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Fluorinated Carbonyl and Olefinic Compounds: Basic Character and Asymmetric Catalytic Reactions†

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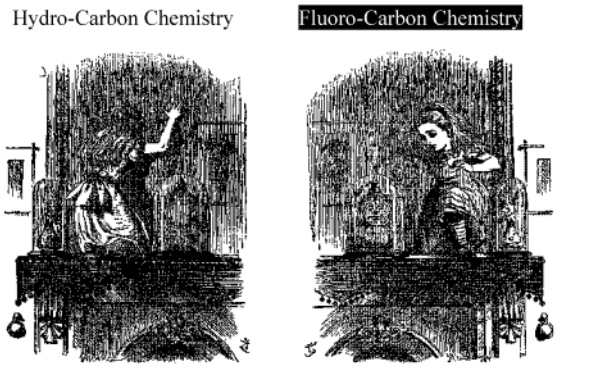
1. Introduction

The synthesis of organofluorine compounds has attracted explosive interest in recent years due to the anomalous physical properties and decreased availability of these compounds when used in physiologically active substances, liquid crystals, and other materials.[1] In the synthesis in which one or three fluorine atoms are introduced in specific absolute configuration, these fluoro-organic compounds exhibit particularly high physiological activity and remarkable physical properties.[2]



Oh, Kitty, how nice it would be if we could only get through into Fluoro-Carbon Chemistry! I'm sure it's got, oh! such beautiful things in it!

A liquid crystal such as 4-{1-(trifluoromethyl)-hexyloxycarbonyl}phenyl 4′-octyloxybiphenyl-4-carboxylate (TFMHPOBC) is an interesting example. TFMHPOBC shows an anti-ferroelectric SmC_A* liquid crystalline phase, while mono- or difluoro analogues, in sharp contrast, exhibit a ferroelectric SmC* phase.[3] Addition of a methyl group in TFMHPOBC shows a significant effect to stabilize a bent conformation for the SmC_A* phase (*anti*-*β*-Me-TFMHPOBC), while the diastereomer (*syn*-*β*-Me-TFMHPOBC) shows an SmC* phase (Figure 1).[4]

9-Fluorohydrocortisone acetate was the first successful example of a fluorinated drug in the modern and hence designed medicinal chemistry (Figure 2).[5] Fried clearly showed the effectiveness of fluorination to enhance the biological activity and to improve the

† Dedicated to the late Prof. Nobuo Ishikawa, one of the pioneering trailblazers in fluorine chemistry, on the occasion of his 13th memorial ceremony.

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Koichi Mikami was born in 1953 in Bousou, Chiba, Japan. He received his Ph.D. in 1982 under the supervision of Professors Takeshi Nakai and Nobuo Ishikawa at the Tokyo Institute of Technology. He was a postdoctoral fellow at Yale University with Professor Frederick E. Ziegler (1982–1983), and then returned to the Tokyo Institute of Technology as an Assistant Professor. He became Associate Professor in 1987. He has received the Tejima Award for stereocontrol based on [2,3]-sigmatropic rearrangements, the Chemical Society of Japan Award (Shinpo-Sho) for asymmetric transmission and asymmetric synthesis based on [2,3]-Wittig rearrangements, the Society of Synthetic Organic Chemistry Japan Award (Asahi-Kasei Award) for asymmetric synthesis based on carbonyl-ene reactions, the IBM award for highly efficient asymmetric catalysis, and the Ichimura Science Award for industrial application of asymmetric Friedel–Crafts reactions. He was the Bristol-Myers-Squibb Lecturer (Colorado State University), the Lilly Research Laboratories Lecturer (The Ohio State University), and the Boehringer Ingelheim Award Lecturer (Université de Montréal) and has held Visiting Professorships at the Université Paris-Sud and in Taiwan.

Yoshimitsu Itoh was born in 1977 in Kanagawa, Japan. He received his M.S. degree under the direction of Professor Koichi Mikami from the Tokyo Institute of Technology in 2003, and then, in the same group, he started his Ph.D. work on reactions of fluorinated compounds with the aid of theoretical studies. His current research interests are mainly in fluorine chemistry, such as new synthetic methods for fluorine compounds, catalytic asymmetric syntheses and reactions of fluorine compounds, and their application to new materials. He is also interested in theoretical calculations to uncover new aspects of fluorine chemistry.

versatility. The recent anti-allergy agent Fluticason propionate for hay fever (kafun-sho, in Japanese) is a further fluorinated analogue.[6]

Synthetic methods for fluorine-containing compounds can be broadly classified into two types: carbon−fluorine bond-forming reactions (fluorination with fluorinating reagents) and carbon−carbon bond-forming reactions (employing fluorine-substituted building blocks such as perfluoro-alkanes and -alkenes, or fluorine-containing carbonyl compounds).

Masahiro Yamanaka was born in 1973 in Chiba, Japan. He received his M.S. degree under the direction of Professor Takahiko Akiyama from Gakushuin University in 1998, and then began his Ph.D. work on the theoretical studies on transition-metal-assisted reactions, based particularly on Cu, Co, and Rh. He received his Ph.D. degree under the supervision of Professor Eiichi Nakamura from The University of Tokyo in 2001. He joined the group of Professor Keiji Morokuma in Emory University for a couple of months. He took a position as an Assistant Professor in the group of Professor Koichi Mikami in the Department of Applied Chemistry, Tokyo Institute of Technology, in 2001. His current research interests lie in the field between theoretical chemistry and organometallic chemistry, particularly the design and development of dynamically controlled asymmetric catalysis systems and the nature of metal–ligand-substrate interactions, further with a third component (chiral controller, activator, and deactivator).

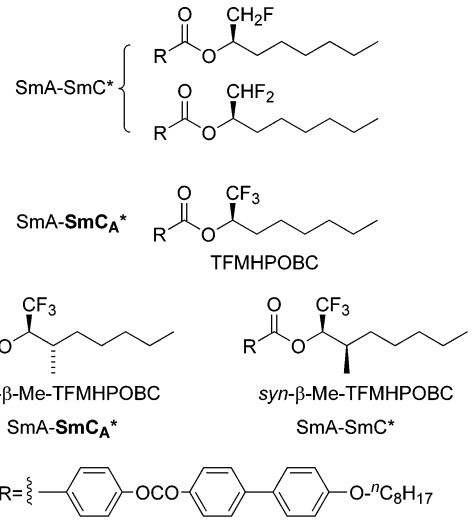


Figure 1. Remarkable effect of the CF_3 group in the fluorine-containing liquid crystals.

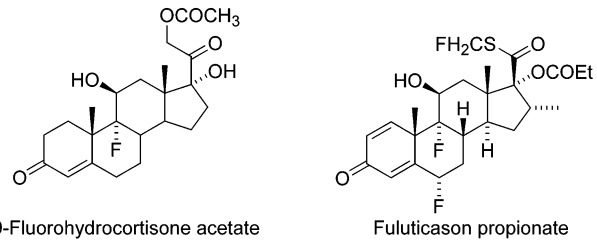


Figure 2. The first and recent examples of fluorinated cortisone.

The former can be further classified into formal electrophilic (F^+) and nucleophilic (F^-) fluorination, and a variety of fluorinating reagents have been developed for these types of specific fluorination.[1a,7]

The carbon−carbon bond-forming reactions involve ionic (electrophilic or nucleophilic) and radical reactions. However, synthetic methods involving ionic (anionic or cationic) carbon−carbon bond-forming reactions, which have already been established for non-fluorinated substrates, are often not applicable to fluorinated substrates. For example, carbon−carbon bond-forming reactions employing stock solutions of perfluoroalkyllithium reagents are not general. Perfluoroalkyllithiums are thermally unstable because of their rapid α- and β-Li−F elimination. A coexisting electrophile can only be used for in situ-generated perfluoroalkyllithium reagents at low temperature. Particularly, trifluoromethyllithium has not yet been reported in synthetic applications.[8] Therefore, trifluoromethyltrimethylsilane ($TMSCF_3$) is useful as a source of "CF_3^-".[9] However, the asymmetric $TMSCF_3$ addition to ketones using cinchona alkaloid fluorides[10] is out of the scope of this review on the asymmetric catalytic reactions of monofluorinated or trifluoromethylated substrates.[11]

Another example is perfluoroalkyl halides. In sharp contrast to normal alkyl halides, perfluoroalkyl halides cannot undergo nucleophilic alkylation because the electronegativities of perfluoroalkyl groups are higher than those of halogens. Thus, the polarization of perfluoroalkyl halides is $R_f^{\delta-}-I^{\delta+}$, and treatment with nucleophile could not produce R_f-Nu. Fluorine-containing carbonyl compounds can also be employed as fluorine-substituted building blocks. However, metal enolates of carbonyl compounds as nucleophiles, which are of central importance in the synthesis of non-fluorinated compounds, have been severely limited on α-F metal enolates to be stabilized by M−F chelate structures.[12] On the other hand, α-CF_3 metal enolates have been generally recognized to be very unstable and hence difficult to prepare because of the rapid β-M−F elimination.[13]

The isolation and purification of asymmetric catalysts after asymmetric catalytic reactions are inevitable but tedious. Quite recently, polyfluorocarbons (PFCs) have been introduced as reaction media for easy separation and purification of products and catalysts in "fluorous biphasic catalysis" (FBC). This is also out of the scope of this review.[14,15]

In this review, we first summarize the unique properties of monofluoro and trifluoromethyl compounds, which have particular significance among these types of fluorine-containing compounds, and then we describe the recent advances in the asymmetric catalytic reactions of these compounds, particularly those using fluorinated carbonyl compounds.

2. General Characteristics of Organo-fluorine Compounds

Important properties of fluorine atom and effects of the fluorine-containing compounds are as follows. (1) Steric effect: F is not sterically demanding and has the smallest van der Waals radius apart from H. (2) Electronic effect: F has the largest electronegativity. (3) Bond energy: the C−F bond is quite stable toward metabolic transformations. (4) Lipophilicity: large lipophilicity assists in distributing the fluorine-containing compounds in an organism. (5) Hydrogen bonding: the lone electron pair of F readily participates in hydrogen bonding. (6) Positron emission tomography (PET): a short-lived isotope ^{18}F ($t_{1/2}$ = 110 min) is useful for PET.

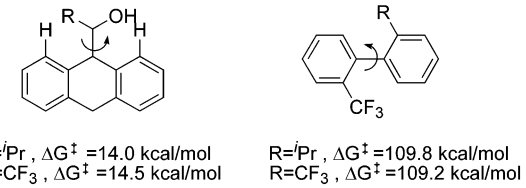


Figure 3. Energy barriers of the single bond rotation.

Table 1. Several Properties of H, F, Cl, and O (OH)

	IP[a] (kcal/mol)	EA[b] (kcal/mol)	vdW radius (Pauling) (Å)	EN[c] (Pauling)	BE[d] CH_3-X (kcal/mol)	CH_3-X (Å)
H	313.6	17.7	1.20	2.1	99	1.09
F	401.8	79.5	1.35	4.0	116	1.39
Cl	299.0	83.3	1.80	3.0	81	1.77
O (OH)	310.4	33.7	1.40	3.5	86	1.43

[a] IP = ionization potential. [b] EA = electron affinity. [c] EN = electronegativity. [d] BE = bond energy.

2.1. Properties of the Fluorine Atom

The van der Waals (vdW) radius of fluorine is the next smallest after hydrogen, and the closest to that of oxygen. The size of CF_3, on the other hand, is relatively large, in the order of Me < ^{i}Pr < CF_3 < ^{t}Bu (Taft's Es values: H = 0, Me = −1.24, ^{i}Pr = −1.71, CF_3 = −2.40, ^{t}Bu = −2.78). When the size of the substituent group is estimated on the basis of single-bond rotational barriers of biphenyl derivatives, CF_3 is approximately equivalent to ^{i}Pr and hence, in sharp contrast to the small vdW radius of fluorine, a rather bulky substituent (Figure 3).[16]

As shown in Table 1, fluorine atom has the highest electronegativity (EN) among all elements. Its ionization potential (IP) is the highest except for those of helium and neon. Therefore, electrons are drawn strongly toward the fluorine nucleus. For this reason, the electron dipole of fluorine atoms is small, and as a result, intermolecular vdW attractive force between fluorine-containing compounds is small. The C−F bond has much greater bond energy than the C−H or C−X (X = Br, Cl) bonds (Table 1). The Si−F bonding energy is even higher (141 kcal/mol) and hence sometimes employed as the driving force for the generation of a nucleophile (Nu^-) from Si−Nu.

The lone electron pair of a fluorine atom can also play a significant role in hydrogen bonding. Although 2-fluorophenol is considered to have two conformations, *syn* and *anti*, only the *syn* conformation has been observed (by microwave spectrometry).[17] The fact that the H−F distance in the *syn* conformation is 2.235 Å, which is smaller than the sum of the vdW radii of hydrogen and fluorine atoms (2.55 Å), is considered to be a proof for hydrogen bonding between OH and F (Figure 4a). Among the enol forms of 2-fluoroacetaldehyde, the *Z*,*syn* conformer is calculated at the MP2 level to be 3.2 kcal/mol more stable because of hydrogen bonding between C=C−OH and F than the *Z*,*anti* isomer (Figure 4b).[18]

Table 2. Comparison of the M−F Length with the Sum of the vdW Radii of the Metals and Fluorine

	metal											
	Li	Na	K	Cs	Al	Ti	Zr	Hf	Sn	Zn	Pd	Ag
M−F (Å)[a]	2.23−2.29	2.15−2.91	2.67−3.39	2.87−3.61	1.77−1.81	2.03−2.10	1.94−2.18	2.31−2.38	2.05−2.46	2.80	3.13−3.16	2.64−2.72
$rF + rM$ (Å)[b]	2.92	3.26	3.70	4.07	2.78	2.82	2.95	2.94	2.93	2.72	2.72	2.79
Δ: (M−F) − ($rF + rM$) (Å)	−0.66	−0.73	−0.67	−0.83	−0.99	−0.76	−0.89	−0.60	−0.68	+0.08	+0.43	−0.11
Δ/($rF + rM$) (%)	−22.6	−22.4	−18.1	−20.4	−35.6	−27.0	−30.2	−20.4	−23.2	+2.9	+15.8	−3.9

[a] Determined by X-ray crystal structure analysis. [b] Sum of vdW radii of M and F.

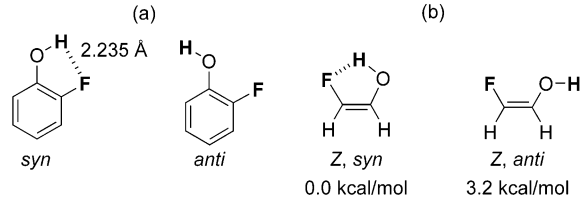


Figure 4. Hydrogen-bonding effect of fluorine-containing compounds.

Table 3. Chelate Stabilization of Alkaline Metal Enolates of 2-Fluoroacetaldehyde

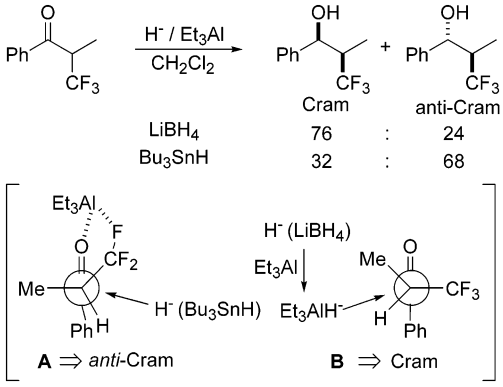
M	ΔE(anti − syn) (kcal/mol)	M−F(syn) (Å)
	1.8	
Li	13.2	1.86
Na	13.6	2.21
K	10.8	2.62

In a manner similar to hydrogen bonding, the fluorine atom can coordinate to metals. The interaction between the metal and fluorine atoms can be confirmed by the difference (Δ) between the metal−fluorine distance determined by X-ray crystal analyses[19] and the sum of the vdW radii of the metal and fluorine ($rF + rM$) (Table 2). The large negative values of Δ/($rF + rM$) for Al (−35.6%) and Ti (−27%) indicate the strong interactions and hence short bond lengths between the metal and fluorine atoms.

The chelate stabilization of alkaline metal enolates of 2-fluoroacetaldehyde has been computationally analyzed. The *Z*(O),*syn*-enolate conformer is calculated to be 11−14 kcal/mol more stable because of a strong chelate structure between H and Li, Na, or K than a *Z*(O),*anti* isomer. The chelate structure is also suggested by the shorter M−F bond lengths: for Li, 1.86 Å; Na, 2.21 Å; and K, 2.62 Å (Table 3).[20]

The M−F chelate structures may control the stereoselectivity of reactions with fluorine-containing compounds, but examples are still limited. The typical example is the reduction of 3,3,3-trifluoro-2-methyl-1-phenylpropan-1-one.[21] Reversal of the stereoselectivity was observed by the use of $LiBH_4$ vs Bu_3SnH in the presence of $AlEt_3$ (Scheme 1). The cyclic intermediate **A** may be formed in the presence of $AlEt_3$, prior to the addition of a reducing reagent. With Bu_3SnH, the reduction proceeds through the cyclic intermediate **A** to give the anti-Cram isomer selectively. On the other hand, with $LiBH_4$, hydride

Scheme 1



can attack the aluminum reagent and destroy the cyclic intermediate to form **B**. As a result, a bulky hydride complex may be generated in situ, and the reduction takes place through the Felkin−Anh model, giving the Cram isomer selectively. These characteristics of fluorine atoms serve as a basis for the following unique effects of these types of organofluorine compounds.

2.2. Fluorine Effects

A fluorine atom has a vdW radius similar to that of hydrogen or oxygen and has a structure that is isoelectronic ($2s^22p^6$ configuration) to oxygen (or alcohol). Therefore, fluoroalkanes, fluoroalkenes, and difluoromethylene groups are referred to as isosteres; they substitute isosterically as hydrogen bond acceptors to the alkanols, amides, and ethers, respectively (bioisosterism) (Figure 5).[1g,22] As a result, fluorine-containing compounds obtained by substitution of hydrogen atoms or hydroxyl groups of physiologically active compounds with fluorine atoms can be dealt with similarly by biological systems. This is referred to as the mimic effect and makes it possible to greatly change the electronic environment of a physiologically active substance without changing its steric environment.

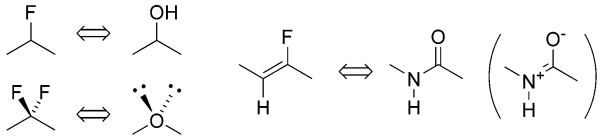


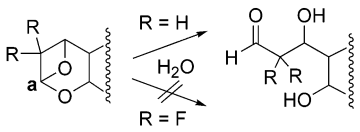
Figure 5. Mimic effect of the fluorine atom.

By virtue of the strong C−F bond energy, physiologically active fluorinated compounds can be resistant to metabolic degradation but similarly recognized. This is referred to as the block effect, which

greatly increases the metabolic resistance of a physiologically active substance. Thus, a fluorinated compound is rendered resistant to oxidation because it has much greater bond energy than C−H or C−X (X = Br, Cl) bonds, thus allowing it to escape or survive metabolic processes. The fluorine atom has reduced lipophilic effects relative to Cl or CH_3, but the SCF_3 group has greater lipophilic effects than CF_3 or OCF_3. Such XCF_3 groups are named pseudohalogens[11] and have significant electron-withdrawing effects, while being more stabilized than halogen atoms.[23] Thus, such XCF_3 molecules readily pass through cell membranes and reach active sites without being broken down. As a result, drug potency is increased, and side effects are suppressed.

The reactivity of some fluorinated compounds can be, sometimes, lowered and hence controlled by the effect of fluorine. For example, oxetane acetals are compounds that are hydrolyzed extremely easily (R = H), but hydrolysis is retarded when the group (R) is changed to F.[24] This effect is due to the decreased electron density of the proximal oxygen atom, resulting from the electron-withdrawing effect of the fluorine atom, and is also due to suppression of cation generation at carbon **a** (Scheme 2).

Scheme 2



Because fluorine atoms have the strongest electronegativity, the LUMO level of fluorinated carbonyl compounds, e.g., trifluoroacetaldehyde (fluoral), is greatly reduced relative to that non-fluorinated acetaldehyde (fluoral, −5.40 eV; acetaldehyde, −4.09 eV at the RHF/6-31G** level).[25] For this reason, the electrophilicity is dramatically increased, and fluoral readily undergoes addition reactions. The hydrate of the fluorinated carbonyl compound (e.g., $CF_3CH(OH)_2$) and the hemiacetal (e.g., $CF_3CH(OH)(OR)$) are more stable than the carbonyl form.[26] Difluoromethylene-ketones are also highly electrophilic to provide their hydrate forms. Their tetrahedral structures mimic the transition state of hydrolysis by protease enzyme, and the tetrahedral intermediates act as reversible protease inhibitors.[27] Orally active protease inhibitors are important for AIDS, metastatic cancer, arthritis, sleeping sickness, etc.

Fluorine has the highest EN and IP (except for He and Ne) (cf. Table 1); therefore, fluorine compounds exhibit characteristic reactivity and physical properties due to the stereoelectronic effect of the F and CF_3 groups (Figure 6). Bis(trifluoromethyl) groups may possess *anti*-periplanar (di-axial) conformations in the ground states and, on the basis of theoretical calculations, in the transition states, because of dipole or steric repulsion resulting from the high electronegativity of the trifluoromethyl group.[28]

Difluoroethane exhibits clear *syn*-clinal conformations on the basis of infrared (IR), Raman,[29] nuclear magnetic resonance (NMR),[30] atomic diffraction,[31] and theoretical calculations,[32] despite dipole or steric

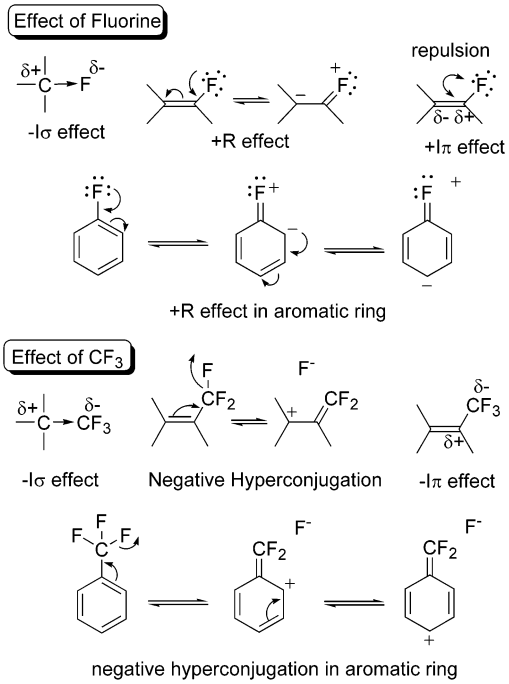


Figure 6. Various effects of the fluorine atom and the trifluoromethyl group.

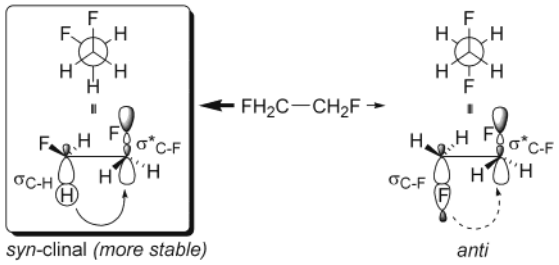


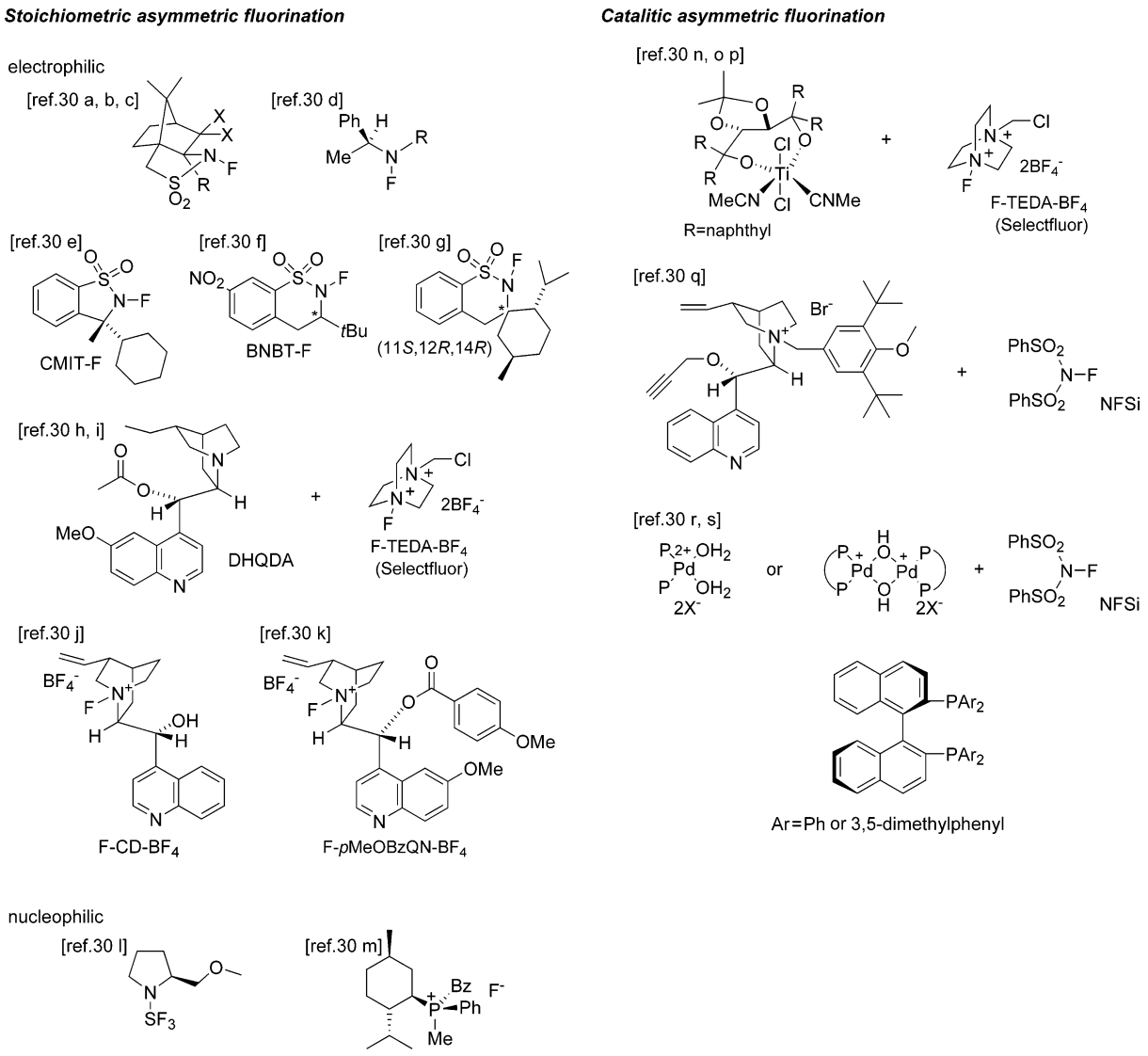
Figure 7. *Syn*-clinal effect of difluoroethane.

repulsion resulting from the high electronegativity of the fluorine atoms. This *syn*-clinal effect is due to the fact that the electron flow toward the σ^*_{C-F} bond from the σ_{C-H} bond is very large relative to the flow toward the σ^*_{C-F} bond from the σ_{C-F} bond in the *anti*-periplanar conformation. As a result, the *syn*-clinal conformation is stabilized (Figure 7). In a similar manner, fluorocarbonyl compounds exhibit clear *anti*-periplanar conformations relative to the incoming "naked" nucleophile in the carbonyl addition reactions on the basis of theoretical calculations. This is due to the effective orbital interaction between the σ^*_{C-F} bond and the π^*_{C-O} double bond, and further with the incoming nucleophile σ in the *anti*-periplanar conformation as compared to the outside or inside orientation of the C−F bond.[33]

3. Catalytic Enantioselective Reactions of Prochiral Fluorine-Containing Carbonyl Compounds or Olefins

As previously noted, enantioselective synthesis of chiral fluorine-containing compounds can be classified into two types: carbon−fluorine bond-forming reactions (fluorination with fluorinating reagents at the α-position of carbonyl compounds) and carbon−carbon bond-forming reactions (employing fluorine-

Chart 1



substituted building blocks such as perfluoro-alkanes and -alkenes, or fluorine-containing carbonyl compounds).

3.1. Asymmetric (Catalytic) Fluorination

A variety of asymmetric fluorinating reagents have been developed, as shown in Chart 1[34] and later described in this review.

3.2. Catalytic Enantioselective Functional Group Transformation: Reduction and Oxidation

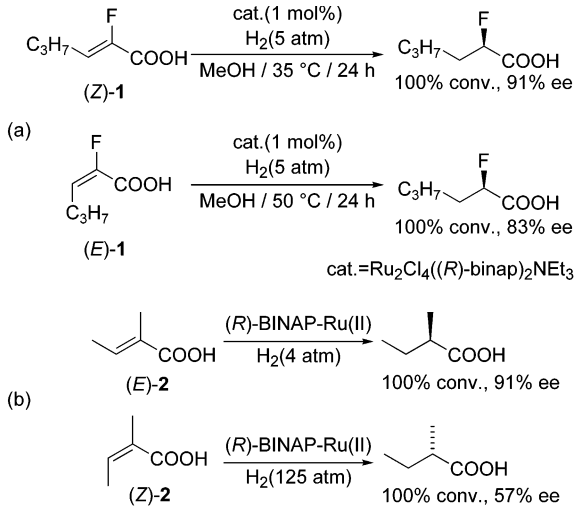
Catalytic enantioselective reactions of prochiral fluorine-containing carbonyl compounds or olefins are the best newcomers in the asymmetric synthesis of chiral organofluorine compounds in either functional group transformation such as reduction and oxidation reactions or carbon−carbon bond-forming reactions.

Standard hydrogenation systems previously established for non-fluorinated substrates have been applied to fluorinated substrates. However, the reactivity or the degree and further the sense of the enantioselectivity critically differ from those of the non-fluorinated substrates. In sharp contrast, the Sharpless oxidation has been so far reported to be equally effective for the fluorinated substrates though in limited numbers of reported examples. Successful examples that give high enantioselectivity are summarized below.

3.2.1. Olefin Hydrogenation

Hydrogenation of monofluoro-olefin with (*R*)-BINAP-Ru systems shows the same sense of (*R*)-enantioselectivity irrespective of the (*E*)- or (*Z*)-geometrical isomer of the olefinic substrates (Scheme 3a).[35] (*Z*)-2-Fluoro-2-hexanoic acid (**1**) underwent hydrogenation in 100% conversion and 91% ee, and (*E*)-**1** also gave 100% conversion and 83% ee (both in the same sense (*R*)). In sharp contrast, the reactivity and the sense of enantioselectivity for non-fluorinated 2-methyl-2-butenoic acid (**2**) both critically depend on the geometry of the substrate isomers (Scheme 3b).[36] (*E*)-**2** underwent reaction at 4 atm in 100% conversion to afford the (*R*)-hydrogenated product with 91%

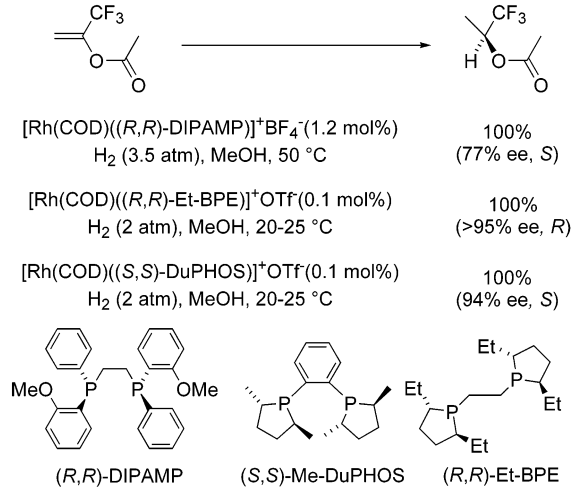
Scheme 3



ee. In contrast, in the case of (*Z*)-**2**, the reaction proceeded slowly even at 125 atm to give only 57% ee in the opposite (*S*) sense.

The first reported successful example of asymmetric hydrogenation of the CF_3-containing olefinic substrates used the (*R*,*R*)-DIPAMP-Rh complex (Scheme 4). The (*R*,*R*)-DIPAMP-Rh complex cata-

Scheme 4

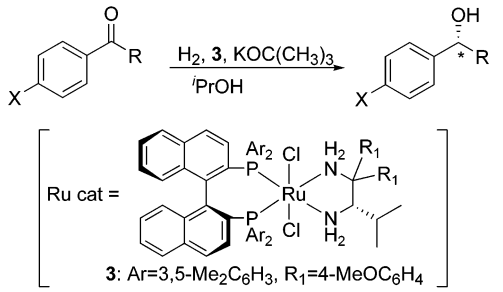


lyzed the enantioselective hydrogenation of 2-acetoxy-1,1,1-trifluoro-2-propene up to 77% ee in the (*S*)-sense.[37] The enantioselectivity was subsequently increased to greater than 95% ee by using (*R*,*R*)-Et-BPE or (*S*,*S*)-Me-DuPHOS as a chiral ligand.[38]

3.2.2. Ketone Reduction

The Nobel-awarded Noyori BINAP-Ru system[39] has also been reported to be effective in the reduction of trifluoromethyl ketones to give enantioselectivity higher than 90% ee, irrespective of the ketonic substrates (Table 4). The electronic effects of para and meta substituents on the enantioselectivities are relatively small in hydrogenation of methyl and

Table 4. Asymmetric Hydrogenation of Aromatic Ketones



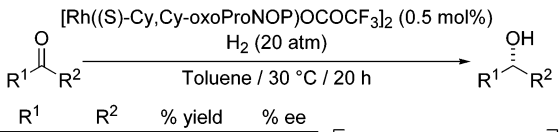
X	R	H_2 (atm)	S/C[a]	time (h)	% yield	% ee
H	CF_3	10	11000	16	100	96
Cl	CF_3	8	2000	4	100	94
OMe	CF_3	8	2000	4	100	96
H	Me	8	100000	60	97	99
Cl	Me	8	20000	16	99.9	99
OMe	Me	10	20000	1	100	100

[a]Substrate/Catalyst molar ratio

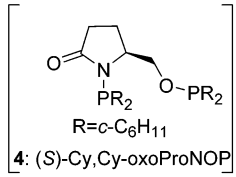
trifluoromethyl ketones. The sense of enantioselectivity is exactly the same as that in the case of non-fluorinated ketonic substrates.[40]

In general, the enantioselective reduction of aliphatic ketones is difficult, apparently because of a similar steric demand of the two aliphatic side chains. It is surprising, however, that good to excellent enantioselectivities have been achieved in the trifluoromethyl ketone reduction catalyzed by the chiral Rh(amidephosphine-phosphinite) complexes. While trifluoromethyloctyl ketone was hydrogenated by the Rh complexes to afford trifluoro-2-decanol quantitatively with 97% ee, the reaction of di- or monofluorinated ketones under the same conditions eventually decreased the % ee values. In addition, both yield and enantioselectivity were greatly suppressed with non-fluorinated methyl ketone reduction (Table 5).[41]

Table 5. Asymmetric Hydrogenation of Aliphatic Ketones

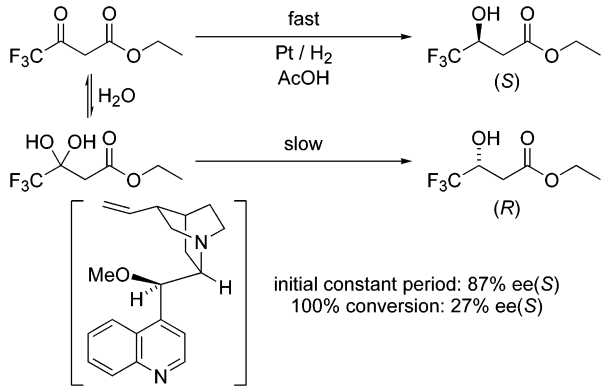


R^1	R^2	% yield	% ee
CF_3	C_8H_{17}	99	97
CF_3	Ph	93	73
CHF_2	C_8H_{17}	100	27
CH_2F	C_8H_{17}	100	15
Me	C_8H_{17}	<1	
Me	Ph	2	8



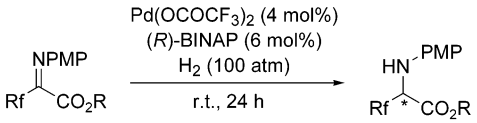
In heterogeneous systems, trifluoroacetoacetate exhibited inversion of enantioselectivity during chirally modified[42] Pt-catalyzed hydrogenation, depending on the presence of even trace amounts of water and trifluoroacetic acid.[43] The enantioselectivity decreased gradually from 87% ee (*S*) to 27% ee (*S*), because of the changeover of the mechanism to hydrogenolysis of the hydrate (Scheme 5) formed in the presence of water and acid.

Scheme 5



Asymmetric reduction of imino ester is effective for the synthesis of fluorinated amino acids but is generally considered to be difficult. However, high enantioselectivities up to 91% ee have been achieved in asymmetric reduction of trifluoromethylimino ester by tuning the solvents employed. The yield and enantioselectivity of the product are moderate in toluene. When trifluoroethanol is employed as solvent, the yield and enantioselectivity are both dramatically increased (Table 6).[44] In contrast to trifluoromethylimino ester, difluoromethylimino ester led to a moderate % ee value, even in trifluoroethanol as a solvent, possibly due to *E*/*Z* isomerization.

Table 6. Asymmetric Hydrogenation of Trifluoromethylimino Esters



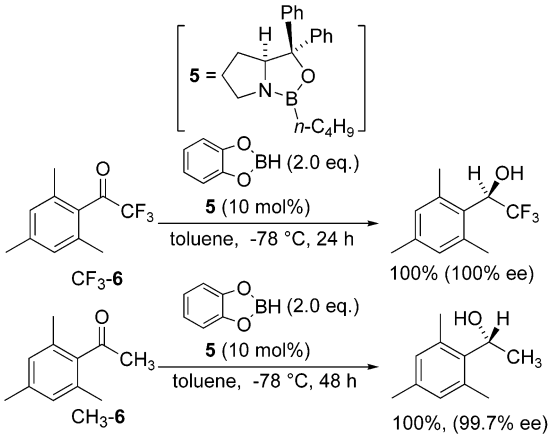
Rf	R	solvent	% yield	% ee
CF_3	Et	toluene	52[a]	39 (*S*)
CF_3	Et	CH_3CH_2OH	29[b]	30 (*R*)
CF_3	Et	CF_3CH_2OH	>99	88 (*R*)
CF_3	Et	CF_3CH_2OH	84[c]	91 (*R*)
CF_3	Bn	CF_3CH_2OH	95	84 (*R*)
CHF_2	Bn	CF_3CH_2OH	75	30 (*R*)

[a] $Pd(OCOCH_3)_2$ was used and the reaction temperature was 35 °C. [b] $CF_3C(OEt)(NHPMP)CO_2Et$ was obtained in 60% yield. [c] Five equivalents of *n*-$BuNHSO_4$ was added.

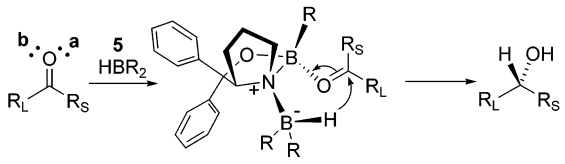
3.2.3. Hydroboration

In hydroboration,[45] the enantioselectivity is determined by the size of the substituents surrounding olefin or ketone substrates. In general, the lone electron pair on the ketone oxygen at the anti-position with respect to the larger substituent is preferentially coordinated to metal complexes, allowing the reduction to progress enantioselectively. It is noted that the sense of enantioselectively is reversed in the Corey−Itsuno reduction of the methyl ketone CH_3-**6** and of the trifluoromethyl ketone CF_3-**6**. Both CH_3-**6** and CF_3-**6** led to high enantioselectivities with reversed absolute configurations (Scheme 6). In the case of CH_3-**6**, the mesityl group is bulkier than the methyl group, and hence oxazaborolidine **5** should coordinate with CH_3-**6** selectively at lone electron pair **a** (*anti* to the mesityl group) to afford the product with *R*-configuration predominantly (Scheme 7, R_S = CH_3, R_L = mesityl). On the other hand, the absolute configuration of the product obtained from CF_3-**6** implies that catalyst **5** should coordinate with CF_3-**6** selectively at lone electron pair **a′** (*anti* to the CF_3 group) (Scheme 7, R_S = mesityl, R_L = CF_3). According to the X-ray structure of 9-anthryl trifluoromethyl ketone **7**, showing displacement of the carbonyl oxygen toward the CF_3 group rather than the 9-anthryl carbon, the CF_3 group could act as a sterically demanding group to cause coordination of catalyst **5** at lone electron pair **a′** (*anti* to the CF_3 group) (Figure 8).[46] This distortion around the carbonyl carbon of CF_3-ketone may be due to delocalization of the lone electron pair of the oxygen into the σ^* orbital of the C−C bond between carbonyl and trifluoromethyl groups.

Scheme 6



Scheme 7



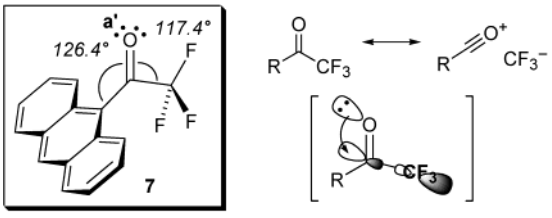


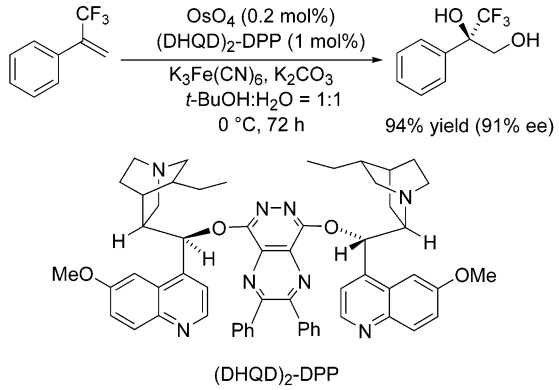
Figure 8. Orbital interaction of the lone electron pair of oxygen and the σ^* orbital of the C−CF_3 bond on the basis of X-ray analysis of the CF_3-containing ketone.

3.2.4. Oxidation

The Nobel-awarded Sharpless oxidation has been reported to be effective also for fluorinated substrates.[47] Asymmetric dihydroxylation using OsO_4 is an example of an enantioselective synthesis of MTPA (Mosher's acid), which is frequently used in order to determine the absolute configuration of secondary alcohols (Mosher's method). By the Sharpless asym-

metric dihydroxylation method, the diol precursor of MTPA is obtained in 91% ee, and after oxidation and recrystallization, MTPA is obtained in 99% ee (Scheme 8).[48]

Scheme 8



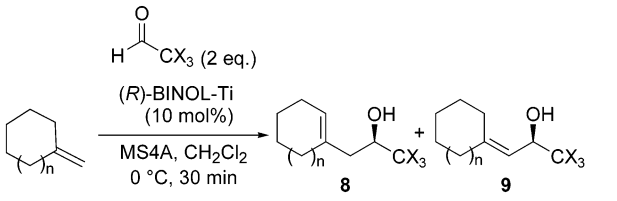
3.3. Catalytic Enantioselective Carbon–Carbon Bond-Forming Reactions

Catalytic enantioselective carbon−carbon bond-forming reactions with prochiral fluorine-containing carbonyl compounds or olefins are among the most chiral-economical processes. Therefore, there is current interest in developing asymmetric catalytic syntheses of organofluorine compounds through carbon−carbon bond formation. In this section, the recent developments in asymmetric catalytic carbonyl−ene, aldol, Friedel−Crafts, carbonyl addition reactions, and cyclopropanation to afford optically active mono- and trifluorinated compounds are reviewed.

3.3.1. Carbonyl-Ene Reaction

C−H bond activation and C−C bond formation are the clues to synthetic exploitation in organic synthesis. In principle, the ene reaction converts readily available alkenes into more functionalized products with activation of an allylic C−H single bond and transposition of the C=C double bond.[49] This intermolecular [1,5]-hydrogen shift is one of the simplest atom-economical processes[50] and hence is a green[51] way for the C−C bond formation. In particular, the class of ene reactions involving a carbonyl compound as the enophile is referred to as "carbonyl-ene reactions".[52] When carbonyl compounds are used as enophiles, alcohols are exclusively formed in a stereoselective manner. The imino derivatives of aldehydes also provide homoallylic amines, while allylic rather than homoallylic amines are sometimes formed in an intramolecular imine-ene reaction via changeover of regioselectivity.[53] In the carbonyl-ene reaction with fluoral, binaphthol (BINOL)-derived titanium (BINOLate-Ti) catalyst, obtained from BINOL and $TiCl_2(O^iPr)_2$ in the presence of 4-Å molecular sieves (MS), gave the ene product **8** and the Friedel−Crafts product **9** (Table 7).[25a] The ratio of **8** and **9** was higher for fluoral than for chloral. This difference can be explained on the basis of the balance of the LUMO energy level of the aldehyde and the charge distribution on the carbonyl carbon. Calculating the charge and LUMO energy in the complex between the aldehyde and acid H^+ used as the chemical model of the Lewis acid at the RHF/6-31G** level; the LUMO energy is lower for fluoral than for chloral, and thus the positive charge on the carbonyl carbon is higher with chloral (Figure 9). The frontier orbital interaction between the ene HOMO and enophile LUMO is the principal interaction in the ene reaction. Consequently, fluoral, having the lower LUMO energy, could show a greater tendency for a concerted ene reaction. In contrast, chloral, having the larger partial positive charge at the carbonyl carbon, more readily undergoes stepwise cationic reactions, the Friedel−Crafts (F−C) one in particular (Scheme 9).[54]

Table 7. BINOLate-Ti-Catalyzed Carbonyl-Ene vs Friedel−Crafts Reactions of Fluoral and Chloral



n	X	% yield	ratio **8**:**9** (% ee)
0	F	78	62 (>95% ee):38 (>95% ee)
1		93	76 (>95% ee):24 (>95% ee)
0	Cl	57	55 (26% ee):45 (75% ee)
1		49	52 (34% ee):48 (66% ee)

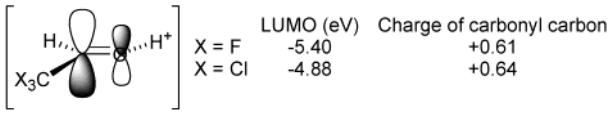
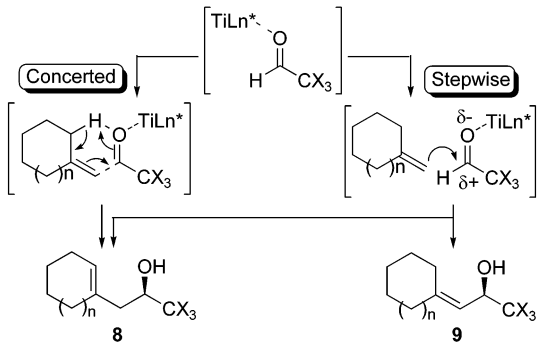


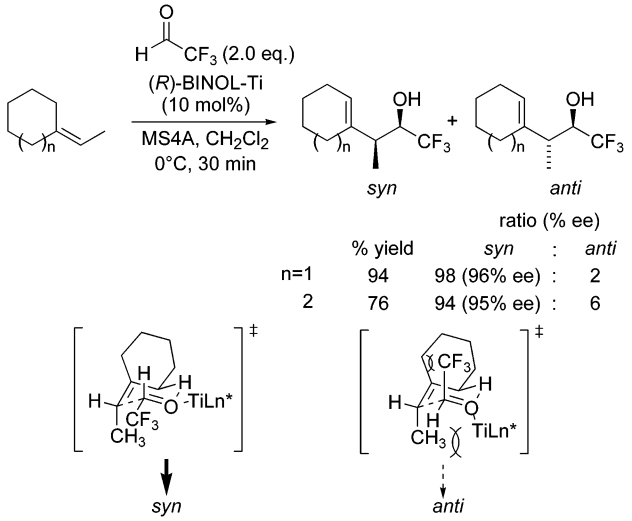
Figure 9. LUMO energy levels and charge distributions of the carbonyl carbon of fluoral and chloral (RHF/6-31G**).

Scheme 9



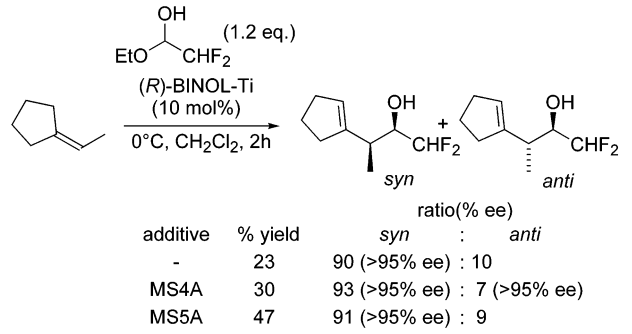
By introducing an electron-donating methyl group on the ene components to increase the HOMO level, the ene reaction was facilitated and, in contrast, the F−C reaction was retarded (Scheme 10).[55] With regard to the diastereoselectivity of the ene reaction, a *syn* product is obtained with nearly perfect selectivity. This selectivity can be explained by considering the six-membered-ring transition state[56] as indicated in Scheme 10. The *syn* isomer is preferentially produced due to destabilization by 1,3-diaxial interactions in the transition state that produces the *anti* isomer.

Scheme 10



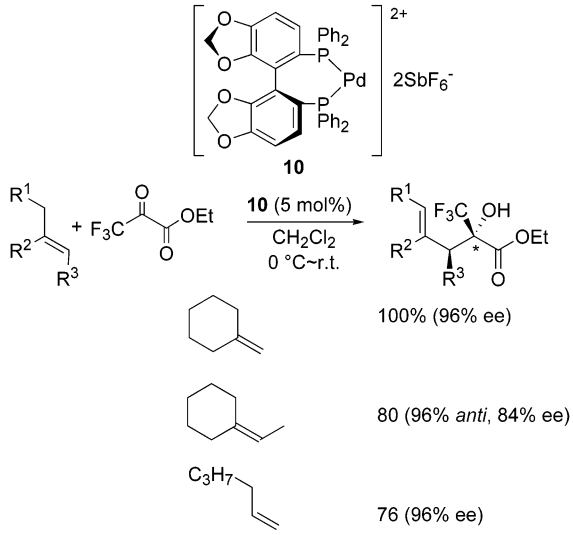
The hemiacetal forms of such aldehydes can also be employed in these carbon−carbon bond-forming reactions. Difluoroacetaldehyde ethyl hemiacetal can also be used in the presence of 5-Å MS rather than 4-Å MS to preferentially trap ethanol generated from the difluoro acetal, showing higher ene selectivity along with higher enantioselectivity of more than 95% ee (Scheme 11).[57]

Scheme 11



Carbonyl-ene reactions with CF_3-ketones are synthetically important as they provide a short access to chiral tertiary α-CF_3-carbinols with homoallylic functionality. However, there has been essentially no successful example of the asymmetric catalysis of ketone-ene reactions,[58] because of low ene reactivity of ketones compared to aldehydes. In relation to the glyoxylate-ene reaction, pyruvate was also examined as a ketonic enophile to give a low yield of the ene product, even with a reactive 1,1-disubstituted olefin, methylenecyclohexane (5 equiv), after 2 days at room temperature to heated conditions (40 °C). The use of a large excess of methylenecyclohexane gave 84% yield using 20 mol % of Cu(II)−bisoxazoline catalyst under the heated conditions after 2 days. The first successful example of asymmetric catalysis of the trifluoromethylpyruvate-ene reaction was reported by use of the "naked" dicationic SEGPHOS-Pd(II) complex in CH_2Cl_2, derived from (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diarylphosphine) (SEGPHOS),[59] $PdCl_2(CH_3CN)_2$, and $AgSbF_6$, to construct the corresponding quaternary carbon center.[60] The cationic SEGPHOS-Pd(II) complex achieves the high chemical yield, (*E*)-olefin selectivity, and *anti*-diastereoselectivity, along with high enantioselectivity even with less reactive mono- and 1,2-disubstituted olefins in this much less reactive carbonyl-ene reaction with ketones (Scheme 12).[61]

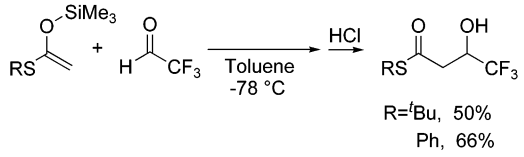
Scheme 12



3.3.2. Aldol Reaction

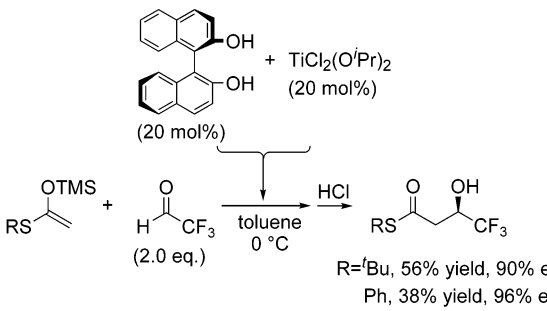
The Mukaiyama aldol reaction of silyl enol ethers is one of the most important carbon−carbon bond-forming reactions for yielding non-fluorinated carbon skeletons in organic synthesis.[62] The fluoral aldol reaction can readily proceed even in the absence of a catalyst, presumably due to the high electrophilicity of fluoral and to the intermolecular interaction between Si and F (Scheme 13).[57] However, simply by

Scheme 13



adding ketene silyl acetal and fluoral simultaneously to a solvent containing the BINOLate-Ti catalyst, it is possible to suppress the uncatalyzed reaction process (Scheme 14). A high level of enantioselectivity

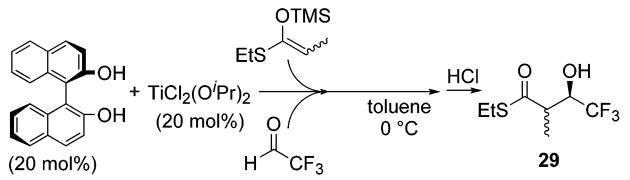
Scheme 14



was achieved (up to 96% ee of the (*R*)-enantiomer). In addition, with ketene silyl thioacetal, having a methyl group at the α-position, the reaction pro-

ceeded with high enantioselectivity, despite its low diastereoselectivity (Scheme 15).

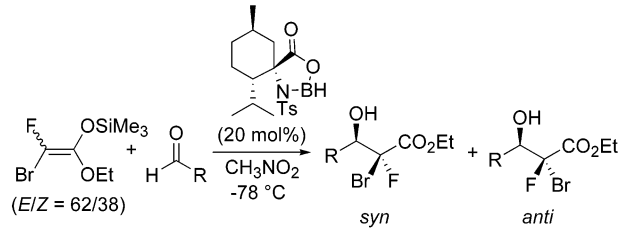
Scheme 15



KSA	% yield	*syn* : *anti*
95%Z	64	48 (55% ee) : 52 (64% ee)
98%E	48	44 (89% ee) : 56 (83% ee)

Ketene silyl acetal bearing a fluorine atom has also been employed for the enantioselective aldol reaction (Scheme 16). The bromofluoro ketene silyl acetal (*E*/*Z* = 62/38) reacted with various aldehydes in nitromethane, with use of Masamune's catalyst, to afford a mixture of the *syn*- and *anti*-aldol products. Although the diastereoselectivity was low, both diastereomers were obtained with high enantioselectivity (90−99% ee).[63]

Scheme 16

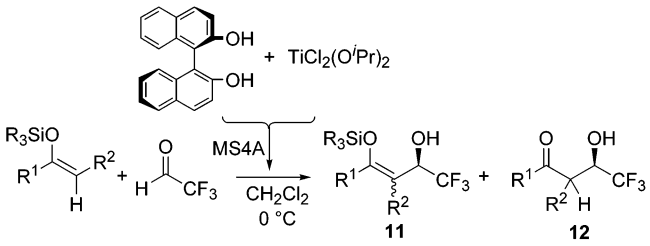


R	% yield	syn : anti
Ph	90	69 (96% ee) : 31 (90% ee)
CH_2CH_2Ph	89	46 (98% ee) : 54 (98% ee)
CH_2OBn	81	57 (97% ee) : 43 (97% ee)
$CHEt_2$	70	54 (99% ee) : 46 (98% ee)

3.3.3. Friedel–Crafts Reaction

The Friedel−Crafts (F−C) reactions also constitute some of the most useful carbon−carbon bond-forming processes in organic synthesis.[64] There have been very few reports on the asymmetric catalytic F−C reaction. Recently, the asymmetric catalytic F−C reactions of the prochiral fluorine-containing carbonyl compounds leading to the chiral tertiary α-CF_3-carbinols have been investigated. The asymmetric catalytic F−C reaction of silyl enol ethers has been reported under the Mukaiyama aldol reaction conditions. The F−C reaction of *tert*-butyldimethylsilyl or triisopropylsilyl enol ether with fluoral was carried out using the (*R*)-BINOLate-Ti complex to afford the F−C product **11** with high % ee, rather than the usual aldol product **12** (Table 8). The amount of the F−C product depends greatly on the bulkiness of the silyl group. Indeed, triisopropylsilyl enol ether overwhelmingly afforded **11**, in contrast to trimethylsilyl enol ether, which gave not **11** but **12**. The Mukaiyama aldol reaction, namely Lewis acid-promoted carbonyl addition of a silyl enol ether to aldehydes or ketones, is well accepted to proceed via the desilylated β-metaloxy carbonyl chelate intermediates. However, the generation of the silyl enol ether

Table 8. Asymmetric Friedel−Crafts Reactions of Silyl Enol Ethers with Fluoral



SiR_3	R^1	R^2	cat. (mol %)	% yield **11** (*E*:*Z*)	% yield **12**	% ee[a]
TMS	4′-Me-Ph	Me	20	0	27[b]	0
TBDMS	Ph	H	5	67 (1:5)	14	98
TIPS	Ph	H	1	90 (1:5)	4	96

[a] The enantiomeric excess of (*Z*)-**11**. [b] The usual aldol product was obtained as the TMS ether. The diastereomeric ratio = 1:4.

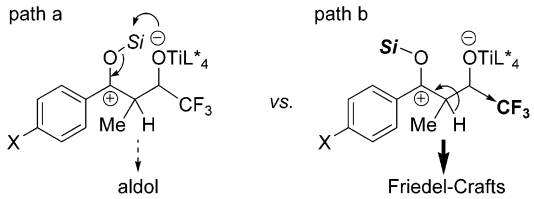
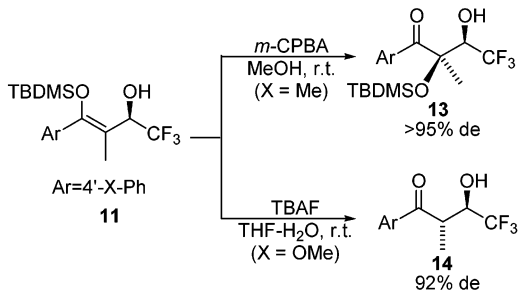


Figure 10. Comparison of the aldol pathway (path a) and the Friedel−Crafts pathway (path b) in the zwitterionic intermediate.

form as the F−C product is found under the Lewis acid-catalyzed Mukaiyama aldol conditions. This is due to the bulkiness of the silyl group, which gives rise to inhibition of the nucleophilic substitution reaction on the silyl group (path a in Figure 10), giving priority to the deprotonation reaction pathway to produce a silyl enol ether (path b in Figure 10). Furthermore, the strongly electron-withdrawing CF_3 group could lower the nucleophilicity of the titanium alkoxide in the zwitterionic intermediate to retard the reaction path a.

In addition, the sequential diastereoselective reactions of the silyl enol ether as the F−C product with electrophiles could thus yield highly functionalized fluorinated aldols that are of material and pharmaceutical interests. The oxidation by *m*-CPBA or desilylation by TBAF of **11** leads selectively to monoprotected *syn*-diol **13** and *anti*-aldol **14** with high diastereoselectivity, respectively (Scheme 17).[65]

Scheme 17



An industrial process to yield 4,4,4-trifluoro-3-hydroxybutyrophenone and the butyric acid phenyl

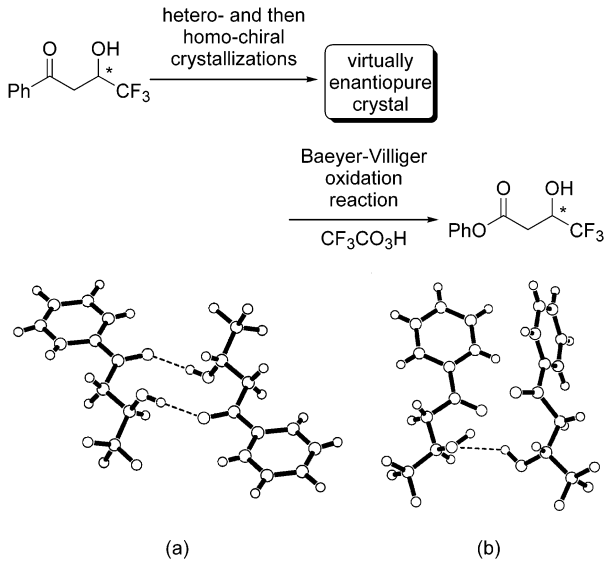
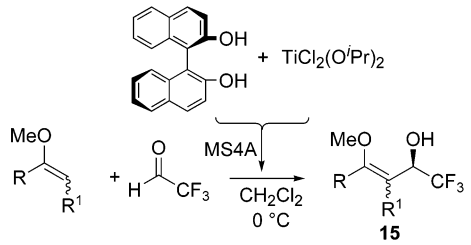


Figure 11. ORTEP drawings of (a) heterochiral crystal and (b) (*R*)-homochiral crystal.

ester is established via heterochiral crystallization through double hydrogen-bonding assembly between −OH and $-CF_3$ in head-to-tail fashion and sequential Baeyer−Villiger oxidation reaction by trifluoroperacetic acid.[66]

The asymmetric F−C reaction of a vinyl ether with fluoral catalyzed by (*R*)-BINOLate-Ti complex, derived from BINOL and $TiCl_2(O^iPr)_2$, has also been carried out. In a manner similar to the F−C reaction of silyl enol ether, reactive vinyl ether was obtained as the F−C product, which can sequentially react with *m*-CPBA to afford the highly functionalized organofluorine compounds. Using enol ether gave only the F−C product with high enantioselectivity (up to 85% ee), and the aldol product was essentially not obtained (Scheme 18). When vinyl ether possess-

Scheme 18

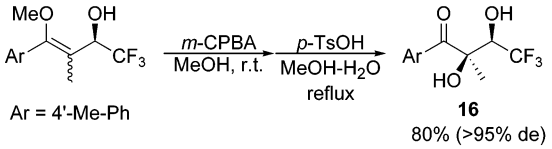


R	R^1	cat.	**15** (*E*:*Z*)	% ee
Ph	Me	10mol %	54 % (1:2)	72
4'-Me-Ph	H	20mol %	64 % (5:1)	85

ing a *β*-methyl substituent was employed, (*E*)-**15** was predominantly obtained, irrespective of the geometry of the substrate. The sequential diastereoselective oxidation of the F−C products by *m*-CPBA provided diastereoselectively *syn*-α,*β*-dihydroxy ketones **16** with high chemical yields (Scheme 19).[67]

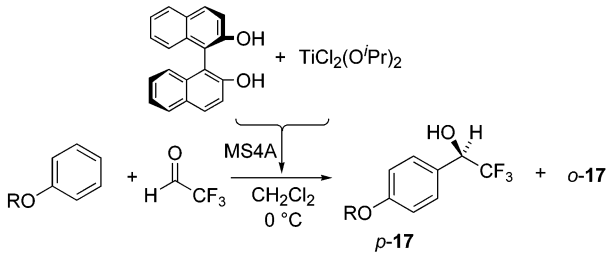
Aromatic compounds have low nucleophilicity relative to silyl enol ethers or vinyl ethers, and hence the asymmetric F−C reaction needs a Lewis acidic metal catalyst such as BINOLate-Ti catalyst. Consequently, both the yield and the enantioselectivity

Scheme 19



of the F−C product are increased when a catalyst with high Lewis acidity is used and an electron-withdrawing group (Br) is introduced onto BINOL. The asymmetric F−C reaction of phenyl ethers gave selectively *p*-**17** rather than *o*-**17**. The regioselectivity of the F−C product was increased by using *n*-butyl phenyl ether (*p*-**17**:*o*-**17** = 8:1). When (*R*)-6,6′-Br_2-BINOL was added,[68] the yield and enantioselectivity were further increased (89% yield, 90% ee), and an asymmetric activation effect was observed (Table 9).[69,70]

Table 9. Asymmetric Friedel−Crafts Reactions of Aromatic Compounds with Fluoral

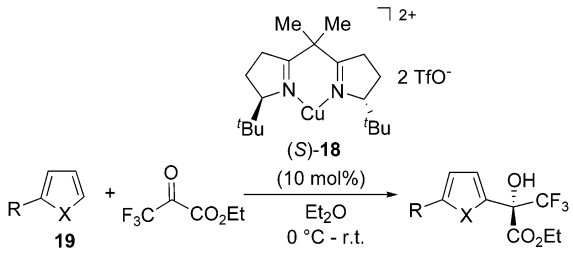


R	cat. (mol %)	additive (mol %)	% yield	*p*-**17**: *o*-**17**	% ee[a]
Me	30		82	4:1	73
Me	5		94	4:1	84
n-Bu	15		85	8:1	83
Ph	10		90	3:1	54
Me	10	(*R*)-6,6′-Br_2-BINOL (**10**)	89	4:1	90
n-Bu	10	(*R*)-6,6′-Br_2-BINOL (**10**)	90	8:1	90

[a] The enantiomeric excess of *p*-**17**.

The reactions with CF_3-ketones are synthetically important to give chiral tertiary α-CF_3-alcohols. The asymmetric catalysis of the F−C reaction has been reported using Cu(II) complexes with bisoxazoline. The enantioselective F−C reaction of trifluoromethyl pyruvate with aromatic and heteroaromatic compounds (Scheme 20) has also been catalyzed by the chiral bisoxazoline−copper(II) complex **18**. When pyrroles **19** were employed as heteroaromatic sub-

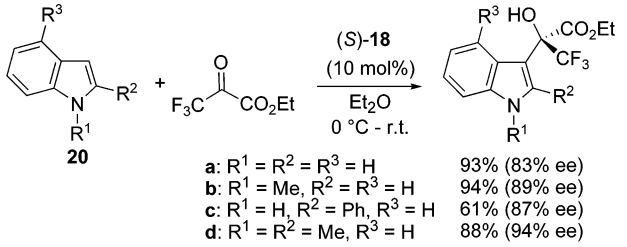
Scheme 20



X	R	
a: NH	H	80% (83% ee)
b: NMe	H	42% (93% ee)
c: NMe	C(O)Me	69% (89% ee)
d: O	Me	65% (93% ee)
e: S	Me	16% (79% ee)

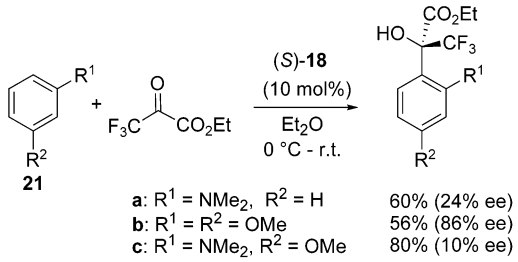
strates for the asymmetric F−C reaction, a hydroxytrifluoromethyl ethyl ester group was induced enantioselectively in the 2-position (**19a** in 80% yield, 83% ee). The reactions proceeded with high enantioselectivity; however, *N*-methylpyrroles **19b**,**c** led to lower yields but with high enantioselectivities, as in furan **19d**. The reaction of both protected and unprotected indoles **20** with trifluoromethyl pyruvate afforded the product with high chemical yields and enantioselectivity, in which a hydroxytrifluoromethyl ethyl ester group was induced in the 3-position (Scheme 21: **20a**

Scheme 21



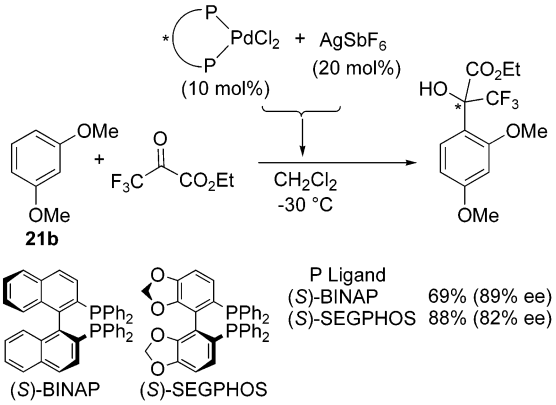
in 93% yield, 83% ee; **20b** in 94% yield, 89% ee). Sterically demanding substituents in the 2-position such as Me and Ph did not affect the enantioselectivity but the yields were slightly lowered (**20c**, 61%; **20d**, 88%). When aromatic compounds **21** are employed, electron-donating substituents such as OMe and NMe_2 are needed on the substrates to give the F−C product (Scheme 22). However, only *m*-methoxyanisole **21b** achieved high enantioselectivity (86% ee).[71]

Scheme 22



Recently, the asymmetric F−C reaction of trifluoromethyl pyruvate with aromatic compounds, catalyzed by a Pd(II) complex with BINAP or SEGPHOS, was found. This reaction can proceed at lower reaction temperatures (−30 °C) to afford the product with high enantioselectivity. The F−C product obtained by using the Pd(II) catalyst shows higher chemical yield and enantioselectivity than that obtained by using the Cu(II) catalyst (Scheme 23).[72] In sharp contrast to the situation with the carbonyl-ene reaction, BINAP ligand provides higher enantioselectivity than SEGPHOS.

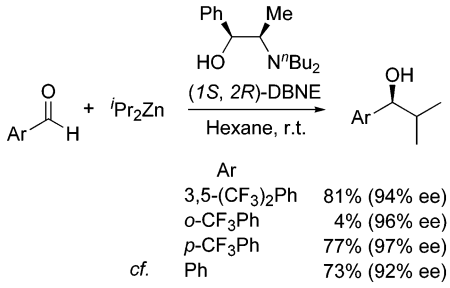
Scheme 23



3.3.4. Carbonyl Addition of Dialkylzinc Reagents

Asymmetric synthesis of fluorine-containing alcohols is an important issue in pharmaceutical chemistry as well as materials science. The catalytic enantioselective addition of dialkylzinc reagents to aldehydes affords optically active secondary alcohols. Since the initial report by Oguni,[73,74] various chiral ligands bearing a β-amino alcohol unit have been explored. Soai reported the first example of the asymmetric catalysis of carbonyl addition of dialkylzinc reagents to fluorine-containing trifluoromethyl benzaldehydes to afford optically active trifluoromethyl-containing secondary alcohols (Scheme 24).

Scheme 24



All trifluoromethyl-containing benzaldehydes gave the corresponding secondary alcohols with high enantioselectivity (up to 97% ee), but *o*-trifluoromethylbenzaldehyde afforded the product with very low chemical yield (4%). This is caused by the steric bulkiness of both the nucleophilic isopropyl group on Zn and the trifluoromethyl group at the ortho position in the aldehyde. It is noted that the enantioselectivity of the fluorine-containing secondary alcohols is as high as in the case with non-fluorinated benzaldehyde.[75]

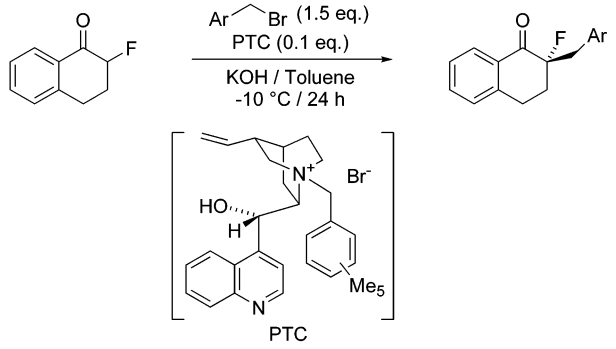
3.3.5. Alkylation of α-Fluorotetralone

Enolate alkylation of carbonyl compounds is one of the most basic methodologies for carbon−carbon bond-forming reactions.[76] The catalytic asymmetric alkylation of α-fluorotetralone can be promoted by a phase-transfer catalyst using the chiral quaternary ammonium salt of cinchonine.[77] The alkylation reaction proceeded smoothly to give up to 91% ee, much higher than that obtained in the case of α-methyltetralone, without epimerization and polyalkylation, which are problematic with the non-fluorinated tetralone (Table 10).

3.3.6. Cyclopropanation of Fluoro-olefins

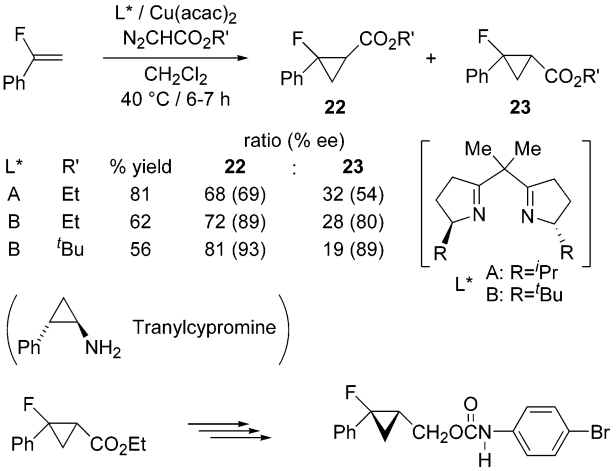
The cyclopropanation reaction has a long history in asymmetric catalysis.[78] Quite recently, an asymmetric catalytic cyclopropanation reaction has been

Table 10. Alkylation of α-Fluorotetralone



Ar	% yield	% ee
2-Me-C_6H_4	60	84
3-Me-C_6H_4	45	84
4-Me-C_6H_4	58	82
2,3,4,5,6-Me_5-C_6	44	91
β-naphthyl	60	79
(*E*)-PhCH=CH	33	70

Table 11. Cyclopropanation of Fluoro-olefins



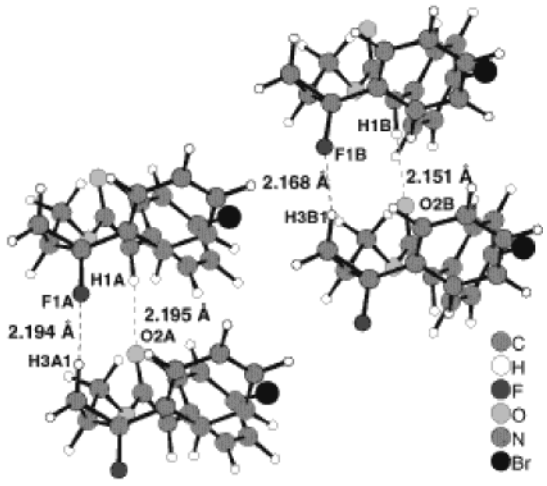


Figure 12. X-ray structure of *N*-(4-bromophenyl)carbamate of (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methanol and its intermolecular C−H- - -F−C interaction.

reported on α-fluorostyrene to give cyclopropanecarboxylate in optically active form using *tert*-butyl diazoacetate in the presence of 2 mol % of an enantiopure bis(oxazoline)−copper complex.[79] The 81:19 mixture of *tert*-butyl *trans*- and *cis*-2-fluoro-2-phenylcyclopropanecarboxylate was obtained with a high ee of 93% or 89%, respectively (Table 11). The product can be transformed to the cis- and trans-isomers of the analogues of Tranylcypromine, an anti-depressive drug. The X-ray crystallographic analysis showed extremely close intermolecular C−H- - -F−C contacts in the product derivative. The shortest of these distances (2.17 Å) was found in the crystal structure of *N*-(4-bromophenyl)carbamate of (1*S*,2*R*)-(2-fluoro-2-phenylcyclopropyl)methanol (Figure 12).

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