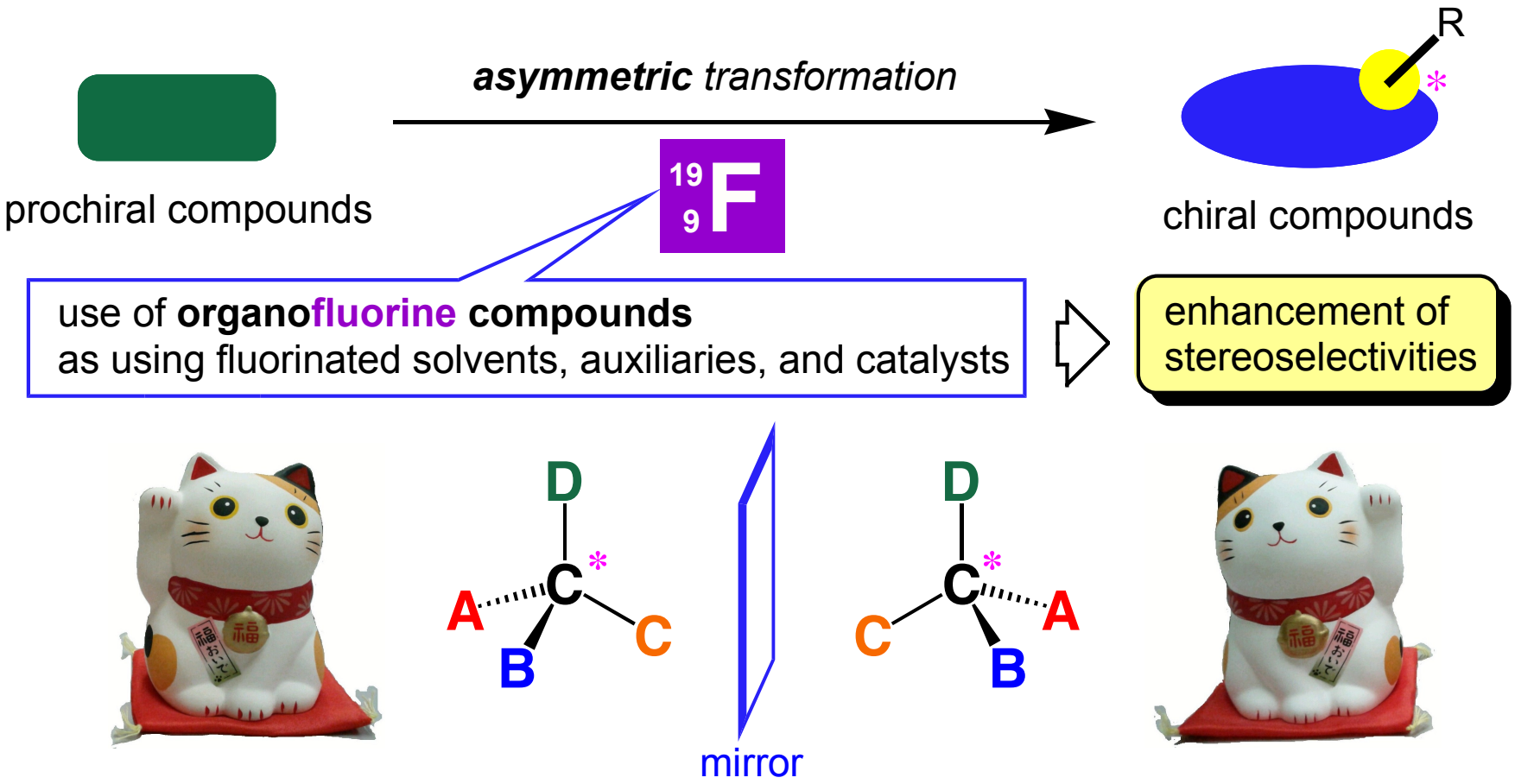
RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

In this review, the drastic changes using fluorinated solvents, additives, auxiliaries, and catalysts in catalytic asymmetric transformations are presented.



Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

REVIEW

Enhancement of stereoselectivities in asymmetric synthesis using fluorinated solvents, auxiliaries, and catalysts

Tsuyuka Sugiishi,[a] Masato Matsugi,[b] Hiromi Hamamoto,[b] and Hideki Amii*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

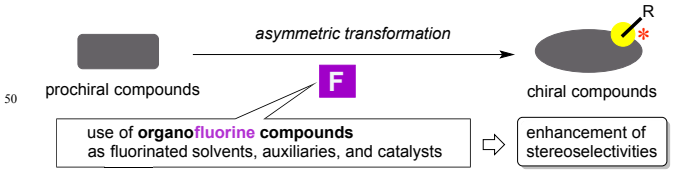
DOI: 10.1039/b000000x

Organofluorine compounds find diverse applications in the medicinal, agricultural, and material sciences. As a new application, certain organofluorine compounds have been used as ancillary materials in asymmetric synthesis. In this paper, we introduce the asymmetric transformations in which fluorinated solvents, additives, auxiliaries, and catalysts function to improve the stereoselectivities and/or the chemical yields.

1. Introduction

The development of asymmetric synthesis continues to grow exponentially over the last three decades.[1] Production of single enantiomers is quite important because most of chiral drugs exhibit the different pharmacological effects between their homochiral and racemate forms. Due to the increased demand of optically active substances in academic and industrial fields, catalytic asymmetric transformations are vigorously studied all over the world for the effectiveness of synthetic processes. However, even now, asymmetric synthesis of chiral molecules is still often faced with problems such as low stereoselectivities of the reactions. Therefore, a new technology for highly selective synthesis of enantiomerically pure compounds has been required.

Organofluorine compounds are the substances of considerable interest in various industrial fields.[2] Introducing of fluorine atoms often endows the parent (non-fluorinated) organic molecules with attractive properties. Fluorine is now an important element by virtue of unique properties associated with the atom and its bond to carbon, its high electronegativity and the relatively small size. Due to these attractive properties, organofluorine compounds have been widely used in the design of pharmaceuticals, agrochemicals, refrigerants, dyes, liquid crystals, optical fibers, and highly durable polymers. Recently, certain fluoroorganic compounds have been applied as ancillary materials in asymmetric synthesis. For instance, the conformational study of organofluorine compounds has impacted on asymmetric catalysts.[3,4] In 2014, Cahard and Bizet have published the excellent tutorial reviews titled 'the influence of fluorine in asymmetric catalysis' and 'fluorine as a control element in asymmetric synthesis'.[5] They introduced the unique properties of organofluorine compounds as mainly substrates and catalysts in asymmetric transformations. Herein, we focus on the asymmetric transformations in which fluorinated solvents, auxiliaries, and catalysts play important roles to enhance the stereoselectivities and/or the chemical yields (Scheme 1).



Scheme 1 Asymmetric synthesis with fluorinated compounds as controlling tools

2. Organocatalysis in fluoroaromatic solvents

Benzotrifluoride (BTF), fluorobenzene (PhF), and hexafluorobenzene (C_6F_6) are well-known commercially available fluoroaromatic materials, which can be used in screening of solvent effects (Fig. 1). In particular, it was reported that BTF can behave as an alternative solvent to dichloromethane because of its dissolving potential in organic synthesis.[6] Not only in order to substitute for the other solvents avoiding shortcomings in the original reactions, but also to find unique physical properties fluoroaromatic solvents have, it is significant to survey the asymmetric synthesis in which fluoroaromatic solvents are employed.

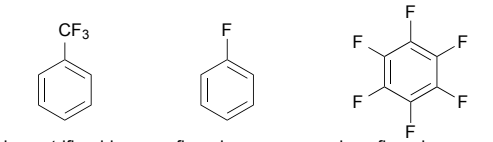
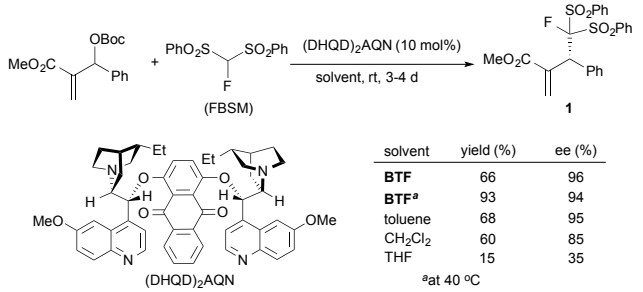


Fig. 1 Representatives of fluoroaromatic compounds

First, the examples using BTF solvent are introduced. Shibata *et al.* reported asymmetric allylic monofluoromethylation of Morita–Baylis–Hillman carbonates with fluorobis(phenylsulphonyl)methane (FBSM) using a bis(cinchona alkaloid), which provides chiral α-methylene β-monofluoromethyl esters with high ee values (Scheme 2).[7] Toluene and BTF were found to be suitable for this reaction with a catalytic amount of $(DHQD)_2AQN$. The yield of **1** was

improved at a slightly higher reaction temperature.

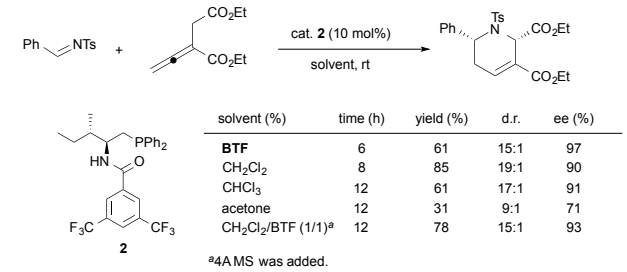


solvent	yield (%)	ee (%)
BTF	66	96
BTF[a]	93	94
toluene	68	95
CH_2Cl_2	60	85
THF	15	35

[a]at 40 °C

Scheme 2 Asymmetric organocatalysed allylic monofluoromethylation of Morita–Baylis–Hillman carbonates

BTF was also used for *N*-acylaminophosphine-catalysed asymmetric [4+2] cycloaddition of allenoates and imines reported by Zhao and coworkers.[8] An examination of the solvent effects revealed that BTF, which has no hydrogen-bonding acceptor atom (O or N) but is a polar aromatic solvent, was favorable in terms of the enantioselectivity and reaction time, albeit with moderate yields (Scheme 3). As a compromise between yield and ee value, the reaction could be performed in a co-solvent of CH_2Cl_2 and BTF (v/v=1/1).

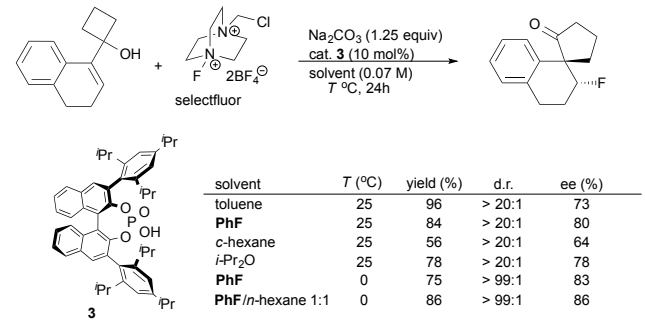


solvent (%)	time (h)	yield (%)	d.r.	ee (%)
BTF	6	61	15:1	97
CH_2Cl_2	8	85	19:1	90
$CHCl_3$	12	61	17:1	91
acetone	12	31	9:1	71
CH_2Cl_2/BTF (1/1)[a]	12	78	15:1	93

[a]4A MS was added.

Scheme 3 Asymmetric [4+2] cycloaddition

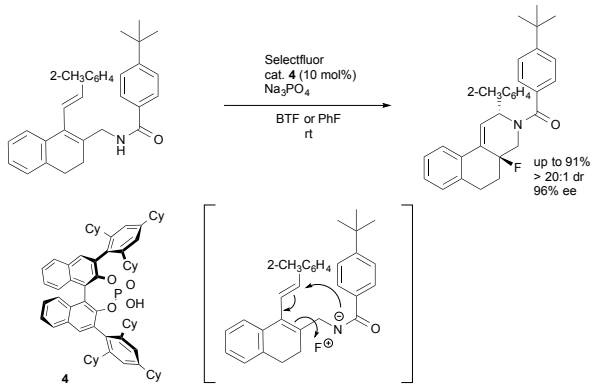
Fluorobenzene and hexafluorobenzene are common chemicals. In 2013, Alexakis *et al.* reported that fluorobenzene was effective as a solvent for the enantioselective fluorination-induced Wagner-Meerwein rearrangement because of the highly hydrophobic, yet strongly solubilizing ability (Scheme 4).[9] Since nonpolar solvents favor ion pairing, the asymmetric synthesis is an example of anionic phase-transfer catalysis, where a lipophilic chiral anion extracts the insoluble fluorinating reagent such as selectfluor into the organic layer, thus rendering it chiral. Accordingly, employing a 1:1 mixture of fluorobenzene and *n*-hexane, and lower temperature led to an increase of the enantioselectivity obtained to 86% ee.



solvent	*T* (°C)	yield (%)	d.r.	ee (%)
toluene	25	96	> 20:1	73
PhF	25	84	> 20:1	80
c-hexane	25	56	> 20:1	64
i-Pr_2O	25	78	> 20:1	78
PhF	0	75	> 99:1	83
PhF/*n*-hexane 1:1	0	86	> 99:1	86

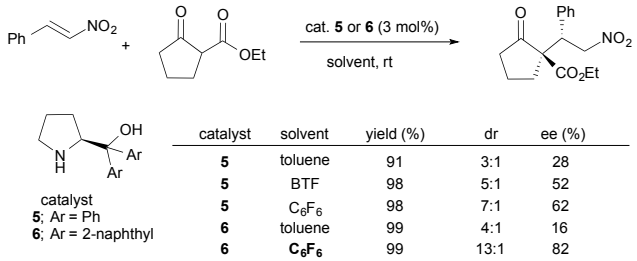
Scheme 4 Asymmetric Wagner-Meerwein rearrangement

The enantioselective fluorocyclisations using Selectfluor and anionic phase-transfer phosphoric acid catalysts in nonpolar solvents was developed by Toste.[10] Both BTF and fluorobenzene were effective for the enantioselective fluoroamination *via* 1,4-addition to conjugated dienes (Scheme 5).[11] Screening of the reaction conditions afforded the complete conversion of the starting materials with high enantioselectivity (96% *ee*) in BTF or PhF.



Scheme 5 Enantioselective fluoroamination *via* 1,4-addition to conjugated dienes

Hexafluorobenzene, an electron-poor arene, is very famous by the π-π interaction with benzene to make C_6F_6-C_6H_6 cocrystals.[12] The effect of C_6F_6 on the asymmetric α,α-L-diaryl prolinol-catalysed nitro-Michael addition was disclosed by Lattanzi and Cavallo *et al* (Scheme 6).[13] Optimisation study with trans-β-nitrostyrene, cyclic *β*-keto ester, and catalyst **5** or **6** in toluene afforded modest values of the diastereo- and enantioselectivity. However, when catalyst **5** was employed, screening in fluoroaromatic solvents such as BTF and C_6F_6 showed significant improvement of diastereo and enantioselectivity. Moreover, much higher stereoselectivity was observed in the reaction with catalyst **6** performed in C_6F_6. DFT calculations indicate C_6F_6 would have electrostatic interaction with electron density delocalised on the enolate π orbitals on the stereoselectivity determining step. C_6F_6 ring stacked over the enolate moieties would generate steric interactions with the reaction system to increase the optimal preference.



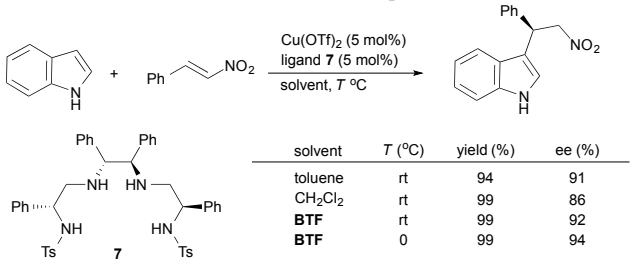
catalyst	solvent	yield (%)	dr	ee (%)
5	toluene	91	3:1	28
5	BTF	98	5:1	52
5	C_6F_6	98	7:1	62
6	toluene	99	4:1	16
6	**C_6F_6**	99	13:1	82

Scheme 6 Asymmetric α,α-L-diaryl prolinol-catalysed nitro-Michael addition

3. Metal-catalysed reactions in fluoroaromatic solvents

Development of novel catalyst systems involving transition metals for enantioselective transformation is one of the most fascinating and important subjects in organic synthesis. To date,

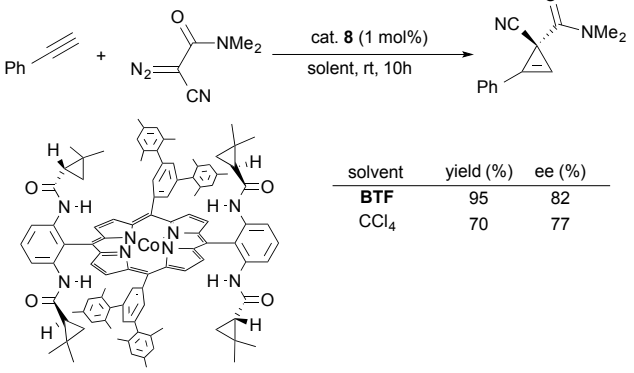
asymmetric catalysis in fluoroaromatic solvents have been investigated.[14] In the study of asymmetric copper(II)-catalysed Friedel-Crafts alkylation of indols with nitroalkanes, BTF was the best solvent which led to the high ee value keeping quantitive conversion of the substrate at a lower temperature (Scheme 7).[15]



solvent	T (°C)	yield (%)	ee (%)
toluene	rt	94	91
CH_2Cl_2	rt	99	86
BTF	rt	99	92
BTF	0	99	94

Scheme 7 Asymmetric copper(II) catalysed Friedel-Crafts alkylation of indoles with nitroalkanes

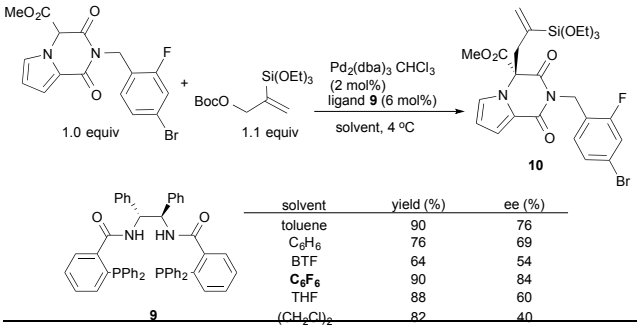
Enantioselective [2+1] cycloaddition of alkynes with carbenes is one of the most powerful methods for the synthesis of chiral cyclopropenes. For asymmetric reactions of alkynes with acceptor/acceptor-substituted diazo reagents involving cobalt(II)-based metalloradical catalysis, BTF performed significantly better than other solvents screened (Scheme 8).[16] The reaction did not proceed in high yields, and neither high ee values were observed even in the cases other aromatic solvents such as PhCl, PhF, PhMe, and PhH were used.



solvent	yield (%)	ee (%)
BTF	95	82
CCl_4	70	77

Scheme 8 Asymmetric [2+1] cycloaddition *via* cobalt(II)-based metalloradical catalysis

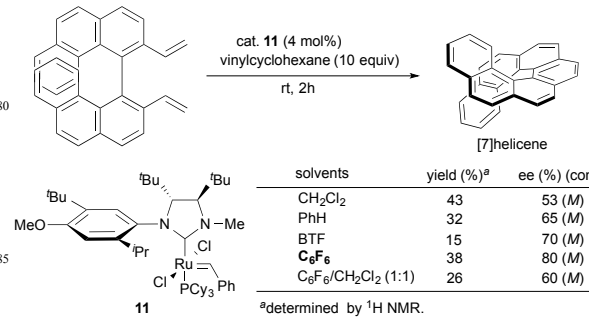
Trost *et al*. employed palladium-catalysed asymmetric allylic alkylation of malonates as a key transformation for synthesis of (-)-ranirestat, an aldose reductase inhibitor (Scheme 9).[17] In the optimisation study of reaction conditions, enantioselectivities were improved with the use of aromatic solvents. Hexafluorobenzene proved to be the optimal solvent for this transformation, providing the allylated product **10** in 90% yield and 84% ee.



solvent	yield (%)	ee (%)
toluene	90	76
C_6H_6	76	69
BTF	64	54
C_6F_6	90	84
THF	88	60
$(CH_2Cl)_2$	82	40

Scheme 9 Asymmetric palladium-catalysed allylic alkylation of malonates

For [7]helicene synthesis *via* asymmetric olefin metathesis, Collins and Grandbois examined aromatic solvents in the screening of reaction conditions (Scheme 10).[18] With regard to enantioselectivity, a modest increase was produced by switching from CH_2Cl_2 to benzene as the solvent, and a further increase was observed when BTF was used. The use of hexafluorobenzene afforded the highest ee, however the reaction in a 1:1 mixture of CH_2Cl_2 and C_6F_6 resulted in a decrease in ee and conversion. The solvent obviously plays an important role in the stereochemistry of [7]helicene, and plausibly interact with the substrate.

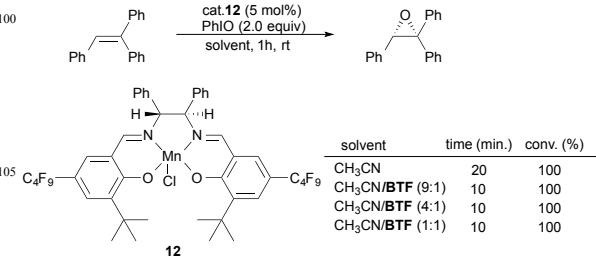


solvents	yield (%)[a]	ee (%) (conf.)[b]
CH_2Cl_2	43	53 (*M*)
PhH	32	65 (*M*)
BTF	15	70 (*M*)
C_6F_6	38	80 (*M*)
C_6F_6/CH_2Cl_2 (1:1)	26	60 (*M*)

[a]determined by ^{1}H NMR.
[b]Enantiomeric excesses were determined by chiral HPLC.

Scheme 10 [7]Helicene synthesis via asymmetric olefin metathesis

Fluoroaromatic solvents are also utilised for oxidation of organic compounds.[19] Asymmetric epoxidation of aromatic olefins using salen catalyst was reported by Matsugi and co-workers.[20] During the study, to use the co-solvent of acetonitrile and BTF was found to be effective for the enantioselectivity (Scheme 11). The enantiomeric excess was increased by addition of BTF with acetonitrile to 65% ee in 1:1 ratio of BTF and acetonitrile.



solvent	time (min.)	conv. (%)	ee (%)
CH_3CN	20	100	49
CH_3CN/**BTF** (9:1)	10	100	52
CH_3CN/**BTF** (4:1)	10	100	60
CH_3CN/**BTF** (1:1)	10	100	65

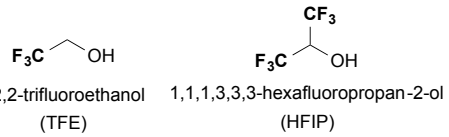
Scheme 11 Asymmetric epoxidation of aromatic olefins using salen catalyst **11**

4. Catalytic asymmetric hydrogenation in fluoroalcohol solvents

Fluoroalcohols attract attentions since they differ from other usual alcohols in following properties: 1) high polarity, 2) high acidity, 3) excellent proton donor, 4) low nucleophilicity, and 5) strong tolerance to oxidation.[21] Among fluorinated solvents, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) are representative commercially available

fluoroalcohols, so that some of asymmetric reactions have been achieved using TFE or HFIP (Fig. 2).

tolerance toward oxidation

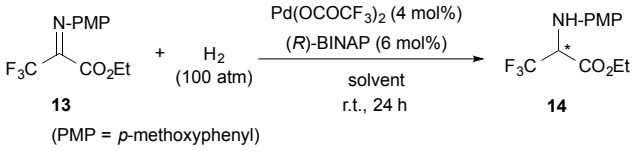


2,2,2-trifluoroethanol (TFE) 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP)

Fig. 2 Typical examples of fluoroalcohols

Catalytic asymmetric synthesis of fluorinated amino acids is a subject of considerable interest.[22] For the construction of chiral centres of α-amino acids, enantioselective reactions of the imino (C=N) moieties in fluorinated iminoesters provide a promising route. In general, enantioselective transformation of imines have been still a challenging subject in organic chemistry.[23] Uneyama *et al.* have reported the first successful asymmetric transition-metal-catalysed hydrogenation of acyclic α-iminoesters for synthesis of β-fluorinated α-amino esters, which was achieved by the use of fluorinated alcohol solvents. In ordinary (nonfluorinated) solvents, when α-iminoester **13** was subjected to hydrogen pressure in the presence of a small amount of chiral palladium complex, α-aminoester **14** formed in low to moderate ee (Table 1).[24] Nucleophilic solvents such as ethanol and methanol attacked the imino carbon of **13** to give α-alkoxylated aminoesters. In 2,2,2-trifluoroethanol (TFE), both the yield and ee were dramatically improved.

Table 1 Effects of solvents on asymmetric hydrogenation.

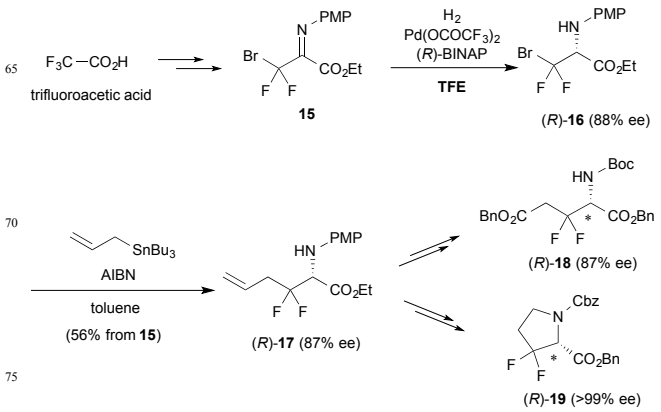


(PMP = *p*-methoxyphenyl)

entry	solvent	yield, %[a]	ee, %[b]
1	toluene[c,d]	52	39 (*S*)
2	CH_3CO_2H[c]	39	4 (*R*)
3	*i*-PrOH[c]	trace	61 (*S*)
4	**TFE**	> 99	88 (*R*)
5[e]	**TFE**	84	91 (*R*)
6	$CF_3CF_2CH_2OH$	94	88 (*R*)
7	**HFIP**	> 99	69 (*R*)

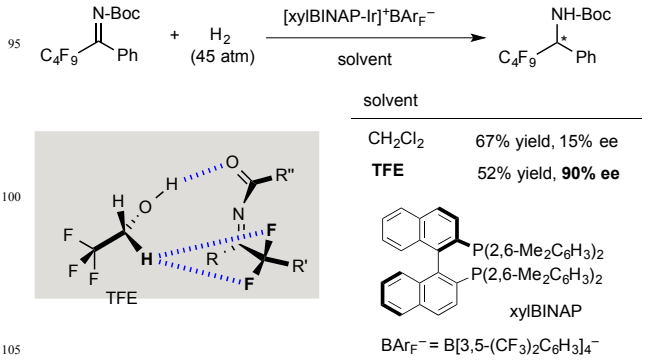
[a] Isolated yields. [b] Determined by HPLC. [c] $Pd(OCOCH_3)_2$ was used. [d] Reaction temperature was 35 °C. [e] 5 eq of n-Bu_4NHSO_4 was added.

As a practical application, they succeeded in the asymmetric hydrogenation of the bromodifluoromethyl iminoester **15** to the synthesis of optically active β,β-difluoroglutamic acid derivative **18** and β,β-difluoroproline derivative **19** (Scheme 12).[25] The present application suggests that the Pd/BINAP/TFE system for catalytic asymmetric hydrogenation gave successful outcomes from the viewpoint of the development of biologically active fluorinated compounds.

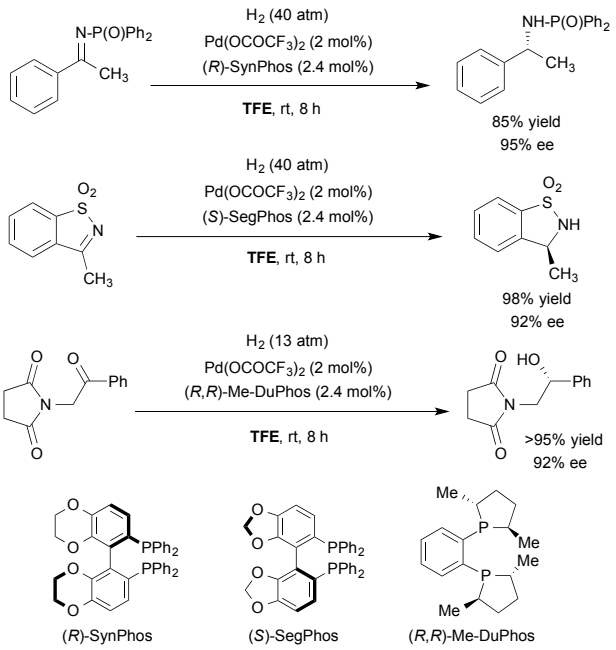


Scheme 12 Application of asymmetric hydrogenation with fluorinated iminoester **15** and Pd/BINAP/TFE system

A study of fluoroalcohol effects on catalytic asymmetric hydrogenation was carried out by Mikami and co-workers. Mikami *et al.* demonstrated asymmetric synthesis of perfluoroalkyl amines catalysed by iridium complex with BINAP. When an electron-withdrawing benzonitrile-derived imine, which has a sterically demanding phenyl group at the α-position, was employed, the use of acidic TFE as a solvent led to the significant increase in enantioselectivity. Comparing with the lower ee value in the case of the reaction in CH_2Cl_2, the hydrogen bonding network between TFE solvent and the perfluoroalkyl substituted imine including the weak electrostatic attraction of C-H/F-C type might stabilise the geometry of the imine to prevent it from isomerizing (Scheme 13).[26]

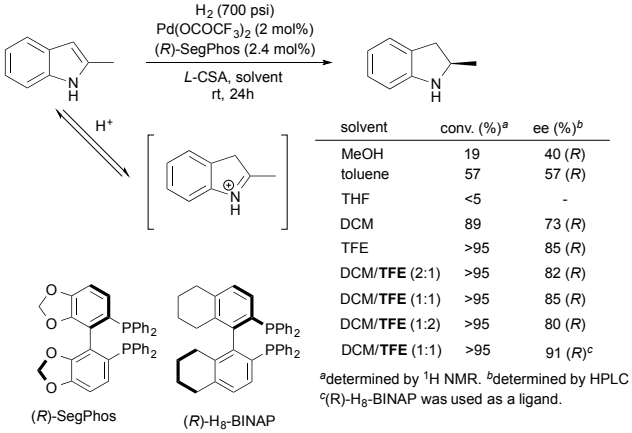


Scheme 13 Iridium-catalysed asymmetric hydrogenation



Scheme 14 Palladium-catalysed asymmetric hydrogenation of non-fluorinated imines and functionalised ketones

Independently, Zhou *et al.* explored the palladium-catalysed asymmetric hydrogenation of non-fluorinated imines[27a,27b] and functionalised ketones[27c] to find only TFE is effective in terms of the conversion and enantioselectivity (Scheme 14). In 2010, they reported palladium-catalysed asymmetric hydrogenation of unprotected indoles (Scheme 15).[28] In the reaction, unprotected indoles undergo the hydrogenation through formation of iminium salt by addition of camphorsulfonic acid (CSA). TFE has been the best solvent, and combination of dichloromethane (DCM) and TFE in 1:1 ratio resulted in complete conversion and higher ee.



solvent	conv. (%)[a]	ee (%)[b]
MeOH	19	40 (*R*)
toluene	57	57 (*R*)
THF	<5	-
DCM	89	73 (*R*)
TFE	>95	85 (*R*)
DCM/**TFE** (2:1)	>95	82 (*R*)
DCM/**TFE** (1:1)	>95	85 (*R*)
DCM/**TFE** (1:2)	>95	80 (*R*)
DCM/**TFE** (1:1)	>95	91 (*R*)[c]

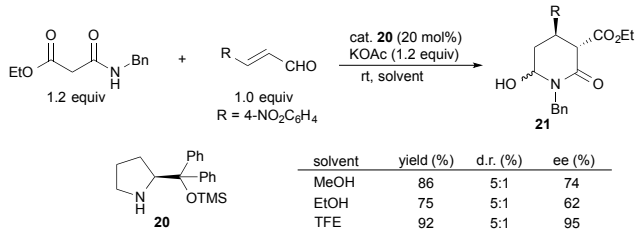
[a]determined by ^{1}H NMR. [b]determined by HPLC
[c](R)-H$_8$-BINAP was used as a ligand.

Scheme 15 Palladium-catalysed asymmetric hydrogenation of unprotected indoles

Fluorinated alcohols such as TFE and HFIP have been employed for stereoselective hydrogenation of unsaturated organic molecules.[21b, 29] As overviewed above, several beneficial effects using fluoro alcohol solvents on the selectivities in asymmetric hydrogenation have been observed. Fluorinated alcohols will be widely used for good candidates of solvent for catalytic hydrogenation.

5. Enantioselective transformation using fluoroalcohol additives

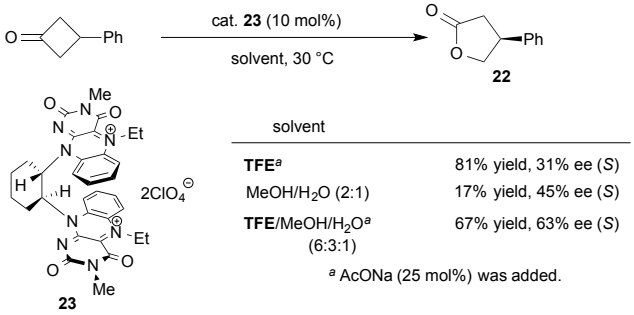
Besides enantioselective hydrogenations, carbon-carbon and carbon-heteroatom bond forming reactions have been explored to date. In asymmetric piperidine synthesis, polar protric acids such as MeOH and EtOH performed well, but the enantioslectivities were moderate (Scheme 16).[30] Desired compound **21** was obtained with higher enantioinselectivity in TFE, a more acidic solvent.



solvent	yield (%)	d.r. (%)	ee (%)
MeOH	86	5:1	74
EtOH	75	5:1	62
TFE	92	5:1	95

Scheme 16 Organocatalysed asymmetric piperidine synthesis

The flavin-catalysed asymmetric Baeyer-Villiger reaction[31] in TFE as a sole solvent gave (*S*)-**21** with low enantioselectivity, because the non-catalysed reaction with hydrogen peroxide occurs fast. When a mixture of solvents (TFE/MeOH/water 6:3:1) was used, both non-catalysed reaction and ketalisation were retarded, and higher enantioselectivity was observed (Scheme 17). A protic solvent is essential to obtain higher enantioselectivity, which indicates that the hydrophobic π-π stacking between the aromatic ring of the catalyst **23** and that of a substrate seems to play an important role in asymmetric induction.

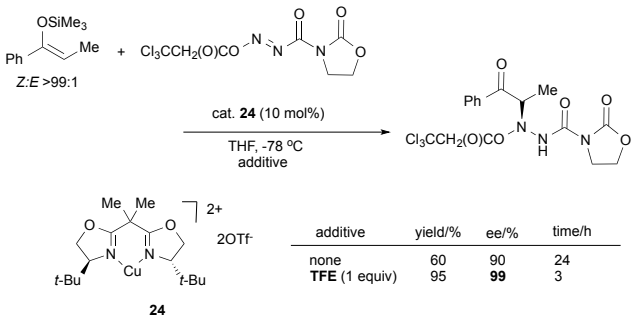


solvent	
TFE[a]	81% yield, 31% ee (*S*)
MeOH/H_2O (2:1)	17% yield, 45% ee (*S*)
TFE/MeOH/H_2O[a] (6:3:1)	67% yield, 63% ee (*S*)

[a] AcONa (25 mol%) was added.

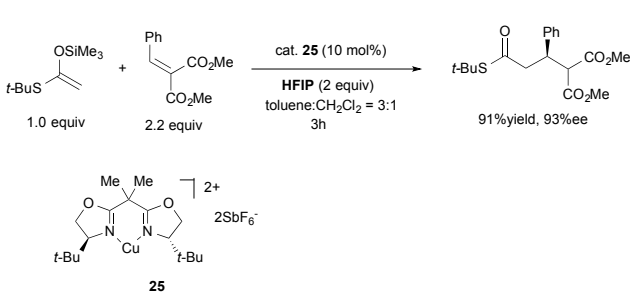
Scheme 17 Flavin-catalysed asymmetric Baeyer-Villiger reaction

Evans *et al*. succeeded in the development of asymmetric amination of silylenolates with a chiral bis(oxazoline) copper(II) complex, in which rate-limiting catalyst turnover was improved by addition of 1 equiv of TFE (Scheme 18).[32] On the other hand, in the Michael reactions of silylenolates to alkylidene malonates (Scheme 19)[33] or imides (Scheme 20),[34] HFIP was utilised in order to promote catalyst turnover and to inhibit oligomerisation of silyl enolates.

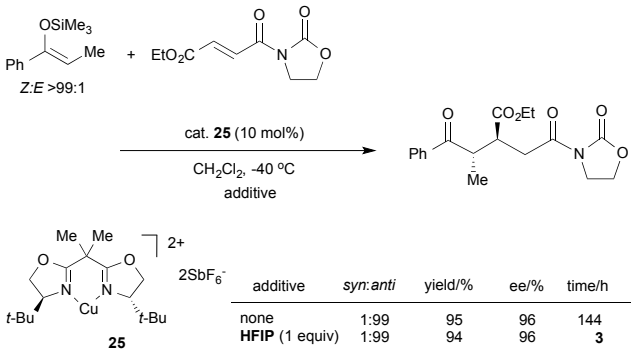


additive	yield/%	ee/%	time/h
none	60	90	24
TFE (1 equiv)	95	**99**	3

Scheme 18 Asymmetric amination of silylenolates with a bis(oxazoline) copper(II) complex



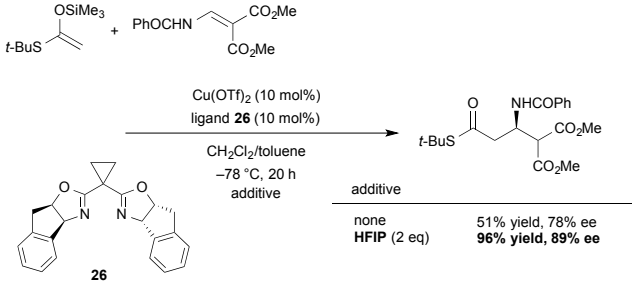
Scheme 19 Asymmetric Michael addtion of silylenolates to alkylidene malonates



additive	*syn*:*anti*	yield/%	ee/%	time/h
none	1:99	95	96	144
HFIP (1 equiv)	1:99	94	96	**3**

Scheme 20 Asymmetric Michael addition of silylenolates to imides

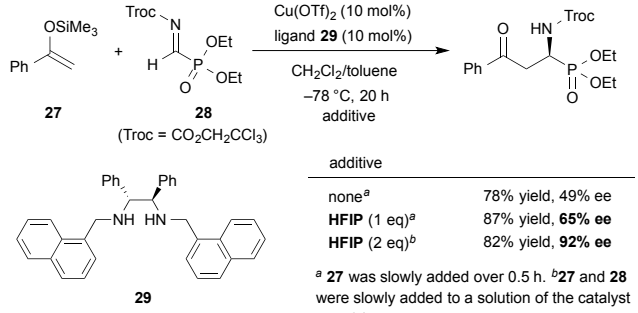
In the case of asymmetric conjugate addition of silylenolates to *β*-enamidomalonates reported by Sibi *et al.*, nonuse of HFIP as an additive had a negative influence on both yield and enantioselectivity (Scheme 21).[35] However, the HFIP is not absolutely necessary for turnover in contrast to Evans' results. It may be that the enamide may function as a proton source in the absence of HFIP.



additive		
none	51% yield, 78% ee	
HFIP (2 eq)	**96% yield, 89% ee**	

Scheme 21 Asymmetric conjugate addition of silylenolates to β-enamidomalonates

Kobayashi *et al*. demonstrated an approach to the synthesis of α-aminophosphonates from silylenolates and *N*-acyl α-iminophosphonates catalysed by a chiral copper(II)-diamine complex (Scheme 22).[36] It was found that HFIP was suitable as an additive for the reaction to improve the yields and enantioselectivity. Considering the reaction mechanism, HFIP would release the copper catalyst from the product α-aminophosphonates, which is a strong Lewis base.

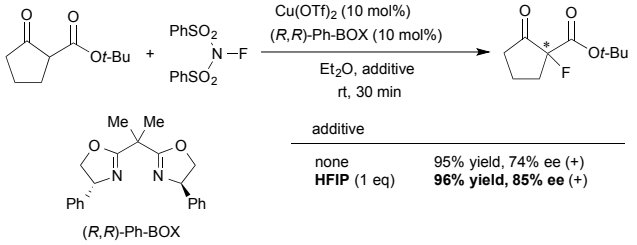


additive	
none[a]	78% yield, 49% ee
HFIP (1 eq)[a]	87% yield, **65% ee**
HFIP (2 eq)[b]	82% yield, **92% ee**

[a] **27** was slowly added over 0.5 h. [b]**27** and **28** were slowly added to a solution of the catalyst over 8 h.

Scheme 22 Copper(II)-diamine-catalysed addition of silylenolates to *N*-acyl α-iminophosphonates

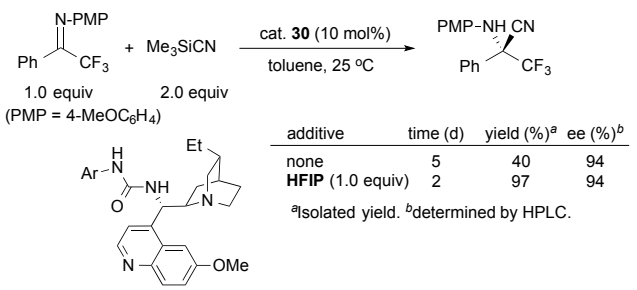
Fluorination and fluoroalkylation of organic molecules are one of the most useful approaches to organofluorine compounds.[37] Cahard *et al.* reported asymmetric copper(II)-bis(oxazoline)-catalysed fluorination of β-ketoesters (Scheme 23).[38] Interestingly, addition of one equivalent of HFIP led to an increase in enantioselectivity.



additive	
none	95% yield, 74% ee (+)
HFIP (1 eq)	**96% yield, 85% ee** (+)

Scheme 23 Copper(II)-bis(oxazoline)-catalysed asymmetric fluorination

Wang and Zhou *et al*. speculated the use of alcoholic additives to improve the reactivity of the asymmetric Strecker reaction (Scheme 24).[39] HFIP (1.0 equiv) was able to promote the reaction without loss of ee, most of the other alcohols or phenols decreased enantioselectivity instead.



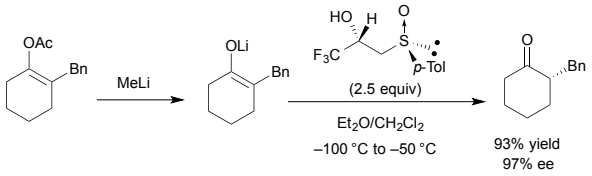
additive	time (d)	yield (%)[a]	ee (%)[b]
none	5	40	94
HFIP (1.0 equiv)	2	97	94

[a]Isolated yield. [b]determined by HPLC.

Scheme 24 Asymmetric Strecker reaction

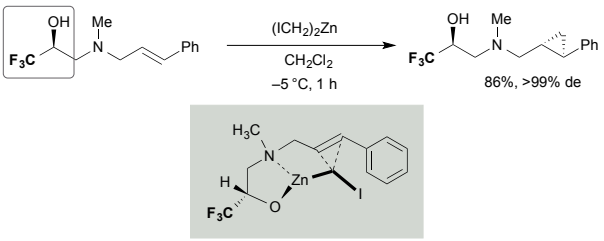
6. The use of fluoroalcohols as chiral auxiliaries and catalyst ligands

Asymmetric protonation of prochiral lithium enolates was achieved in 97% ee using a chiral β-hydroxy sulfoxide which has a chiral trifluoromethylalcohol moiety (Scheme 25).[40] The reaction completed below -50 °C due to the considerably high acidity of the proton induced by strong electron-withdrawing CF_3-substituted.



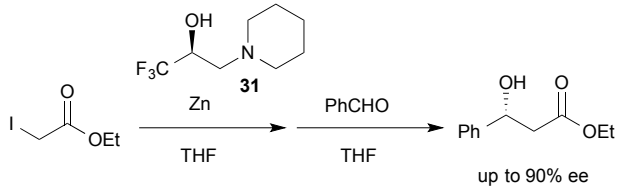
Scheme 25 Asymmetric protonation of lithium enolates

Katagiri and Uneyama *et al.* developed asymmetric Simmons-Smith cyclopropanation of allylic amines taking advantage of the α-trifluoromethyl-β-aminoalcohol auxiliary (Scheme 26).[41] The cyclopropanation resulted in not only dramatic acceleration of reaction rate by the strong electron-withdrawing trifluoromethyl group but also excellent diastereoselectivity by bulkiness of the trifluoromethyl group.



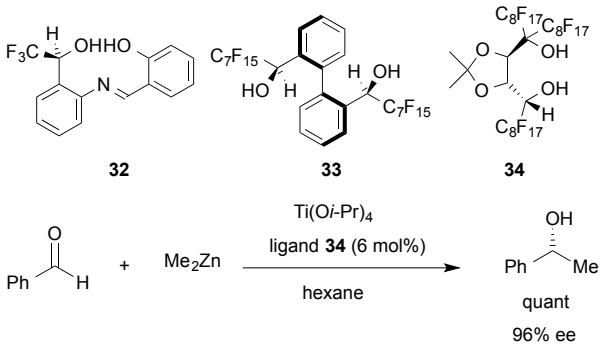
Scheme 26 Asymmetric cyclopropanation with the fluoroalcohol auxiliary

α-Trifluoromethyl-β-aminoalcohol **31** worked effectively as a chiral ligand in asymmetric Reformatsky reaction (Scheme 27).[42] The Reformatsky reagent which was prepared from ethyl iodoacetate underwent 1,2-addition to benzaldehyde to give β-hydroxyesters in a highly stereo-controlled manner.



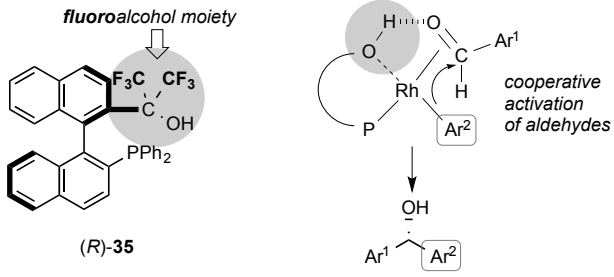
Scheme 27 Asymmetric Reformatsky reaction with α-trifluoromethyl- β-aminoalcohol

Omote *et al.* developed various fluoroalcohols **32**-**34** as chiral organo catalysts (Scheme 28).[43] Particularly, perfluoroalkylated ligand **34** showed an excellent asymmetric induction on the addition of dimethylzinc to aldehydes, although only a small number of studies on the methylation have been reported with the other catalysts probably due to the lower reactivity of dimethylzinc than those of its higher homologues.[43a]

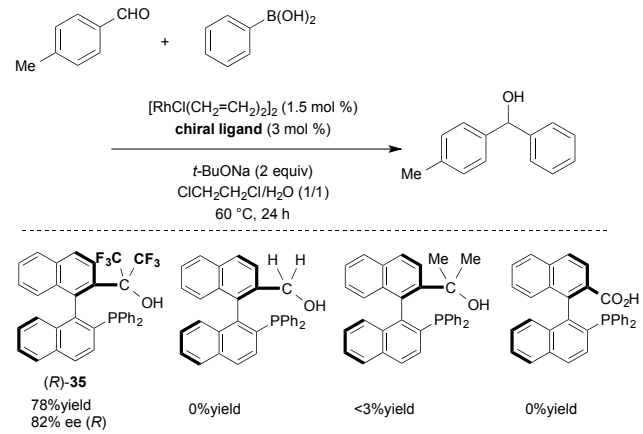


Scheme 28 Various fluoroalcohols designed for chiral organocatalysts

Amii *et al.* found the axially chiral phosphine compound (*R*)-**35** endowed with a fluoroalcohol moiety to be an effective ligand for Rh(I)-catalysed asymmetric arylation of aromatic aldehydes with arylboronic acids (Scheme 29).[44] Despite the difficulty of high enantioselective synthesis with arylboronic acids, the presence of a weakly acidic fluoroalcohol moiety in the ligand (*R*)-**35** afforded enantiomerically enriched diaryl methanol (Scheme 30). The substrate scope in the Rh-catalysed arylation using ligand (*R*)-**35** is shown in Table 2 with higher enantioselectivities. It was suggested that ligand (*R*)-**35** with transition metals would form the suitable catalysts, in which structure bulky trifluoromethyl groups would create the chiral coordination environment.

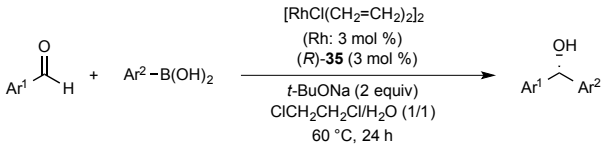


Scheme 29 Axially chiral phosphine ligand with a fluoroalcohol moiety



Scheme 30 Effect of a fluoroalcohol moiety in axially chiral phosphine ligand (*R*)-**35**

Table 2 Rhodium-catalysed 1,2-addition of arylboronic acids to aromatic aldehydes

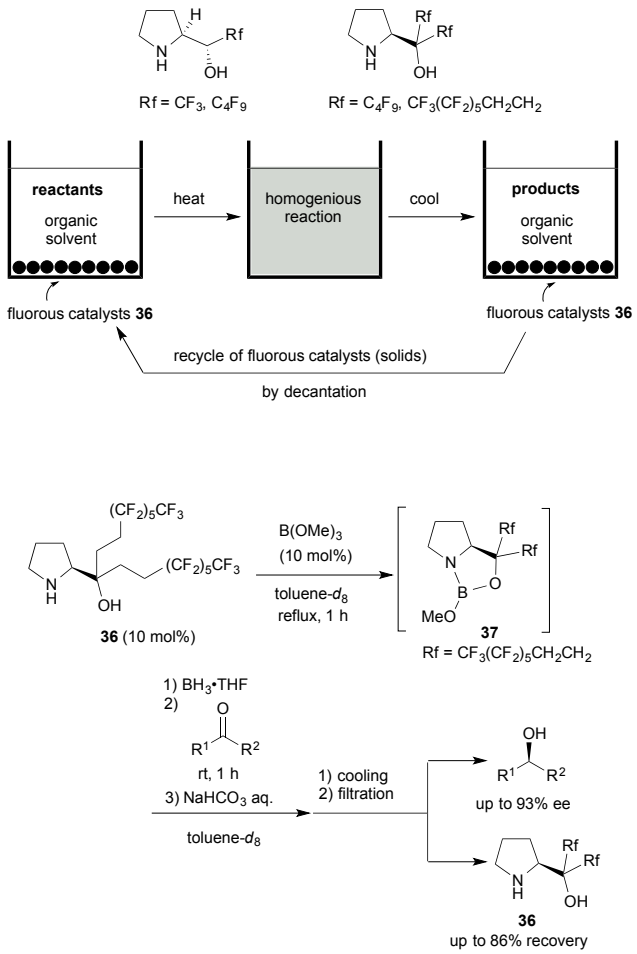


entry	Ar^1	Ar^2	yield/% [a]	ee/% [b]
1	4-MeC_6H_4	Ph	78	82 (*R*)
2	2,4-$Me_2C_6H_3$	Ph	75	82 (*R*)
3[c]	4-^{i}PrC_6H_4	Ph	68	86 (*R*)
4[c]	4-$MeOC_6H_4$	Ph	56	90 (*R*)
5	3,4-$(OCH_2O)C_6H_3$	Ph	96	81 (*R*)
6	4-MeC_6H_4	4-AcC_6H_4	57	80 (+)
7[c]	Ph	4-ClC_6H_4	99	87 (*S*)
8[c]	4-MeC_6H_4	4-ClC_6H_4	64	88 (*S*)
9[c]	4-$MeOC_6H_4$	4-ClC_6H_4	84	89 (*S*)
10[c]	4-$MeOC_6H_4$	3-ClC_6H_4	73	92 (*S*)
11[c]	2-thienyl	4-ClC_6H_4	93	90 (*S*)
12[c]	2-thienyl	3-ClC_6H_4	74	91 (*S*)

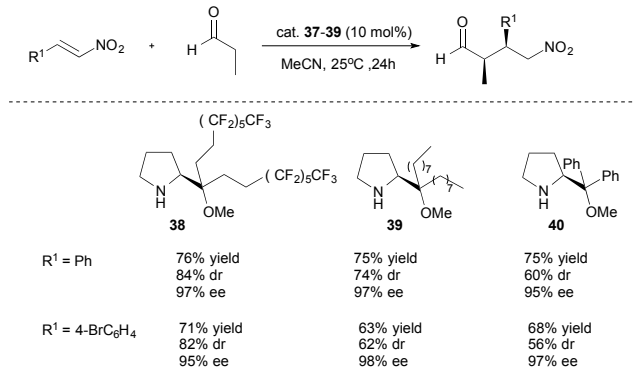
[a] Isolated yield. [b] Enantiomeric excesses were determined by HPLC analyses.
[c] These reactions were carried out at 30 °C for 24 h.

7. Application of perfluoroalkylated molecular catalysts to asymmetric synthesis

Funabiki *et al.* investigated the application of fluoroalkylated prolinols as chiral molecular catalysts (Scheme 31).[45] Particularly, as the purification of product and the recycle of the catalyst are facile, fluorous[46] oxaborolidine boran complex **37** showed high functionality as a chiral reduction catalyst. They also prepared prolinol methyl ether **38**, which is the derivative of prolinol **36**, and investigated its application as an asymmetric organocatalyst for the Michael reactions of nitroalkenes with aldehydes (Scheme 32).[47] The diastereoselectivity with **38** was much higher than that with non-fluorinated prolinol methyl ethers **39** and **40**, which have two *n*-octyl groups or two phenyl groups respectively in place of (perfluorohexyl)ethyl groups. From the advantageous point of reusability, the catalyst **38** was recoverable by solid-phase extraction using fluorous reverse-phase silica gel.



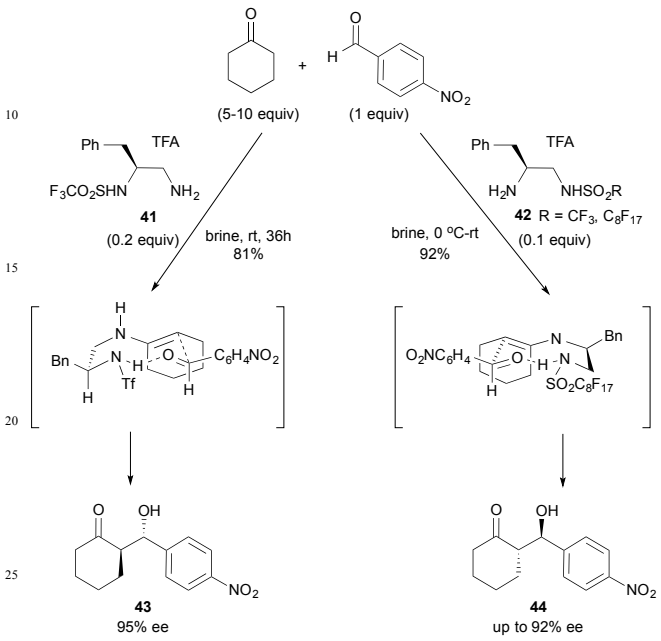
Scheme 31 Application of fluoroalkylated prolino



Scheme 32 Effect of fluoroalkyl chains in chiral prolinol ethers on diastereoselectivity

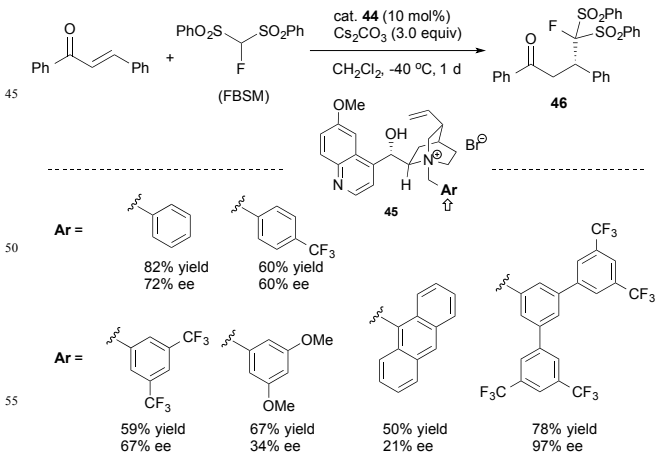
Perfluoroalkylsulphonyl groups in chiral organic molecules can act as a controlling tool in asymmetric synthesis. Direct asymmetric aldol reactions in brine in the presence of fluoroalkyl sulphonamides **41** and **42** yield *anti*-aldol products **43** and **44**, respectively (Scheme 33).[48] Interestingly, by the use of the same chiral source, the positional difference of fluoroalkylsulfonyl groups between organocatalysts **41** and **42** afforded the opposite

absolute configuration of products **43** and **44** to each other. The acidity of sulphoamides **41** and **42** might be enhanced by the electron withdrawing effect of fluoro alkyl groups. It is possible that the acidic proton of sulphonamide group in the enamine intermediate coordinates to aldehyde to stabilise the rigid transition state.



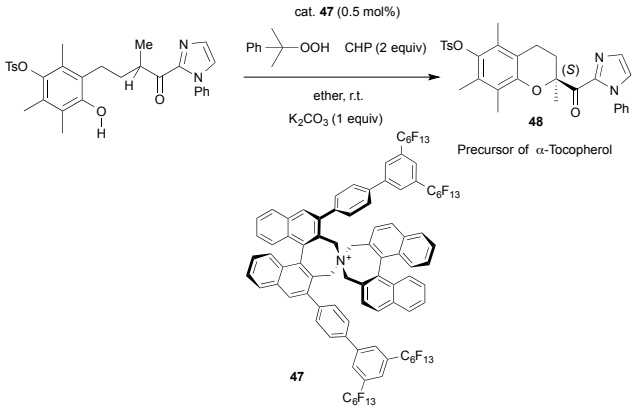
Scheme 33 Asymmetric aldol reactions with chiral fluoroalkyl sulphonamides

Fluoroalkyls groups on aryl rings in organocatalysts are a key element for stereoselective synthesis. In the screening of cinchona alkaloid catalysts for asymmetric Michael addition of 1-fluorobis(phenylsulphonyl)methane (FBSM) to α,β-unsaturated ketones, the quinidiniums bearing various benzyl substituents on each quaternary nitrogen atom were examined. The benzyl substituent which has two 3,5-bis(trifluoromethyl)phenyl groups provided Michael adduct (*S*)-**46** in high yield with excellent enantioselectivity (Scheme 34).[49]



Scheme 34 Asymmetric Michael addition of FBSM

In 2014, Ishihara and co-workers reported asymmetric synthesis of tocopherols *via* oxidative cyclisation by using chiral ammonium iodides and hydroperoxides. The biphenyl groups at the 3,3' positions in chiral ammonium iodide (*R*,*R*)-**47** led generation of product (*S*)-**48** in major, and the fluoroalkyl-substituents of the 3,3'-binaphthyl moiety in (*R*,*R*)-**47** had drastic effects on enantioselectivity and reactivity (Scheme 35).[50]



Scheme 35 Asymmetric synthesis of tocopherols *via* oxidative cyclisation using chiral ammonium iodides

8. Fine-tuning of stereoselectivity by a C-F bond

Concerning with C-F bond, which is the fundamental unit of organofluorine compounds, O'Hagan highlighted the electrostatic character,[51] and Hunter introduced the conformational effect in the review.[3] And Gilmour *et al.* published the reviews about molecular design of organocatalysts comprehensively.[4] Configurations of fluoroaliphatic compounds depend not only on their steric requirements but also on their electronic properties, relating with the explanation of the fluorine "*gauche* effect". The high electronegativity of fluorine polarizes the $C^{\delta+}$-$F^{\delta-}$ bond, and hyperconjugative electron-donation from a vicinal C-H bonding σ orbital to antibonding orbital of the C-F bond stabilises the *gauche* conformation. Contrast to the steric repulsion of fluorine with the heteroatom (X), the *gauche* conformation is preferable rather than *anti* conformation (Figure 3).

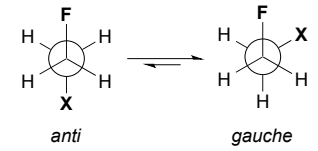
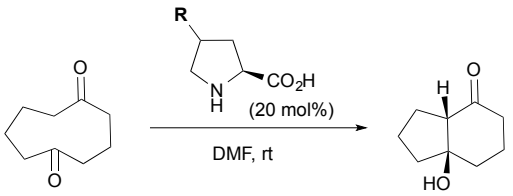


Figure 3

Accordingly, the configurationally defined fluorine substituents are able to behave differently from other substituents. Therefore catalysis tuning by a C-F bond is one of the splendid stereocontrol strategies because fluorine substituents can stabilize preferential molecular conformations and enhance the enantioselectivities.[52] List *et al.* noticed that proline catalysts bearing a substituent at the 4-position could give elevated levels

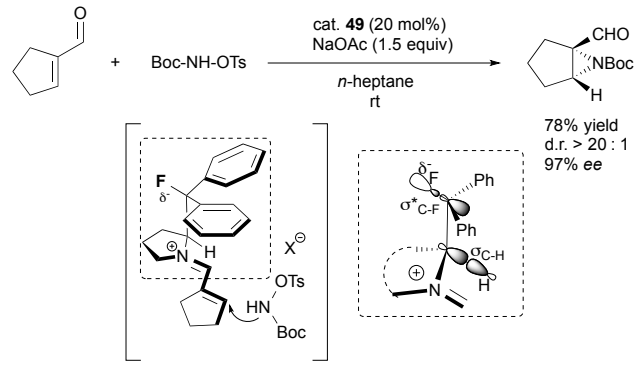
of enantiocontol, in addition to (*S*)-proline itself catalysing asymmetric reactions. The *trans*-4-fluoro derivative gave the highest enantioselectivity in the transannular aldol reaction (Scheme 36).[53] The configulationally stabilised iminium intermediates would contribute to the stereoselectivity.



R	conversion (%)[a]	*ee* (%)[b]
H	60	54
trans-OH	50	64
trans-O^{t}Bu	95	60
cis-F	50	58
trans-F	75	80

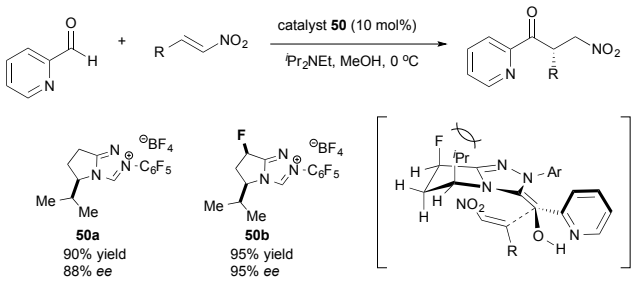
Scheme 36 Proline-catalysed asymmetric transannular aldol reaction

Gilmour and co-workers *et al.* revealed the *gauche* effect of β-fluoroiminium ion with design of (*S*)-2-(fluorodiphenylmethyl) pyrrolidine **49**.[54] Furthermore, application of catalyst **49** to enantioselective aziridination of enals was achieved (Scheme 37).[55] Asymmetric catalytic epoxidation using *trans*-cinnamaldehydes proceeded diastereo- and enantioselectively due to the stable β-fluoroiminium ion intermediate. Electrostatic/charge-dipol ($\sigma_{C\text{-}H} \rightarrow \sigma^*_{C\text{-}F}$; $F^{\delta-}\text{---}N^+$) interactions would render the C-H and C-F bonds antiperiplanar and the torsion angle $F^{\delta-}\text{-}C_\beta\text{-}C_\alpha\text{-}N^+$ small in the intermediate.



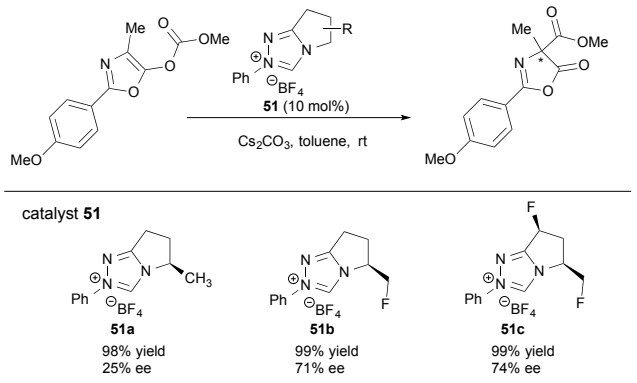
Scheme 37 Fluorinated pyrrolidine-catalysed enantioselective aziridination

Triazolium salts have been employed as NHC (*N*-heterocyclic carbene) catalysts **50** for enantioselective reactions. Rovis and co-workers demonstrated that fluorinated bicyclic triazolium salt **50b** improved the enantioselectivity in Stetter reaction. (Scheme 38).[56] It is proposed that the fluorine atom would induce a conformational stabilisation of transition state with a *gauche* effect to orient the incoming nitroalkene electrophile.



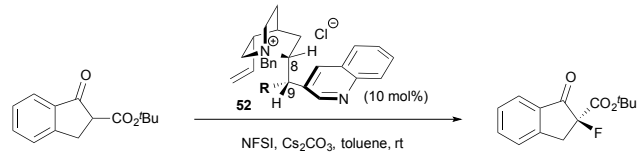
Scheme 38 Fluorinated NHC catalyst for intermolecular asymmetric Stetter reaction

Another example of NHC catalyst **51** was developed for asymmetric Steglich rearrangement of oxazolecarbonates (Scheme 39).[57] A couple of fluorines located on each position of $F^{\delta-}\text{-}C_\beta\text{-}C_\alpha\text{-}N^+$ systems in catalyst **51** confer the most significant advantage as far as Gilmour *et al.* investigated.



Scheme 39 Fluorination of NHC catalyst for asymmetric Steglich rearrangement

Cinchona alkaloids are versatile catalysts for asymmetric synthesis because of the remarkable performance in transformations, the natural abundance, and commercial availability. Gilmour and co-workers designed C9-substituted alkaloid catalysts **52** expecting fluorine stereoelectronic and electrostatic effects for conformational control (Scheme 40). [58] Comparison of C9-fluorinated catalyst **52a** with the other functionalized catalysts **52b-52e** elucidates the restricted internal rotation around C8-C9 ($F^{\delta-}\text{-}C_\beta\text{-}C_\alpha\text{-}N^+$) by *gauche* effect of β-fluoroiminiumes. They applied fluorinated cinchona alkaloids to heterogeneous asymmetric hydrogenation of α-ketoesters. [59]



R	X	cat.	yield (%)	*ee* (%)
F	Cl	**52a**	96	78
H	Br	**52b**	94	10
OH	Cl	**52c**	90	8
OMe	Cl	**52d**	86	64
OTMS	Cl	**52e**	86	57

Scheme 40 C9-Substituted alkaloid catalysts for asymmetric fluorination

As highlighted so far, a fluoro group can stabilise preferential molecular conformations and enhance the enantioselectivities. Besides asymmetric transformation, Grubbs and co-workers demonstrated that fluorinated NHC ligands showed a significant rate enhancement in Ru-catalysed olefin metathesis through intramolecular F---Ru interaction.[60] Recently, a drastic change of regioselectivity taken place by fluorine acting as a steering group has been reported by Yu *et al*.[61] A fluorine atom incorporated in the directing group of the starting material amines effects on the *meta*-selective C-H olefination.

9. Conclusion

In summary, the notable examples of catalytic stereoselective transformations with assistance provided by organofluorine compounds have been described. Needless to say, fluorine-containing molecules have been utilised in many areas including medicine, agriculture, electronics, materials. As highlighted here, organofluorine compounds (as solvents, auxiliaries, additives, and catalysts) exhibit profound effects on stereoselectivities in asymmetric transformations. New exciting advances of organofluorine compounds as a powerful tool for selective transformations to afford useful materials will undoubtedly emerge in the future.

Acknowledgment

The financial support of the Ministry of Education, Culture, Sports, Science and Technology of Japan and Japan Science and Technology Agency (JST) (ACT-C: Creation of Advanced Catalytic Transformation for the Sustainable Manufacturing at Low Energy, Low Environmental Load). We would like to thank Prof. Tsuyoshi Miura (Tokyo University of Pharmacy and Life Sciences) and Prof. Kazuaki Ishihara (Nagoya University) for their useful suggestions.

References

[a] *Division of Molecular Science, Graduate School of Science and Technology, Gunma University, 1-5-1 Tenjin-cho, Kiryu, Gunma 376-8515, Japan. E-mail: amii@gunma-u.ac.jp; Fax: (+81)277-30-1280*
[b] *Faculty of Agriculture, Meijo University, 1-501 Shiogamaguchi, Tempaku-ku, Nagoya 468-8502, Japan. E-mail: matsugi@meijo-u.ac.jp; Fax: (+81) 52-835-7450*

1 (*a*) R. Noyori, *Asymmetric Catalysis In Organic Synthesis*; Wiley, 1994; (*b*) I. Ojima, ed. *Catalytic Asymmetric Synthesis: 3rd Edition*; Wiley, 2010.

2 For books of organofluorine chemistry, see: (*a*) R. E. Banks, B. E. Smart, and J. C. Tatlow; *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press, New York, 2000; (*b*) T. Hiyama, K. Kanie, T. Kusumoto, Y. Morizawa, and M. Shimizu, *Organofluorine Compounds: Chemistry and Application*; Springer-Verlag, Berlin, 2000; (*c*) P. Kirsch, *Modern Fluoroorganic Chemistry*; Wiley-VCH, Weinheim, 2004; (*d*) R. D. Chambers, *Fluorine in Organic Chemistry*; Blackwell, Oxford, 2004; (*e*) K. Uneyama, *Organofluorine Chemistry*; Blackwell, Oxford, 2006; (*f*) J.-P. Bégué, and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc., Hoboken, NJ, 2008; (*g*) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell, Chichester, West Sussex, 2009; (*h*) V. Gouverneur, and K. Mü ller, *Fluorine in Pharmaceutical and Medicinal Chemistry*: *From Biophysical Aspects to Clinical Applications*; World Scientific Publishing Company, London, 2012. For reviews of organofluorine chemistry, see: (*i*)A. M. Thayer, *Chem. Eng. News.,* 2006, **84***,* 15; (*j*) W. K. Hagmann, *J. Med. Chem.,* 2008, **51**, 4359.

3 L. Hunter, *Beilstein J. Org. Chem*. 2010, **6**, 38.

4 (*a*) L. E. Zimmer, C. Sparr, R. Gilmour. *Angew. Chem. Int. Ed.* 2011, **50**, 11860. (*b*) M. Christmann and S. Bräse, *Asymmetric Synthesis: More Methods and Applications*; Wiley-VCH Verlag GmbH & Co. KGaA., 2012.

5 (*a*) D. Cahard and V. Bizet, *Chem. Soc. Rev*., 2014, **43**, 135; (*b*) V. Bizet and D. Cahard, *Chimia*, 2014, **68**, 378.

6 A. Ogawa, and D. P. Curran, *J. Org. Chem.,* 1997, **62**, 450.

7 T. Furukawa, J. Kawazoe, W. Zhang, T. Nishimine, E. Tokunaga, T. Matsumoto, M. Shiro, and N. Shibata, *Angew. Chem. Int. Ed.*, 2011, **50**, 9684.

8 H. Xiao, Z. Chai, H.-F. Wang, X.-W. Wang, D.-D. Cao, W. Liu, Y.-P. Lu, Y.-Q. Yang, and G. Zhao, *Chem. Eur. J.*, 2011, **17**, 10562.

9 F. Romanov-Michailidis, L. Guenee, and A. Alexakis, *Angew. Chem. Int. Ed.*, 2013, **52**, 9266.

10 (*a*) V. Rauniyar, A. D. Lackner, G. L. Hamilton, and F. D. Toste, *Science*, 2011, **334**, 1681. (*b*) R. J. Phipps, K. Hiramatsu, and F. D. Toste, *J. Am. Chem. Soc.* 2012, **134**, 8376.

11 H. P. Shunatona, N. Früh, Y.-M. Wang, V. Rauniyar, and D. Toste, *Angew. Chem. Int. Ed.* 2013, **52**, 7724.

12 (*a*) C. R. Patrick and G. S. Prosser, *Nature,* 1960, **187**, 1021; (*b*) E. A. Meyer, R. K. Castellano, and F. Diederich, *Angew. Chem. Int. Ed.*, 2003, **42**, 1210.

13 A. Lattanzi, C. De Fusco, A. Russo, A. Poater, and L. Cavallo, *Chem. Commun.*, 2012, **48**, 1650.

14 Y. Nakamura, S. Takeuchi, S. Zhang, K. Okumura, and Y. Ohgo, *Tetrahedron Lett.,* 2002, **43**, 3053.

15 J. Wu, X. Li, F. Wu, and B. Wan, *Org. Lett.*, 2011, **13**, 4834.

16 X. Cui, X. Xu, H. Lu, S. Zhu, L. Wojitas, and X. P. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 3304.

17 B. M. Trost, M. Osipov, and G. Dong, *Org. Lett.*, 2010, **12**, 1276.

18 A. Grandbois and S. K. Collins, *Chem. Eur. J.,* 2008, **14**, 9323.

19 N. Havare, and D. A. Plattner, *Helv. Chim. Acta,* 2009, **92**, 623.

20 Y. Kobayashi, S. Inukai, N. Asai, M. Oyamada, S. Ikegawa, Y. Sugiyama, H. Hamamoto, T. Shioiri, and M. Matsugi, *Tetrahedron: Asymmetry*, 2014, **25**, 1209.

21 (*a*) J.-P. Bégué, D. Bonnet-Delpon, and B. Crousse, *Synlett*, 2004, 18; (*b*) I. A. Shuklov, N. V. Dubrovina, and A. Börner, *Synthesis*, 2007, 2925; (*c*) J. Ichikawa, *"Cationic Cyclizations of Fluoro Alkenes: Fluorine as a Controller and an Activator" in Current Fluoroorganic Chemistry*; New Synthetic Directions, Technologies, Materials and Biological Applications, ACS Symposium Series 949, V. A. Soloshonok, K. Mikami, T. Yamazaki, J. T. Welch, and J. Honek, ed., American Chemical Society, Washington, D.C., 2006, Chapter 9, pp. 155; (*d*) A. Saito, *Yakugaku Zasshi* 2008, **128**, 1133; (*e*) T. Dohi, N. Yamaoka, and Y. Kita, *Tetrahedron,* 2010, **66**, 5727.

22 For books, see (*a*) V. A. Soloshonok, *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Ed. Wiley, Chichester, 1999; (*b*) V. P. Kukhar´, and V. A. Soloshonok, *Fluorine-containing Amino Acids: Synthesis and Properties*; Eds., Wiley, Chichester, 1994; For reviews, see (*c*) K. Mikami, Y. Itoh, and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1; (*d*) J. A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119; (*e*) J. A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, 1; (*f*) J. Nie, H.-C. Guo, D. Cahard, and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455.

23 (*a*) S. Kobayashi, and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069; (*b*) J.-H. Xie, S.-F. Zhu, and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713; (*c*) S. Kobayashi, Y. Mori, J. S. Fossey, and M. M. Salter, *Chem. Rev.*, 2011, **111**, 2626.

24 H. Abe, H. Amii, and K. Uneyama, *Org. Lett*., 2001, **3**, 313.

25 A. Suzuki, M. Mae, H. Amii, and K. Uneyama, *J. Org. Chem.*, 2004, **69**, 5132.

26 K. Mikami, T. Murase, L. Zhai, S. Kawauchi, Y. Itoh, and S. Ito, *Tetrahedron Lett.,* 2010, **51**, 1371.

27 (*a*) Y.-Q. Wang, and Y.-G. Zhou, *Synlett,* 2006, 1189; (*b*) Y.-Q. Wang, S.-M. Lu, and Y.-G. Zhou, *J. Org. Chem.*, 2007, **72**, 3729; (*c*) Y.-Q. Wang, S.-M. Lu, and Y.-G. Zhou, *Org. Lett.*, 2005, **7**, 3235.

28 D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 8909.

29 (*a*) M. J. Burk, C. S. Kalberg, and A. Pizzano, *J. Am. Chem. Soc.*, 1998, **120**, 4345; (*b*) Y. Hsiao, N. R. Rivera, Th. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, and J. D. Armstrong, III, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, and C. Malan, *J. Am. Chem. Soc.*, 2004, **126**, 9918; (*c*) F. Fache and O. Piva, *Synlett*, 2004, 1294; (*d*) N. V. Dubrovina, V. I. Tararov, A. Monsees, A. Spannenberg, I. D. Kostas, and A. Börner, *Tetrahedron: Asymmetry*, 2005, **16**, 3640; (*e*) N. V. Dubrovina, I. A. Shuklov, M.-N. Birkholz, D. Michalik, R. Paciello, and A. Börner, *Adv. Synth. Catal.*, 2007, **349**, 2183; (*f*) W. Zhang, and X. Zhang, *J. Org. Chem.*, 2007, **72**, 1020; (*g*) D. Clarisse, B. Fenet, and F. Fache. *Org. Biomol. Chem.*, 2012, **10**, 6587.

30 G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano, and R. Rios, *Tetrahedron Lett.*, 2009, **50**, 1943.

31 S.-I. Murahashi, S. Ono, and Y. Imada, *Angew. Chem. Int, Ed.*, 2002, **41**, 2366.

32 D. A. Evans, and D. S. Johnston, *Org. Lett.*, 1999, **1**, 595.

33 D. A. Evans, T. Rovis, M. C. Kozlowski, and J. S. Tedrow, *J. Am. Chem. Soc.*, 1999, **121**, 1994.

34 D. A. Evans, K. A. Scheidt, J. N. Johnston, and M. C. Willis, *J. Am. Chem. Soc.*, 2001, **123**, 4480.

35 M. P. Sibi and J. Chen, *Org. Lett.,* 2002, **4**, 2933.

36 S. Kobayashi, H. Kiyohara, Y. Nakamura, and R. Matsubara, *J. Am. Chem. Soc.*, 2004, **126**, 6558.

37 J.-H. Lin, and J.-C. Xiao, *Tetrahedron Lett.,* 2014, **55**, 6147.

38 J.-A. Ma, and D. Cahard, *Tetrahedron: Asymmetry*, 2004, **15**, 1007.

39 Y.-L. Liu, T.-D. Shi, F. Zhou, X.-L. Zhao, X. Wang, and J. Zhou, *Org. Lett.*, 2011, **13**, 3826.

40 H. Kosugi, K. Hoshino, and H. Uda, *Tetrahedron Lett.*, 1997, **38**, 6861.

41 T. Katagiri, N. Iguchi, T. Kawate, S. Takahashi and K. Uneyama, *Tetrahedron: Asymmetry*, 2006, **17**, 1157.

42 (*a*) Y. Fujiwara, T. Katagiri, and K. Uneyama, *Tetrahedron Lett.*, 2003, **44**, 6161; (*b*) Y. Fujiwara, T. Katagiri, and K. Uneyama, *Tetrahedron Lett.*, 2003, **44**, 6161.

43 (*a*) M. Omote, N. Tanaka, A. Tarui, K. Sato, I. Kumadaki, and A. Ando, *Tetrahedron Lett.*, 2007, **48**, 2989; (*b*) Y. S. Sokeirik, M. Omote, K. Sato, I. Kumadaki, and A. Ando, *Tetrahedron: Asymmetry*, 2006, **17,** 2654; (*c*) Y. S. Sokeirik, H. Mori, M. Omote, K. Sato, A. Tarui, I. Kumadaki, and A. Ando, *Org. Lett.*, 2007, **9**, 1927.

44 S. Morikawa, K. Michigami, and H. Amii, *Org. Lett.*, 2010, **12**, 2520.

45 (*a*) S. Goushi, K. Funabiki, M. Ohta, K. Hatano, and M. Matsui, *Tetrahedron*, 2007, **63**, 4061; (*b*) K. Funabiki , A. Shibata, K. Hatano, and M. Matsui, *J. Fluorine Chem.*, 2009, **130**, 444; (*c*) K. Funabiki, A. Shibata, H. Iwata, K. Hatano, Y. Kubota, K. Komura, M. Ebihara, and M. Matsui, *J. Org. Chem.*, 2008, **73**, 4694.

46 For books of fluorous chemistry, see: (*a*) J. A. Gladysz, D. P. Curran and I. T. Horváth eds., *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim, 2004; (*b*) I. T. Horváth ed. *Fluorous Chemistry* （Topics in Current Chemistry, Vol. 308, Springer, 2012, For recent reviews on fluorous chemistry: (*c*) I. Ryu, H. Matsubara, H. Nakamura, D. P. Curran, *Chem. Rec.* 2008, **8**, 351; (*d*) W., Zhang, *Chem. Rev.*, 2009, **109**, 749; (*e*) M. Cametti, B. Crousse, P. Metrangolo, R. ilani, and G. Resnati, *Chem. Soc. Rev.*, 2012, **41**, 31.

47 K. Funabiki, M. Ohta, Y. Sakaida, K. Oida, Y. Kubota, and M. Matsui, *Asian J. Chem.*, 2013, **2**, 1048.

48 (*a*) T. Miura, Y. Yasaku, N. Koyata, Y. Murakami, and N. Imai, *Tetrahedron Lett.*, 2009, **50**, 2632; (*b*) T. Miura, M. Ina, K. Imai, K. Nakashima, A, Masuda, N. Tada, N. Imai, and A. Itoh, *Synlett*, 2011, 410; (*c*) T. Miura, H. Kasuga, K. Imai, M. Ina, N. Tada, N. Imai, and A. Itoh, *Org. Biomol. Chem.*, 2012, **10**, 2209.

49 T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, and M. Shiro, *Angew. Chem. Int. Ed.*, 2008, **47**, 8051.

50 M. Uyanik, H. Hayashi, and K. Ishihara, *Science*, 2014, **345**, 291.

51 D. O'Hagan, *Chem. Soc. Rev.* 2008, **37**, 308.

52 Examples of organoctalysts fluorinated at the β-position relative to the amino center; (*a*) C. M. Marson and R. C. Melling, *Chem. Commun.* 1998, 1223; (*b*) C. M. Marson and R. C. Melling, *J. Org. Chem.* 2005, **70**, 9771; (*c*) C.-Y. Ho, Y.-C. Chen, M.-K. Wong, and D. Yang, *J. Org. Chem.* 2005, **70**, 898; (*d*) C. E. Jakobsche, G. Peris, S. J. Miller, *Angew. Chem.* 2008, **120**, 6809; *Angew. Chem. Int. Ed.* 2008, **47**, 6707; (*e*) C. Sparr, E.-M. Tanzer, J. Bachmann, R. Gilmour, *Synthesis* 2010, 1394; (*f*) C. Sparr and R. Gilmour, *Angew. Chem. Int. Ed.* 2010, **49**, 6520; (*g*) D. Seebach, U. Grošelj, W. B. Schweizer, S. Grimme, and C. Mück-Lichtenfeld, *Helv. Chim. Acta,* 2010, **93**, 1; (*h*) Y. P. Rey, L. E. Zimmer, C. Sparr, E.-M. Tanzer, W. B. Schweizer, H. M. Senn, S. Lakhdar, and R. Gilmour, *Eur. J. Org. Chem.* 2014, 1202.

53 C. L. Chandler and B. List, *J. Am. Chem. Soc.* 2008, **130**, 6737.

54 (*a*) C. Sparr, W. B. Schweizer, H. M. Senn, and R. Gilmour, *Angew. Chem. Int. Ed.* 2009, **48**, 3065; (*b*) E.-M. Tanzer, L. E. Zimmer, W. B. Schweizer and R. Gilmour, *Chem. Eur. J.* 2012, **18**, 11334.

55 I. G. Molnar, E.-M. Tanzer, C. Daniliuc and R. Gilmour, *Chem. Eur. J.* 2014, **20**, 794.

56 D. A. DiRocco, K. M. Oberg, D. M. Dalton, and T. Rovis, *J. Am. Chem. Soc.* 2009, **131**, 10872.

57 Y. Rey and R. Gilmour, *Beilstein J. Org. Chem.* 2013, **9**, 2812.

58 E.-M. Tanzer, W. B. Schweizer, M.-O. Ebert, and R. Gilmour, *Chem. Eur. J.* 2012, **18**, 2006.

59 C. Mondelli, C. Bucher, A. Baiker and R. Gilmour, *J. Mol. Catal. A: Chem.* 2010, **327**, 87.

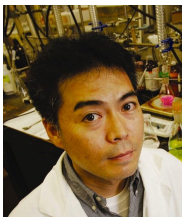
60 T. Ritter, M. W. Day, and R. H. Grubbs, *J. Am. Chem. Soc.* 2006, **128**, 11768.

61 R.-Y. Tang, G. Li, and J.-Q. Yu, *Nature*, 2014, **507**, 215.

Author Profiles

Tsuyuka Sugiishi was born in Tokyo. She received PhD in Chemistry from Gakushuin University under the direction of Prof. Hiroyuki Nakamura (2012). And she has worked as a postdoctoral fellow in Institute for Molecular Science for 2 years with Prof. Hidehiro Sakurai (2012-2014). Now, she belongs to Gunma University as an assistant professor. Her interests are discoveries and developments of novel reactions in organic synthesis.

Masato Matsugi was born in Aichi, Japan. He received his B.S. and M.S. degrees from Toyama University and received his Ph.D. degree from Osaka University (Supervisor: Prof. Yasuyuki Kita). After working at Otsuka Pharmaceutical Co., Ltd., he moved to Osaka University (Prof. Masatomo Nojima group) as an Assistant Professor in 2000. As a visiting scientist he joined the group of Prof. Dennis P. Curran at University of Pittsburgh (2003-2005). He moved to Meijo University and promoted to Professor in 2010. His current research interests are process chemistry including fluorous chemistry, asymmetric synthesis, and natural product synthesis.



Hiromi Hamamoto was born in Kyoto, Japan, in 1974. He received his B.S. and M.S. degrees from Okayama University and received his Ph.D. (2003) degree from Osaka University under the direction of Professor Yasuyuki Kita. He joined the group of Professor Shiro Ikegami at Teikyo University as a research associate. Then he moved to Kinki University. Since 2012 he is an associate professor at Meijo University. He received the Pharmaceutical Society of Japan Award for a Young Chemist in 2011. His present research focuses on the development of novel synthetic methodology and its application to biologically important compounds.

Hideki Amii was born in Hyogo in 1968. He graduated from Kyoto University, where he received his Doctorate degree in 1996 under the direction of Prof. Yoshihiko Ito and Prof. Masahiro Murakami. During 1996-2003, he worked as Research Associate of Okayama University (Prof. Kenji Uneyama's group). He carried out postdoctoral work in France with Dr. Guy Bertrand at Université Paul Sabatier during 2000-2001. In 2003, he was appointed to Associate Professor of Kobe University. Now, he joins Gunma University as Professor of Chemistry. His research interest focuses in the synthesis of organofluorine compounds by the use of metal reagents.