophilic fluorination of the intermediate enolate by NFSI. The β-amino-α-fluoro ester **43** was obtained quantitatively with 64% de (Scheme 15).[104]

Scheme 15



2.1.1.3. α-Fluoro Phosphonates. α-Monofluoroalkylphosphonates are more effective analogues of phosphate esters than alkyl phosphates because the CHF group is a better phosphate mimic.[105] Among the numerous entries to α-monofluoroalkylphosphonates, the direct electrophilic fluorination of alkylphosphonate carbanions is a convenient method. Early work by Differding and co-workers described the reaction of NFSI at −78 °C with phosphonate carbanions generated by KDA. Unfortunately, when chiral centers were present on the alkyl chain, the diastereoselectivity was not provided.[106] The search for effective enzyme inhibitors motivated the development of asymmetric fluorination of alkylphosphonates. Taylor and co-workers prepared enantiomerically pure α-monofluoroalkylphosphonic acids for evaluation as inhibitors of protein tyrosine phosphatase 1B. The key step was a diastereoselective electrophilic fluorination of phosphonamidates bearing *trans*-(*R*,*R*)-1,2-bis(*N*-methylamino)cyclohexane or (−)-ephedrine as a chiral auxiliary (Table 3). The

Table 3. Selected Results for the Fluorination of Chiral Phosphonamidates



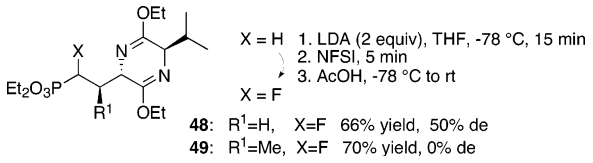
substrate	Ar	base	yield, %	de, %
44	2-naphth	*n*-BuLi	68	68
44	2-naphth	LiHMDS	81	70
trans-**46**	2-naphth	NaHMDS	62	72
cis-**46**	2-naphth	NaHMDS	54	58
trans-**46**	*m*-(Ph)Ph	NaHMDS	85	25
cis-**46**	*m*-(Ph)Ph	NaHMDS	68	26
trans-**46**	Ph	NaHMDS	47	29
cis-**46**	Ph	NaHMDS	44	33

diastereoselectivity was strongly dependent on the nature of the base and counterion with de's ranging from 2% to 72%. While LiHMDS gave good results with **44**, NaHMDS was preferred in the case of **46** (Table 3). Separation of the diastereomeric products **47** by flash chromatography was followed by a racemization-free removal of the ephedrine auxiliary to obtain enantiomerically pure α-fluoro phosphonic acids. The absolute stereochemistry was established by X-ray crystallography.[107]

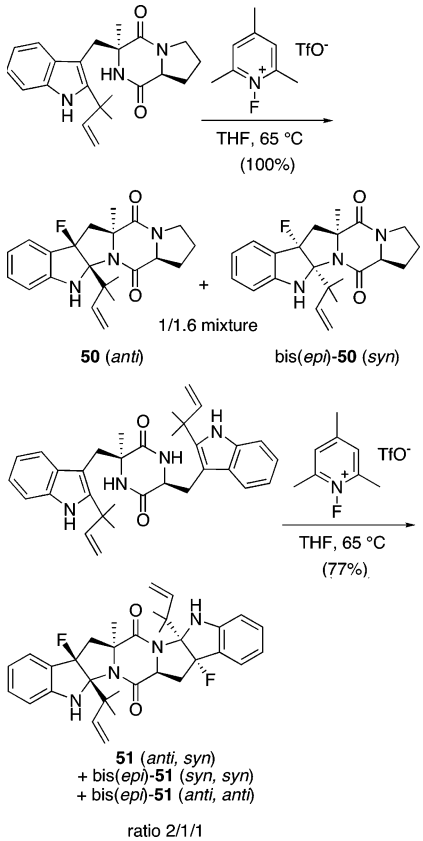
α-Monofluorinated phosphonate mimics of phosphoserine and phosphothreonine were synthesized via electrophilic fluorination of Schöllkopf's bislactim ethers derived from cyclo[L-(2-amino-4-phosphonobutanoic acid)-D-valine]. However, the chiral auxiliary only produced moderate to no diastereoselectivity in the fluorination with NFSI (Scheme 16).[108]

2.1.1.4. Miscellaneous Compounds. Shibata and co-workers reported the synthesis of fluorobrevianamide E (**50**) and fluorogypsetin (**51**) by a novel tandem electrophilic fluorination−cyclization. Despite an elegant synthetic route, the diastereoselectivity was poor for **50** and the sequence of reactions was nonselective for **51** (Scheme 17).[109]

Scheme 16



Scheme 17



Few reports described electrophilic fluorination of sulfoxides and sulfones. Some α-fluoro-β-keto sulfoxides[110−112] and sulfones[113,114] were synthesized but are not of interest for this review since the fluorinated stereogenic centers are configurationally labile. Moreover, the chirality is often lost in further transformations (bis-α-fluorination and elimination reactions).

2.1.2. Enantioselective Fluorination

One of the most fascinating aspects of modern organofluorine chemistry is the discovery of efficient reagents and methods for enantioselective fluorination.[115,116] The formation of a carbon−fluorine bond with concomitant generation of a new stereogenic center from an achiral substrate is now considered state-of-the-art. A variety of chiral nonracemic N−F fluorinating agents were developed for direct enantioselective fluorination of C−H acidic substrates. More recently, the enantioselective electrophilic fluorination with the aid of an achiral fluorinating agent and a catalytic chiral complex of a transition metal and a chiral ligand was reported. Other approaches

involve phase-transfer catalysis, fluorodesilylation of allylsilanes, and the use of chiral bases.

2.1.2.1. Chiral *N*-Fluoro Reagents. The pioneering work of Differding and Lang in 1988 led to the development of the *N*-fluorocamphorsultams **52** and **53** (Figure 4) as the first enantioselective fluorinating

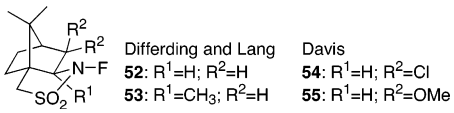
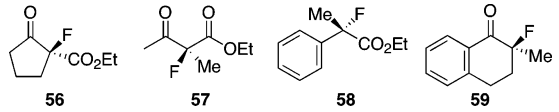


Figure 4. *N*-Fluorocamphorsultams.

agents.[117] Their syntheses require several steps from camphorsulfonyl chloride and the use of molecular fluorine in the last step to create the N−F bond.

Although the fluorination of various prochiral metal enolates proceeded in low to moderate enantioselectivities, these results demonstrated the possibility of reagent-controlled asymmetric fluorination by reaction with an electrophilic fluorine atom (Table 4).

Table 4. Enantioselective Fluorination of Carbonyl Compounds Using *N*-Fluorocamphorsultams 52 and 53



N−F reagent	conditions	product	yield, %	ee,[a] %
52	NaH, Et_2O, 0 °C to rt	**56**	63	70
53	KH, toluene/THF, 0 °C to rt	**56**	<5	<10
52	LiH, Et_2O, rt	**57**	31	<10
52	LDA, THF, −78 °C to rt	**58**	27	35
53	LDA, THF, −78 °C to rt	**58**	34	<10
52	LDA, THF, −78 °C to rt	**59**	<5	35

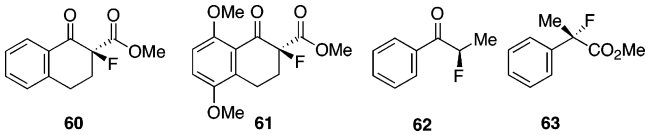
[a] The absolute stereochemistry was not determined.

Further studies on *N*-fluorocamphorsultams **52**, **54**, and **55** (Figure 4) were carried out by Davis and coworkers on tertiary enolates, affording quaternary α-fluoro carbonyl compounds in modest yields and enantiomeric excesses (Table 5). The secondary enolate of propiophenone gave racemic **62** due to facile base-catalyzed epimerization. Both enantiomers of reagent **54** were synthesized to give access to the two optically enriched enantiomers of the fluorinated products.[118,119]

To develop novel chiral electrophilic fluorinating agents, Takeuchi and co-workers exploited phenylglycine and α-phenethylamine as chiral starting materials, which were fluorinated with either perchloryl fluoride ($FClO_3$) or diluted F_2 to produce reagents **64**−**66** (Figure 5). Four model substrates were fluorinated via in situ generation of metal enolates; the best results did not exceed 54% ee for 26% yield (Table 6).[120]

Subsequently, Takeuchi's group embarked on the design of three new chiral N−F sulfonamides (**69**,[121] **70**,[122] and **71**;[123] Figure 6). These reagents were generally more efficient than the previous ones, albeit their direct comparison is difficult due to different reaction conditions. Nevertheless, reagent **69** led to

Table 5. Enantioselective Fluorination of Enolates with *N*-Fluorocamphorsultams 52, 54, and 55



N−F reagent	conditions	product	yield, %	ee, %
52	NaH, Et_2O, 0 °C to rt	**56**	63	70
54	NaH, Et_2O, −78 °C to rt	**56**	59	34
55	NaH, Et_2O, −78 °C	**56**	57	<5
52	NaH, Et_2O, 0 °C to rt	**59**	28	25
54	NaHMDS, −78 °C	**59**	53	76
55	NaHMDS, −78 °C to rt	**59**	61	<5
52	NaHMDS, THF, −78 °C to rt	**60**	8	14
54	KHMDS, THF, −78 °C	**60**	90	41
52	NaH, Et_2O, 0 °C to rt	**61**	28	25
54	NaH, Et_2O, 0 °C to rt	**61**	95	46
55	NaHMDS, −78 °C	**61**	83	14
54	NaHMDS, THF, −78 °C to rt	**62**	41	0
54	NaHMDS, THF, −78 °C	**63**	54	33

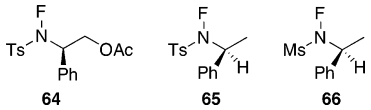
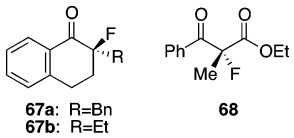


Figure 5. Chiral electrophilic fluorinating agents by Takeuchi and co-workers.

Table 6. Enantioselective Fluorination with Reagents 64−66



N−F reagent	conditions	product	yield, %	ee, %
66	NaH, 0 °C	**56**	6	30
64	KHMDS, −40 °C to 0 °C	**59**	8	8
65	KHMDS, −40 °C to 0 °C	**59**	46	46
66	LDA, −40 °C to rt	**59**	11	20
65	LDA, −40 °C to −20 °C	**67a**	26	54
65	NaH, 0 °C	**68**	21	18

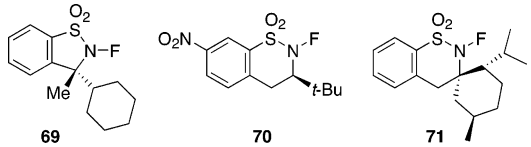


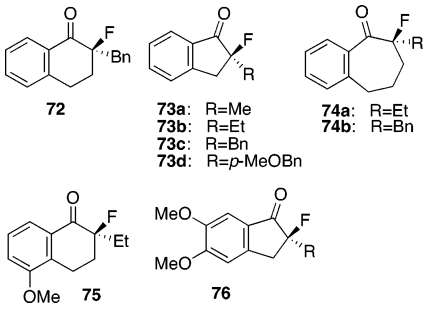
Figure 6. Chiral N−F sulfonamides by Takeuchi and coworkers.

2-fluoro-2-benzyl-1-tetralone (**67a**) in an excellent 88% ee and with 79% isolated yield.[121] Selected results with reagents **69**−**71** are summarized in Table 7.

A general feature of all the N−F fluorinating agents so far described is their arduous multistep synthesis, and the handling of molecular fluorine or perchloryl fluoride. In addition, these N−F reagents have drawbacks such as insufficient levels of enantioselectivity and limited scope for the substrates.

A major breakthrough in the field of enantioselective electrophilic fluorination was the introduction of a fundamentally new class of reagents derived from

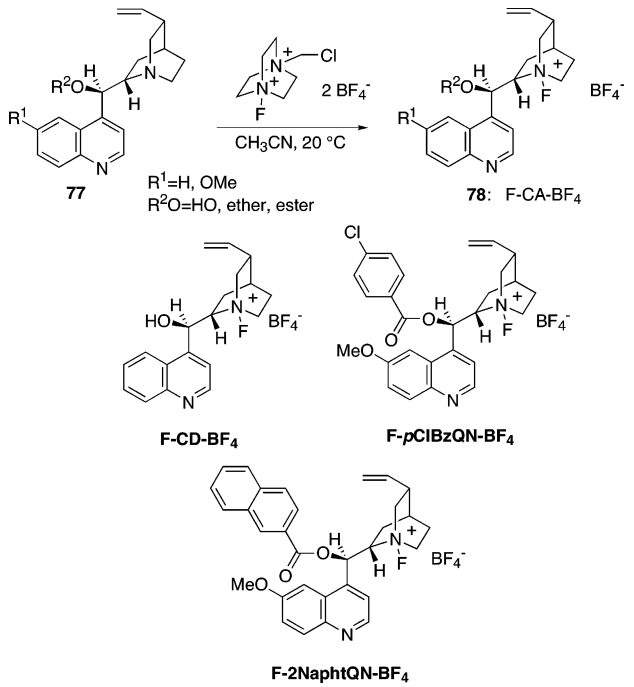
Table 7. Enantioselective Fluorination with Reagents 69−71



N−F reagent	conditions	product	yield, %	ee, %
69	LDA, THF, −50 °C	**59**	67	74
70	LiHMDS, THF, −50 °C	**60**	73	43
69	LDA, THF, −50 °C	**67a**	79	88
69	LDA, THF, −50 °C	**72**	70	72
69	LDA, THF, −50 °C	**73a**	54	54
69	LDA, THF, −50 °C	**73b**	73	20
71	LiHMDS, THF, −40 °C	**73c**	59	54
70	LiHMDS, THF, −50 °C	**73d**	70	69
69	LDA, THF, −50 °C	**74a**	48	43
69	LDA, THF, −50 °C	**74b**	39	18
70	LiHMDS, THF, −50 °C	**75**	59	60
70	LiHMDS, THF, −50 °C	**76**	56	60

naturally occurring cinchona alkaloids. Simultaneously and independently, we[124,125] and Shibata's group[126,127] reported a substantially similar approach to prepare *N*-fluoroammonium salts of cinchona alkaloids. A one-step transfer fluorination[128] on cinchona alkaloids (CAs) **77** with the aid of Selectfluor gave the fluorinating reagents (F-CA-BF_4) **78** (Scheme 18).

Scheme 18



In our case, these new reagents were synthesized, isolated as pure products, and applied in the enantioselective fluorination of enolates and silyl enol ethers of various ketones. We further demonstrated that the transfer fluorination on cinchona alkaloids with the aid of an achiral N−F fluorine-transfer reagent was also effective with NFSI, Accufluor (NFTh), and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate. Moreover, the stereoselectivities observed using the reagents prepared in that way were comparable to those observed using Selectfluor for the transfer fluorination.[129] For their part, Shibata and co-workers did not isolate the reagent, preferring the in situ generation from a combination of alkaloid and Selectfluor. We obtained the X-ray structure of one $[N-F]^+$ reagent (F-CD-BF_4, *N*-fluorocinchonidinium tetrafluoroborate), which allowed us to ascertain its structure.[130] Advantageously, cinchona alkaloids are readily available in diastereomeric forms [cinchonidine (CD)/cinchonine (CN) and quinidine (QD)/quinine (QN)], known to behave as pseudoenantiomers in asymmetric synthesis. We also designed this new class of reagents for their stronger fluorinating power (charged $[N-F]^+$ versus neutral N−F); thus, fluorination of enol derivatives such as silyl enol ethers can now be considered. Both our results and Shibata's data are brought together in Table 8. Our isolated pure $[N-F]^+$ reagents are presented using the general descriptor F-CA-BF_4, whereas CA/Selectfluor combinations are given for Shibata's reagents. In Figure 7 are depicted some of the cinchona alkaloid derivatives used by Shibata and co-workers. The fluorination of metal enolates was only tackled by us, whereas Shibata's group evaluated spontaneously enolizable β-keto esters and β-cyano esters as well as oxindoles. A tentative comparison of the two approaches is only possible for the fluorination of silyl enol ethers; however, a precise comparison of the results is difficult.

To date, attempts to render catalytic in cinchona alkaloid the electrophilic fluorination failed because the fluorination is faster than the transfluorination step, consequently leading to racemic fluorinated products.

We applied our successful enantioselective fluorination approach to the synthesis of α-fluoro-α-phenylglycine derivatives. A study of the relationship between structure and enantioselectivity led to a new range of $[N-F]^+$ reagents that displayed enantiomeric excesses as high as 94% in the synthesis of α-fluoro-*N*-phthaloylphenylglycinonitrile (**94b**) with *O*-(*p*-methoxybenzoyl)-*N*-fluoroquininium tetrafluoroborate (F-pMeOBzQN-BF_4) (Scheme 19).[131]

The significantly higher ee's observed for the nitrile derivative, compared to the ethyl ester, could be explained by the different natures of the corresponding metalated intermediates. Deprotonation of esters typically leads to a prochiral sp^2 enolate (eventually as a mixture of *Z* and *E* isomers), and the asymmetric step consists of a facial enantiodifferentiation. On the other hand, nitrile anions presumably exist as metalated ketenimines bearing an axial chirality, in which racemization occurs rapidly even at low temperature. In this case, enantioselective fluorination results in a kinetic dynamic resolution of the two enantiomers (Scheme 20). With continuing interest in the development of fluorinated bioactive compounds, we further investigated the asymmetric fluorination of dipeptides either by enantioselective fluorination with the

Table 8. Enantioselective Fluorination of Various Substrates by the Groups of Cahard and Shibata

Fluorination of metal enolates[124]

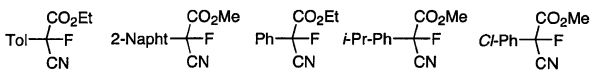
N-F reagent	conditions	product	yield, %	ee, %
F-CD-BF_4		**56**	98	40
F-CD-BF_4	NaH (2 equiv)	**59**	98	50
F-CD-BF_4	THF/CH_3CN	**67a**	96	42
F-*p*ClBzQN-BF_4	-40 °C to rt	**73a**	98	33
F-2NaphtQN-BF_4		**73c**	90	50

Fluorination of trimethylsilyl enol ethers[124,127]

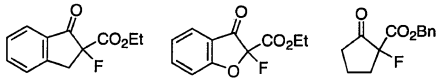
N-F reagent	conditions[a]	product	yield, %	ee, %
*p*ClBzDHQN / Selectfluor	A	**59**	94	40
F-CD-BF_4	B	**59**	93	61
*p*ClBzDHQN / Selectfluor	A	**67a**	95	71
F-*p*ClBzQN-BF_4	B	**67a**	67	66
*p*ClBzDHQN / Selectfluor	A	**67b**	71	67
*p*ClBzDHQN / Selectfluor	A	**73a**	93	53
F-*p*ClBzQN-BF_4	B	**73a**	90	64
*p*ClBzDHQN / Selectfluor	A	**73b**	100	73
F-*p*ClBzQN-BF_4	B	**73b**	97	82
*p*ClBzDHQN / Selectfluor	A	**73c**	86	91
F-2NaphtQN-BF_4	B	**73c**	98	84

[a] Conditions A : alkaloid (1.2 equiv)/Selectfluor, CH_3CN, MS 3Å, 1h, rt, then addition of the silyl enol ether at -20 °C, overnight.
Conditions B : -40 °C, CH_3CN, 20 h

Fluorination of β-ketoesters and β-cyanoesters[127]



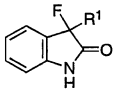
79 **80** **81** **82** **83**



84 **85** **86**

N-F reagent	conditions	product	yield, %	ee, %
DHQD / Selectfluor		**60**	79	59
AcDHQD / Selectfluor	alkaloid (2 equiv)	**79**	80	87
AcDHQD / Selectfluor	Selectfluor (1.5 equiv)	**80**	87	76
AcDHQD / Selectfluor	CH_3CN, MS 3Å, 1h, rt,	**81**	81	83
AcDHQD / Selectfluor	then addition of	**82**	82	87
AcDHQD / Selectfluor	the substrate	**83**	56	68
AcDHQD / Selectfluor	CH_2Cl_2, -80 °C, 2 h	**84**	89	78
AcDHQD / Selectfluor		**85**	92	80
DHQN / Selectfluor		**86**	55	43

Fluorination of oxindoles[127]



87: R^1=Bn
88: R^1=*p*-MeOBn
89: R^1=Me
90: R^1=Et
91: R^1=*i*-Pr
92: R^1=CO_2Et

N-F reagent	conditions	product	yield, %	ee, %
$(DHQ)_2AQN$ / Selectfluor	alkaloid (1.5 equiv)	**87**	100	78
$(DHQD)_2PYR$ / Selectfluor	Selectfluor (1.5 equiv)	**88**	79	82
$(DHQD)_2PYR$ / Selectfluor	CH_3CN, 1h, rt,	**89**	94	67
$(DHQD)_2PYR$ / Selectfluor	then addition of	**90**	79	76
$(DHQ)_2PHAL$ / Selectfluor	the substrate	**91**	12	40
$(DHQD)_2PYR$ / Selectfluor	0 °C, 1-2 days	**92**	93	37

aid of chiral [N−F]$^+$ reagents or by diastereoselective fluorination of enantiopure dipeptides.[132]

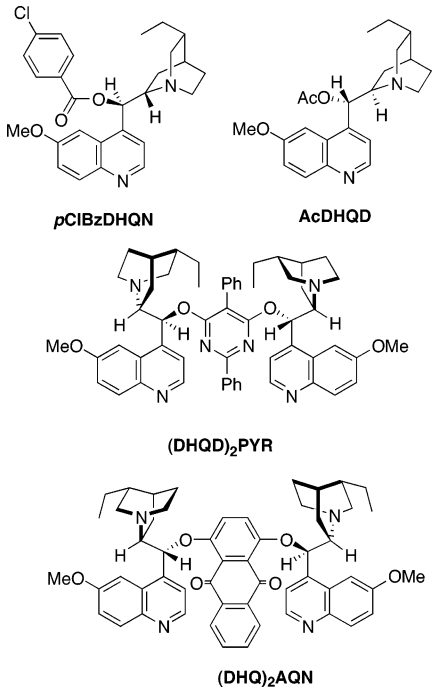
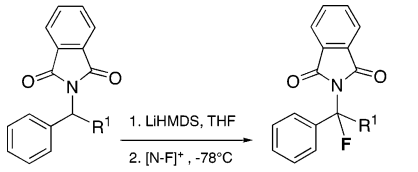


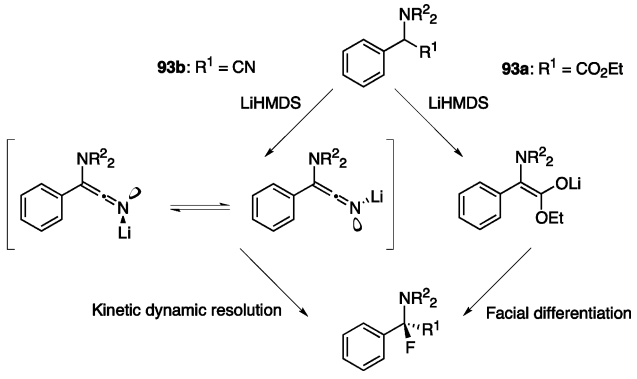
Figure 7. Some cinchona alkaloid derivatives used in combination with Selectfluor as described by Shibata's group.

Scheme 19



94a: R^1 = CO_2Et
79% yield, 76% ee (with F-*p*ClBzDHQN-BF_4)
94b: R^1 = CN
56% yield, 94% ee (with F-*p*MeOBzQN-BF_4)

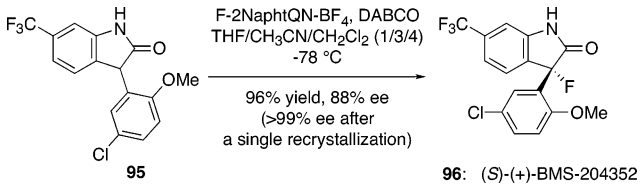
Scheme 20



One of the most remarkable demonstrations of the effectiveness of [N−F]$^+$ reagents came from our application to the enantioselective synthesis of BMS-204352 (MaxiPost, **96**), a potent opener of maxi-K channels, which is evaluated in a worldwide phase III clinical trial for treatment of acute ischemic stroke. Oxindole **95**, prepared in five steps from 3-trifluoromethylaniline, reacted with the *N*-fluoroammonium salt F-2NaphtQN-BF_4 in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) as base, producing the target product (*S*)-BMS-204352 in excel-

lent yield and high enantioselectivity, a single recrystallization allowing enantiomerically pure **96** to be obtained (Scheme 21).[133] Shibata's group also

Scheme 21

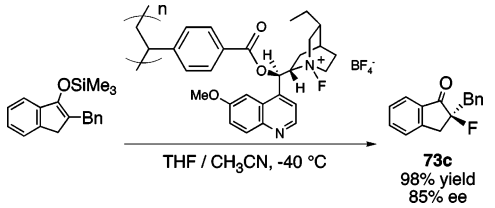


reported the synthesis of BMS-204352 in a slightly lower ee of 84% using the combination $(DHQ)_2AQN$/Selectfluor.[134]

Although the chiral $[N-F]^+$ reagents are efficient and of wide scope, some limitations remain, such as the poor choice of solvents (restricted to acetonitrile or acetone), the requirement for low temperature to reach high enantioselectivity, and the difficult recovery of the cinchona alkaloid. With the aim to circumvent these limitations, we have demonstrated that fluorination can be performed in ionic liquids (ILs), for instance, [hmim][PF_6] (1-butyl-3-methylimidazolium hexafluorophosphate), at 0 °C instead of acetonitrile at −40 °C, with comparable, indeed somewhat higher, enantioselectivities. In addition, ILs selectively dissolve cinchona alkaloids, in preference to diethyl ether, allowing IL and cinchona alkaloid recycling without significant alteration in the enantioselectivity.[135]

The development of recoverable and recyclable reagents supported on polymeric matrixes is a valuable approach. We prepared a collection of new polystyrene-bound cinchona alkaloids for the design of unprecedented enantioselective electrophilic fluorinating agents. For example, soluble polymeric cinchona alkaloids were easily synthesized by polymerization of the dihydro cinchona alkaloid O_9-(4-vinylbenzoate) in the presence of a catalytic amount of AIBN in refluxing dry benzene. Compared to nonsupported $[N-F]^+$ reagents, the polystyrene-bound *N*-fluoroammonium salts of cinchona alkaloids showed comparable efficiency and ready purification of the fluorinated reaction products (Scheme 22).

Scheme 22

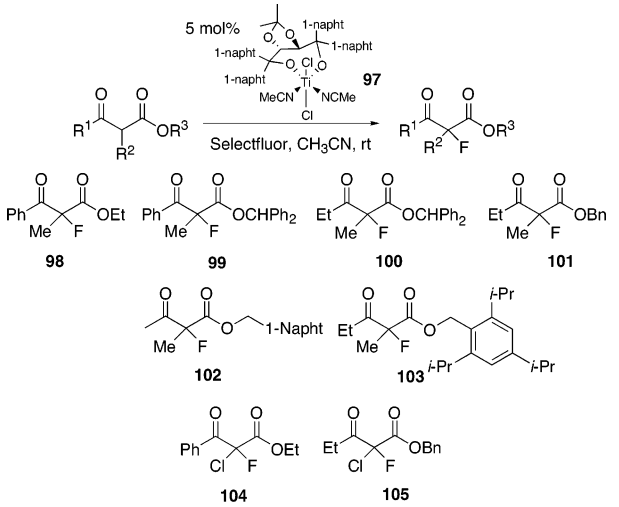


Poly[O_9-(4-vinylbenzoate)-DHQN] was recycled three times without loss of stereochemical performance.[136]

2.1.2.2. Transition-Metal Catalysts. This section is concerned with the synthesis of α-fluoro-β-keto esters by catalytic enantioselective electrophilic fluorination, nicely illustrating the fourth generation of asymmetric synthesis. However, this approach is, so far, strictly limited to the fluorination of β-keto esters for the ease of enolate formation.

Simultaneously with the work on cinchona alkaloid *N*-fluoroammonium salts, the first transition-metal-catalyzed fluorination has been achieved by Togni and co-workers. In this reaction, it was anticipated that catalytic transition-metal complexes would accelerate enolization of β-keto esters. The fluorination of various acyclic β-keto esters, with Selectfluor in the presence of 5 mol % of [$TiCl_2$((*R*,*R*)-TADDOLato)] catalyst **97**, was reported to give high yields (≥80%), and up to 90% ee (Table 9).[137,138] In this approach,

Table 9. Enantioselective Fluorination Catalyzed by TADDOL−Titanium Complexes



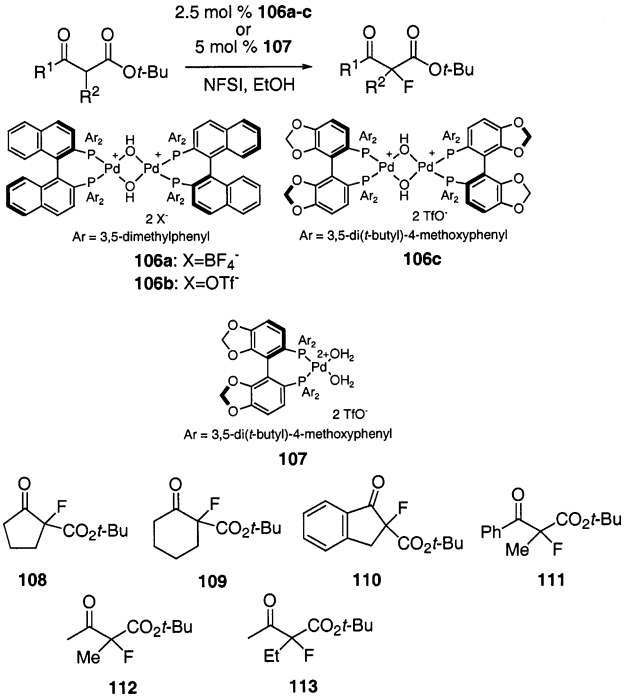
product	yield, %	ee, %	product	yield, %	ee, %
98	≥80	62	**102**	≥80	68
99	≥80	82	**103**	89	90
100	≥80	81	**104**	53	33
101	82	71	**105**	57	60

computational and experimental studies strongly supported a single-electron-transfer (SET) mechanism as a pathway for the fluorination.[139] Interestingly, compounds **104** and **105** were synthesized in a one-pot enantioselective heterodihalogenation of the β-keto esters with *N*-chlorosuccinimide and Selectfluor by sequential addition.[140]

Following Togni's pioneering work, Sodeoka and coworkers reported an efficient enantioselective fluorination of various β-keto esters using chiral BINAP−palladium complexes.[141] The fluorination was carried out with NFSI in ethanol in the presence of 2.5 mol % catalyst **106a,c** or **107**, leading to excellent enantiomeric excesses up to 94% (Table 10). The reaction is not sensitive to water, can be run on a 1 g scale, and proceeds via a palladium enolate complex as already mentioned for the titanium−TADDOL catalyst. Furthermore, the palladium complexes were immobilized in ionic liquids, and their application to catalytic enantioselective fluorination was demonstrated. Efficiently, catalyst **106b** was reused 10 times with a level of enantioselectivity comparable to those obtained in the usual organic solvents.[142]

Inspired by these results, we evaluated nitrogen-containing ligands, which are complementary to the oxygen- and phosphorus-containing ligands investigated, respectively, by Togni and Sodeoka. We re-

Table 10. Enantioselective Fluorination Catalyzed by BINAP−Palladium Complexes



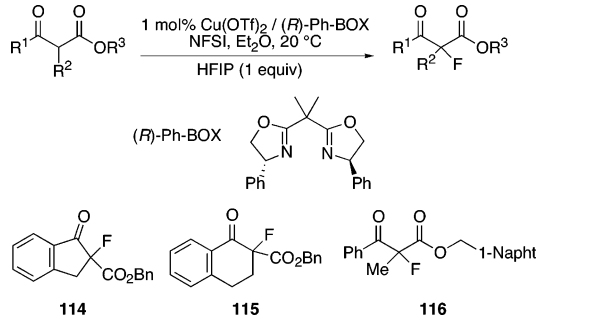
catalyst	temp, °C	time, h	product	yield, %	ee, %
107[a]	0	72	**108**	89	90
106c	20	18	**108**	90	92
106a	−10	20	**109**	91	94
106b	−20	36	**110**	85	83
106a	20	40	**111**	92	91
106c	20	72	**112**	49	91
106b	20	42	**113**	88	87

[a] THF was used as the solvent.

cently reported a new efficient catalytic enantioselective electrophilic fluorination of both cyclic and acyclic β-keto esters by means of chiral bis(oxazoline)−copper complexes. As low as 1 mol % bis(oxazoline)−copper triflate catalyzed the fluorination with NFSI. Selectfluor and *N*-fluoropyridinium triflate produced ee's ca. 10% lower than that of NFSI. In addition, the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), as an additive, allowed 10−15% enantiomeric excess to be gained in all the reactions (Table 11).[143] Other combinations of chiral ligand (sparteine, cinchona alkaloids, PyBOX, Trost's ligand, BINOL) and metal (Zn, Mg, Al, Sc, La) as well as various N−F reagents were screened, leading to enantioenriched α-fluoro-β-keto esters in high yields and moderate enantioselectivities (up to 67% ee).[144]

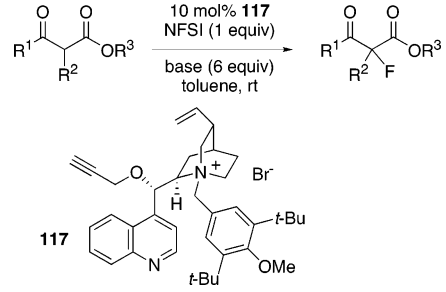
2.1.2.3. Phase-Transfer Catalysis. The first example of catalytic enantioselective electrophilic fluorination under phase-transfer conditions with the aid of quaternary ammonium salts derived from cinchona alkaloids was reported by Kim and Park.[145] This organocatalytic approach is limited, here again, to the fluorination of β-keto esters. Treatment of β-keto esters with NFSI in the presence of 10 mol % chiral phase-transfer catalyst and 6 equiv of base afforded the α-fluoro-β-keto esters in excellent yields and moderate enantioselectivities (Table 12). It is claimed in this paper that the reactions were completed

Table 11. Enantioselective Fluorination Catalyzed by BOX−Copper Complexes



product	time, h	yield, %	ee, %
99	48	72	52
108	0.5	96	85
109	3	92	63
111	96	56	43
114	0.5	94	35
115	0.5	92	38
116	2	88	40

Table 12. Catalytic Enantioselective Fluorination by Phase-Transfer Catalysis



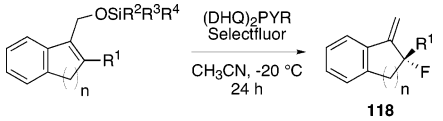
R^1	R^2	R^3	base	yield, %	ee, %
indanone		Me	K_2CO_3	92	69
indanone		Et	Cs_2CO_3	91	63
tetralone		Me	Cs_2CO_3	88	48
tetralone		Et	CsOH	78	52
Ph	Me	Et	NaH	89	40[a]

[a] *O*-(9)-allylcinchonium bromide was used instead of the *O*-(9)-propargyl catalyst **117**.

within 10 min; however, the trick behind this success is the preformation of the enolate for up to 10 h prior to the slow addition of NFSI. Among the various cinchoninium salts evaluated, **117** provided the highest enantioselectivity; surprisingly, diastereomeric cinchonidine as well as quinine and quinidine were not discussed.

2.1.2.4. Fluorodesilylation. α-Fluorocarbonyl compounds are the targets of most of the above-mentioned studies. Interestingly, Gouverneur and coworkers developed a regio- and enantioselective synthesis of allylic fluorides **118** by electrophilic fluorodesilylation of allylsilanes.[146] The in situ generation of the fluorinated cinchona alkaloids was preferred in this reaction, leading to allylic fluorides with excellent enantioselectivity of 96% and high conversion (Scheme 23). The best alkaloid for this transformation was $(DHQ)_2PYR$, leading to high ee values. Additionally, the steric bulk of the silyl group

Scheme 23. Enantioselective Fluorodesilylation of Allylsilanes



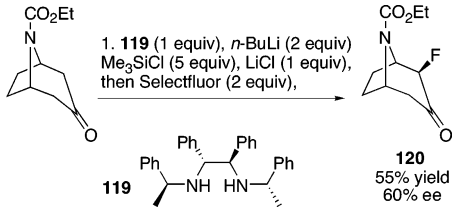
118

n	R^1	R^2	R^3	R^4	ee, %
1	Bn	Me	Me	Me	96
1	H	Ph	Ph	Ph	87
1	H	Me	Me	Ph	73
2	Bn	Me	Me	Me	83
2	Me	Me	Me	Me	45
2	Me	Me	Me	Me	22

was important with regard to enantioselectivity, with the triphenylsilyl group being responsible for higher enantioselectivities.

2.1.2.5. Chiral Bases. Armstrong and co-workers realized a chiral lithium amide base desymmetrization via in situ generation of an intermediate silyl enol ether, which was fluorinated with Selectfluor to afford the enantiomerically enriched chiral α-fluoro-*N*-carbethoxytropinone (**120**) in 55% yield and 60% ee (Scheme 24).[75]

Scheme 24



119

120
55% yield
60% ee

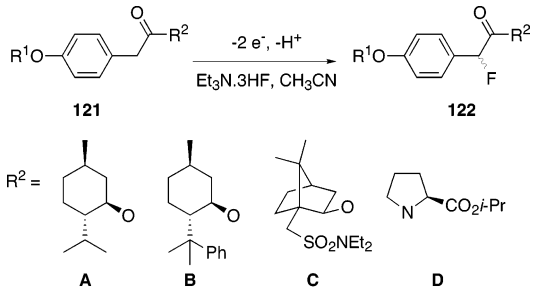
2.2. Nucleophilic Fluorination Reactions

2.2.1. Asymmetric Anodic Fluorination

Asymmetric anodic fluorination was generally very difficult due to the small size of the fluoride ion and the use of polar solvents for electric conductivity. Nevertheless, some studies have been reported. For instance, Laurent and co-workers observed a diastereoselective fluorination at the benzylic position of **121** by oxidation at a platinum anode in $Et_3N{\cdot}3HF/CH_3CN$; moderate diastereomeric excesses in the range 10−60% were recorded (Scheme 25).[147] The best results were obtained with the 8-phenylmenthyl chiral auxiliary.

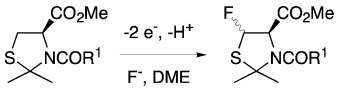
Following this pioneering work, Fuchigami's group embarked on several studies on diastereoselective anodic fluorination. They obtained much lower de's (≤20%) in the anodic fluorination of α-phenylthioacetates having chiral auxiliaries similar to those explored by Laurent.[148] Next, *N*-protected thiazolidines **123** derived from L-cysteine were electrofluorinated in $Et_3N{\cdot}4HF$/DME with moderate yield and high diastereoselectivity favored by the steric hindrance of the *N*-substituent. The reaction was assumed to proceed in a Pummerer-type reaction mechanism (Table 13).[149] Electrofluorination on a platinum anode of 1,3-oxazolidines **125** derived from L-serine and L-threonine gave the α-fluorinated products in moderate yields with observed diastereoselectivity only for the L-threonine derivative.[150] Under similar conditions, a single diastereomer was obtained in the fluorination of chiral 1,3-oxathiolan-5-ones **127** derived from camphorsulfonamides and thioglycol acid.[151] Sulfide **129**, having a dioxolane moiety, was fluorinated via a Pummerer mechanism with good diastereoselectivity (up to 80% de).[152] Other diol protections and various *para*-substituted phenyls were investigated by electrofluorination; however,

Scheme 25



R^1	R^2	yield, %	de, %
Me	A	74	20
i-Pr	A	50	20
Me	B	65	60
Me	C	37	54
Me	D	61	10

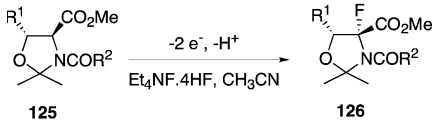
Table 13. Fuchigami's Diastereoselective Anodic Fluorinations



123 124

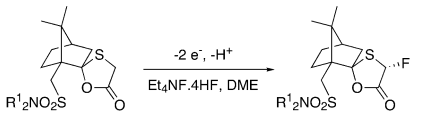
F^- electrolyte	R^1	charge	yield, %	de, %
$Et_3N.4HF$	Ph	5.0 F/mol	50	94
$Et_4N.5HF$	Ph	5.0 F/mol	53[a]	99
$Et_3N.4HF$	Me	5.5 F/mol	53	80
$Et_3N.4HF$	H	5.5 F/mol	40	59
$Et_3N.4HF$	Tol	5.0 F/mol	60	95

[a] Conversion determined by ^{19}F NMR



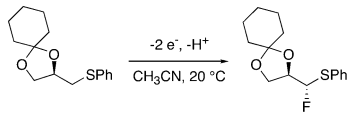
125 126

R^1	R^2	yield, %	de, %
H	Ph	56	0
Me	Ph	73	81



127

128: R^1 = *i*-Pr, 88% yield
R^1 = Me, 76% yield



129

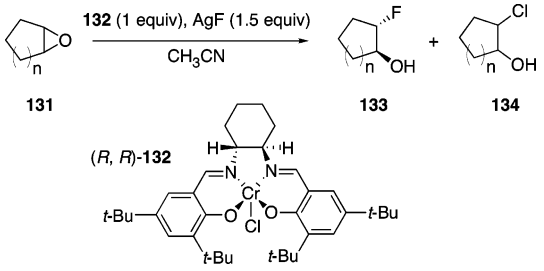
130
40% yield
80% de

lower diastereoselectivities were obtained.[152] In some of the studies, Fuchigami attempted the chemical fluorination using electrophilic N−F reagents, but the method failed to produce the fluorinated compounds, thus showing the advantage of anodic fluorination.

2.2.2. Enantioselective Nucleophilic Fluorination

The first and only example of enantioselective nucleophilic fluorination, described by Haufe and coworkers, concerned the ring-opening of *meso*-epoxides **131** with hydrofluorinating reagents mediated by Jacobsen's (Salen)chromium chloride complex **132**.[153] Ring-opening reaction of racemic terminal epoxides, such as styrene oxide, almost exclusively lead to the fluorine in the primary position; therefore, the fluorine atom was not introduced on a stereogenic center. Initial attempts of ring-opening of *meso*-epoxides with 5−10 mol % $Eu(hfc)_3$ or zinc tartrate led to poor enantioselectivity (4−10% ee). Higher enantiodifferentiation was observed with the aid of a stoichiometric amount of Jacobsen's catalyst, whereas the enantiomeric excess dropped dramatically with a catalytic amount of the chiral Lewis acid. In addition, chlorohydrin **134** was formed as a side product in nonnegligible amounts. Various fluorinating agents were tested [$Et_3N{\cdot}3HF$, KHF_2 (+18-crown-6), $Bu_4N^+H_2F_3^-$, AgF]; better results were obtained with 1.5 equiv of silver fluoride in CH_3CN (Table 14).[154,155]

Table 14. Nucleophilic Enantioselective Ring-Opening of *meso*-Epoxides

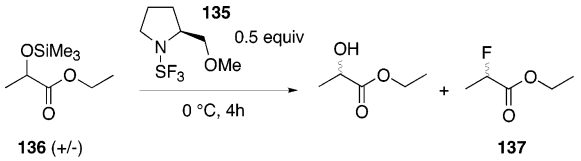


n	temp, °C	time, h	yield,[a] %	ee, %
1	50	72	80	62
2	50	50	90	72
3[b]	60	20	82	65
4	70	190	0	

[a] Calculated on the basis of consumed epoxide. [b] A 50 mol % concentration of **132** was used.

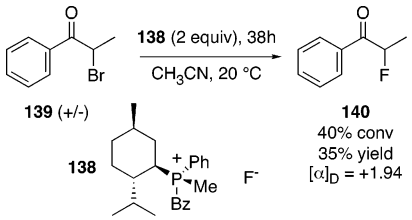
Although kinetic resolutions are not asymmetric syntheses in the strict sense, we think it is of interest to mention two examples of kinetic resolution by fluorodehydroxylation and fluorodebromination. The first case was reported in 1989 by Sampson and Hann, who have synthesized the first chiral aminofluorosulfurane **135** as a chiral analogue of DAST (diethylaminosulfur trifluoride) to conduct an enantioselective fluorodehydroxylation (Scheme 26).[156] The kinetic resolution of 2-trimethylsilyloxypropionic acid ethyl ester (**136**) resulted in a poor enantiomeric excess of 16% for the 2-fluoropropionic acid ethyl ester (**137**).

Scheme 26



Beaumont and co-workers reported the second example in 2001. Chiral phosphonium salt **138**, prepared from (−)-menthyl chloride, was used in the asymmetric nucleophilic fluorination of 2-bromopropiophenone (**139**) to give enantiomerically enriched 2-fluoropropiophenone (**140**) in 35% yield; unfortunately, the enantiomeric excess was not provided (Scheme 27).[157]

Scheme 27



3. Asymmetric Trifluoromethylation Reactions

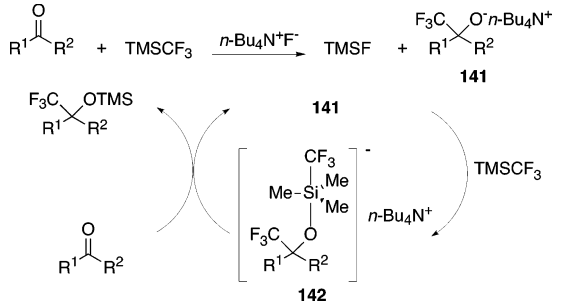
Among fluoroorganic compounds, trifluoromethyl-substituted molecules have gained growing interest during the past decade.[20,158] The introduction of a trifluoromethyl group with strong electron-withdrawing ability can lead to significant changes in the physical, chemical, and biological properties of the molecules. As a consequence, the development of asymmetric approaches for the direct introduction of a trifluoromethyl group is an important synthetic challenge. Methods for the incorporation of the trifluoromethyl group into organic molecules may be considered as nucleophilic, electrophilic, or free radical processes. Nucleophilic trifluoromethylation is now tamed thanks to the extensive use of Ruppert's compound $(TMS)CF_3$ (TMS = Me_3Si),[159−161] while electrophilic trifluoromethylation has been developed relatively slowly.[162]

3.1. Nucleophilic Trifluoromethylation Reactions

Since the initial report in 1989 by Prakash and coworkers on the trifluoromethylating properties of $(TMS)CF_3$, the utilization of this compound as a nucleophilic trifluoromethylating agent has rapidly become the method of choice.[160,163−165] Indeed, $(TMS)CF_3$ was used as a precursor to the trifluoromethide anion, which was liberated by activation with a fluoride source (nucleophilic initiator). Most commonly, tetraalkylammonium fluorides are used as initiators. For example, upon addition of a catalytic amount of TBAF to the reaction mixture of a carbonyl compound and $(TMS)CF_3$ in a suitable solvent, the process commences with the initial formation of Me_3SiF and alkoxide adduct **141**, stabilized by the tetrabutylammonium cation. The reaction between $(TMS)CF_3$ and **141** leads to the formation of the pentavalent complex **142**[166,167] followed by the transfer of the trifluoromethyl group to the electrophilic

carbon of the carbonyl function until all of the starting material has reacted (Scheme 28). Other

Scheme 28

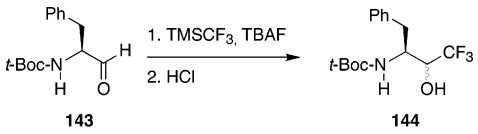


nucleophilic initiators such as alcoholates, amines, phosphines, and even derivatives of arsenic and antimony are also suitable for this purpose. This method has proven to be successful for asymmetric addition to a large number of electrophiles.

3.1.1. Diastereoselective Trifluoromethylation

3.1.1.1. Trifluoromethylation of Amino Acid Derivatives. (TMS)CF_3 was employed to prepare trifluoromethylated amino alcohols from the corresponding protected amino acid derivatives such as *t*-Boc-L-phenylalanal (**143**) (Scheme 29). The reaction

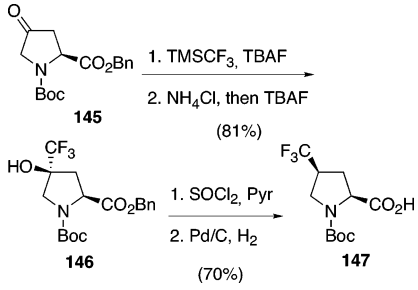
Scheme 29



of (TMS)CF_3 with **143** in the presence of a catalytic amount of TBAF afforded the trifluoromethylated amino alcohol **144** as a mixture of (*S*,*S*) and (*S*,*R*) diastereomers (ratio not provided). Appropriate deprotection gave good yields of amino alcohol, which was used to prepare trifluoromethyl-substituted tripeptides as potential inhibitors of human leukocyte elastase.[168]

Recently, Qing and co-workers described an efficient approach for the synthesis of *N*-Boc-*cis*-4-trifluoromethyl-L-proline (**147**) (Scheme 30).[169] The

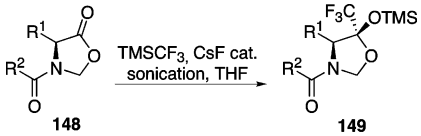
Scheme 30



reaction of *N*-Boc-4-oxo-L-proline **145** with (TMS)CF_3 in the presence of a catalytic amount of TBAF gave the adduct **146** with the CF_3 group *trans* to the ester group. **146** was further dehydrated, hydrogenated, and debenzylated to yield diastereomerically pure **147**. This group also reported trifluoromethylation of Garner's aldehyde with (TMS)CF_3; unfortunately, the diastereoselectivity was not provided.[170]

Ruppert's compound was reacted with a variety of amino acid derived *N*-substituted oxazolidin-5-ones **148** to produce compounds **149** in excellent yields. Replacement of TBAF by CsF and sonication resulted in substantially improved yields. Although the chirality was lost in the end, the trifluoromethylation step was highly diastereoselective since products were obtained as single diastereomers (Scheme 31).[171−173]

Scheme 31

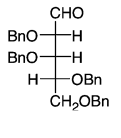
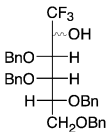
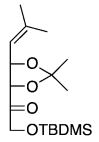
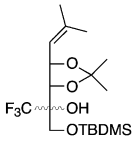
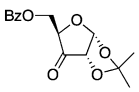
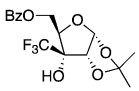
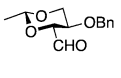
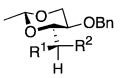
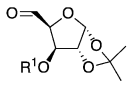
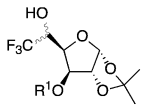
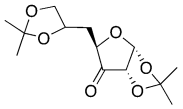
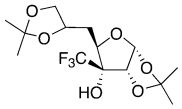
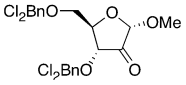
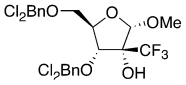
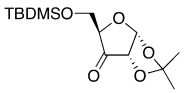
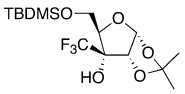
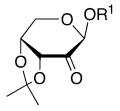
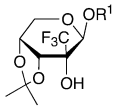


R^1	R^2	yield, %
Bn	BnO	95
Me	BnO	69
$MeO_2C(CH_2)_2$	BnO	73
Bn	*t*-BuO	98
Me	*t*-BuO	85
i-Pr	*t*-BuO	84
i-Bu	*t*-BuO	95
$BnSCH_2$	*t*-BuO	77

3.1.1.2. Trifluoromethylation of Carbohydrate and Inositol Derivatives. Introduction of the hydrophobic trifluoromethylated moiety in place of the methyl group of carbohydrates is suggested to play an important role in molecular recognition.[174] Furthermore, the inductive effect of the trifluoromethyl group decreases the rate of hydrolysis, thus leading to more stable carbohydrates with increased lifetime that are regarded as useful tools for in vivo ^{19}F NMR spectroscopy and for biomedical purposes.[175,176] In particular, the construction of 2-*C*-trifluoromethyl carbohydrates is expected to inhibit the development of a positive charge at the anomeric center, as in the case of 2-*C*-fluoro derivatives.[177,178] The trifluoromethyl group can also modify the cyclization equilibrium between pyranose and furanose. Synthetic methods for preparing carbohydrates bearing a *C*-branched fluoroalkyl substituent have been recently reviewed.[179]

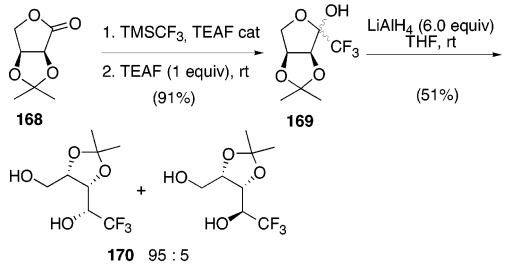
Toyokuni and co-workers have developed trifluoromethylation of an acyclic derivative of D-lyxose (**150**) with (TMS)CF_3 and a catalytic amount of TBAF to give trifluoromethyl adduct **151** in 79% yield, but without stereoselectivity (entry 1, Table 15).[174] Kozak and Johnson reported that ribulose derivative **152** reacted with (TMS)CF_3 in the presence of TBAF to give trifluoromethylated alcohol analogue **153** in 69% yield as a mixture of D-*ribo* and L-*lyxo* epimers in a 4/1 ratio (entry 2, Table 15).[180] They also realized the synthesis of 3′-*C*-trifluoromethyl ribonucleosides, which involved a diastereoselective addition of (TMS)CF_3 to 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose (**154**). The reaction is catalytic in fluoride, but 1.5 equiv of TBAF was used also to cleave the TMS-protected alcohol (entry 3, Table 15).[181]

Table 15. Trifluoromethylation of Carbohydrate Derivatives

entry	carbohydrate	product	yield, %	dr	ref.
1	 **150**	 **151**	79	50/50	174
2	 **152**	 **153**	69	D-ribo/L-lyxo 80/20	180
3	 **154**	 **155**	70	100	181
4	 **156**	 **157a**: R^1=CF_3, R^2=OH **157b**: R^1=OH, R^2=CF_3	71	**157a/157b** 60/40	182
5	 **158a**: R^1=Bn **158b**: R^1=Allyl	 **159a,b**	95 98	L-ido/D-gluco 80/20 (**159a**) 88/12 (**159b**)	183
6	 **160**	 **161**	88	100	183
7	 **162**	 **163**	45	100	184
8	 **164**	 **165**	88	100	185
9	 **166a**: R^1=Me **166b**: R^1=Bn	 **167a,b**	64 65	100 (**167a**) 100 (**167b**)	186

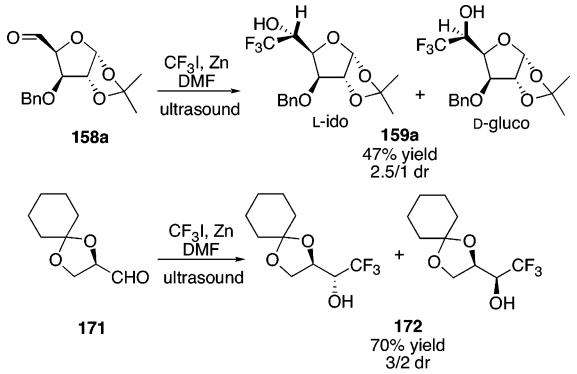
Trifluoromethylation of the cyclic D-erythrose derivative **156** was described by Anker and co-workers in the aim to circumvent the previously encountered stereoselectivity problems in the trifluoromethylation of noncyclized carbohydrate. However, the stereoselectivity was poor despite the more strained cyclic structure (entry 4, Table 15).[182] Because of the low diastereoselectivity, the addition of the CF_3 group was realized on lactone **168**, which provided hemiketal **169** as an equilibrium mixture of α- and β-isomers.[187] It is worth noting that subsequent reduction showed different selectivity depending on the reducing agent, and tuning of the conditions allowed the preparation of CF_3-substituted diol **170** in high stereoselectivity (Scheme 32).[188]

Scheme 32



Pentodialdose derivatives **158a,b** were trifluoromethylated with $(TMS)CF_3$ in the presence of a catalytic amount of $[Ph_3SnF_2]^-n$-Bu_4N^+ to give quantitatively the corresponding products **159a,b** as mixtures of L-*ido* and D-*gluco* epimers with good stereoselectivity, whereas a similar reaction on 3-oxoglucose **160** gave the d-*allo* adduct **161** with complete stereoselectivity (entries 5 and 6, Table 15).[183] Trifluoromethylation of chiral aldehyde **158a** was also carried out by slow addition of trifluoromethyl iodide to a mixture of zinc and aldehyde in DMF under ultrasonication, allowing a comparison with the $(TMS)CF_3$ reaction. The trifluoromethyl iodide procedure afforded **159a**, in a moderate 47% yield with a lower ratio of L-*ido* to D-*gluco* epimers of 2.5/1, clearly demonstrating the superiority of $(TMS)CF_3$ in this reaction (Scheme 33).[189] Under identical

Scheme 33



conditions, trifluoromethylation of D-glyceraldehyde derivative **171** also gave a mixture of diastereomers **172** (Scheme 33).[189]

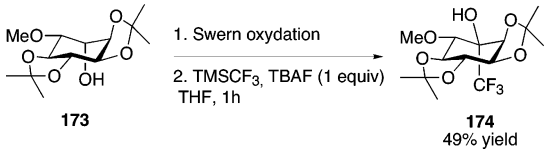
Schmit employed ketone **162** as the starting material for the synthesis of the 2′-trifluoromethylcarbinol **163** (entry 7, Table 15).[184] The reaction afforded a single stereomer resulting from the attack of the CF_3 group of $(TMS)CF_3$ by the β-face of the sugar ring. Further treatment including radical deoxygenation with tributyltin hydride and coupling with bis(silylated) thymine furnished the corresponding β-nucleoside.

Portella and co-workers disclosed an interesting sequence of nucleophilic trifluoromethylation with

(TMS)CF_3 followed by radical deoxygenation to obtain 3-deoxy-3-*C*-trifluoromethyl-D-ribose derivatives. Reaction of the silyl ether **164** with (TMS)CF_3 under catalytic fluoride activation led to the single 3-*C*-trifluoromethyl-D-ribose derivative **165** (entry 8, Table 15).[185] Burger and co-workers reported the synthesis of 2-*C*-trifluoromethyl-D- and -L-ribose via trifluoromethylation of pentopyranosid-2-uloses **166** with Ruppert's compound; only one diastereomer of **167** was formed by preferential attack of the trifluoromethyl anion from the *si* face of the carbonyl group (entry 9, Table 15).[186]

Fluorinated inositols have demonstrated excellent biological activities and enzymatic inhibitory effects.[190,191] Starting from L-quebrachitol diacetonide (**173**), Kozikowski and co-workers prepared 3-*C*-trifluoromethyl-*myo*-inositol derivative **174** by a Swern oxidation followed by trifluoromethylation of the unstable ketone with the aid of Ruppert's compound (Scheme 34). A single configuration was assigned at C-3 due to complete α-face selectivity.[192]

Scheme 34



3.1.1.3. Trifluoromethylation of Steroidal Derivatives. Asymmetric introduction of a trifluoromethyl group into a strategic position of the steroidal skeleton is expected to influence the biological activity. Olah and Prakash demonstrated that (TMS)CF_3 activated by a catalytic amount of TBAF allowed conversion of the ketonic function of steroids into the corresponding trifluoromethylcarbinols as single stereomers (**175** and **176**; Figure 8).[164] Wang and co-

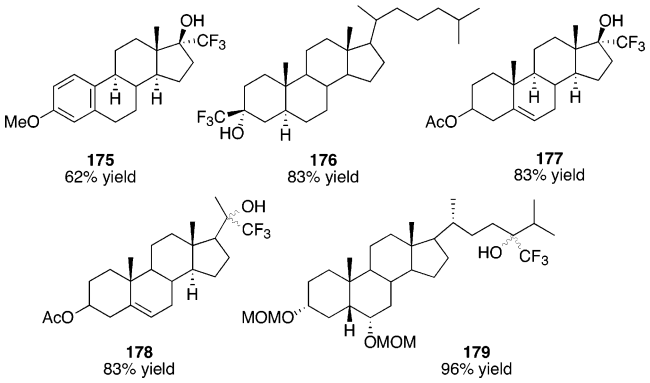
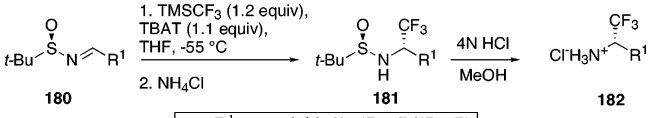


Figure 8. Trifluoromethylated steroidal derivatives.

workers developed a similar procedure for the preparation of trifluoromethylated silyl ethers from ketones in which tetramethylammonium fluoride (TMAF) having a small ammonium cation was found to be superior to TBAF in promoting the CF_3 group transfer, particularly for hindered ketones. The *O*-silylated products were readily converted into trifluoromethylated carbinols by means of 40% aqueous HF (**177**−**179**; Figure 8).[193]

3.1.1.4. Trifluoromethylation of Sulfinimines and Azirines. Trifluoromethylated chiral amines are important fluorinated building blocks for pharmaceutical research and asymmetric synthesis. Direct asymmetric synthesis of trifluoromethylated amines was recently achieved by Prakash and co-workers.[194] The reactivity and stereoselectivity of the reaction are dependent on the fluoride source. Chiral sulfinimines **180** reacted with (TMS)CF_3 in the presence of DeShong's tetrabutylammonium difluorotriphenylsilicate (TBAT)[195] in THF to give the trifluoromethylated products **181** with high diastereoselectivities and yields, which can be hydrolyzed to the chiral amine salts **182** (Scheme 35).

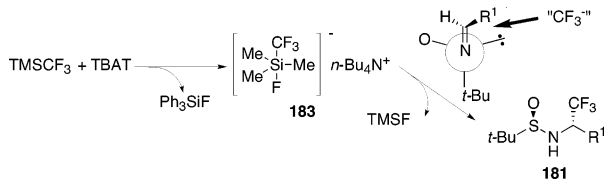
Scheme 35



R^1	yield, %	(*Rs*, *S*)/(*Rs*, *R*)
p-ClC_6H_4	95	>99/1
p-BrC_6H_4	90	>99/1
p-$CF_3C_6H_4$	84	95/5
2-pyridyl	95	99/1
3-pyridyl	92	99/1
2-furyl	85	97/3
Ph	80	97/3
2-naphthyl	83	96/4
9-anthryl	90	99/1
cyclohexyl	88	99/1
t-Bu	75	99/1
$PhCH_2CH_2$	84	90/10

In marked contrast, a stoichiometric amount of CsF provided the trifluoromethylated sulfinamides **181** only in 50−65% yields with moderate diastereoselectivity (50−80% de). The authors described a mechanistic rationale to account for this high stereoselectivity (Scheme 36). In the presence of a stoichiometric

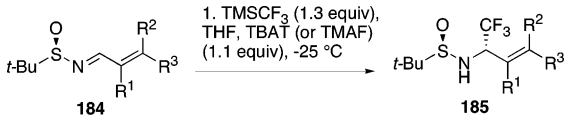
Scheme 36



amount of fluoride source, the pentavalent intermediate **183** preferably adds to the imines from the less hindered *re* face to give the selective Cram products **181**.

The same group has also developed the asymmetric synthesis of trifluoromethylated allylic amines **185** using α,β-unsaturated *N*-2-methyl-2-propanesulfinimines **184** and (TMS)CF_3 (Scheme 37).[196] Nucleophilic addition reactions depended not only on the electrophilicity of the substrates but also on the steric volume of the nucleophiles. Due to the steric congestion, long allyl chain substitutions at the α-position of the substrates gave lower yields of adducts; however, complete diastereoselectivity was observed. On the other hand, reducing the steric volume of the effective nucleophile increased the yields of the

Scheme 37



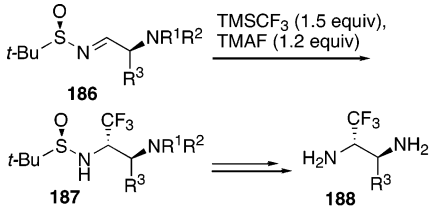
R^1	R^2	R^3	yield, %	(*R*s, *S*)/(*R*s, *R*)
H	H	Ph	55	90/10
Me	H	Ph	73	>99/1
H	H	Furyl	76	92/8
Me	H	Furyl	50	98/2
H	Ph	Ph	62	>99/1
n-C_5H_{11}	Ph	H	25	>99/1
n-C_5H_{11}	Ph	H	82	90/10[a]
n-C_6H_{13}	Ph	H	20	>99/1
n-C_6H_{13}	Ph	H	75	92/8[a]
Ph	Ph	H	62	93/7[a]

[a] TMAF was used as the fluoride source.

products. Indeed, when TMAF was used as a fluoride source, the sterically bulky sulfinimines gave the corresponding adducts in good yields.

Somewhat later, Prakash and co-workers showed that the trifluoromethylated vicinal ethylenediamines **188** can be obtained in high yields and stereoselectivities by treatment of α-amino *N*-2-methyl-2-propanesulfinimines **186** with (TMS)CF_3 (Scheme 38).[197]

Scheme 38

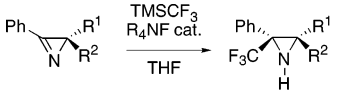


R^1	R^2	R^3	yield, %	dr
Bn	Bn	Me	86	>99/1
Bn	Bn	*n*-C_3H_7	85	>99/1
Bn	Bn	Bn	81	>99/1
Bn	Bn	*i*-Pr	66	>99/1
Bn	Bn	*i*-Pr	71	>99/1
Bn	-C_3H_6-		>99/1	79

By using TMAF as the fluoride source, sulfinimines **186** derived from the L-amino aldehydes were trifluoromethylated to give the vicinal ethylenediamine adducts **187** in good to high yields with excellent diastereoselectivities. However, the imine derived from the D-amino aldehydes gave the corresponding adduct in an 80/20 diastereomeric ratio in 60% yield for the major diastereomer ($R^1 \simeq R^2 \simeq R^3 \simeq$ Bn). These observations suggested that both the chiral centers present in the molecule direct the incoming nucleophile to the *re* face of the imines.

The addition of (TMS)CF_3 was studied on the carbon nitrogen double bond of azirines **189** to obtain exclusively the (*E*)-aziridines **190** in satisfactory yields.[198] The high strain release upon addition of CF_3 to the azirine with concomitant formation of the relatively weak silicon nitrogen bond renders this reaction catalytic in fluoride source (Scheme 39).

Scheme 39

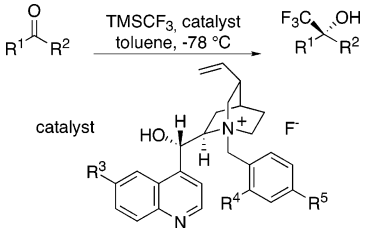


R^1	R^2	R_4NF	yield, %
Me	H	Et_4NF	51
Ph	H	Et_4NF	86
CO_2Me	H	Bu_4NF	67

3.1.2. Enantioselective Trifluoromethylation

The importance of enantiopure trifluoromethylated compounds in medicinal chemistry, agrochemistry, electronics, and optics (liquid crystals) has been well recognized.[20,23,199] Several reports deal with attempts of enantioselective trifluoromethylation of aldehydes and ketones with (TMS)CF_3. According to the mechanism of the trifluoromethylation by (TMS)CF_3 mediated by a tetraalkylammonium fluoride, the ammonium cation is closely associated with the alkoxy adduct during the reaction. It is therefore reasonable to expect that the process could show enantioselectivity if a chiral ammonium cation is used. Prakash and co-workers reported that the use of *N*-benzylquinidinium fluoride in dichloromethane at −78 °C allowed the trifluoromethylation of 9-anthraldehyde in 95% ee (entry 1, Table 16).[200,201] Iseki and co-

Table 16. Enantioselective Nucleophilic Trifluoromethylation



entry	R^1	R^2	R^3	R^4	R^5	yield, %	ee, %	ref
1	9-anth	H	MeO	H	H		95	200, 201
2	Ph	H	H	H	CF_3	>99	37	202
3	Ph	H	H	CF_3	CF_3	>99	46	202
4	*n*-C_3H_7	H	H	H	CF_3	>99	15	202
5	9-anth	H	H	H	CF_3	98	45	202
6	Ph	Me	H	H	CF_3	91	48	202
7	Ph	*i*-Pr	H	H	CF_3	87	51	202

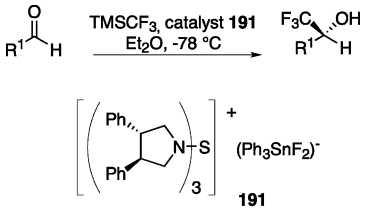
workers employed 1−20 mol % *N*-[4-(trifluoromethyl)benzyl]cinchonium fluoride as an effective catalyst for asymmetric introduction of the trifluoromethyl group into carbonyl compounds to give the corresponding alcohols in high yields and with moderate enantiomeric excesses (entries 2−7, Table 16).[202]

Noteworthy, quinine itself was capable of enantioselective trifluoromethylation of aldehydes using

related Et_3SiCF_3, although with low enantioselectivities and yields.[203,204]

Iseki and co-workers have developed the chiral triaminosulfonium salt **191**, which functions as a Lewis base catalyst in the enantioselective trifluoromethylation.[205] $(TMS)CF_3$ reacted with aldehydes in the presence of 10 mol % chiral salt **191** at −78 °C in diethyl ether to give the corresponding alcohols with ee's ranging from 10% to 52% (Scheme 40).

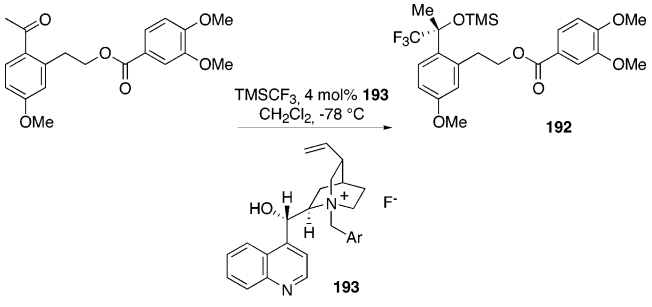
Scheme 40



R^1	yield, %	ee, %
Ph	96	52
p-MeOPh	97	37
p-CF_3Ph	90	24
p-ClPh	93	30
o-MePh	98	33
1-napht	71	12
(*E*)-PhCH=CH	99	18
C_6H_{11}	88	10

With the aim of obtaining the enantiomerically enriched trifluoromethylated silylated alcohol **192**, an in-depth catalyst structure−enantioselectivity relationship study was undertaken by Caron and co-workers.[206] They found that the introduction of a bulky subunit at the quinuclidine nitrogen atom of cinchona alkaloids led to an enhancement of the stereoselectivity. Alkaloids having the *O*-(9)-hydroxyl group etherified did not promote the reaction. Easily prepared cinchonine-derived catalysts **193** were used in amounts as low as 4 mol % in the trifluoromethylation to afford the desired product **192** in up to 92% ee (Scheme 41). However, these catalysts did not prove to be generally applicable to a variety of model

Scheme 41



Ar	conv, %	ee, %
3,5-$(MeO)_2C_6H_3$	98	83
3-$MeOC_6H_4$	86	74
9-anthracenyl	95	85
1-naphthyl	97	92
4-biphenyl	86	68

aldehydes and ketones, albeit no optimization was conducted.

We did not find any example of reagent-controlled nucleophilic trifluoromethylation. However, efforts directed toward the design of enantioselective nucleophilic trifluoromethylating reagents are ongoing in the group of Langlois and Billard. Indeed, they have recently reported enantiopure trifluoroacetamide **194** (Figure 9) derived from ephedrine, which

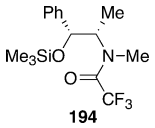


Figure 9. Potential enantioselective nucleophilic trifluoromethylating reagent.

was able to trifluoromethylate benzophenone, benzaldehyde, and acetophenone in the presence of 10 mol % cesium fluoride or TBAT in 58−89% yields.[207] Unfortunately, the enantioselectivity was not discussed at this stage.

3.2. Electrophilic Trifluoromethylation Reactions

Asymmetric electrophilic trifluoromethylation has been developed relatively slowly. Yagupol'skii reported in 1984 the first electrophilic trifluoromethylating reagents **195a,b** (Figure 10), which showed low

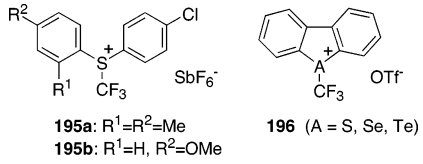


Figure 10. Electrophilic trifluoromethylating reagents.

reactivity.[208] The research work of Umemoto and co-workers in the early 1990s led to the development of highly reactive trifluoromethyl dibenzoheterocyclic salts **196** (Figure 10) as electrophilic trifluoromethylating agents.[209−213]

Umemoto and co-workers reported a comparison of diastereoselectivity for the trifluoromethylation of the trimethylsilyl enol ether **197** and the boron-mediated trifluoromethylation of the corresponding potassium enolate **199** with **196** (A = S).[210,211] The α/β ratio of product **198** was 3.6/1 for the former reaction and 1/2.5 for the latter one (entries 1 and 2, Table 17). The conformation of the intermediate complex **200**, in which the bulky Lewis acid is complexed with the enolate oxygen from the less hindered α-face of the potassium enolate, would force the trifluoromethylating agent to attack the complex from the β-face, predominantly giving the β-isomer (Figure 11). The preferential formation of β-CF_3 steroid isomer **202** can be explained by a similar rationale (entry 3, Table 17).

The first and only example to date of enantioselective electrophilic trifluoromethylation was achieved by the same group. In the presence of optically active boron compound **206** or **207**, the potassium enolate of propiophenone **203** was reacted with **196** (A = S), giving moderate enantioselectivities and low yields

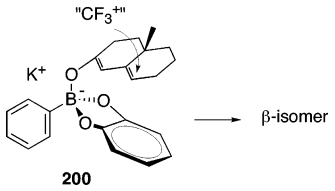
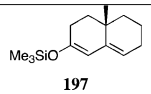
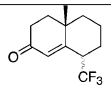
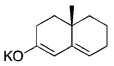
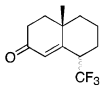
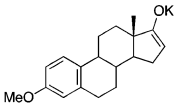
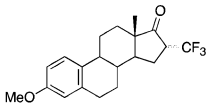
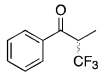
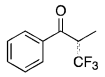
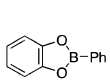
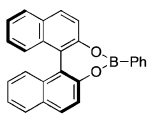
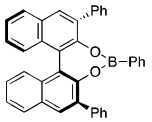


Figure 11. Proposed intermediate for the boron-mediated trifluoromethylation of enolate **199**.

Table 17. Enantioselective Electrophilic Trifluoromethylation

entry	substrate	boron	product	yield, %	de or ee, %
1	 **197**	-	 **198**	69	α/β = 3.6/1
2	 **199**	**205**	 **198**	81	α/β = 1/2.5
3	 **201**	**205**	 **202**	58	α:β = 2/3
4	 **203**	**206**	 **204**	31	12 (ee)
5	 **203**	**207**	 **204**	20	45 (ee)
	 **205**		 **206**  **207**		

(entries 4 and 5, Table 17). The enantioselectivity could arise from the attack of the resulting chiral borate complex by the trifluoromethylating agent.

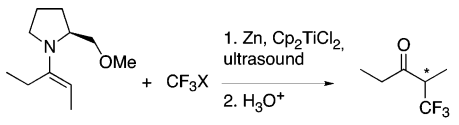
Surprisingly, 10 years later, this research area has not experienced any progress. We have recently initiated a research program dedicated to new approaches in electrophilic trifluoromethylation.[162] Promising results were obtained under phase-transfer catalysis with the aid of cinchona alkaloid ammonium salts; optimization of the enantioselectivity is the subject of active research.[214]

A diastereoselective approach, according to the second generation of asymmetric synthesis, employing chiral enamine **208** was described by Kitazume and Ishikawa.[215] The asymmetric introduction of the trifluoromethyl group in the presence of zinc powder and a catalytic amount of dichlorobis(π-cyclopentadienyl)titanium was promoted by ultrasound; up to 76% ee was obtained with CF_3Br (Scheme 42).

3.3. Radical Trifluoromethylation Reactions

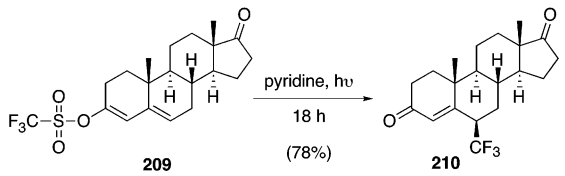
Early work by Elliot and co-workers concerned dienyl enol triflate **209** of a steroidal system. Irradiation of **209** in pyridine photochemically gave 6β-trifluoromethyl α,β-unsaturated ketone **210** (Scheme

Scheme 42



CF_3X	yield, %	ee, %
CF_3I	38	62
CF_3Br	46	76

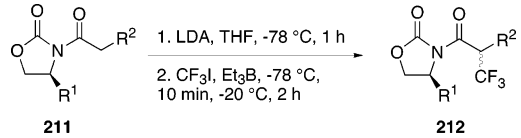
Scheme 43



43). A radical process was suggested for the fragmentation−rearrangement reaction.[216]

The trifluoromethylation of lithium enolates of chiral *N*-acyloxazolidinones **211** with iodotrifluoromethane mediated by triethylborane was achieved by Iseki and co-workers.[217,218] The trifluoromethylation proceeded in good yields and diastereoselectivities to afford α-trifluoromethyl carboximides **212**, which were treated with $LiBH_4$ to provide the corresponding β-trifluoromethyl alcohols without racemization (Scheme 44).

Scheme 44



R^1	R^2	yield, %	de, %[a]
i-Pr	Me	70	64 (*S*)
i-Pr	Bn	61	74
i-Pr	Ph	45	67 (*S*)
i-Pr	*n*-Bu	75	76
i-Pr	*t*-Bu	67	86
Bn	Me	70	72 (*S*)

[a] In parentheses is given the configuration of the major isomer.

The lack of reaction in the absence of triethylborane, or with added galvinoxyl (a radical scavenger) presented evidence for the proposed radical mechanism. The diastereoselectivity of the reaction can be explained by the trifluoromethyl radical reaction on the *si* face of the lithium-chelated transition state (Figure 12).

To synthesize 7α-perfluoroalkylestradiol, Blazejewski and co-workers developed an approach for direct introduction of the trifluoromethyl group by reaction of silyl enol ether **213** of a steroidal ketone with Umemoto's reagent **196** (A = S). Under thermal conditions similar to those employed by Umemoto, the yield was low (15%), while UV irradiation of the reaction mixture led to an excellent yield (90%) of the ketone **214**, although in a poorer selectivity (α/β = 5/4) than that observed in the perfluoroalkyl series (vide infra) (Scheme 45).[219]

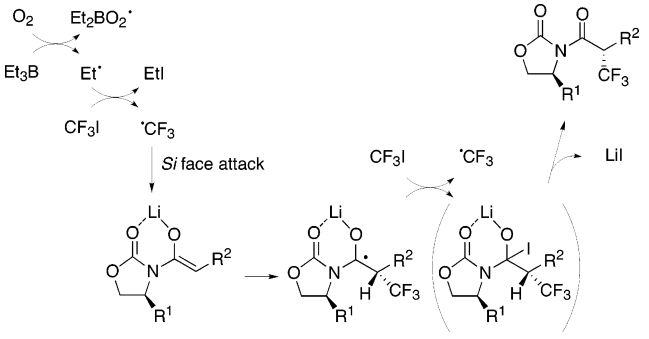
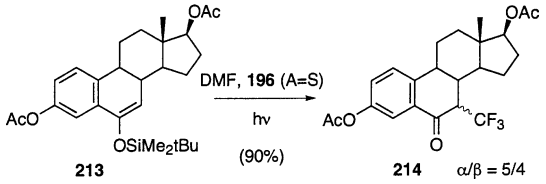


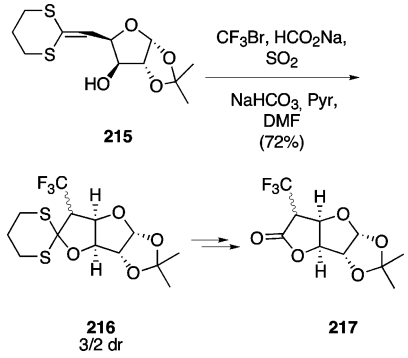
Figure 12. Proposed radical mechanism.

Scheme 45



A tandem radical trifluoromethylation−nucleophilic cyclization of the glucose-derived ketene dithioacetal **215** has been proposed as the key step toward trifluoromethylated lactone **217** (Scheme 46).[220] The

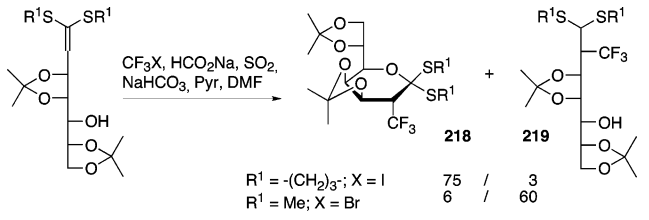
Scheme 46



reaction exhibited poor diastereoselectivity (dr = 3/2), with the two diastereomers of **216** being separable by silica gel chromatography.

A higher degree of diastereoselection (>90/10) was reached starting from a mannose-derived substrate. Depending on the sulfur substitution and the trifluoromethyl halide, the dithioketal lactone **218** or the acyclic sugar **219** was predominantly obtained (Scheme 47).[221]

Scheme 47



4. Asymmetric Perfluoroalkylation Reactions

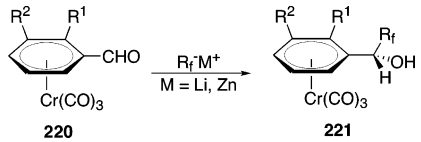
The presence of one or more perfluoroalkyl groups in molecules can be used for various purposes taking advantage of several useful properties of these units.[26] For example, the CF_2 group is known for its isosteric and isopolar relation to oxygen, a property which has been explored in the area of difluorinated analogues of carbohydrates and other oxygenated biomolecules.[222] Additionally, the introduction of a difluoromethylene group into peptides has brought about the discovery of potent protease inhibitors which function as transition-state mimics.[223] In the case of long-chain perfluoroalkylations, some perfluoroalkylated carbohydrates have been synthesized, for example, for the formation of biocompatible oxygen carriers.[224] The development of asymmetric procedures for the straightforward introduction of a perfluoroalkyl group has been the subject of continuous investigations in recent years.

4.1. Nucleophilic Perfluoroalkylation Reactions

4.1.1. Diastereoselective Perfluoroalkylation

The addition of pentafluoroethyllithium and some perfluoroalkylzinc derivatives to chiral arenechromium tricarbonyl aldehydes **220** has been carried out by Solladié-Cavallo and co-workers (Table 18).[225−227]

Table 18. Diastereoselective Perfluoroalkylation of Arenechromiun Tricarbonyl Aldehydes



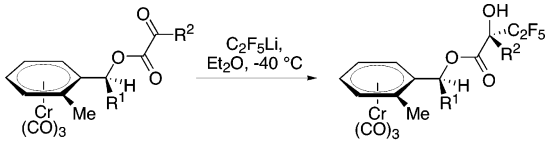
R^1	R^2	R_f	M	yield, %	de, %	ref
Me	H	C_2F_5	Zn	85	44	225
Me	H	i-C_3F_7	Zn	100	66	225
Me	H	C_6F_{13}	Zn	73	46	225
CF_3	H	C_2F_5	Zn	95	33	227
CF_3	H	i-C_3F_7	Zn	95	76	227
Me	H	C_2F_5	Li	87	88	226
Me	H	i-C_3F_7	Li	40	76	226
OMe	H	C_2F_5	Li	72	100	226
OMe	OMe	C_2F_5	Li	72	100	226
OMe	OMe	i-C_3F_7	Li	51	100	226
Me	H	C_2F_5	Li	95	80	226
CF_3	H	C_2F_5	Li	90	94	227
CF_3	H	i-C_3F_7	Li	95	90	227

The preferred diastereomer of **221** was the same in the two cases (from lithium compounds or from zinc compounds). The addition of the perfluoroalkyl group occurred *trans* to the $Cr(CO)_3$ tripod, and the asymmetric induction was highly dependent on the R^1 ring substituent. On decomplexation under irradiation, optically active perfluoroalkylcarbinols were obtained.

Some of the obtained complexed alcohols **221** proved to be good inducers of chirality in the Prelog-type asymmetric synthesis of α-hydroxy acids **222** (Scheme 48).[228]

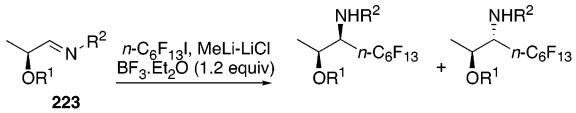
Perfluoroalkyllithiums, generated in situ from the reaction of primary perfluoroalkyl iodides and MeLi−LiBr, in the presence of boron trifluoride, reacted with chiral aldimines **223** and **224** derived from lactic acid or from aldehyde and chiral amines (Table 19). The diastereofacial selectivity observed in the reaction did not agree with Cram's chelation model; thus,

Scheme 48

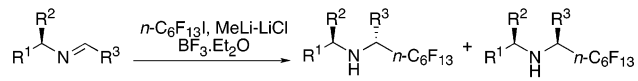


R^1	R^2	yield, %	de, %
C_2F_5	Ph	95	89
C_2F_5	Me	84	84
Et	Ph	76	88
Et	Me	87	90

Table 19. Diastereoselective Perfluorohexylation of Imines



R^1	R^2	solvent	yield, %	dr
t-BuMe$_2$Si	allyl	Et_2O	81	85/15
Me	*n*-Pr	toluene	47	19/81
MOM	*n*-Pr	toluene	42	3/97
MOM	allyl	Et_2O	40	19/81



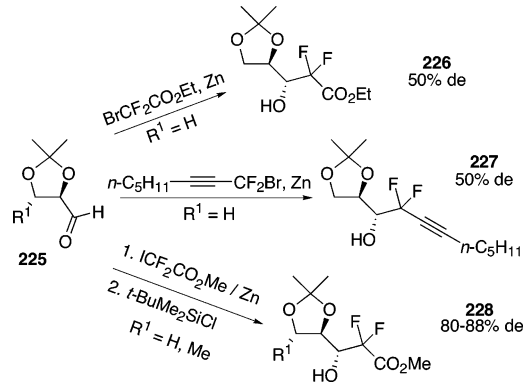
R^1	R^2	R^3	solvent	yield, %	dr
Me	Ph	*i*-Pr	Et_2O	90	84/16
Me	Ph	Ph	Et_2O	63	77/23
Me	Ph	CO_2*n*-Bu	Et_2O	53	77/23
i-Pr	CO_2Me	Ph	Et_2O	54	98/2
i-Bu	CO_2Et	Ph	Et_2O	73	94/6
Bn	CO_2Et	Ph	toluene	75	96/4
Bn	CO_2Et	allyl	Et_2O	43	96/4
Bn	CO_2Et	*n*-Pr	Et_2O	78	88/12

the authors proposed a model involving an interaction of BF_3 with the perfluoroalkyllithium.[229]

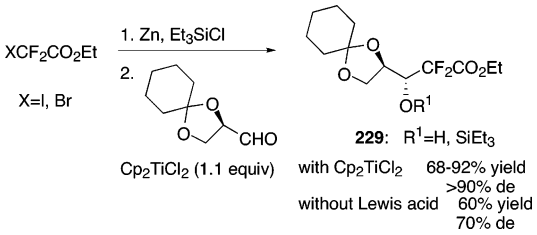
Since the report of Fried,[230] the Reformatsky reaction of difluoroorganozinc with chiral aldehydes has become a frequently used methodology for the preparation of interesting biomolecules with a difluoromethylene moiety. For example, condensation of the zinc derivative of ethyl bromodifluoroacetate[231] and *n*-pentylbromodifluoromethylacetylene[232] with glyceraldehyde acetonide **225** (R^1 = H) gave the desired difluorohydroxy products **226** and **227** with moderate diastereoselectivities (Scheme 49). It is worth noting that difluoroketene acetal generated in situ from methyl iododifluoroacetate, zinc, and trialkylchlorosilane was applied to this reaction, allowing higher diastereoselectivities to be reached for compound **228**.[233]

The diastereoselective synthesis of α,α-difluoro-β,γ-dihydroxy esters **229** can also be promoted by Lewis acids to enhance face differentiation. Cp_2TiCl_2 allowed a higher *anti* selectivity than the reaction run without Lewis acid to be reached (Scheme 50).[234]

Scheme 49

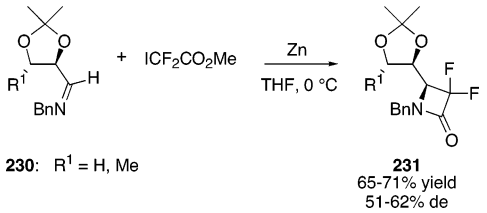


Scheme 50



When diol-protected glyceraldehydes were used in the Reformatsky reaction, the *anti* condensation products were formed preferentially and the stereochemical course was rationalized according to Felkin's model. In contrast, the formation of the *syn* compounds was favored when benzylimines **230** were used as electrophilic species (Scheme 51). In this case

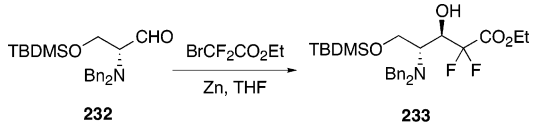
Scheme 51



a chelation between the imine and zinc halide was proposed to rationalize the preferential formation of *syn*-lactams **231**.[235]

When chiral α-amino aldehyde **232** was employed as an electrophile in the Reformatsky reaction, the *anti* compound **233** was obtained as a single diastereomer and was further transformed into 2′-difluoro nucleoside analogues (Scheme 52).[236]

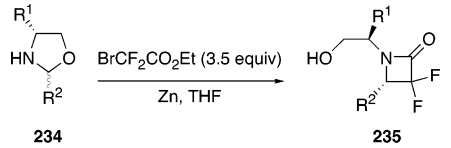
Scheme 52



Alternatively, chiral oxazolidines **234** derived from (*R*)-phenylglycinol or (*R*)-aminobutanol were diastereoselectively perfluoroalkylated with $BrCF_2CO_2Et$ in the presence of activated zinc dust to furnish difluoroazetidinones **235** with up to 99% de (Scheme 53).[237]

Somewhat less diastereoselective was the addition of $BrCF_2CO_2Et$ to alkyl- and aryl-substituted *N-tert*-

Scheme 53

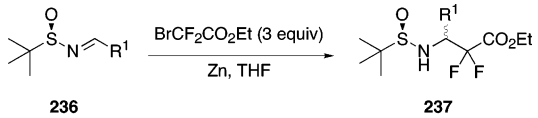


234 235

R^1	R^2	yield, %	de, %
Ph	Ph	65	>99
Et	Ph	69	96
Et	*n*-C_5H_{11}	35	90
Et	2-furyl	62	85
Et	*trans* CH=CHCH$_3$	32	96

butylsulfinimines **236**, furnishing *β-N-tert*-butylsulfinamyl *β*-substituted α,α-difluoropropionates **237** in de's ranging from 60% to 90% (Scheme 54).[238]

Scheme 54



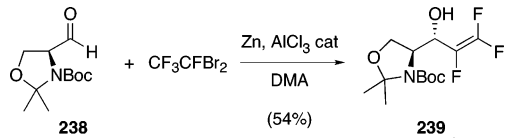
236 237

R^1	yield, %	de, %
i-C_4H_9	51	62
n-C_3H_7	55	60
Ph	82	80
c-C_6H_{11}	81	74
2-thiazolyl	58	90

A considerable number of papers dealing with the Reformatsky reaction employing ethyl bromodifluoroacetate appeared in the literature, but the stereochemistry was sometimes poor or not always discussed; consequently, these examples will not be detailed in this review.[168,239−250]

Another readily available bromofluorocarbon is 1,1-dibromoperfluoroethane (CF_3CFBr_2), which was reacted with Garner's aldehyde **238**. The reaction proceeded smoothly in the presence of zinc powder and catalytic $AlCl_3$ and was highly diastereoselective, affording the *anti* product **239** in 54% yield with a diastereomeric excess greater than 98% (Scheme 55).[251]

Scheme 55



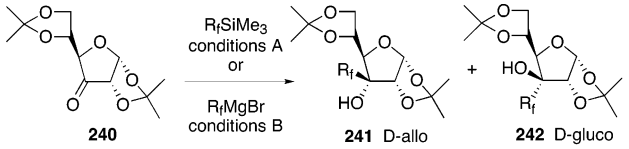
238 239 >98% de

Portella and co-workers described the perfluoroalkylation of carbohydrate **240** with perfluoroalkylmagnesium reagents and perfluoroalkyltrimethylsilanes. A comparison of the two types of reagents was provided. Silyl reagents added with complete stereoselectivity to the *β*-face, giving the D-*allo* derivatives **241** as unique observable products, whereas a mixture of D-*allo* and D-*gluco* epimers **241** and **242** was obtained from magnesium reagents (Scheme 56).[183]

4.1.2. Enantioselective Perfluoroalkylation

In 1995, Braun and co-workers disclosed the enantioselective Reformatsky reaction of bromodifluoro-

Scheme 56



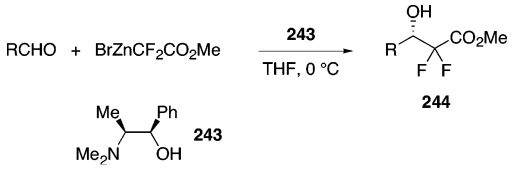
240 241 D-allo 242 D-gluco

Conditions A: 1. R_fSiMe_3 (1.1 equiv), $Bu_4N^+Ph_3SnF_2^-$ cat, CH_2Cl_2, rt
2. H_3O^+ or TBAF
Conditions B: 1. R_fMgBr (1.2 equiv), Et_2O, -45 °C
2. H_3O^+

R_fM	yield, %	**241**/**242**
CF_3SiMe_3	88	100/0
$C_4F_9SiMe_3$	70	100/0
C_4F_9MgBr	68	78/22
$C_6F_{13}MgBr$	59	73/27

acetate with aldehydes. The reaction proceeded with an excess of the Reformatsky reagent in the presence of (1*R*,2*S*)-*N*-methylephedrine (**243**) to provide the corresponding α,α-difluoro-*β*-hydroxy esters **244** in good yields and enantioselectivities. Interestingly, the enantioselection was dependent on the amount of chiral ligand. Use of 10 mol % ligand **243** led to a dramatic decrease of enantioselectivity. In addition, aromatic aldehydes gave rather better optical yields than aliphatic aldehydes (Scheme 57).[252]

Scheme 57

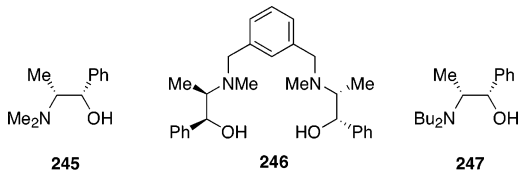


244

243

R	**243**, equiv	yield, %	ee , %
Ph	2	61	84
Ph	0.3	47	79
Ph	0.1	45	54
*p*ClPh	2	56	67
2,5-(MeO)$_2$Ph	2	71	71
i-Pr	2	63	46

Andrés and co-workers also reported the asymmetric synthesis of optically active α,α-difluoro-*β*-hydroxy esters mediated by chiral amino alcohol ligands **245**−**247** (Figure 13). Aromatic aldehydes led



245 246 247

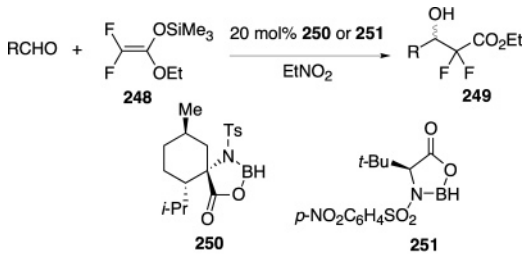
Figure 13. Chiral amino alcohol ligands for enantioselective Reformatsky reaction of bromodifluoroacetate with aldehydes.

to good enantioselectivities (60−83% ee), while aliphatic ones gave up to 58% ee. Chiral ligands **245** and **246** were equipotent, and **247** was somewhat less efficient.[253]

The Mukaiyama aldol reaction of silyl enol ethers is one of the most important carbon−carbon bond

forming reactions in organic synthesis. The asymmetric Mukaiyama aldol reaction of difluoroketene silyl acetal **248** with various aldehydes, in nitroethane, using Masamune's catalyst **250**[254] or Kiyooka's catalyst **251**[255] yielded α,α-difluoro-β-hydroxy esters **249** with excellent yields and high enantioselectivities (Scheme 58). Kiyooka's catalyst was more efficient in the enantioselection with secondary aldehydes than Masamune's catalyst.[256,257]

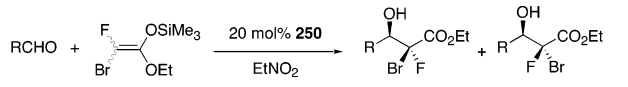
Scheme 58



R	cat.	temp, °C	yield, %	ee, %
Ph	**250**	-78	>99	97 (*R*)
Ph	**251**	-20	96	65 (*R*)
$BnOCH_2$	**250**	-78	94	98
(*E*)-PhCH=CH	**250**	-78	>99	96
c-C_6H_{11}	**250**	-78	87	76
c-C_6H_{11}	**251**	-45	97	94
Et_2CH	**250**	-78	81	64
Et_2CH	**251**	-45	90	95

Additionally, the bromofluoroketene silyl acetal **252** (*E*/*Z* = 62/38) was reacted with various aldehydes in the presence of Masamune's catalyst **250** to afford a mixture of *syn*- and *anti*-aldol products **253**. Although the diastereoselectivity was low, both diastereomers were obtained with high enantioselectivities (90−99% ee) (Scheme 59).[258] It is noteworthy that the stereochemical outcome was found to be dependent on the reaction temperature. The reaction of aldehydes with difluoroketene acetal at −78 and −45 °C (−20 °C in the case of bromofluoroketene acetal) afforded aldol products having opposite signs of optical rotation (Scheme 59). Different transition structures might account for the reversal of the enantioselection.[24]

Scheme 59

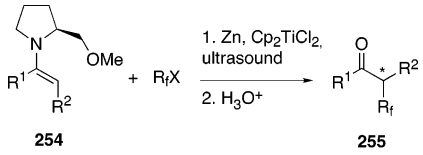


R	-78 °C		-20 °C	
	yield, % (*syn*/*anti*)	ee, % (*syn*/*anti*)	yield, % (*syn*/*anti*)	ee, % (*anti*)
$PhCH_2CH_2$	89 (46/54)	98/98 (+)	85 (13/87)	92 (-)
$BnOCH_2$	81 (57/43)	97/97 (+)	80 (26/74)	72 (-)
c-C_6H_{11}	74 (52/48)	94/89 (+)	90 (20/80)	81 (-)
Et_2CH	70 (54/46)	99/98 (+)	85 (23/77)	74 (-)

4.2. Electrophilic Perfluoroalkylation Reactions

An excellent review on electrophilic perfluoroalkylating reagents has been published by Umemoto; however, no example of asymmetric electrophilic perfluoroalkylation (R_f > CF_3) was reported.[212] The first report with stereochemical information concerned the perfluoroalkylation of chiral enamine **254** derived from (*S*)-proline (Scheme 60).[215] Treatment of enamines **254** with a perfluoroalkyl halide in the presence of Cp_2TiCl_2, Zn powder, and ultrasound afforded the corresponding α-perfluoroalkyl ketones **255** with moderate stereoselection.

Scheme 60

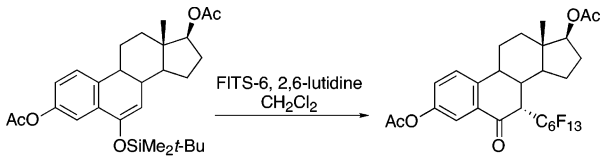


R_fX	R^1	R^2	yield, %	ee, %
C_2F_5I	Me	Et	51	54
n-C_3F_7I	Me	Et	48	59
n-C_4F_9Br	Me	Et	58	64
n-$C_6F_{13}I$	-$(CH_2)_4$-		57	68
n-$C_8F_{17}I$	Me	Et	56	72[a]

[a] Reaction run with an (*R*)-proline auxiliary.

Blazejewski and co-workers described the synthesis of 7α-perfluorohexylestradiol. Reaction of FITS-6 (perfluorohexylphenyliodonium trifluoromethanesulfonate) with silyl enol ether **213** provided the perfluorohexyl steroid **256** in 80% yield with high diastereoselectivity (α/β = 10/1) (Scheme 61).

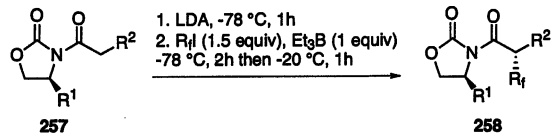
Scheme 61



4.3. Radical or Carbene Perfluoroalkylation Reactions

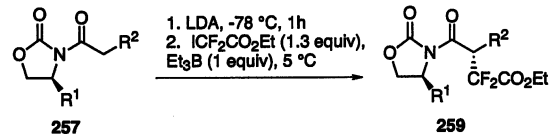
Triethylborane is an effective radical initiator for perfluoroalkyl iodides, which induced the asymmetric trifluoromethylation of chiral *N*-acyloxazolidinones as reported by Iseki and co-workers.[217,218] The same group extended the method to diastereoselective perfluoroalkylation (R_f)[259] of **257**, but also to ethoxycarbonyl difluoromethylation (EtO_2CCF_2),[260] diethylphosphonate difluoromethylation [$(EtO)_2POCF_2$],[261] and bromodifluoromethylation[262,263] (Scheme 62). Various perfluoroalkyl iodides were applicable to the perfluoroalkylation of lithium enolates of *N*-acyloxazolidinones **257** employing the triethylborane-mediated radical procedure; the corresponding α-perfluoroalkylated carboximides **258** were produced in good yields and diastereoselectivities (55−93% de).[259] The diastereoselective introduction of the EtO_2CCF_2 group into **257** proceeded under similar conditions provided the chiral imide enolate is added to a solution of ethyl difluoroiodoacetate and triethylborane.[260,264] Diethyl difluoroiodophosphonate [$ICF_2PO(OEt)_2$] also reacted with the lithium enolate of *N*-acyloxazolidinone **260**

Scheme 62



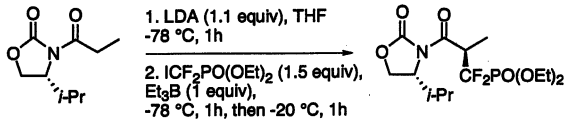
257 258

R^1	R^2	R_f	yield, %	de, %
i-Pr	Me	*n*-C_6F_{13}	79	71
i-Pr	Me	C_2F_5	74	74
i-Pr	Me	$(CF_3)_2CF(CF_2)_2$	75	79
Bn	Me	*n*-C_6F_{13}	81	83
i-Pr	Bn	*n*-C_6F_{13}	70	81
i-Pr	*n*-Bu	*n*-C_6F_{13}	73	83
i-Pr	*t*-Bu	*n*-C_6F_{13}	57	93
i-Pr	Ph	*n*-C_6F_{13}	63	57
i-Pr	OBn	*n*-C_6F_{13}	59	55

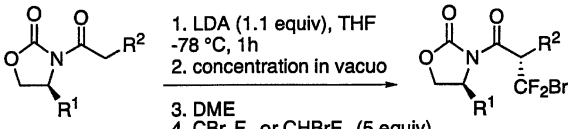


257 259

R^1	R^2	yield, %	de, %
i-Pr	Me	74	88
i-Pr	Me	61	86
i-Pr	*n*-Bu	64	88
i-Pr	*t*-Bu	19	>98
Bn	Me	70	87



260 261
92% yield
77% de



257 262

R^1	R^2	yield, %[a]	de, %[a]
i-Pr	Me	59 (45)	68 (61)
i-Pr	Bn	52 (45)	67 (62)
i-Pr	*n*-Bu	60 (42)	67 (61)
i-Pr	*t*-Bu	42 (42)	92 (93)
Bn	Me	55 (43)	71 (51)
i-Pr	OBn	42	70
i-Pr	$N(Bn)_2$	30	64

[a] In parentheses are given the results of reactions run with $CHBrF_2$.

in the presence of Et_3B to provide the diethylphosphonodifluoromethylated product **261** in 92% yield and 77% de.[261] Interestingly, triethylborane was not necessary for the diastereoselective bromodifluoromethylation of **257** using either dibromodifluoromethane or bromodifluoromethane. An ionic mechanism involving the insertion of difluorocarbene can account for the observations.[265]

5. Concluding Remarks

Outstanding progress has been recently made in the development of reagents and methodologies in asymmetric fluorination, trifluoromethylation, and perfluoroalkylation. High levels of diastereoselectivity are frequently observed in nucleophilic and electrophilic fluorination as well as in nucleophilic perfluoroalkylations (CF_3 and R_f), whereas diastereoselective electrophilic perfluoroalkylations clearly require more investigations to elevate these reactions to the high standard of diastereoselective synthesis. Enantioselective approaches represent a much more challenging area. Within the examples described in this review, enantioselective electrophilic fluorination of various substrates with the aid of chiral *N*-fluoroammonium salts and transition-metal catalysts is now considered state-of-the-art. On the contrary, enantioselective nucleophilic fluorination is currently limited to the ring-opening of *meso*-epoxides. For enantioselective nucleophilic perfluoroalkylations, good methods are available, but the level of enantioselectivity is not globally satisfactory. The scarcity of reports on enantioselective electrophilic perfluoroalkylations is perhaps the consequence of the lack of efficient and easily available electrophilic reagents. The success of this approach will be dependent on the discovery of new efficient electrophilic reagents.

Despite the remarkable advancements in asymmetric introduction of fluorine atoms and perfluorinated groups, further developments are necessary for chiral nonracemic fluorinated molecules to be increasingly used in pharmacy, medicine, agriculture, and material science.

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