Pergamon

Tetrahedron 54 (1998) 13887–13914

TETRAHEDRON

Tetrahedron report number 472

Catalytic Asymmetric Synthesis of Chiral Fluoroorganic Compounds

Katsuhiko Iseki*

MEC Laboratory, Daikin Industries, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305-0841, Japan

Received 25 July 1998

Contents

E-mail: iseki@mec.daikin.co.jp FAX: +298 58 5082

PII: S0040-4020(98)00740-6

1. Introduction

Chirality is essential for molecular recognition in a wide range of biochemical reactions responsible for metabolism and numerous biological functions, because enzymes, biological receptors and other natural binding sites stereospecifically combine with substrates bearing specific chirality [1]. In recent decades, this has greatly promoted the remarkable development of the enantiocontrolled synthesis of single enantiomers, especially asymmetric catalysis, to provide a deeper insight into the implications of chirality for molecular recognition and many homochiral compounds of biological and pharmaceutical interest [2,3].

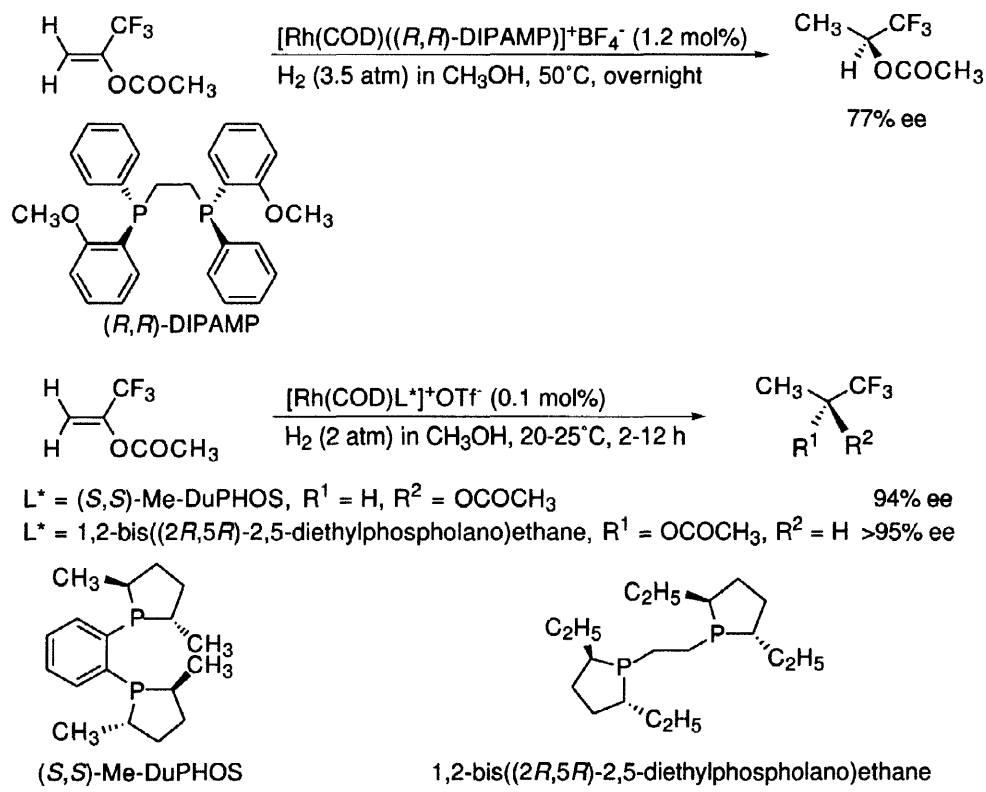
Modification of the physiological activity of bioactive compounds by introducing fluorine into the molecules, owing to the influence of fluorine's unique properties, frequently leads to the discovery of novel and potent biochemical tools and medicinal agents which have a fluorine substituent at a stereogenic center in many cases [4-9]. The steric requirement of fluorine resembles that of hydrogen as shown by their van der Waals radii (1.29 vs. 1.35 Å). Therefore, replacement of a hydrogen by a fluorine as an isosteric substituent usually allows the fluorinated analogs to follow the metabolic pathway of the parent hydrogen compounds, and the strong C-F bond (485.7 kJ/mol) can be often protected from unwanted metabolic transformations. Fluorine can also function as a hydrogen bond acceptor, and the substitution of hydroxyl by fluorine in bioactive compounds, due to the similarity of typical C-F and C-O bond lengths (1.39 vs. 1.43 Å), often retains the biological properties. Furthermore, the extremely high electronegativity of fluorine has important effects, such as changes in the electron density, basicity and acidity, on its neighboring groups in a molecule. The perfluoroalkyl group is highly lipophilic, generally making the absorption and transport of the perfluoroalkylated analogs easy. Thus, the asymmetric synthesis of homochiral fluoroorganic compounds is now an important challenge in biological and medicinal chemistry [10-16]. These compounds are also useful in the development of optoelectronic materials with new properties, *e.g.*, chiral dopants for ferroelectric liquid crystal mixtures [17-19].

Fluorine-containing compounds often show unexpected and generally unusual reactivity and stereochemical outcome, giving rise to the term "flustrates" by Seebach [20]. Thus, asymmetric reactions developed for nonfluorinated chiral compounds are frequently inapplicable. The strongly electronegative nature of fluorine frequently disturbs or alters the course of the reactions established for hydrocarbon patterns. Moreover, the existence of a fluorine or a fluorine-containing group often inverts the stereochemical results of the reactions. Therefore, optically active compounds bearing a fluorine atom or fluorine-containing group at a stereogenic center have been thus far mainly prepared by chemical or biocatalytic resolutions of racemates, selective fluorination of chiral nonfluorinated substances and enzymatic or biological methods. However, much attention has been directed toward the asymmetric synthesis of such chiral molecules during the last decade. Especially, enantiocontrolled synthesis using asymmetric catalysis has been reported in increasingly significant numbers in recent years and can now be said to rival the biological approach. This report focuses on the recent advances in catalytic asymmetric synthesis of chiral fluoroorganic compounds.

2. Asymmetric hydrogenation

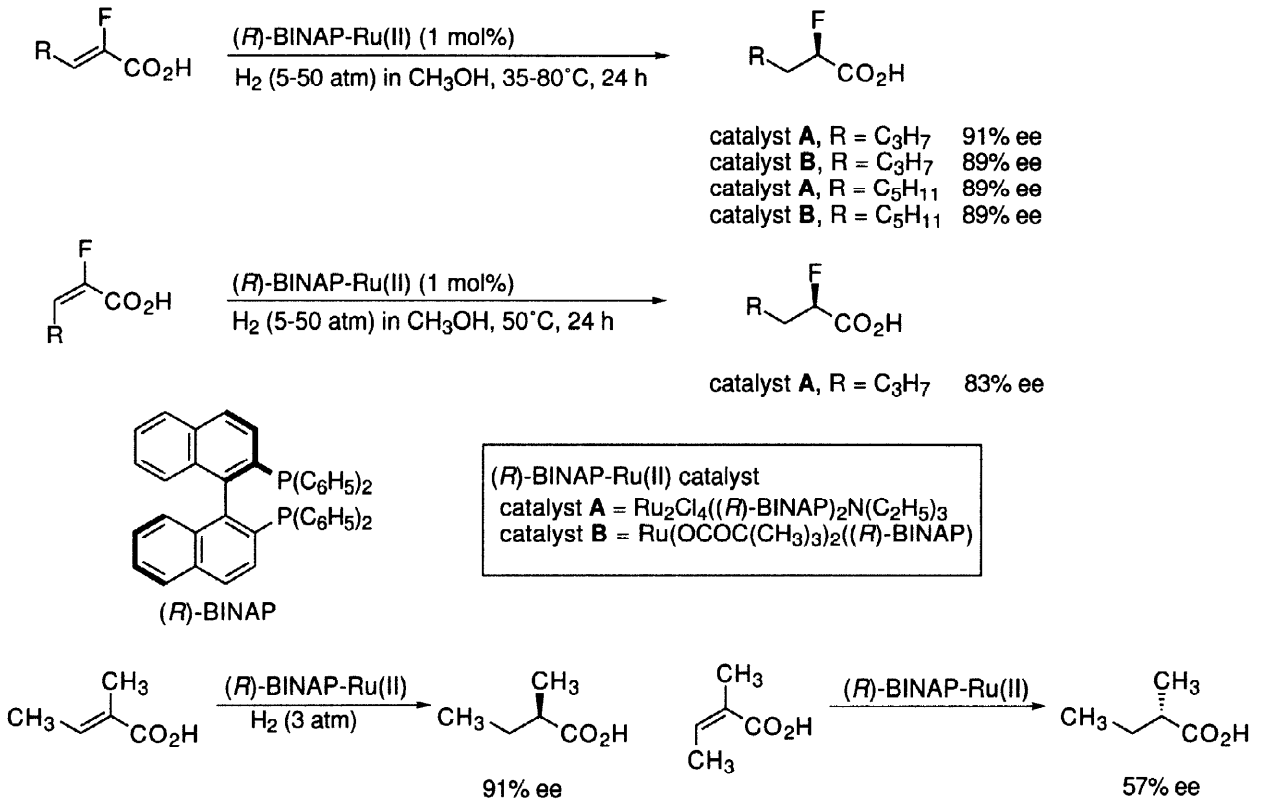
2.1. Asymmetric hydrogenation of olefins

Homogeneous asymmetric hydrogenation with transition metal complexes bearing chiral tertiary phosphines has significantly developed since the 1968 reports by Knowles and Horner and is now regarded as one of the most powerful and industrially feasible tools to prepare enantiomerically enriched organic molecules [21-25]. In fluoroorganic chemistry, the first successful example of catalytic asymmetric hydrogenation was recorded by Koenig and coworkers. A DIPAMP-rhodium(I) complex catalyzes the enantioselective hydrogenation of 1,1,1-trifluoro-2-(acetyloxy)-2-propene to produce optically active 1,1,1-trifluoro-2-(acetyloxy)-2-propane with up to 77% ee [26]. Burk developed novel, excellent C_2-symmetric chiral bidentate ligands, a series of bis(phospholanes)s [27-29], and applied them to the hydrogenation of 1,1,1-trifluoro-2-(acetyloxy)-2-propene to improve the enantioselectivity reported by Koenig *et al.* [30]. The rhodium complexes modified by the incorporation of (*S*,*S*)-Me-DUPHOS and 1,2-bis((2*R*,5*R*)-diethylphospholano)ethane provide the corresponding hydrogenated acetate with 94% ee and >95% ee, respectively (Scheme 1). However, no asymmetric hydrogenation of 3-substituted-1,1,1-trifluoro-2-(acetyloxy)-2-propenes with chiral catalysts has been thus far reported, although the corresponding products, optically active 1,1,1-trifluoroalkanols, are considered to have a widely general applicability as chiral building blocks.



Scheme 1. Enantioselective hydrogenation of 1,1,1-trifluoro-2-(acetyloxy)-2-propene.

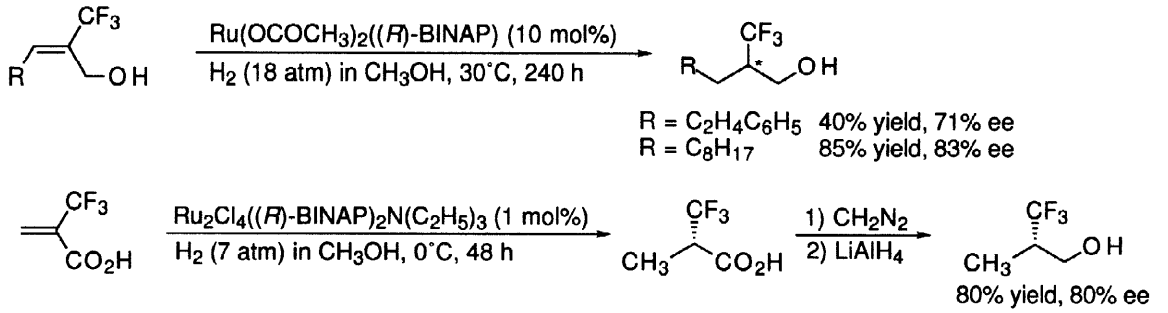
In 1992, Saburi and coworkers reported that ruthenium complexes containing a chiral BINAP ligand catalyzed the asymmetric hydrogenation of 2-fluoro-2-alkenoic acids with high enantioselectivities [31]. Treatment of (*Z*)-2-fluoro-2-hexenoic acid and (*Z*)-2-fluoro-2-octenoic acid with $Ru_2Cl_4((R)\text{-BINAP})_2N(C_2H_5)_3$ gives the corresponding saturated acids bearing the *R* configuration with 91% ee and 89% ee, respectively. A mononuclear dicarboxylate complex, $Ru(OCOC(CH_3)_3)_2((R)\text{-BINAP})$, also provides similar levels of enantioselectivity compared to the dinuclear complex. Interestingly, the hydrogenation of (*E*)-2-fluoro-2-hexenoic acid with $Ru_2Cl_4((R)\text{-BINAP})_2N(C_2H_5)_3$ affords (*R*)-2-fluorohexanoic acid, the same enantiomer as obtained from the corresponding (*Z*)-acid, with 83% ee. This is in sharp contrast to the case of 2-methyl-2-butenoic acid [32]: Ru-BINAP catalyzed hydrogenation of (*E*)- and (*Z*)-isomers of 2-methyl-butenoic acid gives rise to the corresponding (*R*)-saturated acid and its antipodal isomer, respectively, with 91% ee and 57% ee (Scheme 2).



Scheme 2. Enantioselective hydrogenation of 2-fluoro-2-alkenoic acids.

Iseki *et al.* reported the asymmetric hydrogenation of (*E*)-2-(trifluoromethyl)-2-alken-1-ols [33,34]. Treatment of (*E*)-5-phenyl-2-(trifluoromethyl)-2-pentenol and (*E*)-2-(trifluoromethyl)-2-undecenol with a BINAP-Ru(II) complex, $Ru(OCOCH_3)((R)\text{-BINAP})$, affords the corresponding saturated 2-(trifluoromethyl)alkanols with 71% ee and 83% ee, respectively. However, the reaction is very sluggish and needs a large amount of the catalyst. The hydrogenation of 2-(trifluoromethyl)acrylic acid in the presence of 1 mol% of $Ru_2Cl_4((R)\text{-BINAP})_2N(C_2H_5)_3$ provides optically active 2-(trifluoromethyl)propionic acid which is treated

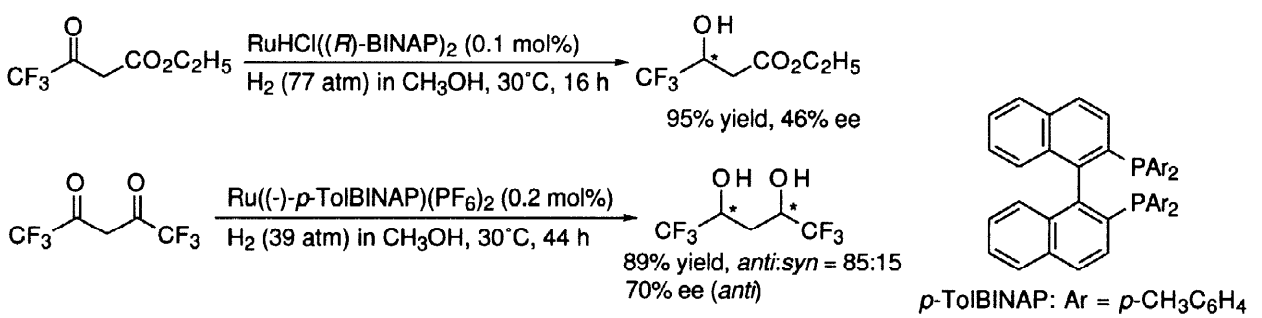
with CH_2N_2 and reduced with $LiAlH_4$ to give (*S*)-2-(trifluoromethyl)propanol with 80% ee in 80% overall yield (Scheme 3).



Scheme 3. Synthesis of optically active 2-(trifluoromethyl)alkanol.

2.2. *Asymmetric hydrogenation of ketones*

Halogen-containing diphosphine-Ru complexes are well-known to be excellent catalysts for the hydrogenation of a wide range of functionalized ketones including α-dialkylamino ketones, β-keto esters and β-diketones to provide the corresponding secondary alcohols with exceptionally high enantiomeric excesses [35]. Sayo *et al.* reported that ethyl 4,4,4-trifluoroacetoacetate was reduced in the presence of 0.1 mol% of RuHCl((*R*)-BINAP)$_2$ to give the corresponding β-hydroxy ester with 46% ee [36]. This unexpected enantiomeric excess may be possibly caused by the high electronegativity of fluorine atoms, because the same catalyst also causes low enantioselectivity in the hydrogenation of methyl 4-bromoacetoacetate (45% ee) and methyl 4-chloroacetoacetate (67% ee). The reduction of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione catalyzed by Ru((-)-*p*-TolBINAP)$(PF_6)_2$ produced an 85:15 mixture of optically active *anti*-1,1,1,5,5,5-hexafluoro-2,4-pentanediol and the *meso*-isomer in 80% yield. The *anti*-isomer showed an enantiomeric purity of 70% [37] (Scheme 4).



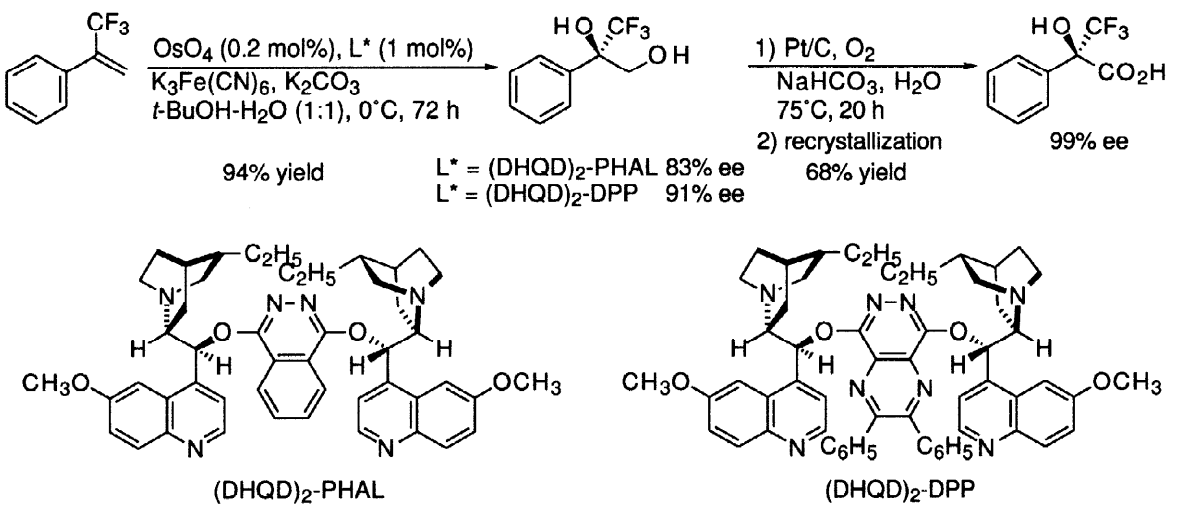
Scheme 4. Asymmetric hydrogenation of trifluoromethyl ketones.

3. Asymmetric oxidation

Catalytic asymmetric dihydroxylation (AD) reactions of olefins catalyzed by chiral tertiary amine ligand-osmium tetroxide complexes are important methods of stereospecifically creating

cis vicinal diols and simultaneously introducing two asymmetric centers into a prochiral molecule. In 1992, Sharpless and coworkers developed an excellent asymmetric catalysis using novel cinchona alkaloid derivatives as chiral ligands [38-40]. Bis-DHQD (dihydroquinidine) and bis-DHQ (dihydroquinine) ethers of phthalazine-1,4-diol (PHAL) coordinate with OsO_4 and accelate the AD reaction of a variety of olefins including olefins substituted by electron-withdrawing groups to give the corresponding *vic*-diols with high enantiopurities.

α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), Mosher's acid, is a useful agent for the enantiomeric excess determination of alcohols and amines. In 1994, the enantioselective synthesis of (*R*)–MTPA using the AD reaction as a key step was disclosed by Bennani *et al.* [41]. Treatment of α-(trifluoromethyl)styrene with 0.2 mol% of OsO_4 and 1 mol% of $(DHQD)_2PHAL$ under the AD-mix conditions gives (*R*)-2-phenyl-3,3,3-trifluoropropane-1,2-diol in 83% optical yield. Use of the ligand bearing a new heterocyclic spacer (DPP), $(DHQD)_2DPP$, causes a reaction with a similar yield and with higher enantioselectivity (91% ee). The diol produced by the AD reaction is oxidized using Pt/C as a catalyst in a sodium bicarbonate solution and recrystallized from toluene-hexane to give enantiomerically pure (*R*)-α-hydroxy-α-(trifluoromethyl)phenylacetic acid which is converted to (*R*)-MTPA according to reported procedures (Scheme 5).

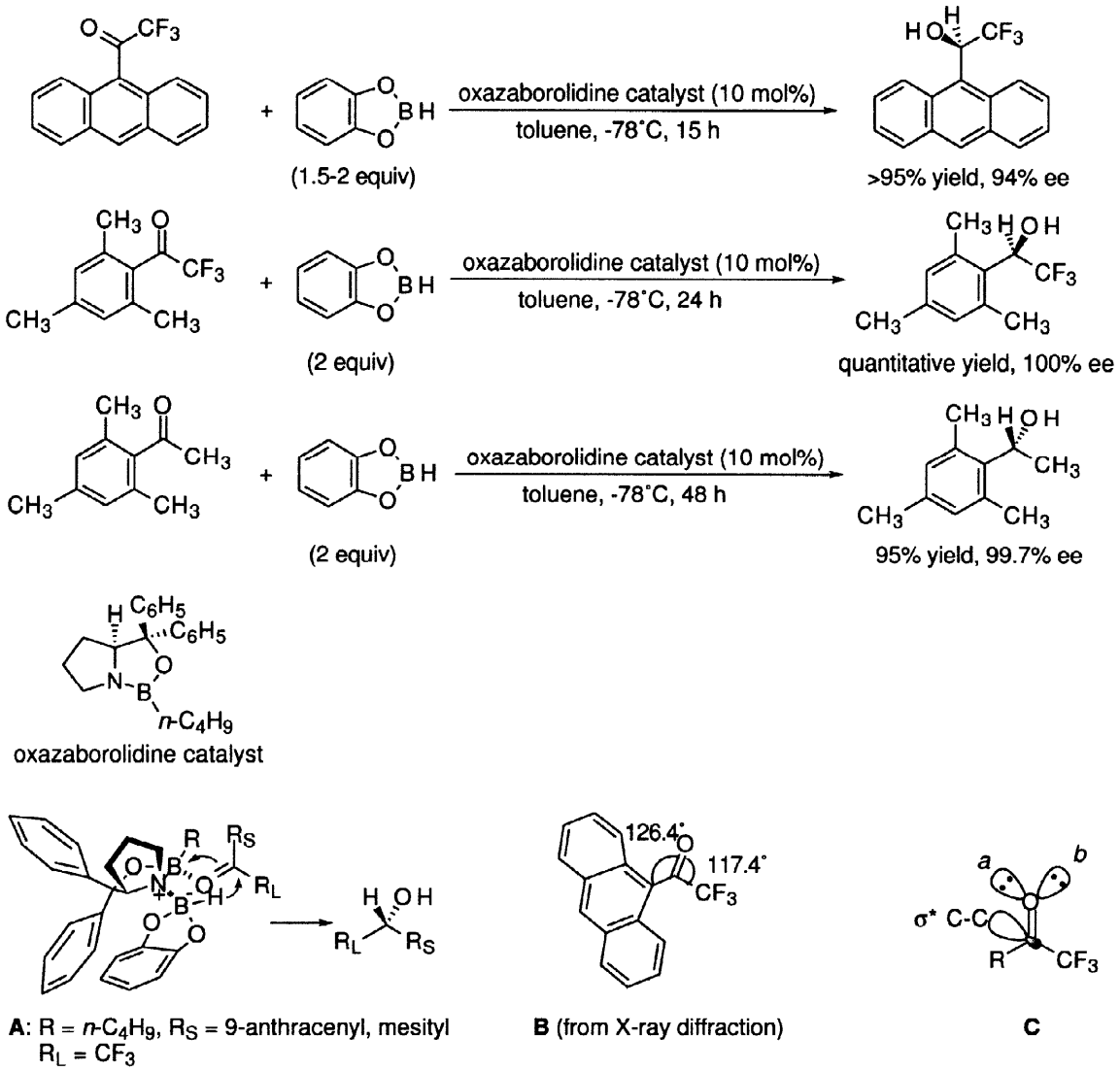


Scheme 5. Enantioselective synthesis of MTPA via asymmetric dihydroxylation (AD) reaction.

4. Asymmetric hydroboration of ketones

Asymmetric reduction of ketones is one of the most useful methods for preparing chiral secondary alcohols which are versatile synthetic intermediates for the synthesis of a variety of biologically active compounds. This has encouraged many organic chemists to undertake efforts to develop the methodologies including biocatalytic transformations using baker's yeasts and stoichiometric and catalytic asymmetric reductions with metal hydrides. In 1987, Corey and coworkers reported the catalytic, highly enantioselective borane reduction of ketones using the oxazaborolidines derived from (*S*)-proline as chiral ligands [42-44].

This catalytic system was also applied to the reduction of trifluoromethyl ketones. Reaction of 9-anthryl trifluoromethyl ketone and mesityl trifluoromethyl ketone with catecholborane as stoichiometric reductant in toluene in the presence of 10 mol% of a chiral oxazaborolidine as catalyst at -78°C provides (*R*)-9-anthryl trifluoromethyl carbinol and (*R*)-mesityl-2,2,2-trifluoroethanol, respectively, with 94% ee and 100% ee [45,46] (Scheme 6).

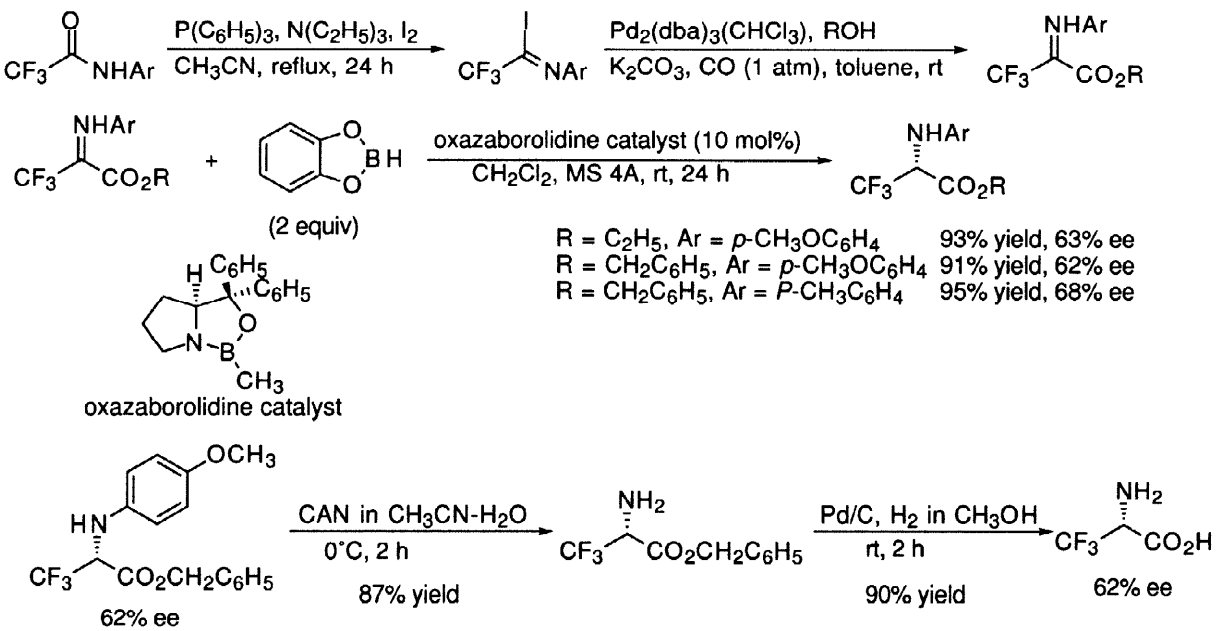


Scheme 6. Enantioselective hydroboration of trifluoromethyl ketones.

A possible mechanism for the asymmetric hydroboration can be expained by a transition state assembly shown in **A** (R_S = smaller group, R_L = larger group) [47] (Scheme 6). For example, the reduction of acetylmesitylene with the same catalyst gave (*R*)-mesitylethanol with 99.7% ee (R_S = CH_3, R_L = mesityl). Thus, it is notable that the trifluoromethyl group acts as a larger group than 9-anthracenyl or mesityl in the reduction of the trifluoromethyl ketones. This result indicates that the oxazaborolidine coordinates with trifluoromethyl ketones selectively at the lone pair *a* (*anti* to CF_3) as shown in **C**, and this has been explained on the basis of the X-

ray analysis of the ketones [48]. The anthryl ketone was found to be locked firmly in the conformation shown in **B** where the carbonyl oxygen is placed away from the 9-anthryl carbon, thus favoring the catalyst coordination at lone pair *a*. This distorted structure implies that lone pair *a* is delocalized into the *anti*-bonding σ* orbital of the carbon-carbon bond between the carbonyl and the CF_3 group [48]. Homochiral 9-anthryl trifluoromethylcarbinol and mesityl-2,2,2-trifluoroethanol are useful tools for analytical work including NMR studies.

Sakai *et al.* reported that optically active 3,3,3-trifluoroalanine was synthesized via the borane reduction of CF_3-substituted imines with a *B*-methyloxazaborolidine catalyst [49]. 2-(*N*-Arylimino)-3,3,3-trifluoropropanoates, prepared from *N*-aryl-trifluoroacetamides in two steps, were treated with 2 equiv of catecholborane and 10 mol% of the oxazaborolidine in CH_2Cl_2 in the presence of 4Å molecular sieves at room temperature to provide the corresponding (*R*)-3,3,3-trifluoroalanine derivatives in good yields. The optical yields were moderate, and the highest enantioselectivity was obtained with benzyl 2-(*N*-*p*-tolylimino)-3,3,3-trifluoropropanoate (68% ee). *N*-*p*-Anisyl-3,3,3-trifluoroalanine benzyl ester (62% ee) was reacted with $(NH_4)_2Ce(NO_3)_6$ (CAN) in CH_3CN-H_2O to give 3,3,3-trifluoroalanine benzyl ester (87% yield) which was deprotected by hydrogenolysis with Pd/C as catalyst in methanol to afford (*R*)-3,3,3-trifluoroalanine in 90% yield and with 62% ee (Scheme 7).



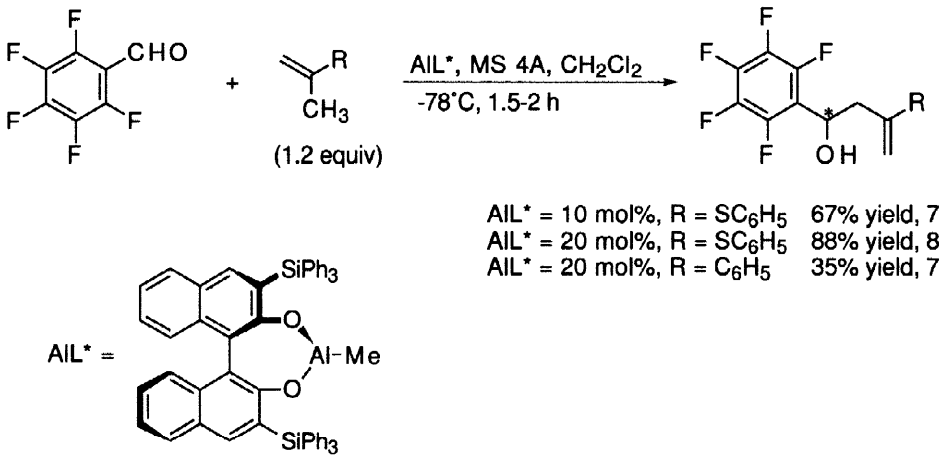
Scheme 7. Enantioselective synthesis of 3,3,3-trifluoroalanine via asymmetric reduction of imines.

5. Asymmetric carbon-carbon bond forming reactions

5.1. Asymmetric ene reaction

The first catalytic enantioselective ene reaction of prochiral aldehydes and alkenes has been accomplished by Maruoka *et al.* using a fluorine-containing aldehyde as substrate and a chiral

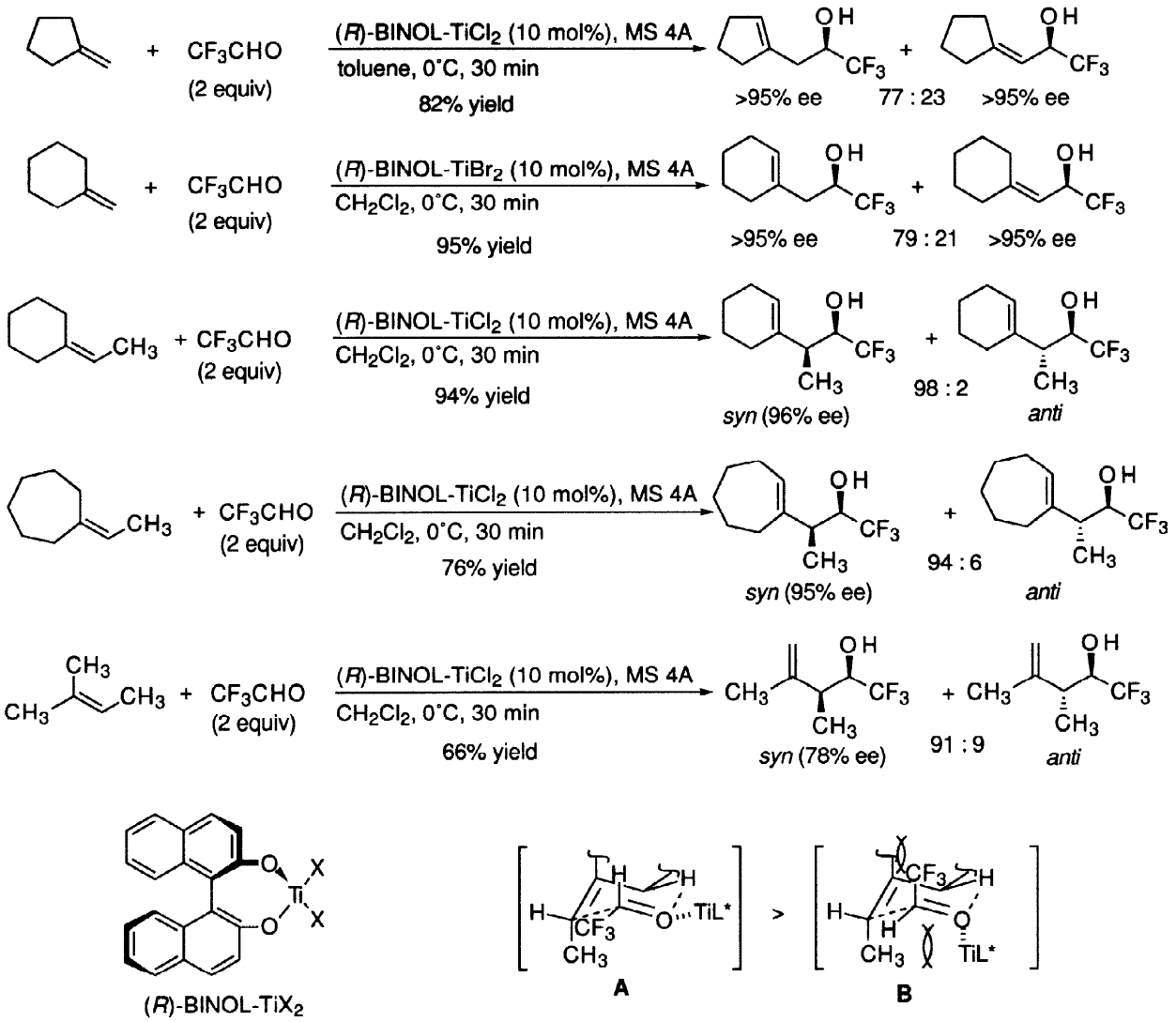
aluminum complex as Lewis acid catalyst as shown in Scheme 8 [50]. The ene reaction of pentafluorobenzaldehyde with 2-(phenylthio)propene is carried out in the presence of 20 mol% of the chiral catalyst (AlL*), derived from $(CH_3)_3Al$ and (*R*)-3,3'-bis(triphenylsilyl)-1.1'-bi-2-naphthol, and molecular sieves 4A in CH_2Cl_2 at -78°C to afford the corresponding, optically active homoallylic alcohol in 88% chemical and 88% optical yields.



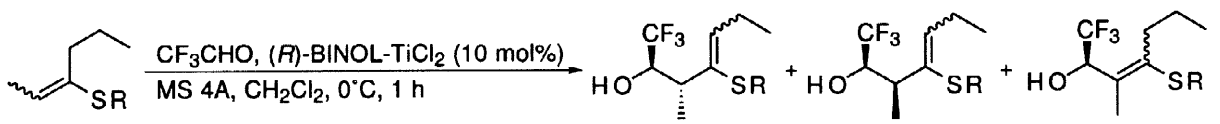
Scheme 8. Enantioselective ene reaction of pentafluorobenzaldehyde.

Mikami and coworkers showed that chiral binaphthol (BINOL)-modified titanium(IV) complexes are extremely efficient catalysts for the ene reaction of glyoxylic esters with a variety of olefins [51-54]. The chiral catalysts have been also applied to the enantioselective ene reaction of trifluoroacetaldehyde (fluoral) to give the corresponding homoallylic alcohols with high enantioselectivities [55-57]. The titanium catalyst can be easily prepared *in situ* from (*R*)-BINOL and diisopropoxytitanium dihalide in the presence of molecular sieves (4Å) which is considered to accelerate the replacement of isopropoxyl moieties by the binaphthol ligand. Reaction of 1,1-disubstituted olefins with fluoral smoothly proceeds in the presence of 10 mol% of (*R*)-BINOL-TiX_2 (X = Cl, Br) at 0°C to give a mixture of the homoallylic and allylic alcohols in good chemical yields. Both alcohols are obtained with excellent enantiomeric excesses (>95% ee), and their major enantiomers have the *R* configuration. The ene reaction of trisubstituted olefins has been also achieved with 10 mol% of (*R*)-BINOL-$TiCl_2$ catalyst. The reaction shows extremely high *syn*-diastereoselectivity (up to 98:2), and the enantiomeric excesses of the *syn*-homoallylic alcohol products are up to 96%. The *syn*-selectivity can be explained by assuming that the fluoral-ene reaction proceeds preferentially via the chair-like cyclic transition structure **A** because the transition state **B** to afford the *anti*-isomer is disfavored by 1,3-diaxial repulsion (Scheme 9).

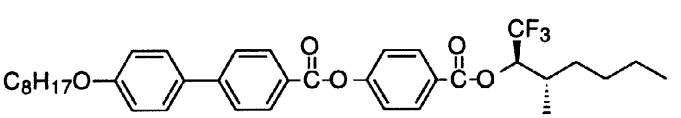
As shown in Scheme 10, the binaphthol-titanium complex-catalyzed fluoral-ene reaction is also applicable to vinylsulfides [58]. The ene reactions of (*E*)-3-*t*-butylthio-2-hexene and (*Z*)-3-phenylthio-2-hexene mediated by 10 mol% of (*R*)-BINOL-$TiCl_2$ give mainly the *anti*-alcohol [*ul* ($R\alpha$,$S\beta$)] and *syn*-alcohol [*lk* ($R\alpha$,$R\beta$)], respectively, with 93% ee and 92% ee. These optically active products were converted to liquid-crystalline molecules.



Scheme 9. Enantioselective ene reaction of trifluoroacetaldehyde (fluoral).

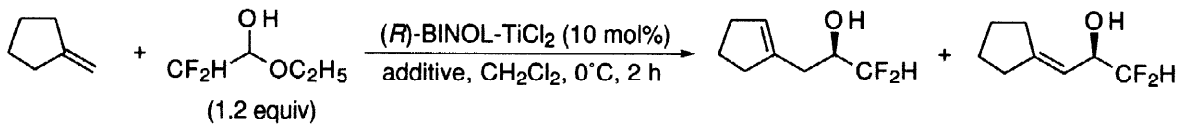


vinylsulfide (R)	yield (%)	*ul* (R_α,S_β)		*lk* (R_α,R_β)		
t-Bu, 98% *E*	80	62.9 (93% ee)	:	25.5	:	11.6
C_6H_5, 94% *Z*	99	13.6	:	30.3 (92% ee)	:	56.1 (86% ee)



Scheme 10. Enantioselective fluoral-ene reaction with vinylsulfides.

The titanium-binaphthol-catalyzed ene reaction was also examined with difluoroacetaldehyde [57]. Difluoroacetaldehyde ethyl hemiacetal was used in place of the aldehyde which is extremely difficult to isolate. The reaction of methylenecyclopentane with the hemiacetal in the presence of 10 mol% of (*R*)-BINOL-$TiCl_2$ at 0°C provided a mixture of the homoallylic and allylic alcohols in low chemical yield (23%). However, the use of molecular sieves (5Å), due to their trapping effect for ethanol, improved the chemical yield (47%). The homoallylic alcohol product was obtained in high optical yield (>95% ee) (Scheme 11).

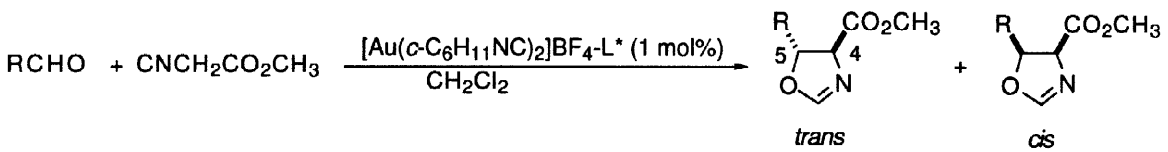


additive	yield (%)			
-	23	90 (>95% ee)	:	10
MS 4A	30	93 (>95% ee)	:	7 (>95% ee)
MS 5A	47	91 (>95% ee)	:	9

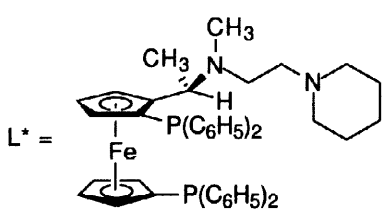
Scheme 11. Enantioselective ene reaction of difluoroacetaldehyde hemiacetal.

5.2. *Asymmetric aldol and related reactions*

Chiral ferrocenylphosphine-gold(I) complexes have been shown by Ito and Hayashi to be highly effective catalysts for an asymmetric Knoevenagel reaction [59-61]. The reaction of aldehydes with isocyanoacetates is catalyzed by the Au(I)-ferrocenylphosphine catalysts to predominantly provide *trans*-5-substituted-2-oxazoline-4-carboxylates with high enantiomeric excess.



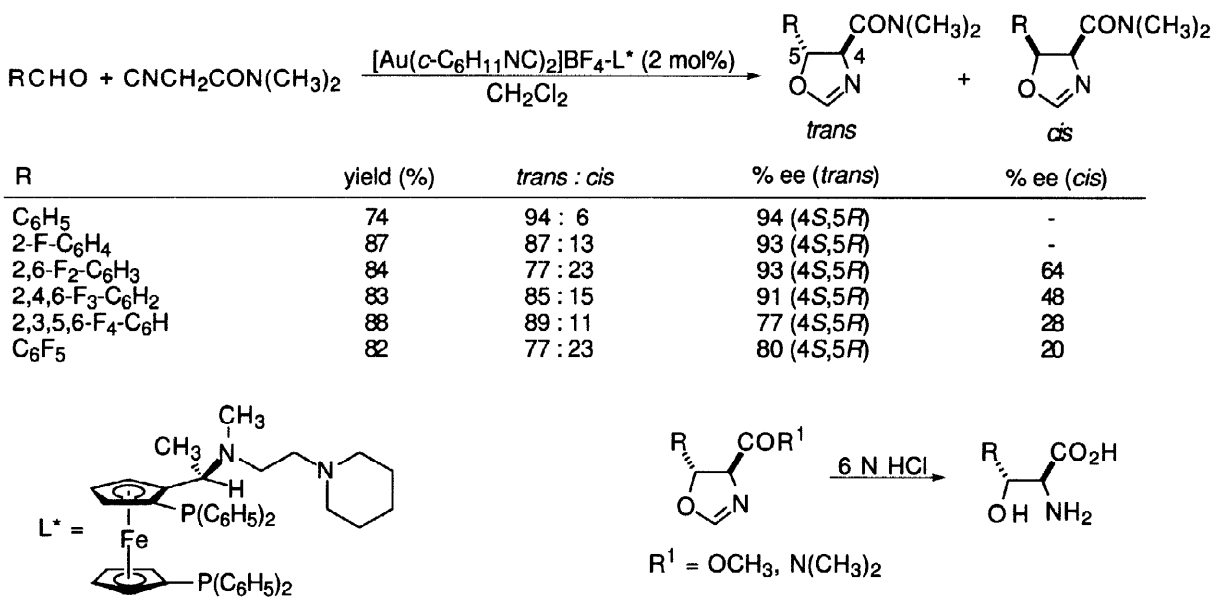
R	yield (%)	*trans* : *cis*	% ee (*trans*)	% ee (*cis*)
C_6H_5	94	94 : 6	95 (4*S*,5*R*)	49 (4*R*,5*R*)
2-F-C_6H_4	99	89 : 11	90 (4*S*,5*R*)	40
2,6-F_2-C_6H_3	98	75 : 25	86 (4*S*,5*R*)	78
2,4,6-F_3-C_6H_2	96	67 : 33	73 (4*S*,5*R*)	82
2,3,5,6-F_4-C_6H	90	47 : 53	48 (4*S*,5*R*)	89
C_6F_5	99	57 : 43	36 (4*S*,5*R*)	78 (4*S*,5*S*)



Scheme 12. Gold(I)-catalyzed asymmetric aldol reaction of fluorinated benzaldehydes with methyl isocyanoacetate.

Soloshonok and Hayashi applied the Au(I)-ferrocenylphosphine catalyst (1 mol%) to the reaction between fluorinated benzaldehydes and methyl isocyanoacetate [62,63]. As shown in Scheme 12, while the reaction of benzaldehyde gives the corresponding *trans*-oxazoline with high diastereo- and enantioselectivity (*trans*/*cis* = 94/6, 95% ee), increasing the number of fluorine atoms in the phenyl ring of benzaldehyde brings about a remarkable decrease in both the *trans*-selectivity and enantiomeric excess of the *trans*-isomer. Contrastingly however, the enantioselectivity of the *cis*-isomer is gradually enhanced (up to 89% ee). With perfluorobenzaldehyde, the *trans-cis* ratio is 57:43 and the *trans*-(4*S*,5*R*)- and *cis*-(4*S*,5*S*)-isomers are obtained, respectively, in optical yields of 36% and 78%.

As shown in Scheme 13, use of *N*,*N*-dimethyl-α-isocyanoacetamide in place of methyl isocyanoacetate was found to improve the *trans*-selectivity and enantiomeric excesses of the dominant *trans*-oxazolines [63,64]. The reaction of 2,3,5,6-tetrafluorobenzaldehyde gives the corresponding (4*S*,5*R*)-*trans*-isomer with 77% ee (*trans*/*cis* = 89/11). Hydrolysis of the *trans*-oxazoline esters and amides with 6 N HCl, followed by dehydrochlorination with propylene oxide in methanol, affords optically active β-(mono- and polyfluorophenyl)serines.

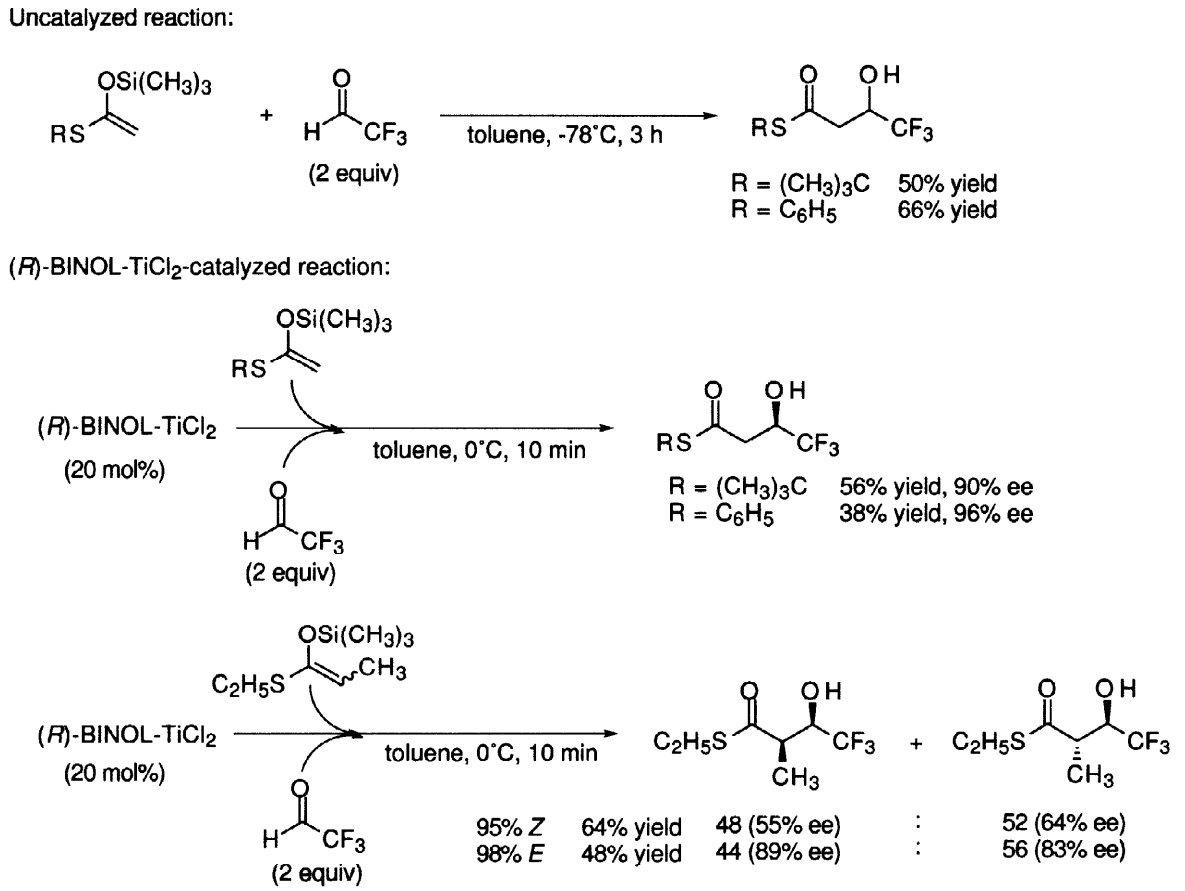


R	yield (%)	*trans* : *cis*	% ee (*trans*)	% ee (*cis*)
C_6H_5	74	94 : 6	94 (4*S*,5*R*)	-
2-F-C_6H_4	87	87 : 13	93 (4*S*,5*R*)	-
2,6-F_2-C_6H_3	84	77 : 23	93 (4*S*,5*R*)	64
2,4,6-F_3-C_6H_2	83	85 : 15	91 (4*S*,5*R*)	48
2,3,5,6-F_4-C_6H	88	89 : 11	77 (4*S*,5*R*)	28
C_6F_5	82	77 : 23	80 (4*S*,5*R*)	20

Scheme 13. Gold(I)-catalyzed asymmetric aldol reaction of fluorinated benzaldehydes with *N*,*N*-dimethyl isocyanoacetamide.

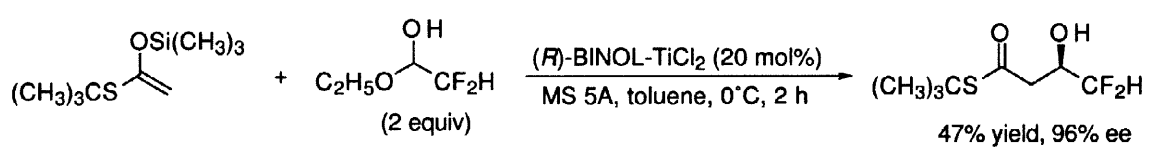
The enantioselective Mukaiyama-type aldol reaction of trifluoroacetaldehyde (fluoral) has been accomplished by Mikami and coworkers using a titanium-binaphthol complex as chiral catalyst [57,65]. Because of its high electrophilicity, fluoral easily condenses with ketene silyl acetals, derived from a thioester, even at -78°C in the absence of a Lewis acid catalyst. Therefore, it was critical for the enantioselective aldol reaction to suppress the uncatalyzed reaction process, which was overcome by improving the addition procedure: fluoral and the ketene silyl acetal are added separately but simultaneously to the catalyst solution. *S*-*tert*-Butyl and *S*-phenyl 4,4,4-trifluoro-3-hydroxybutanethioates having the *R* configuration are obtained in moderate yields and with high enantioselectivity (90% ee and 96% ee, respectively).

Although neither the *E*- nor the *Z*-isomer of *S*-ethyl *O*-(trimethylsilyl) methylketene thioacetal shows any diastereoselectivity, both *syn*- (89% ee) and *anti*- (83% ee) products are obtained with good enantioselectivity from the (*E*)-acetal (Scheme 14).



Scheme 14. Asymmetric aldol reaction of fluoral with ketene silyl acetal.

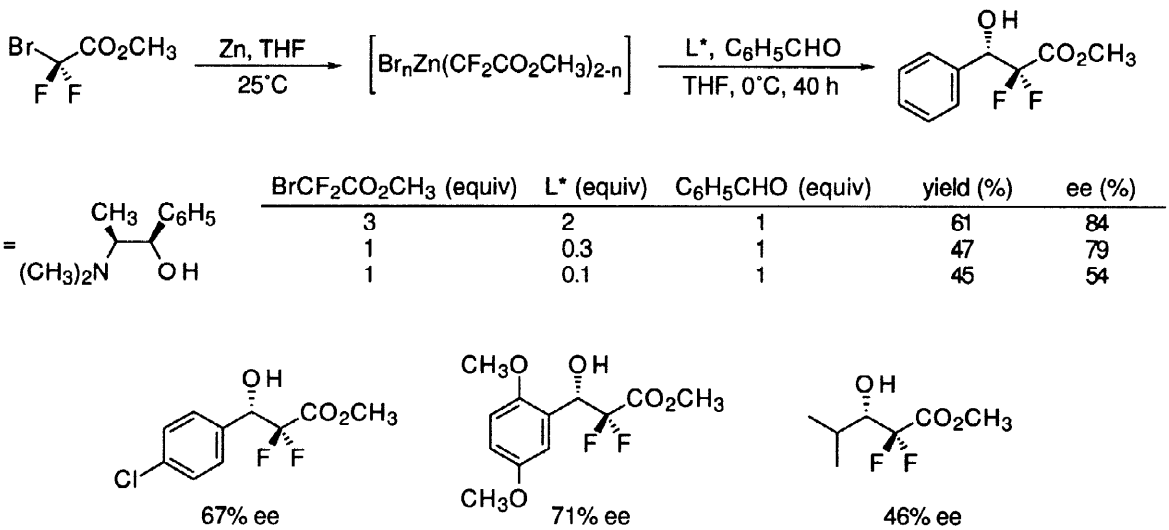
Mikami and coworkers also reported that the titanium-binaphthol complex can catalyze the asymmetric aldol reaction of difluoroacetaldehyde ethyl hemiacetal [57]. *S-tert*-Butyl *O*-(trimethylsilyl) ketene thioacetal reacts with the difluoroacetaldehyde hemiacetal (2 equiv) in the presence of 20 mol% of (*R*)-BINOL-$TiCl_2$ at 0°C to provide the corresponding (*R*)-aldol in an optical yield of 96%, although the chemical yield is not satisfactory (Scheme 15).



Scheme 15. Asymmetric aldol reaction of difluoroacetaldehyde hemiacetal with ketene silyl acetal.

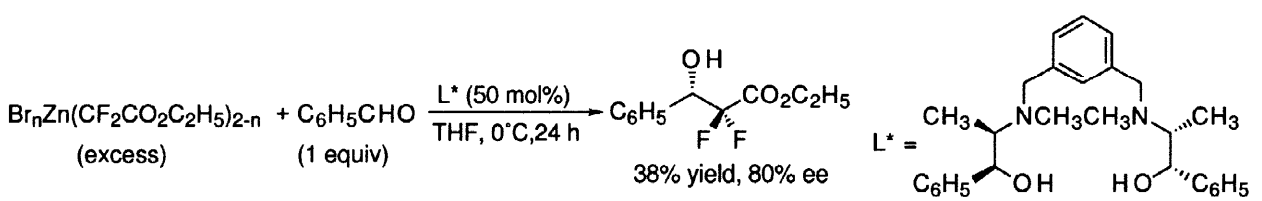
The introduction of a difluoromethylene moiety into biologically active peptides has brought about the discovery of potent protease inhibitors which function by mimicking the transition

state for hydrolytic amide bond cleavage [66-68]. Thus, chiral α,α-difluoro β-hydroxy carboxylates are considered to be the useful building blocks for the enantiocontrolled synthesis of these fluorinated peptides. In 1995, Braun *et al.* disclosed the enantioselective Reformatsky reaction of a bromodifluoroacetate [69]. Benzaldehyde reacts with an excess of the Reformatsky regent, prepared from zinc and methyl bromodifluoroacetate (3 equiv), in the presence of 2 equivalents of a chiral aminoalcohol, (1*R*,2*S*)-*N*-methylephedrine, in THF at 0°C for 40 h to provide the corresponding α,α-difluoro β-hydroxy ester in 61% yield and with 84% ee. However, the decrease in the amount of the chiral ligand markedly suppresses the optical yield. Use of 10 mol% of the aminoalcohol affords the product with 54% ee. Aromatic aldehydes give rather good optical yields, but aliphatic aldehydes provide the products with modest enantiomeric excesses (Scheme 16).



Scheme 16. Asymmetric Reformatsky reaction of methyl bromodifluoroacetate.

Andres and coworkers also reported the asymmetric synthesis of optically active α,α-difluoro β-hydroxy esters using chiral aminoalcohol ligands [70]. However, both chemical and optical yields were insufficient (Scheme 17).

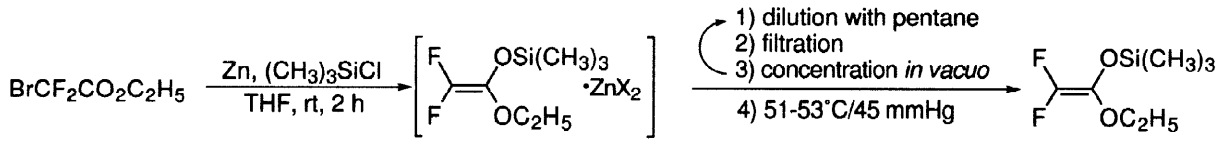


Scheme 17. Asymmetric Reformatsky reaction of ethyl bromodifluoroacetate.

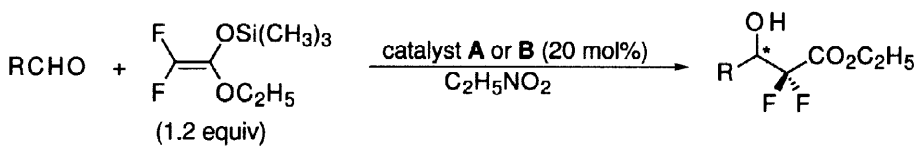
The first example of the asymmetric Mukaiyama aldol reaction of difluoroketene silyl acetals catalyzed by chiral Lewis acids was described in 1997 by Iseki and coworkers [71,72]. Difluoroketene silyl acetals generated *in situ* from α-halo-α,α-difluoroacetate, zinc and

trialkylchlorosilane have been applied to some useful reactions which are not asymmetric syntheses [73-76]. However, this impure acetal containing zinc salt is not suitable for the asymmetric aldol reaction because the salt itself acts as a Lewis acid. Thus, the salt-containing acetal solution is diluted with pentane and filtered to remove the salt, and the filtrate is concentrated. The dilution-filtration-concentration sequence is repeated two more times to provide difluoroketene ethyl trimethylsilyl acetal in pure form (51-53°C/45 mmHg). The aldol reaction of the salt-free difluoroketene acetal has been examined using several chiral Lewis acid catalysts. As shown in Scheme 18, two chiral boron complexes, Masamune's (**A**) and Kiyooka's (**B**) catalysts, gave good results in nitroethane. Masamune's catalyst induces favorable chemical yields and excellent enantioselection at -78°C for benzaldehyde, (*E*)-cinnamaldehyde, benzyloxyacetaldehyde, butanal and decanal. The highest enantioselectivity is obtained with benzyloxyacetaldehyde (98% ee). Kiyooka's catalyst (-45°C) is more effective in the enantioselectivity with secondary aldehydes than Masamune's catalyst (-78°C).

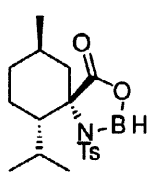
Isolation of difluoroketene ethyl trimethylsilyl acetal:



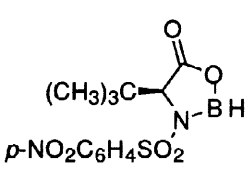
Asymmetric aldol reaction catalyzed by chiral Lewis acids:



aldehyde R	catalyst (20 mol%)	temp. (°C)	product yield (%)	ee (%)
C_6H_5	**A**	-78	99	97 (*R*)
(*E*)-C_6H_5CH=CH	**A**	-78	99	96
$C_6H_5CH_2CH_2$	**A**	-78	98	76
$C_6H_5CH_2OCH_2$	**A**	-78	94	98
c-C_6H_{11}	**B**	-45	97	94
$CH_3CH_2CH_2$	**A**	-78	91	97
$CH_3(CH_2)_8$	**A**	-78	93	92
$(CH_3)_2CHCH_2$	**B**	-45	85	96
$(C_2H_5)_2CH$	**B**	-45	90	95



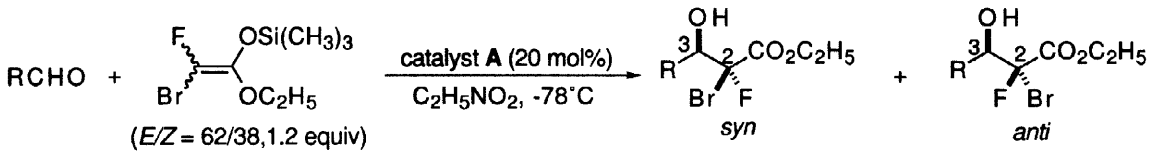
A



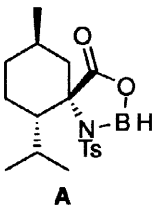
B

Scheme 18. Asymmetric aldol reaction of difluoroketene silyl acetal.

Salt-free bromofluoroketene ethyl trimethylsilyl acetal can be also prepared as an *E*/*Z* mixture (*E*/*Z* = 62/38) from ethyl dibromofluoroacetate in a manner similar to the difluoroketene silyl acetal. The enantioselective aldol reaction of various aldehydes with the bromofluoroketene acetal is carried out in nitroethane at -78°C using 20 mol% of Masamune's catalyst (**A**) to provide a mixture of the *syn*- and *anti*-α-bromo-α-fluoro-β-hydroxycarboxylates. Although *syn*/*anti* diastereoselectivity is not observed, both diastereomers are obtained with high enantioselectivities (up to 99% ee) [77].



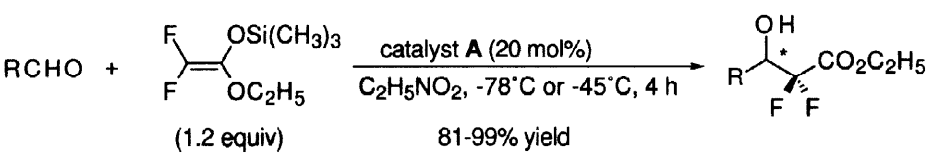
aldehyde (R)	yield (%)	*syn/anti*	ee (*syn*) (%)	ee (*anti*) (%)
C_6H_5	90	69/31	98 (2*S*,3*R*)	90 (2*R*,3*R*)
(*E*)-C_6H_5CH=CH	96	57/43	83	83
$C_6H_5CH_2CH_2$	89	46/54	98	98
$C_6H_5CH_2OCH_2$	81	57/43	97	97
c-C_6H_{11}	74	52/48	94	89
$CH_3CH_2CH_2$	90	46/54	97	98
$(CH_3)_2CHCH_2$	96	48/52	98	98
$(C_2H_5)_2CH$	70	54/46	99	98



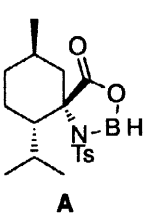
A

Scheme 19. Asymmetric aldol reaction of bromofluoroketene silyl acetal.

The enantioselective aldol reactions of the difluoroketene and bromofluoroketene silyl acetals catalyzed by Masamune's catalyst (**A**) are carried out by the addition of an aldehyde to a solution of the acetal and the catalyst in nitroethane at -78°C over 3 h, followed by stirring at the same temperature for 1 h prior to quenching. Interestingly, the stereochemical outcome was found to depend on the reaction temperature [72]. The reactions of aldehydes with difluoroketene ethyl trimethylsilyl acetal at -78 and -45°C afford the aldol products having opposite signs of optical rotation. For example, cyclohexanecarboxaldehyde provides the corresponding (+)-aldol preferentially in an optical yield of 76% at -78°C, while the reaction at -45°C gives the antipodal (-)-aldol as the major enantiomer with 92% ee (Scheme 20).



aldehyde R	ee (%) -78°C	-45°C
C_6H_5	97 (*R*)	33 (*S*)
$C_6H_5CH_2OCH_2$	98 (+)	81 (-)
c-C_6H_{11}	76 (+)	92 (-)
$CH_3CH_2CH_2$	97 (+)	79 (-)
$(CH_3)_2CHCH_2$	82 (+)	75 (-)
$(C_2H_5)_2CH$	64 (+)	88 (-)

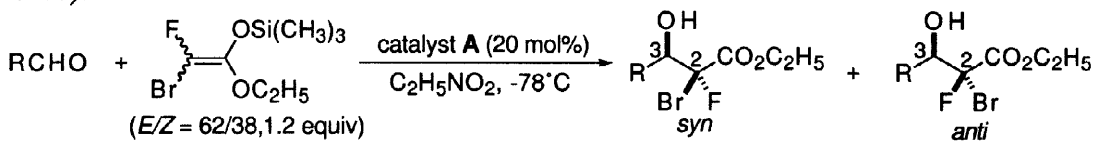


A

Scheme 20. Effects of reaction temperature on the stereoselectivity in the aldol reaction with difluoroketene silyl acetal.

The reaction of bromofluoroketene ethyl trimethylsilyl acetal at -20°C provides different results in diastereoselectivity and enantiofacial selection from those of the reaction at -78°C [78]. While the reaction at -78°C results in a nearly 1:1 mixture of *syn*- and *anti*-aldols, *anti* diastereoselection is observed at -20°C. The aldol reaction of butanal at -20°C gives the corresponding aldol with an *anti*/*syn* ratio of 89/11. The *anti*-isomers obtained at -78°C show

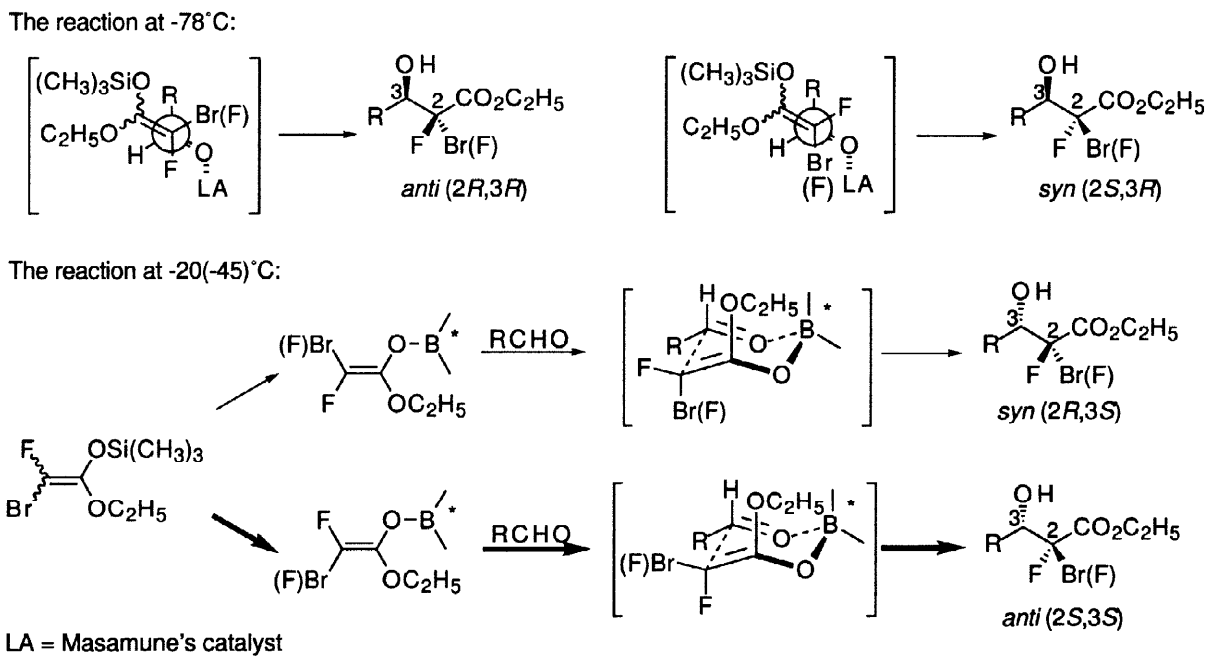
dextrorotation. On the contrary, those at -20°C are levorotatory, and the highest enantiomeric excess is 93% with butanal. It is notable that the reactions at -78 and -20°C provide (+)- and (-) -*anti*-α-bromo-α-fluoro-β-hydroxy esters, respectively, with significant enantioselectivities (Scheme 21).



aldehyde R	-78°C yield (%)	syn/anti	ee (*anti*) (%)	-45°C yield (%)	syn/anti	ee (*anti*) (%)
$C_6H_5CH_2CH_2$	89	46/54	98 (+)	85	13/87	92 (-)
$C_6H_5CH_2OCH_2$	81	57/43	97 (+)	80	26/74	72 (-)
c-C_6H_{11}	74	52/48	89 (+)	90	20/80	81 (-)
$CH_3CH_2CH_2$	90	46/54	98 (+)	87	11/89	93 (-)
$(CH_3)_2CHCH_2$	96	48/52	98 (+)	87	11/89	91 (-)
$(C_2H_5)_2CH$	70	54/46	98 (+)	85	23/77	74 (-)

Scheme 21. Effects of reaction temperature on the stereoselectivity in the aldol reaction with bromofluoroketene silyl acetal.

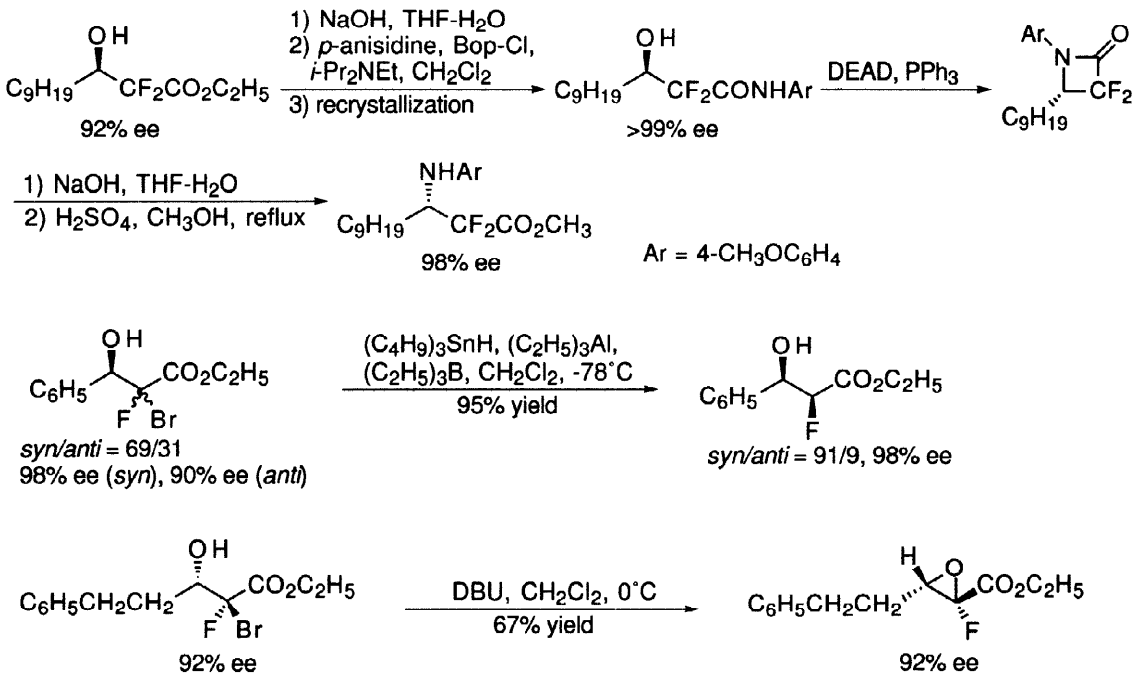
Although the reason is not clear for the *anti* selectivity in the reaction with bromofluoroketene silyl acetal, the reversal of the enantioselection may be possibly explained by some transition structures shown in Scheme 22. The reaction at -78°C proceeds through the extended open transition states, and the bromofluoroketene and difluoroketene acetals react preferentially on the *si* face of the aldehyde. On the other hand, the reaction at -20°C (-45°C in the case of the bromofluoroketene acetal) proceeds with *re* facial selection via transmetallation to the boron enolate and the cyclic chair transition state [78].



Scheme 22. Possible mechanism of asymmetric aldol reactions of difluoroketene and bromofluoroketene silyl acetals.

Optically active α,α-difluoro and α-bromo-α-fluoro β-hydroxy esters are versatile synthetic intermediates for various fluorinated bioactive compounds. As shown in Scheme 23, the hydrolysis of ethyl (+)-2,2-difluoro-3-hydroxydodecanoate (92% ee) with aqueous NaOH-THF and treament with *p*-anisidine in the presence of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl) and *N,N*-diisopropylethylamine gives the corresponding amide which can be purified to enantiomerically pure form by a single recrystallization. The amide is converted to the homochiral β-lactam without racemization using a Mitsunobu protocol. Hydrolysis of the β-lactam, followed by the esterification of the resulting acid, provides the β-amino α,α-difluoro ester with 98% ee [72].

A mixture of optically active *syn*- and *anti*-2-bromo-2-fluoro-3-hydroxy-3-phenylpropanoates [*syn/anti* = 69/31, 98% ee (*syn*), 90% ee (*anti*)] is reduced with $(C_4H_9)_3SnH$ in the presence of $(C_2H_5)_3Al$ and $(C_2H_5)_3B$ in CH_2Cl_2 at -78°C according to the procedure given by Ishihara and coworkers to afford (2*S*,3*R*)-2-fluoro-3-hydroxy-3-phenylpropanoate with high diastereo- and enantioselectivities (*syn/anti* = 91/9, 98% ee) (Scheme 23) [77,79]. Ethyl (2*S*,3*S*)-2-bromo-2-fluoro-3-hydroxy-5-phenylpentanoate (92% ee) is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.9 equiv.) in CH_2Cl_2 at 0°C to give ethyl (2*S*,3*S*)-2,3-epoxy-2-fluoro-5-phenylpentanoate in 67% yield and with 92% ee (Scheme 23).



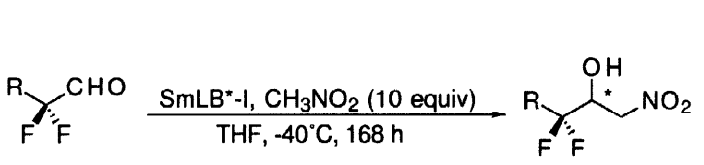
Scheme 23. Stereoselective conversion of α,α-difluoro and α-bromo-α-fluoro β-hydroxy esters to chiral useful intermediates.

5.3. Asymmetric nitroaldol reaction

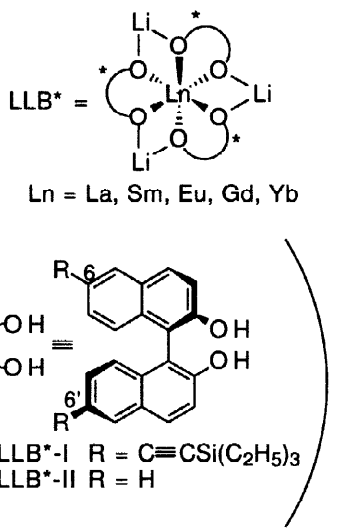
Shibasaki and coworkers have developed a series of highly selective heterobimetallic catalysts for a variety of catalytic asymmetric reactions [80]. Lanthanoid (Ln)-lithium-BINOL

(LLB catalyst) complexes are the most efficient catalysts for the asymmetric nitroaldol reaction (Henry reaction) and catalyze the reaction of aldehydes with nitroalkanes to provide the nitroaldols with very good enantio- and diastereoselectivities [81-88].

In 1996, Iseki *et al.* reported the nitroaldol reaction of α,α-difluoroaldehydes using the lanthanoid-lithium-BINOL complexes which can be easily prepared *in situ* from Ln(O-*i*-Pr)3, BuLi, H_2O and (*R*)-BINOL [89]. After surveying various rare earth (lanthanoid) metals, samarium was found to be the most suitable for the asymmetric nitroaldol reaction of α,α-difluoroaldehydes. The reaction of the aldehydes with nitromethane is carried out at -40°C in THF in the presence of samarium-lithium-(*R*)-BINOL (SmLB) catalysts to afford the optically active nitroaldols, and samarium-lithium-(*R*)-6,6'-bis((triethylsilyl)ethynyl)-BINOL (SmLB*-I) (5-8 mol%) gives the best enantioselectivity (74-95% ee) although the chemical yields are moderate. 2,2-Difluoro-5-phenylpentanal provides (*S*)-3,3-difluoro-6-phenyl-1-nitro-2-hexanol with 92% ee, and the highest enantiomeric excess (95% ee) is obtained with 2-cyclohexyl-2,2-difluoroacetaldehyde (Scheme 24).



aldehyde (R)	SmL* (mol%)	yield (%)	ee (%)
$C_6H_5(CH_2)_3$	5	55	92 (*S*)
$CH_3(CH_2)_6$	5	55	74
$C_6H_5CH_2O(CH_2)_2$	5	52	80
$(CH_3)_2CHSCH_2$	5	55	85
4-$(CH_3OC_2H_4)C_6H_4O$	8	52	77
c-C_6H_{11}	8	58	95

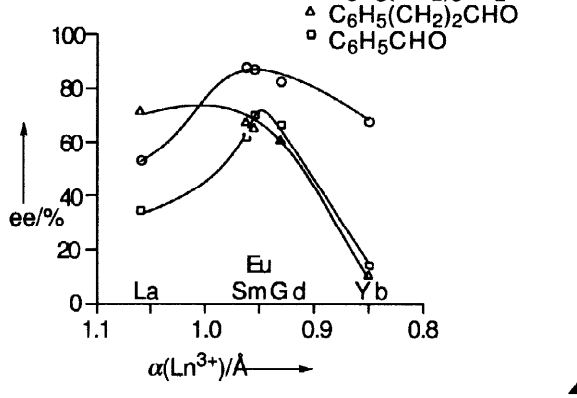


Scheme 24. Asymmetric nitroaldol reaction of α,α-difluoroaldehydes.

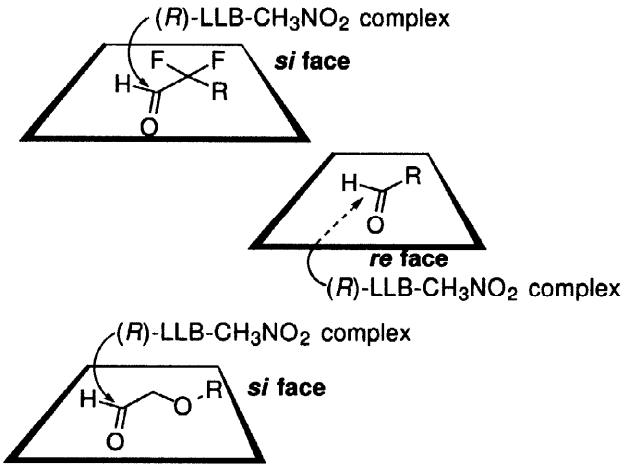
The unique relationship between the ionic radii of the rare-earth metals and the optical purities of the nitroaldols, which was examined using the lanthanoid-lithium-(*R*)-BINOL complex (LLB*-II catalyst), is depicted in Scheme 25. α,α-Difluoroaldehydes showed a different relationship from nonfluorinated aliphatic aldehydes. For example, the nitroaldol reaction of 2,2-difluoro-5-phenylpental gives the highest enantioselectivity with the samarium complex, while the best result for 3-phenylpropanal is obtained with the lanthanum catalyst (LaLB). The relationship given by α,α-difluoroaldehydes may be rather similar to that of an aromatic aldehyde, benzaldehyde.

Lanthanoid-lithium-(*R*)-BINOL complexes generally direct the attack of the nitronate with a *re* face preference to aldehydes. Interestingly, the enantiotopic facial selection of α,α-difluoroaldehydes is the reverse of that of nonfluorinated aldehydes employed in the usual catalytic asymmetric nitroaldol reaction. This stereoselection of α,α-difluoroaldehydes is indentical with that of β-oxa-aldehydes, suggesting that the fluorine atoms at the α-position

exert a pronounced influence on the enantiotopic facial selection. The difluoromethylene moiety is frequently thought to function as a mimic of ether-oxygen (Scheme 26).

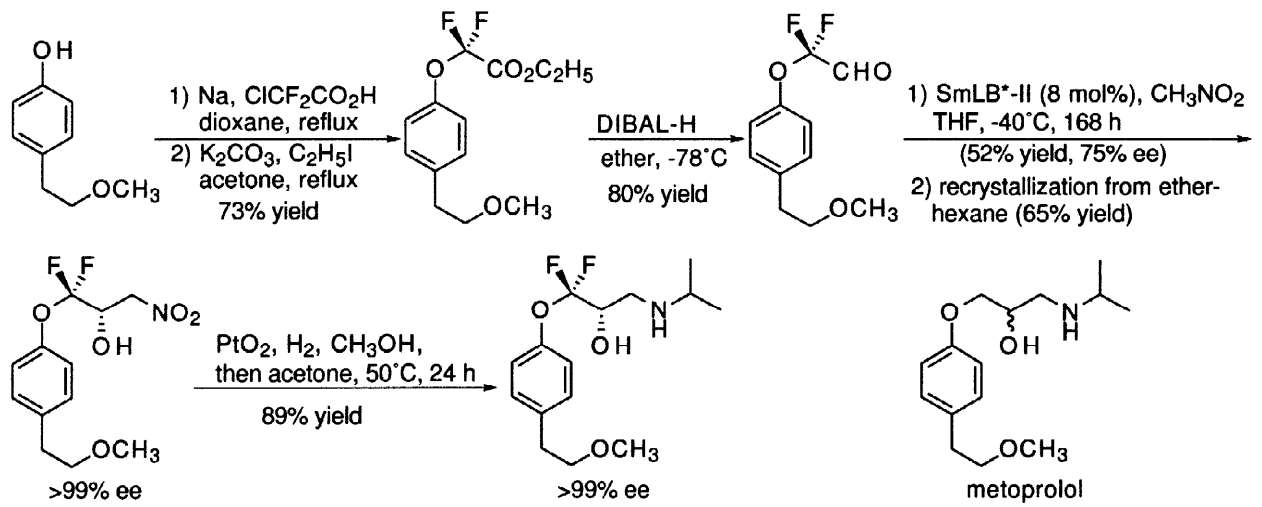


Scheme 25. Effect of the ionic radii α of the rare-earth elements on the optical yield of nitroaldols.



Scheme 26. Stereochemical course of asymmetric nitroaldol reaction.

An optically active nitroaldol product obtained from an α,α-difluoroaldehyde has been applied to the synthesis of a difluorinated analog of the β_1-selective β-adrenergic blocking agent, metoprolol [90]. As shown in Scheme 27, the α,α-difluoroaldehyde prepared from 4-(2-methoxyethyl)phenol reacted with nitromethane in the presence of 8 mol% of Sm-Li-(*R*)-BINOL, followed by recrystallization, to give the corresponding nitroaldol in enantiomerically pure form. Reductive alkylation of the nitroaldol thus obtained was accomplished by PtO_2-catalyzed hydrogenation in the presence of acetone in methanol to afford the homochiral metoprolol analog bearing the *S* configuration. The fluorinated analog showed a slightly lower affinity to the β-receptor and was less potent in β_1-adrenergic activity compared to metoprolol.

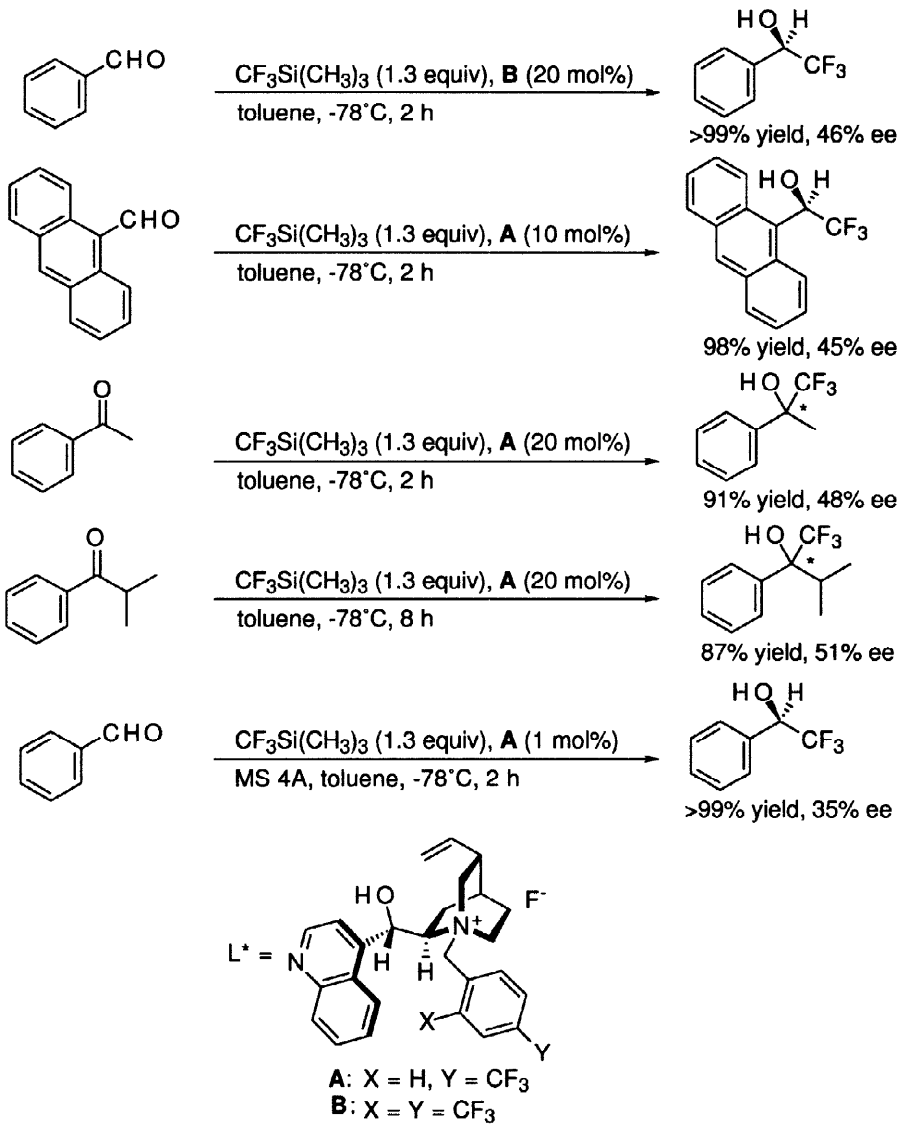


SmLB*-II = Sm-Li-(*R*)-BINOL

Scheme 27. Synthesis of a fluorinated analog of the β-adrenergic blocking agent, metoprolol.

5.4. Asymmetric addition to carbonyl compounds

Trifluoromethyltrimethylsilane [$(CH_3)_3SiCF_3$] has been shown by Prakash *et al.* to be an excellent reagent for the trifluoromethylation of carbonyl compounds [91-93]. The reaction of aldehydes or ketones with $(CH_3)_3SiCF_3$ is catalyzed by a catalytic amount of tetrabutylammonium fluoride (TBAF) to afford the α-trifluoromethylated alcohols in good yields.

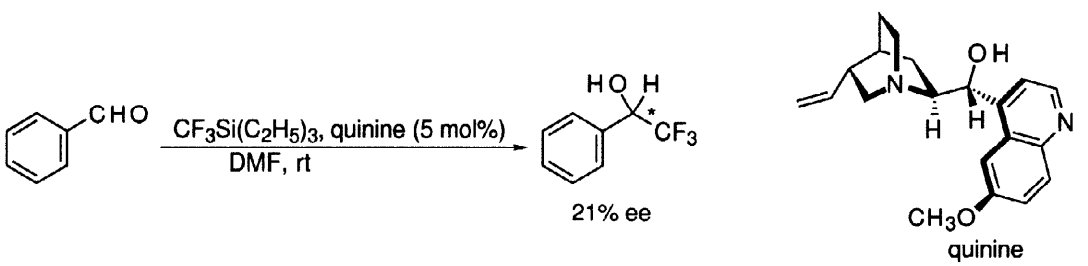


Scheme 28. Asymmetric trifluoromethylation of carbonyl compounds catalyzed by chiral quaternary ammonium fluorides.

In 1994, Iseki *et al.* disclosed the catalytic asymmetric trifluoromethylation of aldehydes and ketones with $(CH_3)_3SiCF_3$ mediated by chiral quarternary ammonium fluorides [94]. The reaction of benzaldehyde with $(CH_3)_3SiCF_3$ is carried out in the presence of 20 mol% of *N*-2,4-bis(trifluoromethyl)benzylcinchonium fluoride (**B**) in toluene at -78°C for 2 h to give (*R*)-

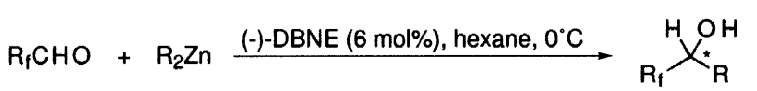
α-(trifluoromethyl)benzyl alcohol in quantitative chemical yield and with 46% ee. The trifluoromethylation of 9-anthraldehyde mediated by 10 mol% of *N*-4-(trifluoromethyl)benzylcinchonium fluoride (**A**) produces (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol in an optical yield of 45%. Ketones are also suitable substrates for enantioselective trifluoromethylation. For example, the reaction of acetophenone or isobutyrophenone in the presence of 20 mol% of catalyst **A** gives the corresponding tertiary alcohols, respectively, in 48% ee and 51% ee. Use of molecular sieves (4Å) can lead to a reduction in the amount of the catalyst, and 1 mol% of catalyst **A** catalyzes the trifluoromethylation of benzaldehyde at -78°C for 2 h to afford the optically active trifluoromethylated alcohol in quantitative yield and with 35% ee (Scheme 28).

Hagiwara *et al.* also reported the catalytic asymmetric trifluoromethylation of benzaldehyde [95]. However, the use of 5 mol% quinine as a Lewis base catalyst in combination with trifluoromethyltriethylsilane [$(C_2H_5)_3SiCF_3$] in DMF produced optically active α-(trifluoromethyl)benzyl alcohol in only 11% chemical yield and 21% ee (Scheme 29).

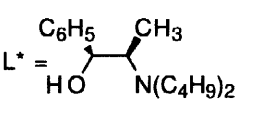


Scheme 29. Asymmetric trifluoromethylation of benzaldehyde catalyzed by quinine.

Soai and coworkers disclosed that the enantioselective addition of dialkylzinc reagents to fluorine-containing aldehydes was mediated by chiral aminoalcohol ligands to provide the optically active secondary alcohols with high enantioselectivities [96]. Reaction of *p*-trifluoromethylbenzaldehyde with diethylzinc or dimethylzinc proceeded in the presence of 6 mol% of (1*S*,2*R*)-(-)-*N*,*N*-dibutylnorephedrine [(-)-DBNE] in hexane at 0°C to afford (*S*)-1-(*p*-trifluoromethyl)phenylpropanol and (*S*)-1-(*p*-trifluoromethyl)phenylethanol, respectively, with 91% ee and 81% ee. The method is also applicable to monofluorinated benzaldehydes and polyfluorinated aliphatic alcohols, and the corresponding fluorinated alcohols are obtained in good-to-high optical yields (Scheme 30).



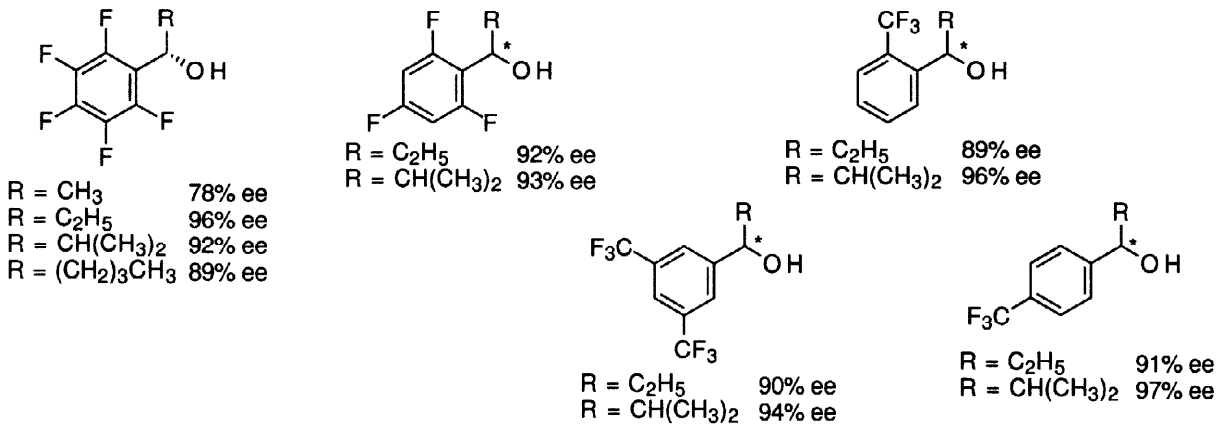
R_fCHO	R_2Zn (equiv)	time (h)	yield (%)	ee (%)
p-$CF_3C_6H_4CHO$	$(C_2H_5)_2Zn$ (2.2)	22	92	91 (*S*)
p-$CF_3C_6H_4CHO$	$(CH_3)_2Zn$ (3.0)	214	80	81 (*S*)
p-FC_6H_4CHO	$(C_2H_5)_2Zn$ (2.2)	24	83	93
o-FC_6H_4CHO	$(C_2H_5)_2Zn$ (2.2)	24	65	85
$CF_3(CF_2)_5(CH_2)_2$	$(C_2H_5)_2Zn$ (2.2)	12	43	73



(1*S*,2*R*)-(-)-DBNE

Scheme 30. Asymmetric alkylation of fluorine-containing aldehydes (1).

After further studies, the asymmetric addition reaction using 20 mol% of (1*S*,2*R*)-(-)-DBNE at room temperature was found to provide the best enantioselectivity, and a variety of optically active fluorine-containing aromatic alcohols were obtained with high enantiomeric excesses (78-97% ee) as shown in Scheme 31 [97].



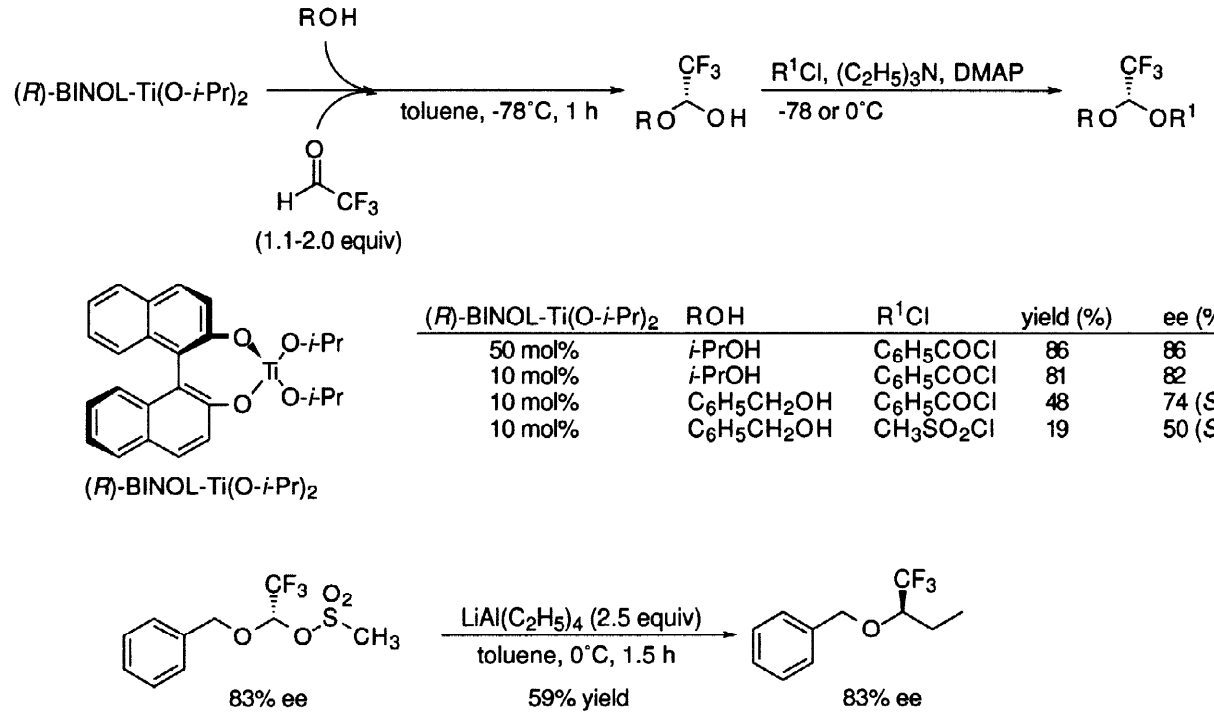
Scheme 31. Asymmetric alkylation of fluorine-containing aldehydes (2).

6. Other methods for chiral fluoroorganic compounds

The first example of enantioselective synthesis of optically active trifluoroacetaldehyde hemiacetals was reported by Hiyama and coworkers using a binaphthol-titanium (IV) complex as chiral catalyst [98]. The reaction is carried out by simultaneously adding trifluoroacetaldehyde (fluoral) and isopropanol or benzyl alcohol to a solution of (*R*)-BINOL-Ti(O-*i*-Pr)$_2$ in toluene at -78°C, followed by stirring for 1 h at -78°C. The resulting hemiacetal is benzoylated at -78°C or mesylated at 0°C to give the corresponding optically active benzoates and mesylates, respectively. The benzoate of 1-isopropoxy-2,2,2-trifluoroethanol having an optical purity of 82% is produced in 81% yield using 10 mol% of the titanium catalyst. In the same manner, the benzoate of (*S*)-1-benzyloxy-2,2,2-trifluoroethanol is obtained as the major enantiomer from benzyl alcohol and benzoyl chloride (74% ee). Optically active 1-benzyloxy-2,2,2-trifluoroethanol, prepared from benzyl alcohol and 10 mol% of the catalyst, is then trapped with methanesulfonyl chloride to provide the corresoponding (*S*)-mesylate with 50% ee. The relatively low enantiomeric excess may be possibly ascribed to partial racemization of the hemiacetal at 0°C, the temperature required for the mesylation (Scheme 32).

The obtained optically active mesylate must be a useful chiral building block and has been applied to the carbon-carbon bond-forming reactions. Treatment of (*S*)-1-benzyloxy-2,2,2-trifluoroethanol methanesufonate having an enantiomeric excess of 83% with lithium tetraethylaluminate [LiAl(C_2H_5)$_4$] in toluene at 0°C for 1.5 h provides (*R*)-(+)-2-benzyloxy-1,1,1-trifluorobutane of 83% ee in 59% yield and with complete inversion of configuration. Other lithium tetraalkylaluminates are also applicable to convert the benzyloxy mesylates to the corresponding optically active 2-benzyloxy-1,1,1-trifluoroalkanes with excellent chirality

transfer. The reaction of the mesylates with lithium tetraalkylaluminates is the first example of stereospecific and nucleophilic carbon-carbon bond-forming substitution at a CF_3-substituted carbon (Scheme 32).



(*R*)-BINOL-Ti(O-*i*-Pr)$_2$	ROH	R^1Cl	yield (%)	ee (%)
50 mol%	*i*-PrOH	C_6H_5COCl	86	86
10 mol%	*i*-PrOH	C_6H_5COCl	81	82
10 mol%	$C_6H_5CH_2OH$	C_6H_5COCl	48	74 (*S*)
10 mol%	$C_6H_5CH_2OH$	CH_3SO_2Cl	19	50 (*S*)

Scheme 32. Enantioselective synthesis of optically active trifluoroacetaldehyde hemiacetals.

7. Concluding remarks

Significant progress has been recently made in the development of *catalytic asymmetric synthesis of chiral fluoroorganic compounds*. However, only less than ten reactions are comparable in efficiency, especially in enantioselectivity, to the asymmetric reactions for chiral fluorine-free compounds, implying that the theories established for the fluorine-free compounds are not always applicable to the preparation of chiral fluoroorganic compounds. Thus, an accurate understanding of the properties of fluorine atoms and fluoroorganic molecules and the design of chiral catalysts suitable for fluorine-containing substrates is essential for breakthroughs in the catalytic asymmetric synthesis of chiral fluoroorganic compounds. In addition, detailed mechanistic studies of the interaction between key catalytic species and fluorine-containing substrates in asymmetric induction steps are thought to be extremely important.

Although the term "chirotechnology" denotes a new technology spawned by the current and future direction of the chiral drugs arena, I would like to emphasize that a wide variety of applications of chiral fluoroorganic compounds are not only for physiologically active compounds and their synthetic intermediates but also for new materials, such as color liquid crystals and nonlinear optics. These depend on further advances in the fluorine version of

"chirotechnology" and catalytic asymmetric synthesis should play a central role in the technology. I am confident that many efficient and practical chiral catalysts will be developed and various chiral fluorinated compounds will be produced using catalytic asymmetric reactions on an industrial scale in the near future.

Acknowledgments: I am grateful to Professor Masakatsu Shibasaki for his valuable comments on the typed manuscript of this review.

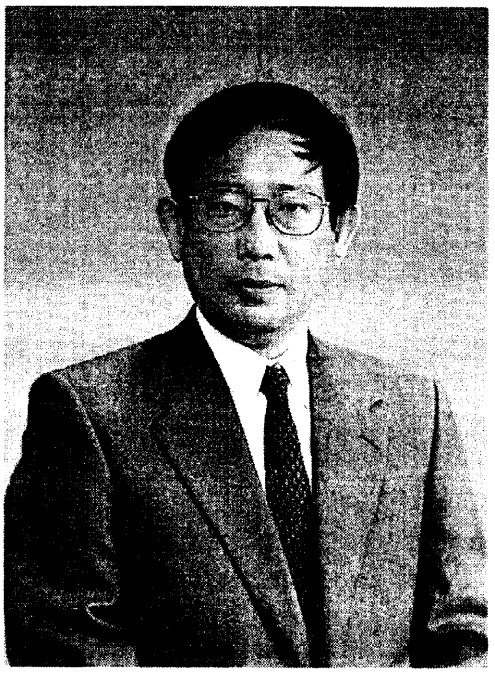
References

[1] For example: Crossley R. Tetrahedron 1992;48;8155-8178.
[2] Ojima I, editor. Catalytic asymmetric synthesis. Weinheim: VCH, 1993.
[3] Noyori R. Asymmetric catalysis in organic synthesis. New York: John Wiley, 1994.
[4] Filler R, Kobayashi Y, editors. Biomedical aspects of fluorine chemistry. Tokyo and Amsterdam: Kodansha and Elsevier, 1982.
[5] Welch JT, Eswarakrishnan S. Fluorine in bioorganic chemistry. New York: John Wiley, 1991.
[6] Welch JT, editor. Selective fluorination in organic and bioorganic chemistry. Washington: American Chemical Society, 1991.
[7] Filler R, Kobayashi Y, Yagupolskii LM, editors. Organofluorine compounds in medicinal chemistry and biomedical applications. Amsterdam: Elsevier, 1993.
[8] Ojima I, McCarthy JR, Welch JT, editors. Biomedical frontiers of fluorine chemistry. Washington: American Chemical Society, 1996.
[9] Welch JT. Tetrahedron 1987;43;3123-3197.
[10] Bravo P, Resnati G. Tetrahedron:Asymm. 1990;1;661-692.
[11] Resnati G. Tetrahedron 1993;49;9385-9445.
[12] Iseki K, Kobayashi Y. J. Synth. Org. Chem. Jpn. 1994;52;40-48.
[13] Hayashi T, Soloshonok VA, editors. Enantiocontrolled synthesis of fluoro-organic compounds. Tetrahedron:Asymm. 1994;5;No. 6.
[14] Iseki K, Kobayashi Y. Rev. Heteroatom Chem. 1995;12;211-237.
[15] Resnati G, Soloshonok VA, editors. Fluoroorganic chemistry: synthetic challenges and biomedicinal rewards. Tetrahedron 1996;52;No. 1.
[16] Soloshonok VA, editor. Enantiocontrolled synthesis of fluoro-organic compounds: stereochemical challenges and biomedical targets. New York: John Wiley, 1998.
[17] Bömelburg J, Heppke G, Ranft A. Z. Naturforsch. 1989;1127-1131.
[18] Buchecker R, Kelly SM, Fünfschilling J. Liquid Cryst. 1990;8;217-227.
[19] Arakawa S, Nito K, Seto J. Mol. Cryst. Liq. Cryst. 1991;204;15-25.
[20] Seebach D. Angew. Chem. Int. Ed. Engl. 1990;29;1320-1367.
[21] Horner L, Siegel H, Büthe H. Angew. Chem. Int. Ed. Engl. 1968;7;942.
[22] Knowles WS, Sabacky MJ. J. Chem. Soc., Chem. Commun. 1968;1445-1446.
[23] Knowles WS, Sabacky MJ, Vineyard BD. J. Chem. Soc., Chem. Commun. 1972;10-11.
[24] Takaya H, Ohta T, Noyori R. Asymmetric hydrogenation. In: Ojima I, editor. Catalytic asymmetric synthesis. Weinheim: VCH, 1993:1-39.
[25] Noyori R. Homogeneous asymmetric hydrogenation. In: Asymmetric catalysis in organic synthesis. New York: John Wiley, 1994:16-94.
[26] Koenig KE, Bachman GL, Vineyard BD. J. Org. Chem. 1980;45;2362-2365.
[27] Burk MJ, Feaster JE, Harlow RL. Organometallics 1990;9;2653-2655.
[28] Burk MJ, Harlow RL. Angew. Chem., Int. Ed. Engl. 1990;29;1462-1464.
[29] Burk MJ, Feaster JE. Tetrahedron:Asymm. 1991;2;569-592.
[30] Burk MJ. J. Am. Chem. Soc. 1991;13;8518-8519.
[31] Saburi M, Shao L, Sakurai T, Uchida Y. Tetrahedron Lett. 1992;33;7877-7880.
[32] Ohta T, Takaya H, Kitamura M, Nagai K, Noyori R. J. Org. Chem. 1987;52;3176-3178.
[33] Iseki K, Kuroki Y, Nagai T, Kobayashi Y. J. Fluorine Chem. 1994;69;5-6.
[34] Iseki K, Kuroki Y, Nagai T, Kobayashi Y. Chem. Pharm. Bull. 1996;44;477-480.
[35] Kitamura M, Ohkuma T, Inoue S, Sayo N, Kumobayashi H, Akutagawa S, Ohta T, Takaya H, Noyori R. J. Am. Chem. Soc. 1988;110;629-631.
[36] Sayo N, Akutagawa S, Saito T, Noyori R, Kumobayashi H, Takaya H. EP 1988;295109 A1.
[37] Sayo N, Saito T, Akutagawa S, Noyori R, Takaya H. EP 1989;297752 A2.

[38] Sharpless KB, Amberg W, Bennani YL, Crispino GA, Hartung J, Jeong KS, Kwong HL, Morikawa K, Wang ZM, Xu D, Zhang XL. J. Org. Chem. 1992;57;2768-2771.
[39] Amberg W, Bennani YL, Crispino GA, Chadha RK, Davis W, Hartung J, Jeong KS, Ogino Y, Shibata T, Sharpless KB. J. Org. Chem. 1993;58;844-849.
[40] Kolb HC, Anderson PG, Bennani YL, Crispino GA, Jeong KS, Kwong HL, Sharpless KB. J. Am. Chem. Soc. 1993;115;12226-12227.
[41] Bennani YL, Vanhessche KPM, Sharpless KB. Tetrahedron:Asymm. 1994;5;1473-1476.
[42] Corey EJ, Bakshi RK, Shibata S. J. Am. Chem. Soc. 1987;109;5551-5553.
[43] Corey EJ, Bakshi RK, Shibata S, Chen CP, Singh VK. J. Am. Chem. Soc. 1987;109;7925-7926.
[44] Corey EJ, Shibata S, Bakshi RK. J. Org. Chem. 1988;53;2861-2863.
[45] Corey EJ, Bakshi RK. Tetrahedron Lett. 1990;31;611-614.
[46] Corey EJ, Cheng XM, Cimprich KA, Sarshar S. Tetrahedron Lett. 1991;32;6835-6838.
[47] Corey EJ, Link JO, Bakshi RK. Tetrahedron Lett. 1992;33;7107-7110.
[48] Corey EJ, Link JO, Sarshar S, Shao Y. Tetrahedron Lett. 1992;33;7103-7106.
[49] Sakai T, Yan F, Kashino S, Uneyama K. Tetrahedron 1996;52;233-244.
[50] Maruoka K, Hoshino Y, Shirasaka T, Yamamoto H. Tetrahedron Lett. 1988;29;3967-3970.
[51] Mikami K, Terada M, Nakai T. J. Am. Chem. Soc. 1989;111;1940-1941.
[52] Mikami K, Terada M, Nakai T. J. Am. Chem. Soc. 1990;112;3949-3954.
[53] Mikami K, Terada M, Narisawa S, Nakai T. Org. Synth. 1992;71;14-21.
[54] Mikami K, Shimizu M. Chem. Rev. 1992;92;1021-1050.
[55] Mikami K, Yajima T, Terada M, Uchimaru T. Tetrahedron Lett. 1993;34;7591-7594.
[56] Mikami K, Yajima T, Terada M, Kato E, Maruta M. Tetrahedron:Asymm. 1994;5;1087-1090.
[57] Mikami K, Yajima T, Takasaki T, Matsukawa S, Terada M, Uchimaru T, Maruta M. Tetrahedron 1996;52;85-98.
[58] Mikami K, Yajima T, Siree N, Terada M, Suzuki Y, Kobayashi I. Synlett 1996;837-838.
[59] Ito Y, Sawamura M, Hayashi T. J. Am. Chem. Soc. 1986;108;6405-6406.
[60] Hayashi T, Sawamura M, Ito Y. Tetrahedron 1992;48;1999-2012.
[61] Pastor SD, Togni A. J. Am. Chem. Soc. 1989;111;2333-2334.
[62] Soloshonok VA, Hayashi T. Tetrahedron Lett. 1994;35;2713-2716.
[63] Soloshonok VA, Kacharov AD, Hayashi T. Tetrahedron 1996;52;245-254.
[64] Soloshonok VA, Hayashi T. Tetrahedron:Asymm. 1994;5;1091-1094.
[65] Mikami K, Takasaki T, Matsukawa S, Maruta M. Synlett 1995;1057-1058.
[66] Gelb MH, Svaren JP, Abeles RH. Biochemistry 1985;24;1813-1817.
[67] Gelb MH. J. Am. Chem. Soc. 1986;108;3146-3147.
[68] Kirk KL. Synthesis and biochemical applications of fluorine-containing peptides and proteins. In: Kukhar' VP, Soloshonok VA, editors. Fluorine-containing amino acids. New York: John Wiley, 1995:343-401.
[69] Braun M, Vonderhagen A, Waldmüller D. Liebigs Ann. Chem. 1995;1447-1450.
[70] Andres JM, Martinez MA, Pedrosa R, Perez-Encabo A. Synthesis 1996;1070-1072.
[71] Iseki K, Kuroki Y, Asada D, Kobayashi Y. Tetrahedron Lett. 1997;38;1447-1448.
[72] Iseki K, Kuroki Y, Asada D, Takahashi M, Kishimoto S, Kobayashi Y. Tetrahedron 1997;53;10271-10280.
[73] Kitagawa O, Taguchi T, Kobayashi Y. Tetrahedron Lett. 1988;29;1803-1806.
[74] Taguchi T, Kitagawa O, Suda Y, Ohkawa S, Hashimoto A, Iitaka Y, Kobayashi Y. Tetrahedron Lett. 1988;29;5291-5294.
[75] Burton DJ, Easdon JC. J. Fluorine Chem. 1988;38;125-129.
[76] Kitagawa O, Hashimoto A, Kobayashi Y, Taguchi T. Chem. Lett. 1990;1307-1310.
[77] Iseki K, Kuroki Y, Kobayashi Y. Tetrahedron Lett. 1997;38;7209-7210.
[78] Iseki K, Kuroki Y, Kobayashi Y. Synlett in press.
[79] Ishihara T, Kuwahata S, Yamanaka H. 72nd National Meeting of the Chemical Society of Japan, Tokyo, March 1997, Abstr., No. 3G247.
[80] Shibasaki M, Sasai H, Arai T. Angew. Chem. Int. Ed. Engl. 1997;36;1236-1256.
[81] Sasai H, Suzuki T, Arai S, Arai T, Shibasaki M. J. Am. Chem. Soc. 1992;114;4418-4420.
[82] Sasai H, Suzuki T, Itoh N, Shibasaki M. Tetrahedron Lett. 1993;34;851-854.
[83] Sasai H, Itoh N, Suzuki T, Shibasaki M. Tetrahedron Lett. 1993;34;855-858.
[84] Sasai H, Suzuki T, Itoh N, Arai S, Shibasaki M. Tetrahedron Lett. 1993;34;2657-2660.
[85] Sasai H, Kim WS, Suzuki T, Shibasaki M, Mitsuda M, Hasegawa J, Ohashi T. Tetrahedron Lett. 1994;35;6123-6126.
[86] Sasai H, Yamada YMA, Shibasaki M. Tetrahedron 1994;50;12313-12318.
[87] Sasai H, Suzuki T, Itoh N, Tanaka K, Date T, Okamura K, Shibasaki M. J. Am. Chem. Soc. 1993;115;10372-10373.
[88] Sasai H, Tokunaga T, Watanabe S, Suzuki T, Itoh N, Shibasaki M. J. Org. Chem. 1995;60;7388-7389.
[89] Iseki K, Oishi S, Sasai H, Shibasaki M. Tetrahedron Lett. 1996;37;9081-9084.
[90] Iseki K, Oishi S, Sasai H, Shibasaki M. Bioorg. Med. Chem. Lett. 1997;7;1273-1274.
[91] Prakash GKS, Krishnamurti R, Olah GA. J. Am. Chem. Soc. 1989;111;393-395.
[92] Krishnamurti R, Bellew DR, Prakash GKS. J. Org. Chem. 1991;56;984-989.
[93] Prakash GKS, Yudin AK. Chem. Rev. 1997;97;757-786.

[94] Iseki K, Nagai T, Kobayashi Y. Tetrahedron Lett. 1994;35;3137-3138.
[95] Hagiwara T, Kobayashi T, Fuchikami T. 14th International Symposium on Fluorine Chemistry, Yokohama, 1994, Abstr., No. 1P07.
[96] Soai K, Hirose Y, Niwa S. J. Fluorine Chem. 1992;59;5-8.
[97] Hayase T, Sugiyama T, Suzuki M, Shibata T, Soai K. J. Fluorine Chem. 1997;84;1-5.
[98] Matsutani H, Yaruva J, Poras H, Kusumoto T, Hiyama T. 44th Symposium on Organometallic Chemistry, Japan, Osaka, 1997, Abstr., No. B109.

Biographical sketch



Katsuhiko Iseki

Katsuhiko Iseki was born in Yokosuka, Japan in 1951 and graduated from the University of Tokyo in 1974. He worked as an organic chemist in Mitsubishi Chemical Corporation (1974-1990). In 1978 he joined Teikyo University, Sagamiko as a visiting scientist to carry out research on the synthesis of some prostanoids and natural triquinane products under supervision of Professors M. Shibasaki and S. Ikegami and received his Ph.D. degree from the University of Tokyo in 1984. In 1990 he moved to MEC Laboratory, Daikin Industries, Ltd. where his current research interests include the development of catalytic asymmetric synthesis and the design of chiral catalysts.