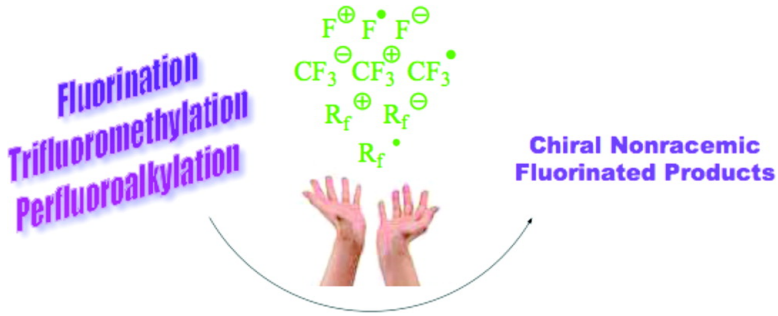
CHEMICAL REVIEWS

Review

Update 1 of: Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions

Jun-An Ma, and Dominique Cahard

Chem. Rev., 108 (9), PR1-PR43 • DOI: 10.1021/cr800221v • Publication Date (Web): 10 September 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Update 1 of: Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions

Jun-An Ma[†] and Dominique Cahard[*,‡]

Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, China, and UMR 6014 CNRS, laboratoire COBRA de l'IRCOF (Institut de Recherche en Chimie Organique Fine), Université et INSA de Rouen, Rue Tesniere, F-76130 Mont Saint Aignan, France

This is a Chemical Reviews Perennial Review. The root paper of this title was published in Chem. Rev. **2004**, *104, 6119−6146. Updates appear in red.*

Received March 11, 2008

Contents

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.[2−12] 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).[13] 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)[14] 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.[15,16] Nevertheless, the controversy remains on the existence of hydrogen bonds between the C−F group and -OH or -NH donors.[17−19] 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.[20] The CF_3 group has an electronegativity similar to that of oxygen[21] and a large hydrophobic parameter.[22] 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.[23]

One of the most fascinating aspects of organofluorine chemistry is the asymmetric synthesis of fluorinated molecules.[24−29] 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.[30] 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, ring-opening of epoxides with $Et_3N{\bullet}3HF$, or replacements of tertiary deactivated hydrogen in steroids) and classical resolutions, which are not asymmetric syntheses, will not be considered, with the exception

* To whom correspondence should be addressed. Fax: (33) 2 35 52 29 62. E-mail: dominique.cahard@univ-rouen.fr.
† Tianjin University.
‡ Université et INSA de Rouen.

10.1021/cr800221v CCC: $71.00
Published on Web 09/10/2008

Jun-An Ma was born in Henan Province, China. He received his B.S. degree from Henan University in 1991 and his M.S. degree from Nankai University in 1994. Then, he joined Guangzhou Baihua Flavor & Fragrance Co. as a Senior Research Fellow. From 1996 to 1999, he completed his Ph.D. under the supervision of Professor Run-Qiu Huang at Nankai University. Then, he stayed there to work with Professor Qi-lin Zhou before taking up postdoctoral fellowships with Dr. D. Cahard in 2003 and Professor M. T. Reetz (Germany) in 2004 and 2005. In July 2005, he joined the Department of Chemistry at Tianjin University, where he was appointed as a full Professor. His research interests focus on new methodologies in asymmetric synthesis and catalysis, fluorine chemistry, and the synthesis of biologically active compounds.

Dominique Cahard was born in 1968 in Fecamp (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 and was promoted to Directeur de Recherche in 2007. He has authored 74 publications and 5 patent applications. His current research interests concern the asymmetric synthesis of fluorinated molecules, with emphasis on electrophilic fluorination and trifluoromethylation, as well as the chemistry of peptidomimetics.

of kinetic resolutions, which will be mentioned. The electrophilic fluorination−nucleophilic addition reaction upon glycals and other ethylenic systems was intentionally not covered.[31,32] 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 December 2007.

2. Asymmetric Fluorination Reactions

2.1. Electrophilic Fluorination Reactions

A wide variety of electrophilic fluorinating agents have been developed over the past few decades.[33−35] 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;[36] however, it is quite indiscriminate as a reagent in asymmetric synthesis. Cationic fluorine, F^+, has only been observed spectroscopically in the gas phase;[37] 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.[38,39] Some reviews covering specific electrophilic fluorinating reagents and recent advances in electrophilic fluorination have been published.[35,40,41]

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.[42,43] 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, dipeptides, nucleosides).

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,

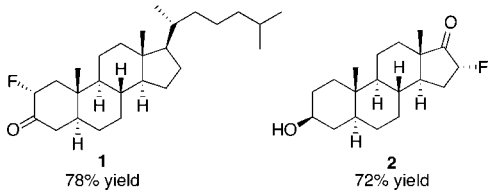
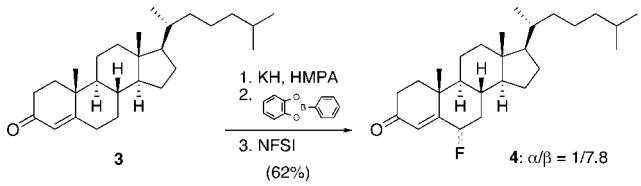
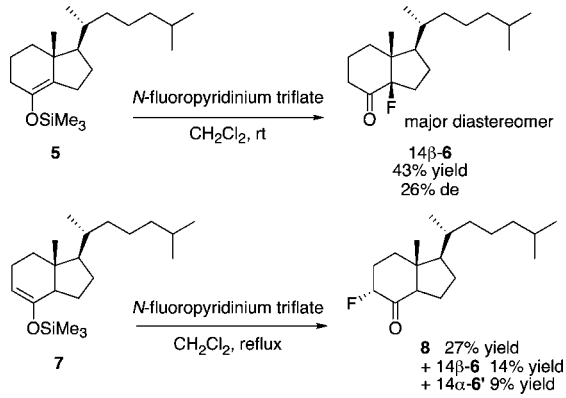


Figure 1.

Scheme 1



Scheme 2



as single diastereomers by selective α-face fluorination (Figure 1).[44]

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,[45–48] enol acetates,[46,49–54] enamides,[55] or enamines.[56,57]

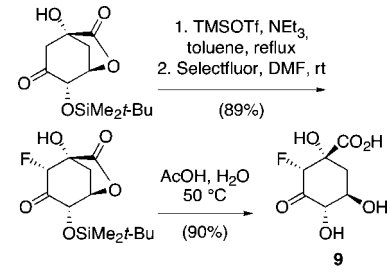
Using conjugated enol ethers raised the problem of regioselectivity. Selective γ-fluorination of various steroids was realized by Poss and co-workers as exemplified on 4-cholesten-3-one (**3**), leading to an α/β-isomer ratio of 1/7.8 (Scheme 1).[58] The potassium dienoxyboronate generated in situ was 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.[49,51,59–66]

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.[67,68]

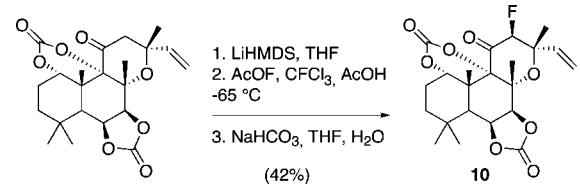
Dauben and Greenfield reported fluoro C/D ring ketones as fluorinated chirons for vitamin D_3 syntheses.[69] Kinetic and thermodynamic silyl enol ethers **5** and **7** reacted with *N*-fluoropyridinium triflate to afford mixtures of fluorinated products, in poor yields and diastereoselectivities, and 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(tetrafluorobo-

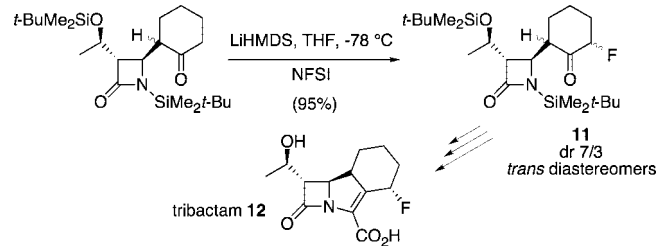
Scheme 3



Scheme 4



Scheme 5



rate)] (Scheme 3). After recrystallization, a single diastereomer was obtained in 89% yield.[70]

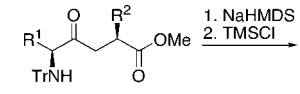
In the synthesis of 12-fluoroforskolin, the fluoro intermediate **10** was obtained by reaction of the lithium enolate with acetyl hypofluorite; a single diastereomer was obtained in 42% yield (Scheme 4).[71]

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).[72,73]

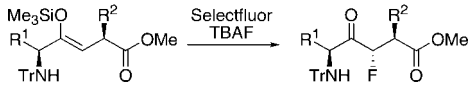
Monofluoro ketone peptide isosteres possess therapeutic potential as enzyme−inhibitors. The first synthesis of such fluoro peptides utilized fluorination of a silyl enol ether with the aid of XeF_2 in a mixture acetonitrile/1,1,2-trichlorotrifluoroethane, leading to the desired product in 71% yield without any diastereoselectivity.[74] The incorporation of fluorine into dipeptides was further developed by Hoffman and co-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 (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.[75–77]

We examined the diastereoselective electrophilic fluorination of two dipeptides of a C^{α} quaternary chiral amino acid ((*S*)-MPBrG) and racemic phenylglycine (Scheme 7). The electrophilic fluorination was conducted with the aid of NFSI, and the stereoselectivity is directed intramolecularly by the enantiomerically pure substrate Phth-(*S*)-MPBrG-(*N*-Me-Phg)-OR **15**. A diastereoselectivity of 91:9 was obtained with a phenylglycine methyl ester derived dipeptide, and a

Scheme 6



13



14

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

Scheme 7

15

R	conv, % (yield)	dr
Me	>98	91:9
Bn	>98 (86)	>98:2

diastereoselectivity of >98:2 was obtained with a phenylglycine benzyl ester analogue.[78] Interestingly, this approach gives access to a dipeptide possessing two consecutive enantiopure quaternary amino acids which could be incorporated into a longer peptide.

In the nucleoside family, the first synthesis of 1′-fluoronucleosides was achieved by electrophilic fluorination of 2′-ketouridine lithium enolates. A mixture of anomeric 1′-fluoronucleosides **16** and **17** (hydrate form) was obtained whatever the fluorinating agent (NFSI, Selectfluor, or *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate) and the reaction conditions (Scheme 8).[79]

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 **18**, 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 **18**.[80] The same group also reported the quite lengthy synthesis of the biphenyl-based ketone **19** requiring two fluorination steps by Selectfluor and epimerization in tri-

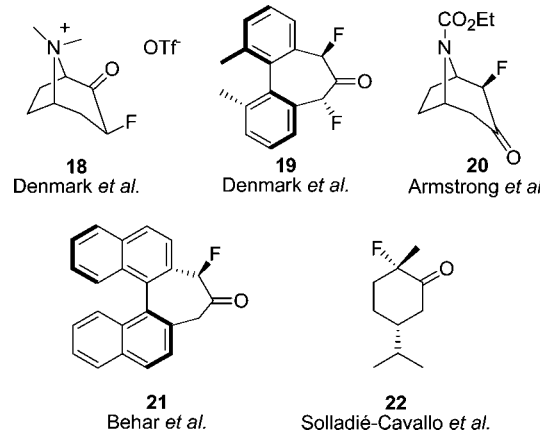


Figure 2. α-Fluoro ketones used in asymmetric epoxidation.

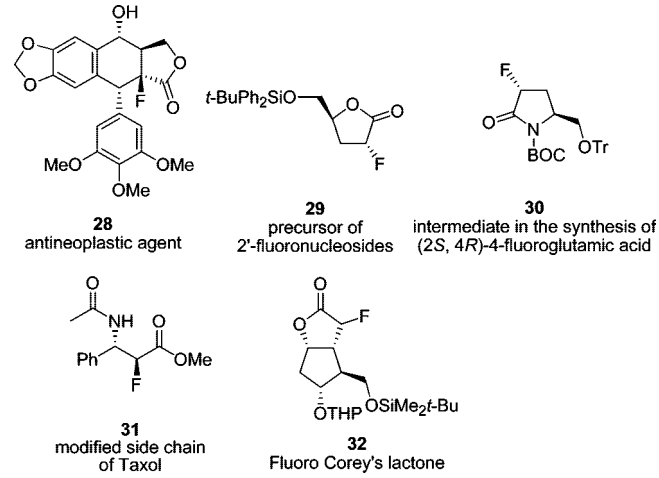
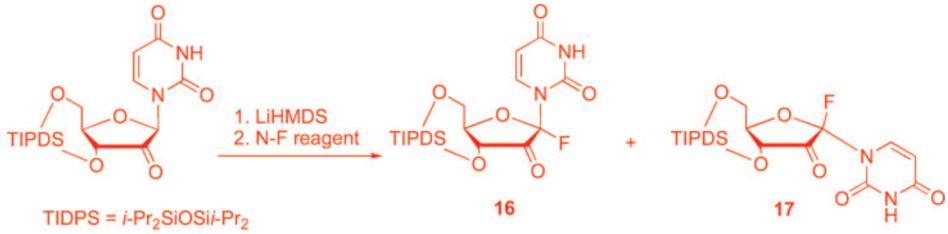


Figure 3. Examples of α-fluoro esters and amides.

Scheme 8

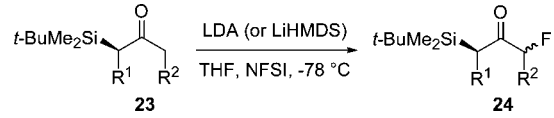


TIDPS = i-Pr_2SiOSi-Pr_2

N–F reagent	conditions	yield, %	α:β
NFSI	THF, –78°C	87	2.4:1
NFSI	THF, –78°C[a]	72	6.2:1
NFSI	DMF-THF (1:2), –78°C	57	1:1
NFSI	DMF-THF (4:1), –40°C	58	1:1.4
N-fluoro-2,6-dichloropyridinium BF_4	DMF-THF (4:1), rt	52	1:1.9
Selectfluor	DMF-THF (9:1), –40°C	57	1:3.3

[a] KHMDS was used instead of LiHMDS.

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



23 **24**

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 square brackets, for reactions employing LiHMDS. [b] Yield (or de) for reactions with LDA generated enolates and, in parenthesis, for reactions with LiHMDS generated enolates.

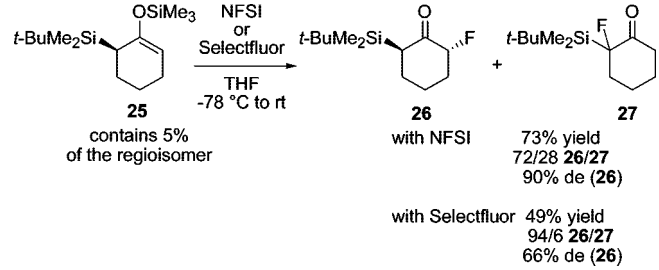
ethylamine to afford a single diastereomer.[80] Armstrong and co-workers have synthesized 2-fluoro-*N*-carbethoxytropinone (**20**) via a silyl enol ether and 2 equiv of Selectfluor in 63% yield. The fluorination occurred exclusively on the less hindered exo face of the silyl enol ether.[81] An enantioselective version of the synthesis of **20** 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 **21** in 77% yield (other distributions of fluorine atoms were also reported).[82] Solladie-Cavallo and co-workers synthesized the α-fluoro ketone **22** by fluorination of the silyl enol ether with Selectfluor, providing a mixture of two diastereomers (54/46) which were separated by column chromatography.[83,84] Other structurally similar α-fluoro ketones were evaluated by the same group in asymmetric oxidation of silyl enol ethers.[85]

Enantiopure α-silyl ketones **23** 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.[86,87] Lithium enolates of **23** generated by LDA were fluorinated with 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.

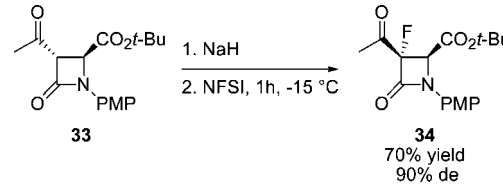
This concept was also applied to silyl enol ether **25**; however, the fluorination gave rise to a significant amount of regioisomers **26** and **27** (Scheme 9).[87] The unpredictable formation in various amounts (up to 100%) of the regioisomer bearing the fluorine atom on the side of the silyl group 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-Fluoropodophyllotoxin (**28**), a potent

Scheme 9

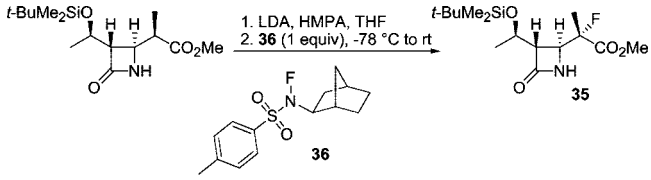


Scheme 10

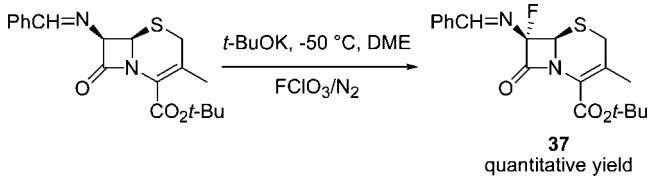


antitumor agent, was obtained by a completely diastereoselective fluorination of the sodium enolate with NFSI in 99% yield; the stereochemistry at the ring junction was *trans*.[88,89] Liotta and co-workers have also reported a completely diastereoselective electrophilic fluorination of a chiral nonracemic lactone which was further transformed into 2′-fluoronucleosides. Indeed, fluorolactone **29** could be obtained in 50−70% yield with 100% de.[90] Enantiomerically pure 2-pyrrolidinone derived from L-glutamic acid was fluorinated to give **30** in 57% yield and 100% de by reaction with LDA, followed by NFSI in THF at −78 °C. **30** was further converted to the desired (2*S*,4*R*)-4-fluoroglutamic acid as a single stereomer.[91] 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 **31** in 65% yield and a moderate 62% de.[92] The α-fluoro analogue of Corey's lactone (**32**), 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.[60]

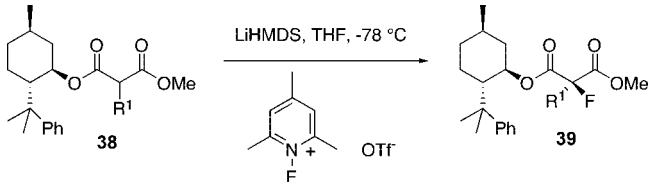
Scheme 11



Scheme 12



Scheme 13



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

The fluorolactone **32** could also be obtained using NFSI, but was immediately converted to the desired difluorolactone for the synthesis of difluoroprostacyclins.[93]

Elaboration of fluorinated antibiotics was conducted via electrophilic fluorination of functionalized azetidinone **33** by means of NFSI. Attack of the fluorine atom by the less hindered face of the stabilized sodium enolate gave predominantly **34** having the fluorine atom *trans* to the ester moiety (Scheme 10).[94]

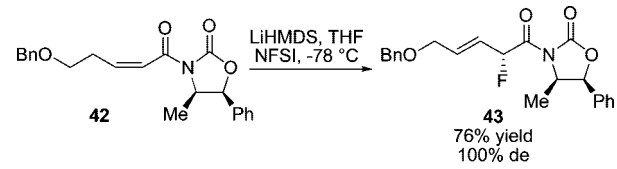
In the chemistry of carbapenems, Wildonger and co-workers prepared 1-fluoro-1-methylcarbapenem **35** by fluorination of the corresponding enolate using *N*-fluoro-*N*-(*exo*-2-norbornyl)-*p*-toluenesulfonamide (**36**).[95] The desired diastereoisomer was purified and isolated pure in 35% yield; however, the diastereoselectivity was not reported (Scheme 11).[96]

An early example of diastereoselective fluorination with perchloryl fluoride was the preparation of 7α-fluorocephalosporin Schiff base **37** (Scheme 12).[97]

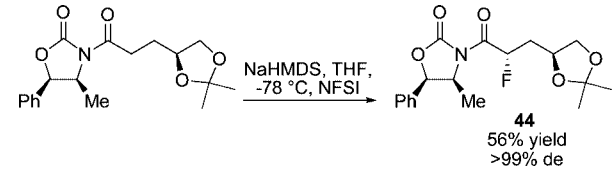
Examples of second-generation asymmetric fluorination are more frequent in the literature. Fukumoto and co-workers published a series of papers on diastereoselective fluorination of malonates **38** bearing a chiral phenylmenthyl auxiliary for the construction of quaternary fluorinated stereogenic centers (Scheme 13).[98–100]

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.[101] Other diastereoselective fluorinations of β-keto esters bearing a chiral auxiliary (e.g., cholesteryl ester[102] and menthyl esters[103,106]) have been conducted in the presence of a chiral transition-metal catalyst (see section 2.1.2.2). In these reactions, a double stereodifferentiation was expected; however, the stereoselectivity was lower or equal to that observed with achiral ester derivatives.

Scheme 14



Scheme 15



Scheme 16

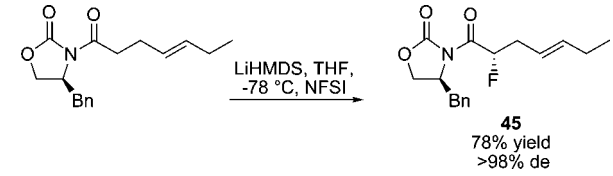
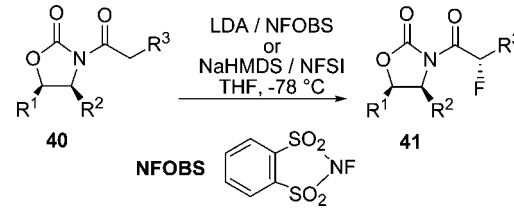


Table 2. Diastereoselective Fluorination of Chiral Imide Enolates



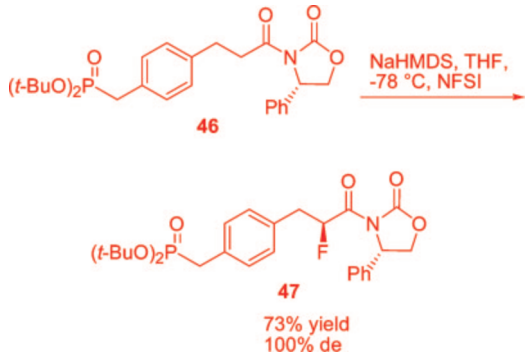
using LDA/NFOBS					using NaHMDS/NFSI				
R^1	R^2	R^3	yield, %	de, %	R^1	R^2	R^3	yield, %	de, %
Ph	Me	*n*-Bu	88	97		Me	Ph	85	>97
H	*i*-Pr	*n*-Bu	85	96	Ph	Me	Me	77	86
Ph	Me	*t*-Bu	86	96	Ph	Me	CH=CH$_2$	69	84
H	*i*-Pr	*t*-Bu	80	97	Ph[a]	Me[a]	CH$_2$OBn	78	94
Ph	Me	Bn	84	89					
Ph	Me	Ph	86	86					

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

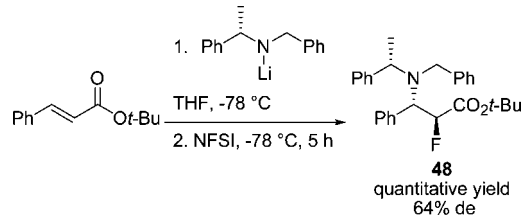
Davis and co-workers greatly contributed to diastereoselective electrophilic fluorinations. They selected Evans' oxazolidinones as chiral auxiliaries and *N*-fluoro-*O*-benzenedisulfonimide (NFOBS) or NFSI as the fluorinating agent.[107–109] Good to excellent diastereoselectivities were obtained by selective approach of the fluorinating agent from the less hindered *si* face of the chiral imide enolate (Table 2). The authors suggested that the fluorination occurred by an S_N2-type mechanism for transfer of fluorine to enolate species.[110] 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 **41** 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

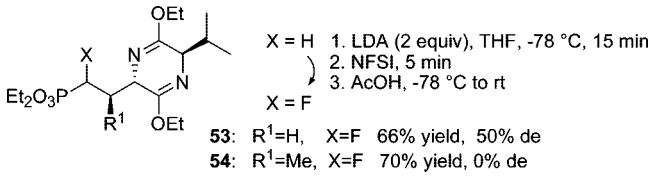
Scheme 17



Scheme 18



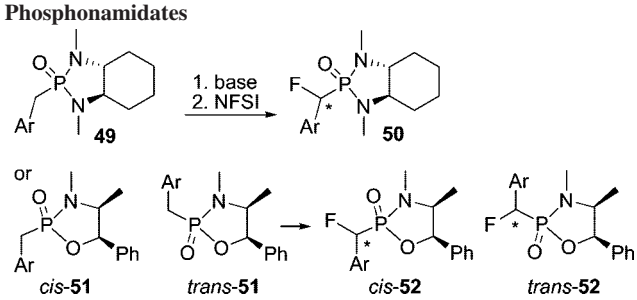
Scheme 19



reagents provided the corresponding α-fluoro ketones without racemization.[108] This synthetic route complements Enders' method (vide supra).

Diastereoselective fluorination of α,β-unsaturated chiral oxazolidinone **42** was conducted by reaction of LiHMDS followed by addition of NFSI to produce a single diastereomer in 76% yield (Scheme 14). 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 **43** was employed in the synthesis of fluoro carbohydrates.[111,112]

Table 3. Selected Results for the Fluorination of Chiral Phosphonamidates



substrate	Ar	base	yield, %	de, %
49	2-naphth	*n*-BuLi	68	68
49	2-naphth	LiHMDS	81	70
trans-**51**	2-naphth	NaHMDS	62	72
cis-**51**	2-naphth	NaHMDS	54	58
trans-**51**	*m*-(Ph)Ph	NaHMDS	85	25
cis-**51**	*m*-(Ph)Ph	NaHMDS	68	26
trans-**51**	Ph	NaHMDS	47	29
cis-**51**	Ph	NaHMDS	44	33

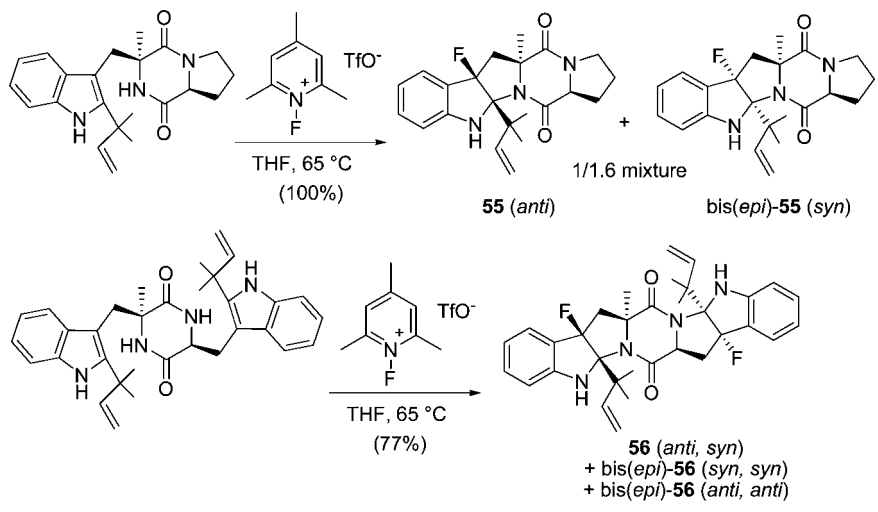
The success of the method stimulated significant efforts to improve the scope of the process. Marquez and co-workers synthesized the key fluorinated intermediate **44** for the preparation of active anti-HIV compounds FddA and FddC. The fluorination proceeded with complete diastereoselectivity (Scheme 15).[113]

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 **45** as a biosynthetic precursor of the ionophore antibiotic tetronasin (Scheme 16).[114]

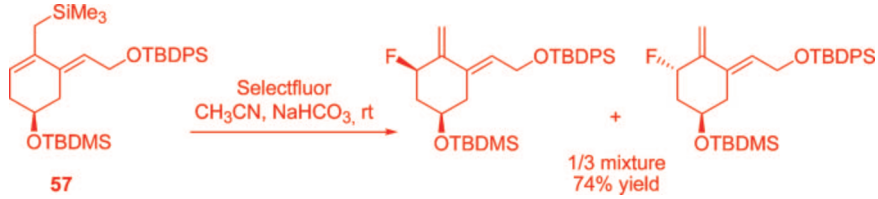
Burke and co-workers utilized the commercially available Evans auxiliary (*S*)-(+)-4-phenyl-2-oxazolidinone for a diastereoselective electrophilic fluorination in the synthesis of a new fluorophosphotyrosyl mimetic. Treatment of **46** with NaHMDS followed by reaction with NFSI gave the (*S*)-α-fluoro derivative **47** without any evidence of the (*R*)-diastereomer (Scheme 17).[115]

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 **48** was obtained quantitatively with 64% de (Scheme 18).[116]

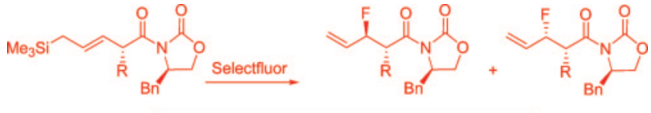
Scheme 20



Scheme 21



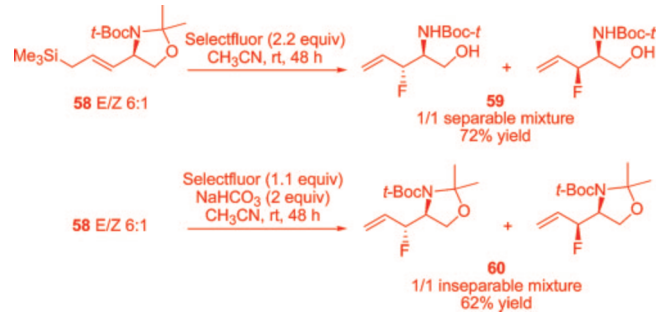
Scheme 22



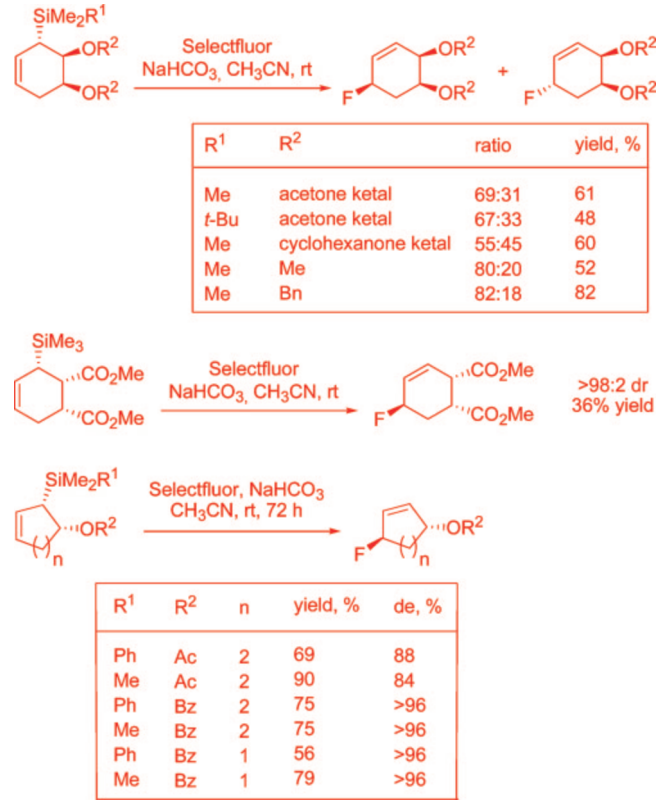
R	conditions	yield, %	anti/syn
Bn	acetone, $NaHCO_3$	100[a]	2:1
Bn	CH_3CN	95	1.2:1
Me	CH_3CN	82	1:1

[a] conversion

Scheme 23



Scheme 24



R^1	R^2	ratio	yield, %
Me	acetone ketal	69:31	61
t-Bu	acetone ketal	67:33	48
Me	cyclohexanone ketal	55:45	60
Me	Me	80:20	52
Me	Bn	82:18	82

R^1	R^2	n	yield, %	de, %
Ph	Ac	2	69	88
Me	Ac	2	90	84
Ph	Bz	2	75	>96
Me	Bz	2	75	>96
Ph	Bz	1	56	>96
Me	Bz	1	79	>96

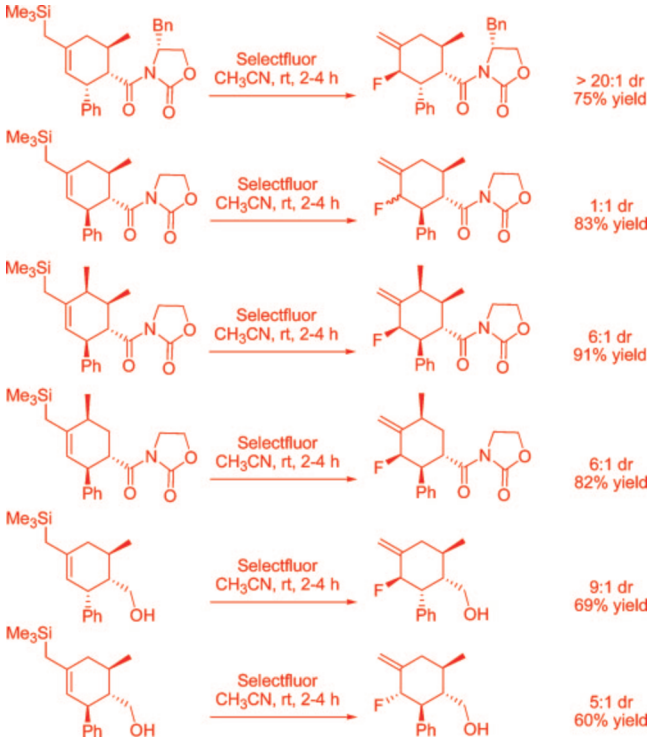
2.1.1.3. α-Fluoro Phosphonates. α-Monofluoroalkylphosphonates are more effective analogues of phosphate esters than alkyl phosphates because the CHF group is a better phosphate mimic.[117] Among the numerous entries to α-monofluoroalkylphosphonates, the direct electrophilic fluorination of alkylphosphonate 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.[118] 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 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 **49**, NaHMDS was preferred in the case of **51** (Table 3). Separation of the diastereomeric products **52** 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.[119]

α-Monofluorinated phosphonate mimics of phosphoserine and phosphothreonine were synthesized via electrophilic fluorination of Schollkopf'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 19).[120]

2.1.1.4. Miscellaneous Compounds. Shibata and co-workers reported the synthesis of fluorobrevianamide E (**55**) and fluorogypsetin (**56**) by a novel tandem electrophilic fluorination-cyclization. Despite an elegant synthetic route, the diastereoselectivity was poor for **55** and the sequence of reactions was nonselective for **56** (Scheme 20).[121]

Gouverneur and co-workers described several examples of diastereoselective as well as enantioselective (see section 2.1.2.4) electrophilic fluorodesilylation of allylsilanes. A substrate-controlled, first generation asymmetric synthesis, diastereoselective fluorodesilylation of the dienylsilane **57** provided a useful intermediate for the preparation of fluorinated vitamin D_3 analogues. A ratio anti/syn 3:1 was obtained, and products were separated by preparative TLC (Scheme 21).[122] *β*-Fluorinated *γ*,*δ*-unsaturated carboxylic acids and the corresponding alcohols were prepared by electrophilic diastereoselective fluorodesilylation carried out in the presence of Selectfluor. The selectivity did not exceed a ratio anti/syn 2:1; however, the products were separated by careful column chromatography (Scheme 22).[123] Allylsilane **58** synthesized from Garner's aldehyde reacted with an excess of Selectfluor to give product **59** as a mixture of two diastereomers, ratio 1:1, which can be separated by careful silica gel chromatography (Scheme 23). In the presence of $NaHCO_3$, product **60** was obtained but in an

Scheme 25



inseparable 1:1 ratio (Scheme 23).[124] Further, highly functionalized fluorinated carbocycles were prepared by means of electrophilic fluorodesilylation of allylsilanes, as demonstrated in the synthesis of intermediates toward fluorinated cyclitols (Scheme 24)[125,126] as well as in Scheme 25.[127]

Few reports described electrophilic fluorination of sulfoxides and sulfones. Some α-fluoro-β-keto sulfoxides[128–130] and sulfones[131,132] 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

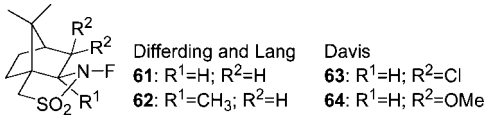
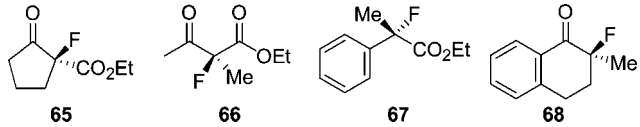


Figure 4. *N*-fluorocamphorsultams.

Table 4. Enantioselective Fluorination of Carbonyl Compounds Using *N*-Fluorocamphorsultams 61 and 62

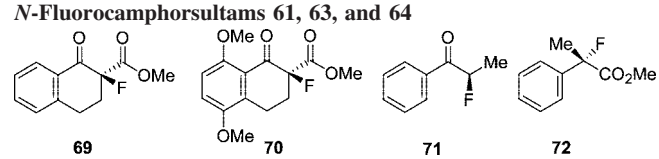


65 66 67 68

N–F reagent	conditions	product	yield, %	ee,[a] %
61	NaH, Et_2O, 0 °C to rt	**65**	63	70
62	KH, toluene/THF, 0 °C to rt	**65**	<5	<10
61	LiH, Et_2O, rt	**66**	31	<10
61	LDA, THF, −78 °C to rt	**67**	27	35
62	LDA, THF, −78 °C to rt	**67**	34	<10
61	LDA, THF, −78 °C to rt	**68**	<5	35

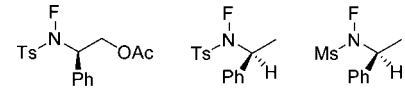
[a] The absolute stereochemistry was not determined.

Table 5. Enantioselective Fluorination of Enolates with *N*-Fluorocamphorsultams 61, 63, and 64



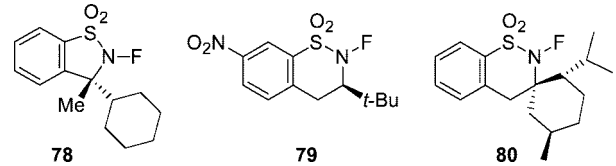
69 70 71 72

N–F reagent	conditions	product	yield, %	ee, %
61	NaH, Et_2O, 0 °C to rt	**65**	63	70
63	NaH, Et_2O, −78 °C to rt	**65**	59	34
64	NaH, Et_2O, −78 °C	**65**	57	<5
61	NaH, Et_2O, 0 °C to rt	**68**	28	25
63	NaHMDS, −78 °C	**68**	53	76
64	NaHMDS, −78 °C to rt	**68**	61	<5
61	NaHMDS, THF, −78 °C to rt	**69**	8	14
63	KHMDS, THF, −78 °C	**69**	90	41
61	NaH, Et_2O, 0 °C to rt	**70**	28	25
63	NaH, Et_2O, 0 °C to rt	**70**	95	46
64	NaHMDS, −78 °C	**70**	83	14
63	NaHMDS, THF, −78 °C to rt	**71**	41	0
63	NaHMDS, THF, −78 °C	**72**	54	33



73 74 75

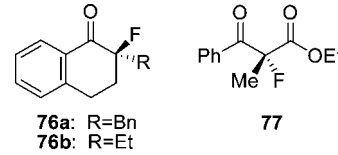
Figure 5. Chiral electrophilic fluorinating agents by Takeuchi and co-workers.



78 79 80

Figure 6. Chiral N−F sulfonamides by Takeuchi and co-workers.

Table 6. Enantioselective Fluorination with Reagents 73−75

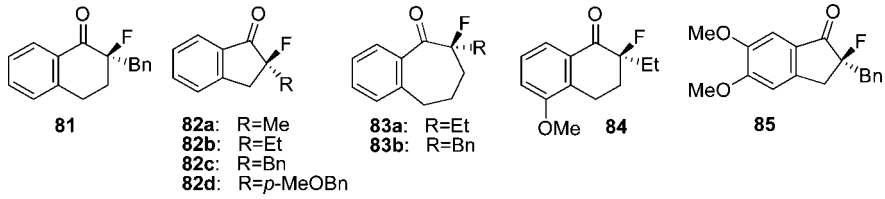


76a: R=Bn
76b: R=Et
77

N–F reagent	conditions	product	yield, %	ee, %
75	NaH, 0 °C	**65**	6	30
73	KHMDS, −40 to 0 °C	**68**	8	8
74	KHMDS, −40 to 0 °C	**68**	46	46
75	LDA, −40 °C to rt	**68**	11	20
74	LDA, −40 to −20 °C	**76a**	26	54
74	NaH, 0 °C	**77**	21	18

methods for enantioselective fluorination.[133–139] 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. From 2000, 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 has received considerable attention. More recently, enantioselective organocatalytic α-fluorinations of aldehydes were reported in very high enantioselectivities. Other approaches involve phase-transfer catalysis, fluorodesilylation of allylsilanes, and the use of chiral bases.

Table 7. Enantioselective Fluorination with Reagents 78−80



N−F reagent	conditions	product	yield, %	ee, %
78	LDA, THF, −50 °C	**68**	67	74
79	LiHMDS, THF, −50 °C	**69**	73	43
78	LDA, THF, −50 °C	**76a**	79	88
78	LDA, THF, −50 °C	**81**	70	72
78	LDA, THF, −50 °C	**82a**	54	54
78	LDA, THF, −50 °C	**82b**	73	20
80	LiHMDS, THF, −40 °C	**82c**	59	54
79	LiHMDS, THF, −50 °C	**82d**	70	69
78	LDA, THF, −50 °C	**83a**	48	43
78	LDA, THF, −50 °C	**83b**	39	18
79	LiHMDS, THF, −50 °C	**84**	59	60
79	LiHMDS, THF, −50 °C	**85**	56	60

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 **61** and **62** (Figure 4) as the first enantioselective fluorinating agents.[140] 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).

Further studies on *N*-fluorocamphorsultams **61**, **63**, and **64** (Figure 4) were carried out by Davis and co-workers on tertiary enolates, affording quaternary α-fluoro carbonyl compounds in modest yields and enantiomeric excesses (Table 5). The secondary enolate of propiophenone gave racemic **71** due to facile base-catalyzed epimerization. Both enantiomers of reagent **63** were synthesized to give access to the two optically enriched enantiomers of the fluorinated products.[141,142]

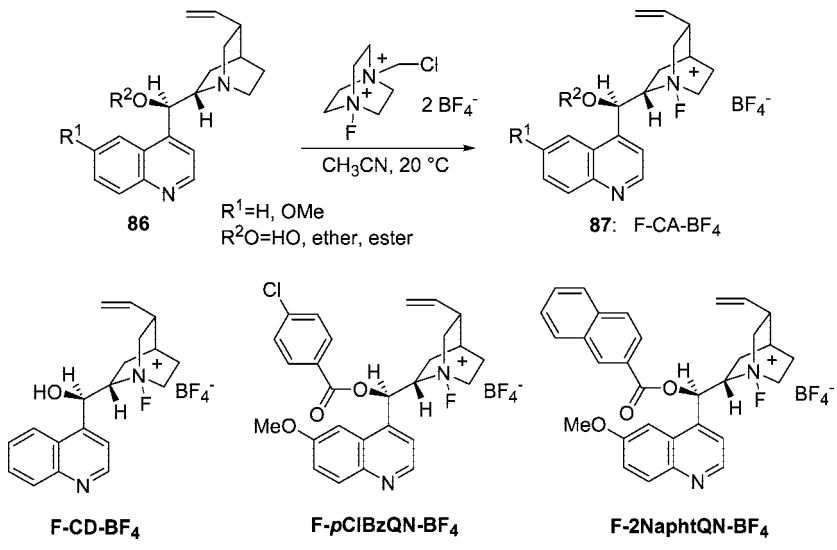
To develop novel chiral electrophilic fluorinating agents, Takeuchi and co-workers exploited phenylglycine and α-phenethylamine as chiral starting materials, which were fluorinated with either perchloryl fluoride ($FClO_3$) or diluted F_2 to produce reagents **73**−**75** (Figure 5). Four model substrates were fluorinated via in situ generation of metal enolates; the best results did not exceed 54% ee for 26% yield (Table 6).[143]

Subsequently, Takeuchi's group embarked on the design of three new chiral N−F sulfonamides (**78**,[144] **79**,[145] and **80**;[146] 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 **78** led to 2-fluoro-2-benzyl-1-tetralone (**76a**) in an excellent 88% ee and with 79% isolated yield.[144] Selected results with reagents **78**−**80** 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 naturally

Scheme 26



occurring cinchona alkaloids. Simultaneously and independently, we[147,148] and Shibata's group[149,150] reported a substantially similar approach to prepare *N*-fluoroammonium salts of cinchona alkaloids. A one-step transfer fluorination[151] on cinchona alkaloids (CAs) **86** with the aid of Selectfluor gave the fluorinating reagents (F-CA-BF_4) **87** (Scheme 26).

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.[152] 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.[153] 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.

In 2007, Togni and co-workers demonstrated that several α-nitro esters can be α-fluorinated with either isolated $[N-F]^+$ reagents or a combination Selectfluor/cinchona alkaloid under basic conditions. The enantioselectivities are modest, up to 40% ee (Scheme 27).[154]

Attempts to render catalytic in cinchona alkaloid the electrophilic fluorination led to moderate enantioselectivities; up to 54% ee. Because the fluorination of silyl enol ethers by Selectfluor is faster than the transfluorination step, consequently leading to racemic fluorinated products, Shibata and co-workers decided to use acyl enol ethers **102** that are less reactive than silyl enol ethers and not reactive enough toward Selectfluor. With these substrates, enantioselective fluorination occurred in the presence of a catalytic amount of cinchona alkaloid and 2 equiv of sodium acetate at room temperature for 2−4 days (Scheme 28).[155] In addition, a β-keto ester can also be fluorinated by a bulky analogue of NFSI, *N*-fluoro-(3,5-di*tert*-butyl-4-methoxy)benzenesulfonimide (NFBSI), in the presence of 10 mol % of $(DHQD)_2PYR$ and cesium hydroxide in 56% yield with 87% ee (Scheme 29).[156,355]

We applied our successful enantioselective fluorination approach to the synthesis of α-fluoro-α-phenylglycine derivatives. A study of the relationship between structure and

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

Fluorination of metal enolates[147]

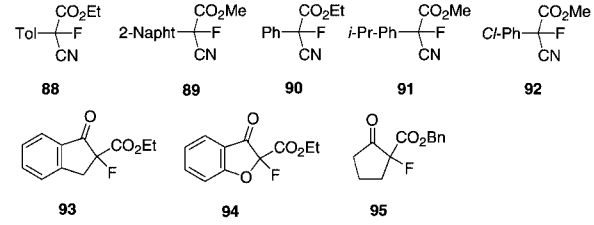
N-F reagent	conditions	product	yield, %	ee, %
F-CD-BF_4		**65**	98	40
F-CD-BF_4	NaH (2 equiv)	**68**	98	50
F-CD-BF_4	THF/CH_3CN	**76a**	96	42
F-*p*ClBzQN-BF_4	-40 °C to rt	**82a**	98	33
F-2NaphtQN-BF_4		**82c**	90	50

Fluorination of trimethylsilyl enol ethers[147,150]

N-F reagent	conditions[a]	product	yield, %	ee, %
*p*ClBzDHQN / Selectfluor	A	**68**	94	40
F-CD-BF_4	B	**68**	93	61
*p*ClBzDHQN / Selectfluor	A	**76a**	95	71
F-*p*ClBzQN-BF_4	B	**76a**	67	66
*p*ClBzDHQN / Selectfluor	A	**76b**	71	67
*p*ClBzDHQN / Selectfluor	A	**82a**	93	53
F-*p*ClBzQN-BF_4	B	**82a**	90	64
*p*ClBzDHQN / Selectfluor	A	**82b**	100	73
F-*p*ClBzQN-BF_4	B	**82b**	97	82
*p*ClBzDHQN / Selectfluor	A	**82c**	86	91
F-2NaphtQN-BF_4	B	**82c**	98	84

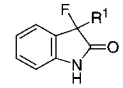
[a] Conditions A : alkaloid (1.2 equiv)/Selectfluor, CH_3CN, MS 3Å, 1h, rt, then addition of the silyl enol ether at -20 °C, overnight.
Conditions B : -40 °C, CH_3CN, 20 h

Fluorination of β-ketoesters and β-cyanoesters[150]



N-F reagent	conditions	product	yield, %	ee, %
DHQD / Selectfluor		**69**	79	59
AcDHQD / Selectfluor	alkaloid (2 equiv)	**88**	80	87
AcDHQD / Selectfluor	Selectfluor (1.5 equiv)	**89**	87	76
AcDHQD / Selectfluor	CH_3CN, MS 3Å, 1h, rt,	**90**	81	83
AcDHQD / Selectfluor	then addition of	**91**	82	87
AcDHQD / Selectfluor	the substrate	**92**	56	68
AcDHQD / Selectfluor	CH_2Cl_2, -80 °C, 2 h	**93**	89	78
AcDHQD / Selectfluor		**94**	92	80
DHQN / Selectfluor		**95**	55	43

Fluorination of oxindoles[150]



96: R^1=Bn
97: R^1=*p*-MeOBn
98: R^1=Me
99: R^1=Et
100: R^1=*i*-Pr
101: R^1=CO_2Et

N-F reagent	conditions	product	yield, %	ee, %
$(DHQ)_2AQN$ / Selectfluor	alkaloid (1.5 equiv)	**96**	100	78
$(DHQD)_2PYR$ / Selectfluor	Selectfluor (1.5 equiv)	**97**	79	82
$(DHQD)_2PYR$ / Selectfluor	CH_3CN, 1h, rt,	**98**	94	67
$(DHQD)_2PYR$ / Selectfluor	then addition of	**99**	79	76
$(DHQ)_2PHAL$ / Selectfluor	the substrate	**100**	12	40
$(DHQD)_2PYR$ / Selectfluor	0 °C, 1-2 days	**101**	93	37

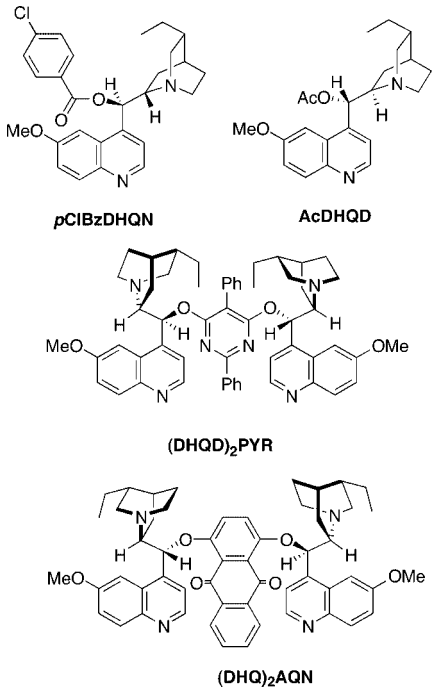


Figure 7.

Scheme 27

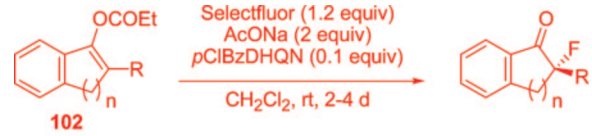
R	method	[N–F]$^+$ reagent[a]	yield, %	ee, %
Me	A	F-CD-BF_4[b]	59	25
Me	A	F-QN-BF_4	65	40
Me	A	F-AcQN-BF_4	68	40
i-Pr	A	F-AcCD-BF_4	78	23
Ph	A	F-AcQN-BF_4	8	27
Ph	B	F-AcCD-BF_4	85[c]	31
Bn	A	F-AcQN-BF_4	78	24
Bn	B	F-AcQN-BF_4	84[c]	16

[a] in situ prepared reagents
[b] isolated reagent
[c] reaction run at –40°C

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 (**104b**) with *O*-(*p*-methoxybenzoyl)-*N*-fluoroquininium tetrafluoroborate (F-pMeOBzQN-BF_4) (Scheme 30).[157]

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 31). With continuing interest in the development of fluorinated bioactive compounds, we further investigated

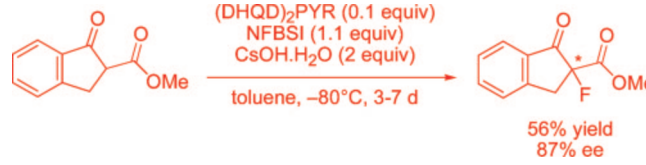
Scheme 28



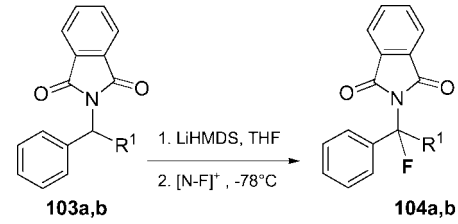
R	n	yield, %	ee, %
Bn	1	72	53 (*R*)
Bn	1	65[a]	54 (*R*)
Me	1	88	37 (*R*)
Et	1	84	43 (*R*)
$pMeOC_6H_4CH_2$	1	77	51
$pClC_6H_4CH_2$	1	69	52
Me	2	65	3
Me	2	83[b]	45 (*R*)
Bn	2	17	24 (*S*)

[a] Acetyl enol ether and AcONa.3H_2O were used
[b] $(DHQ)_2AQN$ (0.1 equiv) was used

Scheme 29

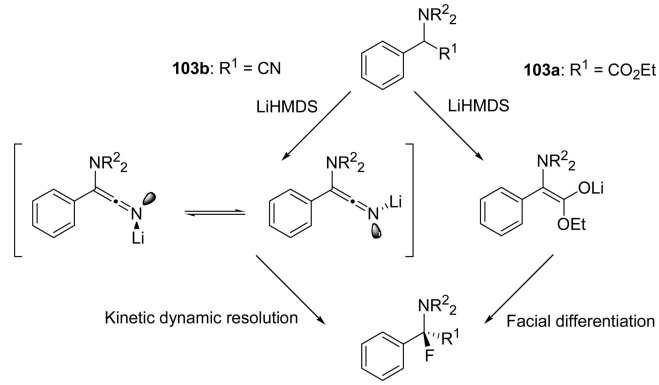


Scheme 30



104a: $R^1 = CO_2Et$
79% yield, 76% ee (with F-*p*ClBzDHQN-BF_4)
104b: $R^1 = CN$
56% yield, 94% ee (with F-*p*MeOBzQN-BF_4)

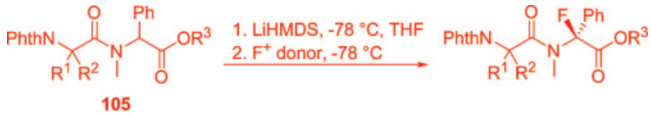
Scheme 31



the asymmetric fluorination of dipeptides **105** by enantioselective fluorination with the aid of chiral [N−F]$^+$ reagents (Scheme 32).[78]

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, **107**), a potent opener of maxi-K channels, which is evaluated in a worldwide phase III clinical trial for treatment of acute ischemic stroke. Oxindole **106**, prepared in five steps from

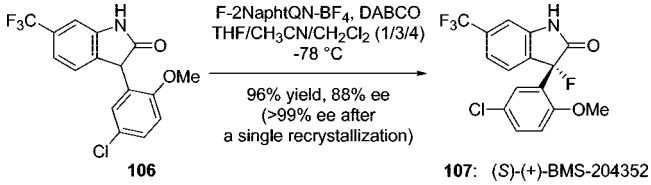
Scheme 32



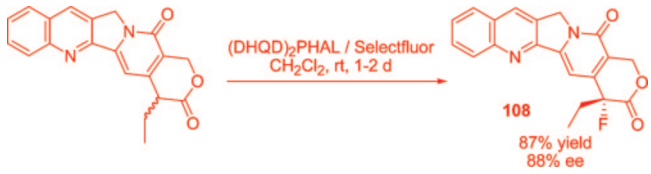
105

R^1	R^2	R^3	fluorinating reagent	conv, % (yield)	er
$-(CH_2)_4-$		Me	F-*p*ClBzQN-BF_4	>98	67:33
$-(CH_2)_4-$		Me	F-*p*ClBzQD-BF_4	>98	36:64
$-(CH_2)_4-$		Me	F-*p*ClBzCN-BF_4	95	47:53
$-(CH_2)_4-$		Me	F-*p*ClBzCD-BF_4	95	58:42
$-(CH_2)_4-$		Bn	F-*p*ClBzQN-BF_4	>98 (92)	73:27
Me	Me	Me	F-*p*ClBzQN-BF_4	>98	66:34
Me	Me	Bn	F-*p*ClBzQN-BF_4	95 (88)	72:28

Scheme 33



Scheme 34



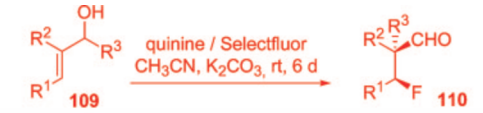
3-trifluoromethylaniline, reacted with the *N*-fluoroammonium salt F-2NaphtQN-BF_4 in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) as base, producing the target product (*S*)-BMS-204352 in excellent yield and high enantioselectivity, a single recrystallization allowing enantiomerically pure **107** to be obtained (Scheme 33).[158,159] Shibata's group also reported the synthesis of BMS-204352 in a slightly lower ee of 84% using the combination $(DHQ)_2$AQN/Selectfluor.[160]

By means of in situ generated *N*-fluoroammonium salts of cinchona alkaloids, Shibata and co-workers synthesized both enantiomers of 20-deoxy-20-fluorocamptothecin **108** as an isosteric analogue of camptothecin with 88% ee for the *R* enantiomer (Scheme 34) and with 81% ee for the *S* enantiomer using the pseudoenantiomeric bis-cinchona alkaloid $(DHQ)_2$PHAL.[161]

The quinine/Selectfluor combination was further developed by Tu and co-workers to induce asymmetric semipinacol rearrangement of allylic alcohols **109**, leading to an enantioselective approach to α-quaternary β-fluoro aldehydes **110** with up to 82% ee (Scheme 35).[162]

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-hexyl-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

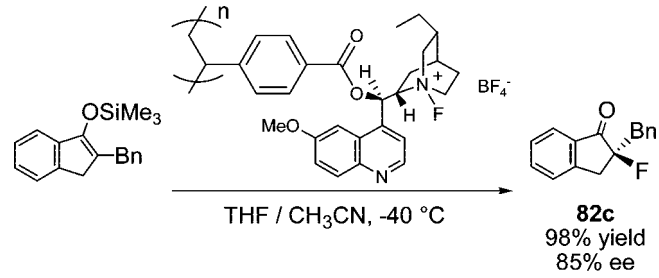
Scheme 35



109 110

R^1	R^2	R^3	yield, %	ee, %
$-(CH_2)_4-$		3,4-$(OCH_2O)C_6H_3$	39	74
$-(CH_2)_4-$		3,4-$(MeO)_2C_6H_3$	42	73
$-(CH_2)_4-$		2-$MeOC_6H_4$	50	71
$-(CH_2)_4-$		3-$MeOC_6H_4$	48	54
$-(CH_2)_4-$		4-$MeOC_6H_4$	41	76
$-(CH_2)_4-$		4-MeC_6H_4	35	70
$-(CH_2)_4-$		C_6H_5	33	67
$-(CH_2)_4-$		1-Naphthyl	45	82
$-(CH_2)_5-$		3,4-$(OCH_2O)C_6H_3$	34	65
n-Pr	*n*-Bu	3,4-$(OCH_2O)C_6H_3$	37	61

Scheme 36



preference to diethyl ether, allowing IL and cinchona alkaloid recycling without significant alteration in the enantioselectivity.[163]

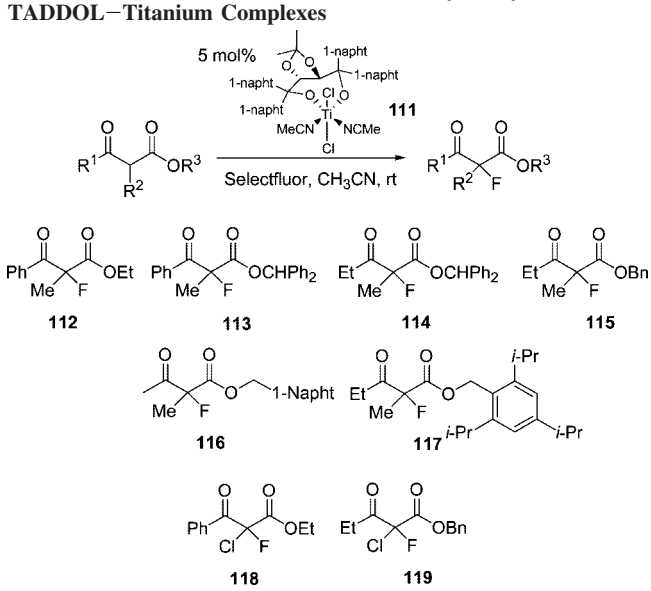
The development of recoverable and recyclable reagents supported on polymeric matrixes is a valuable approach. We prepared a collection of new polystyrene-bound cinchona alkaloids[164] for the design of unprecedented enantioselective electrophilic fluorinating agents. For example, soluble polymeric cinchona 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 36). Poly[O_9-(4-vinylbenzoate)-DHQN] was recycled three times without loss of stereochemical performance.[165]

For a similar purpose, Shibata and co-workers developed a fluorous-BzDHQN as a fluorous-phase soluble cinchona alkaloid for performing reactions in biphasic systems.[156]

2.1.2.2. Transition-Metal Catalysts. Among the various ways to produce enantiopure compounds, metal-mediated catalytic reactions provide one of the most powerful synthetic approaches. Since the early 1980s, intense research effort has greatly expanded the scope of catalytic asymmetric reactions that can be performed in highly enantioselective fashion. With the dawn of the new century, we have been fortunate enough to witness the development of metal−catalytic asymmetric fluorination.[135,156,166–169]

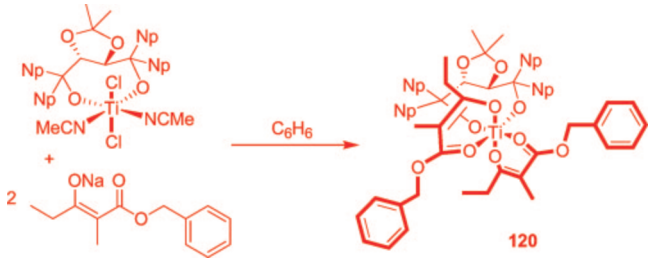
Simultaneously with the work on cinchona alkaloid *N*-fluoroammonium salts, the first transition-metal-catalyzed fluorination has been achieved by Togni and co-workers. In this reaction, it was anticipated that catalytic transition-metal complexes would accelerate enolization of β-keto esters. The fluorination of various acyclic β-keto esters, with Selectfluor in the presence of 5 mol % of [$TiCl_2$((*R*,*R*)-TADDOLato)]

Table 9. Enantioselective Fluorination Catalyzed by TADDOL−Titanium Complexes



product	yield, %	ee, %	product	yield, %	ee, %
112	≥80	62	**116**	≥80	68
113	≥80	82	**117**	89	90
114	≥80	81	**118**	53	33
115	82	71	**119**	57	60

Scheme 37



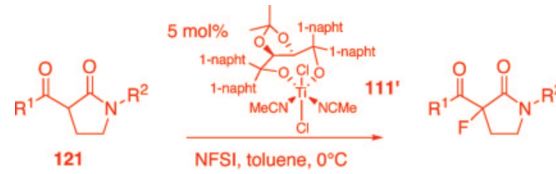
catalyst **111**, was reported to give high yields (≥80%) and up to 90% ee (Table 9).[102,170] In this approach, computational and experimental studies strongly supported a single-electron-transfer (SET) mechanism as a pathway for the fluorination.[171]Interestingly, compounds **118** and **119** were synthesized in a one-pot enantioselective heterodihalogenation of the β-keto esters with *N*-chlorosuccinimide and Selectfluor by sequential addition.[103]

The complex **120** of [$TiCl_2$(1-Np-TADDOLato)] catalyst with β-keto ester was prepared and structurally characterized by NMR and X-ray crystallography (Scheme 37).[172] It was found that there are two main diastereoisomeric forms in solution and, for the major C_2-symmetric isomer, the *face-on* naphthyl group of the chiral ligand shields the *si* side of the coordinated enolate. Therefore, electrophilic attack of the fluorinating agent can only occur at the *re* side of the substrate.

In addition to β-keto esters, Togni and co-workers employed α-acyl-γ-lactams **121** as substrates. The catalytic asymmetric fluorination was performed with NFSI in toluene at 0 °C, with 5 mol % of the Ti(TADDOLato) catalyst. All substrates were successfully fluorinated in good yields with scarce to good enantioselectivities (Scheme 38).[172]

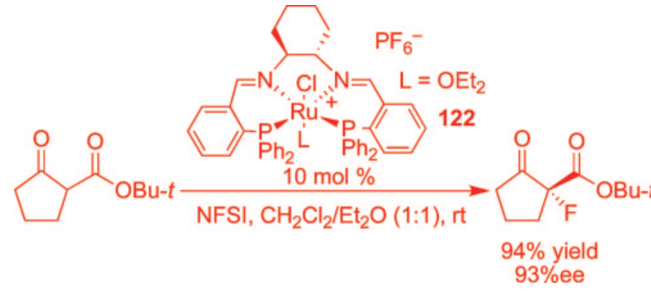
Togni and co-workers also demonstrated that relatively soft late transition-metal Lewis acids are also suitable catalysts for electrophilic fluorination. Indeed, cationic chiral

Scheme 38



R^1	R^2	yield, %	ee, %
Me	Bn	75	26
Ph	Bn	78	15
Ph	Me	75	6
Me	Ph	75	87 (*R*)
Cy	Me	60	50
Me	Cy	–	46
t-Bu	Me	40	20

Scheme 39



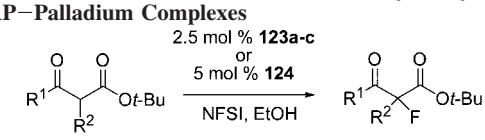
ruthenium(II)−Salen complex **122** is a powerful catalyst for the enantioselective fluorination of β-keto esters (Scheme 39).[135,173]

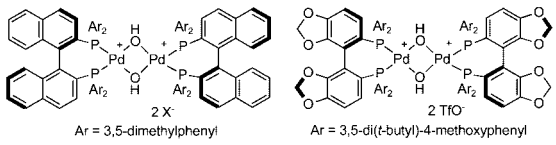
Following Togni's pioneering work, Sodeoka and co-workers reported an efficient enantioselective fluorination of various β-keto esters using chiral BINAP−palladium complexes.[174,175] The fluorination was carried out with NFSI in ethanol in the presence of 2.5 mol % catalyst **123a,c** or **124**, leading 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 **123b** was reused 10 times with a level of enantioselectivity comparable to those obtained in the usual organic solvents.[176]

In 2005, the same research group reported a highly efficient catalytic enantioselective fluorination of oxindoles **131** by using catalyst **123b**.[177] The reaction proceeded well without exclusion of air and moisture to give fluorinated oxindoles **132** in good yields with high to excellent enantioselectivities (79−96% ee) (Table 11). This catalytic asymmetric reaction was applied to the synthesis of BMS-204352 (MaxiPost, **107**) in 90% yield with 71% ee. Deprotection and recrystallization furnished optically pure MaxiPost (>99% ee). It should be noted that the optically active α-fluoro-α-arylacetate derivatives were readily obtained by treatment of the fluorinated oxindoles with MeONa in MeOH. In addition, tandem asymmetric fluorination−methanolysis of an *N*-Boc-protected oxindole afforded a chiral monofluorinated aryl acetate in 53% yield with 93% ee (Scheme 40).

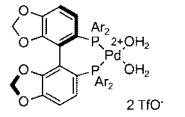
Recently, Sodeoka and co-workers extended their asymmetric catalytic system to *tert*-butoxycarbonyl lactones and lactams. Reactions with lactones proceeded smoothly in an

Table 10. Enantioselective Fluorination Catalyzed by BINAP−Palladium Complexes

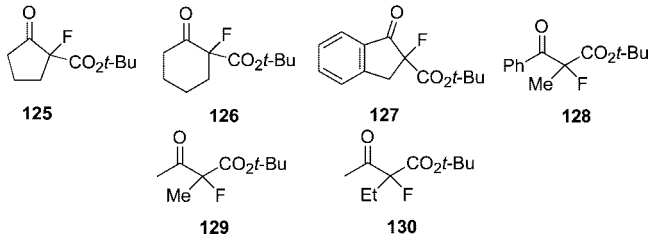




123a: X=BF_4^-
123b: X=OTf
123c



124



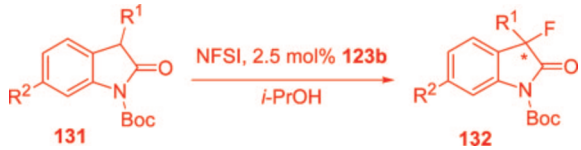
125 **126** **127** **128**

129 **130**

catalyst	temp, °C	time, h	product	yield, %	ee, %
124[a]	0	72	**125**	89	90
123c	20	18	**125**	90	92
123a	−10	20	**126**	91	94
123b	−20	36	**127**	85	83
123a	20	40	**128**	92	91
123c	20	72	**129**	49	91
123b	20	42	**130**	88	87

[a] THF was used as the solvent.

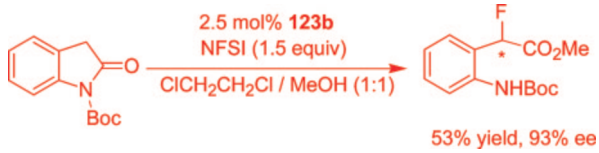
Table 11. Catalytic Enantioselective Fluorination of Oxindoles



131 **132**

R^1	R^2	temp	time, h	yield, %	ee, %
Ph	H	0 °C	18	96	90
4-MeC_6H_4	H	0 °C	18	92	88
4-FC_6H_4	H	rt	3	94	84
2-$MeOC_6H_4$	CF_3	rt	3	80	75
Me	H	0 °C	18	85	96
Et	H	rt	10	85	92
$CH_2C(O)Me$	H	rt	2	85	86
Bn	H	rt	4	72	80
i-Bu	H	rt	2	85	75

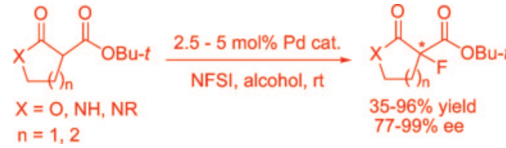
Scheme 40



53% yield, 93% ee

alcoholic solvent with 2.5 mol % catalyst **123c**. In the case of the less acidic lactam substrates, concurrent use of the Pd complex and 2,6-lutidine as a cocatalyst was effective. Under the reaction conditions, the fluorinated lactones and

Scheme 41



lactams were obtained in good yields with excellent enantioselectivities (94−99% ee) (Scheme 41).[178]

Simultaneously and independently, Sodeoka, Kim, and Jørgensen's groups developed the enantioselective electrophilic fluorination of β-keto phosphonates using their catalytic systems (Scheme 42). The group of Sodeoka employed chiral palladium complexes **123b,c, 124, 133,** and **134** in the catalytic fluorination reaction of cyclic and acyclic β-keto phosphonates with excellent enantiomeric excesses (up to 98% ee).[179,180] Kim and-co-workers exploited the chiral palladium complexes **135** to get α-fluoro-β-keto phosphonates in the range 87−97% ee.[181] Jørgensen and co-workers developed a combination of the chiral tridentate ligand **136** [(*R*,*R*)-Ph-DBFOX] and $Zn(ClO_4)_2$ or $Zn(SbF_6)_2$ to afford α-fluoro-β-keto phosphonates in moderate to good yields with up to 91% ee.[182]

Kim and co-workers also reported the catalytic enantiomeric fluorination of α-cyano acetates **137** catalyzed by the chiral palladium complex **135b** (X = PF_6), leading to α-cyano-α-fluoro acetates **138** with excellent enantiomeric excesses (Table 12).[183]

Concerning the synthesis of α-fluoro-α-cyano-α-aryl phosphonates, the groups of Sodeoka and Kim, again independently, described a similar catalytic system involving chiral Pd(II) complexes in the presence of an organic base such as pyridine derivatives. The Pd(II) complexes activate the substrates through coordination of the nitrile group, and pyridine derivatives abstract an acidic proton, thereby affording the desired fluorinated products in good yields with good to high enantioselectivities (Scheme 43).[184,185] Unfortunately, the reaction was not applicable to α-alkyl-α-cyano phosphonates.

Inspired by the pioneering findings, in 2004 we evaluated nitrogen-containing ligands, which are complementary to the oxygen- and phosphorus-containing ligands investigated, respectively, by Togni and Sodeoka. We first 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 (NFPY-OTf) 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 13).[186] 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) (Scheme 44).[187]

One of us (Prof. Ma's group) exploited an interesting catalytic stereoselective tandem transformation via Nazarov cyclization−electrophilic fluorination. This sequence is efficiently promoted by a Cu(II) complex to afford fluorine-containing 1-indanone derivatives with two new stereocenters with high diastereoselectivity (*trans*/*cis* up to 49/1). Further attempts to extend this protocol to a catalytic enantioselective

Scheme 42

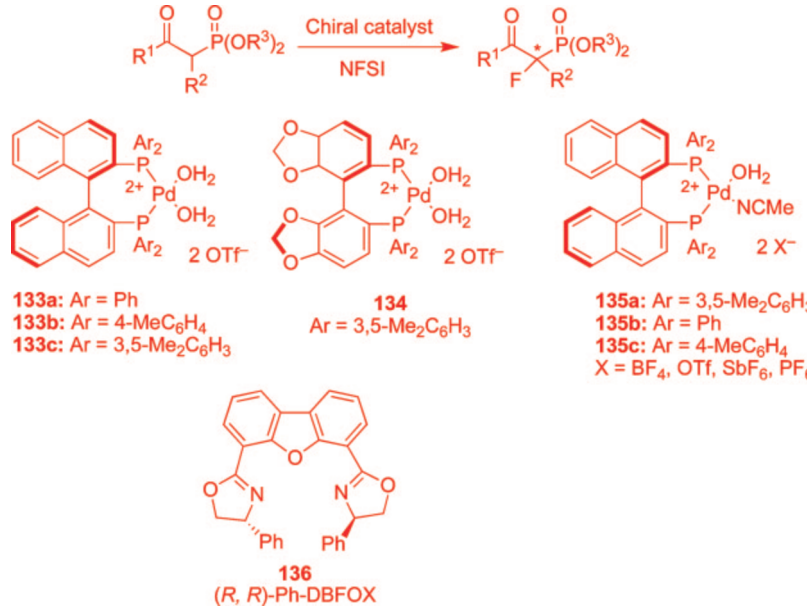
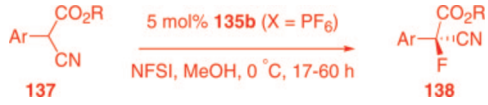


Table 12. Catalytic Enantioselective Fluorination of α-Cyano Acetates



Ar	R	yield, %	ee, %
Ph	Me	56	67
Ph	Et	79	79
Ph	Bn	75	81
Ph	*t*-Bu	83	99
4-ClC$_6$H$_4$	*t*-Bu	94	85
4-MeC$_6$H$_4$	*t*-Bu	85	93
4-MeOC$_6$H$_4$	*t*-Bu	85	99
2-naphthyl	*t*-Bu	88	93
9-anthryl	*t*-Bu	42[a]	91

[a] Reaction carried out at rt in THF−MeOH (1:1).

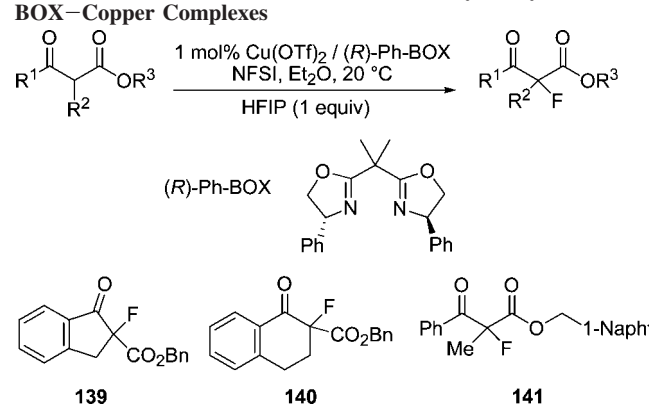
Scheme 43

	Sodeoka's catalytic system 2.5 mol% **123b** (Ar = Ph) 2,6-lutidine (1 equiv), EtOH, –20 °C		Kim's catalytic system 5 mol% **135a** (X = OTf), EtOH, rt 2,6-*t*-Bu$_2$-4-MePyridine (2 equiv)	
Ar	yield, %	ee, %	yield, %	ee, %
Ph	95	66	90	85
4-MeC$_6$H$_4$	96	44	96	80
4-ClC$_6$H$_4$	95	24	98	91
1-Naphthyl	92	78	73	83

transformation by using Cu(OTf)$_2$/(*R*)-Ph-bis(oxazoline) gave the tandem products in good yields with moderate to high enantioselectivities (up to 95.5% ee) (Scheme 45).[188] This catalytic enantioselective tandem transformation can be used for synthesis of organofluorine compounds with adjacent carbon- and fluorine-substituted tertiary and quaternary stereocenters.

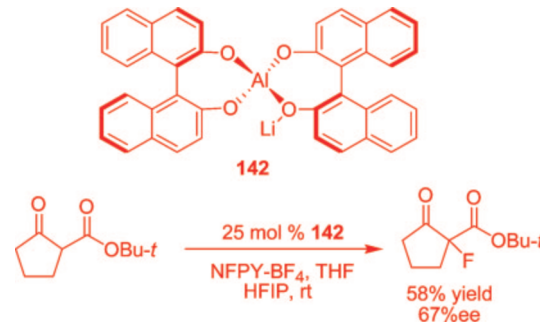
Just after the publication of our work on copper(II) triflate−bis(oxazoline)-catalyzed enantioselective electrophilic fluorination of β-keto esters, Shibata and co-workers

Table 13. Enantioselective Fluorination Catalyzed by BOX−Copper Complexes



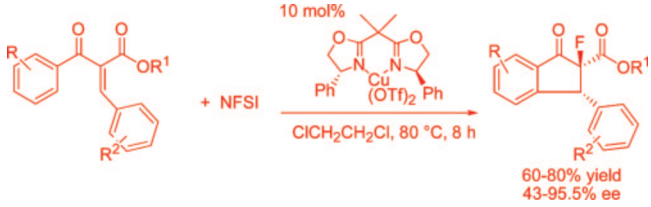
product	time, h	yield, %	ee, %
113	48	72	52
125	0.5	96	85
126	3	92	63
128	96	56	43
139	0.5	94	35
140	0.5	92	38
141	2	88	40

Scheme 44

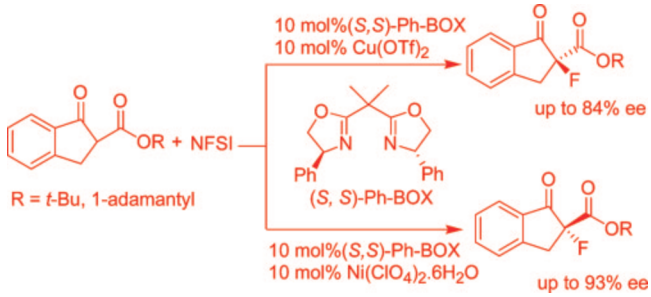


also reported the use of enantiopure bis(oxazoline)−Cu(II) and bis(oxazoline)−Ni(II) complexes as catalysts in the enantioselective electrophilic fluorination of β-keto esters. The main finding in NFSI-mediated fluorination is that the (*S*,*S*)-Ph-BOX-Ni(II) complex provides the fluorinated prod-

Scheme 45



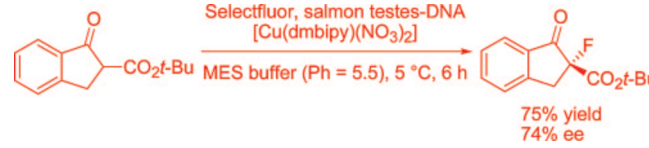
Scheme 46



uct with opposite configuration to that obtained with the (*S*,*S*)-Ph-BOX-Cu(II) complex (Scheme 46). The origin of the reversed sense of stereoinduction could be a consequence of a change in the metal-center geometry from distorted square-planar (Cu complex) to square-pyramidal (Ni complex) in the reactive intermediates.[104]

Shibata and co-workers demonstrated that a combination of the chiral tridentate ligand Ph-DBFOX **136** and $Ni(ClO_4)_2 \cdot 6H_2O$ catalyzed the enantioselective electrophilic fluorination of cyclic carbonyl compounds that are capable

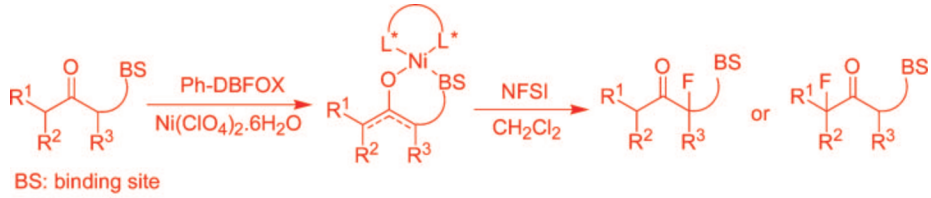
Scheme 47

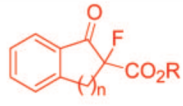
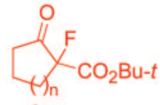
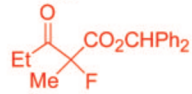
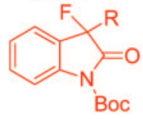
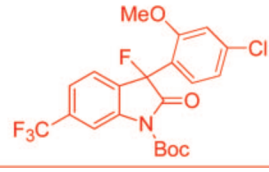


of two-point binding. The fluorination reactions of a series of β-keto esters and oxindoles with Boc-protecting groups were carried out to afford the desired products in high yields with high to excellent enantioselectivities (Table 14).[105] One of the fluorinated oxindoles was converted into Maxipost by cleavage of the Boc group. This example provides another catalytic enantioselective preparation of Maxipost. It was noted that a positive nonlinear effect of chiral amplification was observed in the fluorination of β-keto esters.[156]

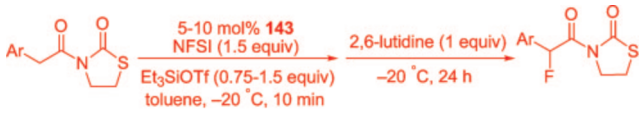
It is well-known that biocatalyst-mediated fluorination is extremely rare. O'Hagan and co-workers have isolated a bacterial fluorinating enzymes' "fluorinase" from *Streptomyces cattleya* which catalyzes the fluorination reaction of *S*-adenosyl-L-methonine to 5′-fluoro-5′-deoxyadenosine. However, the corresponding process does not involve any stereoselective reaction.[189,190] Recently, Shibata and Toru reported one example of DNA-mediated enantioselective electrophilic fluorination. A catalytic system comprised of DNA, an achiral ligand, 4,4′-dimethyl-2,2′-bipyridine (dmbipy), and a Cu(II) salt displays ability in biocatalysis in that it forms a chiral C−F bond at the quaternary carbon center in β-keto esters. Enantioselectivities with ee values up to 74% were achieved for the fluorine transfer from Selectfluor to substrates in water (Scheme 47).[191]

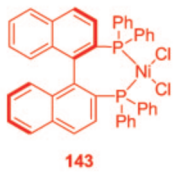
Table 14. Enantioselective Catalytic Fluorination of Carbonyl Compounds Capable of Two-Point Binding



Product		yield, %	ee, %
	R = *t*-Bu, n = 1 R = Ad, n = 1 R = L-Men, n = 1 R = Ad, n = 2	76 71 66 88	99 99 99 95
	n = 1 n = 2	84 86	93 99
		75	83
	R = Me R = Ph	73 72	93 96
		71	93 (*S*)

Scheme 48



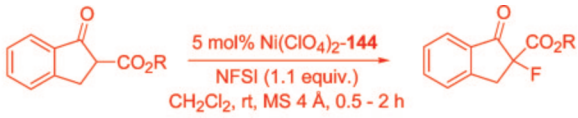


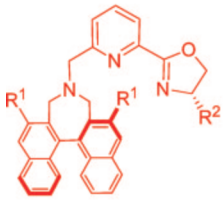
143

Ar	yield, %	ee, %
Ph	99	88
Ph[a]	95	87
4-FC_6H_4	90	83
4-$MeOC_6H_4$	92	81
3-$MeOC_6H_4$	95	82
2-$MeOC_6H_4$	87	78
2-Naphthyl	99	83
1-Naphthyl	94	87

[a] Oxazolidinone substrate was used.

Scheme 49





144a: R^1 = H, R^2 = *i*-Pr
144b: R^1 = H, R^2 = Bn
144c: R^1 = H, R^2 = Ph
144d: R^1 = H, R^2 = *t*-Bu
144e: R^1 = Ph, R^2 = Ph

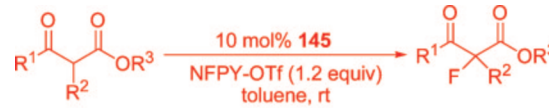
R	ligand	yield, %	ee, %
t-Bu	**144a**	99	94
t-Bu	**144b**	99	88
t-Bu	**144c**	98	92
t-Bu	**144d**	99	89
t-Bu	**144e**	68	20
Bn	**144c**	99	86

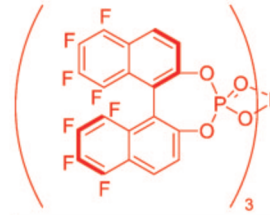
On Sodeoka's group side, they presented another remarkable advance in the catalytic enantioselective fluorination of acyclic (2-aryl acetyl)thia- and oxazolidin-2-ones with the unique combination system of Ni(II)-BINAP/R_3SiOTf/2,6-ludidine (Scheme 48).[192] In this reaction, a substoichiometric amount of Et_3SiOTf and a stoichiometric amount of the base were required for a high chemical yield. Therefore, cooperative activation by a cationic metal complex and an organic base could promote the formation of a metal enolate from the two-point binding substrates.[193] The monofluorinated compounds were formed in excellent yield with high enantioselectivity (up to 88% ee). Unfortunately, the reaction with (2-alkyl acetyl)thiazolidin-2-ones failed to provide good results.

Iwasa and co-workers designed and synthesized the optically active *N*,*N*,*N*-tridentate ligand **144**, having both axial chirality on the binaphthyl backbone and carbon-centered chirality on the oxazoline ring. The Ni(II) complex of this ligand catalyzed enantioselective direct fluorination of β-keto esters in excellent yields and enantioselectivities (Scheme 49). It is interesting to note that the use of ligands that have the opposite absolute configuration on the axial chiral binaphthyl backbone showed poor enantioselectivity.[106]

Interestingly, Inanaga and co-workers described a series of chiral rare earth metal complexes **145** (M = Sc, La, Gd, Yb, In) bearing polyfluorinated binaphthyl phosphate ligand F_8BNP (5,5′,6,6′,7,7′,8,8′-octafluoro-1,1′-binaphthyl-2,2′-diyl phosphate) as catalysts for the enantioselective electrophilic fluorination reaction of β-keto esters. The use of Sc[(*R*)-$F_8BNP]_3$ catalyst in combination with NFPY-OTf as a fluorinating agent was found to give the desired fluorinated products in high yields with good enantioselectivities under mild conditions (Scheme 50).[194]

Scheme 50

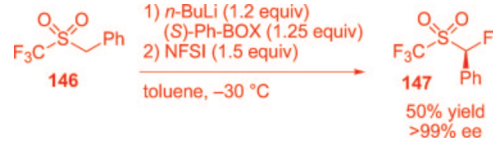




145 M = Sc : Sc[(*R*)-$F_8BNP]_3$

R^1	R^2	R^3	yield, %	ee, %
$-(CH_2)_3-$		*t*-Bu	94	84
$-(CH_2)_3-$		Me	97	84
$-(CH_2)_3-$		Et	87	76
$-(CH_2)_3-$		*i*-Pr	90	74
$-(CH_2)_3-$		Bn	87	47
$-(CH_2)_4-$		Me	77	81
Ph	Me	Me	63	75
Ph	Me	*t*-Bu	16	78

Scheme 51



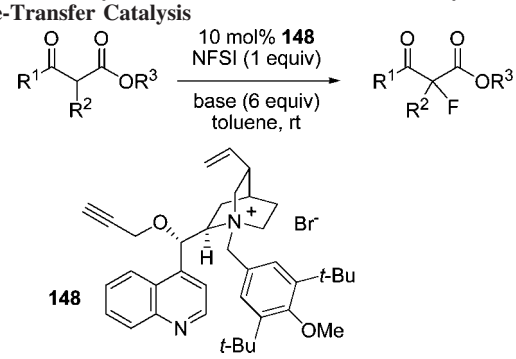
Finally, the preparation of α-fluorobenzyl sulfones has been investigated by Nakamura, Toru, and co-workers in order to obtain α-fluorinated sulfur compounds. Fluorination of **146** with NFSI in the presence of (*S*)-Ph-BOX afforded (*R*)-**147** exclusively in 50% yield (Scheme 51).[195]

2.1.2.3. Organocatalysis. Organocatalysis is an alternative approach that can induce high to very high enantioselectivities. The first example of organocatalytic enantioselective electrophilic fluorination under phase-transfer conditions with the aid of quaternary ammonium salts derived from cinchona alkaloids was reported by Kim and Park.[196] 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 15). It is claimed in this paper that the reactions were completed 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, **148** provided the highest enantioselectivity; surprisingly, diastereomeric cinchonidine as well as quinine and quinidine were not discussed.

In 2004, the same group widened the study to α-cyano esters, which give slightly higher enantioselectivities; up to 76% (Scheme 52).[197]

Due to particular experimental conditions, we decided to look for standard phase-transfer catalysis conditions that allow simultaneous introduction of all the reaction partners. We found that the fluorination of indanone 2-methylcar-

Table 15. Catalytic Enantioselective Fluorination by Phase-Transfer Catalysis



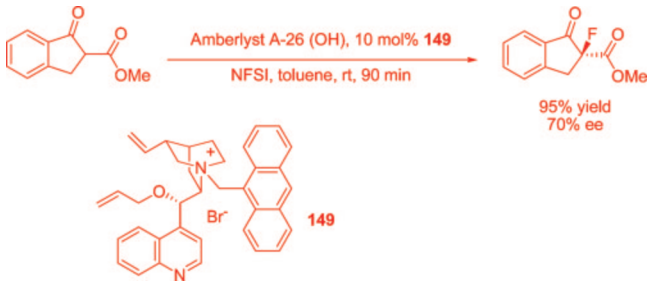
R^1	R^2	R^3	base	yield, %	ee, %
indanone		Me	K_2CO_3	92	69
indanone		Et	Cs_2CO_3	91	63
tetralone		Me	Cs_2CO_3	88	48
tetralone		Et	CsOH	78	52
Ph	Me	Et	NaH	89	40[a]

[a] *O*-(9)-Allylcinchonium bromide was used instead of the *O*-(9)-propargyl catalyst **148**.

Scheme 52

Ar	yield, %	ee, %
Ph	76	73
2-Naphthyl	71	76
4-MeC_6H_4	64	72
4-FC_6H_4	76	73
4-ClC_6H_4	72	76

Scheme 53



boxylate with NFSI in the presence of catalyst **149** proceeded smoothly on Amberlyst A-26(OH) in toluene at room temperature; complete conversion was attained after 1.5 h in 95% yield with 70% ee (Scheme 53).[198]

Small organic molecules have recently been established as highly selective and efficient catalysts in a wide range of reactions that include electrophilic enantioselective fluorination. Indeed, direct organocatalytic asymmetric fluorination of aldehydes and ketones has been described by Enders and Hüttl in 2005 employing L-proline and derivatives as catalysts and Selectfluor as the electrophilic fluorine source. α-Fluoro aldehydes and α-fluoro ketones were obtained in moderate yields with asymmetric induction of 36% ee at the best in the case of 2-fluorocyclohexanone (Scheme 54). Several derivatives of proline were evaluated; however, the enantiomeric excesses were low, ranging from 0% to 34% ee.[199]

Enantioselective organocatalytic α-fluorination of aldehydes has been described simultaneously by the groups of Barbas, Jørgensen, and MacMillan with moderate to very

Scheme 54

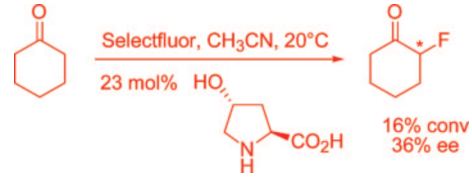
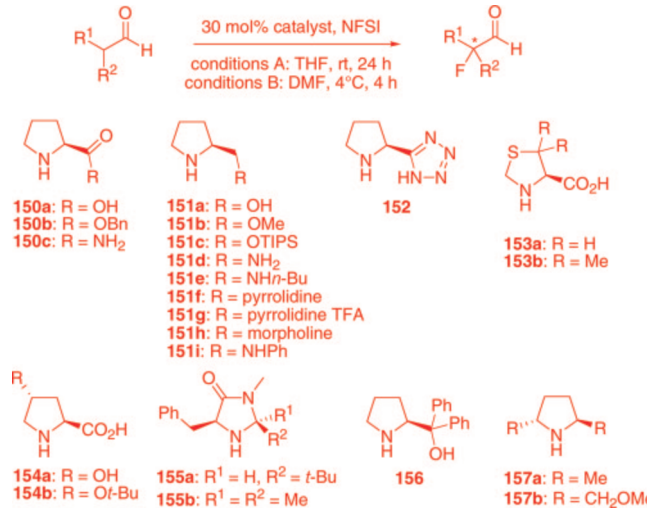


Table 16. Organocatalyzed Enantioselective Electrophilic Fluorination of Aldehydes by Barbas and Co-workers



R^1	R^2	conditions	catalyst	yield, %	ee, %
Ph	Me	A	150a	94	28
Ph	Me	A	150b	75	28
Ph	Me	A	151a	70	24
Ph	Me	A	151b	83	24
Ph	Me	A	151c	90	44
Ph	Me	A	151g	85	16
Ph	Me	A	152	99	38
Ph	Me	A	153b	75	28
Ph	Me	A	154a	93	22
Ph	Me	A	154b	65	27
Ph	Me	A	155a	77	16
Ph	Me	A	156	34	24
Ph	Me	A	157a	19	18
1-indanyl-		B	151c	98	66
n-C_8H_{17}	H	B	155a	65	76
n-C_8H_{17}	H	B	155b	30	88
n-C_8H_{17}	H	B	155b[a]	90	88
n-Pr	H	B	155b	74	96
oct-2-enyl	H	B	155b	59	93
n-C_6H_{13}	H	B	155b	94	86
n-C_4H_9	H	B	155b	40	92
Bn	H	B	155b	97	88

[a] With stoichiometric amounts of **155b**.

high enantioselectivities. Barbas and co-workers developed an organocatalytic α-fluorination of linear and branched aldehydes. A screening of electrophilic fluorinating reagents showed a preference for NFSI rather than Selectfluor, Accufluor, *N*-fluoropyridinium tetrafluoroborate, or 1,1′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate). A considerable number of organocatalysts **150**−**157** (Table 16) were also screened for α-fluorination of 2-phenylpropionaldehyde and decanal, in particular. Linear aldehydes allowed high enantioselectivities of up to 96% ee while branched aldehydes that deliver a quaternary stereogenic center gave only moderate enantioselectivities of up to 66% ee (Table 16). Standard conditions require 30 mol % of catalyst; however, it is important to note that the best yields and ee values were

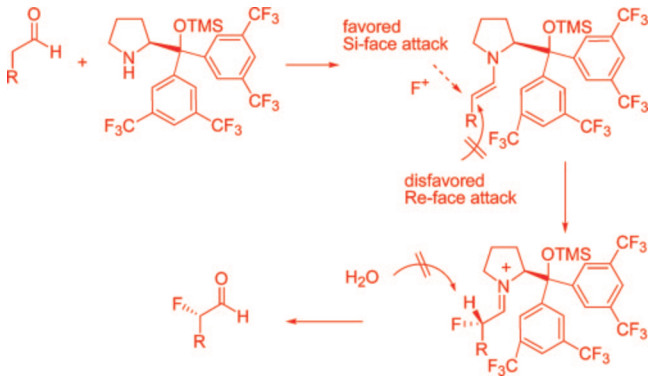
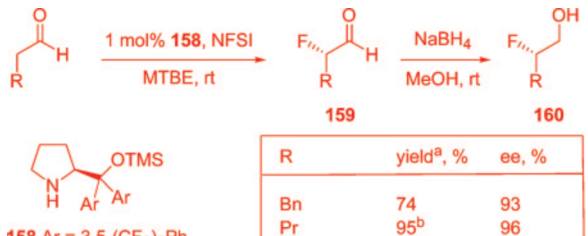


Figure 8. Transition-state model accounting for the stereodifferentiation and the configurative stability.

Scheme 55



R	yield[a], %	ee, %
Bn	74	93
Pr	95[b]	96
Bu	90[b]	91
Hex	55	96
$BnO(CH_2)_3$	64	91
Cy	69	96
t-Bu	90[b]	97
1-Ad	75	96

[a] yield of **160** from starting aldehyde
[b] yield of **159** from starting aldehyde

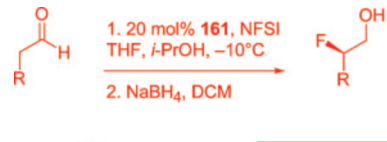
obtained when the reactions were run with stoichiometric amounts of chiral promoters.[200]

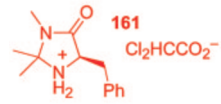
Jørgensen and co-workers demonstrated that a range of aldehydes can be directly fluorinated with NFSI in the presence of 1 mol % of the sterically encumbered chiral pyrrolidine **158**, which was obtained in four steps from L-proline. L-Proline, L-prolinamide, and *C*2 symmetric 2,5-diphenyl-pyrrolidine gave low yields and enantioselectivities in the range 30%−48% ee. The optically active α-fluorinated aldehydes **159** were directly reduced without loss of enantioselectivity to α-fluorinated alcohols **160**, which are configurationally stable. Linear and branched aldehydes were studied. Linear aldehydes resulted in high enantioselectivities of up to 97% ee (Scheme 55). On the other hand, the formation of a quaternary stereocenter from branched 2-methylpropionaldehyde occurred with a modest 48% ee.[201,356]

The fluorination proceeds through an E-configured enamine with the big substituents of the pyrrolidine ring that shield the *re* face of the enamine. The *si* face attack is favored, leading to the S configuration of the α-fluorinated aldehyde. In addition, the hydrogen atom at the stereogenic center is located in a sort of hydrophobic pocket, which prevents a nucleophilic attack by a molecule of water. Consequently, the high configurative stability of the α-fluorinated imine avoids racemization and difluorination reactions (Figure 8).[201]

Finally, MacMillan and Beeson reported the highly enantioselective organocatalytic α-fluorination of aldehydes with NFSI in the presence of 2.5−20 mol % of chiral imidazolidinone **161** (Scheme 56). The fluorination of cyclohexylacetaldehyde with L-proline and imidazolidinone•TFA led to lower enantioselectivities of 26% and 63% ee, respectively.

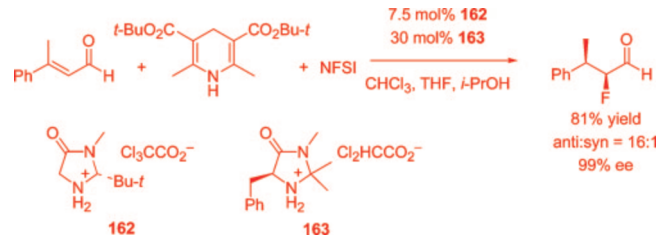
Scheme 56



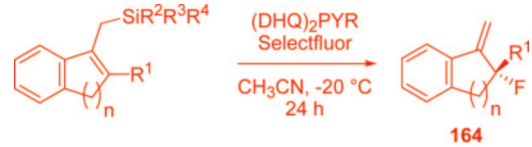


R	yield, %	ee, %
n-C_9H_{19}	70	94
non-8-enyl	79	94
Z-oct-5-enyl	81	94
but-(4-ethyl carboxylate)-yl	77	91
c-Hex	96	99
N-Boc 4-piperidinyl	85	98
Ph	54	99
Bn	71	96
1-Ad	82	98

Scheme 57



Scheme 58. Enantioselective Fluorodesilylation of Allylsilanes.



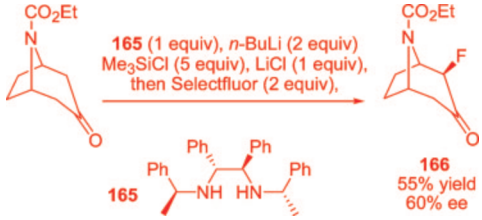
n	R^1	R^2	R^3	R^4	ee, %
1	Bn	Me	Me	Me	96
1	H	Ph	Ph	Ph	87
1	H	Me	Me	Ph	73
2	Bn	Me	Me	Me	83
2	Me	Me	Me	Me	45
2	H	Me	Me	Me	22

The α-fluorinated aldehydes were not isolated but were directly reduced with sodium borohydride to the corresponding α-fluorinated alcohols.[202]

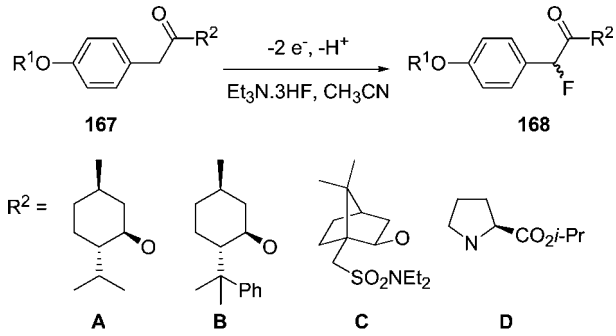
Exposure of α,β-unsaturated aldehydes to a tandem reaction that combines transfer hydrogenation conditions using Hantzsch esters and NFSI in the presence of one or a combination of two organocatalysts allows the formal addition of hydrogen fluoride with very high levels of enantio- and diastereoselection (Scheme 57).[203]

2.1.2.4. Fluorodesilylation. α-Fluorocarbonyl compounds are the targets of most of the above-mentioned studies. Interestingly, Gouverneur and co-workers developed a regio- and enantioselective synthesis of allylic fluorides **164** by electrophilic fluorodesilylation of allylsilanes.[204] 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 58). The best alkaloid for this transformation was $(DHQ)_2PYR$, leading to high ee values. Additionally, the steric bulk of

Scheme 59



Scheme 60



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

the silyl group was important with regard to enantioselectivity, with the triphenylsilyl group being responsible for higher enantioselectivities. For a catalytic version of this reaction recently published in 2008 by Shibata and coworkers, see ref 355.

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 (**166**) in 55% yield and 60% ee (Scheme 59).[81]

2.2. Nucleophilic Fluorination Reactions

2.2.1. Asymmetric Anodic Fluorination

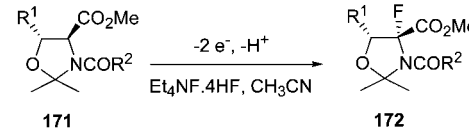
Asymmetric anodic fluorination was generally very difficult due to the small size of the fluoride ion and the use of polar solvents for electric conductivity. Nevertheless, some studies have been reported. For instance, Laurent and coworkers observed a diastereoselective fluorination at the benzylic position of **167** by oxidation at a platinum anode in $Et_3N \cdot 3HF/CH_3CN$; moderate diastereomeric excesses in the range 10−60% were recorded (Scheme 60).[205] 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.[206] Next, *N*-protected thiazolidines **169** derived from L-cysteine were

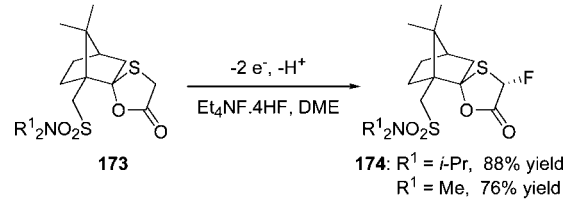
Table 17. Fuchigami's Diastereoselective Anodic Fluorinations

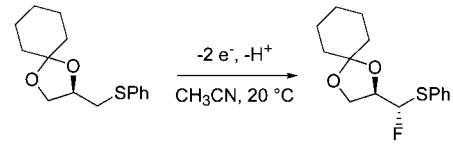
F^- electrolyte	R^1	charge	yield, %	de, %
$Et_3N.4HF$	Ph	5.0 F/mol	50	94
$Et_4N.5HF$	Ph	5.0 F/mol	53[a]	99
$Et_3N.4HF$	Me	5.5 F/mol	53	80
$Et_3N.4HF$	H	5.5 F/mol	40	59
$Et_3N.4HF$	Tol	5.0 F/mol	60	95

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



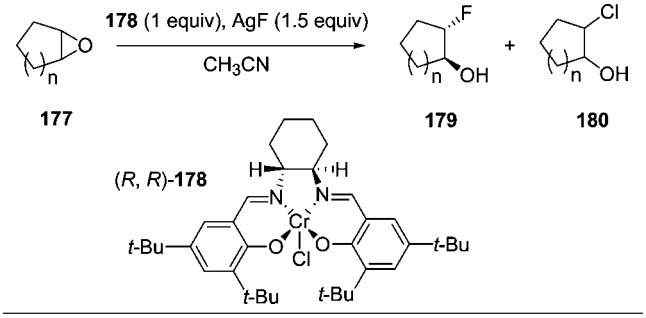
R^1	R^2	yield, %	de, %
H	Ph	56	0
Me	Ph	73	81





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 17).[207] Electrofluorination on a platinum anode of 1,3-oxazolidines **171** derived from L-serine and L-threonine gave the α-fluorinated products in moderate yields with observed diastereoselectivity only for the L-threonine derivative.[208] Under similar conditions, a single diastereomer was obtained in the fluorination of chiral 1,3-oxathiolan-5-ones **173** derived from camphorsulfonamides and thioglycol acid.[209] Sulfide **175**, having a dioxolane moiety, was fluorinated via a Pummerer mechanism with good diastereoselectivity (up to 80% de).[210] Other diol protections and various *para*-substituted phenyls were investigated by electrofluorination; however, lower diastereoselectivities were obtained.[210] 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.

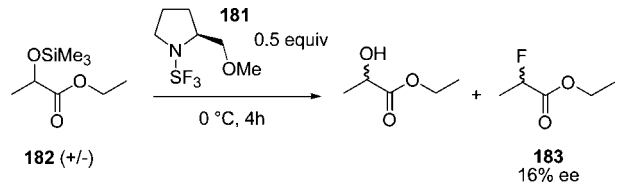
Table 18. Nucleophilic Enantioselective Ring-Opening of *meso*-Epoxides



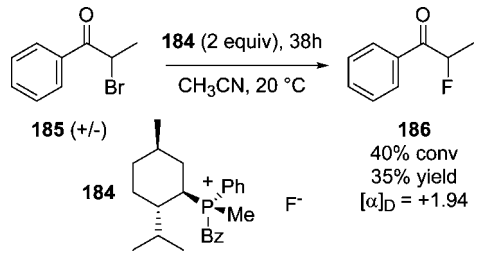
n	temp, °C	time, h	yield,[a] %	ee, %
1	50	72	80	62
2	50	50	90	72
3[b]	60	20	82	65
4	70	190	0	

[a] Calculated on the basis of consumed epoxide. [b] A 50 mol % concentration of **178** was used.

Scheme 61



Scheme 62

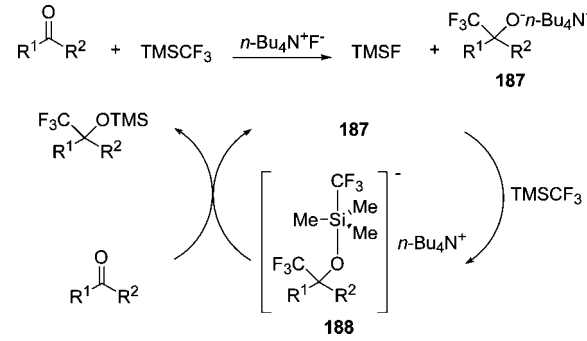


2.2.2. Enantioselective Nucleophilic Fluorination

The first and only example of enantioselective nucleophilic fluorination, described by Haufe and co-workers, concerned the ring-opening of *meso*-epoxides **177** with hydrofluorinating reagents mediated by Jacobsen's (Salen)chromium chloride complex **178**.[211] 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 **180** 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 18).[212,213]

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

Scheme 63



aminofluorosulfurane **181** as a chiral analogue of DAST (diethylaminosulfur trifluoride) to conduct an enantioselective fluorodehydroxylation (Scheme 61).[214] The kinetic resolution of 2-trimethylsilyloxypropionic acid ethyl ester (**182**) resulted in a poor enantiomeric excess of 16% for the 2-fluoropropionic acid ethyl ester (**183**).

Beaumont and co-workers reported the second example in 2001. Chiral phosphonium salt **184**, prepared from (−)-menthyl chloride, was used in the asymmetric nucleophilic fluorination of 2-bromopropiophenone (**185**) to give enantiomerically enriched 2-fluoropropiophenone (**186**) in 35% yield; unfortunately, the enantiomeric excess was not provided (Scheme 62).[215]

3. Asymmetric Trifluoromethylation Reactions

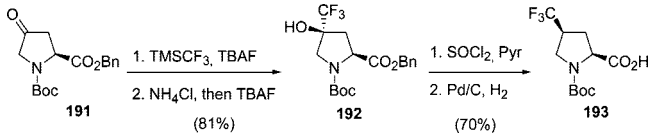
Among fluoroorganic compounds, trifluoromethyl-substituted molecules have gained growing interest during the past decade.[22,216] The introduction of a trifluoromethyl group with strong electron-withdrawing ability can lead to significant changes in the physical, chemical, and biological properties of the molecules. As a consequence, the development of asymmetric approaches for the direct introduction of a trifluoromethyl group is an important synthetic challenge.[217] 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),[218–220] while electrophilic trifluoromethylation has been developed relatively slowly.[221]

3.1. Nucleophilic Trifluoromethylation Reactions

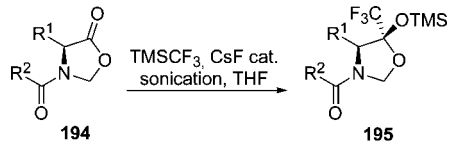
Since the initial report in 1989 by Prakash and co-workers on the trifluoromethylating properties of $(TMS)CF_3$, the utilization of this compound as a nucleophilic trifluoromethylating agent has rapidly become the method of choice.[219,222–224] Indeed, $(TMS)CF_3$ was used as a precursor to the trifluoromethide 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 **187**, stabilized by the tetrabutylammonium cation. The reaction between $(TMS)CF_3$ and **187** leads to the formation of the pentavalent complex **188**[225,226] 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 63). Other nucleophilic initiators such as alcoholates, amines,

Scheme 64

Scheme 65



Scheme 66



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

N-oxides, dimethylformamide, dimethylsulfoxide, various carbonates, acetates, phosphates, phosphines, and even derivatives of arsenic and antimony are also suitable for this purpose.[217] 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 (**189**) (Scheme 64). The reaction of $(TMS)CF_3$ with **189** in the presence of a catalytic amount of TBAF afforded the trifluoromethylated amino alcohol **190** 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.[227]

Recently, Qing and co-workers described an efficient approach for the synthesis of *N*-Boc-*cis*-4-trifluoromethyl-L-proline (**193**) (Scheme 65).[228] The reaction of *N*-Boc-4-oxo-L-proline **191** with $(TMS)CF_3$ in the presence of a catalytic amount of TBAF gave the adduct **192** with the CF_3 group *trans* to the ester group. **192** was further dehydrated, hydrogenated, and debenzylated to yield diastereomerically pure **193**. This group also reported trifluoromethylation of Garner's aldehyde with $(TMS)CF_3$; unfortunately, the diastereoselectivity was not provided.[229]

Ruppert's compound was reacted with a variety of amino acid derived *N*-substituted oxazolidin-5-ones **194** to produce compounds **195** 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 66).[230–232]

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.[233] 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.[234,235] 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.[236,237] 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.[238]

Toyokuni and co-workers have developed trifluoromethylation of an acyclic derivative of D-lyxose (**196**) with $(TMS)CF_3$ and a catalytic amount of TBAF to give trifluoromethyl adduct **197** in 79% yield, but without stereoselectivity (entry 1, Table 19).[233] Kozak and Johnson reported that ribulose derivative **198** reacted with $(TMS)CF_3$ in the presence of TBAF to give trifluoromethylated alcohol analogue **199** in 69% yield as a mixture of D-*ribo* and L-*lyxo* epimers in a 4/1 ratio (entry 2, Table 19).[239] 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 (**200**). The reaction is catalytic in fluoride, but 1.5 equiv of TBAF was used also to cleave the TMS-protected alcohol (entry 3, Table 19).[240]

Trifluoromethylation of the cyclic D-erythrose derivative **202** 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 19).[241] Because of the low diastereoselectivity, the addition of the CF_3 group was realized on lactone **214**, which provided hemiketal **215** as an equilibrium mixture of α- and β-isomers.[246] 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 **216** in high stereoselectivity (Scheme 67).[247]

Scheme 67

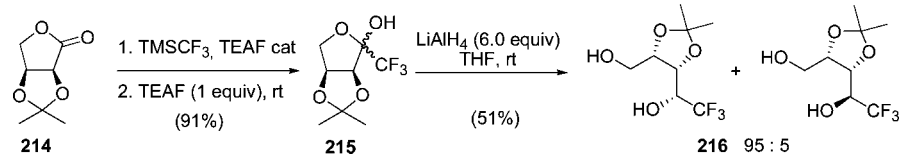
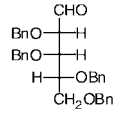
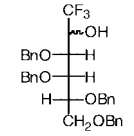
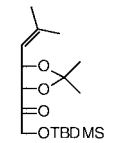
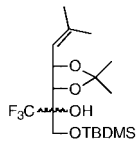
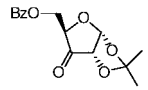
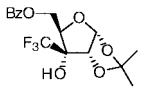
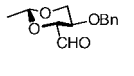
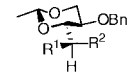
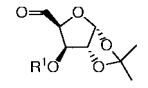
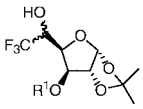
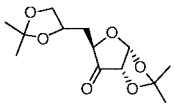
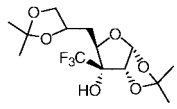
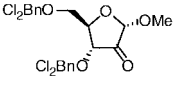
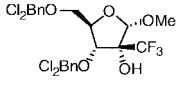
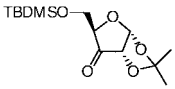
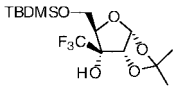
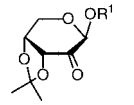
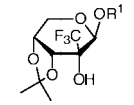
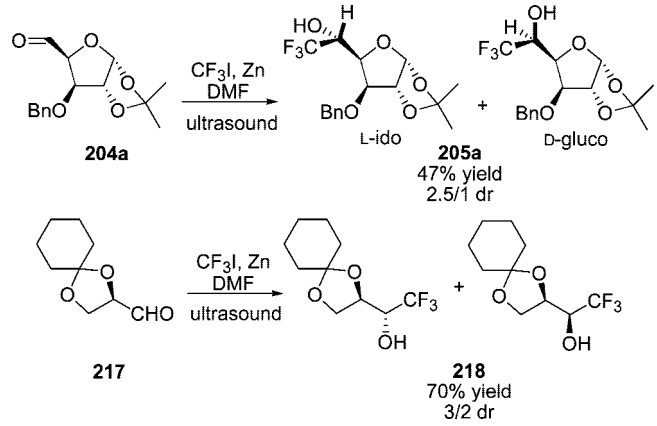


Table 19. Trifluoromethylation of Carbohydrate Derivatives

entry	carbohydrate	product	yield, %	dr	ref.
1	 **196**	 **197**	79	50/50	233
2	 **198**	 **199**	69	D-ribo/L-lyxo 80/20	239
3	 **200**	 **201**	70	100	240
4	 **202**	 **203a**: R^1=CF_3, R^2=OH **203b**: R^1=OH, R^2=CF_3	71	**203a/203b** 60/40	241
5	 **204a**: R^1=Bn **204b**: R^1=Allyl	 **205a,b**	95 98	L-ido/D-gluco 80/20 (**205a**) 88/12 (**205b**)	242
6	 **206**	 **207**	88	100	242
7	 **208**	 **209**	45	100	243
8	 **210**	 **211**	88	100	244
9	 **212a**: R^1=Me **212b**: R^1=Bn	 **213a,b**	64 65	100 (**213a**) 100 (**213b**)	245

Pentodialdose derivatives **204a,b** were trifluoromethylated with $(TMS)CF_3$ in the presence of a catalytic amount of $[Ph_3SnF_2]^-n\text{-}Bu_4N^+$ to give quantitatively the corresponding products **205a,b** as mixtures of L-*ido* and D-*gluco* epimers

Scheme 68



with good stereoselectivity, whereas a similar reaction on 3-oxoglucose **206** gave the D-*allo* adduct **207** with complete stereoselectivity (entries 5 and 6, Table 19).[242] Trifluoromethylation of chiral aldehyde **204a** 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 **205a**, 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 68).[248] Under identical conditions, trifluoromethylation of D-glyceraldehyde derivative **217** also gave a mixture of diastereomers **218** (Scheme 68).[248]

Schmit employed ketone **208** as the starting material for the synthesis of the 2′-trifluoromethylcarbinol **209** (entry 7, Table 19).[243] 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 **210** with $(TMS)CF_3$ under catalytic fluoride activation led to the single 3-*C*-trifluoromethyl-D-ribose derivative **211** (entry 8, Table 19).[244] Burger and co-workers reported the synthesis of 2-*C*-trifluoromethyl-D- and -L-ribose via trifluoromethylation of pentopyranosid-2-uloses **212** with Ruppert's compound; only one diastereomer of **213** was formed by preferential attack of the trifluoromethyl anion from the *si* face of the carbonyl group (entry 9, Table 19).[245]

Fluorinated inositols have demonstrated excellent biological activities and enzymatic inhibitory effects.[249,250] Starting from L-quebrachitol diacetonide (**219**), Kozikowski and coworkers prepared 3-*C*-trifluoromethyl-*myo*-inositol derivative **220** by a Swern oxidation followed by trifluoromethylation of the unstable ketone with the aid of Ruppert's compound (Scheme 69). A single configuration was assigned at C-3 due to complete α-face selectivity.[251]

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

Scheme 69

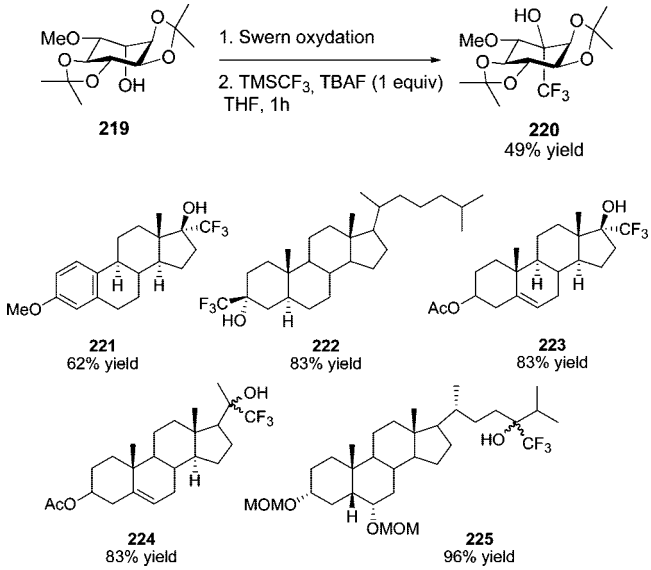
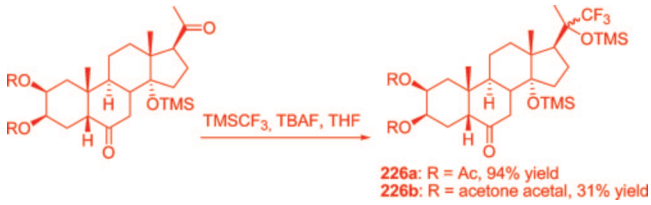
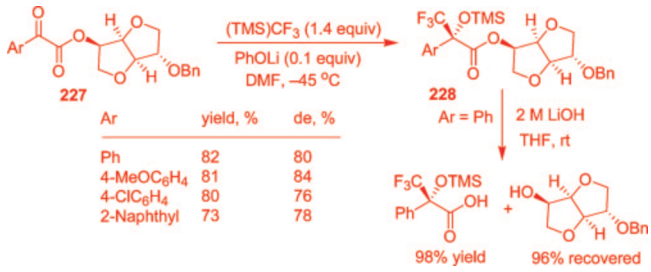


Figure 9. Trifluoromethylated Steroidal Derivatives.

Scheme 70



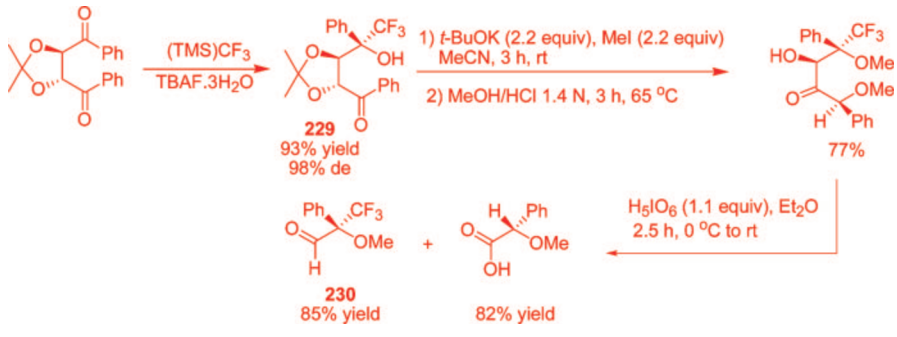
Scheme 71



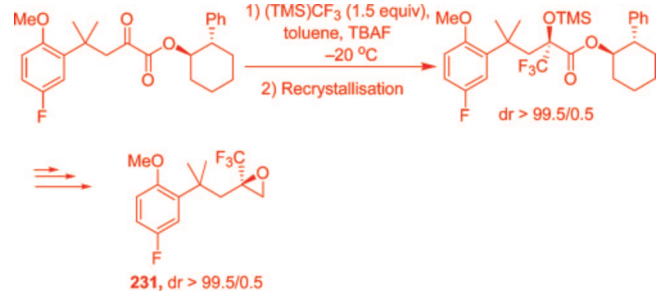
Ar	yield, %	de, %
Ph	82	80
4-MeOC$_6$H$_4$	81	84
4-ClC$_6$H$_4$	80	76
2-Naphthyl	73	78

stereomers (**221** and **222**; Figure 9).[223] Wang and co-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 (**223**−**225**; Figure 9).[252]

Scheme 72



Scheme 73



In the ecdysteroid series, Odinokov and co-workers reported the trifluoromethylation of poststerone with (TMS)CF_3 in the presence of TBAF; however, two singlets (1:1) were observed by ^{1}H NMR for the C-21 H_3 of **226**, indicating a racemic mixture of diastereomers (Scheme 70).[253]

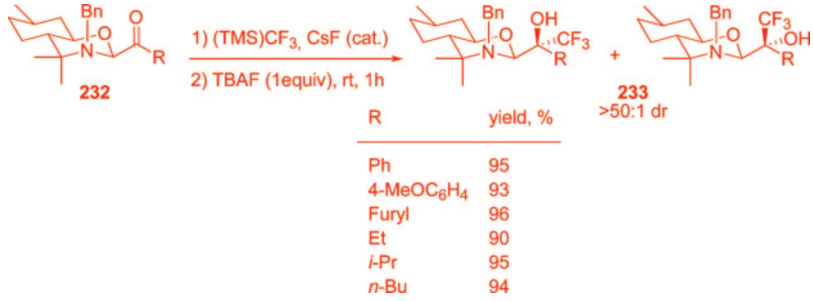
3.1.1.4. Trifluoromethylation of Diverse Carbonyl Compounds. Mosher's acid is a valuable reagent for the determination of the enantiomeric excess of alcohols or amines. For the purpose of its synthesis, a diastereoselective trifluoromethylation of chiral α-keto esters **227** derived from isosorbide with (TMS)CF_3 with the aid of a Lewis base catalyst provided the corresponding trifluoromethylated α-hydroxy esters **228** in good yields with moderate to high diastereomeric excesses.[254] Further hydrolysis with LiOH afforded the (*S*)-Mosher's acid, while the chiral auxiliary was recovered quantitatively (Scheme 71).

Somewhat later, an alternative methodology was developed for the synthesis of the precursor of Mosher's acid. A highly diastereoselective nucleophilic monotrifluoromethylation of the tartaric acid-derived diketone with (TMS)CF_3 provided the corresponding α-keto trifluoromethylcarbinol **229** in 98% diastereomeric excess. Bis(*O*-methylation) under basic conditions, followed by acidic hydrolysis and oxidative cleavage, gave two different enantiopure products. The functionalized trifluoromethyl derivative **230** is a potential precursor of Mosher's acid (Scheme 72).[255]

Recently, Song and co-workers developed a practical asymmetric process for the synthesis of pharmaceutically active intermediate **231**: α-trifluoromethyl-α-alkyl epoxide. The fluoride-initiated CF_3 addition to the starting chiral α-keto ester proceeded with a diastereoselectivity up to 86:14. The major diastereomer was readily obtained with over 99% diastereomeric excess by crystallization and further transformed to the desired epoxide **231** with excellent purity (99.5:0.5 er) on a kilogram scale (Scheme 73).[256]

Pedrosa and co-workers presented the diastereoselective addition of (TMS)CF_3 to chiral 2-acyl-1,3-perhydrobenzoxazine **232** derived from (−)-8-benzylamino menthol. The

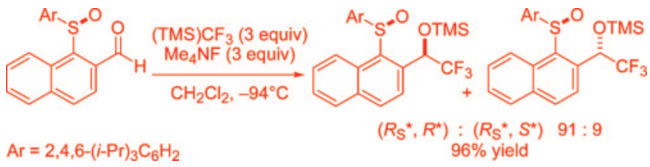
Scheme 74



R	yield, %
Ph	95
4-MeOC$_6$H$_4$	93
Furyl	96
Et	90
i-Pr	95
n-Bu	94

Scheme 75

Scheme 76



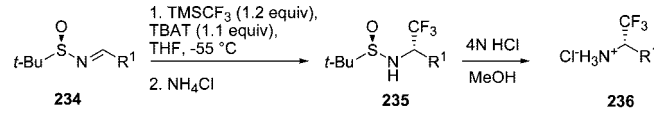
trifluoromethylated adducts **233** were obtained in very good yields (80−96%) with high to excellent diastereoselectivities. In terms of reactivity and diastereoselectivity, CsF was a better catalyst than TBAF. Further transformation of the addition products allowed for the synthesis of enantioenriched 1,2-diols and 1,2-amino alcohols possessing a quaternary stereocenter (Scheme 74).[257]

Enders and Herriger developed an efficient asymmetric synthesis of 2-trifluoromethylated 1,2,3-triols. The α-alkylated dioxanones, which were obtained via the SAMP/RAMP hydrazone methodology, were trifluoromethylated by nucleophilic 1,2-addition of the CF_3 group by means of (TMS)CF_3 and TBAF in high diastereoselectivities (de ≥ 96%). Deprotection of dioxanol under acidic conditions gave the corresponding trifluoromethylated triols in essentially enantiomerically pure form (ee 95−96%). (Scheme 75).[258]

Toru and co-workers reported an asymmetric trifluoromethylation induced by a remote chiral sulfinyl group. The reaction was initiated using tetramethylammonium fluoride to give trifluoromethylated products in high yields with high diastereoselectivity (Scheme 76). The reaction run on ketones or imines failed to give the trifluoromethylated products. Further desilylation, recrystallization, and cleavage of the sulfinyl group afforded the enantiomerically pure 1-(2-naphthyl)-2,2,2-trifluoroethanol.[259]

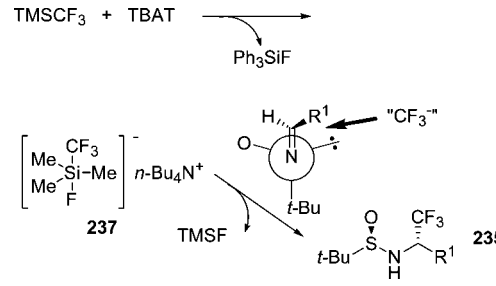
3.1.1.5. Trifluoromethylation of Sulfinimines and Azirines. Trifluoromethylated chiral amines are important fluorinated building blocks for pharmaceutical research and asymmetric synthesis. Direct asymmetric synthesis of trifluoromethylated amines was recently achieved by Prakash and co-workers.[260] The reactivity and stereoselectivity of the reaction are dependent on the fluoride source. Chiral sulfinimines **234** reacted with (TMS)CF_3 in the presence of DeShong's tetrabutylammonium difluorotriphenylsilicate (TBAT)[261] in THF to give the trifluoromethylated products **235** with high diastereoselectivities and yields, which can be hydrolyzed to the chiral amine salts **236** (Scheme 77).

Scheme 77



R^1	yield, %	(*Rs*, *S*)/(*Rs*, *R*)
p-ClC$_6$H$_4$	95	>99/1
p-BrC$_6$H$_4$	90	>99/1
p-CF$_3$C$_6$H$_4$	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$_2$CH$_2$	84	90/10

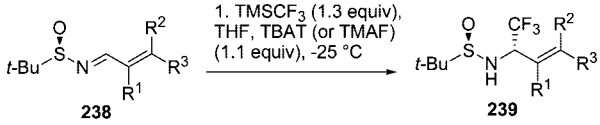
Scheme 78



In marked contrast, a stoichiometric amount of CsF provided the trifluoromethylated sulfinamides **235** only in 50−65% yields with moderate diastereoselectivity (50−80% de). The authors described a mechanistic rationale to account for this high stereoselectivity (Scheme 78). In the presence of a stoichiometric amount of fluoride source, the pentavalent intermediate **237** preferably adds to the imines from the less hindered *re* face to give the selective Cram products **235**.

The same group has also developed the asymmetric synthesis of trifluoromethylated allylic amines **239** using α,β-unsaturated *N*-2-methyl-2-propanesulfinimines **238** and (TMS)CF_3 (Scheme 79).[262] 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 products. Indeed,

Scheme 79



R^1	R^2	R^3	yield, %	(*Rs*, *S*)/(*Rs*, *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.

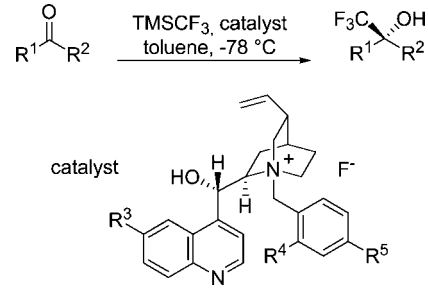
when TMAF was used as a fluoride source, the sterically bulky sulfinimines gave the corresponding adducts in good yields.

Somewhat later, Prakash and co-workers showed that the trifluoromethylated vicinal ethylenediamines **242** can be obtained in high yields and stereoselectivities by treatment of α-amino *N*-2-methyl-2-propanesulfinimines **240** with (TMS)CF_3 (Scheme 80).[263]

By using TMAF as the fluoride source, sulfinimines **240** derived from the L-amino aldehydes were trifluoromethylated to give the vicinal ethylenediamine adducts **241** 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 ($R^1 \cong R^2 \cong R^3 \cong$ Bn). These observations suggested that both the chiral centers present in the molecule direct the incoming nucleophile to the *re* face of the imines.

Mukaiyama and Kawano disclosed the trifluoromethylation of chiral *N*-sulfinylimines with (TMS)CF_3 under mild conditions by using a Lewis base. The corresponding trifluoromethylated adducts **243** were obtained in good to high yields with good diastereoselectivities when the reactions were carried out by using an equimolar amount of tetrabutylammonium acetate at −40 °C. Aliphatic aldimines having no

Table 20. 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	269, 270
2	Ph	H	H	H	CF_3	>99	37	271
3	Ph	H	H	CF_3	CF_3	>99	46	271
4	*n*-C_3H_7	H	H	H	CF_3	>99	15	271
5	9-anth	H	H	H	CF_3	98	45	271
6	Ph	Me	H	H	CF_3	91	48	271
7	Ph	*i*-Pr	H	H	CF_3	87	51	271

Scheme 81

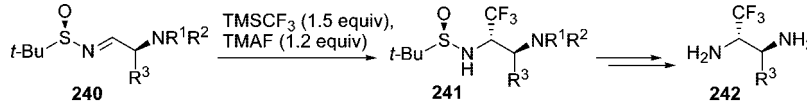
R	Lewis base	yield, %	(S_s, *R*) / (S_s, *S*)
Ph	$AcONBu_4$-*n*	91	96/4
4-MePh	$AcONBu_4$-*n*	90	95/5
4-ClPh	$AcONBu_4$-*n*	94	95/5
2-ClPh	$AcONBu_4$-*n*	92	96/4
3-ClPh	$AcONBu_4$-*n*	93	95/5
1-Naphthyl	$AcONBu_4$-*n*	92	96/4
3-Pyridyl	$AcONBu_4$-*n*	85	94/6
2-Furyl	$AcONBu_4$-*n*	93	95/5
t-Bu	$AcONBu_4$-*n*	91	96/4
c-Hex	$PhONBu_4$-*n*	75	95/5
$PhCH_2CH_2$	$PhONBu_4$-*n*	53	92/8

α-proton adjacent to the imino group reacted smoothly to afford the desired adducts in high yields, whereas those that have α-protons gave the adducts in moderate to good yields in the presence of an equimolar amount of $PhONBu_4$-*n* (Scheme 81).[264]

The addition of (TMS)CF_3 was studied on the carbon nitrogen double bond of azirines **244** to obtain exclusively the (*E*)-aziridines **245** in satisfactory yields.[265] 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 82).

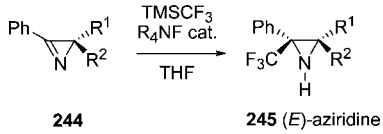
Trifluoromethyl iodide has been employed for the purpose of nucleophilic trifluoromethylation of carbonyl compounds

Scheme 80



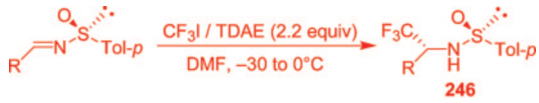
R^1	R^2	R^3	yield, %	dr
Bn	Bn	Me	86	>99/1
Bn	Bn	*n*-C_3H_7	85	>99/1
Bn	Bn	Bn	81	>99/1
Bn	Bn	*i*-Pr	66	>99/1
Bn	Bn	*i*-Pr	71	>99/1
Bn	-C_3H_6-		>99/1	79

Scheme 82



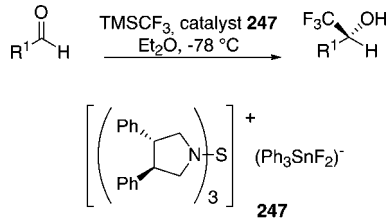
R^1	R^2	R_4NF	yield, %
Me	H	Et_4NF	51
Ph	H	Et_4NF	86
CO_2Me	H	Bu_4NF	67

Scheme 83



R	yield, %	dr
Ph	66	87/13
4-MePh	73	86/14
4-MeOPh	71	82/18
4-FPh	69	85/15
4-CF_3Ph	74	88/12
4-ClPh	67	88/12
1-Naphthyl	42	94/6
n-C_6H_{13}	48	72/28

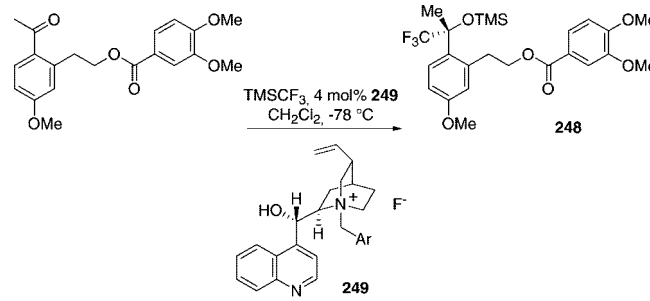
Scheme 84



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

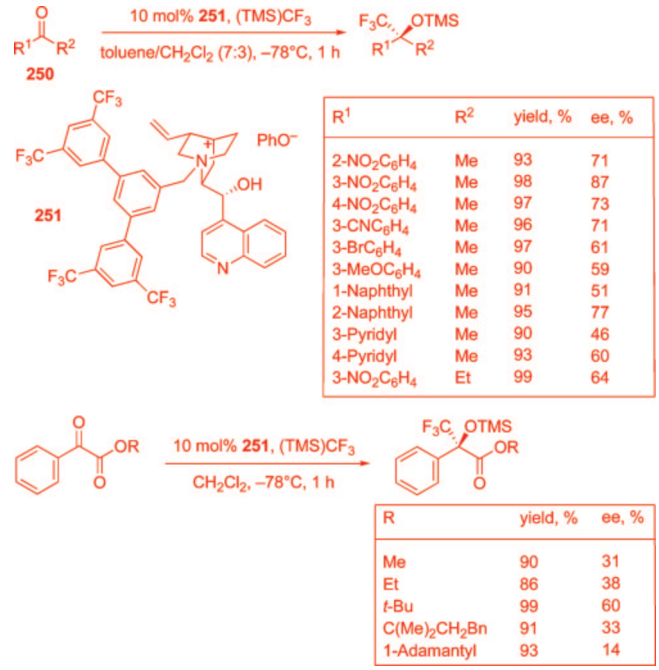
via its derived organometallic reagents. However, some drawbacks have limited their utility in synthesis. Recently, Dolbier and co-workers developed an alternative approach to nucleophilic trifluoromethylation based on the formation of a charge-transfer complex between CF_3I and TDAE, followed by stepwise, photoinduced single-electron transfers of two electrons from TDAE to CF_3I to generate a complex between CF_3^- anion and $TDAE^{2+}$ dication, which presumably is the active nucleophilic trifluoromethylating agent.[266,267] A variety of nonenolizable aldehydes, ketones, and aromatic aldimines were trifluoromethylated by using this reagent to give the desired adducts in moderate to high yields. Furthermore, when nucleophilic trifluoromethylation of *p*-

Scheme 85



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

Scheme 86



R^1	R^2	yield, %	ee, %
2-$NO_2C_6H_4$	Me	93	71
3-$NO_2C_6H_4$	Me	98	87
4-$NO_2C_6H_4$	Me	97	73
3-CNC_6H_4	Me	96	71
3-BrC_6H_4	Me	97	61
3-$MeOC_6H_4$	Me	90	59
1-Naphthyl	Me	91	51
2-Naphthyl	Me	95	77
3-Pyridyl	Me	90	46
4-Pyridyl	Me	93	60
3-$NO_2C_6H_4$	Et	99	64

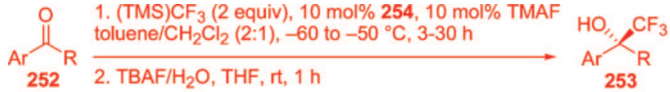
R	yield, %	ee, %
Me	90	31
Et	86	38
t-Bu	99	60
$C(Me)_2CH_2Bn$	91	33
1-Adamantyl	93	14

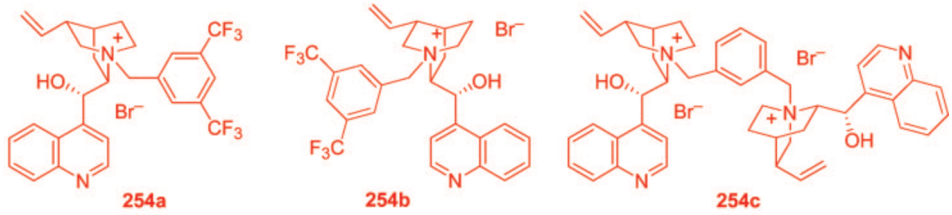
toluenesulfinimides **246** was carried out under these conditions, good diastereoselectivities were observed for a series of substrates (Scheme 83).[267]

3.1.2. Enantioselective Trifluoromethylation

The importance of enantiopure trifluoromethylated compounds in medicinal chemistry, agrochemistry, electronics, and optics (liquid crystals) has been well recognized.[22,25,268] 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

Scheme 87





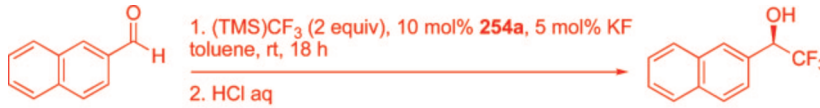
Ar	R	catalyst	yield, %	ee, %
2-Naphthyl	Me	**254c**	87	85
2-Naphthyl	Me	**254a**	65	81
2-Naphthyl	Me	**254b**	70	77[a]
Ph	Et	**254c**	65	82
Ph	Pr	**254c**	83	76
4-BrC_6H_4	Me	**254c**	81	86
4-BrC_6H_4	Et	**254c**	84	93[b]
4-$NO_2C_6H_4$	Me	**254a**	97	52[c]
1-tetralone		**254c**	75	94
1-indanone		**254c**	34	74
1-benzosuberon		**254c**	53	73
PhCH=CH	Me	**254c**	85	70
2-Naphthyl	H	**254c**	93	41
$PhCH_2CH_2$	Me	**254c**	37	10

[a] (*S*)-**253** was obtained.

[b] The reaction was carried out at −80 to −70 °C.

[c] 20 mol % of TMAF was used.

Scheme 88



9-anthraldehyde in 95% ee (entry 1, Table 20).[269,270] Iseki and co-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 20).[271]

Noteworthy, quinine itself was capable of enantioselective trifluoromethylation of aldehydes using related Et_3SiCF_3, although with low enantioselectivities and yields.[272–274]

Iseki and co-workers have developed the chiral triaminosulfonium salt **247**, which functions as a Lewis base catalyst in the enantioselective trifluoromethylation.[275] $(TMS)CF_3$ reacted with aldehydes in the presence of 10 mol % chiral salt **247** at −78 °C in diethyl ether to give the corresponding alcohols with ee's ranging from 10% to 52% (Scheme 84).

With the aim of obtaining the enantiomerically enriched trifluoromethylated silylated alcohol **248**, an in-depth catalyst structure−enantioselectivity relationship study was undertaken by Caron and co-workers.[276] 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 **249** were used in amounts as low as 4 mol % in the trifluoromethylation to afford the desired product **248** in up to 92% ee (Scheme 85). However, these catalysts did not prove to be generally applicable to a variety of model aldehydes and ketones, albeit no optimization was conducted.

In 2007, four new publications in the field appeared, providing new directions toward highly enantioselective nucleophilic trifluoromethylation. Based on the fact that metal alkoxides are efficient nucleophilic initiators of the Ruppert−Prakash reagent, Mukaiyama and co-workers demonstrated that cinchonidine-derived quaternary ammonium phenoxides catalyzed the asymmetric trifluoromethylation of ketones with $(TMS)CF_3$. The structure of the ammonium salt and also the solvent of the reaction were investigated. Next, several ketones **250** were trifluoromethylated in the presence of catalyst **251** in high yields with moderate to high enantioselectivities (Scheme 86).[277] Five alkyl 2-oxo-2-phenylacetates were also used as substrates, leading to trifluoromethylated products in high yields with 14−60% ee (Scheme 86).[278]

Shibata, Toru, and co-workers devised an operationally simple procedure based on a combination of a chiral quaternary ammonium salt derived from cinchona alkaloid

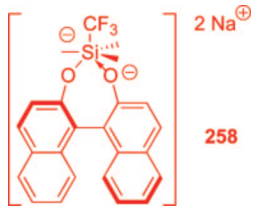


Figure 10

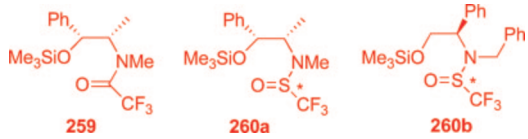


Figure 11

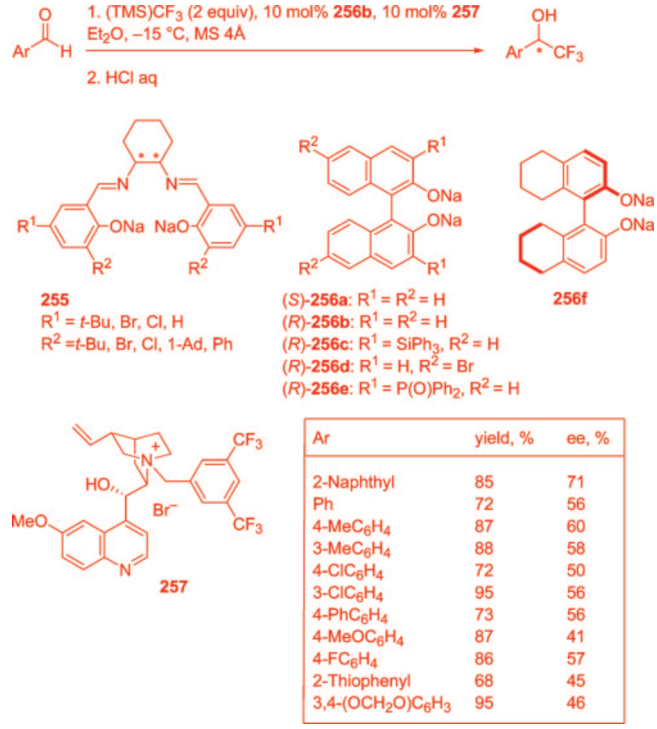
and tetramethylammonium fluoride (TMAF) for the catalytic nucleophilic enantioselective trifluoromethylation of aryl ketones **252**. In this case of dual activation, the fluoride anion acts as the nucleophilic activator of the Ruppert−Prakash reagent and the chiral ammonium activates the carbonyl group of **252**. Very good enantioselectivities were recorded (up to 94% ee), in particular with the biscinchoninium derivative **254c** (Scheme 87).[279] Unfortunately, both aryl aldehyde and aliphatic ketones gave much lower ee values in the range 10−41%.

In a search for efficient asymmetric induction in the case of aldehydes, Shibata, Toru, and co-workers developed a similar strategy using a mixture of KF and a chiral ammonium bromide in the trifluoromethylation of 2-naphthaldehyde. This way, the troublesome use of anhydrous ammonium fluoride is bypassed. A screening of a variety of chiral ammonium salts was conducted that include cinchonium bromides, *N*-spiro C_2-symmetric Maruoka's ammonium salts, and Shibasaki's bisammonium diiodide derived from L-tartaric acid. A combination of KF and cinchonium bromide **254a** gave a moderate 40% ee (Scheme 88).[280]

Improved enantioselectivity was reported by Feng and co-workers, who utilized a combination of a chiral quaternary ammonium salt either with a disodium salt of chiral Schiff base **255** or with a disodium (*R*)-binaphtholate **256** as counteranion. The disodium (*R*)-binaphtholate **256** in combination with chiral ammonium **257** exhibited the best ee values in the trifluoromethylation of 2-naphthaldehyde and was selected to study the scope of the reaction. This catalytic system was generated in situ and developed for the enantioselective trifluoromethylation of aromatic aldehydes in up to 71% yield (Scheme 89). Importantly, the reaction did not proceed with a monosodium binaphtholate. A mechanism was proposed that involves a hexavalent intermediate **258** (Figure 10) for the activation of $(TMS)CF_3$ and an activation of the carbonyl group of the aromatic aldehyde by the positively charged N atom of **257**.[281]

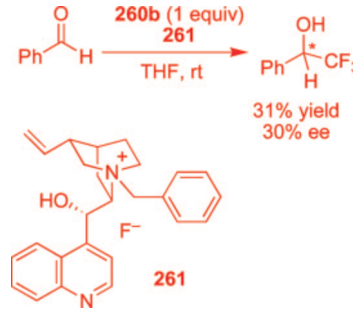
A single example of reagent-controlled nucleophilic trifluoromethylation has been reported in the literature by Langlois and co-workers. In 2003−2004, Langlois' group designed novel trifluoroacetamides **259** and trifluoromethanesulfinamides **260** derived from *O*-silylated *vic*-aminoalcohols (Figure 11). For example, ephedrine derivative **259** was able to trifluoromethylate both enolizable and nonenolizable ketones, as well as reactive aldehydes in good to excellent yields under activation by fluoride anion. Unfortunately, the enantioselectivity was not discussed at this stage.[282] In 2005, this group employed various chiral trifluoromethanesulfinamides as chiral trifluoromethylating agents. In the trifluoromethylation of benzaldehyde, low ee values in the range 1−20% were observed with trifluoromethanesulfinamide **260b**. In order to improve enantioselectivity, a chiral ammonium fluoride **261** was employed as initiator for the trifluoromethylation reaction of benzaldehyde with **260b**; enantioselectivity was improved to 30% ee in 31% yield (Scheme 90).[283,284]

Scheme 89



Ar	yield, %	ee, %
2-Naphthyl	85	71
Ph	72	56
4-MeC_6H_4	87	60
3-MeC_6H_4	88	58
4-ClC_6H_4	72	50
3-ClC_6H_4	95	56
4-PhC_6H_4	73	56
4-$MeOC_6H_4$	87	41
4-FC_6H_4	86	57
2-Thiophenyl	68	45
3,4-$(OCH_2O)C_6H_3$	95	46

Scheme 90



3.2. Electrophilic Trifluoromethylation Reactions

Asymmetric electrophilic trifluoromethylation has been developed relatively slowly. Yagupol'skii reported in 1984 the first electrophilic trifluoromethylating reagents **262a,b** (Figure 12), which showed low reactivity.[285] The research work of Umemoto and co-workers in the early 1990s led to the development of highly reactive trifluoromethyl dibenzoheterocyclic salts **263** (Figure 12) as electrophilic trifluoromethylating agents.[286–291]

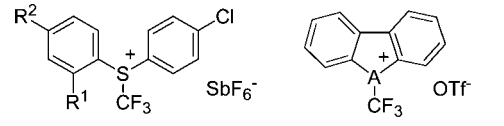
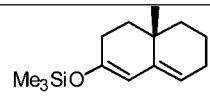
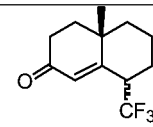
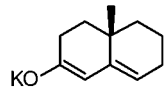
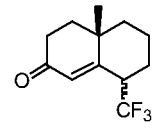
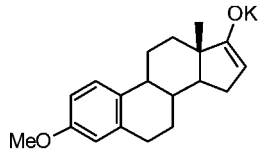
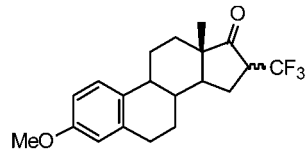
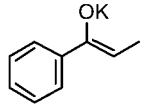
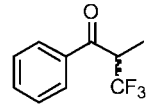
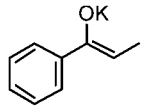
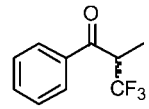
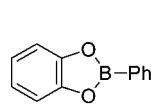
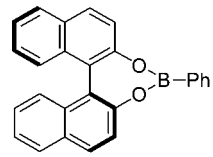


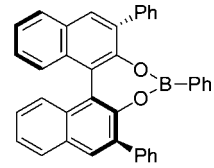
Figure 12. Electrophilic trifluoromethylating reagents.

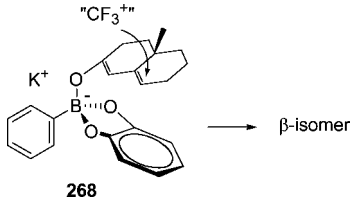
Table 21. Enantioselective Electrophilic Trifluoromethylation

entry	substrate	boron	product	yield, %	de or ee, %
1	 **264**	-	 **265**	69	α/β = 3.6/1
2	 **266**	**273**	 **267**	81	α/β = 1/2.5
3	 **269**	**273**	 **270**	58	α:β = 2:3
4	 **271**	**274**	 **272**	31	12 (ee)
5	 **271**	**275**	 **272**	20	45 (ee)


273


274


275



268

Figure 13. Proposed intermediate for the boron-mediated trifluoromethylation of enolate **266**.

Umemoto and co-workers reported a comparison of diastereoselectivity for the trifluoromethylation of the trimethylsilyl enol ether **264** and the boron-mediated trifluoromethylation of the corresponding potassium enolate **266** with **263** (A = S).[287,288] The α/β ratio of product **265** was 3.6/1 for the former reaction and 1/2.5 for the latter one (entries 1 and 2, Table 21). The conformation of the intermediate complex **268**, 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 13). The preferential formation of β-CF_3 steroid isomer **270** can be explained by a similar rationale (entry 3, Table 21).

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 **274** or **275**, the potassium enolate of propiophenone **271** was reacted with **263** (A = S), giving moderate enantioselectivities and low yields (entries 4 and 5, Table 21). The enantioselectivity could arise from the attack of the resulting chiral borate complex by the trifluoromethylating agent.

Surprisingly, 13 years later, this research area has not experienced any progress. In 2003, we initiated a research program dedicated to new approaches in electrophilic trifluoromethylation.[221] We examined the use of chiral ammonium salts such as **276** acting as chiral phase-transfer catalysts in enantioselective electrophilic trifluoromethylation. 1-Oxo-indan-2-carboxylic acid methyl ester was selected as model substrate, and a screening approach was adopted for the identification of suitable reaction conditions (base, solvent, PTC, temperature). So far, the best enantiomeric excess recorded was 19% (Scheme 91). This approach looks

Scheme 91

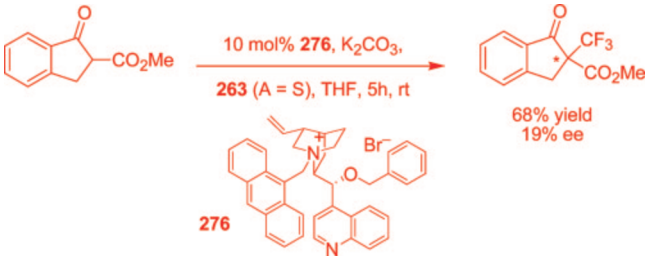
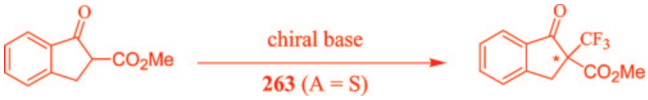


Table 22



solvent	chiral base	temp, °C	time, h	yield, %	ee, %
CH_2Cl_2	4-ClBzQN	−78	48	0	
CH_2Cl_2	QN	−78	12	30	10
CH_2Cl_2	HQD	−78	12	73	13
CH_2Cl_2	HQN	−78	3.5	51	29
$CHCl_3$	HQN	20	96	42	25
$CHCl_3$	HQN	−60	96	55	35
CH_2Cl_2/hexane: 1/1	HQN	−78	72	45	56
CH_2Cl_2/hexane: 1/2	HQN	−78	96	53	71
CH_2Cl_2/hexane: 1/3	HQN	−78	96	34	52

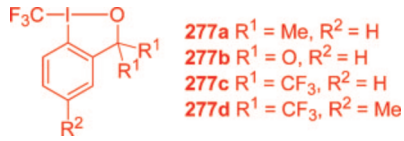


Figure 14. Togni's electrophilic trifluoromethylating reagents.

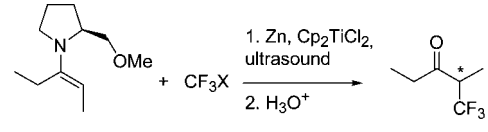
promising, and more experiments must be carried out to improve the enantioselectivity.[217]

The poor enantioselection observed in this reaction may be attributed to the trifluoromethylation of the potassium enolate rather than the chiral quaternary ammonium enolate. The undesirable process of interfacial trifluoromethylation of the "wrong" ion-pair possessing the potassium cation should be disfavored and the extraction of the potassium enolate into the bulk organic phase by ion exchange with the chiral quaternary ammonium would be the preferred pathway. To banish the presence of achiral enolates, we decided to use cinchona alkaloids as chiral tertiary bases for promoting enolization of the β-keto ester and subsequent enantioselective electrophilic trifluoromethylation of the chiral ammonium enolates. Preliminary results allowed us to obtain the trifluoromethylated product in 53% yield with 71% enantiomeric excess (Table 22). Such a level of enantioselectivity is attained for the first time for an enantioselective electrophilic trifluoromethylation.[217]

Although the asymmetric electrophilic trifluoromethylation reaction is very important and extremely challenging, chiral reagents are not currently known. The new hypervalent iodine (III)−CF_3 reagents **277** (Figure 14) recently described by Togni and co-workers open new possibilities to design chiral enantiopure trifluoromethylation reagents.[292,293]

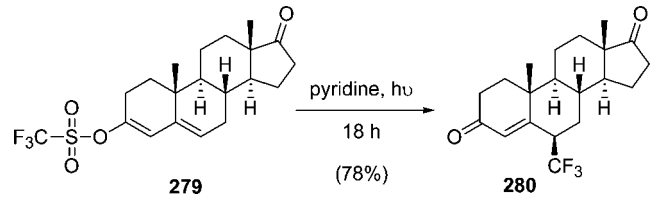
A diastereoselective approach, according to the second generation of asymmetric synthesis, employing chiral enamine **278** was described by Kitazume and Ishikawa.[294] The asymmetric introduction of the trifluoromethyl group in the presence of zinc powder and a catalytic amount of dichlorobis(π-cyclopentadienyl)titanium was promoted by ultrasound; up to 76% ee was obtained with CF_3Br (Scheme 92).

Scheme 92

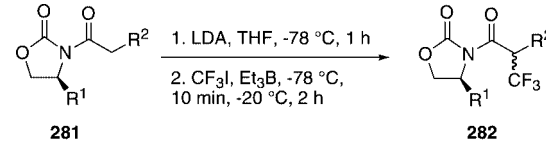


CF_3X	yield, %	ee, %
CF_3I	38	62
CF_3Br	46	76

Scheme 93



Scheme 94



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.

3.3. Radical Trifluoromethylation Reactions

Early work by Elliot and co-workers concerned dienyl enol triflate **279** of a steroidal system. Irradiation of **279** in pyridine photochemically gave 6β-trifluoromethyl α,β-unsaturated ketone **280** (Scheme 93). A radical process was suggested for the fragmentation−rearrangement reaction.[295]

The trifluoromethylation of lithium enolates of chiral *N*-acyloxazolidinones **281** with iodotrifluoromethane mediated by triethylborane was achieved by Iseki and co-workers.[296,297] The trifluoromethylation proceeded in good yields and diastereoselectivities to afford α-trifluoromethyl carboximides **282**, which were treated with $LiBH_4$ to provide the corresponding β-trifluoromethyl alcohols without racemization (Scheme 94).

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 15).

To synthesize 7α-perfluoroalkylestradiol, Blazejewski and co-workers developed an approach for direct introduction of the trifluoromethyl group by reaction of silyl enol ether **283** of a steroidal ketone with Umemoto's reagent **263** (A = S). Under thermal conditions similar to those employed by Umemoto, the yield was low (15%), while UV irradiation

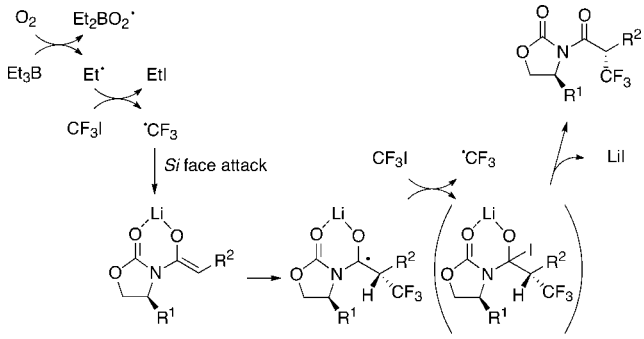
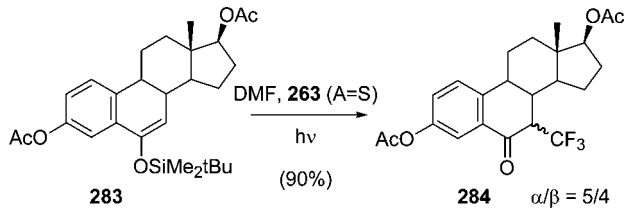
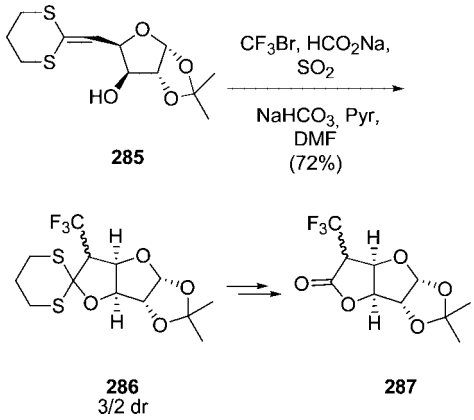


Figure 15. Proposed Radical Mechanism.

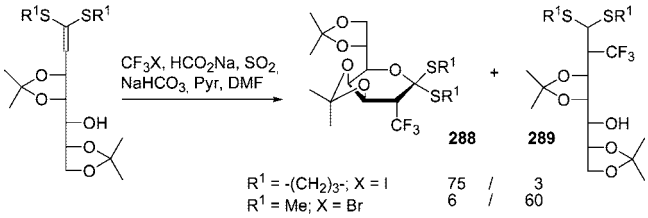
Scheme 95



Scheme 96



Scheme 97



of the reaction mixture led to an excellent yield (90%) of the ketone **284**, although in a poorer selectivity (α/β = 5/4) than that observed in the perfluoroalkyl series (vide infra) (Scheme 95).[298]

A tandem radical trifluoromethylation−nucleophilic cyclization of the glucose-derived ketene dithioacetal **285** has been proposed as the key step toward trifluoromethylated lactone **287** (Scheme 96).[299] The reaction exhibited poor diastereoselectivity (dr = 3/2), with the two diastereomers of **286** 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 **288** or the acyclic sugar **289** was predominantly obtained (Scheme 97).[300]

A single example of radical enantioselective trifluoromethylation has been recently reported by Mikami and co-workers. The radical trifluoromethylation was performed at the α position of 2-phenyl cyclohexanone through the corresponding lithium enolate generated from the enol silane **290**. Noteworthy, the defluorination of the α-CF_3 ketone product during the reaction was not observed. A bidentate ligand, (*S*,*S*)-hydrobenzoin or (−)-sparteine, was added to the reaction mixture to coordinate lithium enolate **291** and to induce asymmetric radical trifluoromethylation. Although low yields and ee values were measured, this approach has great potential and further developments are imminent (Scheme 98).[301,302] Moreover, this approach complements the diastereoselective trifluoromethylation reported by Iseki and Kobayashi in the nineties.

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.[28] 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.[303] Additionally, the introduction of a difluoromethylene group into peptides has brought about the discovery of potent protease inhibitors which function as transition-state mimics.[304] In the case of long-chain perfluoroalkylations, some perfluoroalkylated carbohydrates have been synthesized, for example, for the formation of biocompatible oxygen carriers.[305] 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

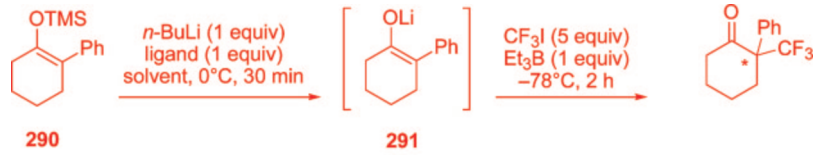
The addition of pentafluoroethyllithium and some perfluoroalkylzinc derivatives to chiral arenechromium tricarbonyl aldehydes **292** has been carried out by Solladie-Cavallo and co-workers (Table 23).[306–308] The preferred diastereomer of **293** was the same in the two cases (from lithium compounds 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 **293** proved to be good inducers of chirality in the Prelog-type asymmetric synthesis of α-hydroxy acids **294** (Scheme 99).[309]

Perfluoroalkyllithiums, generated in situ from the reaction of primary perfluoroalkyl iodides and MeLi−LiBr, in the presence of boron trifluoride, reacted with chiral aldimines **295** and **296** derived from lactic acid or from aldehyde and chiral amines (Table 24). The diastereofacial selectivity observed in the reaction did not agree with Cram's chelation model; thus, the authors proposed a model involving an interaction of BF_3 with the perfluoroalkyllithium.[310]

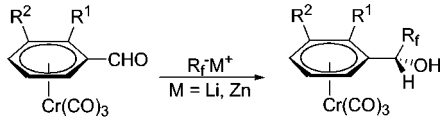
Since the report of Fried,[311] the Reformatsky reaction of difluoroorganozinc with chiral aldehydes has become a frequently used methodology for the preparation of interesting biomolecules with a difluoromethylene moiety. For example, condensation of the zinc derivative of ethyl bromodifluoroacetate[312] and *n*-pentylbromodifluoromethylacetylene[313] with glyceraldehyde acetonide **297** (R^1 = H)

Scheme 98



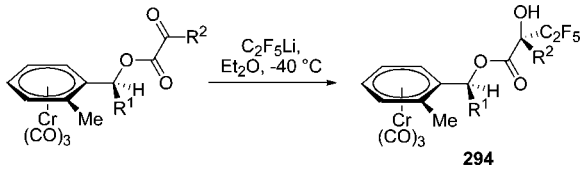
ligand	solvent	yield, %	ee, %
(*S*,*S*)-hydrobenzoin	Et_2O	39	27
(–)-sparteine	*t*-BuOMe	13	44

Table 23. Diastereoselective Perfluoroalkylation of Arenechromiun Tricarbonyl Aldehydes



R^1	R^2	R_f	M	yield, %	de, %	ref
Me	H	C_2F_5	Zn	85	44	306
Me	H	*i*-C_3F_7	Zn	100	66	306
Me	H	C_6F_{13}	Zn	73	46	306
CF_3	H	C_2F_5	Zn	95	33	308
CF_3	H	*i*-C_3F_7	Zn	95	76	306
Me	H	C_2F_5	Li	87	88	307
Me	H	*i*-C_3F_7	Li	40	76	306
OMe	H	C_2F_5	Li	72	100	306
OMe	OMe	C_2F_5	Li	72	100	306
OMe	OMe	*i*-C_3F_7	Li	51	100	306
Me	H	C_2F_5	Li	95	80	306
CF_3	H	C_2F_5	Li	90	94	308
CF_3	H	*i*-C_3F_7	Li	95	90	306

Scheme 99



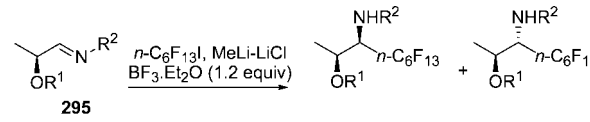
R^1	R^2	yield, %	de, %
C_2F_5	Ph	95	89
C_2F_5	Me	84	84
Et	Ph	76	88
Et	Me	87	90

gave the desired difluorohydroxy products **298** and **299** with moderate diastereoselectivities (Scheme 100). 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 **300**.[314]

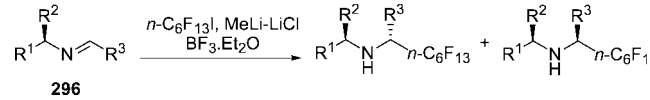
The diastereoselective synthesis of α,α-difluoro-β,γ-dihydroxy esters **301** can also be promoted by Lewis acids to enhance face differentiation. Cp_2TiCl_2 allowed a higher *anti* selectivity than the reaction run without Lewis acid to be reached (Scheme 101).[315]

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

Table 24. Diastereoselective Perfluorohexylation of Imines

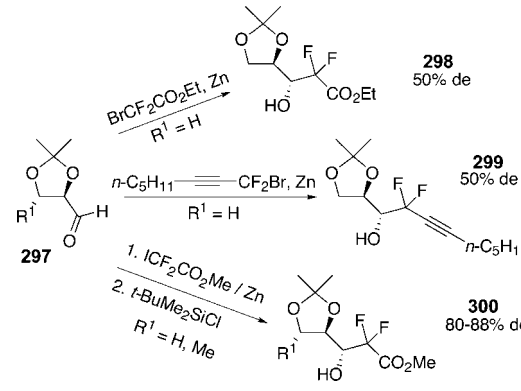


R^1	R^2	solvent	yield, %	dr
t-$BuMe_2Si$	allyl	Et_2O	81	85/15
Me	*n*-Pr	toluene	47	19/81
MOM	*n*-Pr	toluene	42	3/97
MOM	allyl	Et_2O	40	19/81



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_2n-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

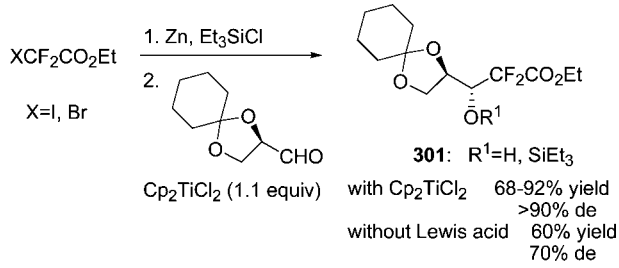
Scheme 100



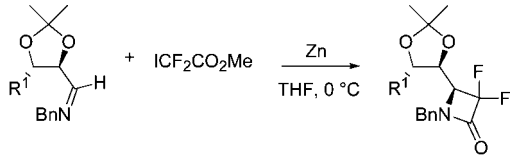
formation of the *syn* compounds was favored when benzylimines **302** were used as electrophilic species (Scheme 102). In this case a chelation between the imine and zinc halide was proposed to rationalize the preferential formation of *syn*-lactams **303**.[316]

When chiral α-amino aldehyde **304** was employed as an electrophile in the Reformatsky reaction, the *anti* compound

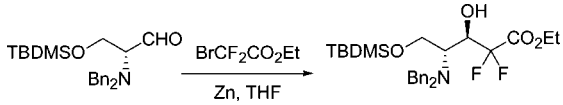
Scheme 101



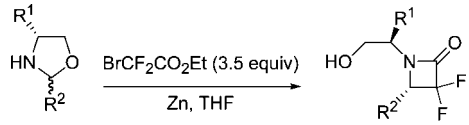
Scheme 102



Scheme 103



Scheme 104



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

305 was obtained as a single diastereomer and was further transformed into 2′-difluoro nucleoside analogues (Scheme 103).[317]

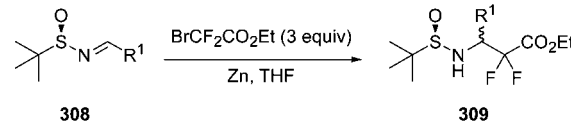
Alternatively, chiral oxazolidines **306** derived from (*R*)-phenylglycinol or (*R*)-aminobutanol were diastereoselectively perfluoroalkylated with $BrCF_2CO_2Et$ in the presence of activated zinc dust to furnish difluoroazetidinones **307** with up to 99% de (Scheme 104).[318]

Somewhat less diastereoselective was the addition of $BrCF_2CO_2Et$ to alkyl- and aryl-substituted *N*-*tert*-butylsulfinimines **308**, furnishing *β*-*N*-*tert*-butylsulfinamyl *β*-substituted α,α-difluoropropionates **309** in de's ranging from 60% to 90% (Scheme 105).[319]

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.[227,320−331]

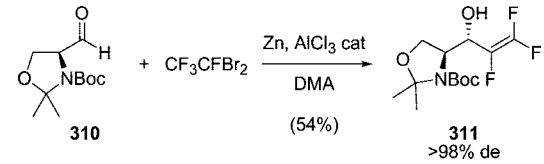
Another readily available bromofluorocarbon is 1,1-dibromoperfluoroethane (CF_3CFBr_2), which was reacted with Garner's aldehyde **310**. The reaction proceeded smoothly in

Scheme 105

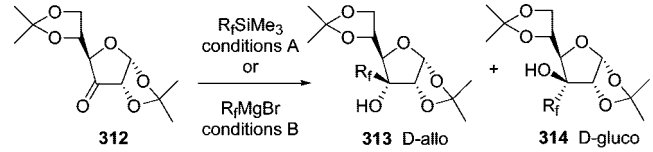


R^1	yield, %	de, %
i-C_4H_9	51	62
n-C_3H_7	55	60
Ph	82	80
c-C_6H_{11}	81	74
2-thiazolyl	58	90

Scheme 106



Scheme 107



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, %	**313/314**
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

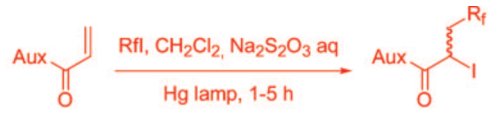
the presence of zinc powder and catalytic $AlCl_3$ and was highly diastereoselective, affording the *anti* product **311** in 54% yield with a diastereomeric excess greater than 98% (Scheme 106).[332]

Portella and co-workers described the perfluoroalkylation of carbohydrate **312** 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 **313** as unique observable products, whereas a mixture of D-*allo* and D-*gluco* epimers **313** and **314** was obtained from magnesium reagents (Scheme 107).[242]

Acrylic acid derivatives bearing a chiral auxiliary were perfluoroalkylated by a series of perfluoroalkyl iodides in the presence of an aqueous solution of $Na_2S_2O_3$ under UV irradiation. The reaction is regioselective and diastereoselective; however, the iodoperfluoroalkylation occurred with moderate diastereoselectivities (Scheme 108).[333] In these examples, the perfluoroalkyl group is not attached to the created stereogenic center but at the α carbon atom. Products **315** are direct precursors of chiral fluorine-containing amino acids.

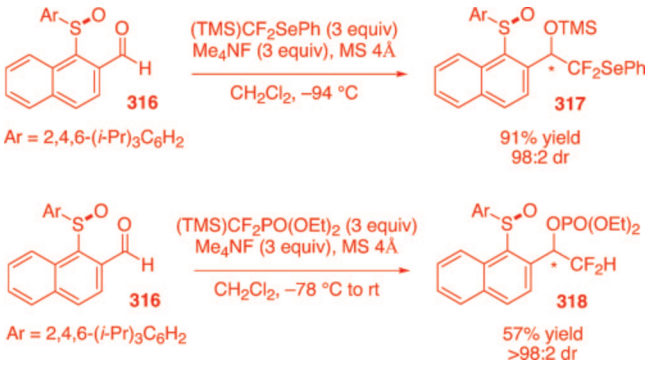
In 2006, Toru and co-workers reported the diastereoselective difluoromethylation of 2-naphthaldehyde bearing a

Scheme 108



Aux	R_fI	yield, %	dr
Ph, O	*n*-C_6F_{13}I	80	50:50
O, O, O	*n*-C_6F_{13}I	82	60:40
Ph, O	*n*-C_6F_{13}I	87	76:24
Bn, O, N, O	*n*-C_6F_{13}I	69	76:24
S, N, O_2	*n*-C_6F_{13}I *n*-C_3F_7I *i*-C_3F_7I C_2F_5I CF_3I	73 73 75 68 63	77:23 81:19 83:17 79:21 80:20

Scheme 109

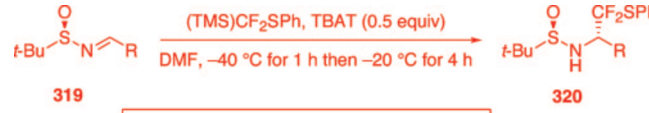


chiral sulfinyl group at C_1 **316**. The difluoromethylation was carried out with either (TMS)CF_2SePh or (TMS)-$CF_2PO(OEt)_2$ in the presence of TMAF. At low temperature, high yield and high diastereoselectivities were attained (Scheme 109).[259] Completion of the reaction between **316** and (TMS)$CF_2PO(OEt)_2$ required higher temperature, and product **318** was obtained as a result of a intramolecular rearrangement.

In 2007, Hu and Li demonstrated that (TMS)CF_2SPh is also able to serve as difluoromethylating agent under activation by TBAT. Various chiral sulfinylimines **319** reacted successfully, providing very high diastereoselectivities (Scheme 110).[334] The difluoro(phenylthio)methyl group in **320** can easily be reduced into the CF_2H group.

Alternatively, the same group utilized difluoro- and monofluoromethylphenyl sulfone as versatile reagent for the transfer of CF_2H and CFH_2 groups, respectively. Although the monofluoromethylation reaction described by Hu and Li is not a perfluoroalkylation, we think it is of interest to

Scheme 110



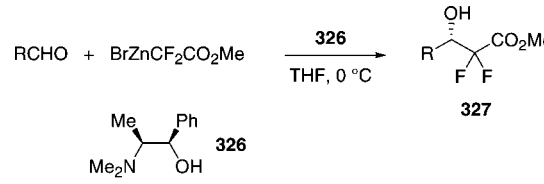
R	yield, %	dr
Ph	75	≥99:1
4-$MeOC_6H_4$	85	≥98:2
4-ClC_6H_4	89	≥99:1
2-Naphthyl	85	≥98:2
2-Furyl	72	≥98:2
i-Pr	75	≥99:1
c-Hex	74	≥99:1
(1-(*S*)-NBn_2-3-Me)Bu	58	≥99:1
n-Pr	30	≥99:1
t-Bu	71	≥99:1

mention this reaction in this section. In these two cases, deprotonation by a strong base generates the fluorinated anions that react diastereoselectively with chiral sulfinylimines (Table 25).[335–337]

4.1.2. Enantioselective Perfluoroalkylation

In 1995, Braun and co-workers disclosed the enantioselective Reformatsky reaction of bromodifluoroacetate with aldehydes. The reaction proceeded with an excess of the Reformatsky reagent in the presence of (1*R*,2*S*)-*N*-methylephedrine (**326**) to provide the corresponding α,α-difluoro-*β*-hydroxy esters **327** in good yields and enantioselectivities. Interestingly, the enantioselection was dependent on the amount of chiral ligand. Use of 10 mol % ligand **326** led to a dramatic decrease of enantioselectivity. In addition, aromatic aldehydes gave rather better optical yields than aliphatic aldehydes (Scheme 111).[338]

Scheme 111

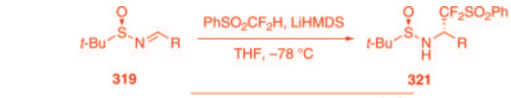


R	**326**, equiv	yield, %	ee , %
Ph	2	61	84
Ph	0.3	47	79
Ph	0.1	45	54
*p*ClPh	2	56	67
2,5-$(MeO)_2$Ph	2	71	71
i-Pr	2	63	46

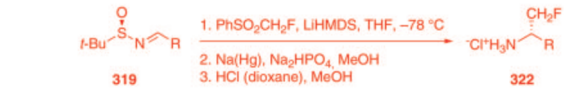
Andres and co-workers also reported the asymmetric synthesis of optically active α,α-difluoro-*β*-hydroxy esters mediated by chiral amino alcohol ligands **328**−**330** (Figure 16). Aromatic aldehydes led to good enantioselectivities (60−83% ee), while aliphatic ones gave up to 58% ee. Chiral ligands **328** and **329** were equipotent, and **330** was somewhat less efficient.[339]

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 **331** with various aldehydes, in nitroethane, using Masamune's catalyst **333**[340]

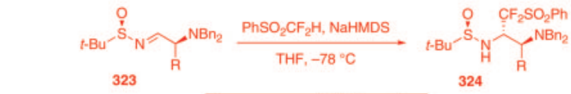
Table 25. Diastereoselective Mono- and Difluoromethylation of SulfinylimineSubstrates have opposite absolute configuration at the carbon center



R	yield, %	dr, %
Ph	95	>99
4-MeOC$_6$H$_4$	96	>99
4-ClC$_6$H$_4$	95	>99
2-Naphthyl	98	>99
2-Furyl	90	>99
Et	95	>99
i-Pr	94	>99
t-Bu	85	>99

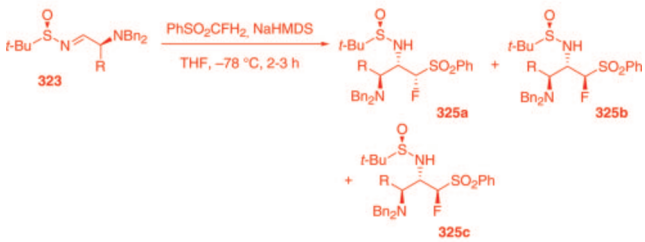


R	yield, %	dr
Ph	77	99:1
4-ClC$_6$H$_4$	73	99:1
2-Naphthyl	74	99:1
4-MeOC$_6$H$_4$	76	99:1
4-NMe$_2$C$_6$H$_4$	75	98:2
2-Furyl	71	99:1
t-Bu	73	99:1
i-Pr	70	99:1
n-Pr	70	99:1
i-Bu	74	99:1



R	yield, %	dr
Bn	80	99:1
Bn[a]	85	95:5
i-Bu	83	99:1
i-Pr	74	99:1
Ph	73	99:1
s-Bu	83	98:2
Me	95	99:1

[a] Substrate have opposite absolute configuration at the carbon center



R	yield, %[a]	dr[b]	325a : 325b
Bn	99	>99:1	1.5:1
i-Bu	97	>99:1	2.2:1
i-Pr	87	>99:1	3.3:1

[a] yield of **325a** + **325b**
[b] facial selectivity [(**325a** + **325b**):**325c**]

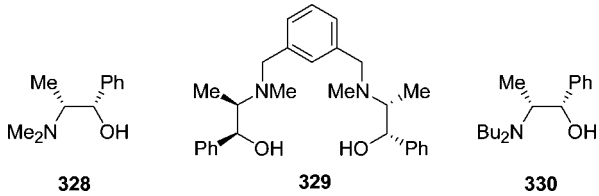
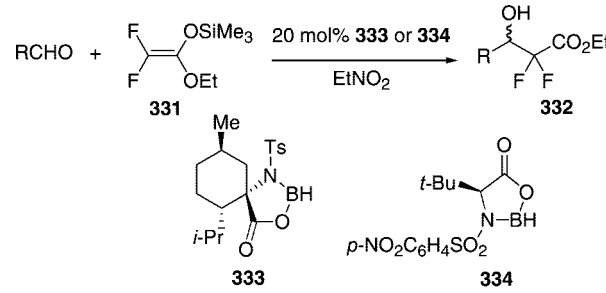


Figure 16. Chiral amino alcohol ligands for enantioselective Reformatsky reaction of bromodifluoroacetate with aldehydes.

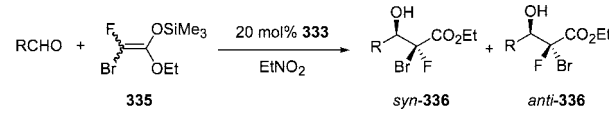
or Kiyooka's catalyst **334**[341] yielded α,α-difluoro-*β*-hydroxy esters **332** with excellent yields and high enantioselectivities (Scheme 112). Kiyooka's catalyst was more efficient in the

Scheme 112



R	cat.	temp, °C	yield, %	ee, %
Ph	**333**	-78	>99	97 (*R*)
Ph	**334**	-20	96	65 (*R*)
BnOCH$_2$	**333**	-78	94	98
(*E*)-PhCH=CH	**333**	-78	>99	96
c-C$_6$H$_{11}$	**333**	-78	87	76
c-C$_6$H$_{11}$	**334**	-45	97	94
Et$_2$CH	**333**	-78	81	64
Et$_2$CH	**334**	-45	90	95

Scheme 113



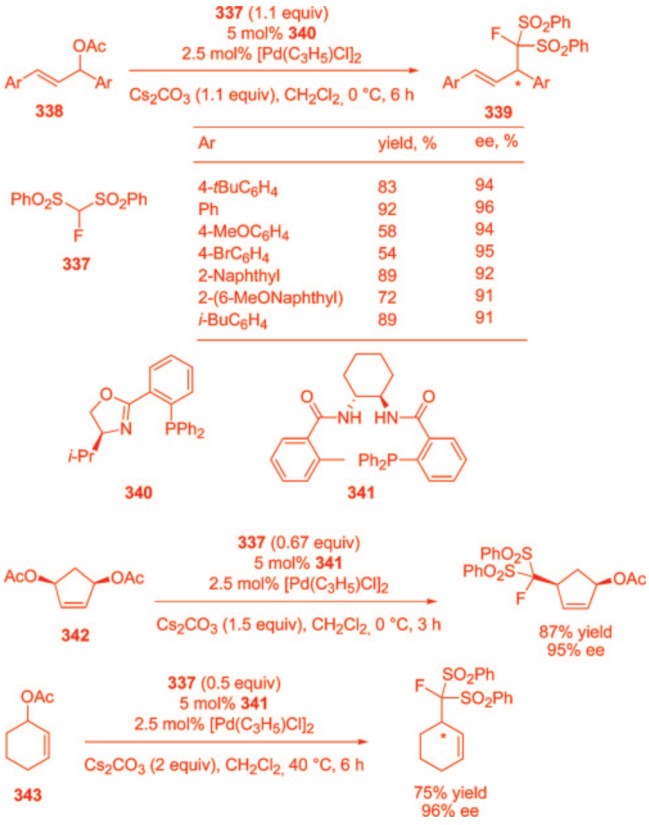
R	-78 °C		-20 °C	
	yield, % (*syn*/*anti*)	ee, % (*syn*/*anti*)	yield, % (*syn*/*anti*)	ee, % (*anti*)
PhCH$_2$CH$_2$	89 (46/54)	98/98 (+)	85 (13/87)	92 (-)
BnOCH$_2$	81 (57/43)	97/97 (+)	80 (26/74)	72 (-)
c-C$_6$H$_{11}$	74 (52/48)	94/89 (+)	90 (20/80)	81 (-)
Et$_2$CH	70 (54/46)	99/98 (+)	85 (23/77)	74 (-)

enantioselection with secondary aldehydes than Masamune's catalyst.[342,343]

Additionally, the bromofluoroketene silyl acetal **335** (*E*/*Z* = 62/38) was reacted with various aldehydes in the presence of Masamune's catalyst **333** to afford a mixture of *syn*- and *anti*-aldol products **336**. Although the diastereoselectivity was low, both diastereomers were obtained with high enantioselectivities (90−99% ee) (Scheme 113).[344] 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 113). Different transition structures might account for the reversal of the enantioselection.[26]

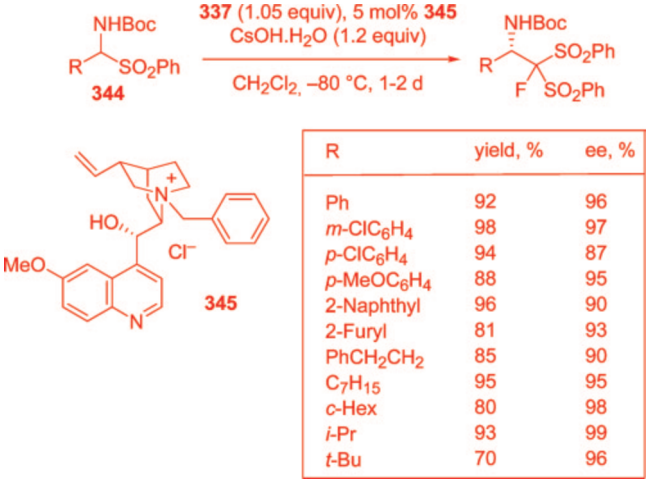
Monofluoromethylation by means of fluorobis(phenylsulfonyl)methane **337**, a fluoromethide equivalent, was recently investigated by Shibata, Toru, and co-workers. They found that the palladium catalyzed asymmetric allylic fluorobis(phenylsulfonyl)methylation reaction of allyl acetates **338** proceeds with very high enantioselectivities (up to 97%) to afford products **339**. Of the catalysts tested, (*S*)-PHOX **340** works well with allyl acetates **338** whereas (*R*,*R*)-DPPBA **341** was preferred in the case of allyl acetates **342** and **343** (Scheme 114). The removal of the two sulfonyl groups at

Scheme 114



Ar	yield, %	ee, %
4-*t*BuC$_6$H$_4$	83	94
Ph	92	96
4-MeOC$_6$H$_4$	58	94
4-BrC$_6$H$_4$	54	95
2-Naphthyl	89	92
2-(6-MeONaphthyl)	72	91
i-BuC$_6$H$_4$	89	91

Scheme 115



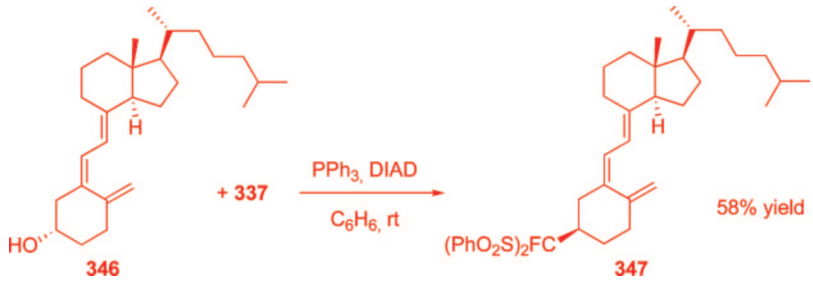
R	yield, %	ee, %
Ph	92	96
m-ClC$_6$H$_4$	98	97
p-ClC$_6$H$_4$	94	87
p-MeOC$_6$H$_4$	88	95
2-Naphthyl	96	90
2-Furyl	81	93
PhCH$_2$CH$_2$	85	90
C$_7$H$_{15}$	95	95
c-Hex	80	98
i-Pr	93	99
t-Bu	70	96

the fluorinated carbon can be achieved with activated magnesium in methanol.[345]

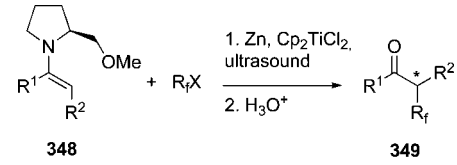
An organocatalytic variant was next developed by the same group in a Mannich-type reaction. Indeed, catalytic enantioselective fluorobis(phenylsulfonyl)methylation using reagent **337** was realized with in situ generated imines from α-amido sulfones **344**. The use of cinchona alkaloid phase-transfer catalyst **345** allowed us to attain very high enantioselectivities (Scheme 115).[346] Here again, the reductive desulfonylation with magnesium provides interesting monofluoromethylated products.

Prakash, Olah, and co-workers also employed reagent **337** with chiral enantiopure alcohols in a stereospecific Mitsunobu reaction that proceeds through an S_N2 pathway with Walden inversion. The formation of the C−R_f bond with concomitant stereospecific inversion at the existing stereogenic center was observed on simple chiral enantiopure secondary alcohols such as 2-octanol, 1-phenylethanol, and 1-(naphthalen-2-yl)ethanol but also on vitamin D_3 (Scheme 116).[347] The reductive desulfonylation provided the monofluoromethylated vitamin D_3.

Scheme 116



Scheme 117



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]

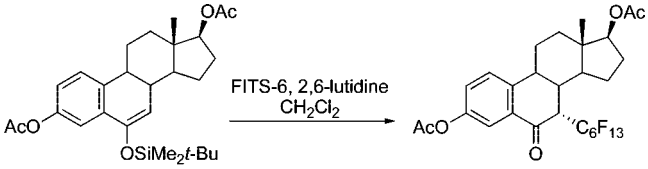
[a] Reaction run with (*R*)-proline auxiliary.

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.[289] The first report with stereochemical information concerned the perfluoroalkylation of chiral enamine **348** derived from (*S*)-proline (Scheme 117).[294] Treatment of enamines **348** with a perfluoroalkyl halide in the presence of Cp_2TiCl_2, Zn powder, and ultrasound afforded the corresponding α-perfluoroalkyl ketones **349** with moderate stereoselection.

Blazejewski and co-workers described the synthesis of 7α-perfluorohexylestradiol. Reaction of FITS-6 (perfluorohexylphenyliodonium trifluoromethanesulfonate) with silyl enol

Scheme 118



283 350

ether **283** provided the perfluorohexyl steroid **350** in 80% yield with high diastereoselectivity (α/β = 10/1) (Scheme 118).[298]

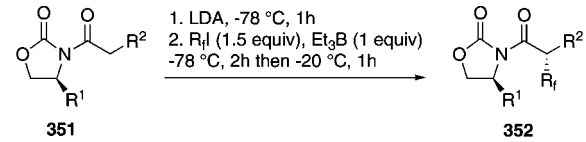
4.3. Radical or Carbene Perfluoroalkylation Reactions

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.[296,297] The same group extended the method to diastereoselective perfluoroalkylation (R_f)[348] of **351**, but also to ethoxycarbonyl difluoromethylation (EtO_2CCF_2),[349] diethylphosphonate difluoromethylation [$(EtO)_2POCF_2$],[350] and bromodifluoromethylation[351,352] (Scheme 119). Various perfluoroalkyl iodides were applicable to the perfluoroalkylation of lithium enolates of *N*-acyloxazolidinones **351** employing the triethylborane-mediated radical procedure; the corresponding α-perfluoroalkylated carboximides **352** were produced in good yields and diastereoselectivities (55−93% de).[348] The diastereoselective introduction of the EtO_2CCF_2 group into **351** proceeded under similar conditions provided the chiral imide enolate is added to a solution of ethyl difluoroiodoacetate and triethylborane.[349,353] Diethyl difluoroiodophosphonate [$ICF_2PO(OEt)_2$] also reacted with the lithium enolate of *N*-acyloxazolidinone **354** in the presence of Et_3B to provide the diethylphosphonodifluoromethylated product **355** in 92% yield and 77% de.[350] Interestingly, triethylborane was not necessary for the diastereoselective bromodifluoromethylation of **351** using either dibromodifluoromethane or bromodifluoromethane. An ionic mechanism involving the insertion of difluorocarbene can account for the observations.[354]

5. Concluding Remarks

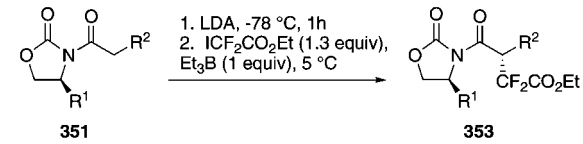
Outstanding progress has been recently made in the development of reagents and methodologies in asymmetric fluorination, trifluoromethylation, and perfluoroalkylation. High levels of diastereoselectivity are frequently observed in nucleophilic and electrophilic fluorination as well as in nucleophilic 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, transition-metal catalysts, and organocatalysis 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, excellent methods are now available, in particular for trifluoromethylation, leading to very high level of enantioselectivity. However, the enantioselective nucleophilic trifluoromethy-

Scheme 119



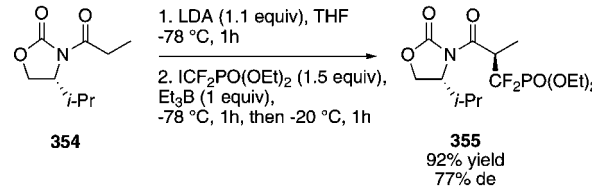
351 352

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

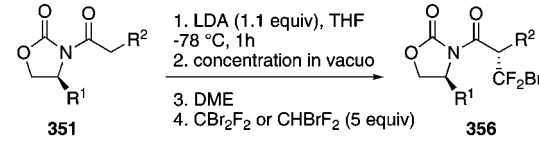


351 353

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



354 355
92% yield
77% de



351 356

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, results of reactions run with $CHBrF_2$.

lation of aldehydes remains problematic. 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.

6. Acknowledgments

The authors wish to sincerely thank their co-workers listed in the references. Financial support by NSFC (China) and CNRS (France) is acknowledged.

7. References

(1) Schofield, H. *J. Fluorine Chem.* **1999**, *100*, 7.
(2) Filler, R.; Kobayashi, Y.; Yagupolskii, Y. L. *Organofluorine Compounds in Medicinal Chemistry and Biological Applications*; Elsevier: Amsterdam, 1993.
(3) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994.
(4) Welch, J. T. *Selective Fluorination*; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991.
(5) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II. A Critical Review*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.
(6) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(7) *Organofluorine Compounds. Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000.
(8) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505.
(9) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381.
(10) *Biomedical Fontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; Washington, DC, 1996.
(11) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004..
(12) Thayer, A. *Chem. Eng. News* **2006**, *84*, 15.
(13) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(14) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1.
(15) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3, and references therein.
(16) Parsch, J.; Engels, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 5664.
(17) Dunitz, J. D.; Taylor, R. *Chem.—Eur. J.* **1997**, *3*, 89.
(18) Barbarich, T. J.; Rithner, C. D.; Miller, S. M.; Anderson, O. P.; Strauss, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 4280.
(19) DesMarteau, D. D.; Xu, Z. Q.; Witz, M. *J. Org. Chem.* **1992**, *57*, 629.
(20) Seebach, D. *Angew. Chem., Int. Ed.* **1990**, *29*, 1320.
(21) Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284.
(22) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.
(23) Gladysz, J. A.; Curran, D. P. *Fluorous chemistry; Tetrahedron 58*; Elsevier: 2002.
(24) Ramachandran, P. V. *Asymmetric fluoroorganic chemistry. Synthesis, applications, and future directions*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000.
(25) Soloshonok, V. A. *Enantiocontrolled synthesis of fluoro-organic compounds*; Wiley: Chichester, 1999.
(26) Iseki, K. *Tetrahedron* **1998**, *54*, 13887.
(27) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.
(28) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661.
(29) Enantiocontrolled Synthesis of Fluoro-organic Compounds. Hayashi, T., Soloshonok, V. A., Eds.; *Tetrahedron: Asymmetry* 1994; Vol. 5 (6).
(30) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1.
(31) Vincent, S. P.; Burkart, M. D.; Tsai, C. Y.; Zhang, Z. Y.; Wong, C. H. *J. Org. Chem.* **1999**, *64*, 5264.
(32) Rozen, S. In *Synthetic Fluorine Chemistry*; Olah, G. A., Chambers, R. D., Prakash, G. K. S., Eds.; Wiley: New York, 1992.
(33) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.
(34) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717.
(35) Baudoux, J.; Cahard, D. *Org. React. (Hoboken, NJ, U. S.); John Wiley & Sons, Inc.* **2007**, *69*, 347.
(36) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307.
(37) Zhang, X.; Wang, H.; Guo, Y. *Rapid Commun. Mass Spectrom.* **2006**, 1877.
(38) Differding, E.; Rüegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815.
(39) Differding, E.; Wehrli, M. *Tetrahedron Lett.* **1991**, *32*, 3819.
(40) Singh, R.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31.
(41) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431.
(42) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111.
(43) Davis, F. A.; Kasu, P. V. N. *Org. Prep. Proced. Int.* **1999**, *31*, 125.
(44) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, *17*, 2609.
(45) Thomas, M. G.; Suckling, C. J.; Pitt, A. R.; Suckling, K. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3191.
(46) Patrick, T. B.; Mortezania, R. *J. Org. Chem.* **1988**, *53*, 5153.
(47) Pataki, J. *Tetrahedron* **1973**, *29*, 4053.
(48) Königsberger, K.; Chen, G.-P.; Vivelo, J.; Lee, G.; Fitt, J.; McKenna, J.; Jenson, T.; Prasad, K.; Repic, O. *Org. Process. Res. Dev.* **2002**, *6*, 665.
(49) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *Chem. Commun.* **1992**, 595.
(50) Poss, A. J.; Van Der Puy, M.; Nalewajek, D.; Shia, G. A.; Wagner, W. J.; Frenette, R. L. *J. Org. Chem.* **1991**, *56*, 5962.
(51) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *16*, 19.
(52) Barnette, W. E.; Wheland, R. C.; Middleton, W. J.; Rozen, S. *J. Org. Chem.* **1985**, *50*, 3698.
(53) Rozen, S.; Lerman, O. *J. Am. Chem. Soc.* **1979**, *101*, 2782.
(54) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.
(55) Nakanishi, S.; Jensen, E. V. *J. Org. Chem.* **1962**, *27*, 702.
(56) Gabbar, R.; Jensen, E. *J. Org. Chem.* **1958**, *23*, 1406.
(57) Nakanishi, S.; Jensen, E. V. *Chem. Pharm. Bull.* **1977**, *25*, 3395.
(58) Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1995**, *36*, 4721.
(59) *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J., Eds.; Van Nostrand Reinhold: New York, 1972; Vol. 8.
(60) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
(61) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.
(62) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.
(63) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563.
(64) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379.
(65) Umemoto, T.; Nagayoshi, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2287.
(66) Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1999**, *40*, 2673.
(67) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Tewson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2365.
(68) Schlosser, M.; Heinz, G. *Chem. Ber.* **1969**, *102*, 1944.
(69) Dauben, W. G.; Greenfield, L. J. *J. Org. Chem.* **1992**, *57*, 1597.
(70) Manthey, M. K.; Gonzalez-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 625.
(71) Shutske, G. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1544.
(72) Padova, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *Chem. Commun.* **1995**, 661.
(73) Padova, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *Tetrahedron* **1996**, *52*, 263.
(74) Garrett, G. S.; Emge, T. J.; Lee, S. C.; Fischer, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.* **1991**, *56*, 4823.
(75) Hoffman, R. V.; Saenz, J. E. *Tetrahedron Lett.* **1997**, *38*, 8469.
(76) Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 4195.
(77) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 126.
(78) Mohar, B.; Sterk, D.; Ferron, L.; Cahard, D. *Tetrahedron Lett.* **2005**, *46*, 5029.
(79) Kodama, T.; Matsuda, A.; Shuto, S. *Tetrahedron* **2006**, *62*, 10011.
(80) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479.
(81) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610.
(82) Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943.
(83) Solladié-Cavallo, A.; Bouérat, L. *Tetrahedron: Asymmetry* **2000**, *11*, 935.
(84) Solladié-Cavallo, A.; Bouérat, L.; Jierry, L. *Eur. J. Org. Chem.* **2001**, 4557.
(85) Solladié-Cavallo, A.; Lupattelli, P.; Jierry, L.; Bovicelli, P.; Angeli, F.; Antonioletti, R.; Klein, A. *Tetrahedron Lett.* **2003**, *44*, 6523.
(86) Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2362.
(87) Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307.
(88) VanVliet, D. S.; Lee, K. H. *Tetrahedron Lett.* **1999**, *40*, 2259.
(89) VanVliet, D. S.; Tachibana, Y.; Bastow, K. F.; Huang, E.-S.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 1422.
(90) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem.* **1998**, *63*, 2161.
(91) Konas, D. W.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 8831.
(92) Davis, F. A.; Reddy, R. E. *Tetrahedron: Asymmetry* **1994**, *5*, 955.
(93) Nakano, T.; Makino, M.; Morizawa, Y.; Matsumura, Y. *Angew. Chem., Int. Ed.* **1996**, *35*, 1019.

(94) Gênet, J. P.; Durand, J. O.; Roland, S.; Savignac, M.; Jung, F. *Tetrahedron Lett.* **1997**, *38*, 69.
(95) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452.
(96) Wildonger, K. J.; Leanza, W. J.; Ratcliffe, R. W.; Springer, J. P. *Heterocycles* **1995**, *41*, 1891.
(97) Slusarchyk, W. A.; Applegate, H. E.; Funke, P.; Koster, W.; Puar, M. S.; Young, M.; Dolfini, J. E. *J. Org. Chem.* **1973**, *38*, 943.
(98) Ihara, M.; Kai, T.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2357.
(99) Ihara, M.; Taniguchi, N.; Kai, T.; Satoh, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 221.
(100) Ihara, M.; Kawabuchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1041.
(101) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587.
(102) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359.
(103) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709.
(104) Shibata, N.; Ishimura, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703.
(105) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, 4204.
(106) Shibatomi, K.; Tsuzuki, Y.; Nakata, S.-i.; Sumikawa, Y.; Iwasa, S. *Synlett* **2007**, 551.
(107) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.
(108) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135.
(109) Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546.
(110) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730.
(111) Davis, F. A.; Qi, H. Y. *Tetrahedron Lett.* **1996**, *37*, 4345.
(112) Davis, F. A.; Qi, H. Y.; Sundarababu, G. *Tetrahedron* **2000**, *56*, 5303.
(113) Siddiqui, M. A.; Marquez, V. E.; Driscoll, J. S.; Barhi, J. J. *Tetrahedron Lett.* **1994**, *35*, 3263.
(114) Less, S. L.; Handa, S.; Millburn, K.; Leadlay, P. F.; Dutton, C. J.; Staunton, J. *Tetrahedron Lett.* **1996**, *37*, 3515.
(115) Shi, Z.-D.; Liu, H.; Zhang, M.; Yang, D.; Burke, T. R., Jr *Synth. Commun.* **2004**, *34*, 3883.
(116) Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A. M.; McCarthy, T. D. *Synlett* **2004**, 791.
(117) Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13.
(118) Differding, E.; Duthaler, R. O.; Krieger, A.; Rüegg, G. M.; Schmit, C. *Synlett* **1991**, 395.
(119) Kotoris, C. C.; Wen, W.; Lough, A.; Taylor, S. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, *8*, 1271.
(120) Ruiz, M.; Ojea, V.; Quintela, J. M.; Guillin, J. J. *Chem. Commun.* **2002**, 1600.
(121) Shibata, N.; Tarui, T.; Doi, Y.; Kirk, K. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4461.
(122) Giuffredi, G.; Bobbio, C.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 5361.
(123) Tredwell, M.; Tenza, K.; Pacheco, C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 4495.
(124) Teare, H.; Huguet, F.; Tredwell, M.; Thibaudeau, S.; Luthra, S.; Gouverneur, V. *Arkivoc* **2007**, 232.
(125) Purser, S.; Odell, B.; Claridge, T. D. W.; Moore, P. R.; Gouverneur, V. *Chem.—Eur. J.* **2006**, *12*, 9176.
(126) Purser, S.; Wilson, C.; Moore, P. R.; Gouverneur, V. *Synlett* **2007**, 1166.
(127) Lam, Y.-h.; Bobbio, C.; Cooper, I. R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5106.
(128) Posner, G. H.; Frye, L. L. *J. Fluorine Chem.* **1985**, *28*, 151.
(129) Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani, F.; Zanda, M.; Zappala, C. *J. Fluorine Chem.* **1997**, *84*, 79.
(130) Caille, J.-C.; Miel, H.; Armstrong, P.; McKervey, M. A. *Tetrahedron Lett.* **2004**, *45*, 863.
(131) Wnuk, S. F.; Robins, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2519.
(132) Iwasaki, Y.; Shimizu, M.; Hirosawa, T.; Yamada, S. *Tetrahedron Lett.* **1996**, *37*, 6753.
(133) Muñiz, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1653.
(134) Muñiz, K. In *Organic Synthesis Highlight V*; Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH Verlag GmbH & KGaA: Weinheim, Germany, 2003.
(135) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147.
(136) Surya Prakash, G. K.; Beier, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2172.
(137) Pihko, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544.
(138) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065.
(139) Audouard, C.; Ma, J.-A.; Cahard, D. *Adv. Org. Synth.* **2006**, *2*, 431–461.
(140) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087.
(141) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971.
(142) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B. C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273.
(143) Takeuchi, Y.; Satoh, A.; Suzuki, T.; Kameda, A.; Dohrin, M.; Satoh, T.; Koizumi, T.; Kirk, K. L. *Chem. Pharm. Bull.* **1997**, *45*, 1085.
(144) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708.
(145) Shibata, N.; Liu, Z.; Takeuchi, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1954.
(146) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583.
(147) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699.
(148) Desmurs, J.-R.; Hébrault, D.; Cahard, D.; Audouard, C.; Plaquevent, J.-C. PCT Int. Appl. (Rhodia Chimie, Fr.) Wo 2001090107, 2001.
(149) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728.
(150) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.
(151) Abdul-Ghani, M.; Banks, R. E.; Besheesh, M. K.; Sharif, I.; Syvret, R. G. *J. Fluorine Chem.* **1995**, *73*, 255.
(152) Baudequin, C.; Loubassou, J. F.; Plaquevent, J.-C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122*, 189.
(153) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867.
(154) Ramirez, J.; Huber, D. P.; Togni, A. *Synlett* **2007**, 1143.
(155) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2006**, *127*, 548.
(156) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469.
(157) Mohar, B.; Baudoux, J.; Plaquevent, J.-C.; Cahard, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4214.
(158) Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*, 1833.
(159) Laumonnier, F.; Roger, S.; Guérin, P.; Molinari, F.; M'Rad, R.; Belhaj, A.; Helayem, M.; Persico, A. M.; Cahard, D.; Chaabouni, H.; Colleaux, L.; Constant, J.; Guennec, J.-Y. L.; Moraine, C.; Briault, S. *Am. J. Psychiatry* **2006**, *163*, 1622.
(160) Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem.* **2003**, *68*, 2494.
(161) Shibata, N.; Ishimaru, T.; Nakamura, M.; Toru, T. *Synlett* **2004**, 2509.
(162) Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C.-A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. *Chem. Commun.* **2005**, *44*, 5580.
(163) Baudequin, C.; Plaquevent, J.-C.; Audouard, C.; Cahard, D. *Green Chem.* **2002**, *4*, 584.
(164) Thierry, B.; Plaquevent, J. C.; Cahard, D. *Mol. Diversity* **2005**, *9*, 277.
(165) Thierry, B.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synlett* **2004**, 856.
(166) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941.
(167) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, *10*, 1467.
(168) Sodeoka, M.; Hamashima, Y. *Shokubai* **2007**, *49*, 20.
(169) Shibata, N. *Yuki Gosei Kagaku Kyokaishi* **2006**, *64*, 14.
(170) Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55*, 801.
(171) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979.
(172) Perseghini, M.; Massaccesi, M.; Liu, Y.; Togni, A. *Tetrahedron* **2006**, *62*, 7180.
(173) Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Organometallics* **2007**, *26*, 5902.
(174) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.
(175) Sodeoka, M.; Hamashima, Y. *Jpn. Kokai Tokkyo Koho* (Takasago Perfumery Co., Ltd., Japan); Japanese Patent JP, 2004.
(176) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225.
(177) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164.
(178) Suzuki, T.; Goto, T.; Hamashima, Y.; Sodeoka, M. *J. Org. Chem.* **2007**, *72*, 246.
(179) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447.
(180) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.-i.; Goto, T.; Sodeoka, M. *Tetrahedron* **2006**, *62*, 7168.
(181) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309.
(182) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324.
(183) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115.
(184) Moriya, K.-i.; Hamashima, Y.; Sodeoka, M. *Synlett* **2007**, 1139.
(185) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135.
(186) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007.
(187) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2004**, *125*, 1357.

(188) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053.
(189) O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. *Nature* **2002**, *416*, 279.
(190) Dong, C.; Huang, F.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004**, *427*, 561.
(191) Shibata, N.; Yasui, H.; Nakamura, S.; Toru, T. *Synlett* **2007**, 1153.
(192) Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5435.
(193) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.
(194) Suzuki, S.; Furuno, H.; Yokoyama, Y.; Inanaga, J. *Tetrahedron: Asymmetry* **2006**, *17*, 504.
(195) Nakamura, S.; Hirata, N.; Kita, T.; Yamada, R.; Nakane, D.; Shibata, N.; Toru, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7648.
(196) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.
(197) Park, E. J.; Kim, H. R.; Joung, C. U.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451.
(198) Cahard, D.; Petit, S.; Plaquevent, J.-C. Unpublished results.
(199) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991.
(200) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.
(201) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.
(202) Beeson, T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.
(203) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051.
(204) Greedy, B.; Paris, J. M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291.
(205) Kabore, L.; Chebli, S.; Faure, R.; Laurent, E.; Marquet, B. *Tetrahedron Lett.* **1990**, *31*, 3137.
(206) Narizuka, S.; Koshiyama, H.; Konno, A.; Fuchigami, T. *J. Fluorine Chem.* **1995**, *73*, 121.
(207) Baba, D.; Ishii, H.; Higashiya, S.; Fujisawa, K.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 7020.
(208) Baba, D.; Fuchigami, T. *Tetrahedron Lett.* **2002**, *43*, 4805.
(209) Baba, D.; Yang, Y.-J.; Uang, B.-J.; Fuchigami, T. *J. Fluorine Chem.* **2003**, *121*, 93.
(210) Suzuki, K.; Fuchigami, T. *J. Org. Chem.* **2004**, *69*, 1276.
(211) Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104*, 247.
(212) Haufe, G.; Bruns, S.; Runge, M. *J. Fluorine Chem.* **2001**, *112*, 55.
(213) Haufe, G.; Bruns, S. *Adv. Synth. Catal.* **2002**, *344*, 165.
(214) Hann, G. L.; Sampson, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1650.
(215) Beaumont, A. J.; Kiely, C.; Rooney, A. D. *J. Fluorine Chem.* **2001**, *108*, 47.
(216) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635.
(217) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975.
(218) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195.
(219) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.
(220) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123.
(221) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726.
(222) Stahly, G. P.; Bell, D. R. *J. Org. Chem.* **1989**, *54*, 2873.
(223) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.
(224) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.
(225) Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2252.
(226) Kolomeitsev, A.; Bissky, G.; Lork, E.; Movchun, V.; Rusanov, E.; Kirsch, P.; Röschenthaler, G.-V. *Chem. Commun.* **1999**, 1107.
(227) Skiles, J. W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K. G.; Mauldin, S. C.; Vitous, J.; Mui, P. W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S. M.; Possanza, G.; Keirns, J.; Letts, G.; Rosenthal, A. S. *J. Med. Chem.* **1992**, *35*, 641.
(228) Qiu, X. L.; Qing, F. L. *J. Org. Chem.* **2002**, *67*, 7162.
(229) Qing, F.-L.; Peng, S.; Hu, C.-M. *J. Fluorine Chem.* **1998**, *88*, 79.
(230) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Chuhan, J.; Schofield, C. J. *Tetrahedron Lett.* **1995**, *36*, 7761.
(231) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *Tetrahedron* **1997**, *53*, 7275.
(232) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J. Org. Chem.* **1998**, *63*, 5179.
(233) Bansal, R. C.; Dean, B.; Hakomori, S.-I.; Toyokuni, T. *Chem. Commun.* **1991**, 796.
(234) Taylor, N. F. *Fluorinated Carbohydrates*; ACS Symposium Series 374; American Chemical Society: Washington, DC, 1988.
(235) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; J. Wiley & Sons: New York, 1991.
(236) Braun, C.; Brayer, G. D.; Withers, S. G. *J. Biol. Chem.* **1995**, *270*, 26778.
(237) Stuetz, A. E. *Angew. Chem., Int. Ed.* **1996**, *35*, 1926.
(238) Plantier-Royon, R.; Portella, C. *Carbohydr. Res.* **2000**, *327*, 119.
(239) Kozak, J.; Johnson, C. R. *Nucleosides Nucleotides* **1998**, *17*, 2221.
(240) Johnson, C. R.; Bhumralkar, D. R.; De Clercq, E. *Nucleosides Nucleotides* **1995**, *14*, 185.
(241) Munier, P.; Picq, D.; Anker, D. *Tetrahedron Lett.* **1993**, *34*, 8241.
(242) Lavaire, S.; Plantier-Royon, R.; Portella, C. *Tetrahedron: Asymmetry* **1998**, *9*, 213.
(243) Schmit, C. *Synlett* **1994**, 241.
(244) Lavaire, S.; Plantier-Royon, R.; Portella, C. *J. Carbohydr. Chem.* **1996**, *15*, 361.
(245) Eilitz, U.; Böttcher, C.; Hennig, L.; Burger, K.; Haas, A.; Gockel, S.; Sieler, J. *J. Heterocycl. Chem.* **2003**, *40*, 329.
(246) Munier, P.; Giudicelli, M. B.; Picq, D.; Anker, D. *J. Carbohydr. Chem.* **1994**, *13*, 1225.
(247) Munier, P.; Giudicelli, M. B.; Picq, D.; Anker, D. *J. Carbohydr. Chem.* **1996**, *15*, 739.
(248) Hanzawa, Y.; Uda, J.-I.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. *Chem. Pharm. Bull.* **1991**, *39*, 2459.
(249) Marecek, J. F.; Prestwich, G. D. *Tetrahedron Lett.* **1989**, *30*, 5401.
(250) Kozikowski, A. P.; Fauq, A. H.; Powis, G.; Melder, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 4528.
(251) Kozikowski, A. P.; Ognyanov, V. I.; Fauq, A. H.; Wilcox, R. A.; Nahorski, S. R. *Chem. Commun.* **1994**, 599.
(252) Wang, Z.; Ruan, B. *J. Fluorine Chem.* **1994**, *69*, 1.
(253) Odinokov, V. N.; Nazmeeva, S. R.; Savchenko, R. G. *Russian J. Org. Chem.* **2003**, *39*, 1733.
(254) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 304.
(255) Massicot, F.; Monnier-Benoit, N.; Deka, N.; Plantier-Royon, R.; Portella, C. *J. Org. Chem.* **2007**, *72*, 1174.
(256) Song, J. J.; Tan, Z.; Xu, J.; Reeves, J. T.; Yee, N. K.; Ramdas, R.; Gallou, F.; Kuzmich, K.; DeLattre, L.; Lee, H.; Feng, X.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 292.
(257) Pedrosa, R.; Sayalero, S.; Vicente, M.; Maestro, A. *J. Org. Chem.* **2006**, *71*, 2177.
(258) Enders, D.; Herriger, C. *Eur. J. Org. Chem.* **2007**, 1085.
(259) Sugimoto, H.; Nakamura, S.; Shibata, Y.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2006**, *47*, 1337.
(260) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589.
(261) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.
(262) Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847.
(263) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538.
(264) Kawano, Y.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 894.
(265) Félix, C. P.; Khatimi, N.; Laurent, A. J. *Tetrahedron Lett.* **1994**, *35*, 3303.
(266) Pawelke, G. *J. Fluorine. Chem.* **1991**, *52*, 229.
(267) Xu, W.; Dolbier, W. R. *J. Org. Chem.* **2005**, *70*, 4741.
(268) Asep, R.; Nohira, H. *Mol. Cryst. Liq. Cryst.* **2003**, *400*, 31.
(269) Prakash, G. K. S. 29th Western Regional Meeting of the American Chemical Society and 32nd Annual Meeting of the Southern California Section of the Society for Applied Spectroscopy, Pasadena, CA, October 19−23, 1993.
(270) Yudin, A. K., University of Southern California, 1996.
(271) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137.
(272) Hagiwara, T.; Kobayashi, T.; Fuchikami, T. 14th International Symposium on Fluorine Chemistry, Yokohama, Abstr. No. 1, P07, 1994.
(273) Hagiwara, T.; Kobayashi, T.; Fuchikami, T. *Main Group Chem.* **1997**, *2*, 13.
(274) Iseki, K.; Kobayashi, Y. *Rev. Heteroat. Chem.* **1995**, *12*, 211.
(275) Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231.
(276) Caron, S.; Do, N. M.; Arpin, P.; Larivée, A. *Synthesis* **2003**, *11*, 1693.
(277) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666.
(278) Nagao, H.; Kawano, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2406.
(279) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707.
(280) Mizuta, S.; Shibata, N.; Hibino, M.; Nagano, S.; Nakamura, S.; Toru, T. *Tetrahedron* **2007**, *63*, 8521.
(281) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822.
(282) Joubert, J.; Roussel, S.; Christophe, C.; Billard, T.; Langlois, B. R.; Vidal, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3133.
(283) Roussel, S.; Billard, T.; Langlois, B. R.; Saint-Jalmes, L. *Chem.—Eur. J.* **2005**, *11*, 939.
(284) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891.
(285) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 103.
(286) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579.
(287) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156.
(288) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692.
(289) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.
(290) Umemoto, T.; Ishihara, S. *J. Fluorine Chem.* **1998**, *92*, 181.
(291) Umemoto, T.; Adachi, K.; Ishihara, S. *J. Org. Chem.* **2007**, *72*, 6905.

(292) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.−Eur. J.* **2006**, *9*, 2579–2586.
(293) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754–757.
(294) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186.
(295) Lan-Hargest, H.-Y.; Elliott, J. D.; Eggleston, D. S.; Metcalf, B. W. *Tetrahedron Lett.* **1987**, *28*, 6557.
(296) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169.
(297) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961.
(298) Blazejewski, J.-C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11*, 335.
(299) Foulard, G.; Brigaud, T.; Portella, C. *J. Fluorine Chem.* **1998**, *91*, 179.
(300) Foulard, G.; Brigaud, T.; Portella, C. *J. Org. Chem.* **1997**, *62*, 9107.
(301) Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62*, 7199.
(302) Mikami, K.; Itoh, Y. *Jpn. Kokai Tokkyo Koho* (Tosoh F-Tech Inc., Japan; Tokyo Institute of Technology). Jp, 2007.
(303) Lopin, C.; Gautier, A.; Gouhier, G.; Piettre, S. *J. Am. Chem. Soc.* **2002**, *124*, 14668, and references therein.
(304) Kirk, K. L. In *Fluorine-containing Amino Acids*; Kukhar′, V. P., Soloshonok, V. A., Eds.; Wiley: New York, 1995.
(305) Riess, J. G.; Greiner, J. In *Carbohydrates as Organic Raw Materials II*; Descotes, G., Ed.; VCH: Weinheim, 1992.
(306) Solladié-Cavallo, A.; Farkhani, D.; Fritz, S.; Lazrak, T.; Suffert, J. *Tetrahedron Lett.* **1984**, *25*, 4117.
(307) Solladié-Cavallo, A.; Suffert, J. *Synthesis* **1985**, 659.
(308) Solladié-Cavallo, A.; Farkhani, D.; Dreyfuss, A. C.; Sanch, F. *Bull. Soc. Chim. Fr.* **1986**, *6*, 906.
(309) Solladié-Cavallo, A.; Suffert, J. *Tetrahedron Lett.* **1984**, *25*, 1897.
(310) Uno, H.; Okada, S.-I.; Ono, T.; Shiraishi, Y.; Suzuki, H. *J. Org. Chem.* **1992**, *57*, 1504.
(311) Hallinan, E. A.; Fried, J. *Tetrahedron Lett.* **1984**, *25*, 2301.
(312) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406.
(313) Hanzawa, Y.; Inazawa, K.; Kon, A.; Aoki, H.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 659.
(314) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803.
(315) Matsumura, Y.; Fujii, H.; Nakayama, T.; Morizawa, Y.; Yasuda, A. *J. Fluorine Chem.* **1992**, *57*, 203.
(316) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 5291.
(317) Evans, G. B.; Furneaux, R. H.; Lewandowicz, A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *46*, 3412.
(318) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461.
(319) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276.
(320) Konas, D. W.; Pankuch, J. J.; Coward, J. K. *Synthesis* **2002**, *17*, 2616.
(321) Ding, Y.; Wang, J.; Abboud, K. A.; Xu, Y.; Dolbier, W. R.; Richards, N. G. J. *J. Org. Chem.* **2001**, *66*, 6381.
(322) Meffre, P.; Dave, R. H.; Leroy, J.; Badet, B. *Tetrahedron Lett.* **2001**, *42*, 8625.
(323) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394.
(324) Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, R. E.; Meyer, E. F.; Trainor, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 3368.
(325) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M. *J. Med. Chem.* **1985**, *28*, 1553.
(326) Thaisrivongs, S.; Pals, D. T.; Kati, W. M.; Turner, S. R.; Thomasco, L. M.; Watt, W. *J. Med. Chem.* **1986**, *29*, 2080.
(327) Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.* **1987**, *30*, 1617.
(328) Schirlin, D.; Baltzer, S.; Altenburger, J. M. *Tetrahedron Lett.* **1988**, *29*, 3687.
(329) Sham, H. L.; Rempel, C. A.; Stein, H.; Cohen, J. *Chem. Commun.* **1990**, 904.
(330) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7195.
(331) Chou, T. S.; Heath, P. C.; Patterson, L. E.; Poteet, L. M.; Lakin, R. E.; Hunt, A. H. *Synthesis* **1992**, 565.
(332) Peng, S.; Qing, F.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3345.
(333) Yajima, T.; Nagano, H. *Org. Lett.* **2007**, *9*, 2513.
(334) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489.
(335) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882.
(336) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693.
(337) Liu, J.; Li, Y.; Hu, J. *J. Org. Chem.* **2007**, *72*, 3119.
(338) Braun, M.; Vonderhagen, A.; Waldmüller, D. *Liebigs Ann. Chem.* **1995**, 1447.
(339) Andrés, J. M.; Martinez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *Synthesis* **1996**, 1070.
(340) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365.
(341) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276.
(342) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 1447.
(343) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271.
(344) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 7209.
(345) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Yasui, H.; Nakamura, S.; Toru, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4973.
(346) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394.
(347) Surya Prakash, G. K.; Chacko, S.; Alconcel, S.; Stewart, T.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4933.
(348) Iseki, K.; Takahashi, M.; Asada, D.; Nagai, T.; Kobayashi, Y. *J. Fluorine Chem.* **1995**, *74*, 269.
(349) Iseki, K.; Asada, D.; Takahashi, M.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 7399.
(350) Iseki, K.; Takahashi, M.; Kobayashi, Y. Unpublished results.
(351) Iseki, K.; Asada, D.; Takahashi, M.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1995**, *36*, 3711.
(352) Iseki, K.; Asada, D.; Takahashi, M.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 1205.
(353) Iseki, K.; Asada, D.; Takahashi, M.; Nagai, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1314.
(354) Rico, I.; Cantacuzene, D.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1063, and references therein.
(355) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157.
(356) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem.−Eur. J.* **2006**, 6039.

CR800221V