Asymmetric Construction of Stereogenic Carbon Centers Featuring a Trifluoromethyl Group from Prochiral Trifluoromethylated Substrates

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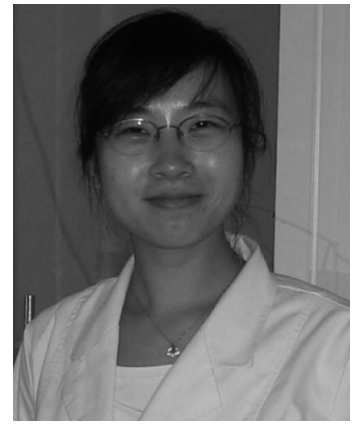
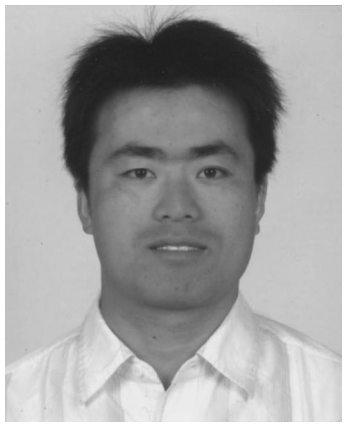
1. Introduction

Organofluorine chemistry is an area of tremendous expansion.[1] The field of applications is impressively wide in scope and has the potential to concern all fields of society. Indeed, fluorine is playing a key role in pharmaceutical, veterinary, agrochemical, and material sciences. Of particular relevance is the emergence of drug candidates featuring fluorine atom(s), which often present a favorable therapeutic profile. As a consequence, the introduction of one or more fluorine atoms is now routine in every new drug discovery and development program. The exceptional high frequency of fluorinated molecules in the pharmaceutical pipeline is truly astonishing considering that only a dozen fluorinated natural products have been identified on Earth.[2] It is universally acknowledged that the presence of fluorine functional groups in a bioactive molecule profoundly modifies its physicochemical and biological properties through concomitant alteration of its steric, electronic, lipophilic, and metabolic characteristics. The excellent therapeutic profile of pharmaceutical drugs featuring fluorine atom(s) for use in either humans or animals stimulates research for new discovery in medicinal chemistry; nevertheless, fluorine continues to challenge the organic chemistry community. In particular, the stereocontrol at carbon center featuring a fluorinated motif that could be a single fluorine, a trifluoromethyl group, or a polyfluoroalkyl substituent is a highly challenging task. Two complementary strategies could be applied: (i) the first one consists of the direct introduction of a single fluorine atom or a fluorinated moiety through nucleophilic, electrophilic, or radical reactants;[3,4] (ii) the second strategy exploits already fluorinated substrates as fluorine-containing building blocks for the construction of chiral fluorinated products. This latter approach is well suited for the valorization of readily available fluorinated building blocks. Accordingly, there has been a continuing interest in the development of highly efficient methods for the asymmetric synthesis of organofluorine compounds exploiting readily available fluorinated substrates. In this context, enantiopure trifluoromethylated molecules are at the forefront of innovation in modern organofluorine chemistry and stimulate high interest due to the increasing occurrence of this motif in a wide range of biologically active compounds but also in chiral reagents or in materials for optoelectronic devices. These compounds are presented in Figures 1−3 in a nonexhaustive fashion. Figure 1 lists the biologically active compounds featuring a trifluorocarbinol motif; Figure 2 shows the biologically active compounds featuring a trifluoroethylamine motif; and Figure 3 provides examples of compounds with a trifluoromethyl group at an all-C tertiary or quaternary chiral carbon center. Figure 1 includes chiral reagents **I**,[5] liquid crystals **II**,[6−9] and several biologically active compounds such as anticonvulsant **III**,[10] selective glucocorticoid receptor agonist (ZK-216348, **IV**),[11−14] NK-1 receptor antagonist (CJ-17493, **V**),[15] HIV reverse transcriptase inhibitor (Efavirenz, Sustiva™, **VI**),[16,17] inhibitor of matrix metalloproteinases **VII**,[18] chlolesteryl ester transfer protein inhibitor **VIII**,[19] progesterone receptor antagonist **IX**,[20] reversible monoamine oxidase A inhibitor (Befloxatone, **X**),[21] molecule used in urinary disorder (KW-7158, **XI**),[22] pyruvate dehydrogenase kinase inhibitor **XII**,[23,24]

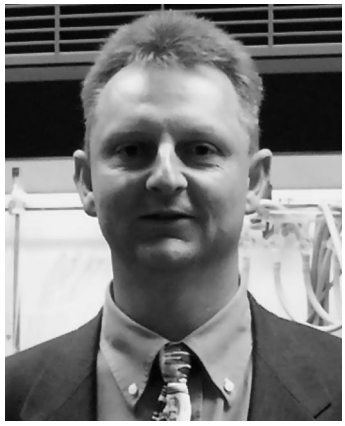
Jun-An Ma was born in He'nan Province, China. He received his B.S. degree from He'nan University in 1991 and his M.S. degree from Nankai University in 1994. Then, he joined Guangzhou Baihua Flavor & Fragrance Co. as a Senior Research Fellow. From 1996 to 1999, he completed his Ph.D. under the supervision of Professor Run-Qiu Huang at Nankai University. Then, he stayed there to work with Professor Qi-Lin Zhou before taking up postdoctoral fellowships with Dr. D. Cahard in 2003 and Professor M. T. Reetz (Germany) in 2004 and 2005. He also spent several months as a JSPS fellow with Professor Mikiko Sodeoka at RIKEN of Japan. Since July of 2005 he joined the Department of Chemistry at Tianjin University, where he was appointed to a full professor. His research interests focus on new methodologies in asymmetric synthesis of fluorinated compounds, and biologically active molecules.



Jing Nie was born in Tianjin, China, in 1980. She received her B.S. degree in chemistry from Shanxi University. In 2004, she pursued her Ph.D. at Tianjin University under the supervision of Professor Wenqin Zhang and Professor Jun-An Ma. In 2009, she joined the Department of Chemistry at Tianjin University, where she continues her research on asymmetric synthesis and developing novel methods for synthesis of organofluorine compounds.



Hong-Chao Guo received his Ph.D. degree from China Agricultural University in 2002. Spending several years for chemical research at Shanghai Institute of Organic Chemistry, Max-Planck-Institut für Kohlenforschung (Muelheim), University of California at Los Angeles, and University of Illinois at Urbana−Champaign, he joined China Agricultural University as an associate Professor in 2010. His research focuses on Lewis base-catalyzed organic reactions and their application in organic synthesis.



Dr. Dominique Cahard is a CNRS Research Director. He received his Ph.D. degree at the University of Rouen under the direction of Prof. Jean Marie Poirier and Prof. Pierre Duhamel. He was a Postdoctoral Research Associate with Prof. Chris McGuigan in Southampton (U.K.) and in Cardiff (Wales) and then with Prof. Tadashi Nakata at RIKEN, Tokyo (Japan). In 1996, he joined the CNRS at the University of Rouen, where he completed his Habilitation in 2001 and was promoted to "Directeur de Recherche" in 2007. He has published around 85 papers, patents, and book chapters. His current research interests concern innovative methodologies for asymmetric synthesis of fluorinated molecules, with emphasis for biologically active compounds such as pseudopeptides and gangliosides.

anticancer agents **XIII**[25] and **XIV**,[26] and antimalarial agents **XV**.[27] Figure 2 includes suicide inhibitor of α-oxamine synthases **XVI**,[28,29] *N*-terminal trifluoromethyl dipeptides **XVII** and α-trifluoromethyl alanine containing tripeptide **XVIII**,[30] tetrapeptide featuring the trifluoroethylamine function [CH(CF_3)NH] **XIX**,[31] neutral endopeptidase inhibitor **XX**,[32] selective inhibitor of cathepsin K for the treatment of osteoporosis (Odanacatib, MK-0822, **XXI**),[33,34] antirheumatic agent **XXII**,[35] and anticancer agents (CF_3−Ac Docetaxel, **XXIII**)[36] and **XXIV**.[37] Finally, Figure 3 shows antiestrogenic compound **XXV**,[38] household insecticide **XXVI**,[39] peptidomimetics **XXVII**,[40] olfactory variant of citronellol **XXVIII**,[41] and chiral fluorinated anesthetics such as Halothane **XXIX**, Isoflurane **XXX**, and Desflurane **XXXI**, which contain a stereogenic carbon atom bearing a trifluoromethyl group but are administered as racemic mixtures.[42]

The reasons for introducing a trifluoromethyl group into a molecule are several. The trifluoromethyl group is a bulky and highly electron-withdrawing group (electronegativity of 3.5 on the Pauling scale) that strongly affects the reactivity of the adjacent functional groups. Incorporation of a trifluoromethyl group into organic molecules generally increases their chemical stability, owing to the high bond strength that can induce increased resistance to metabolic decomposition. It could act as an isostere of the isopropyl group; the van der Waals molar volume of the trifluoromethyl group was calculated to be 21.3 $cm^3\ mol^{-1}$, similar to the molar volume of the isopropyl group.[43] Fluorine certainly participates in hydrogen-bonding interactions with H−C only as acceptor but with a much lower energy than an O···H hydrogen bond (2−3.2 versus 5−10 kcal mol^{-1}).[44] Inspection of the Cambridge Structural Database System revealed that F···H−C interactions are found in the solid-state organization of organofluorine compounds through short C−F···H−X contacts of ≤2.35 Å; however, a precise understanding of these interactions is still lacking in the literature.[45,46] α-Trifluoromethylated alcohols or amines are increasingly popular as chiral enantiopure synthons in the design of new drugs or materials. For instance, peptides incorporating fluoroalkyl amino acids display retarded proteolytic degradation combined with enhanced absorption as well as permeability through biological barriers. The trifluoroethylamine function [CH(CF_3)NH] is emerging as a remarkable surrogate of the natural peptide bond [CONH] in the area of peptide mimics. The replacement of the planar amide bond by a stereogenic 2,2,2-trifluoroethylamine moiety was proposed by Zanda and co-workers on the basis of favorable properties featured by the trifluoroethylamino group, in particular a low NH basicity that maintains hydrogen-bonding donation and a structural analogy with the tetrahedral proteolytic transition state (TS); however, geometry for peptide mimics and polarity concerns are more questionable.[31]

Several commercially available or readily synthesized compounds could be used as prochiral substrates in asymmetric reactions; it includes trifluoroacetaldehyde, 3,3,3-trifluoropyruvates, 4,4,4-trifluoroacetoacetates, trifluoromethyl ketones, trifluoromethyl olefins, and their derivatives. All asymmetric reactions involving these reagents and allowing the creation of a stereogenic carbon center featuring the trifluoromethyl group are recorded in this review. This review is part of a series covering the asymmetric direct fluorination and perfluoroalkylation processes ("Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions" by Ma and Cahard in *Chem. Rev.* **2004**, *104*, 6119[47] and the perennial review *Chem. Rev.* **2008**, *108*, PR1−PR43)[4] as well as asymmetric reactions of fluorinated substrates for the creation of stereogenic carbon centers featuring a fluorine atom ("Fluorine & chirality: How to create a nonracemic stereogenic carbon−fluorine centre?" by Cahard et al. in *Chem. Soc. Rev.* **2010**, *39*, 558)[48] or a CF_3 group (this review). The feature article "Selective difluoromethylation and monofluoromethylation reactions" (by Hu et al. in *Chem. Commun*. **2009**, 7465) nicely complements this series with the CF_2H and CFH_2 motifs.[49] This review includes all examples found in the literature through the end of 2009, with additional references cited that appeared in the first quarter of 2010. The literature survey was conducted by a computer search of Chemical Abstracts and by direct inspection of the literature.

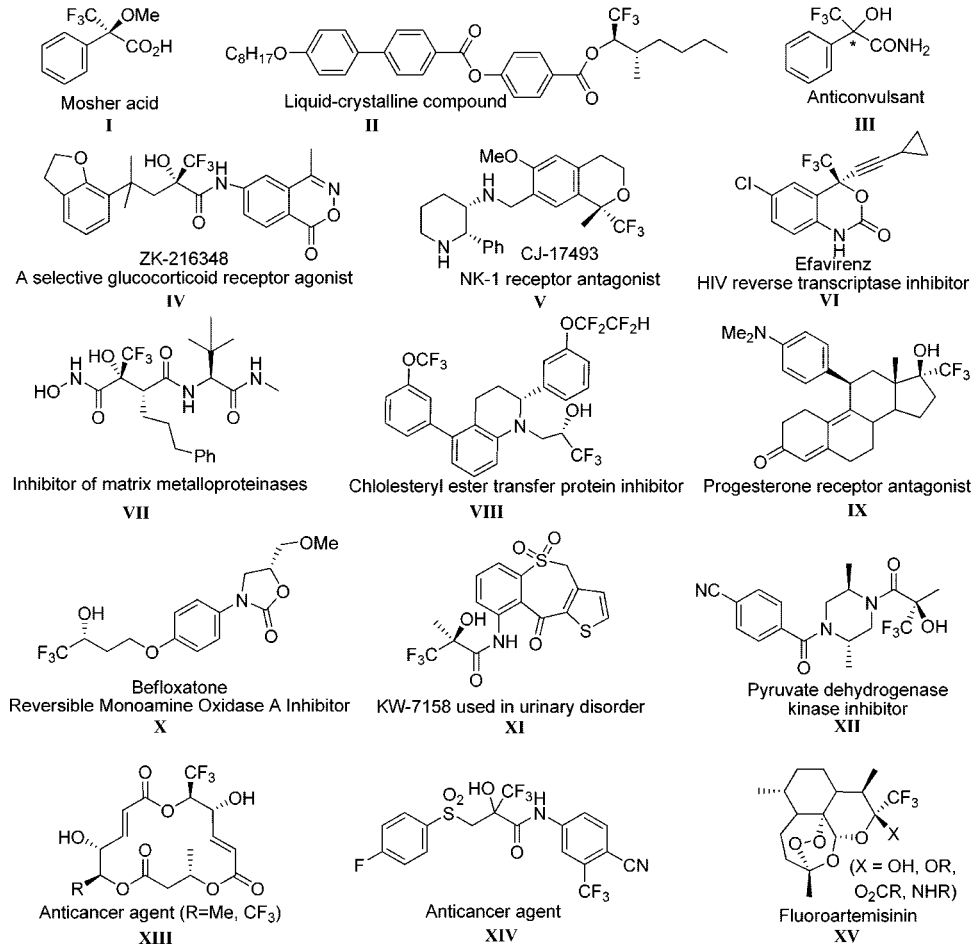


Figure 1. Biologically active compounds featuring a trifluoromethyl carbinol motif.

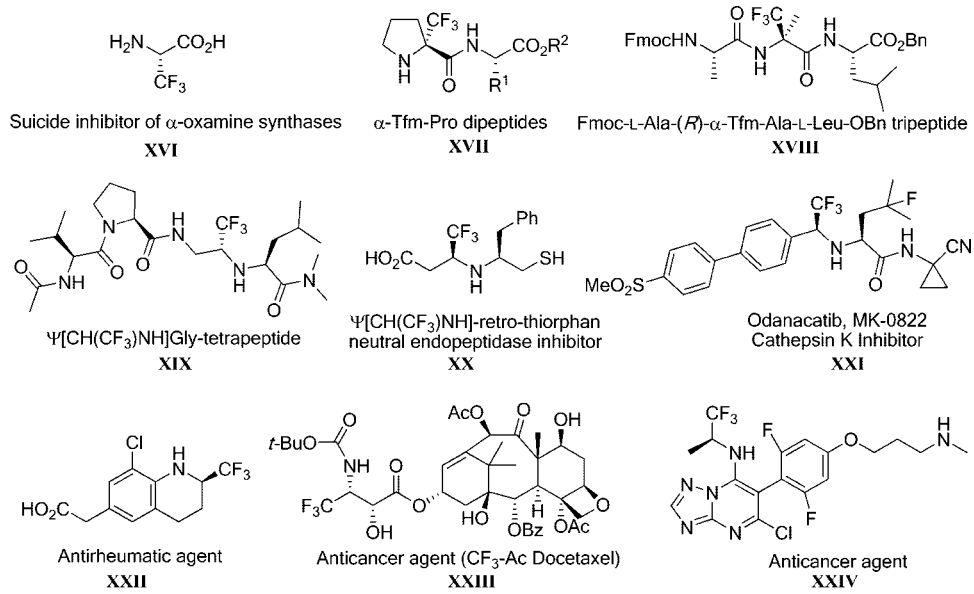


Figure 2. Biologically active compounds featuring a trifluoroethylamine motif.

2. Asymmetric Reactions of Prochiral Trifluoroacetaldehyde and Derivatives

Trifluoroacetaldehyde, also named trifluoroethanal or fluoral, is a gas at ambient temperature with a boiling point of −18 °C. For convenient use, it is stably stored and supplied in bulk at reasonable costs as the monohydrate, or as its methyl hemiacetal or ethyl hemiacetal. Trifluoroacetaldehyde and derivatives (Figure 4, **A**−**E**) are C2 building blocks of choice that can be converted into various trifluoromethyl compounds either directly or, if necessary, after dehydration or dealcoholization.[50]

2.1. From Trifluoroacetaldehyde

Trifluoroacetaldehyde is generated as a vapor by heating the monohydrate or its methyl or ethyl hemiacetal with P_2O_5,[51] polyphosphoric acid (PPA),[52] or concentrated sulfuric

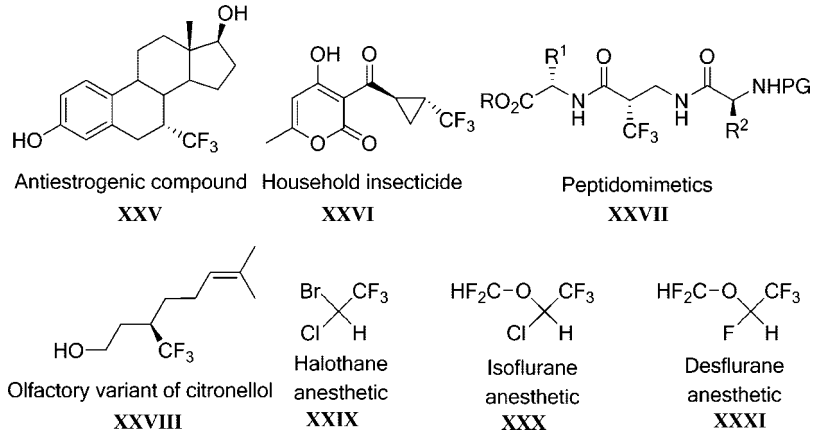


Figure 3. Examples of compounds with a trifluoromethyl group at an all-C tertiary or quaternary chiral carbon center.

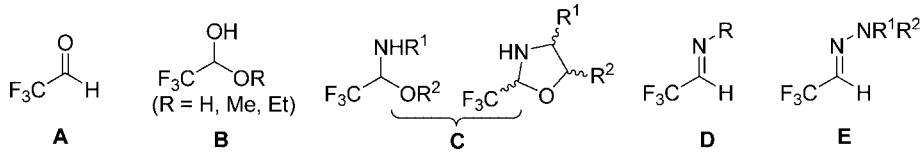


Figure 4. Trifluoroacetaldehyde and derivatives.

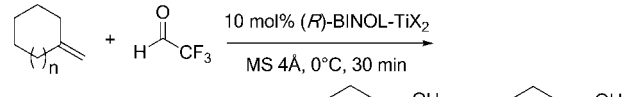
acid.[53] Among other processes for the synthesis of trifluoroacetaldehyde are the fluorination of trichloroacetaldehyde in the gas phase;[54] the reduction of trifluoroacetic acid or trifluoroacetate;[55] and the oxidation of trifluoroethanol.[56,57] The aldehyde vapor is condensed using a cold trap as a neat liquid or directly into the reaction solvent and is used immediately. It is soluble in water, alcohols, ethers, and most organic solvents. To prevent problems of polymerization and autoxidation, the neat liquid or solutions of trifluoroacetaldehyde should be kept cool and used soon after they have been prepared. Trifluoroacetaldehyde is a cancer suspect agent and should be used only in a well-ventilated fume hood, and a direct contact with the chemical should be avoided.

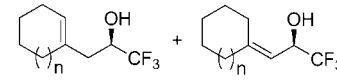
2.1.1. Fluoral−Ene Reactions

The pioneering work of Mikami and co-workers in 1993 on catalytic enantioselective fluoral−ene reaction catalyzed by a chiral Lewis acid provided a synthetically important access to chiral tertiary α-CF_3 carbinols with homoallylic functionality.[58−60] The reaction of freshly distilled fluoral with exocyclic and linear alkenes was promoted by a chiral binaphthol-derived titanium complex, which was prepared from (*R*)- or (*S*)-BINOL and diisopropoxytitanium dihalide in the presence of 4 Å molecular sieves. The expected homoallylic alcohol **1** (ene-type product through a concerted mechanism) was obtained along with the allylic alcohol **2** resulting from a Friedel−Crafts reaction (stepwise mechanism).[61] Irrespective of the solvent or the halide ligand of the catalyst, high enantiomeric excesses (ee) were measured for both the fluoral−ene adducts and the Friedel−Crafts products (ee > 95%) with the same sense of asymmetric induction (Table 1).

Trisubstituted alkenes with a terminal electron-donor methyl group (featuring enhanced ene reactivity) provided the adducts with an additional stereogenic center in allylic position.[62] The Friedel−Crafts reaction was sufficiently retarded to allow the unique formation of the ene-adduct with a high level of diastereoselectivity in favor of the *syn*-products and high enantioselectivity for exocyclic alkenes

Table 1. Enantioselective Fluoral−Ene Versus Friedel−Crafts Reactions Catalyzed by Chiral BINOLate Titanium Complex

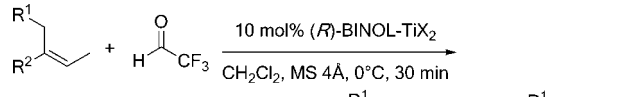


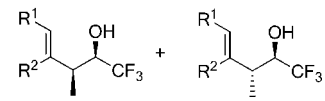


(*R*)-1 >95% ee (*R*)-2 >95% ee

n	X	solvent	yield, %	1:2
0	Cl	CH_2Cl_2	78	62:38
0	Cl	toluene	82	77:23
1	Cl	CH_2Cl_2	93	76:24
1	Br	CH_2Cl_2	95	79:21
1	Cl	toluene	82	79:21

Table 2. Diastereoselective and Enantioselective Fluoral−Ene Reaction Catalyzed by Chiral BINOLate Titanium Complex





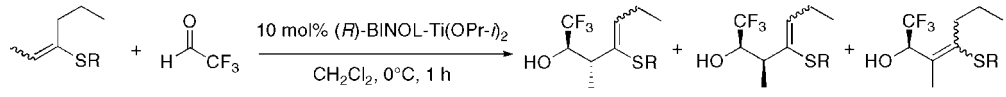
syn-3 *anti*-4

R^1	R^2	X	yield, %	*syn*-3(ee, %):*anti*-4
-$(CH_2)_4$-		Cl	94	98(96):2
-$(CH_2)_4$-		Br	85	96(92):4
-$(CH_2)_5$-		Cl	76	94(95):6
-$(CH_2)_5$-		Br	75	98(93):2
H	Me	Cl	66	91(78):9
H	Me	Br	74	96(74):4

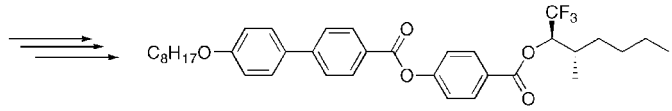
(92−96% ee) but only moderate for the reaction with 2-methyl-2-butene (74−78% ee) (Table 2).

The trifluoromethyl carbinol ene-adducts **3** and **4** served in the elaboration of liquid-crystalline molecules that displayed new phases with high potential applications in electronic and optoelectronic devices.[6,7] Furthermore, the binaphthol−titanium complex catalyzed the fluoral−ene reaction with vinyl sulfides in the synthetic route to antifer-

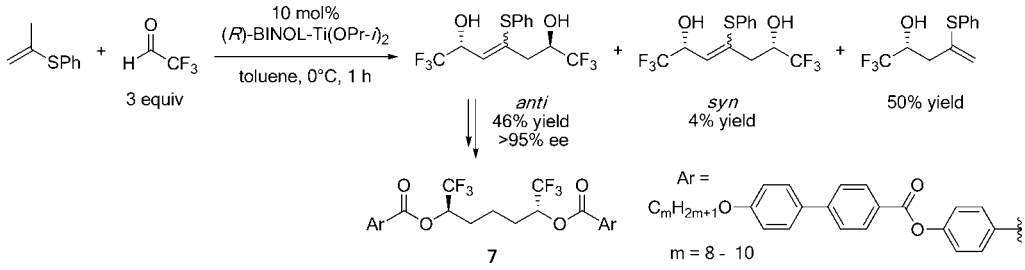
Table 3. Enantioselective Fluoral−Ene Reaction with Vinyl Sulfides Catalyzed by Chiral BINOLate Titanium Complex



R	substrate config.	yield, %	*anti*-**5**(ee, %):*syn*-**5**(ee, %):**6**(ee, %)
t-Bu	98% *E*	80	62.9(93):25.5:11.6
t-Bu	98% *Z*	83	36.7:34.2:29.1
Ph	81% *E*	89	37.5(83):13.1:(92):49.4
Ph	94% *Z*	99	13.6:30.3(92):56.1(86)



Scheme 1



roelectric and ferroelectric liquid-crystalline molecules (Table 3).[63] A dimeric analogue **7** featuring a trimethylene tether was also synthesized based on a one-pot tandem two-directional carbonyl−ene reaction of fluoral with (prop-1-en-2-yl) phenyl sulfide (Scheme 1).[64]

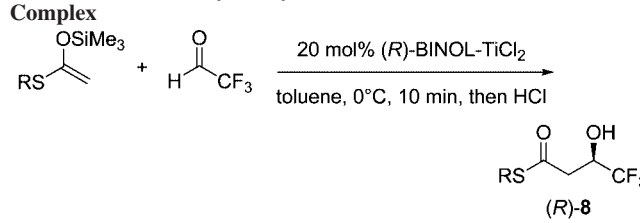
2.1.2. Aldol Reactions

The chiral BINOLate titanium complex that promoted the fluoral−ene reaction was successfully applied by Mikami and co-workers in the Mukaiyama aldol reaction with fluoral and ketene trimethylsilyl acetals derived from thioesters.[65] Provided the two reactants are introduced separately and simultaneously to the chiral catalyst, high enantioselectivities are obtained for **8** (>90% ee, Table 4, top); such a protocol suppressed the uncatalyzed reaction that is due to the high electophilicity of fluoral. With *E*- and *Z*-three-carbon thioesters, the reaction generated *syn*- and *anti*-**9** products but with poor diastereoselectivity and moderate enantioselectivity (Table 4, bottom).

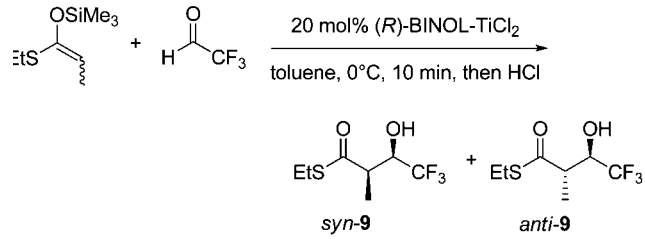
The diastereoselective aldol reaction using fluoral and boron enolate derived from *N*-acyloxazolidinones was described by Kobayashi and co-workers.[66−68] The normal Evans stereoselectivity was not observed, but instead the reaction preferentially occurred on the *Si* face of the enolate to produce *anti*-aldols **10** as major product along with "non-Evans" *syn*-aldols **10**. Acyclic transition states were proposed to account for these stereochemical results (Table 5). In the presence of an additional Lewis acid such as $TiCl_4$ that coordinates fluoral, a different acyclic transition state **TS-C** competes with **TS-A** and **TS-B** to provide the *syn*-stereomer **10**. The diastereoselectivity is superior to that reported in Mikami's work, and enantiomerically pure *syn*- and *anti*-α-alkyl-β-hydroxy-β-CF_3 butyrates could be obtained after separation and cleavage of the oxazolidinone.

Oppolzer's sultam was also investigated by the same group as chiral auxiliary in the aldol reaction of boryl enolates with fluoral. It has been observed that fluoral reacts with partial

Table 4. Enantioselective and Diastereoselective Mukaiyama Aldol Reaction Catalyzed by Chiral BINOLate Titanium Complex



R	yield, %	ee, %
t-Bu	56	90
Ph	38	96



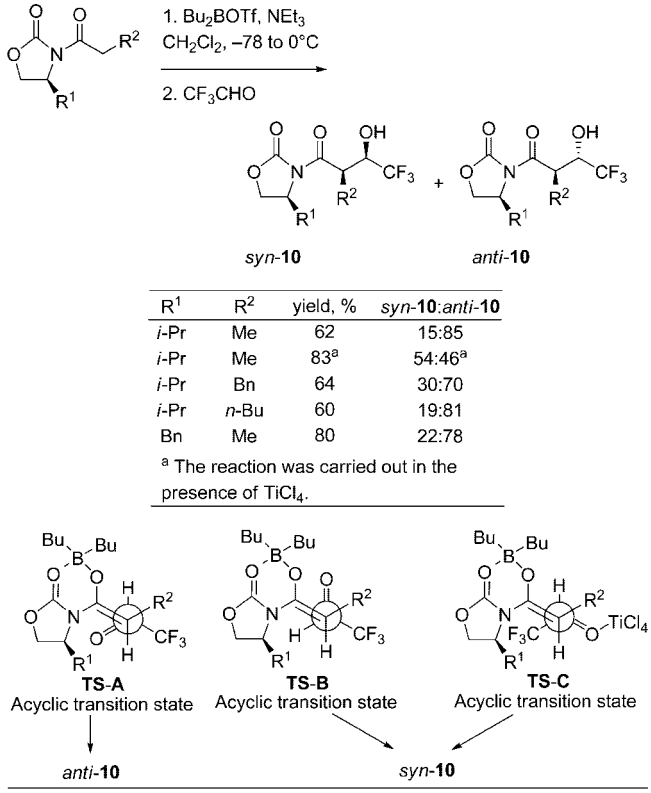
config.	yield, %	*syn*-**9** (ee, %):*anti*-**9** (ee, %)
95% *Z*	56	48(55):52(64)
98% *E*	38	44(89):56(83)

reversal of the "normal" diastereofacial selectivity, leading to unexpected *syn*-**11c** and *anti*-**11d** in significant amounts along with the normal *syn*-aldol **11a**. The addition of titanium tetrachloride prior to fluoral completely reversed the stereochemistry of the reaction, giving the *Re*-face attack aldol *anti*-**11d** via an open transition state (Scheme 2).[69]

2.1.3. Friedel−Crafts Reactions

The Friedel−Crafts reaction is a fundamental carbon−carbon bond-forming reaction that is receiving increasing attention in its catalytic asymmetric version.[70] Ishii and Mikami

Table 5. Diastereoselective Aldol Reaction of Fluoral



R^1	R^2	yield, %	*syn*-**10**:*anti*-**10**
i-Pr	Me	62	15:85
i-Pr	Me	83[a]	54:46[a]
i-Pr	Bn	64	30:70
i-Pr	*n*-Bu	60	19:81
Bn	Me	80	22:78

[a] The reaction was carried out in the presence of $TiCl_4$.

investigated the catalytic enantioselective Friedel−Crafts reaction of fluoral with aromatic substrates in order to get α-aryl-α-CF_3 secondary carbinols.[71] Aromatic substrates with an alkoxyl group to increase the nucleophilicity reacted with fluoral to give mixtures of *para*- and *ortho*-products (**12**, **13**) in favor of the *para*-isomer (from 3:1 to 8:1, Table 6). The regioselectivity of the Friedel−Crafts product reached into a ratio of *p*/*o* = 8:1 with the bulkier *n*-butylphenyl ether. The most effective catalyst featured electron-withdrawing bromine atoms at the 6,6′-positions, and both the yield and enantioselectivity could be improved further in the presence of an acidic additive that presumably changed the structure of the catalyst.[72]

The Friedel−Crafts reaction was extended to methyl vinyl ethers using the optimized catalyst system (*R*)-6,6′-Br_2−BINOL−Ti(OPr-*i*)$_2$/(*R*)-6,6′-Br_2−BINOL; however, only the aldol product **15** was obtained instead of the expected Friedel−Crafts product **14** (Table 7). A reason for that is the hydrolysis of **14** by acidic protons of the catalyst. Accordingly, the catalyst system (*R*)-BINOL/Cl_2Ti(OPr-*i*)$_2$/MS 4 Å afforded only **14** as a mixture of *E* and *Z* isomers with good ee values (Table 7).[73] Enol ether **14** was subsequently subjected to further functionalization such as *m*-CPBA oxidation to afford interesting organofluorine products.

Finally, the asymmetric catalytic Friedel−Crafts reaction of silyl enol ethers with fluoral was reported also by Mikami and co-workers. Under standard Lewis acid-catalyzed Mukaiyama conditions, the Friedel−Crafts products **16** were isolated as main products instead of the usual aldol products **17**. This was particularly true when bulky silyl groups were present on the substrate and when the amount of catalyst was reduced from 20 to 1 mol % (Table 8). The zwitterionic intermediate preferably reacts to give the Friedel−Crafts product for two reasons: (i) the bulkiness of the silyl group inhibits the nucleophilic substitution by the alcoholate; (ii) the electron-withdrawing trifluoromethyl group lowers the nucleophilicity of the titanium alcoholate (Figure 5). From a mechanistic point of view, it was proposed that the generation of the Friedel−Crafts product is a possible intermediate in the Mukaiyama aldol reaction. Importantly, ee values measured for the major *Z* isomer of **16** were all excellent.[74]

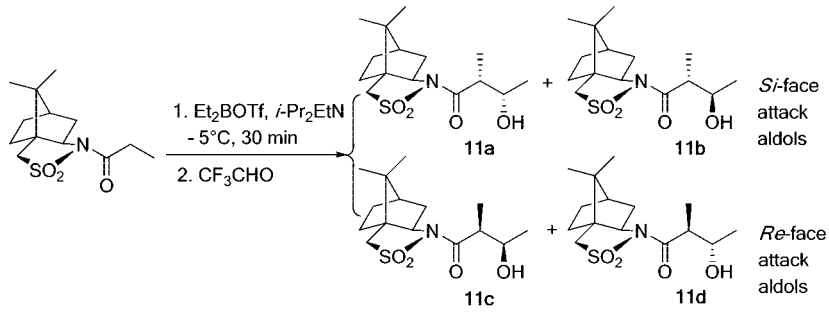
2.1.4. Synthesis of Chiral Hemiacetals

The enantioselective synthesis of trifluoroacetaldehyde hemiacetals was reported by Hiyama and co-workers using (*R*)-BINOL−Ti(OPr-*i*)$_2$ as chiral catalyst. A simultaneous addition of freshly prepared fluoral and R^1OH to a solution of the chiral catalyst in toluene at −78 °C afforded the hemiacetals **18** that were trapped in situ with benzoyl chloride or mesyl chloride (Table 9).[8,75] Hemiacetal tosylates further reacted with various organometallic reagents to give substitution products with inversion of configuration.[76]

2.1.5. Allylboration

The group of Brown examined in detail organoborane chemistry on fluorinated substrates, e.g., the asymmetric reduction of fluoroketones, hydroboration of fluoroalkenes (see later in the text), and allylboration of fluoroaldehydes. This latter reaction was realized with fluoral in the presence

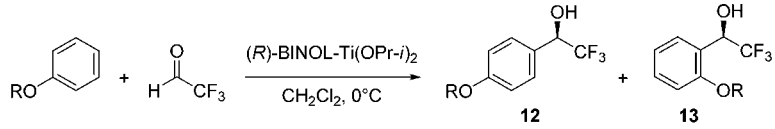
Scheme 2



	Aldols
yield, %	**11a** : **11b** : **11c** : **11d**
96	73 : 1 : 19 : 7
89[a]	0 : 0 : 1 : 99[a]

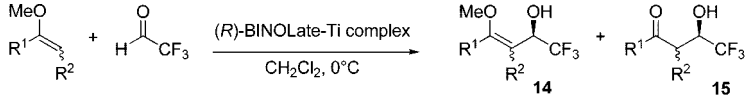
[a] The reaction was carried out in the presence of $TiCl_4$

Table 6. Enantioselective Friedel−Crafts Reactions Catalyzed by Chiral BINOLate Titanium Complex



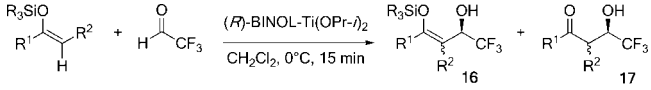
R	ligand (mol%)	additive (mol%)	yield, %	12 : 13	ee, % (12)
Me	(*R*)-BINOL (30)	–	82	4:1	73
Me	(*R*)-H_8-BINOL (5)	–	11	4:1	22
Me	(*R*)-6,6'-Br_2-BINOL (1)	–	99	4:1	72
Me	(*R*)-6,6'-Br_2-BINOL (5)	–	94	4:1	84
Me	(*R*)-6,6'-Br_2-BINOL (10)	–	66	4:1	70
Me	(*R*)-6,6'-Br_2-BINOL (10)	pentafluorophenol (10)	94	3:1	68
Me	(*R*)-6,6'-Br_2-BINOL (10)	(*R*)-BINOL (10)	97	3:1	64
Me	(*R*)-6,6'-Br_2-BINOL (10)	(*R*)-5-Cl-BIPOL (10)	88	4:1	78
Me	(*R*)-6,6'-Br_2-BINOL (10)	(*R*)-6,6'-Br_2-BINOL (10)	89	4:1	90
n-Bu	(*R*)-6,6'-Br_2-BINOL (15)	–	85	8:1	83
n-Bu	(*R*)-6,6'-Br_2-BINOL (10)	(*R*)-6,6'-Br_2-BINOL (10)	90	8:1	90
Ph	(*R*)-6,6'-Br_2-BINOL (10)	–	90	3:1	54

Table 7. Enantioselective Friedel−Crafts Reaction of Methyl Vinyl Ethers with Fluoral Catalyzed by BINOLate Titanium Complex



R^1	R^2	catalyst (mol%)	yield, % 14 (*E*:*Z*)	15	ee, %
Ph	H	(*R*)-6,6'-Br_2-BINOL-Ti(OPr-*i*)$_2$/(*R*)-6,6'-Br_2-BINOL (20)	0	53	70
Ph	H	(*R*)-6,6'-Br_2-BINOL/Cl_2Ti(OPr-*i*)$_2$/MS 4Å (20)	48 (1:2)	7	58
Ph	H	(*R*)-BINOL/Cl_2Ti(OPr-*i*)$_2$/MS 4Å (10)	54 (1:2)	0	72
4-MeC_6H_4	Me	(*R*)-BINOL/Cl_2Ti(OPr-*i*)$_2$/MS 4Å (20)	64 (5:1)	0	85

Table 8. Enantioselective Friedel−Crafts Reaction of Silyl Enol Ethers with Fluoral Catalyzed by BINOLate Titanium Complex



R_3Si	R^1	R^2	cat., mol%	yield, % 16 (*E*:*Z*)	17 (*syn*:*anti*)	ee, %
Me_3Si	4-MeC_6H_4	Me	20	0	27	-
t-BuMe_2Si	4-MeC_6H_4	Me	20	77 (1:6)	10 (1:1)	94
t-BuMe_2Si	Ph	H	5	67 (1:5)	14	98
i-Pr_3Si	Ph	H	1	90 (1:5)	4	96
t-BuMe_2Si	4-MeOC_6H_4	Me	20	68 (1:5)	22 (5:3)	95
t-BuMe_2Si	4-MeSC_6H_4	Me	20	72 (1:6)	18 (2:1)	95

of (*B*)-allyldiisopinocamphenylborane at −100 °C, leading to homoallyl alcohols **19** in high ee. The very low temperature is necessary for a clean reaction and high ee. Unfortunately, the crotylborane derivatives failed to react cleanly, but the alkoxyallylboration gave **21** in high ee and diastereomeric excess (de) when the reaction was conducted with the "ate" complex **20** (Scheme 3).[77−79]

2.2. From Trifluoroacetaldehyde Hemiacetals

From a practical point of view, it is obviously easier to work with stable, liquid trifluoroacetaldehyde hemiacetals that could be used as an alternative to gaseous unstable trifluoracetaldehyde. These hemiacetals, mainly methyl and ethyl hemiacetals, are used as building blocks in the synthesis of fluorinated molecules either directly or through in situ generation of fluoral.

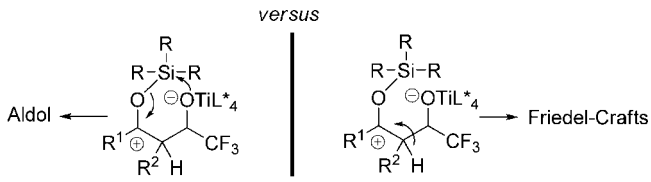


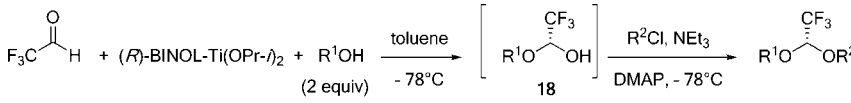
Figure 5. Mechanistic pathways to aldol and Friedel−Crafts products.

2.2.1. Reaction with Chiral Hydrazones and Imines

In a 2001 paper by Fernández, Lassaletta, and co-workers, it was indicated that fluoral ethyl hemiacetal could be used without any previous treatment for in situ generation of fluoral in the diastereoselective synthesis of α-hydroxy-α-CF_3-hydrazone **22**. Contrary to the use of simple aldehydes, the more reactive fluoral did not require addition of promoters such as $ZnCl_2$ or Et_2AlCl for high conversion, but a poor de was measured (Scheme 4).[80]

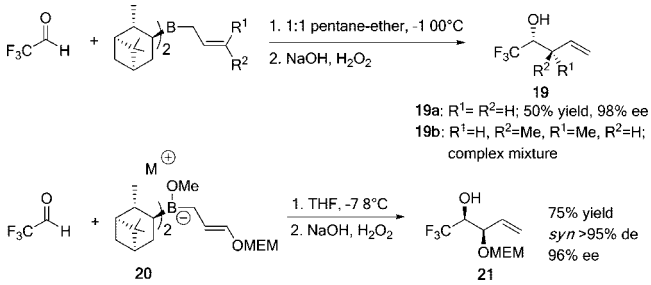
From imines, Funabiki and co-workers conducted the synthesis of trifluoromethylaldols by diastereoselective reaction of chiral imines with in situ generated fluoral.[81−83] Fluoral hemiacetal or fluoral hydrate reacted with an equimolar amount of imine in equilibrium with the enamine form acting successively as base to deprotonate the fluoral precursor, as counter ammonium cation, and as carbon nucleophile to react with fluoral after elimination of ethanol. The reaction was performed preferentially in hexane but can also be done in aqueous media with a similar level of enantioselectivity.[84] The (*R*)-1-(1-naphthyl)ethyl group was the most effective chiral auxiliary for the reaction in terms of diastereoselectivity, up to 86% ee for the aldol products **23** after acidic hydrolysis (Table 10).[85] This approach presents the advantages of an easy generation of an equimolar amount of fluoral and the possibility to recover the chiral auxiliary; however, the reaction conditions, 7 days at 0 °C, are not very practical and can explain the moderate yields.

Table 9. Enantioselective Hemiacetal Synthesis and Formation of Mixed Acetals



fluoral, equiv.	(*R*)-BINOL-Ti(OPr-*i*)$_2$, equiv.	R^1	R^2	yield, %	ee, %
4	1	*i*-Pr	PhCO	85	85
4	0.2	*i*-Pr	PhCO	81	82
4	0.2	Bn	PhCO	61	25
2.2	0.2	Bn	PhCO	48	74
2.2	0.4	Bn	PhCO	54	91
2.2	0.4	$PhCH_2CH_2$	PhCO	57	78
2.2	0.4	*n*-Bu	PhCO	65	65
4	0.4	Et_2CH	PhCO	54	73
2.2	0.4	Bn	$MeSO_2$	35	79

Scheme 3



Scheme 4

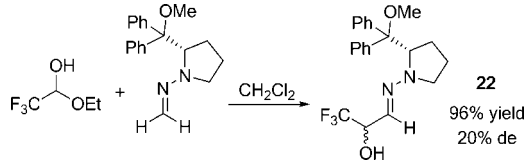
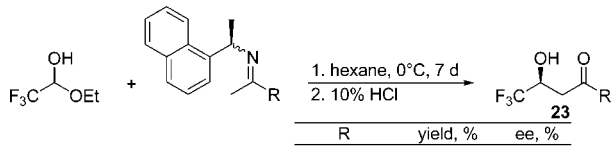


Table 10. In Situ Generation of Fluoral and Diastereoselective C−C Bond-Formation Reaction with Chiral Imines



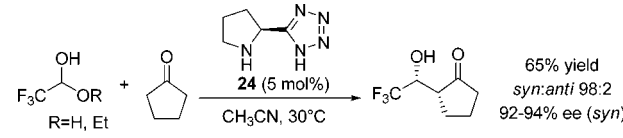
R	yield, %	ee, %
Ph	57	81
Ph	57[a]	78
4-MeC_6H_4	68	79
4-ClC_6H_4	64	75
4-$MeOC_6H_4$	51	72
2-thienyl	37	81
2-MeC_6H_4	14	14
3-MeC_6H_4	70	81
c-Hex	73	86
i-Pr	59	76
t-Bu	24	84

[a] Fluoral hydrate was used.

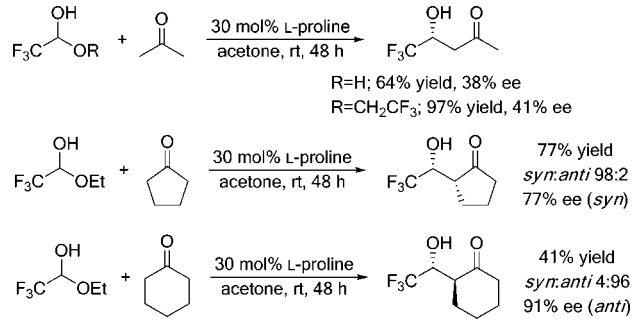
2.2.2. Organocatalyzed Reaction with Ketones

Enantioselective organocatalysis has emerged as a powerful synthetic approach that is complementary to metal-catalyzed transformations and has boosted the development of unprecedented methods for asymmetric synthesis of chiral molecules. The combination of organocatalysis and fluorine chemistry is particularly challenging. In a logical extension of their detailed work done with chloral, Saito, Yamamoto, and co-workers described a catalytic direct enantioselective aldol reaction of in situ generated fluoral with unmodified

Scheme 5



Scheme 6



cyclopentanone. The reaction was assisted by water in the presence of a proline-derived tetrazole catalyst **24** (Scheme 5).[86]

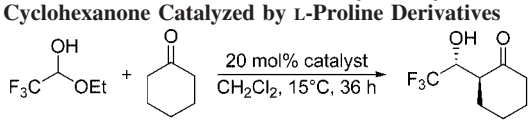
Further work in direct enantioselective aldol reaction was conducted by Funabiki and co-workers to report on the reaction of in situ generated fluoral with three unmodified ketones catalyzed by L-proline. With acetone, the ee's were only moderate, whereas cyclopentanone and cyclohexanone gave 77% and 91% ee, respectively. Interestingly, the two cyclic ketones provided aldol products with excellent but opposite diastereoselectivities; cyclopentanone gave the *syn*-diastereomer (same as in Scheme 5) and cyclohexanone gave the *anti*-diastereomer (Scheme 6).[87,88]

A study of L-proline-derived catalysts was realized by Gong and co-workers in the reaction of fluoral ethyl hemiacetal with cyclohexanone.[89] The results are somewhat different to those obtained by Funabiki and co-workers. Both the *anti*-selectivity and the ee are lower when using L-proline **25**; however, high *anti*/*syn* ratio and good ee were obtained with L-prolinamide **27**. With L-methyl prolinate **26**, a reverse selectivity was observed because the *syn*-aldol became major whereas **28** was not an efficient catalyst under these reaction conditions (Table 11).

2.2.3. Organocatalyzed Three-Component Reactions

Chiral phosphoric acids are powerful Brønsted acid catalysts in several asymmetric reactions, providing excellent enantioselectivities especially for phosphoric acids featuring a binaphthyl scaffold with 3,3′-positions occupied by bulky

Table 11. Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal with Cyclohexanone Catalyzed by L-Proline Derivatives



catalyst	yield, %	*anti* (ee, %) : *syn* (ee, %)
25	57	66 (35) : 34 (10)
26	95	21 (12) : 79 (13)
27	92	90 (88) : 10 (56)
28	<1	/

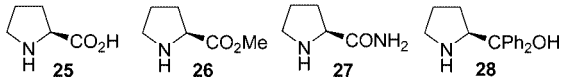
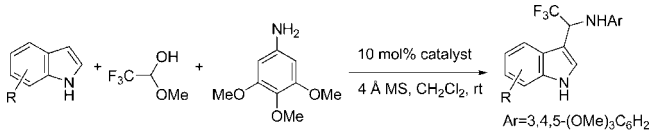
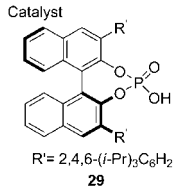


Table 12. Three-Component Friedel−Crafts Aminoalkylation of Indoles





R	time, h	yield, %	ee, %
H	24	99	94 (99.9)[a]
5-Me	72	83	95
5-OMe	24	99	92
5-F	72	99	94
5-CO_2Me	72	90	92
6-Cl	48	95	90
7-Me	48	97	96
7-Et	48	99	98
2-Me	96	80	79

[a] Ee after recrystallization

groups. Ma and co-workers accomplished a highly enantioselective Friedel−Crafts aminoalkylation of indoles with trifluoromethyl imines generated in situ from trifluoroacetaldehyde hemiacetal and aniline derivatives.[90] In the presence of phosphoric acid **29**, this three-component reaction allowed the synthesis of novel 2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethanamine in high yields and excellent enantioselectivities (Table 12). Interestingly, *N*-protected indoles failed to react, clearly indicating activation of the reactant by phosphoric acid through nitrogen atom of indoles.

2.3. From Trifluoroacetaldehyde Hemiaminals

Hemiaminals of fluoral are stable species and useful synthetic equivalents of trifluoromethylated aldimines that have been designed as precursors of trifluoromethylated imines or iminium salts as reviewed hereafter, but also as nucleophilic trifluoromethylating agents[3,91,92] and as chiral auxiliaries.[93] Acyclic hemiaminals and oxazolidines (Figure 4, **C**) are easily prepared from fluoral hydrate or hemiacetal derivatives and an amine in the presence of molecular sieves or *p*-toluene sulfonic acid at room temperature. Condensation

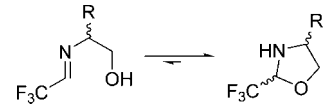


Figure 6. Tautomerization of imines.

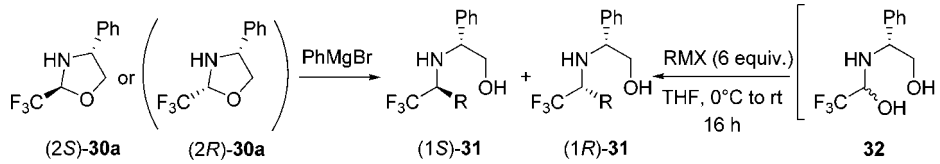
of amino alcohols with trifluoroacetaldehyde hemiacetal with azeotropic removal of water, MeOH, or EtOH did not yield the expected imines but instead the oxazolidines as mixtures of diastereomers. This is due to the highly electron-withdrawing CF_3 group that greatly enhances the electrophilicity of the imine carbon, thus shifting the equilibrium completely to the oxazolidine tautomer (Figure 6).

2.3.1. Addition Reactions of Organometallic Reagents

Ishii, Higashiyama, and Mikami were the first to examine asymmetric addition reaction of Grignard reagents to chiral fluoral hemiaminals.[94] In a first series of experiments, chiral 1,3-oxazolidine **30a** was prepared by condensation of fluoral hydrate with (*R*)-phenylglycinol; then the two diastereomers were separated by column chromatography, and each diastereomer was reacted with PhMgBr (Scheme 7, left). While nonfluorinated 1,3-oxazolidines provided a single diastereomer of addition products whatever the diastereomeric ratio of the oxazolidine, the trifluoromethylated products **31** were obtained with opposite sense of diastereoselectivity when starting from pure (2*S*)- or (2*R*)-**30**. This result indicates that an intermediate imine is not involved in the reaction mechanism, and that phenylmagnesium bromide reacted directly with the 1,3-oxazolidines. Then, acyclic hemiaminals **32** were generated in situ and further reacted with an excess of Grignard reagents. The reaction lead to 1-substituted-2,2,2-trifluoroethylamine **31** in a highly diastereoselective fashion (Scheme 7, right) and presumably proceeded through a metallo-imine; however, a large excess of Grignard is used and the process is self-immolative for the chiral auxiliary after oxidative cleavage with $Pb(OAc)_4$.

More recently, Gosselin and co-workers investigated further the organometallic addition to various trifluoromethyl oxazolidines **30b−g**, which were used as diastereomeric mixtures (from 1.2 to 2.6:1).[95] In this work at Merck laboratories, it was also concluded that direct addition of PhLi or PhMgBr to oxazolidines gave poor diastereomeric ratio (dr) of arylated product (from 2:1 to 5:1).[34] This ratio was significantly improved to 40:1 when the tautomeric imine was used as substrate instead of the oxazolidine, leading the authors to conceive a new procedure keeping the oxazolidines as starting materials. The oxazolidines were first ring-opened with a base (LiHMDS) and *O*-silylated by Me_3SiCl followed by complete isomerization of the generated imine into the *E*-imine that could then react in situ with the organometallic

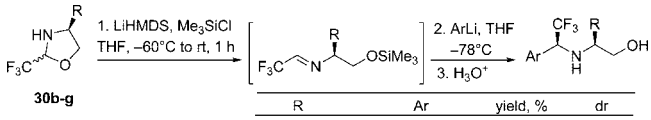
Scheme 7



substrate	yield, %	(1*S*)-**31** : (1*R*)-**31**
(2*S*)-**30**	90	1.2 : 1
(2*R*)-**30**	94	1 : 7.8

RMX	yield, %	(1*S*)-**31** : (1*R*)-**31**
PhMgBr	94	5 : 95
MeMgBr	60	3.5 : 96.5
BnMgCl	83	2.5 : 97.5

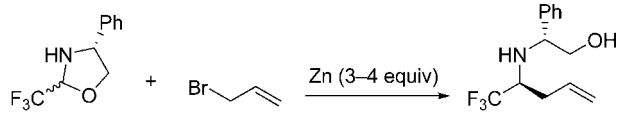
Table 13. Diastereoselective Organometallic Addition to Oxazolidines via In Situ Generated *E*-Imines



30b-g

R	Ar	yield, %	dr
30b; Et	Ph	97	49:1
30c; *i*-Pr	Ph	97	>100:1
30d; *i*-Bu	Ph	64	44:1
30e; Bn	Ph	81	40:1
30f; *t*-Bu	Ph	88	35:1
30g; $(CH_2)_2SMe$	Ph	86	38:1
30d; *i*-Bu	1-naphth	89	40:1
30d; *i*-Bu	4-BrC_6H_4	82	40:1
30d; *i*-Bu	4-$MeOC_6H_4$	89	40:1
30d; *i*-Bu	3-$CF_3C_6H_4$	95	40:1
30d; *i*-Bu	2-$MeSC_6H_4$	74	69:1
30d; *i*-Bu	3-F-4-$MeOC_6H_3$	89	40:1
30d; *i*-Bu	3-pyridyl	76	36:1
30d; *i*-Bu	2-furyl	60	40:1

Scheme 8



conditions	yield, %	dr, %
DMF, rt	65	61
THF, reflux	45	9

species. Diastereoselectivities greater than 35:1 and good yields are observed (Table 13).[95]

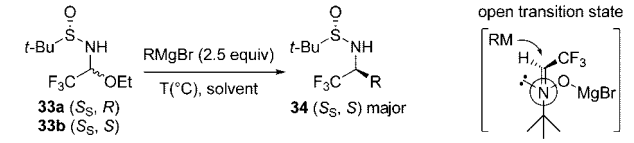
A stereoselective Barbier-type allylation was also performed with oxazolidine **30a** in the presence of zinc dust as reported by Bonnet-Delpon and co-workers (Scheme 8).[96] The dr was only moderate, and the major diastereomer was opposite to the major one obtained in the reaction with allylsilane in the presence of a Lewis acid (see section 2.3.3). The excess of zinc probably caused the formation of an iminium ion as intermediate; however, allylation reactions were best performed from chiral aldimines by means of 1.3 equiv of zinc with better diastereoselectivities (see section 2.4.1).

Apart from the use of phenylglycinol as chiral auxiliairy, Kuduk and co-workers at Merck laboratories have condensed the (*S*)-*tert*-butanesulfinamide with neat fluoral ethyl hemiacetal in $Ti(OEt)_4$ overnight at 70 °C to give a mixture of diastereomeric hemiaminals **33** that were easily separated by column chromatography. Hemiaminals **33a** and **33b** were separately reacted with 2.5 equiv of Grignard reagents to afford the corresponding trifluoroethylamines **34** in good yields with moderate to high diastereoselectivities (Table 14).[97] The diastereoselectivity difference between isomers **33a** and **33b** was found, by variable-temperature ^1H NMR studies, to be dependent on the temperature at which the intermediate imine is generated. The stereochemistry of the newly created stereogenic center is *S* and is likely formed through an open transition state.

2.3.2. Reformatsky Reactions

The Reformatsky reaction between 2-trifluoromethyl-1,3-oxazolidine **30a** and ethyl bromoacetate in the presence of zinc dust was examined by Huguenot and Brigaud to synthesize chiral 4-trifluoromethylazetidin-2-one **35** (Scheme 9).[98] Unlike nonfluorinated amino alcohol-based oxazolidines, both the diastereoselectivity and the yield were only moderate in this case. Ethanolysis under acidic condi-

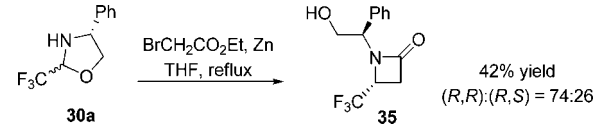
Table 14. Diastereoselective Addition of Grignard Reagents to *tert*-Butanesulfinamide Fluoral Ethyl Hemiaminal



33a (S_S, *R*)
33b (S_S, *S*)
34 (S_S, *S*) major

substrate	R	solvent	time, h	temp, °C	yield, %	(S_S, *S*) : (S_S, *R*)
33a	vinyl	toluene	0.5	0	80	7:1
33b	vinyl	toluene	0.5	0	85	6:1
33a	vinyl	toluene	2	–23	78	11:1
33a	vinyl	toluene	2	–40	58	16:1
33a	vinyl	THF	2	–40	64	13:1
33a	vinyl	CH_2Cl_2	2	–40	58	22:1
33a	vinyl	CH_2Cl_2	2	–30	68	14:1
33a	vinyl	CH_2Cl_2	3	–40 to –20	71	22:1
33b	vinyl	CH_2Cl_2	1	–40	70	14:1
33b	vinyl	CH_2Cl_2	2	–60 to –20	75	22:11
33a	isopropenyl	CH_2Cl_2	2	–40 to –20	81	11:1
33a	allyl	CH_2Cl_2	2	–40 to –20	98	5:1
33a	homoallyl	CH_2Cl_2	2	–40 to –10	74	>30:1
33a	phenyl	CH_2Cl_2	2	–40 to –20	98	6:1
33a	phenyl	THF	0.5	–40 to –20	97	3.5:1

Scheme 9



tions of column-chromatographed pure (*R*,*R*)-**35** was conducted, but this route to β-trifluoromethyl-β-amino esters was abandoned for the reaction of silyl ketene acetal with **30a** (see section 2.3.3), which gave better results.

2.3.3. Reaction with Silylated Nucleophiles

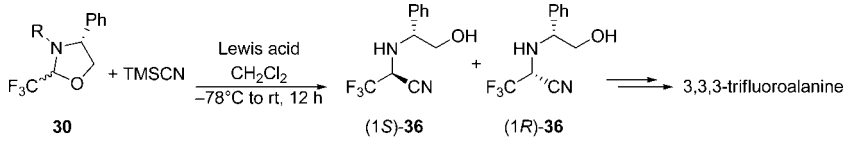
The asymmetric cyanosilylation of imines or derivatives (Strecker-type reactions) is of interest as it allows access to biologically important chiral α-amino acids. Brigaud and co-workers reported the Strecker reaction by means of trimethylsilyl cyanide on chiral 2-trifluoromethyloxazolidines **30** (Table 15).[99,100] Optimization of the reaction was conducted, and it was found that the best results were obtained with a catalytic amount of TMSOTf or with 1.5 equiv of BF_3-Et_2O. From oxazolidine **30a** (R = H), the same diastereomeric ratio of α-amino nitriles **36** was measured whatever the diastereomeric ratio of the oxazolidine **30a**, clearly indicating a unique iminium as intermediate. Oxazolidines derived from (−)-ephedrine and (−)-norephedrine gave the addition products in high yields (80−90%) but with a lower diastereoselectivity, not higher than 33:67.

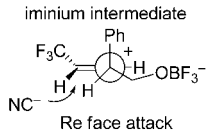
The reaction of oxazolidines **30a** mediated with BF_3-Et_2O was successfully extended to various silylated nucleophiles including allyltrimethylsilane,[101] bistrimethylsilylacetylene, enoxysilanes, and a silyl ketene acetal as shown in Scheme 10.[98,99] Some of these products served as intermediates in the synthesis of a variety of β-trifluoromethyl-β-amino acid, β-amino ketones, and γ-amino alcohols.

2.3.4. Aziridination

Chiral trifluoromethyl-substituted aziridines are useful synthetic intermediates for the synthesis of more elaborated nitrogen-containing compounds. In this aim, the reaction of trifluoroacetaldehyde hemiaminal **37** with diazoacetate **38** derived from (*R*)-pantolactone led to highly diastereoselective

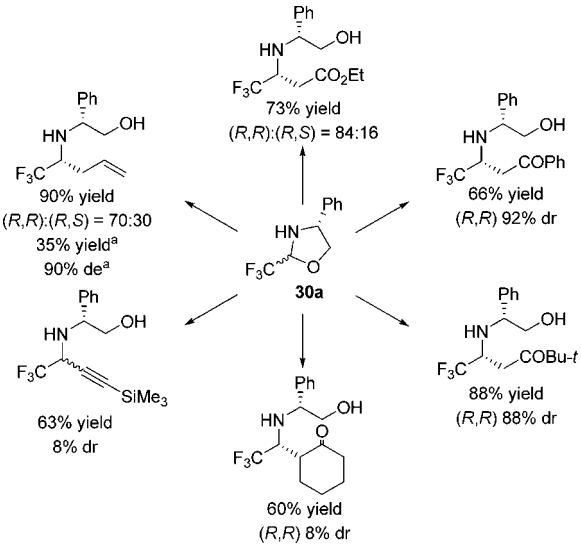
Table 15. Diastereoselective Strecker-Type Reaction on Oxazolidines



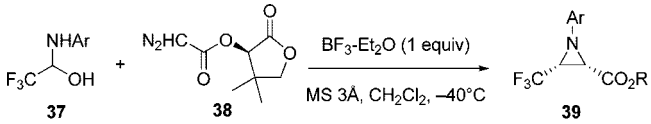


30; (2*S*):(2*R*)	Lewis acid	yield, %	**36**; (1*S*):(1*R*)
30a; 62:38	BF_3·Et_2O (1.5 equiv)	90	17:83
30a; 62:38	TMSOTf (0.1 equiv)	87	18:82
30a; 87:13	TMSOTf (0.1 equiv)	87	19:81
30a; 20:80	TMSOTf (0.1 equiv)	84	17:83
30a' (R=Bn); 67:33	BF_3·Et_2O (1.5 equiv)	87	50:50
30a" (R=Bz); 100:0	BF_3·Et_2O (1.5 equiv)	0	-

Scheme 10



Scheme 11



Ar	yield, %	*cis* (dr, %):*trans*
4-$MeOC_6H_4$	81	>95(94:<5
4-BrC_6H_4	83	>99(92):<1

aziridination. Akiyama and co-workers demonstrated that BF_3−Et_2O was effective for the aziridination providing stereoselectively the *cis* isomer **39** in high yield with excellent diastereoselectivity (Scheme 11). Menthol and binaphthol monomethyl ether were not effective as chiral auxiliaries.[102]

2.4. From Trifluoroacetaldehyde Imines

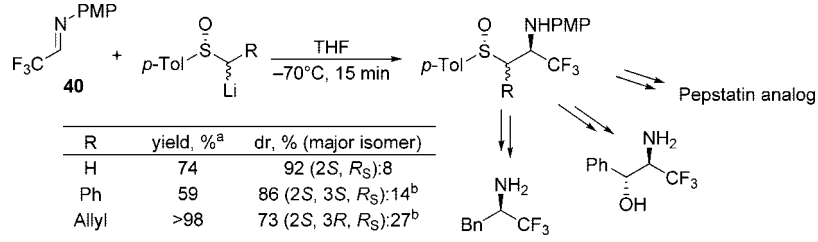
Trifluoromethyl aldimines have emerged as powerful building blocks to construct important molecules in many fields of application.[103] Unlike their nonfluorinated analogues, trifluoromethyl imines are good electrophiles owing to the electron-withdrawing effect of the CF_3 group. Trifluoromethyl aldimines are routinely prepared from fluoral hemiacetal and an amine in toluene at reflux in an azeotropic Dean−Stark distillation apparatus. Readily available chiral amines and amino alcohols used to prepare chiral trifluoromethyl aldimines are optically pure 1-phenylethylamine, 1-(1-naphthyl)ethylamine, (*S*)-leucinol, (*R*)-phenylglycinol, and (*S*)-*N*-*tert*-butanesulfinamide. Aldimines were always obtained as the *E* isomer.

2.4.1. Addition Reactions of Organometallic Reagents

In a joint research project by Bravo, Zanda, Soloshonok, and co-workers, diastereoselective additions of α-lithiated alkyl- and aryl-(*R*)-*p*-tolylsulfoxides to *N*-*p*-methoxyphenyl (*N*-PMP) trifluoromethylaldimine (**40**) were reported (for trifluoromethylketimines, see section 5.2), affording versatile precursors of enantiomerically pure α-trifluoromethylalkylamines and α-CF_3-β-hydroxyalkylamines.[104−106] The choice of the *N*-PMP derivative of fluoral was critical to allow high reactivity of the imine and favorable imine geometry for efficient stereocontrol; indeed, *N*-(alkoxycarbonyl) trifluoromethylaldimines gave only limited success in the studied reaction. Control reactions suggested that the additions occurred irreversibly under kinetic control, which is in sharp contrast to the similar reactions run with nonfluorinated substrates. The diastereoselectivities and yields obtained with different sulfoxides were moderate to good (Scheme 12). However, crystallization of the crude mixtures was achieved to end up with enantiopure products ready for further chemical transformations. For example, the stereospecific displacement of the sulfinyl auxiliary by a hydroxy group provided an efficient synthesis of (*R*, *R*)-trifluoronorephedrine. For R = allyl, a synthesis of a trifluoromethyl analogue of the aspartate protease inhibitor pepstatin featuring two CF_3 groups was developed.[107]

As a privileged chiral auxiliary, the sulfinyl group was also exploited by García Ruano, Fustero, and co-workers in the nucleophilic addition of 2-(*p*-tolylsulfinyl) benzylcarbanions to trifluoromethylimine **40** with excellent diastereocontrol of the configuration of the created stereogenic centers at the benzylic position (R ≠ H) and at the carbon bearing the trifluoromethyl group (Scheme 13).[108,109] In this work and the preceding one, the chiral element is located on the nucleophilic partner of the reaction (i.e., the sulfinyl auxiliary), whereas in all the following examples presented in this section, the diastereodiscriminating elements are positionned on the electrophilic trifluoromethylaldimine. The sulfoxide was deprotonated at its benzylic position with lithium diisopropylamide (LDA) and was subsequently reacted with imine **40** at −78 °C prior to protonation at the same temperature, giving the addition products **41** (major) and **42**. Isolated product **41** was cyclized in the presence of a base into indolines **43** by intramolecular nucleophilic aromatic substitution of the sulfinyl group acting as a leaving group. Advantagenously, the one-pot synthesis of trifluoromethylated indolines **43** was also presented (Scheme 13).

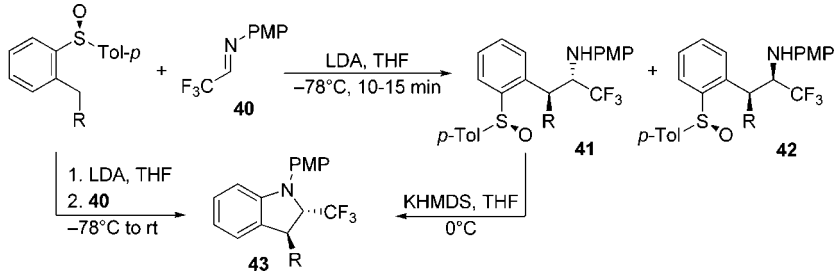
Scheme 12



R	yield, %[a]	dr, % (major isomer)
H	74	92 (2*S*, R_S):8
Ph	59	86 (2*S*, 3*S*, R_S):14[b]
Allyl	>98	73 (2*S*, 3*R*, R_S):27[b]

[a] Isolated yields of the major diastereomer
[b] Ratio of major diastereomer/sum of the 3 minor diastereomers

Scheme 13



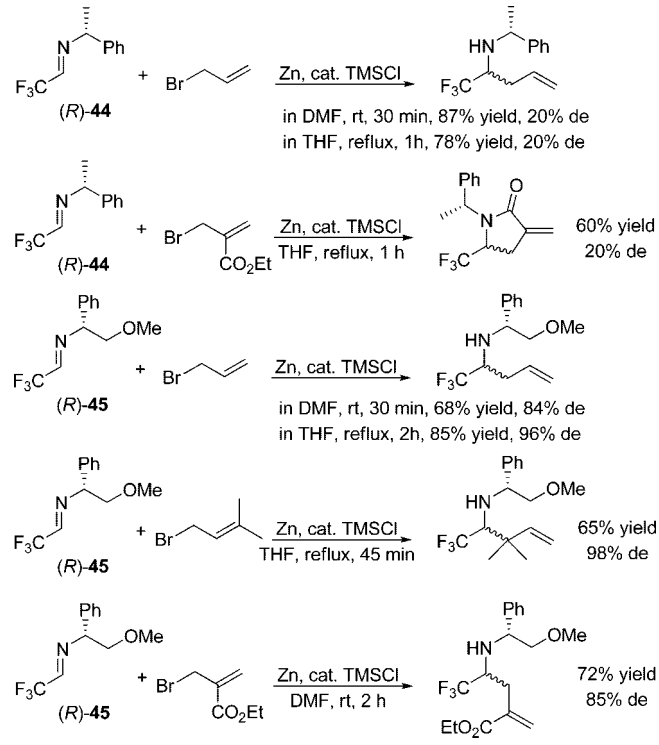
	synthesis of **41** and **42**		one pot synthesis of indolines **43**	
R	dr (**41**:**42**), %	yield, %[a]	dr (1:2), %	yield, %
H	69:31	51	–[b]	61
Me	>98:<2	71	>98:<2	61
Et	>98:<2	60	>98:<2	61
Allyl	>98:<2	51	>98:<2	61
Bn	>98:<2	74	>98:<2	71

[a] Yield of the major diastereomer
[b] In this case, ee was not determined

The synthetic route to homoallyl trifluoromethylamines through the use of organometallics complements the Lewis acid-promoted addition of allylsilanes to trifluoroacetaldehyde hemiaminals or imines (see sections 2.3.3 and 2.4.3, respectively). Crousse, Bonnet-Delpon, and co-workers demonstrated that allylation reaction of trifluoromethyl aldimines occurred under Barbier conditions with zinc (1.3 equiv) activated in situ by trimethylsilyl chloride either in dimethylformamide (DMF) at room temperature (rt) or in tetrahydrofuran (THF) at reflux. Investigation of chiral trifluoromethyl aldimine **44** synthesized from (*R*)-1-phenylethylamine produced only poor dr values, whereas the trifluoromethylaldimine **45** made from (*R*)-phenylglycinol methyl ether gave high diastereoselectivities in the range 84−96% (Scheme 14). This latter chiral auxiliary featuring a methyl ether function was chosen to prevent the formation of the less reactive oxazolidine. The absolute configuration of the new stereogenic center could not be determined.[96,110] Additional studies by the same research group using chiral imine **45** lead to the synthesis of a β-CF_3-β-amino ester by Reformatsky reaction (Scheme 15a) and a α-CF_3-α-alkylamine under Barbier conditions (Scheme 15b) with moderate diastereoselectivities of 81% and 53%, respectively.[111] Highly diastereoselective vinylation[112] by means of a Grignard reagent and alkynylation[113] with various alkynyl lithiums were also reported, de > 98% (Scheme 15c and d). Applications of these chiral fluorinated molecules include the synthesis of peptidomimetics and heterocycles.[114]

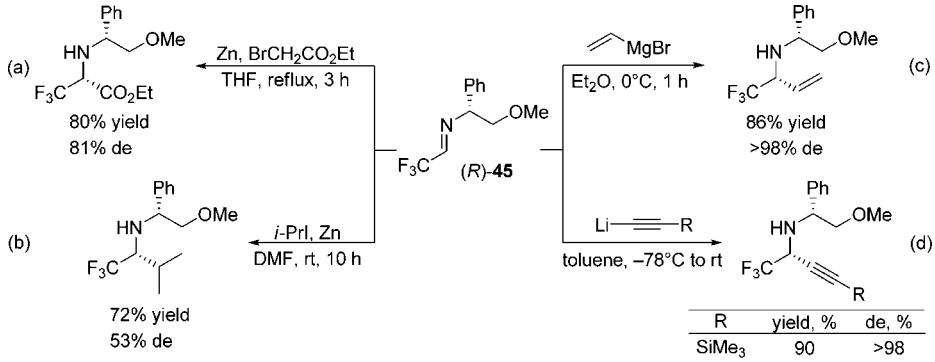
A highly diastereoselective aryllithium addition to fluoral imine **46** bearing the *O*-trialkylsilyl-(*S*)-leucinol chiral auxiliary was reported by researchers at Merck (Scheme 16).[115,116] The protecting group on the oxygen was installed

Scheme 14



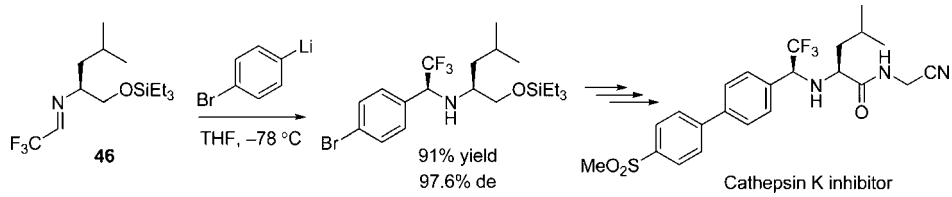
to prevent the ring closure into the corresponding oxazolidine during preparation of the substrate. This approach toward Cathepsin K inhibitors gives high diastereoselectivity, is suitable for multigram-scale synthesis, is complementary to

Scheme 15



R	yield, %	de, %
$SiMe_3$	90	>98
Bu	77	>98
Ph	95	>98

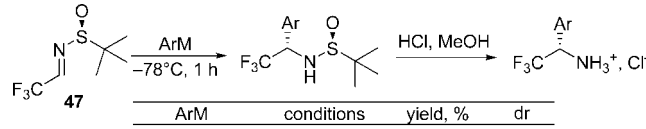
Scheme 16



the in situ generation of imines from oxazolidines described by the same authors (see section 2.3.1), and constitutes an alternative route to that involving the reductive amination of trifluoromethyl aryl ketone through a chiral imine (see section 5.2).[117]

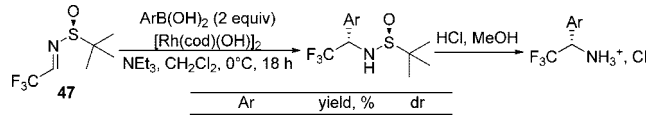
We have already seen that amino alcohols are suitable chiral auxiliaries, better than simple chiral amines, for achieving highly diastereoselective 1,2-addition of organometallic species to fluoral imines. In addition, commercially available *N*-*tert*-butanesulfinamide is a widely used chiral auxiliary by virtue of its excellent diastereocontrol and the mild conditions for its cleavage with possible recovery. Truong and co-workers synthesized sulfinyl imine **47** as a single *E*-isomer from various sources of trifluoroacetaldehyde (hydrate, methyl, or ethyl hemiacetals) in CH_2Cl_2 or toluene at 40 °C in the presence of molecular sieves and used them without purification because only poor yields were obtained when isolation was attempted. Imine **47** was reacted with phenylmagnesium bromide and various aryllithium and phenyl boronic acids to give several 1-aryl-2,2,2-trifluoroethylamines in moderate yields with high diastereoselectivities.[118,119] Lewis acid additives tended to improve both the yield and the stereoselectivity of PhMgBr addition, whereas aryllithium additions did not require additives to reach high levels of diastereoselectivity (Table 16). The obtention of the major diastereomer adduct (S,S_S) is consistent with a nonchelated transition state model even with Grignard reagent. The same group recently investigated the 1,2-addition of aryl boronic acids to chiral imine **47** catalyzed by rhodium complexes. Initial screening of rhodium catalysts showed that $[Rh(cod)(OH)]_2$ afforded the highest yields and the best diastereoselectivities. Therefore, this catalyst was used in the solvent-optimization study that revealed dichloromethane as the optimal solvent for the reaction. Organic and inorganic bases were evaluated, and triethylamine was found to be appropriate in providing the best compromise between yield and diastereoselection. Various arylboronic acids were used, and comparison with aryllithium was possible. In particular, yields of addition of arylboronic acids were higher than those of aryllithium additions and diastereomeric ratios were in the same range (Table 17). The stereochemical outcome of the reaction proceeds also through a nonchelated transition state model.

Table 16. Diastereoselective 1,2-Addition of PhMgBr and Aryllithium to Imine 47



ArM	conditions	yield, %	dr
PhMgBr	toluene	52	72:28
PhMgBr	CH_2Cl_2	54	85:15
PhMgBr	CH_2Cl_2, $AlMe_3$	51	90:10
PhMgBr	CH_2Cl_2, $TiCl_4$	11	93:7
PhLi	THF	66	98:2
4-$MeOC_6H_4Li$	THF	55	97:3
4-$MeSC_6H_4Li$	THF	53	98:2
4-FC_6H_4Li	THF	50	100:1
3,4-$F_2C_6H_4Li$	THF	36	83:17
2-MeC_6H_4Li	THF	40	99:1
pyridin-2-ylLi	THF	15	98:2

Table 17. Rhodium-Catalyzed Diastereoselective 1,2-Addition of Arylboronic Acids to Imine 47



Ar	yield, %	dr
Ph	72	95:5
4-$MeOC_6H_4$	73	91:9
4-$MeSC_6H_4$	55	97:3
4-FC_6H_4	75	97:3
4-$CF_3C_6H_4$	58	>100:1
2-MeC_6H_4	72	91:9
2-naphthyl	62	91:9
4-$NAcC_6H_4$	47	97:3
4-$CO_2MeC_6H_4$	49	97:3
4-$COMeC_6H_4$	66	93:7

Recently, Mimura and co-workers found that the vacuum distillation of (*S*)-*tert*-butylsulfinimine **47** at a low temperature (40 °C, 0.6 kPa) allowed its preparation in a highly pure form in 76% overall yield.[120] 1,2-Addition reactions of organolithium and organozinc reagents to (*S*)-sulfinimine **47**

Scheme 17

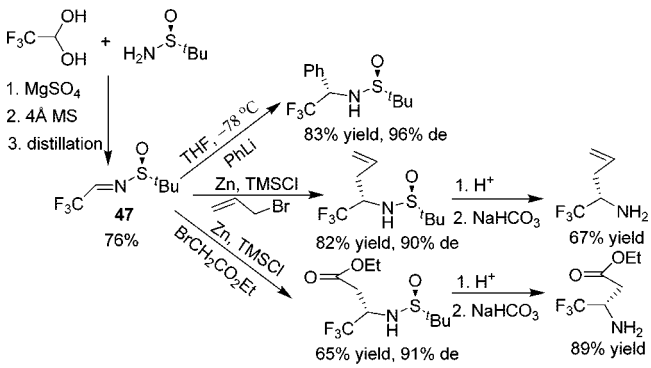
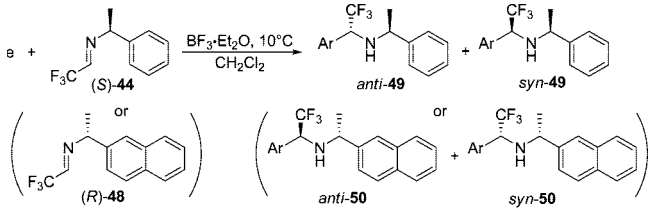
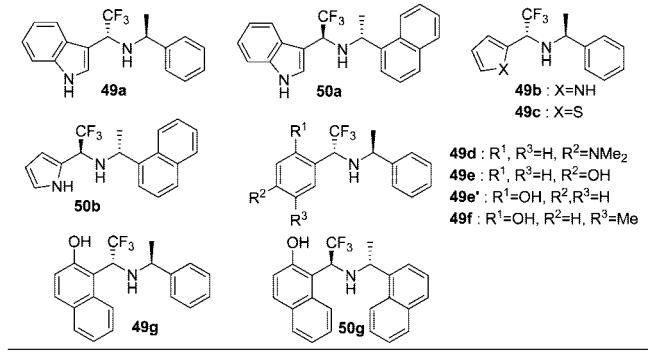


Table 18. Friedel−Crafts Reactions of Arenes with Imines 44 and 48



arene	imine	BF_3-Et_2O, mol%	time, h	product	yield, %	*anti*:*syn*
indole	**44**	10	4	**49a**	21	95:5
indole	**44**	20	4	**49a**	54	92:8
indole	**44**	50	4	**49a**	94	90:10
indole	**48**	50	4	**50a**	92	>99:1
pyrrole	**44**	50	4	**49b**	78	78:22
pyrrole	**48**	50	4	**50b**	82	82:18
thiophene	**44**	50	48	**49c**	18	64:36
thiophene	**44**	100	48	**49c**	46	64:36
$PhNMe_2$	**44**	50	12	**49d**	68	80:20
phenol	**44**	100	48	**49e** + **49e'**	57 and 10	50:50 and 97:3
4-cresol	**44**	100	60	**49f**	52	97:3
2-naphthol	**44**	100	48	**49g**	86	89:11
2-naphthol	**48**	100	48	**50g**	71	>99:1

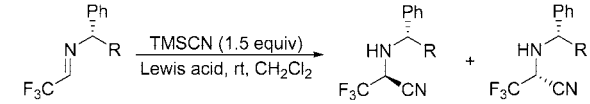


afforded the corresponding α-substituted trifluoroethylamino derivatives in good yields with high diastereoselectivities. Subsequent deprotection under acidic conditions followed by neutralization produced the free amines in good yields (Scheme 17).

2.4.2. Friedel−Crafts Reactions

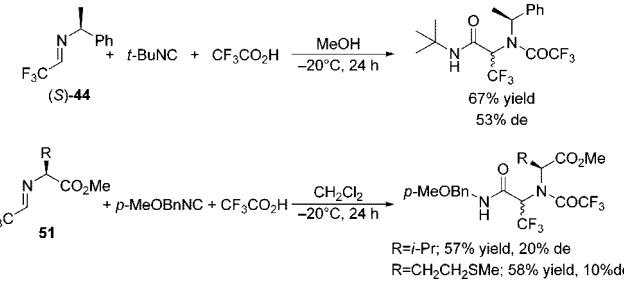
The Friedel−Crafts reactions of chiral *N*-(2,2,2-trifluoroethylidene)-1-arylamines (*S*)-**44** and (*R*)-**48** with various electron-rich aromatics were investigated by Gong and Kato in the presence of BF_3−Et_2O. The reactions proceeded at room temperature with 50−100 mol % of the Lewis acid affording the major *anti*-products (**49** and **50**) with diastereoselectivities up to >99% de (Table 18).[121] Subsequently, the selective removal of the chiral auxiliary by palladium-catalyzed hydrogenolysis conveniently gave the chiral 1-aryl-2,2,2-trifluoroethyl amines as important building blocks for pharmaceutical research.

Table 19. Strecker-Type Reactions of Imines 44 and 45



imine	Lewis acid	yield, %	dr
44	$Yb(OTf)_3$	80	50:50
45	$Yb(OTf)_3$	58	50:50
45	$MgBr_2$	62	80:20

Scheme 18



2.4.3. Strecker-Type Reactions

We have already seen the asymmetric cyanosilylation of chiral 2-trifluoromethyloxazolidines by means of trimethylsilyl cyanide with 83:17 dr at best (see section 2.3.3). The same authors also evaluated the Strecker-type reaction of imines (*S*)-**44** and (*R*)-**45**. The reactions were promoted by a Lewis acid under mild conditions; ytterbium triflate did not induce any diastereoselection, whereas magnesium bromide gave a 80:20 dr from imine **45** (Table 19).[100] However, no enhancement of the diastereoselectivity was achieved when compared to the reactions using oxazolidines.

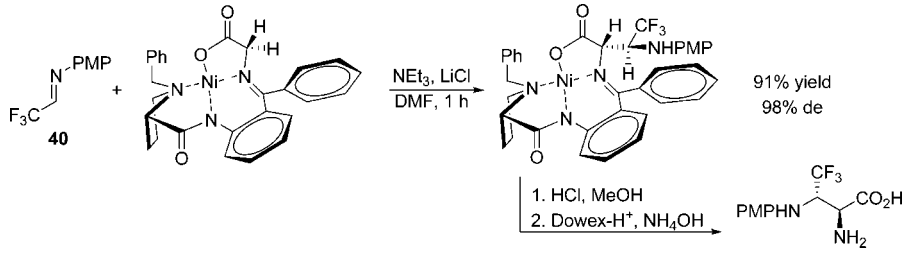
2.4.4. Ugi Reactions

The multicomponent Ugi condensation allows the rapid access to α-aminoacyl amide derivatives with a wide variety of substitution patterns. Röschenthaler, Nenajdenko, and co-workers studied the Ugi reaction with CF_3−carbonyl compounds and imines for the preparation of α-trifluoromethyl amino acids and derivatives. In particular, they have investigated the stereochemistry of the reaction using chiral imines of fluoral having either the (*S*)-α-methylbenzylamine (**44**) or an amino acid (**51**) as chiral auxiliaries. For example, the reaction with imine **44** and *tert*-butyl isocyanide in the presence of trifluoroacetic acid gave the trifluoroalanine derivative in 67% yield with a moderate 53% de (Scheme 18).[122]

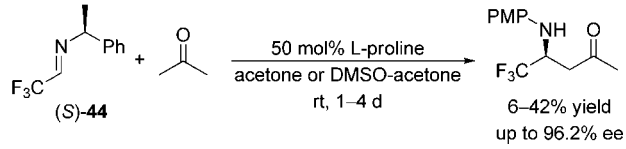
2.4.5. Mannich Reactions

The first diastereoselective Mannich-type reaction was reported by Soloshonok and co-workers in 1997. A chiral nonracemic nickel II complex of glycine Schiff base with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone served as substrate for a Mannich-type addition reaction of trifluoroacetaldehyde *N*-(*p*-methoxyphenyl)imine **40**. The reaction proceeded well in the presence of lithium chloride and triethylamine, affording the adduct in high yield and excellent diastereoselectivity (98% de) under kinetic control (Scheme 19).[123,124] Of particular importance, the addition of LiCl

Scheme 19



Scheme 20



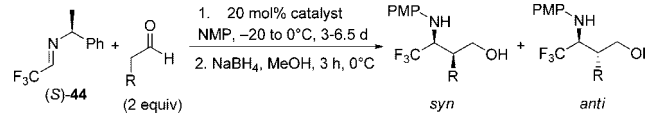
dramatically enhanced both the rate and the stereochemical outcome of the reaction. A second report mentioned an attempt of diastereoselective Mannich reaction with trifluoromethylated imine **40** and a chiral (−)-8-phenylmenthol lithium ester enolate but with only 38% de.[125]

The first organocatalyzed enantioselective Mannich reaction was reported in 2004 by Funabiki and co-workers two years before they disclosed the aldol reaction with trifluoroacetaldehyde hemiacetal (see section 2.2.2). The enantioselective organocatalytic version of this reaction was considered more attractive than the diastereoselective version, and a successful result was obtained with acetone in terms of enantioselectivity although yields were low to moderate (Scheme 20). Unfortunately, acetone was the sole ketone able to react under these conditions since other ketones such as cyclohexanone, ethyl methyl ketone, diethylketone, and acetophenone failed to react.[126] Further work in this field was realized by Fustero, Sanz-Cervera, and co-workers, who demonstrated the high efficiency of proline and derivatives in the organocatalyzed cross-Mannich condensation of fluorinated imine (*S*)-**44** with various aldehydes. The reactions proceeded with 20 mol % of the secondary chiral amine in *N*-methylpyrrolidinone between −20 and 0 °C for up to 6.5 days, followed by reduction of the crude reaction mixture to end up with the corresponding alcohols or by oxidation to get ester derivatives, with the aim being to avoid epimerization at the α-position of the aldehyde function. This way, *β*-alkyl-*γ*-amino-*γ*-trifluoromethyl alcohols and α-alkyl-*β*-amino-*β*-trifluoromethyl esters were produced in optically pure form thanks to an excellent level of enantioselection (entries 1−7, table 20).[127] Noteworthy is that proline provided *syn*-products as major diastereomers whereas diarylproline ethers **52a** and **52b** were effective organocatalyts in *anti*-selective Mannich reactions with excellent diastero- and enantiomeric excesses yet in moderate yields (entries 8−13, Table 20). This simple change in the nature of the catalyst allowed one to obtain either the *syn* or the more challenging *anti*-isomers of the target condensation products; different transition states were proposed by the authors to account for these results.[128]

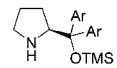
2.4.6. Aziridination

A single example of aziridination of a chiral trifluoromethylimine derived from (*R*)-phenylglycinol methyl ether was described by Higashiyama and co-workers. In this reaction,

Table 20. Organocatalyzed Mannich-Type Reactions of Imine 44 with Aldehydes

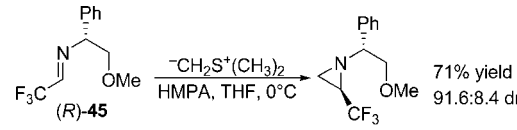


entry	R	catalyst	yield, %	*syn* : *anti*	ee, %
1	Me	L-proline	45	96:4	99
2	Me	L-proline	41	96:4	99
3	Me	L-proline	50	96:4	99
4	Me	D-proline	48	96:4	99
5	Et	L-proline	31	>99:1	99
6	Bn	L-proline	35	>99:1	99
7	Allyl	L-proline	40	96:4	99
8	Me	**52a**	41	14:86	>99
9	Et	**52a**	46	4:96	98
10	*n*-Pr	**52a**	40	3:97	>99
11	Bn	**52a**	50	8:92	98
12	Bn	**52b**	17	8:92	88
13	Allyl	**52a**	60	5:95	97



52a; Ar=Ph
52b; Ar=3,5-$(CF_3)_2C_6H_3$

Scheme 21



dimethylsulfonium methylide was generated from trimethylsulfonium iodide and *n*-butyllithium for reaction with imine **45** to end up with the trifluoromethyl aziridine in 71% yield and 83% diastereomeric excess (Scheme 21).[129] Of the examples provided in that paper, the methyl, *i*-propyl, and *t*-butyl aziridines were all obtained with >98% de; however, the rather low diastereomeric excess measured for the CF_3−aziridine product was not justified but was certainly not due to steric effects. Such a method allows access to simple nonfunctionalized aziridines unlike the case of aziridination that was already disclosed in section 2.3.4 using trifluoroacetaldehyde hemiaminal and a chiral diazoacetate.

Scheme 22

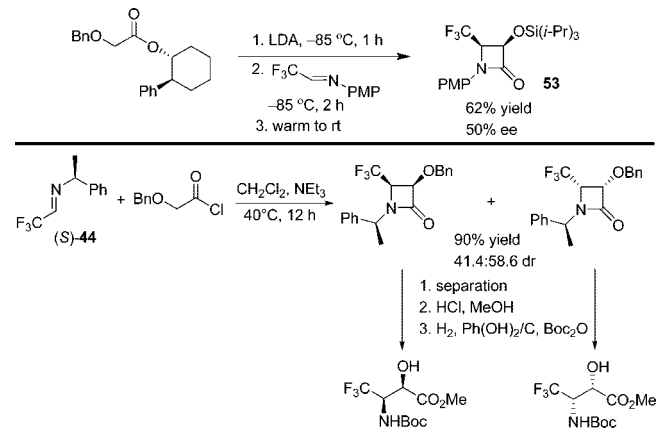
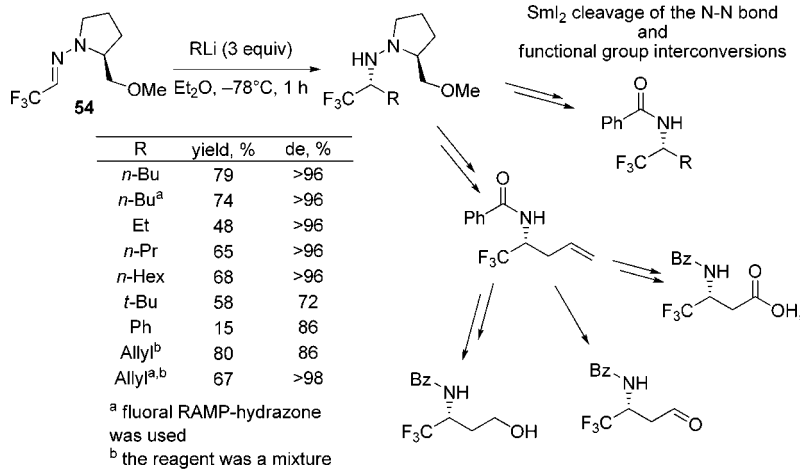


Table 21. Reaction of Trifluoroacetaldehyde SAMP- or RAMP-Hydrazone with RLi



R	yield, %	de, %
n-Bu	79	>96
n-Bu[a]	74	>96
Et	48	>96
n-Pr	65	>96
n-Hex	68	>96
t-Bu	58	72
Ph	15	86
Allyl[b]	80	86
Allyl[a,b]	67	>98

[a] fluoral RAMP-hydrazone was used
[b] the reagent was a mixture of $(Allyl)_4Sn$ (3 equiv) and PhLi (12 equiv)

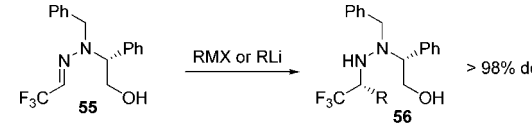
2.4.7. Staudinger Reaction

The [2 + 2]-ketene−imine cycloaddition known as the Staudinger reaction is one of the most convenient methods for the construction of the β-lactam ring. Major applications for enantiopure β-lactams are the synthesis of amino acids, dipeptides, and taxoid anticancer agents. In particular, trifluoromethyl-β-lactams served as intermediates for the preparation of fluorinated docetaxel analogues by coupling with baccatin III.[130] For example, Ojima and Slater disclosed the synthesis of *syn*-4-trifluoromethyl-β-lactam **53** with 50% ee through an inverse electron demand Staudinger-type reaction of a chiral ester−enolate with an electrophilic imine (Scheme 22, top).[131] On the other hand, the Staudinger reaction using chiral trifluoroacetaldehyde imine (*S*)-**44** and an in situ generated ketene gave a mixture of two diastereomeric *syn*-β-lactams albeit with a poor chiral induction (17% de) with the (*S*)-1-phenylethylamine auxiliary. Nevertheless, a separation of the two diastereomers by chromatography and crystallization followed by methanolysis and hydrogenolysis afforded both enantiomers of *syn*-α-hydroxy-β-trifluoromethyl-β-amino esters (*syn*-*N*-Boc-isoserinates) (Scheme 22, bottom).[130,132,133]

2.5. From Trifluoroacetaldehyde Hydrazones

Trifluoroacetaldehyde imines featuring a chiral enantiopure auxiliary present the disadvantage of being self-immolative for the auxiliary because the nitrogen atom is incorporated in the final product and the stereogenic center is lost during the removal step. In this context, the use of hydrazones constitutes a major improvement toward the recovery of the chiral auxiliary after reductive cleavage of the hydrazine N−N bond. Enders and Funabiki demonstrated the high efficiency of trifluoroacetaldehyde (*S*)- or (*R*)-1-amino-2-methyoxymethylpyrrolidine (SAMP/RAMP) hydrazones **54** in the diastereoselective synthesis of α-trifluoromethylated amines via nucleophilic 1,2-addition of organolithium reagents. Hydrazones **54** are easily prepared from trifluoroacetaldehyde ethyl hemiacetal and SAMP or RAMP in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene. They are more stable than the corresponding imines and stable enough to be purified by silica gel column chromatography. The yields were moderate to good, albeit the reaction required the use of 3 equiv of alkyl- or phenyllithium; nevertheless, the diastereomeric excesses were high to very high (Table 21).[134,135] Further development by Funabiki and co-workers allowed access to both enantiomers of α-trifluoromethylated homoallylamine (R = allyl, Table 21), and different functional group interconversions were carried out to provide β-trifluoromethylated-β-amino alcohol, aldehyde, and carboxylic acid derivatives (Table 21).[136−138]

Table 22. Reaction of Trifluoroacetaldehyde Hydrazone 55 with RM



RM (equiv)	conditions	yield, %
n-BuLi (2.2)	THF, –78 °C, 2 h	37
n-BuMgCl (2.2)	THF, –78 °C, 2 h, then rt, 12 h	44
n-BuMgCl (3.3)	THF, –40 °C, 3 h, then rt, 3 h	58
VinylMgCl (4)	THF, –78 °C, 30 min, then rt, 3 h	23
VinylMgCl (3.3)	THF, –50 °C, 2 h, then rt, 4 h	47
n-BuLi (3)	Et_2O, –30 °C, 4 h	65
VinylMgCl (3)	Et_2O, –30 °C, 4 h	75
BnMgCl (3)	Et_2O, –30 °C, 4 h	68

The addition of organometallic reagents to hydrazones, which derived from amino alcohols possessing a free hydroxyl group, is known to proceed with high stereoselectivity; thus, Brigaud and co-workers studied the addition of organolithium and Grignard reagents to a (*R*)-phenylglycinol-derived trifluoromethylhydrazone **55**. Here again, an excess of organometallics was required, with 1 equiv being consumed to generate the alkoxide of the phenylglycinol auxiliary. Addition products **56** were obtained in moderate yields with diastereoselectivities > 98% (Table 22).[139] Removal of the chiral auxiliary was done through controlled hydrogenolysis of hydrazines **56**; however, the chiral auxiliary was not recovered.

3. Asymmetric Reaction of Prochiral 3,3,3-Trifluoropyruvates and Derivatives

Trifluoropyruvates and derivatives (Figure 7, **F**−**I**) are very valuable C3 synthons for construction of trifluoromethyl compounds. They are considerably stable at room temperature as well as not sensitive to atmosphere and humidity, thus, they are easy to handle and readily accessible. Moreover, the trifluoropyruvates and derivatives are characterized by a very electrophilic carbon atom bearing the

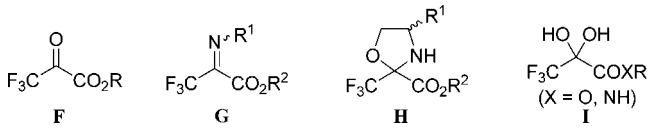
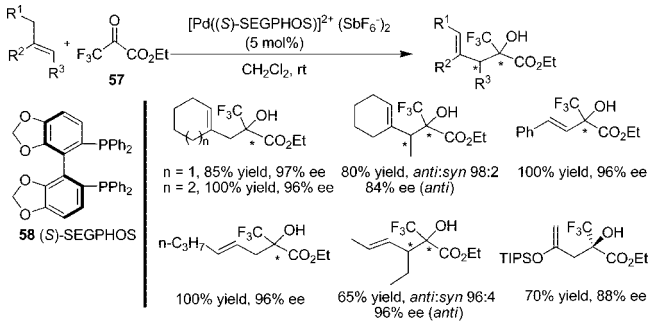


Figure 7. Trifluoropyruvates and derivatives.

Scheme 23



electron-withdrawing groups (CF_3 and CO_2R), thus allowing easy reaction with nucleophilic reagents.

3.1. From Trifluoropyruvates

Methyl and ethyl trifluoropyruvates are the most commonly used substrates, which are liquid at ambient temperature with boiling points of 85 and 95 °C, respectively. There are some available pathways for their preparation. One is from hexafluoropropene oxide and alcohol via decomposition of resulting tetrafluoropropanoate in the presence of sulfuric acid or strong Lewis acid.[140−143] Alternatively, the condensation of oxalate with trifluoromethyl bromide with the aid of zinc powder in pyridine is another synthetic route to trifluoropyruvates.[144]

3.1.1. Carbonyl−Ene Reactions

The carbonyl−ene reaction is an important carbon−carbon formation process for the atom-economic construction of chiral tertiary alcohols with homoallylic moiety.[145,146] The use of ketone in asymmetric catalytic carbonyl−ene reaction is limited due to lower reactivity of the ketone compared with aldehyde. Mikami and co-workers reported successful ketone−ene reactions catalyzed by dicationic SEGPHOS−Pd(II) complex, derived from SEGPHOS **58**, $PdCl_2(CH_3CN)_2$, and $AgSbF_6$, facilitating the asymmetric synthesis of chiral tertiary α-CF_3 carbinols with homoallylic functionality.[147−149] Ethyl trifluoropyruvate **57** was utilized as an appropriate enophile, which was vital for accelerating electrophilic attack on less reactive olefins. Significantly, mono- and 1,2-substituted olefins proceeded smoothly to give the corresponding products in good to high yields with high enantioselectivities and diastereoselectivities, along with (*E*)-selectivity for the olefin moiety (Scheme 23).

Shortly afterward, the same group demonstrated that the enantiopure *atropos* BIPHEP−Pt(II) complex [BIPHEP **59**: 2,2′-bis(diphenylphosphanyl)biphenyl], obtained from resolving racemic *tropos* BIPHEP−Pt(II) complex with (*R*)-2,2′-bis(trifluoromethane sulfonylamino)-1,1′-binaphthyl or (*R*)-2,2′-diamino-1,1′-binapthyl, can promote ketone−ene reactions of ethyl trifluoropyruvate with monosubstituted olefins in high yields and stereoselectivities (Scheme 24).[150]

Doherty, Knight, and co-workers reported a detailed study of asymmetric carbonyl−ene reactions between mono-, di-, or trisubstituted alkenes with ethyl trifluoropyruvate by using

Scheme 24

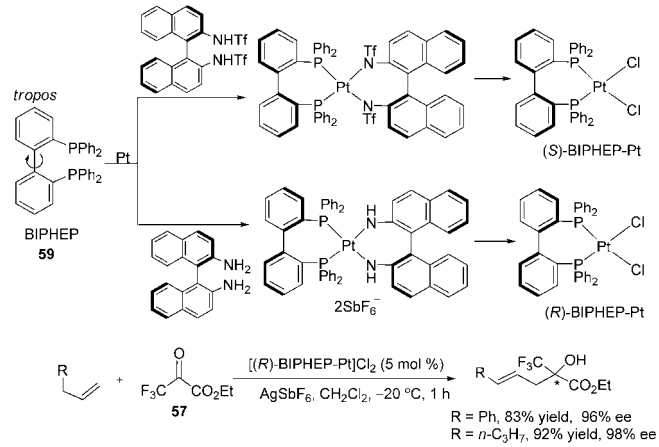
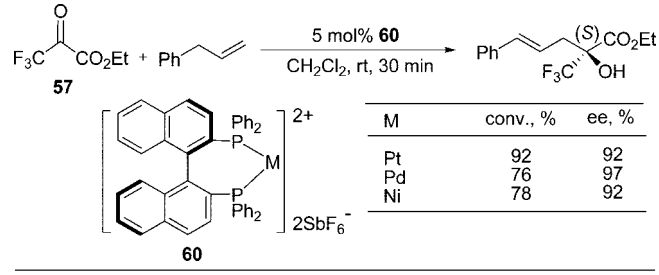


Table 23. Asymmetric Carbonyl−Ene Reaction of Allyl Benzene with Ethyl Trifluoropyruvate

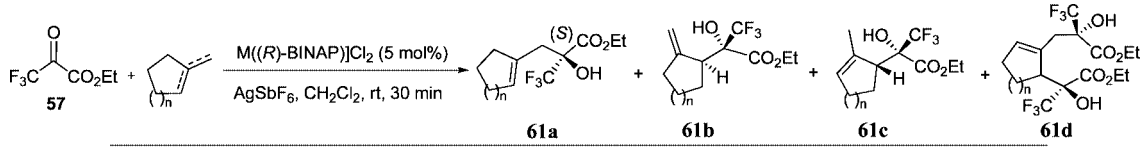


M	conv., %	ee, %
Pt	92	92
Pd	76	97
Ni	78	92

three metal complexes **60** [M((*R*)-BINAP)]$(SbF_6)_2$ (M = Pd, Pt, Ni).[151] In the reaction of allyl benzene with ethyl trifluoropyruvate, each of the catalysts gave good conversions, which increase in the order Pt > Ni ≈ Pd, complete *E* selectivity, and excellent enantioselectivities (Table 23). For 1,1-disubstituted or trisubstituted alkenes, Pd(II) complex provided the expected ene-products **61** in good yields with excellent stereoselectivies (Table 24). In contrast, the Pt- and Ni-complexes catalyzed the same reactions to afford a mixture of α-hydoxy esters arising from alkene isomerization followed by ene reaction as well as from the postreaction isomerization of the ene product. In addition, Pt- and Ni-complexes also promoted two consecutive ene reactions to afford double carbonyl−ene products **61d**. The absolute configuration of **61a** was assigned as (*S*) and is consistent with a *Re* face attack as shown on model **A** (Table 24). In this model, the chiral catalyst is coordinated to trifluoropyruvate, forming a square-planar geometry. The phenyl rings prevent the approach of the alkene to the *Si* face of coordinated trifluoropyruvate, thus rendering favorable *Re* face attack to give the (*S*)-isomer. The high diastereoselectivities for **61b** can be attributed to a preferential *exo* approach to avoid steric interactions between alkene and phenyl rings in the *endo* approach (Table 24, models **B** and **C**).

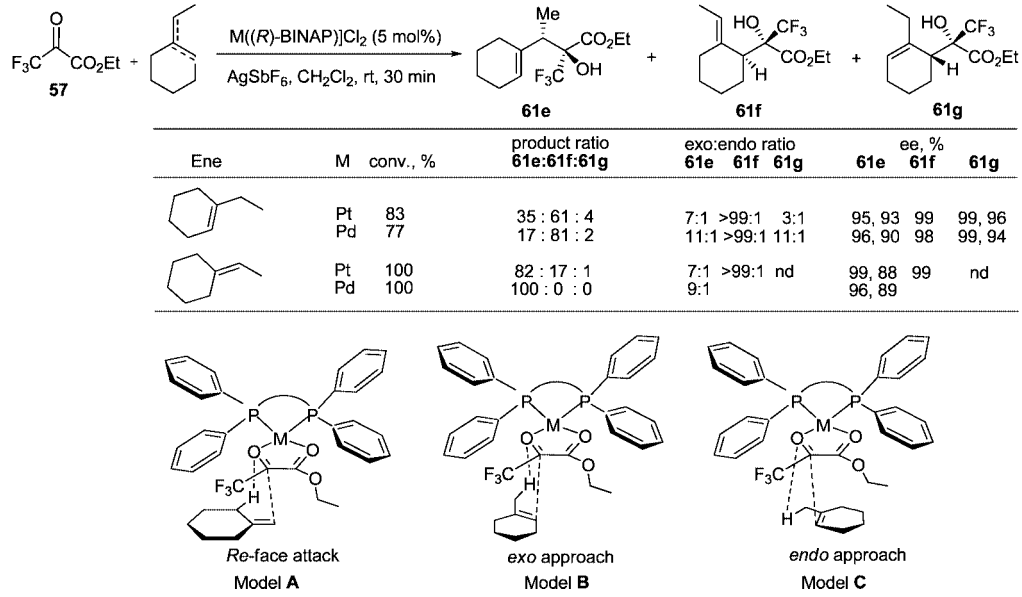
In 2007, ene reactions of α-methylstyrenes with ethyl trifluoropyruvate were discussed by the same group.[152] In this case, carbonyl−ene reaction, dimerization of olefin, along with Friedel−Crafts reaction were altogether catalyzed by M[(*R*)-BINAP] complexes, giving a mixture of products **62a−d** in which regioselectivities were determined by the nature of the metal centers. The palladium complex was entirely selective for the ene reaction, furnishing chiral trifluoromethylated tertiary alcohols in full conversions with good enantioselectivities (up to 88% ee) (Table 25).

Table 24. Asymmetric Carbonyl−Ene Reactions of 1,1-Disubstituted or Trisubstituted Alkenes with Ethyl Trifluoropyruvate



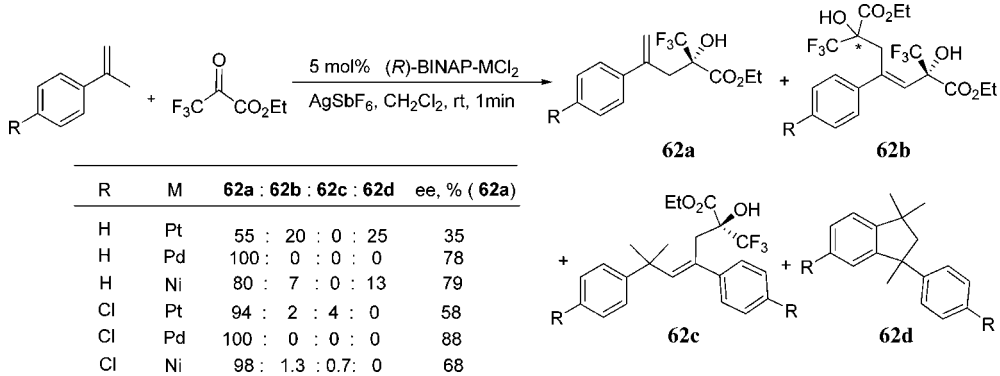
Ene	M	conv., %	product ratio 61a:61b:61c:61d	exo:endo ratio 61b	exo:endo ratio 61C	ee, %[a] 61a	ee, %[a] 61b	ee, %[a] 61c	de, % 61d
	Pt	100	38 : 47 : 10 : 5	>99:1	1:2	77	99	99, 98	91
	Pd	100	100 : 0 : 0 : 0			93			
	Ni	100	57 : 40 : 2 : 1	>99:1	1:2	74	99	86, 82	92
	Pt	99	2 : 91 : 7 : 0	>99:1	1:2	78	99	99, 96	
	Pd	93	1 : 81 : 5 : 0	>99:1	3:1	96	99	99, 94	
	Ni	100	1 : 98 : 1 : 0	>99:1	3:1	77	99	79, 84	
	Pt	100	7 : 68 : 15 : 10	>99:1	3:1	72	99	97, 95	92
	Pd	100	98 : 2 : 0 : 0	>99:1		96	99		
	Ni	98	45 : 26 : 19 : 10	>99:1	7:3	73	99	95, 94	89
	Pt	100	4 : 75 : 16 : 5	>99:1	3:1	69	99	96, 95	89
	Pd	100	4 : 89 : 8 : 0	>99:1	4:1	99	99	92, 91	
	Ni	98	1 : 54 : 32 : 14	>99:1	3:1	76	99	98, 96	80

[a] ee % of **61c** expected as ee % exo and ee % endo.



Ene	M	conv., %	product ratio 61e:61f:61g	exo:endo ratio 61e	61f	61g	ee, % 61e	61f	61g
	Pt	83	35 : 61 : 4	7:1	>99:1	3:1	95, 93	99	99, 96
	Pd	77	17 : 81 : 2	11:1	>99:1	11:1	96, 90	98	99, 94
	Pt	100	82 : 17 : 1	7:1	>99:1	nd	99, 88	99	nd
	Pd	100	100 : 0 : 0	9:1			96, 89		

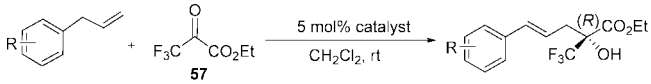
Table 25. Asymmetric Carbonyl−Ene Reactions of α-Methylstyrenes with Ethyl Trifluoropyruvate Catalyzed by M(II)(*R*)-BINAP Complexes



R	M	62a : 62b : 62c : 62d	ee, % (62a)
H	Pt	55 : 20 : 0 : 25	35
H	Pd	100 : 0 : 0 : 0	78
H	Ni	80 : 7 : 0 : 13	79
Cl	Pt	94 : 2 : 4 : 0	58
Cl	Pd	100 : 0 : 0 : 0	88
Cl	Ni	98 : 1.3 : 0.7: 0	68

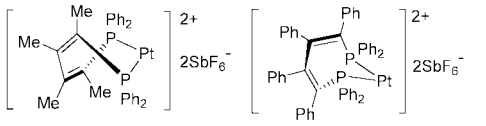
Doherty, Knight, and co-workers also described the application of conformationally flexible 1,4-bis(diphenylphosphino)-1,2,3,4-tetrasubstituted-1,3-butadienes and NUPHOS diphosphines as efficient ligands for enantioselective carbonyl−ene reactions with ethyl trifluoropyruvate, giving similar or higher levels of asymmetric induction than that obtained with atropisomeric BINAP counterpart.[153] Among these new catalytic systems **63a−d**, the platinum complex **63c** has proven to be the most promising in terms of enantioselectivity and conversion. A variety of phenyl-substituted allylbenzene derivatives (Table 26) as well as methylenecycloalkanes, 1-methylcycloalkanes, and 2,4,4-trimethylpent-1-ene (Table 27) were investigated as substrates, generally affording the corresponding carbonyl−ene products (**61a−d**, and **65**) in good to high yields with up to 99% ee. In addition, novel tropos biaryl diphosphine ligands

Table 26. Asymmetric Carbonyl−Ene Reaction between Allylbenzene Derivatives and Ethyl Trifluoropyruvate Catalyzed by Pt NUPHOS, BINAP, or NU-BIPHEP Complexes



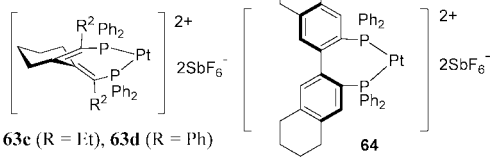
R	catalyst[a]	conv., %	ee, %	R	catalyst[a]	conv., %	ee, %
H	**63a**	64	98	4-Cl	**63a**	61	98
H	**63b**	20	93	4-Cl	**63c**	73	>99
H	**63c**	79	99	4-Cl	**60**	74	>99
H	**63d**	17	94	4-Cl	**64**	60	>99
H	**60**	92	99	2-Cl	**63a**	58	96
H	**64**	67	99	2-Cl	**63c**	66	98
4-Me	**63a**	74	95	2-Cl	**60**	62	98
4-Me	**63c**	79	96	2-Cl	**64**	71	99
4-Me	**60**	90	93	3-Cl	**63a**	83	95
4-Me	**64**	63	99	3-Cl	**63c**	79	99
2-Me	**63a**	51	97	3-Cl	**60**	83	>99
2-Me	**63c**	77	99	3-Cl	**64**	66	99
2-Me	**60**	81	96	4-NO_2	**63a**	84	99
3,5-Me_2	**63a**	95	96	4-NO_2	**63c**	86	>99
3,5-Me_2	**63c**	89	90	4-NO_2	**60**	92	>99
3,5-Me_2	**60**	94	93	4-NO_2	**64**	98	99

[a] **60** (M = Pt)



63a

63b



63c (R = Et), **63d** (R = Ph)

64

NU-BIPHEP were synthesized and applied to the asymmetric carbonyl−ene reaction of ethyl trifluoropyruvate. Treatment of a series of allylbenzenes with 5 mol % platinum complex **64** gave chiral trifluoromethyl tertiary alcohols in 60−98% yields with exceptionally high enantioselectivities (>99% ee) (Table 26).[154]

In 2009, the indium(III)−PyBox (**66**) catalyzed carbonyl−ene reaction of methyl trifluoropyruvate was described by Loh and co-workers.[155] Screening of counterions indicated that they have a marked influence on yields and enantioselectivities. Strong electronegative and less coordinating anion SbF_6^- gave the best results. By combining 10 mol % In(III)−PyBox with 20 mol % $AgSbF_6$ and 4 Å molecular sieves in dichloroethane (DCE), both aromatic and aliphatic 1,1-disubstituted alkenes furnished the trifluoromethylated products in good to high yields and enantioselectivities (Table 28). This reaction illustrates the potential application of stable and easily accessible indium-based Lewis acid catalysts for asymmetric carbonyl−ene reactions.

Recent years have witnessed an explosive growth in the field of organocatalysis, and numerous chiral organocatalysts have been designed and developed for various asymmetric reactions. In this context, Clarke and co-workers reported the first organocatalytic carbonyl−ene reaction of ethyl trifluoropyruvate with various alkenes by means of a chiral enantiopure thiourea **67** although with low enantioselectivity, up to 33% ee (Scheme 25).[156]

Much higher enantioselectivities were reached when using BINOL-derived chiral phosphoric acids[157] as illustrated by the work of Rueping's group in 2008.[158] Chiral phosphoric acid-derived *N*-triflylphosphoramides have been used as very acidic Brønsted acids for the noncovalent activation of the carbonyl group of ethyl trifluoropyruvate. Screening of catalysts revealed that H_8−BINOL-derived *N*-triflylphosphoramide **68** gave the best result. A broad range of α-methylstyrene derivatives were used, leading to α-trifluoromethylated α-hydroxyesters in good to high yields with excellent enantioselectivities (92−97% ee) (Table 29). The enantioselectivity was kept at high levels even with as low as 0.1 mol % catalyst loading.

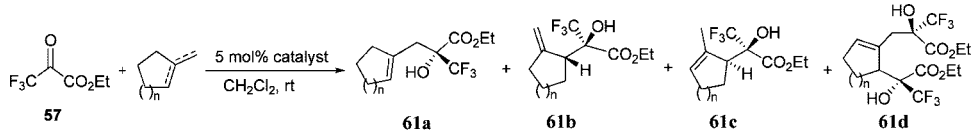
3.1.2. Aldol Reactions

Trifluoropyruvates are nonenolizable ketones and more electrophilic than ethyl pyruvate due to the electron-withdrawing trifluoromethyl group. Trifluoropyruvates and derivatives are often used in many asymmetric aldol reactions. To construct fluorinated peptidomimetic molecules, Zanda and co-workers designed a stereoselective aldol reaction to build α-Tfm-malic units.[159] In a diastereoselective fashion, ethyl trifluoropyruvate smoothly reacted with (*S*)-*N*-acyloxazoline-2-ones **69** in the presence of $TiCl_4$/*i*-Pr_2EtN, affording *syn* and *anti* "non-Evans" diastereomers of four possibilities with low to good stereoselectivity (Scheme 26). The predominant *anti*-diastereomer was rationalized by an "open" TS, wherein the titanium enolate of oxazolidinone was attacked by trifluoropyruvate from the *Re* face. However, this strategy was not practical because of difficult cleavage of the auxiliary and difficult isolation of the stereochemically pure malic units. Subsequently, the same group switched the chiral auxiliary from (*S*)-*N*-acyloxazolidin-2-one to (*S*)-*N*-acyloxazolidin-2-thione, likewise providing the *anti* "non-Evans" diastereomer as the major product in low diastereomeric ratio. The aldol adducts were then subjected to the cleavage of the oxazolidine-2-thione auxiliary under mild conditions. For instance, the *syn*-diastereomer was transformed to the target CF_3 peptidomimetic compound **70** (Scheme 26). Unfortunately, the preliminary study showed a lower inhibitory activity compared to the nonfluorinated analogue.[18]

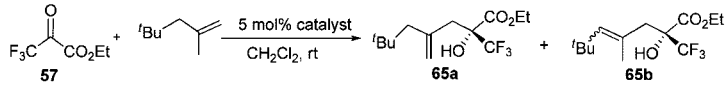
Considering the different electrophilic reactivities between nonfluorinated α-ketoesters and a nonenolizable trifluoropyruvate, Jørgensen and co-workers developed a chiral Lewis acid-promoted asymmetric cross-aldol reaction of α-ketoesters with ethyl trifluoropyruvate.[160] In the presence of 10 mol % (*S*)-*t*-Bu-Box-Cu$(OTf)_2$, the cross-aldol reaction of ethyl pyruvate with ethyl trifluoropyruvate proceeded well in Et_2O with good conversion, but a low enantioseletivity (42% ee) was observed. It is interesting to note that the use of α-ketoesters with substituents at the β-position led to full conversions and high enantioselectivities, albeit with low diastereoselectivities (Table 30). However, the reason for the moderate yields is the result of the formation of isotetronic acid derivatives from the cross-aldol adduct **71**. Moreover, poor ee values were detected for the isotetronic acid derivatives. This observation suggests that two isomers (major) of four diastereomers could have the same absolute configuration at C-3.

The synthetic application of trifluoropyruvates in asymmetric Henry reaction is relatively rare. One example of chiral Lewis acid-promoted enantioselective Henry reaction was attempted by Xu and co-workers.[161,162] Ethyl trifluoropyruvate was reacted with nitromethane in the presence of Et_3N and ligands **72a**−**b** to give the aldol product with 23% ee and 13% ee, respectively (Scheme 27). Both bis(oxazoline)−Cu(II) complex and bis(thiazoline)−Cu(II) complex showed different catalytic activities. Moreover, the yields of trifluoropyruvate were generally lower than that of the "non-fluorinated" analogues.

Table 27. Asymmetric Carbonyl−Ene Reaction of Ethyl Trifluoropyruvate Catalyzed by Pt NUPHOS or BINAP Complexes

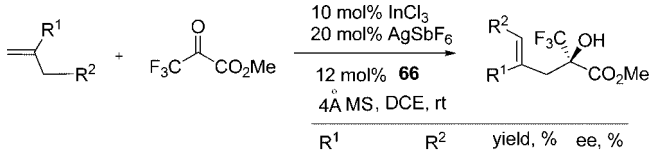


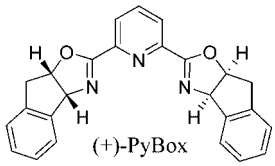
Ene	catalyst	conv., %	61a:61b:61c:61d	exo:endo ratio 61b	exo:endo ratio 61C	ee, % 61a	ee, % 61b	ee, % 61c	de, % 61d
	63a	100	13 : 63 : 18 : 6	>99:1	5:1	61	>99	83, nd	89
	63b	99	7 : 57 : 36 : 0	>99:1	9:1	52	80	58, nd	
	63c	100	11 : 63 : 20 : 6	>99:1	6:1	70	>99	89, nd	91
	63d	65	6 : 64 : 30 : 0	>99:1	2:1	64	80	52, nd	
	63a	100	45 : 49 : 4 : 3	>99:1	1:1	63	99	93, nd	
	63b	>99	20 : 75 : 5 : 0	>99:1	1:1	41	92	99, 99	89
	63c	>99	43 : 55 : 1 : 1	>99:1	3:2	70	>99	99, 99	
	63d	94	26 : 70 : 2 : 0	>99:1	2:1	35	94	64, 55	
	63a	100	0 : 80 : 19 : 0	>99:1	8:1		99	79, nd	93
	63b	65	1 : 63 : 36 : 0	>99:1	3:1	82	80	42, nd	
	63c	100	0 : 75 : 21 : 4	>99:1	8:1		>99	93, 94	89
	63a	96	4 : 93 : 3 : 0	>99:1	2:1	66	98	88, 87	
	63b	25	4 : 95 : 0 : 0	>99:1	2:1	35	93		
	63c	98	4 : 95 : 1 : 0	>99:1	2:1	74	>99	92, 95	



catalyst	conv., %	65a:65b	ee, % (65a)
63a	>99	88:12	98
63b	98	90:10	93
63c	>99	89:11	99
63d	99	91:9	94
60	99	86:14	99

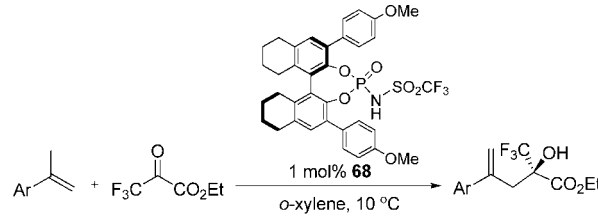
Table 28. In(III)−PyBox Catalyzed Carbonyl−Ene Reaction of Methyl Trifluoropyruvate





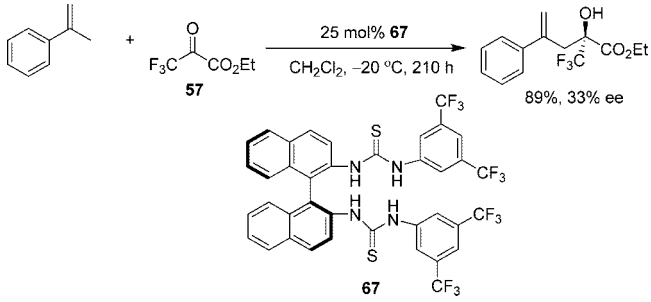
R^1	R^2	yield, %	ee, %
C_6H_5	H	99	95
3-MeC_6H_4	H	99	94
4-MeC_6H_4	H	99	94
2-FC_6H_4	H	56	87
4-FC_6H_4	H	92	92
4-ClC_6H_4	H	90	95
4-BrC_6H_4	H	97	91
2-Naphthyl	H	99	95
2-$MeOC_6H_4$	H	86	85
3-$MeOC_6H_4$	H	99	95
4-$MeOC_6H_4$	H	99	64
-C_4H_8-		95	98
-C_3H_6-		94	98
Me	H	99	64

Table 29. Chiral Phosphoric Acid Catalyzed Enantioselective Carbonyl−Ene Reactions



Ar	yield, %	ee, %	Ar	yield, %	ee, %
Ph	76	96	*p*-^{i}PrC$_6$H$_4$	85	92
p-MeC_6H_4	92	96	*p*-$MeOC_6H_4$	69	92
m-MeC_6H_4	91	96	*p*-EtC_6H_4	96	95
p-FC_6H_4	88	92	*p*-^{t}BuC$_6$H$_4$	83	94
2-naphthyl	95	95	*m,p*-$Me_2C_6H_3$	92	92
biphenyl	87	97	*p*-BrC_6H_4-C_6H_4	87	96
indanyl	93	95	*p*-IC_6H_4	89	97
tetralinyl	96	95	*p*-BrC_6H_4	71	93
p-ClC_6H_4	55	93			

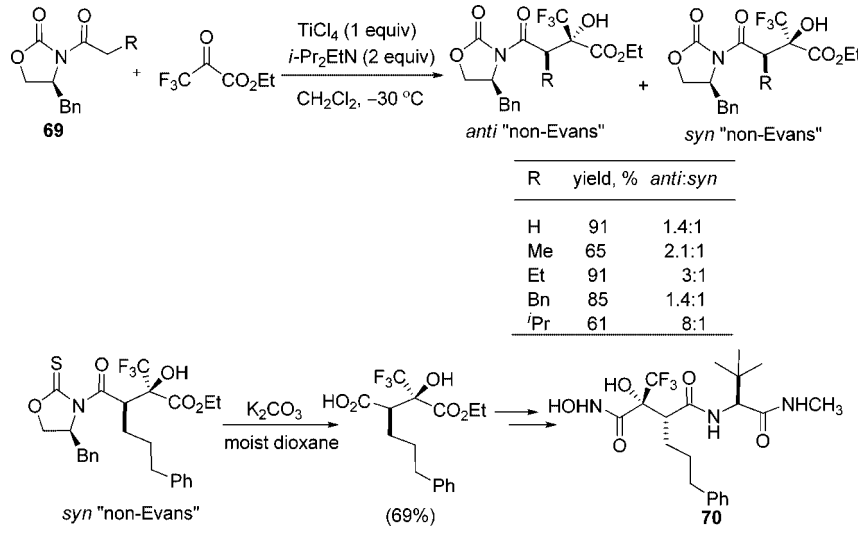
Scheme 25



As the simplest enzyme, (*S*)-proline is a milestone in the field of organocatalysis because of its high efficiency and wide application. Barbas III and co-workers reported the proline-catalyzed cross-ketone aldol reaction for the de novo synthesis of carbohydrates.[163] As a complementary application, trifluoropyruvate was selected as the acceptor in this direct aldol reaction. The screening of catalysts revealed (*S*)-proline to be optimal, giving the *anti*-adduct as the major diastereomer with up to 99% ee. In addition, water proved to be beneficial for diastereoselectivity, albeit at a cost of yield. Thus, the efficiency of this reaction was unsatisfactory (Table 31).

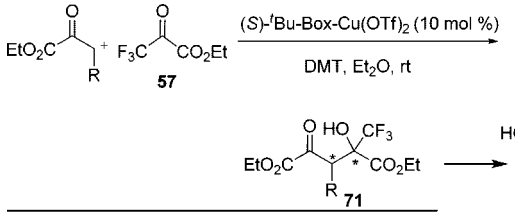
Recently, Landge and Török disclosed microwave-assisted asymmetric aldol reactions of ethyl trifluoropyruvate with ketones in the presence of 30 mol % (*S*)-proline.[164] Compared with standard conditions, the use of microwave irradiation at subzero temperatures (−25 °C) gave more satisfactory results. A series of trifluoromethylated aldol products **73** were obtained in high yields and moderate to high stereoselection (Table 32).

Scheme 26



R	yield, %	*anti*:*syn*
H	91	1.4:1
Me	65	2.1:1
Et	91	3:1
Bn	85	1.4:1
^{i}Pr	61	8:1

Table 30. Cross-Aldol Reaction of α-Ketoesters with Ethyl Trifluoropyruvate Catalyzed by Chiral BOX−Copper Complex



		aldol adduct **71**		
R	time, h	yield, %	dr	ee, %
Me[a]	48	40	1 : 1.8	89, 92
CH_2-*c*-C_6H_{11}	72	32	1 : 1.2	68, 84
$CH_2CH_2CH{=}CH_2$	144	52	1 : 1.4	85, 96
n-C_5H_{11}	110	28	1 : 1.2	92, 91
i-Bu[b]	74	66	1 : 1.2	62, 75

[a] at −15 °C. [b] at −24 °C.

Scheme 27

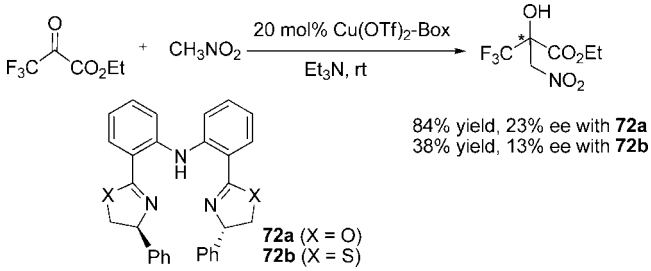
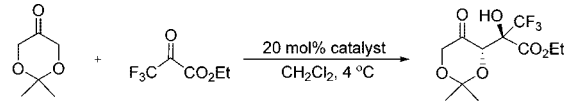


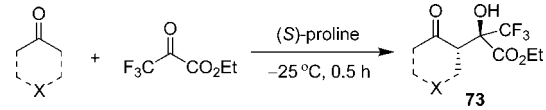
Table 31. Proline-Catalyzed Stereoselective Cross-Aldol Reaction



catalyst	additive	time, h	yield, %	*anti*:*syn*	ee, %
(*S*)-proline	--	48	41	85:15	>99, 38
(*S*)-proline	--	264	83	87:13	>99, 54
(*S*)-proline	H_2O (5 equiv.)	48	3	>95:1	>99
(*S*)-2-pyrrolidine-tetrazole	--	48	39	79:21	58, 75
(*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine	TFA (1 equiv.)	48	11	87:13	>99, 37

In addition to ketones, aldehydes were also used as donors with ethyl trifluoropyruvate in direct catalytic aldol reactions. Jørgensen and co-workers reported an enantioselective pro-

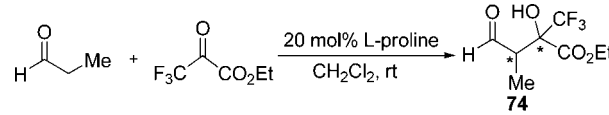
Table 32. Microwave-Assisted Proline-Catalyzed Aldol Reaction of Ethyl Trifluoropyruvate with Ketones



ketone	condition	yield, %	de, %	ee, %
cyclohexanone	standard [a]	49	95	98
	MW	91	97	98
dihydro-2*H*-thiopyran	standard	86	66	25
-4(3*H*)-one	MW	55	87	92
dihydro-2*H*-pyran	standard	2	-	-
-4(3*H*)-one	MW	86	98	99
t-butyl 4-oxopiperidine	standard	5	84	11
-1-carboxylate	MW	76	96	86
4,4-dimethylcyclo	standard	79	60	64
-hexanone	MW	42	88	70
2,2-dimethyl-1,3	standard	3	-	-
-dioxan-5-one	MW	53	70	80
1,4-dioxaspiro[4.5]	standard	88	80	60
-decan-8-one	MW	87	94	94
cyclopentanone	standard [b]	23	60	78
	MW	92	96	80
acetone	standard [b]	95	-	46
	MW	94	-	50
pentan-3-one	standard	traces	-	-
	MW	20	92	99

[a] −78 °C for 48 h. [b] −78 °C for 24 h

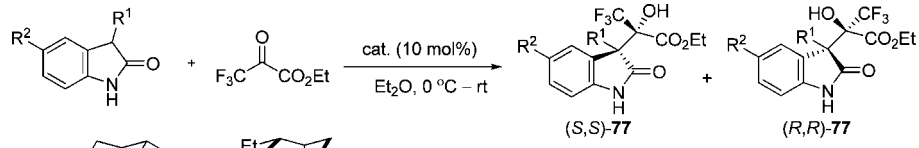
Scheme 28

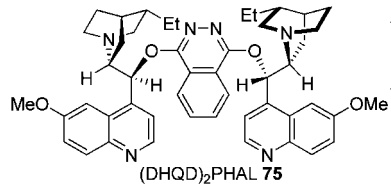


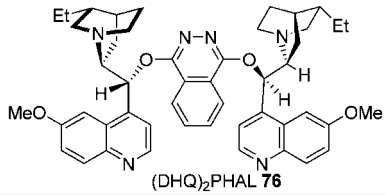
line-catalyzed cross-aldolization of propanal with ethyl trifluoropyruvate. Trifluoromethylated aldol product **74** was obtained in 98% yield with good enantioselectivity, albeit with low diastereoselectivity (Scheme 28).[165]

Cinchona alkaloids are relatively inexpensive, commercially available, and naturally occurring chiral materials. These alkaloids and derivatives have been widely applied in the field of asymmetric synthesis. For example, Shibata, Toru, and co-workers developed a highly enantioselective aldol reaction of oxindoles with ethyl trifluoropyruvate.[166] In the presence of $(DHQD)_2PHAL$ **75** or $(DHQ)_2PHAL$ **76**, both enantiomers of trifluoromethylated oxindole adducts **77**

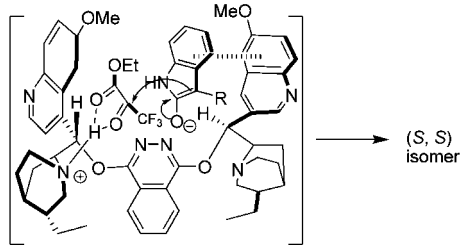
Table 33. Aldol Reaction of Oxindoles with Trifluoropyruvate Catalyzed by Cinchona Alkaloids







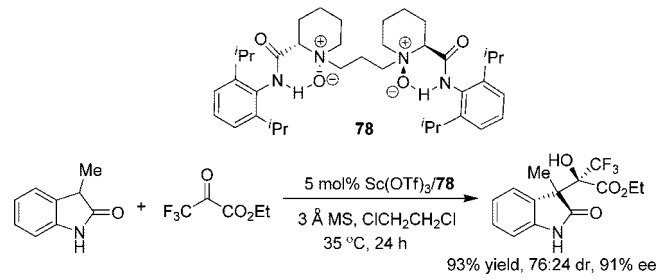
		(*S*,*S*)-**77** [(DHQD)$_2$PHAL]			(*R*,*R*)-**77** [(DHQ)$_2$PHAL]		
R^1	R^2	yield, %	dr	ee, %	yield, %	dr	ee, %
Me	H	99	90:10	95	99	88:12	94
Et	H	90	94:6	95	99	88:12	99
Bn	H	97	89:11	96	95	95:5	98
4-BrC$_6$H$_4$CH$_2$	H	93	86:14	92	90	97:3	98
4-MeC$_6$H$_4$CH$_2$	H	89	89:11	99	81	94:6	97
4-ClC$_6$H$_4$CH$_2$	H	99	90:10	98	99	94:6	99
Et	Me	94	92:8	95	97	95:5	90
Bn	Me	75	85:15	95	78	92:8	95
BocNHCH$_2$CH$_2$	H	99	88:12	79	82	90:10	79
CbzNHCH$_2$CH$_2$	H	91	90:10	83	83	91:9	84
BnNHCH$_2$CH$_2$	H	41	70:10	0	27	71:9	1



could be accessible with high diastereoselectivities and excellent enantioselectivities in most cases (Table 33). Surprisingly, when oxindoles with 3-amidoethyl substituents were used as substrates, a drop-off of enantioselectivity was observed, whereas 3-benzylaminoethyloxindole gave a racemate product, apparently owing to the basicity of the amino moiety. With regard to the reaction mechanism, the intermediate for the *S*,*S*-selective formation of oxindole adducts under the catalysis of (DHQD)$_2$PHAL is presumably an open conformation. The deprotonation of the oxindole is induced by the quinuclidine nitrogen atom, and the resulting enoates might be stabilized in part through hydrogen bonding and π-stacking in the U-shaped cleft of (DHQD)$_2$PHAL. The *Si* face of the oxindole is covered so effectively by the quinoline ring that trifluoropyruvate approaches the *Re* face and is captured by the hydrogen-bonding network through the quinuclidine nitrogen atom. Consequently, the *S*,*S*-isomer is produced predominantly.

Recently, Feng and co-workers gave one example of chiral Sc(III)-*N*,*N*′-dioxide (**78**) complex-catalyzed aldol-type reaction of 3-methyloxindole with ethyl trifluoropyruvate. In the presence of 5 mol % catalyst, the aldol product was obtained in high yield (93%) and enantioselectivity (91% ee), albeit with moderate diastereoselectivity (76:24 dr) (Scheme 29).[167]

Scheme 29

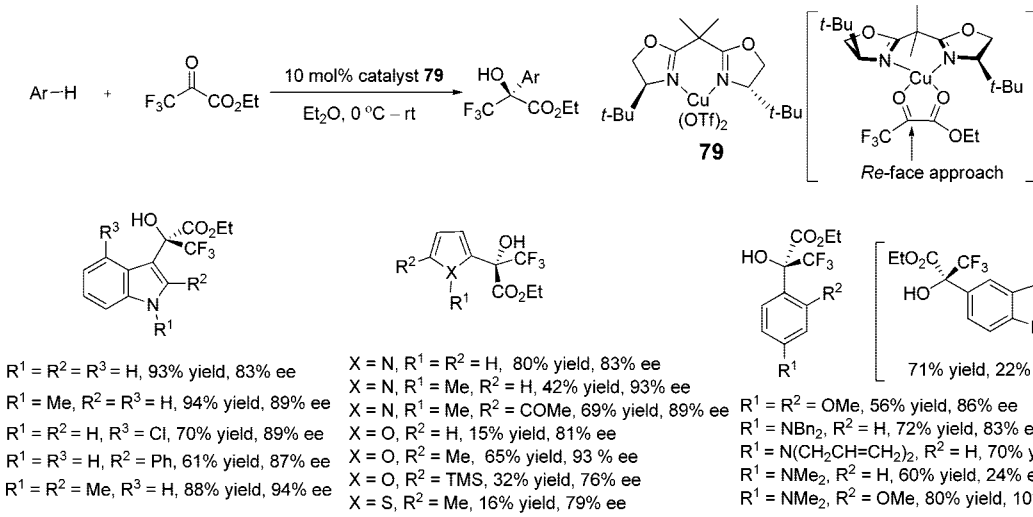


3.1.3. Friedel–Crafts Reactions

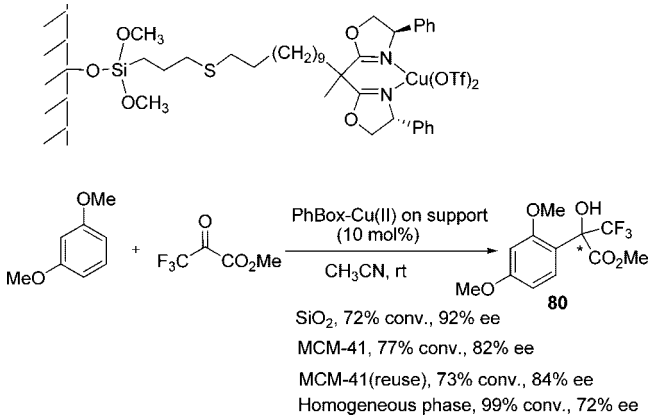
The Friedel–Crafts reaction is one of the classical C–C bond-forming reactions that can be promoted by Lewis or Brønsted acids. The enantioselective Friedel–Crafts alkylation reaction of electron-rich aromatic compounds with activated trifluoropyruvates is synthetically attractive because it provides easy access to optically active trifluoromethyl tertiary alcohols. However, enantiocontrol in these Friedel–Crafts reactions of trifluoropyruvate is difficult, owing to its distinct racemic background reaction. The first asymmetric Friedel–Crafts reaction of trifluoropyruvate was reported by Jørgensen and co-workers in 2000 (Scheme 30).[168] In the presence of chiral bisoxazoline–copper(II) complex **79**, a wide range of aromatic and heteroaromatic compounds underwent the Friedel–Crafts reaction with ethyl trifluoropyruvate. In general, both indoles and pyrroles were subjected to hydroxyalkylation favorably, giving the desired products in good to high yields with up to 94% ee. As for furanes and thiophenes, the reaction proceeded with high enantioselectivities, but in low yields. Aromatic compounds containing an electron-donating substituent such as *m*-methoxyanisole were tolerated with this Lewis acid catalytic system, while the hydroxyalkylation of anilines gave low ee values due to the competitive coordination of nitrogen atom with catalyst. To obtain high enantioselectivities, the anilines should be protected with sterically demanding groups such as benzyl and allyl. On the basis of assignment of the absolute configuration, the mechanism for these catalytic enantioselective Friedel–Crafts reactions was proposed to proceed through a distorted square-planar model.[169] Arene approaches the *Re* face of the activated trifluoropyruvate to give the observed absolute configuration.

Corma and co-workers developed a highly enantioselective heterogeneous Friedel–Crafts arylation of methyl trifluoro-

Scheme 30



Scheme 31



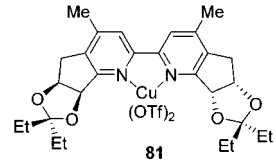
pyruvate with 1,3-dimethoxybenzene.[170] In the presence of 10 mol % PhBox−Cu(II) covalently anchored on silica or MCM-41, the chiral tertiary alcohol **80** was obtained in 92% ee, which rivals those observed in the homogeneous process (72% ee). Additionally, this solid catalyst can be recycled and used in the same asymmetric reaction without sacrificing yield and enantioselectivity (Scheme 31).

As Cu(II) complexes played an important role in asymmetric Friedel−Crafts reactions, several groups independently published their findings on enantioselective Friedel−Crafts arylation of trifluoropyruvate. For another example, Wilson and co-workers reported that the Cu-complex **81** catalyzed Friedel−Crafts alkylation of indoles with methyl or ethyl trifluoropyruvate. Good enantioselectivities were obtained in most cases. When *N*-methylindole was employed as substrate, low asymmetric induction was observed, thereby demonstrating that the hydrogen on the N atom is crucial to stereoselectivity (Table 34).[171]

Furthermore, a highly enantioselective Friedel−Crafts alkylation of aromatic ether with ethyl trifluoropyruvate has been described by Liu and co-workers in 2006.[172] Using as low as 1 mol % DIPhBox−Cu(II) catalyst **82**, various aromatic ethers were subjected to Friedel−Crafts alkylation with excellent enantioselectivities (90−93% ee) under solvent-free conditions (Table 35).

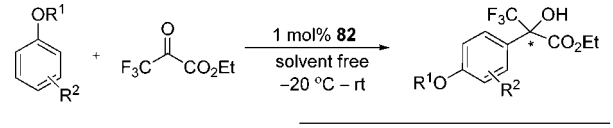
Further studies were carried out by Nakamura, Toru, and co-workers on application of Cu(II)−bis(imidazoline) (Phebim, **83**) complex for enantioselective Friedel−Crafts alkylation of indoles with ethyl trifluoropyruvate.[173] The catalyst loading can be reduced to 0.5 mol % without a significant decrease of the enantiomeric excess. Both enantiomers could be prepared with high enantioselectivity by using different combinations of counterion, chiral ligand, and solvent (Table 36). The Phebim could form a complex with $Cu(OTf)_2$ in a monodentate fashion, which is different from the bidentate chelation of Cu(II)−bisoxazoline catalysts. A dual activation mechanism has been proposed in which a weak hydrogen-bonded complex could be formed between indole and one imidazoline moiety of the Phebim, and the chelating Lewis acid activates trifluoropyruvate. The indole approaches the *Si* face of the carbonyl attached to the trifluoromethyl group. Possibly, the drastic change in the nitrogen-substituent

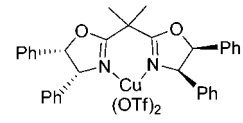
Table 34. Enantioselective Friedel−Crafts Reactions of Indoles with Trifluoropyruvates



R1	R2	R3	R4	yield, %	ee, %
H	H	H	Et	68	74
H	H	H	Me	77	90
H	H	Me	Me	79	86
MeO	H	H	Me	69	72
NO_2	H	H	Me	75	60
H	Me	H	Me	74	18
H	Me	Ph	Me	65	18

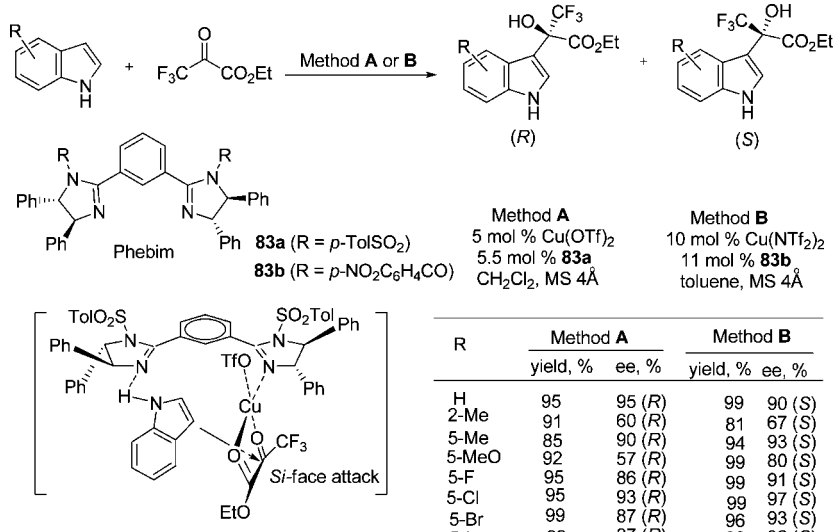
Table 35. Enantioselective Friedel−Crafts Reactions of Aromatic Ethers with Trifluoropyruvate





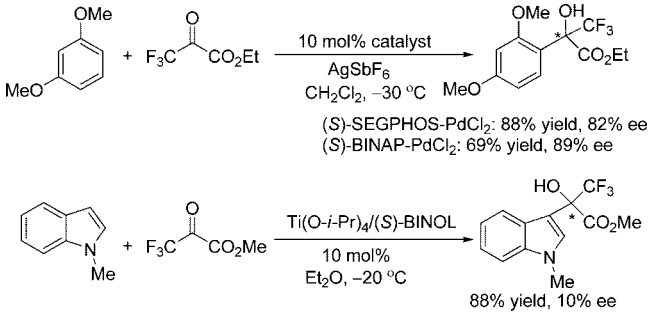
R1	R2	yield, %	ee, %
Me	H	90	90
Me	2-Me	80	90
Me	2-Ph	55	90
n-Bu	H	88	92
Ph	H	62	92
2'-$BrC_6H_4CH_2$	H	96	92
4'-$BrC_6H_4CH_2$	H	85	91
3'-$ClC_6H_4CH_2$	H	78	93
Bn	H	98	90
p-BrBn	H	85	91
Allyl	H	62	93
Allyl	2-Ph	70	93

Table 36. Cu(II)−Phebim-Catalyzed Friedel−Crafts Alkylations of Indoles



R	Method A		Method B	
	yield, %	ee, %	yield, %	ee, %
H	95	95 (*R*)	99	90 (*S*)
2-Me	91	60 (*R*)	81	67 (*S*)
5-Me	85	90 (*R*)	94	93 (*S*)
5-MeO	92	57 (*R*)	99	80 (*S*)
5-F	95	86 (*R*)	99	91 (*S*)
5-Cl	95	93 (*R*)	99	97 (*S*)
5-Br	99	87 (*R*)	96	93 (*S*)
5-I	92	87 (*R*)	99	96 (*S*)
5-CO_2Me	75	51 (*R*)	80	80 (*S*)

Scheme 32



structure of ligands **83a** and **83b** led to the opposite stereochemistry.

Other metal complexes are also efficient Lewis acid catalysts for Friedel−Crafts reactions of trifluoropyruvates.[148] For example, using the combination of (*S*)-SEGPHOS-$PdCl_2$ or (*S*)-BINAP-$PdCl_2$ with $AgSbF_6$, ethyl trifluoropyruvate was enantioselectively arylated with 1,3-dimethoxybenzene with good enantioselectivities (Scheme 32, top). However, in the presence of chiral (*S*)-BINOL-Ti(IV) complex, the reaction of methyl trifluoropyruvate with *N*-methylindole gave the corresponding product in good yield with poor enantioselectivity (Scheme 32, bottom).[174]

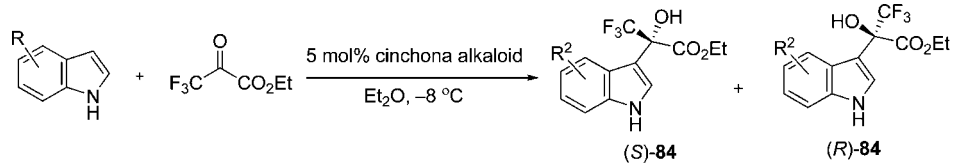
Over the past few years, organocatalysis has emerged as an important tool for various enantioselective Friedel−Crafts reactions of activated alkenes, imines, and carbonyl compounds. In this context, an early contribution to organocatalytic enantioselective Friedel−Crafts reaction of trifluoropyruvate was presented by Török, Prakash, and co-workers in 2005.[175] Cinchona alkaloids catalyzed Friedel−Crafts hydroxyalkylation of indoles with ethyl trifluoropyruvate in high enantioselectivities (83−95% ee). Furthermore, both enantiomers of the products **84** could be obtained by simple selection of the appropriate chiral auxiliary (cinchonidine **85** for (*S*)-product vs. cinchonine **86** for (*R*)-product) (Table 37). The authors emphasized that the specific structure including free 9-OH and nitrogen moieties within cinchona alkaloid along with the unprotected nitrogen of indoles altogether play a crucial role in enantioselection. Cinchona alkaloids could form a weak hydrogen-bonded complex with indole and then anchor trifluoropyruvate to give an active hydrogen-bonded intermediate. Thus, the alkaloids provide a chiral environment and also activate the electrophilic carbonyl group of trifluoropyruvate.

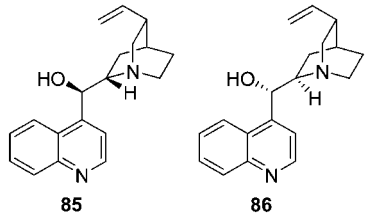
Another example of cinchona alkaloid catalyzed enantioselective Friedel−Crafts reaction of trifluoropyruvate was accomplished by Liu and co-workers.[176] Phenols were selected to test the feasibility of this organocatalytic reaction. A detailed study on optimized conditions has been performed and revealed that, in the presence of cinchona alkaloid derivative **87** having a bulky phenanthrene group, a number of phenols gave the *para*-hydroxyalkylated adducts with good to high enantioselectivities (71−94% ee) (Table 38).

Other organocatalytic Friedel−Crafts reactions of trifluoropyruvate were conducted in the presence of chiral Brønsted acids (Scheme 33). For example, Jørgensen and co-workers employed C_2-symmetric bis-sulfonamide **88** as chiral Brønsted acid in enantioselective Friedel−Crafts alkylations of *N*-methyl indoles with ethyl trifluoropyruvate. Low stereoselectivity was observed (23% ee).[177] In the course of the investigation on Cu(II)−bis(imidazoline) complex-catalyzed Friedel−Crafts reaction, the bis(imidazoline) was found to function as a chiral Brønsted acid to promote this alkylation in the absence of metal. The combination of 10 mol % Phebim **83** with achiral acid, such as TfOH and Tf_2NH, catalyzed the Friedel−Crafts alkylation of indoles with ethyl trifluoropyruvate to afford the desired products in high yields with good enantioselectivities.[173] As ongoing investigation on chiral phosphoric acid-promoted Friedel−Crafts arylations of trifluoromethyl ketones, Ma's group evaluated the feasibility of enantioselective arylation of ethyl trifluoropyruvate with indoles by using Brønsted acid **29**. It was found that the reaction proceeded well, albeit with low to moderate enantioselectivities (20−64% ee).[178]

To suppress the competing background reaction of indoles with trifluoropyruvate, Akiyama and co-workers conducted this transformation in dilute solution at low temperature (−78 °C) by using H_8-BINOL-derived chiral phosphoric acid **89**.[179] It was found that good to high enantioselectivities were obtained for a series of indoles. In particular, electron-deficient indoles gave the corresponding adducts with excellent enantioselectivities (Table 39). Importantly, this organocatalytic asymmetric Friedel−Crafts reaction could be

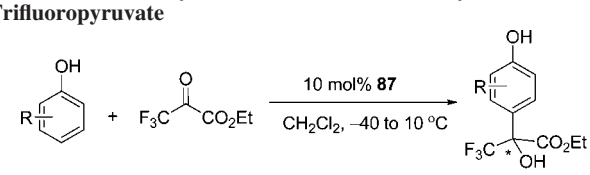
Table 37. Cinchona Alkaloid-Catalyzed Enantioselective Friedel−Crafts Alkylation of Indoles with Trifluoropyruvate

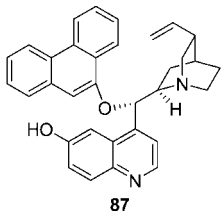




R	(*S*)-**84** (catal-**85**) yield, %	ee, %	(*R*)-**84** (catal-**86**) yield, %	ee, %
H	99	95	99	90
5-Me	98	93	99	92
6-Me	97	95	98	90
5-F	97	92	98	86
5-Cl	96	90	98	86
5-Br	97	87	96	85
5-I	97	87	97	85
5-CO_2Me	96	88	97	85
5-OMe	98	83	96	83

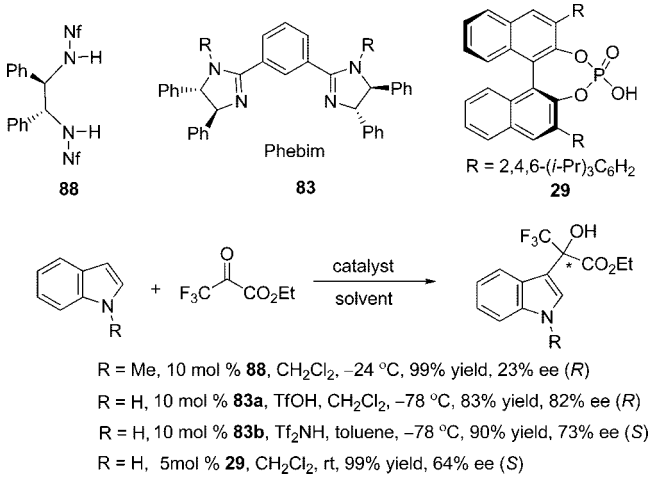
Table 38. Cinchona Alkaloid-Catalyzed Enantioselective Friedel−Crafts Alkylations of Phenols with Ethyl Trifluoropyruvate





R	yield, %	ee, %
H	76	86
2-Me	88	86
2-Ph	67	75
2-OMe	87	71
2,6-Me_2	78	94
2-Me-6-(CH_2=$CHCH_2$)	83	88
2,6-(*i*-Pr)$_2$	75	86
2-(2′-Bu)-6-(CH_2=$CHCH_2$)	96	81
2-OH	82	78
2-(CH_2=$CHCH_2$)	58	91

Scheme 33

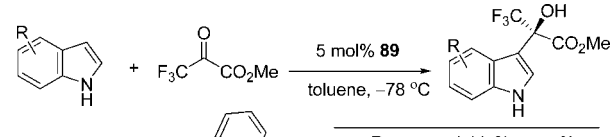


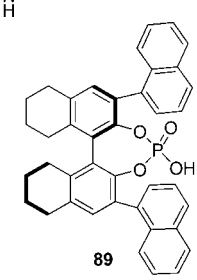
extended to other electron-rich heteroaromatic compounds, such as pyrrole and furan.

3.1.4. Alkylation and Alkynylation Reactions

Asymmetric alkylation and alkynylation reactions of trifluoropyruvates provide another useful access to chiral trifluoromethylated tertiary alcohols. For example, in the presence of a stoichiometric mixture of Et_2Zn and (*R*)-BINOL, ethyl trifluoropyruvate was alkylated with Grignard reagents to give the corresponding adducts **90**, which were

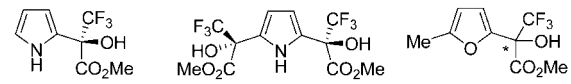
Table 39. Chiral Phosphoric Acid-Catalyzed Enantioselective Friedel−Crafts Reaction of Trifluoropyruvate





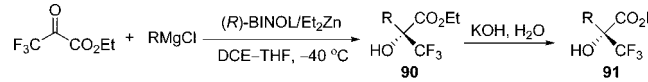
R	yield, %	ee, %
H	100	80
5-F	96	83
5-Cl	100	87
5-Br	98	88
5-I	97	87
5-CO_2Me*	97	90
5-CN*	96	92
5-NO_2*	100	98

* concentration of indole: 0.2 M other indole: 0.01 M.



94%, 70% ee | 86%, 89% de, 96% ee | 100%, 82% ee

Table 40. BINOL-Zincate-Catalyzed Asymmetric Alkylation of Ethyl Trifluoropyruvate

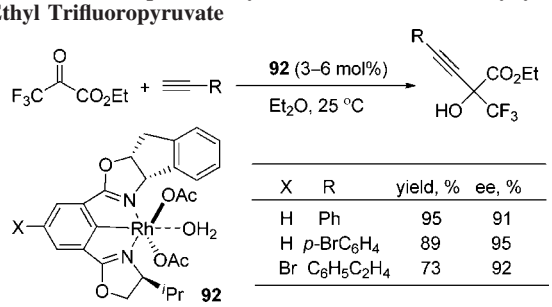


R	**91** yield, %	ee, %
Me	29	50
Et	74	74
n-Pr	34	76
n-Bu	35	83
n-C_5H_{11}	25	83
phenyl	38	69
vinyl	29	13
allyl	37	<4
benzyl	36	<5

directly hydrolyzed with aqueous KOH to afford the enantiomerically enriched α-trifluoromethyl α-hydroxy acids **91** in moderate yields over two steps. However, when vinyl-, allyl-, and benzylmagnesium chlorides were used as nucleophiles, poor enantioselectivities were observed (Table 40).[180]

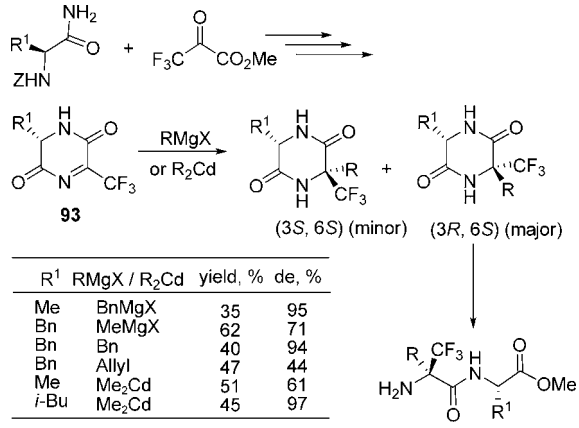
Nishiyama and Ito presented an interesting alkynylation reaction of ethyl trifluoropyruvate.[181] In the presence of the unsymmetric chiral Rh−bis(oxazoline) complex **92**, three propargyl alcohols were obtained in 73−95% yield with high enantioselectivities (Table 41). Unfortunately, the reaction mechanism was not provided at this stage.

Table 41. Rh-Complex-Catalyzed Enantioselective Alkynylation of Ethyl Trifluoropyruvate



X	R	yield, %	ee, %
H	Ph	95	91
H	*p*-BrC_6H_4	89	95
Br	$C_6H_5C_2H_4$	73	92

Table 42. Diastereoselective Alkylation of Diketopiperazines with RMgX or R_2Cd



R^1	RMgX / R_2Cd	yield, %	de, %
Me	BnMgX	35	95
Bn	MeMgX	62	71
Bn	Bn	40	94
Bn	Allyl	47	44
Me	Me_2Cd	51	61
i-Bu	Me_2Cd	45	97

3.2. From Trifluoropyruvate-Derived Imines

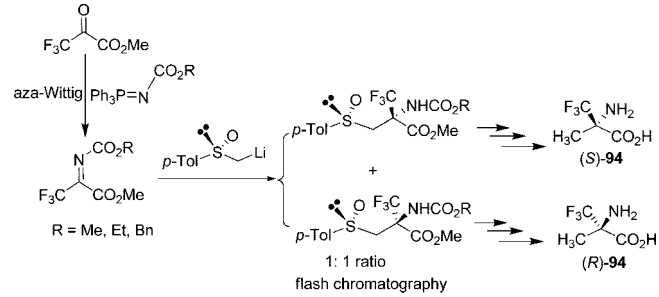
Trifluoropyruvate-derived imines represent one kind of important prochiral candidate because they can be readily converted to optically active trifluoromethyl compounds, which are potentially precursors for synthesis of α-trifluoromethyl amino acids. There are three main approaches to obtain these imines, namely, direct condensation of amines with trifluoropyruvate, Staudinger (aza-Wittig) reactions of phosphazenes with trifluoropyruvate, and palladium-catalyzed alkoxycarbonylation of trifluoroacetoimidoyl iodides.

3.2.1. Addition Reactions to Imines

Asymmetric addition of organometallic species to trifluoropyruvate-derived imines is a versatile approach for stereoselective construction of biologically active α-trifluoromethyl amino acids. In most cases, chiral auxiliaries have been introduced to control the formation of a new stereogenic center. An early example described stereoselective addition of organometallic reagent (RMgX or R_2Cd) to chiral 2,5-diketopiperazines **93**, which were in situ generated via the condensation of methyl trifluoropyruvate and chiral α-aminoamide.[182] Variable levels of asymmetric induction with unpredictable stereoselectivity were observed for a series of 3-alkyl-3-trifluoromethyl-2,5-diketopiperazines. Subsequently, the corresponding homochiral dipeptide esters could be obtained on acidolysis in methanol (Table 42).

In 1994, Zanda and co-workers reported an addition reaction of chiral lithiated sulfoxide to trifluoropyruvate-derived *N*-alkoxycarbonyl imines, which could be synthesized by an aza-Wittig reaction between phosphazenes and methyl trifluoropyruvate.[183] The resulting diastereomers (1:1) were isolated by flash chromatography and then separately subjected to desulfurization and hydrogenation to access

Scheme 34



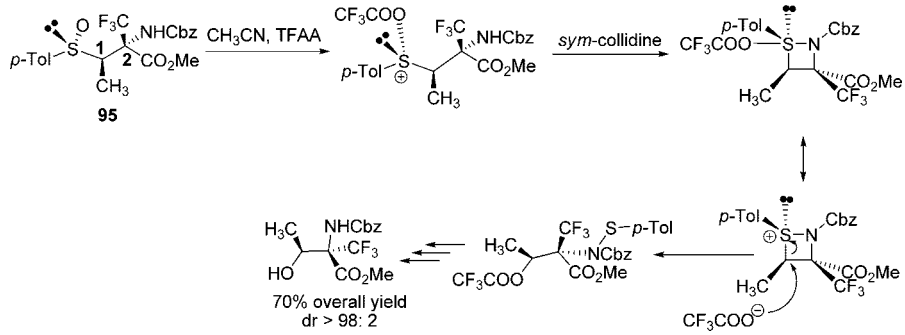
optically pure trifluoroalanines **94** with opposite configuration (Scheme 34).

In addition, the isolated diastereomers of α-sufinylamines **95** were treated with trifluoroacetic anhydride (TFAA) and *syn*-collidine, and then in situ reduced with $NaBH_4$, to give the "non-oxidative" Pummerer reaction products in high yields with up to 96% de.[184] This highly diastereoselective rearrangement has been confirmed to proceed through a four-membered cyclic *σ*-sulfurane intermediate (pentavalent sulfur), which was stabilized by two conjoint electron-withdrawing substituents. The key step was the S_N2-type intermolecular replacement of the sulfinyl auxiliary with a trifluoroacetoxy group, via TFAA-promoted "non-oxidative" Pummerer reaction of the diastereomeric intermediate α-sulfinylamines (Scheme 35). This overall process represents a straightforward route to both enantiomers of α-trifluoromethylthreoninates.[185]

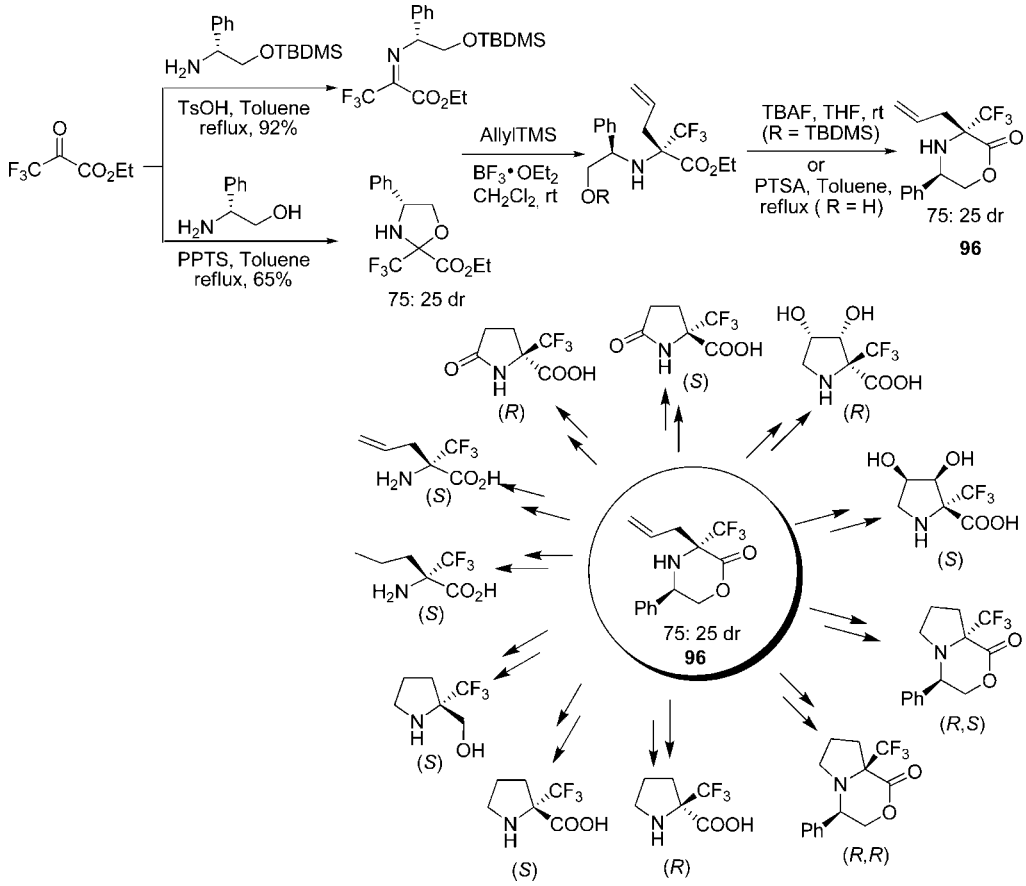
Brigaud and co-workers developed an elegant pathway to obtain a series of enantioenriched trifluoromethylated compounds via a diastereoselective allylation of chiral imine or oxazolidine, originated from condensation of ethyl trifluoropyruvate and (*R*)-phenylglycinol (Scheme 36).[186] The allylation of oxazolidine using $BF_3 \cdot Et_2O$ showed the best results in terms of yield, albeit with a slightly lower diastereoselectivity (75:25 vs 89:19 dr from imine). Notably, the diastereoselectivity was not affected by the initial diastereomeric ratio of oxazolidine, thus indicating the formation of the same iminium from each diastereomer of oxazolidine. Cyclization of both protected and unprotected allylic amino esters afforded α-allyl-α-trifluoromethylmorpholinones **96** in the yields of 88% and 97%, respectively. α-Allyl-α-trifluoromethylmorpholinones are versatile intermediates, which could be further transformed into a series of fluorinated α-amino acids[187] and derivatives.[188]

The use of optically pure sulfoxides as chiral auxiliary of trifluoropyruvate-derived imines also provides an efficient route for the preparation of fluorinated α-amino acids. Zanda and co-workers reported the synthesis of chiral sulfinimines **97** by using (*S*)-*N*-sulfinyl iminophosphorane and trifluoropyruvates via an aza-Wittig condensation.[189] The reaction of these chiral sulfinimines **97** with Grignard reagents afforded a range of nonracemic α-substituted α-trifluoromethylamino esters. A series of benzyl-, allyl-, and alkylmagnesium reagents could tolerate these reaction conditions well, whereas phenylmagnesium and vinylmagnesium reagents show different regioselectivities to give simple sulfoxides. Moreover, benzylmagnesium and allylmagnesium reagents featured low and opposite senses of diastereoselectivities in comparison with alkylmagnesium reagents. Good diastereoselectivities could be obtained with isobutyl and isopropylmagnesium reagents. The resulting diastereomers could be isolated by flash chromatography, and further removal of the

Scheme 35



Scheme 36



chiral auxiliary ended up to both enantiomers of α-trifluoromethylamino esters (Table 43).[190]

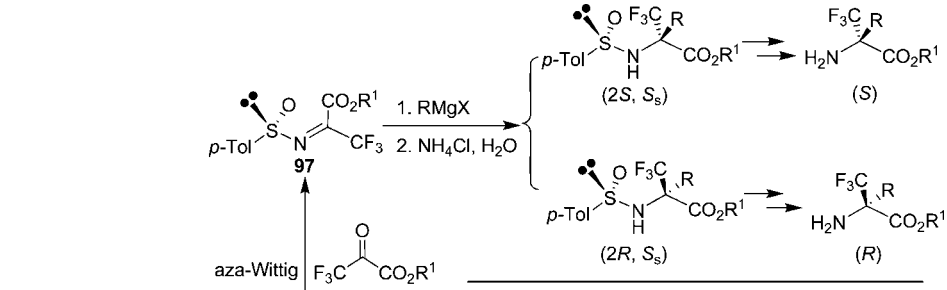
The scope of the reaction was further extended to ethynylmagnesium reagent for the synthesis of α-vinyl α-trifluoroalanine, which was not accessible via addition of vinylmagnesium reagent to chiral sulfinimine **97** (R^1 = Et). Treatment of chiral sulfinimine **97** with ethynylmagnesium bromide afforded the desired adduct with 84% de. Subsequent cleavage of the sulfinyl group and chemoselective hydrogenation either at rt or 0 °C furnished enantiopure α-ethyl α-trifluoroalanine and α-vinyl α-trifluoroalanine, respectively (Scheme 37).[191]

3.2.2. Mannich Reactions

The Mannich-type reaction of trifluoropyruvate-derived imines provides another efficient access to many useful chiral building blocks. 4-Substituted 3-acetyloxazolidin-2-ones are often utilized as chiral auxiliaries to form enolate intermediates in the presence of $TiCl_4$ and *i*-Pr_2NEt. Zanda and coworkers found that the titanium enolate of chiral oxazolidinone accomplished the Mannich-type reaction with (*E*)-*N*-Cbz ketimine of trifluoropyruvate exclusively in two *anti* manners of four possibilities, delivering the "Evans" and "non-Evans" *anti*-products **98** in the ratio of 91:9. In this process, the transition state leading to the major adduct could involve electrophilic addition of (*E*)-imine from its *Si*-face to the unhindered *Si*-face of the (*Z*)-chlorotitanium enolate of (*S*)-3-acetyloxazolidin-2-one. The major diasteromer **98b** is a valuable precursor for the construction of a series of highly functionalized compounds. For instance, an enantiopure α-trifluoromethyl β-hydroxy aspartic acid could be released via the removal of oxazolidinone auxiliary and hydroxyl-protected group (Scheme 38).[192,193]

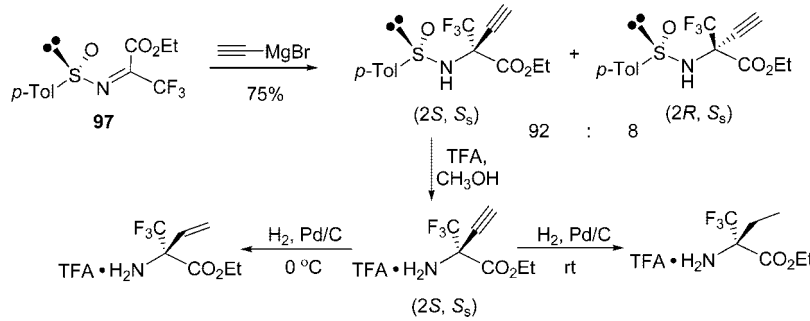
Another example of diastereoselective Mannich reaction was presented by Zanda's group in 2009.[194] In this study, *tert*-butyl acetate was selected as nucleophilic reagent to react

Table 43. Diastereoselective Additions of Grignard Reagents to Chiral Sulfinimines

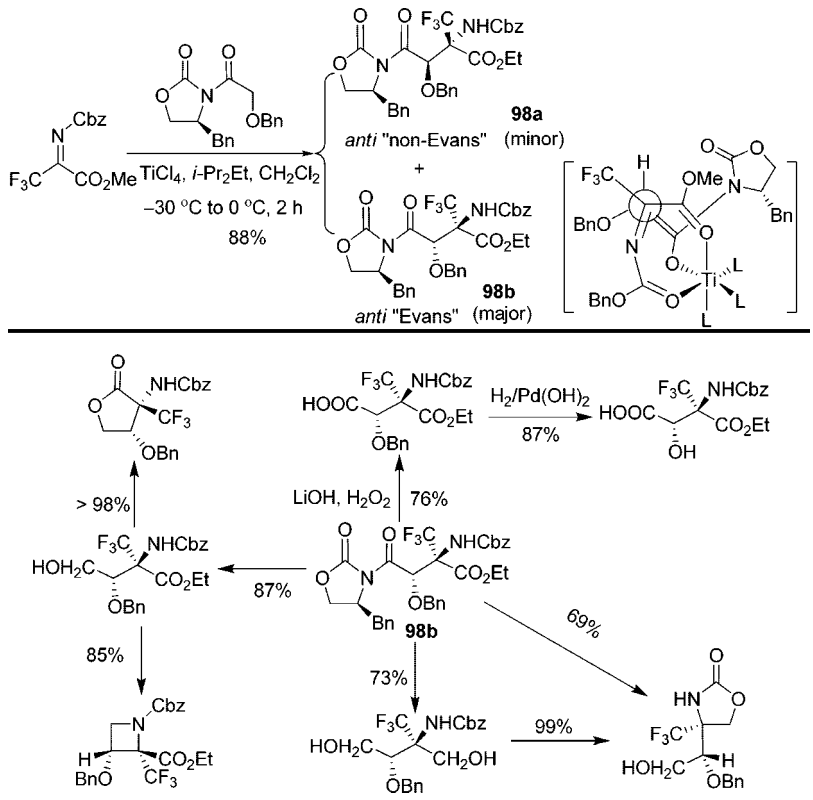


R	R^1	X	yield, %	(2*S*,*Ss*):(2*R*,*Ss*)	ee, %
Bn	Me	Cl	68	30:70	93
Allyl	Et	Cl	55	34:66	85
Me	Et	Cl	52	55:45	>96
Et	Et	Cl	55	72:28	92
i-Pr	Et	Cl	72	84:16	91
i-Bu	Et	Br	65	87:13	88
Bn	Et	Cl	68	30:70	93
n-Bu	Et	Cl	55	74:26	>96

Scheme 37



Scheme 38



with chiral sulfinimine **97**. Screening of different metals revealed that $TiCl(OPr^i)_3$ in combination with LDA gave the best performance, leading to 92% dr and 80% ee of the target adduct. The ee value of major isomer could be improved to 97% by a single recrystallization. The preferential formation of the 2*S* stereomer was interpreted by a transition state in

Scheme 39

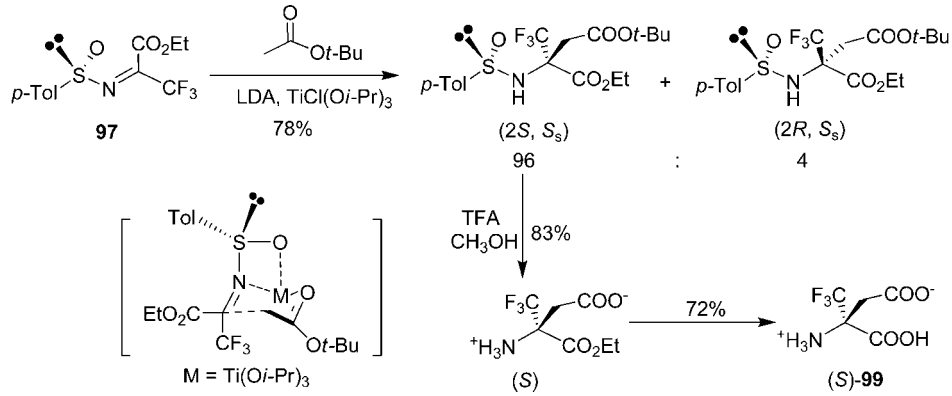
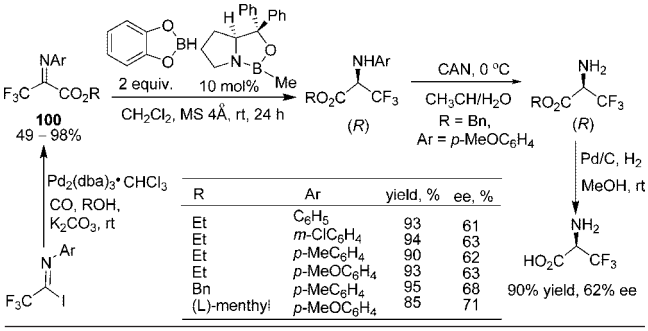
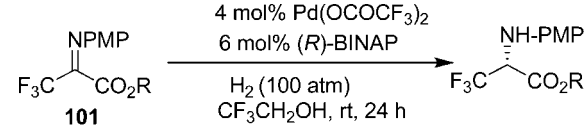


Table 44. Enantioselective Reduction of Trifluoropyruvate-Derived *N*-Arylimines



R	Ar	yield, %	ee, %
Et	C_6H_5	93	61
Et	*m*-ClC_6H_4	94	63
Et	*p*-MeC_6H_4	90	62
Et	*p*-$MeOC_6H_4$	93	63
Bn	*p*-MeC_6H_4	95	68
(L)-menthyl	*p*-$MeOC_6H_4$	85	71

Table 45. Pd(II)−Complex-Catalyzed Asymmetric Reduction of Trifuoropyruvate Imines



R	yield, %	ee, %
Et	>99	88
t-Bu	92	85
Bn	95	84

which the enolate could approach the *Re*-face of the chiral sulfinimine. Finally, functional group deprotection afforded enantiopure α-trifluoromethyl aspartic acid **99** (Scheme 39).

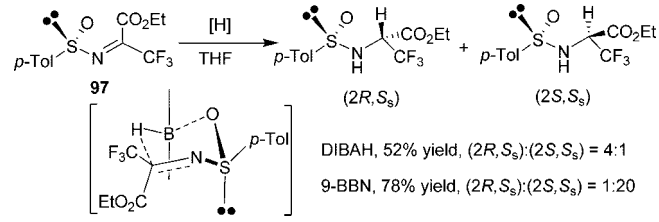
3.2.3. Reduction Reactions

Asymmetric reduction of trifluoropyruvate-derived imines is a straightforward way to obtain the corresponding chiral α-CF_3 amino acid. By means of palladium-catalyzed carbonylation of trifluoroacetoimidoyl iodides, Uneyama and co-workers succeeded in synthesizing prochiral *N*-arylimines of trifluoropyruvate for use in stereoselective reduction.[195,196] Optimization of the reaction conditions was carried out and revealed that *N*-aryliminotrifluoropyruvate **100** underwent enantioselective reduction with 2 equiv of catecholborane in the presence of 10% mol chiral oxazaborolidine. After subsequent deprotecting transformations, (*R*)-α-CF_3 amino acid was obtained in high yield with 62% ee (Table 44).[197,198]

Besides using boron hydride, the same group further described the enantioselective hydrogenation of α-fluorinated iminoesters **101** by using a palladium−BINAP complex.[199] In the presence of 4 mol % $Pd(OCOCF_3)_2$−BINAP complex, a series of α-fluorinated *N*-PMP-iminoesters were hydrogenated in high yields with good enantioselectivities. It was noteworthy that 3,3,3-trifluoroethanol as the solvent was very important for both yield and enantioselectivity. Although the role of trifluoroethanol in this asymmetric hydrogenation has not been clarified yet, it probably can be ascribed to its frail coordination to palladium and its ability to activate the imino group by protonation or hydrogen bonding (Table 45).

Zanda and co-workers presented another straightforward method to prepare enantioenriched 3,3,3-trifluoroalanine derivative via asymmetric reduction. Chiral sulfinimine **97** was used as starting material. By selecting appropriate reducing agents, DIBAH or 9-BBN, the sulfinamides could be obtained with

Scheme 40

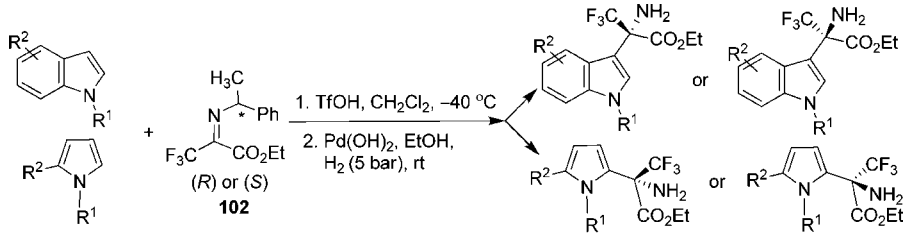


divergent diastereoselectivity. The high stereoselectivity observed with 9-BBN was rationalized by a chairlike transition state, in which the hydride predominantly approaches the *Re*-face of the (*E*)-sulfinimines (Scheme 40).[200]

3.2.4. Friedel−Crafts Reactions

As mentioned earlier in the text, the asymmetric Friedel−Crafts reaction of trifluoropyruvates has been developed in the presence of chiral metal complexes, cinchona alkaloid, and chiral phosphoric acids. In contrast, the asymmetric Friedel−Crafts reactions of trifluoropyruvate-derived imines **102** are rare. Török and co-workers presented a TfOH-catalyzed aminoalkylation of electron-riched heteroaromatic compounds with enantiomeric *N*-methylbenzylimines of trifluoropyruvate.[201] Various indoles and pyrroles were treated with (*R*)- and (*S*)-*N*-methylbenzylimines in the presence of 1.6% (w/v) triflic acid, followed by deprotection of *N*-substituent via Pd-catalyzed hydrogenolysis in one-pot, to give both enantiomers of α-trifluoromethyl α-heteroaromatic glycinates in good yields and ee values. The optically pure products could be obtained via fractional crystallization. Steric factors, generated by the chiral auxiliary, are primarily responsible for the almost exclusive product formation. In this reaction, (*R*)-α-trifluoromethyl-α-ketimino-ester **102** gave (*S*)-α-trifluoromethyl α-heteroaromatic glycinates, whereas (*S*)-**102** furnished the product with predominant (*S*)-configuration (Table 46).

Table 46. Diastereoselective Friedel−Crafts Reactions of Indoles and Pyrroles



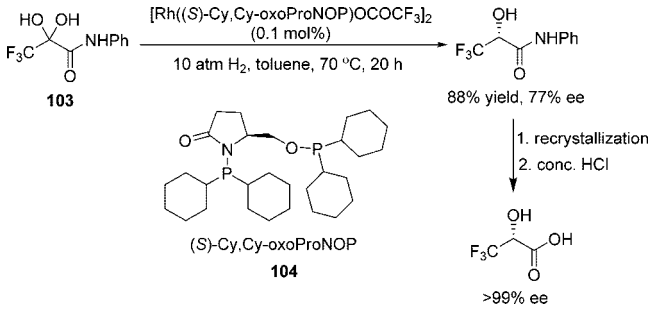
Indoles

R^1	R^2	Imine	Product	yield, %	ee, %
H	H	(*R*)	(*S*)	92	83
H	H	(*S*)	(*R*)	90	82
H	5-MeO	(*R*)	(*S*)	93	83
H	5-MeO	(*S*)	(*R*)	90	73
Me	H	(*R*)	(*S*)	85	85
Me	H	(*S*)	(*R*)	86	84
H	2-CO_2Et	(*R*)	(*S*)	80	75
H	2-CO_2Et	(*S*)	(*R*)	60	79
H	6-^{i}Pr	(*R*)	(*S*)	97	86
H	6-^{i}Pr	(*S*)	(*R*)	97	90
H	7-Me	(*R*)	(*S*)	96	85
H	7-Me	(*S*)	(*R*)	96	84
H	2-Me	(*R*)	(*S*)	86	87
H	2-Me	(*S*)	(*R*)	73	93

Pyrroles

R^1	R^2	Imine	Product	yield, %	ee, %
H	H	(*R*)	(*S*)	82	97
H	H	(*S*)	(*R*)	75	94
Me	H	(*R*)	(*S*)	77	84
Me	H	(*S*)	(*R*)	72	98
H	2-Et	(*R*)	(*S*)	81	91
H	2-Et	(*S*)	(*R*)	74	84

Scheme 41



3.3. From Other Trifluoropyruvate Derivatives

Direct asymmetric reduction of trifluoropyruvates, for the preparation of optically active trifluorolactic acid, remains a challenging task. Kuroki and co-workers employed 3,3,3-trifluoro-2,2-dihydroxypropionanilide **103** as prochiral substrate for the synthesis of (*R*)-trifluorolactic acid.[202] In the presence of 0.1 mol % chiral Rh-((*S*)-Cy,Cy-oxoProNOP) (**104**) complex under 10 atm H_2 at 70 °C for 20 h, the asymmetric hydrogenation of **103** provided (*R*)-3,3,3-trifluoro-2-hydroxy propionanilide in 88% yield with 77% ee. The ee value could be further improved to >99% by a single recrystallization. Subsequent hydrolysis of the (*R*)-amide with concentrated HCl at 80 °C gave useful (*R*)-trifluorolactic acid in 84% yield and >99% ee (Scheme 41). The hydrogenation of simple trifluoromethyl ketones can be found in section 5.1.1.5.

4. Asymmetric Reactions of Prochiral 4,4,4-Trifluoroacetoacetates and Derivatives

4,4,4-Trifluoroacetoacetates are also named 3-oxo-4,4,4-trifluorobutanoates or 3-oxo-4,4,4-trifluorobutyrates. Because ethyl and methyl 4,4,4-trifluoroacetoacetates (**J**) are easy to handle and commercially available, they are two of the most commonly used C4-synthons that can be transformed into various chiral trifluoromethyl products. In addition, 3-enamino-4,4,4-trifluorobutyrates (**K**) are interesting derivatives of 4,4,4-trifluoroacetoacetates and are complementary prochiral building blocks in asymmetric synthesis (Figure 8).

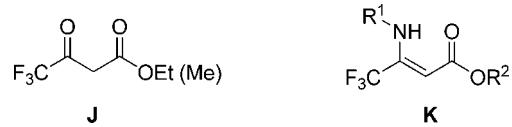


Figure 8. Prochiral 4,4,4-trifluoroacetoacetates and derivatives.

4.1. From 4,4,4-Trifluoroacetoacetates

In 1926, for the first time, Swarts reported the preparation of ethyl 4,4,4-trifluoroacetoacetate by alkaline condensation of ethyl trifluoroacetate with ethyl acetate.[203] Subsequently, a similar procedure was adopted by the use of different bases, such as sodium ethoxide,[204] sodium hydride,[205] and sodium (Scheme 42).[206] Other approaches involved the condensation of trifluoroacetyl chloride with ketene,[207] as well as the reaction of trifluoroacetaldehyde ethylhemiacetal with diazoacetates.[53] The ratio of the tautomeric keto and enol forms was found to be dependent on the temperature[208] and solvent.[209] 4,4,4-Trifluoroacetoacetates are highly reactive toward nucleophiles and are thus important kinds of prochiral synthons.

4.1.1. Reduction of 4,4,4-Trifluoroacetoacetates

Optically active ethyl 3-hydroxy-4,4,4-trifluorobutyrate is a useful intermediate for the preparation of the antidepressant Befloxatone[210] and other enantiopure CF_3-containing compounds.[211,212] Asymmetric reduction of ethyl 4,4,4-trifluoroacetoacetate provides a direct and simple route to this chiral intermediate.

Over the past few decades, catalytic asymmetric hydrogenation became a mature methodology for the production of enantiopure, bioactive ingredients and fine chemicals.[213,214]

Scheme 42

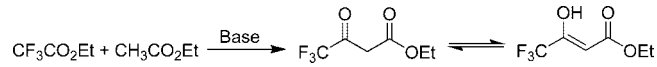
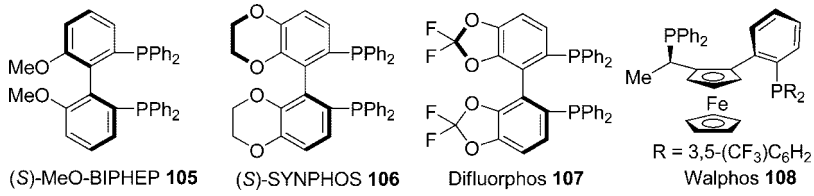
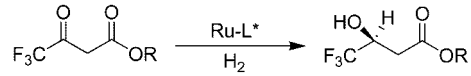


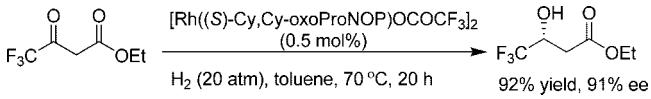
Table 47. Enantioselective Hydrogenation of 4,4,4-Trifluoroacetoacetates





L*	R	Solvent	P (H_2), bar	T, °C	ee, %
(*S*)-BINAP	Et	EtOH	80	30	46
(*S*)-MeO-BIPHEP	Et	EtOH	20	99	42
(*S*)-SYNPHOS	Et	EtOH	20	99	49
(*S*)-Difluorphos	Et	EtOH	10	99	70
Walphos	*i*-Pr	*i*-PrOH	20	77	77

Scheme 43

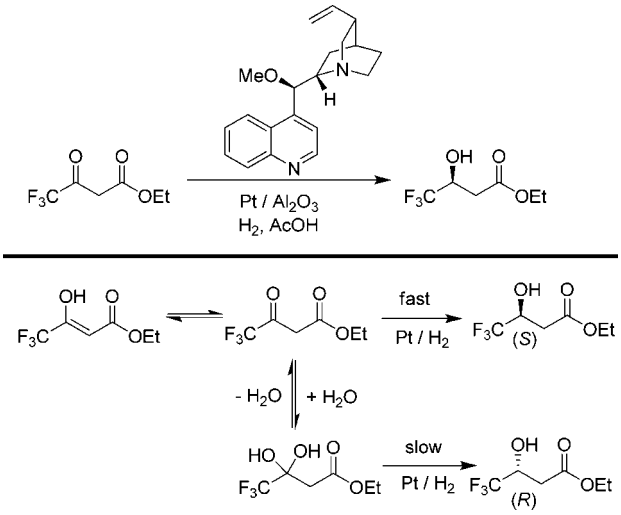


Among the most efficient catalysts for asymmetric reduction of ketones are ruthenium and rhodium complexes of chiral diphosphine ligands.[215,216] Noyori and co-workers gave the first example of a ruthenium-promoted hydrogenation reaction of ethyl 4,4,4-trifluoroacetoacetate. The corresponding β-hydroxy ester was isolated in 95% yield with 46% ee in the presence of RuHCl[(*R*)-BINAP]$_2$ at 80 bar pressure and 30 °C.[217] Next, other biaryl- and ferrocenyl-based chiral diphosphines (such as MeO-BIPHEP **105**,[218] SYNPHOS **106**,[219] Difluorphos **107**,[220] and Walphos **108**[221]) were also applied in the asymmetric hydrogenation of 4,4,4-trifluoroacetoacetates and were found to give unsatisfactory enantioselection under similar conditions (Table 47).

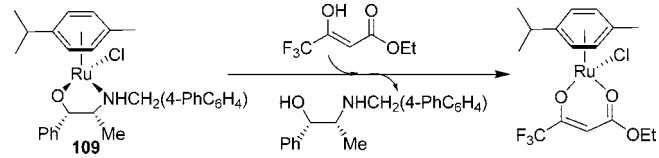
Interestingly, Iseki and co-workers demonstrated that the amidephosphine-phosphinite ligand (**104**[222]), derived from homochiral 5-(hydroxymethyl)-2-pyrrolidinone, was an effective ligand for the rhodium-catalyzed enantioselective hydrogenation reaction of ethyl 4,4,4-trifluoroacetoacetate. Ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate was obtained in 92% yield with 91% ee in toluene under 20 atm H_2 at 70 °C for 20 h (Scheme 43).[223]

On the other hand, heterogeneous asymmetric catalysis is also a powerful tool for the synthesis of various enantiomerically enriched compounds.[224] Cinchona alkaloid-modified metals, with different supports such as activated carbon, Al_2O_3, SiO_2, TiO_2, and zeolites, represent one kind of the most successful heterogeneous enantioselective catalysts.[225] Baiker and co-workers reported that ethyl 4,4,4-trifluoroacetoacetate can be enantioselectively hydrogenated to (*S*)-β-hydroxy ester with a Pt/Al_2O_3 catalyst in the presence of *O*-methyl cinchonidine.[226] The choice of reaction medium has a great impact on the rate and enantioselectivity of the hydrogenation. Up to 93% ee and 640−1850 h^{-1} turnover frequency (TOF) were observed in acetic acid. A further increase in ee to 96% could be achieved at 0 °C by using a mixture of AcOH and THF. Similar high ee values were obtained for the methyl and isopropyl 4,4,4-trifluoroacetoacetate. It was noteworthy that in the presence of even small amounts of water in THF the rate and enantioselection

Scheme 44



Scheme 45

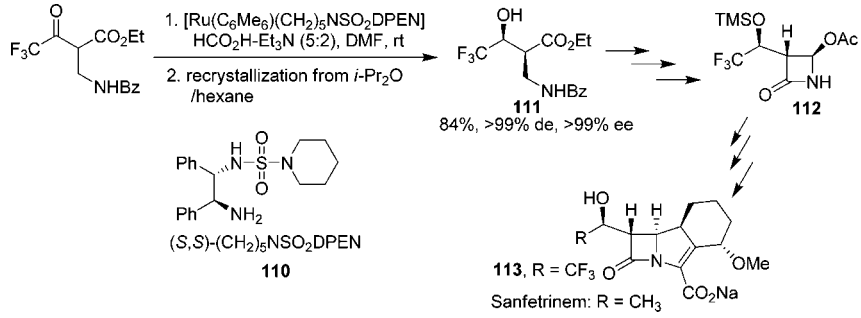


dropped because of hydrate formation and its subsequent hydrogenolysis to (*R*)-β-hydroxy ester (Scheme 44).[227−229]

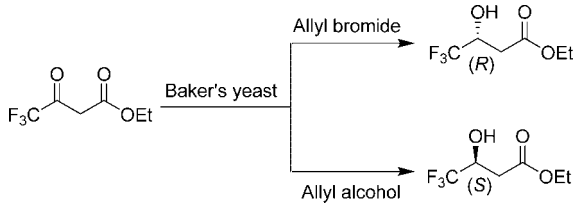
Catalytic asymmetric transfer hydrogenation provides a useful complement to catalytic reduction using molecular hydrogen.[230] In this context, one of the most significant breakthroughs is the use of chlororuthenium(II)arene precursors with chiral monoarylsulfonylated-1,2-diamine or β-amino alcohol ligands.[215,231] However, ethyl 4,4,4-trifluoroacetoacetate failed to be reduced with these hydrogen transfer catalyst systems.[232] Cross-experiments established that 18-electron catalyst precursor **109** reacts rapidly with the enol of β-keto ester to form an inactive diketonato complex, with concomitant release of the chiral α-amino alcohol (Scheme 45). Therefore, this functionalized prochiral substrate could deactivate the catalytic species.

Notably, Mohar and co-workers developed a new and useful stereoselective dynamic kinetic resolution (DKR) via

Scheme 46



Scheme 47

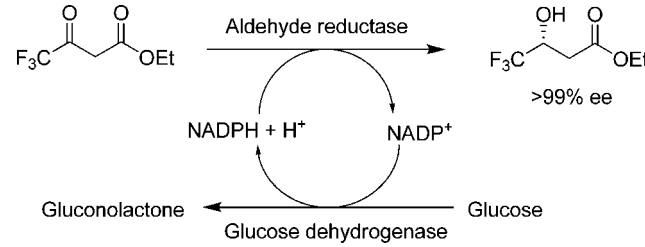


[Ru(C_6Me_6)(*S*,*S*)-$(CH_2)_5NSO_2$DPEN(**110**)]-catalyzed asymmetric transfer hydrogenation of ethyl 2-benzamidomethyl-3-oxo-4,4,4-trifluorobutanoate.[233] The reduction was carried out at room temperature in DMF using HCO_2H-Et_3N (5:2), followed by a single recrystallization from *i*-Pr_2O/hexane, to give the desired *syn*-alcohol **111** in 84% yield with excellent diastereo- and enantioselectivity (>98% de, >99% ee). Subsequently, trifluoromethylated β-lactam intermediate **112** and fluorine-modified sanfetrinem **113** (a tricyclic Carbapenem) were obtained through a set of elegant synthetic transformations (Scheme 46).

Despite the effectiveness of several metal catalysts in such asymmetric transformations, biocatalytic reduction remains a useful alternative: it enables not only green but also economically competitive processes through the use of microorganisms or enzymes. In this respect, many alcohol dehydrogenase-containing microorganisms have been found to catalyze enantioselective reduction of carbonyl groups and have been applied in organic synthesis.[234] For example, Baker's yeast reduction of ethyl 4,4,4-trifluoroacetoacetate afforded only (*R*)-β-hydroxy ester, and because there are various yeast−oxidoreductases with opposite stereochemical preferences that act simultaneously, the enantioselectivity of the reduction is low.[235−238] To obtain the enantiopure isomers, it is necessary to modify the enzymatic equipment of the microorganism. Forni and co-workers found that Baker's yeast reduction of ethyl 4,4,4-trifluoroacetoacetate, in the presence of allyl bromide, gives the corresponding (*R*)-β-hydroxy ester in 100% conversion with 80% ee, whereas allyl alcohol directs the enantioselectivity toward the (*S*)-enantiomer (100% conversion and 65% ee). Therefore, the two additives can act as inhibitors of *Si*- or *Re*-yeast enzymes, respectively (Scheme 47).[239]

The researchers of Lonza developed a water/butyl acetate two-phase system by using whole cells of *Escherichia coli* that contain two plasmids. One carries an aldehyde reductase gene from the yeast *Sporobolomyces salmonicolor*, which catalyzes the reduction of ethyl 4,4,4-trifluoroacetoacetate, and the second carries a glucose dehydrogenase gene from *Bacillus megaterium* to generate NADPH from $NADP^+$ (Scheme 48).[240,241] The (*R*)-enantiomer has an ee value of >99%, and the yield is ~50%. The concentration of $NADP^+$ required for maximum activity is ~0.5 g/L.

Scheme 48



Interestingly, Sun and co-workers reported the enantioselective reduction of ethyl 4,4,4-trifluoroacetoacetate by using whole-cell *Saccharomyces uvarum* SW-58 in an aqueous−organic solvent biphasic system. (*R*)-β-Hydroxy ester was obtained in 85% conversion with 85% ee. The bioconversion in the biphasic system was more efficient compared with that in the monophasic aqueous system, and product concentration as high as 54.6 g/L was reached in the organic phase without addition of the costly cofactors.[242]

The discovery of new enantioselective biocatalysts for this given transformation was recently reported. Li and co-workers described a practical methodology consisting of preselection of microorganisms based on degradation ability and high-throughput screening with a miniaturized system coupled with fast analysis of enantioselectivities. Two novel bacterial alcohol dehydrogenases from phenylalanine- and tyrosine-degrading strains, named as *Klebsiella pneumomiae* Phe-E4 and *Bacillus pumilus* Phe-C3, were identified in the preparation of both enantiomers of ethyl 4,4,4-trifluoro-3-hydroxybutanoate in high ee values (>90%) and high yields (>80%).[243]

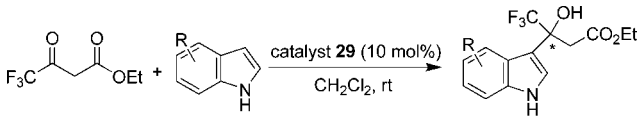
4.1.2. Arylation of 4,4,4-Trifluoroacetoacetates

4,4,4-Trifluoroacetoacetates are electrophilic substrates; however, rapid formation of inactive β-enolate chelate complexes limits their utilization in metal-mediated asymmetric transformations. Asymmetric arylation of 4,4,4-trifluoroacetoacetates remains an important challenge. Ma and co-workers used BINOL-derived phosphoric acids **29**[157] as chiral organocatalysts for the activation of ethyl 4,4,4-trifluoroacetoacetate. Enantioselective arylation proceeds well with a series indoles. The corresponding trifluoromethyl-substituted tertiary alcohols were obtained in moderate to high yields with up to 78% ee. Several enantiopure products were also obtained after single recrystallization (Table 48).[178]

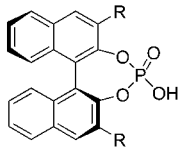
4.2. From 3-Enamino-4,4,4-trifluorobutyrates

Over the past decades, fluorinated analogues of (non)proteinogenic amino acids have received a great deal of attention.[244] In this context, the study of β-amino acids is a

Table 48. Chiral Brønsted Acid-Catalyzed Asymmetric Arylation of Ethyl 4,4,4-Trifluoroacetoacetate with Various Indoles



Catalyst:



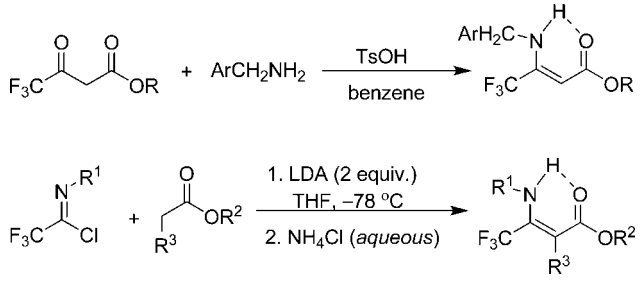
R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

29

R	time, h	yield,%	ee, %
H	96	99	64
5-F	120	89	64 (95)[a]
5-Cl	120	66	61
5-Br	120	36	61
5-Me	96	99	65
5-MeO	96	97	77 (99.9)[a]
7-Me	76	99	74
7-Et	76	99	78 (99.5)[a]

[a] After single recrystallization.

Scheme 49



topic of constant interest due to the applications of such compounds in medicinal and peptide chemistry as well as molecular recognition. 3-Enamino-4,4,4-trifluorobutyrates are useful intermediates for the asymmetric synthesis of β-trifluoromethyl β-amino acids. There are two main strategies that have been followed to synthesize these intermediates (Scheme 49). In the presence of *p*-toluene sulfonic acid or cation-exchange resin, the direct condensation of 4,4,4-trifluoroacetoacetates with benzylamines affords (*Z*)-enamines, stabilized by the intramolecular hydrogen bond. Alternatively, 3-enamino-4,4,4-trifluorobutyrates can also be prepared from the condensation of fluorinated imidoyl chlorides with lithium enolates of alkyl esters.

4.2.1. [1,3]-Proton Shift Reactions

[1,3]-Proton shift reaction, namely, biomimetic reductive amination, makes use of a transposition of an imine functionality via base-catalyzed azomethine−azomethine isomerization.[245] This intramolecular reductive-oxidative process is an external reducing agent-free methodology. Soloshonok and co-workers discovered that the isomerization of ethyl 3-enamino-4,4,4-trifluorobutyrates to the corresponding imines, followed by [1,3]-proton shift reaction in azaallylic system, led to the formation of thermodynamically favored *N*-benzylidene derivative albeit with low enantioselectivity (16% ee) in the presence of a catalytic amount of (−)-cinchonidine **85**. The resulting product was readily hydrolyzed into the corresponding (*R*)-3-amino-4,4,4-trifluorobutanoic acid **114** in 93% yield (Scheme 50).[246,247] Recently, Plaquevent's group reexamined this enantioselective catalytic [1,3]-proton shift reaction by use of a deuterated enamine (derived from deuterated benzylamine).[248] It was found that deuterated *N*-benzylidene derivative is the only product, and an isotopic effect was observed. This observation confirmed that the [1,3]-proton shift reaction involves a suprafacial deprotonation−reprotonation process, and the deprotonation step of the imine seems to be the rate-determining step. On the basis of these results, *p*-NO_2−benzylamine was used for the synthesis of ethyl 3-enamino-4,4,4-trifluorobutyrate, and the bisalkaloid $(DHQ)_2PHAL$ **76** was chosen as the best catalyst, leading to a 71% enantiomeric excess.

On the other hand, Soloshonok et al. also developed 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed diastereoselective [1,3]-proton shift transfer of optically active ethyl 3-[*N*-(α-phenylethyl)]enamino-4,4,4- trifluorobutyrate.[249] Ethyl 3-[*N*-(α-phenyl)ethyl]imine-4,4,4-trifluorobutyrate was obtained in 48% yield with 95% de. However, the major problem in scaling up this procedure is purification and separation of the Schiff base from the excess of DBU. A partial racemization under the reaction conditions was observed, causing preparation of this intermediate in only 80% ee.[250] To avoid these drawbacks, the same group provided an alternative approach using the (*Z*,*R*,*R*)-enamine−amide **115** as starting material for biomimetic transamination (Scheme 51). Higher diastereoselectivity (98% de) and convenient separation of the target products from excess DBU was achieved. Moreover, this method was demonstrated to be practical for large-scale (>25 g) synthesis of the target β-amino acid **114**.[251]

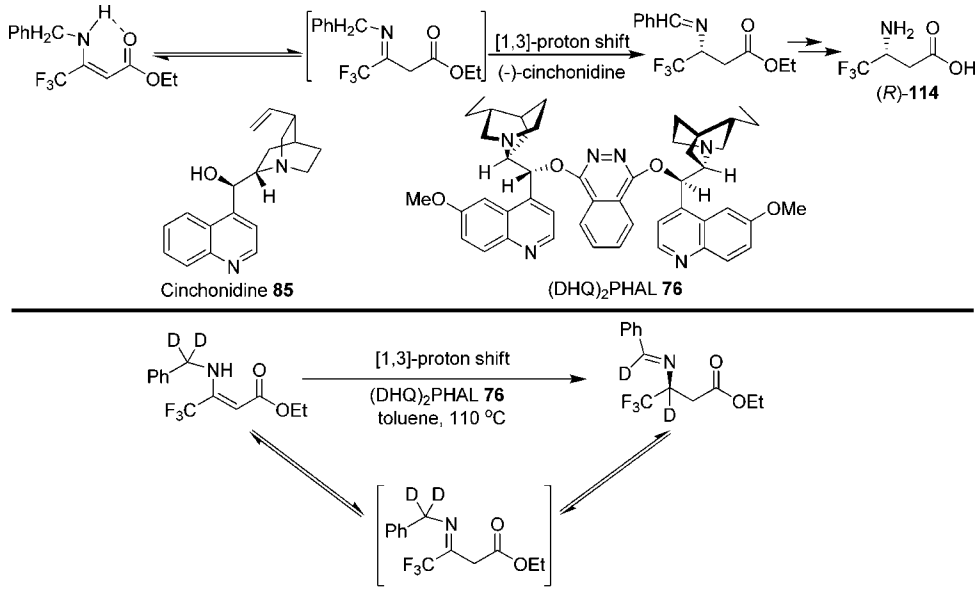
4.2.2. Reduction Reactions

An alternative approach to enantiopure β-trifluoromethyl β-amino acids involves stereoselective reduction of 3-enamino-4,4,4-trifluorobutyrate derivatives. Fustero's group described an efficient two-step method for the preparation of fluorinated β-amino acid derivatives.[252] First, the reaction of optically active α-metalated 2-alkyl-Δ^2-oxazolines with acylimidoyl chlorides gave initially masked β-enamino acid derivatives **116** in 60−92% yields. Then, the treatment of these intermediates with $ZnI_2/NaBH_4$ afforded the corresponding target trifluoromethylated β-amino acid derivatives **117** in good yields, albeit with moderate diastereoselectivities (Table 49).

One year later, Fustero and co-workers prepared a series of fluorinated β-enamino esters **118** by using optically active alkyl esters.[253] The asymmetric reduction of these β-enamino esters proceeded well with $ZnI_2/NaBH_4$ to give the corresponding β-amino esters **119** in good yields as a mixture of two diastereomers (up to 60% de) (Table 50). Both diastereomers were readily isolated in pure forms by column chromatography on silica gel and transformed into the fluorinated γ-amino alcohols by $LiAlH_4$ reduction. Removal of the chiral auxiliary was carried out by Ti(IV) isopropoxide-catalyzed transesterification to isopropyl esters (Scheme 52, top). In addition, the Mannich-like addition of lithium enolates of a chiral ester to trifluoromethyl imine did not provide much better results with regard to chemical yield (58%) and diastereoselectivity (38% de) (Scheme 52, bottom).

More recently, a cyclic β-enamino ester **120** could be obtained through condensation of methyl 4,4,4-trifluoroacetoacetate with (*S*)-2-amino-2-phenylethanol followed by intramolecular transesterification. The asymmetric reduction of β-enamino ester with $NaBH_3CN/HCl$ gave the corresponding cyclic β-amino ester with high diastereoselectivity (94% de). The major isomer of β-amino ester was readily separated by column chromatography and converted into (*S*)-

Scheme 50



Scheme 51

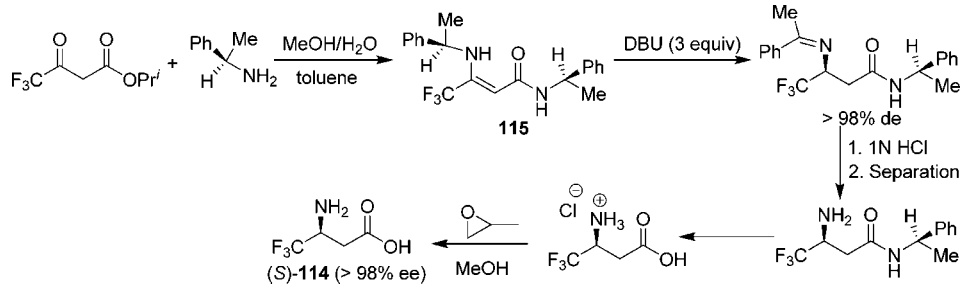
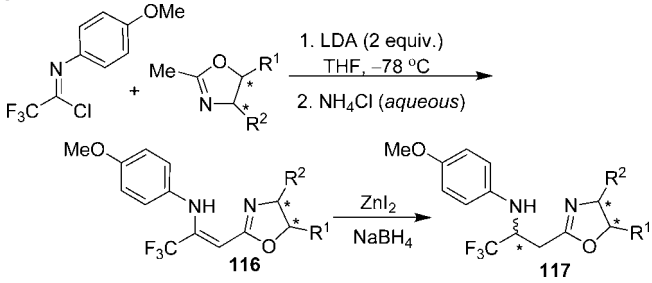
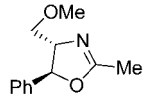
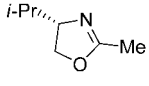
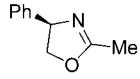
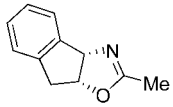


Table 49. Diastereoselective Synthesis of C-Oxazoline-Protected *β*-Amino Acid Derivatives



	enamino acid derivative	amino acid derivative **117**	
	116 yield, %	yield, %	dr (*R*): (*S*)
	72	90	80:20
	92	75	65:35
	90	80	80:20
	60	60	60:40

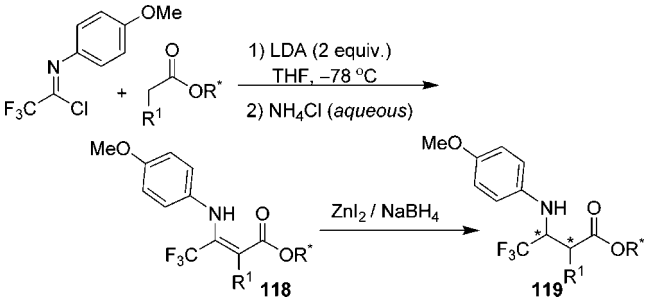
3-amino-4,4,4-trifluorobutanoic acid **114** in 38% overall yield (five steps) with >99% ee (Scheme 53).[254]

Recently, one example of enantioselective hydrogenation of *N*-phenyl-*β*-trifluoromethyl enamino ester involved rhodium complex with the electron-donating bisphosphine Tangphos **121**.[255] Only moderate conversion (48%) and good enantioselectivity (78.9% ee) were observed for this substrate (Scheme 54).

5. Asymmetric Reactions of Prochiral Trifluoromethyl Ketones and Derivatives

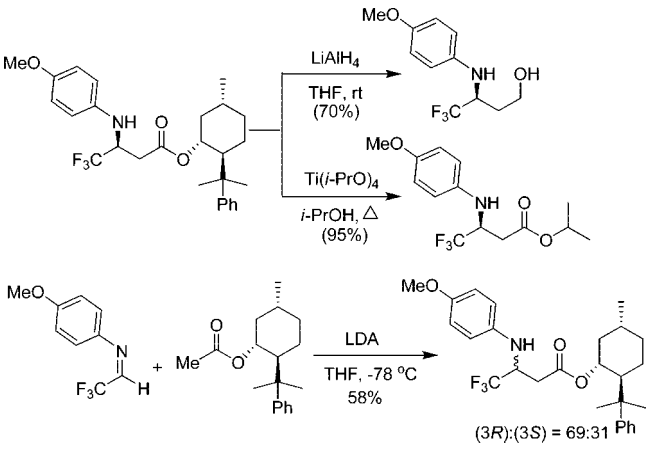
Asymmetric reactions of prochiral trifluoromethyl ketones and derivatives are among the most useful processes in the synthesis of chiral compounds bearing a CF_3 group through functional group transformations such as reduction and carbon−carbon bond-forming reactions. Therefore, significant progress has been made over the past decades. Among the following substrates (**L**, **M**, **N**, and **O** in Figure 9), aryl and alkyl trifluoromethyl ketones (**L**) are the most frequently used substrates because many of them are commercially available or readily prepared. The nitrogen-containing derivatives **M** offer more chances for diverse reactions and provide the direct access to chiral amino compounds. α,*β*-Unsaturated trifluoromethyl ketones (**N**) and trifluoromethyl *β*-diketones (**O**) possess two active functional groups. Substrates **N** and **O** require strict controlling of regioselectivity. On the other hand, tandem reactions become possible because of the presence of two functional groups. At present, only a few tandem reactions involving substrates **N** and **O** have been studied, but they deserve more attention.

Table 50. Diastereoselective Synthesis of Fluorinated β-Amino Esters



		enamino esters **118**	amino esters **119**	
R*	R	yield, %	yield, %	dr (*S*):(*R*)
Ph	H	72	85	80:20
4-I-C_6H_4	H	69	75	72:28
2-Naph	H	70	80	77:23
Ph	Me	-	83	81:19 (2*R*,3*R*,*R**):(2*S*,3*S*,R*)

Scheme 52



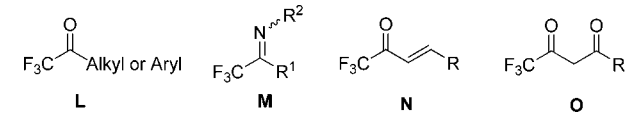


Figure 9. Prochiral trifluoromethyl ketones and derivatives.

5.1. From Aryl and Alkyl Trifluoromethyl Ketones

Because a lot of aryl and alkyl trifluoromethyl ketones are commercially available, and the corresponding chiral products are useful in the field of organic chemistry and pharmaceutical science, asymmetric transformations of these substrates have gained considerable attention. In particular, asymmetric reductions and carbon−carbon bond-forming reactions have been extensively studied, and plentiful excellent results have been recorded in the literature.

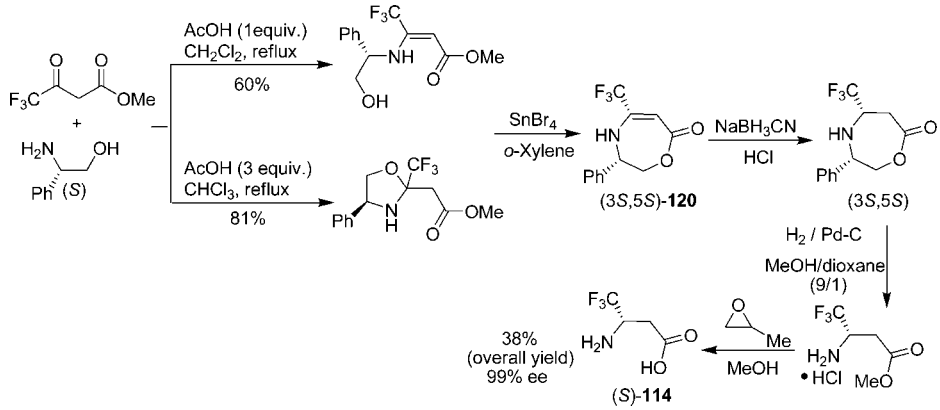
5.1.1. Reduction Reactions

Asymmetric reduction of trifluoromethyl ketones is obviously the method of choice for the synthesis of chiral trifluoromethyl alcohols, which serve as important precursors to a variety of trifluoromethylated chiral products. Usually, standard hydrogenation systems, previously established for nonfluorinated substrates, could be used in the reduction of these fluorinated compounds. Owing to the electron-withdrawing nature and the steric bulk of the trifluoromethyl group, the reactivity and the sense of the enantioselectivity in the reduction of trifluoromethyl ketones are different from that of the nonfluorinated substrates.

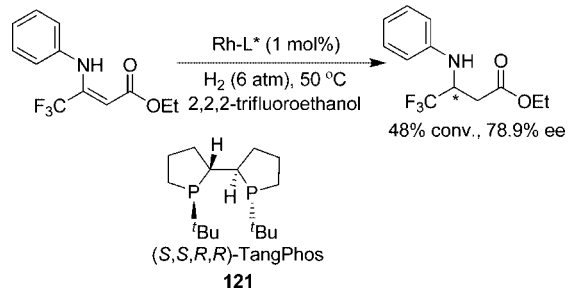
5.1.1.1. Organoborane-Mediated Reductions. Chiral oxazaborolidine-catalyzed reduction of ketones (CBS reduction) with coordinated borane or catecholborane as stoichiometric reductant, developed by Corey and co-workers,[256] provides an efficient access to a broad range of chiral secondary alcohols. This enantioselective catalytic reduction has now been established as a major synthetic method for the asymmetric synthesis of chiral medicines, natural products, synthetic intermediates, and ligands.[257] In the presence of catecholborane and catalyst **122**, the CBS reduction of phenyl, anthryl, and 1-mesityl trifluoromethyl ketones afforded the corresponding (*R*)-alcohols in >95% yield with >90% ee (Scheme 55).[258,259] The product 1-mesityl-2,2,2-trifluoroethanol served as an outstanding chiral controller in Lewis acid-catalyzed Diels−Alder reactions.[260] X-ray diffraction studies of crystalline trihalomethyl ketones and conformational analysis offered deep insights into the origin of high enantioselectivity in CBS reduction. The electron-withdrawing nature and the steric bulk of the trihalomethyl group play a key role for the high reactivity and enantioselectivity.[261,262] Odanacatib (MK-0822), which is a potent and selective inhibitor of Cathepsin K, includes a α-trifluoromethylbenzyl amino stereocenter.[263] This stereocenter was constructed by oxazaborolidine-catalyzed enantioselective reduction of 4-bromophenyl trifluoromethyl ketone with 2.5 mol % of CBS catalyst **122** and catecholborane to furnish the corresponding alcohol in 96% isolated yield with 92% ee.[264] In 2002, Kanth and Brown developed a similar catalyst **123** for CBS reduction. This catalyst, prepared from (−)-α,α-diphenylpyrrolidinemethanol and 9-borabicyclo[3.3.1]nonane, catalyzed the reduction of prochiral trifluoromethyl phenyl ketone with BH_3−THF to give the corresponding alcohol in 93% ee.[265]

Brown and co-workers introduced (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP-chloride **124**][266] as a chiral reagent to reduce prochiral aryl and alkyl perfluorinated ketones.[267] As shown in Table 51, the (−)-DIP-chloride delivered high enantioselectivity and activity. Although the reaction of alkyl trifluoromethyl ketones proceeded at a rate faster than that of the aryl derivatives, both substrates could be reduced to the corresponding chiral alcohols with high ee values. Typically, in the presence of (−)-DIP-chloride, the reduction of 2,2,2-trifluoroacetophenone provided the corresponding alcohol in 90% yield with 90% ee. By a simple recrystallization from pentane, the optical purity of 1-phenyl-2,2,2-trifluoroethanol was improved to >99% ee. Subsequently, several similar catalysts, such as Alpine-borane **125**,[268,269] K-Glucoride **126**,[270] and NB-Enantride **127**,[271] were reported (Figure 10). In comparison with DIP-chloride, these catalysts gave only moderate enantioselectivities in the reduction of trifluoromethyl phenyl ketone.

Scheme 53



Scheme 54



Both (−)-DIP-chloride and (*R*)-Alpine-borane have been used in the asymmetric reduction of prochiral α-acetylenic α′-fluoroalkyl ketones. As shown in Table 52, these trifluoromethyl acetylenic ketones can be reduced with excellent enantioselectivity (>98% ee).[272,273] In addition, Prakash and co-workers applied (−)-DIP-chloride in the reduction of 1,1,1-trifluoro-4-phenyl-3-butyn-2-one to give (*S*)-1,1,1-trifluoro-4-phenyl-3-butyn-2-ol (90% yield, 96% ee), which was further reduced to (*S*)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol using Red-Al without any loss of stereochemical information.[274]

By using (+)- and (−)-DIP-chloride **124**, Brown reported a very efficient one-pot, two-step transformation for the asymmetric synthesis of both enantiomers of (trifluoromethy1)-oxirane **128** in good yields with high enantioselectivities (>96% ee) (Scheme 56).[275] The product **128** appears to be a very versatile synthetic intermediate, which could be converted into a variety of useful chiral α-trifluoromethyl secondary alcohols via the ring-cleavage reaction with appropriate nucleophiles without any loss of optical activity. For example, (*R*)-3-amino-1,1,1-trifluoropropan-2-ol, which is used for large-scale production of a cholesterol ester transfer protein inhibitor, can be prepared by the ring-opening of chiral epoxide **128**.[19]

5.1.1.2. Organoaluminum- and Organomagnesium-Mediated Reductions. In 1991, Chong and co-workers used Noyori's BINAL-H reagent **129** for the reduction of trifluoromethyl aryl ketones.[276] In these reactions, the BINAL-H reduction of hindered aryl trifluoromethyl ketones furnished good to excellent enantioselectivities (up to 98% ee), whereas the less-hindered trifluoromethyl ketones gave poor enantioselectivities (6−27% ee) (Table 53).[276,277] Interestingly, BINAL-H reagent has also been employed in the reduction of trifluoromethyl alkynyl ketones by Kobayashi and co-workers, but very low ee values (<21%) were observed.[272] In the reduction of 9-anthryl trifluoromethyl ketone, three analogous lithium aluminum hydride reagents (Figure 11), prepared from the sulfamide **130**,[278] oxazolylmethanol **131**,[279] and amino alcohol **132**[280] with $LiAlH_4$, provided modest enantioselectivities (30−55% ee) in the reduction of aryl trifluoromethyl ketones.

In 1977, Nasipuri and Bhattacharya studied a series of chiral alkoxyaluminum and -magnesium halides for the reduction of phenyl trifluoromethyl ketone.[281] The reactions were carried out in diethyl ether at 0−25 °C by using a 4-fold excess of these reagents. The aluminum reagents **133** and **135** (Figure 12) could reduce the ketone to afford 2,2,2-trifluoro-1-phenylethanol in moderate enantioselectivities (68% ee and 77% ee, respectively), whereas only 23% ee was obtained by using the magnesium reagent **134**. It was suggested that the reductions proceeded via a Meerwein−Ponndorf−Verley mechanism. In another report, the reduction of phenyl trifluoromethyl ketone, mediated by chiral Grignard reagent of (*S*)-2-phenyl-1-bromoethane-*1,1,2-d*$_3$, gave the corresponding chiral alcohol in 66% yield with 50% ee.[282]

Yong and Chong presented the chiral organomagnesium amide **136** (COMA) as reducing agent for the enantioselective reduction of a series of trifluoromethyl ketones.[283] Deuteration experiments with MeOD suggested that enolization was a major competing pathway in the reduction of acetophenone, and only trace amounts of phenethyl alcohol could be obtained. Trifluoromethyl aryl ketones without α-proton appeared to be suitable substrates. In fact,the reactions proceeded under very mild conditions to give excellent enantioselectivities (up to 96% ee) and chemical yields (>85%) (Table 54). While stoichiometric amounts of COMA reagent **136** were used in these reductions, the chiral ligand could be easily recovered by acid−base extraction.

5.1.1.3. Biocatalyzed Reductions. From a practical point of view, biocatalysis has demonstrated a high potential in the synthesis of chiral alcohols on a preparative scale. Because Baker's yeast is commercially available and could perform a variety of hydrogen-transfer reactions, it has been widely used for the synthesis of chiral trifluoromethyl alcohols. In the 1970s and 1980s, several groups studied Baker's yeast-mediated reduction of trifluoromethyl ketones.[284,285] All these reactions were carried out by treating the substrate with a vigorously fermenting sugar/yeast/water suspension to produce the corresponding trifluoromethyl alcohols with moderate to excellent enantioselectivities. For example, an amazing >99% ee could be obtained in the reduction of cyclohexyl trifluoromethyl ketone (Scheme 57).[286,287]

Basically, the common enzyme system consists of an enzyme, a catalytic amount of coenzyme NAD(P)H, and a

Scheme 55

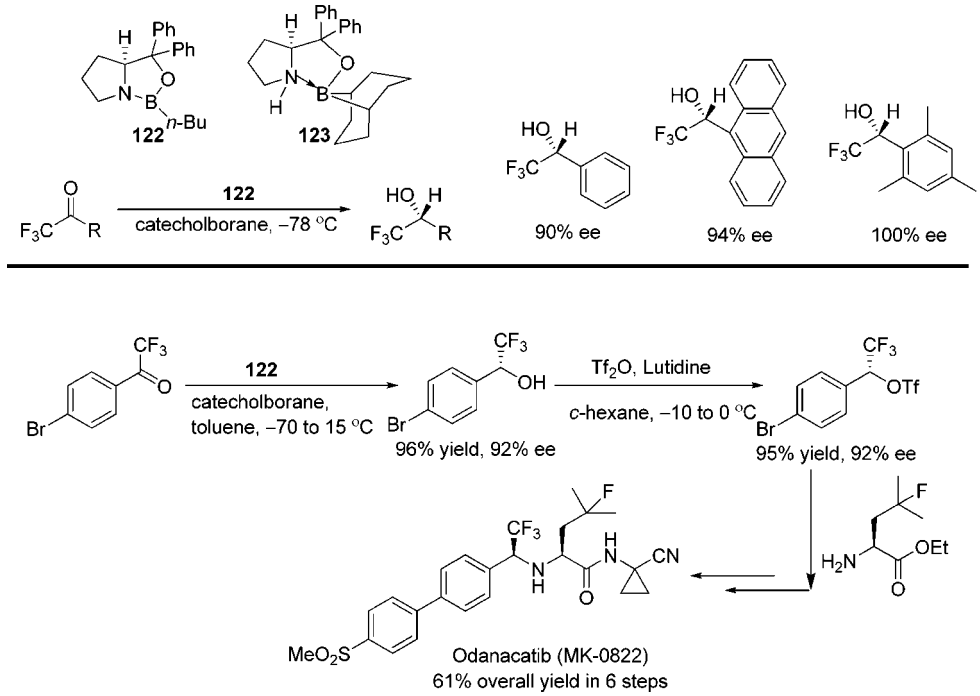
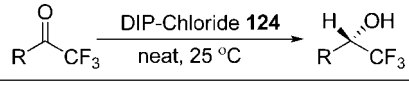


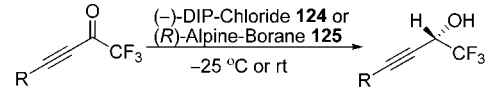
Table 51. Enantioselective Reduction Reactions Catalyzed by DIP-Chloride 124



R	time, h	yield, %	ee, %
Ph	24	90	90
1-Naphthyl	72	93	78
2-Naphthyl	72	92	91
9-Anthryl	30 d	48	82
CH_3	3	70	89
CH_3[a]	96	72	96
n-C_7H_{15}	8	80	92
n-C_8H_{17}	8	87	91
cyclohexyl	12	75	87

[a] Reaction run at –25 °C.

Table 52. Enantioselective Reductions with DIP-Chloride 124 and Alpine-Borane 125



R	(*R*)-Alpine-Borane **124**		(–)-DIP-Chloride **125**	
	yield, %	ee, %	yield, %	ee, %
Ph	81	98	89	98
n-Bu	76	>99	78	98

reducing agent (such as 2-alkanol or cyclopentanol). As the ketone substrates are reduced into alcohols, NAD(P)$^+$ is formed, which in turn is reduced to NAD(P)H by the coupled oxidation of 2-alkanol or cyclopentanol as shown in Scheme 58 (top). Wong and co-workers found that the alcohol dehydrogenase, originated from *Lactobacillus kefir*, simultaneously catalyzed carbonyl reduction and NADPH regeneration in the presence of 2-propanol.[288] With this enzyme system, phenyl trifluoromethyl ketone could be reduced to afford the corresponding alcohol in 71% yield and >99% ee (Scheme 58, bottom). This NADPH-requiring enzyme transfers the hydride from the cofactor to the *Si*-face of the carbonyl group to provide (*R*)-alcohol. The overall stereochemistry is opposite to that of many known alcohol dehydrogenases, which give (*S*)-alcohol. Therefore, this enzyme is enantiocomplementary to the alcohol dehydroge-

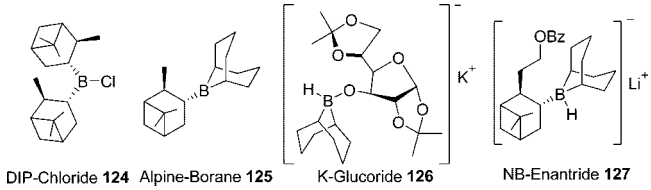
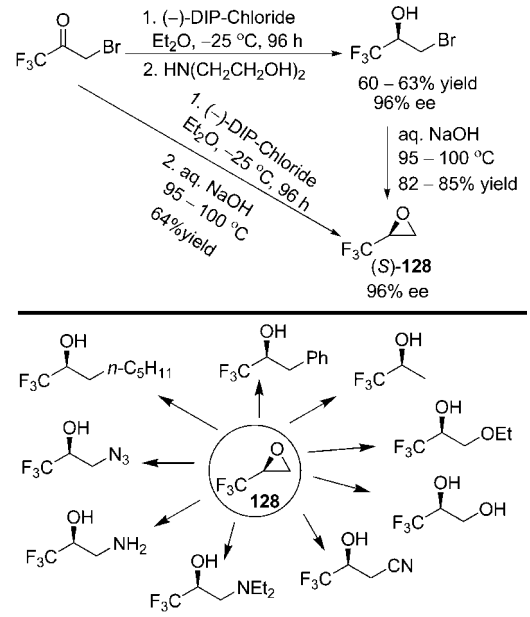


Figure 10. Several borane catalysts derived from chiral natural products.

Scheme 56



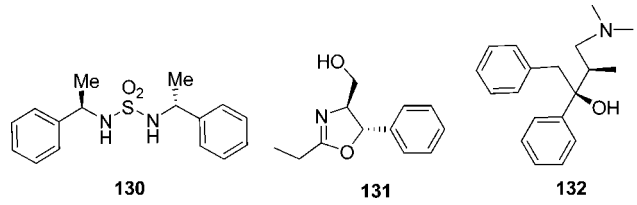


Figure 11. Several chiral ligands.

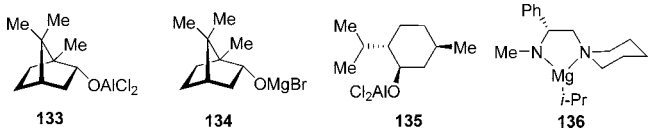
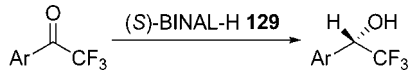


Figure 12. Several chiral alkoxyaluminum and -magnesium halides.

Table 53. Enantioselective Reductions Mediated by (*S*)-BINAL-H



Ar	temp., °C	time, h	yield, %	ee, %
9-anthryl	−20	22	90	98
2-methyl-1-naphthyl	−60	24	85	93
1-naphthyl	−60	24	93	70
2,4,6-trimethylC_6H_2	−60	24	69	97
2-MeC_6H_4	−60	24	81	74
Ph	−60	4	97	27
4-MeOC_6H_4	−60	3	99	6
4-FC_6H_4	0	3	94	14

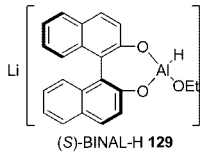
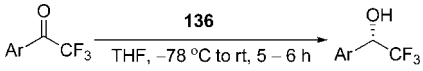
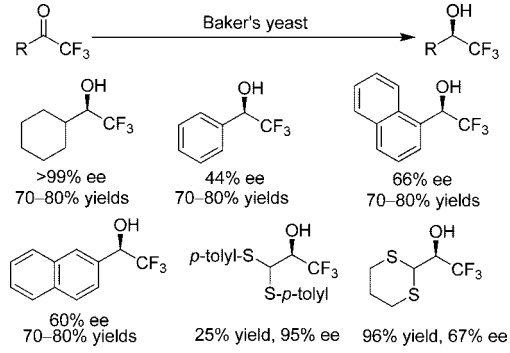


Table 54. Reduction of Trifluoromethyl Aryl Ketones Catalyzed by 136



Ar	yield, %	ee, %
Ph	84	74 (*S*)
1-naphthyl	92	86 (*S*)
2-Me-1-naphthyl	95	86 (*S*)
mesityl	89	94 (*S*)
9-anthryl	95	96 (*S*)
Bu−C≡C-	88	22 (*R*)

Scheme 57



nases from *Thermoanaerobium brockii* and horse liver, and is a useful synthetic catalyst.

Nakamura and co-workers examined another enzymatic reduction system using the dried cells of a dimorphic fungus, *Geotrichum candidum* IFO 4597 (APG4), by which either aromatic or aliphatic trifluoromethyl ketones can be reduced to give optically pure secondary alcohols.[289,290] This APG4 system is very versatile and has a broad scope of substrates. All kinds of substituents including aryl, alkyl, and sulfur functionality can be tolerated (Table 55). Furthermore, both

Scheme 58

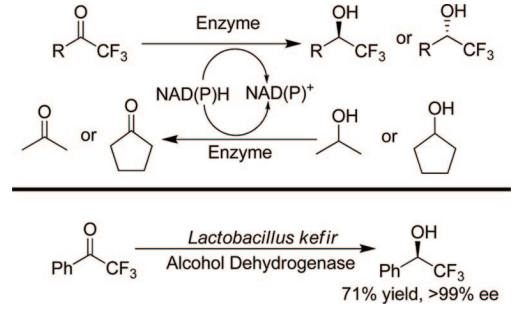
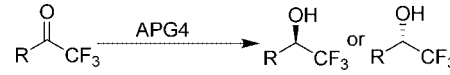


Table 55. Enantioselective Reduction of Trifluoromethyl Ketones Catalyzed by APG4



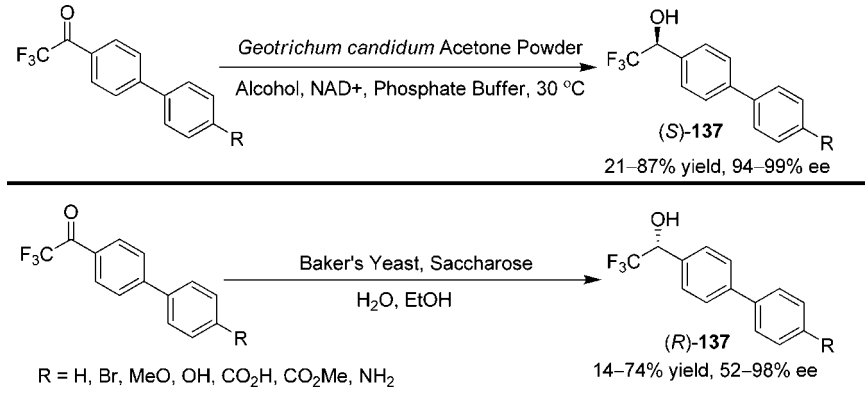
R	Yield, %	ee, %
Ph	>99	98 (*S*)
4-ClC_6H_4	91	>99 (*S*)
4-BrC_6H_4	82	>99 (*S*)
Bn	55	97 (*S*)
2-Thienyl	>99	>99 (*S*)
3-Thienyl	>99	>99 nd
Hexyl	>99	96 (*S*)
Heptyl	>99	96 (*S*)
Octyl	>99	>99 (*S*)
Nonyl	>99	98 (*S*)
$PhSCH_2$	97	98 (*R*)
$PhS(CH_2)_3$	98	>99 (*S*)
OctylSCH_2	60	96 (*R*)
1,3-Dithian-2-yl	67	>99 (+)

APG4 and the isolated enzyme from crude mixture could be used in the reduction of fluorinated ketones on a preparative scale and provided chiral fluorinated alcohols with excellent ee.[291,292] Usually, trifluoromethyl ketones and methyl ketones are reduced by enzymes with an opposite sense of stereoselectivity. Investigation of the mechanism revealed that the stereochemical outcome of the reduction of ketones by the APG4 system depends not only on bulkiness and electronic factor of the trifluoromethyl group, but also on the different substrate properties toward different dehydrogenases participating in the reduction.[293] Interestingly, *Pichia farinose*-mediated reduction of 1,1,1-trifluoro-3-(phenylthio) propan-2-one afforded the corresponding alcohol in 72% yield with 88% ee having the same configuration, identical to that obtained in the reduction of nonfluoroketone.[294]

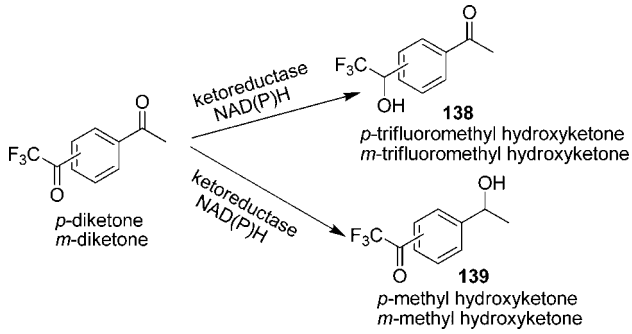
In addition, this APG4 enzymatic reduction system has been successfully applied in the asymmetric reduction of (trifluoroacetyl)biphenyl derivatives by Fujisawa and co-workers.[295] As shown in Scheme 59, both Baker's yeast and *Geotrichum candidum* acetone powder worked very well to afford the corresponding alcohols in satisfatory yields and enantioselectivities. Compared with Baker's yeast, *Geotrichum candidum* acetone powder appeared to be more efficient and enantioselective and gave (*S*)-alcohols **137**, whose configuration is opposite to (*R*)-carbinols from the reduction by Baker's yeast.

Grau and co-workers described a highly chemo- and enantioselective reduction bioprocess for the preparation of chiral fluorinated hydroxyketones from *p*- and *m*-diketones (Scheme 60).[296] Ketoreductases can selectively differentiate

Scheme 59



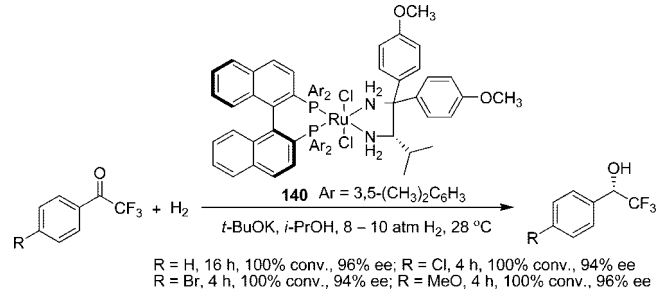
Scheme 60



between acetyl and trifluoroacetyl groups within the same molecule. A commercially available ketoreductase library was screened. In fact, many of the enzymes could offer a mixture of trifluoromethyl hydroxyketone and bisalcohol. With perfect chemoselectivity for *p*-diketone, KRED-112 or KRED-A1i provided (*S*)-*p*-trifluoromethyl hydroxyketone **138** in 100% yield and >99% ee, while KRED-129, KRED-131, KREDA1n, and KRED-A1x produced the (*R*)-*p*-trifluoromethyl hydroxyketone in 100% yield and >99% ee. Two enzymes of ADHCP and KRED-A1p demonstrated chemoselectivity toward the reduction of the methyl carbonyl producing the methyl hydroxyketone **139** with low levels of bisalcohol. The (*S*)-enantiomer of the methyl hydroxyketone can be synthesized on a large scale in 94% yield with 98% ee. Generally, for the *m*-diketone, the chemoselectivity of the catalysts was lower than that for the *p*-diketone. KRED-A1i and KRED-112 gave (*S*)-*m*-trifluoromethyl hydroxyketone in 99% ee with <14% bisalcohol, whereas the (*R*)-enantiomer was obtained using ADH-RE in 82% yield with 99% ee. The enzyme of ADH-CP produced the (*S*)-enantiomer of the *m*-methyl hydroxyketone in 90% ee with moderate chemoselectivity. Importantly, this new method eliminated the need for costly and time-consuming protection/deprotection of the ketone moiety and established a more convergent synthesis of hydroxyketones.

In 2005, Chênevert and co-workers reported the stereoselective reduction of ketones catalyzed by *Daucus carota* hairy root cultures. With phenyl trifluoromethyl ketone as the substrate, the corresponding (*R*)-alcohol was obtained in 90% yield and 97% ee.[297] Subsequently, Nakamura and co-workers found that a germinated radish sprout, which is easily accessible from commercially available vegetable seeds, could be used as a novel type of biocatalyst for the asymmetric reduction of trifluoromethyl phenyl ketone. The reactions proceeded under illumination (4000 Lux) for 1−4 days at 20 °C to give (*S*)-alcohol in 30−40% yield with >99% ee.[298]

Scheme 61

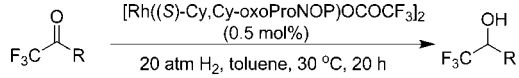


5.1.1.4. Transition Metal-Catalyzed Hydrogenation. Organometal-complex-mediated asymmetric hydrogenation of ketones is a mature area of organic chemistry, and a considerable number of catalytic systems are known to provide a variety of enantiopure secondary alcohols.[299] Recently, many reports involved transition metal complex-catalyzed asymmetric hydrogenation of trifluoromethyl ketones. For example, Noyori and co-workers investigated asymmetric hydrogenation of 2,2,2-trifluoroacetophenone and its derivatives in the presence of the XylBINAP/DAIPEN−ruthenium complex **140**.[300] α-Trifluoromethyl alcohols could be obtained with high enantioselectivities (94−96% ee) in 100% conversion (Scheme 61). This catalytic procedure showed a high turnover number (TON). For several substrates (R = H, Cl, Br, MeO), the substrate/catalyst molar ratio was >2000. It is worth noting that the sense of asymmetric induction is identical to that observed with nonfluorinated acetophenones.

By using chiral rhodium−Cy,Cy-oxoProNOP complexes, Kuroki and co-workers presented another procedure for the asymmetric hydrogenation of trifluoromethyl ketones.[202] Under 20 atm of hydrogen in toluene at 30 °C for 20 h, a variety of trifluoromethyl ketones gave the corresponding products with up to 98% ee (Table 56).

To avoid the use of a volatile epoxide in a closed reactor that is difficult to monitor, Martinez and co-workers developed an alternative access to (*R*)-3-amino-1,1,1-trifluoropropan-2-ol.[301] The process involved an efficient route to α-amino trifluoromethylketone **141** through a modified Dakin−West reaction,[302,303] followed by an asymmetric hydrogenation or an enzymatic reduction of the resulting ketone to the target alcohol **142**. As the key step for introducing the chirality, the reduction reaction proceeded very well in the presence of either a diacetato[(*R*)-(+)-BINAP]−ruthenium(II) catalyst with trifluoroacetyl (TFA)

Table 56. Enantioselective Hydrogenation Reactions Catalyzed by Chiral Rh-Complex



R	yield, %	ee, %
C_8H_{17}	99	97
C_6H_{13}	98	97
c-C_6H_{11}	90	97
c-$C_6H_{11}CH_2$	97	98
$PhCH_2$	97	97
$Ph(CH_2)_2$	99	96
$PhCH_2OCH_2$	100	86
Ph	93	73
p-ClC_6H_4	8	38
p-$CH_3OC_6H_4$	100	83

Scheme 62

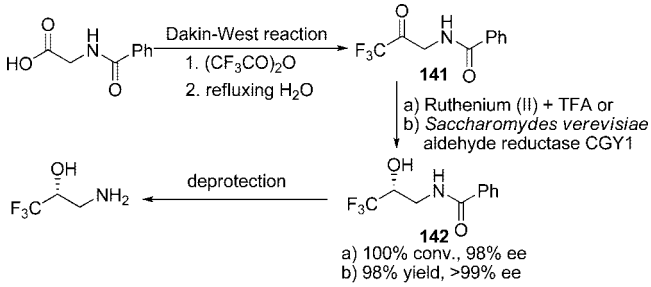
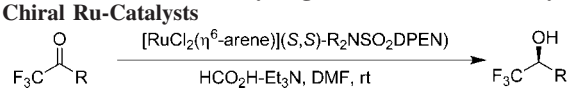
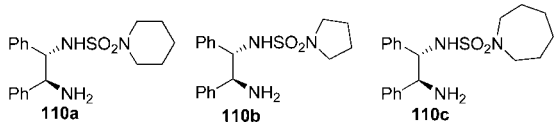


Table 57. Enantioselective Hydrogenation Reactions Catalyzed by Chiral Ru-Catalysts



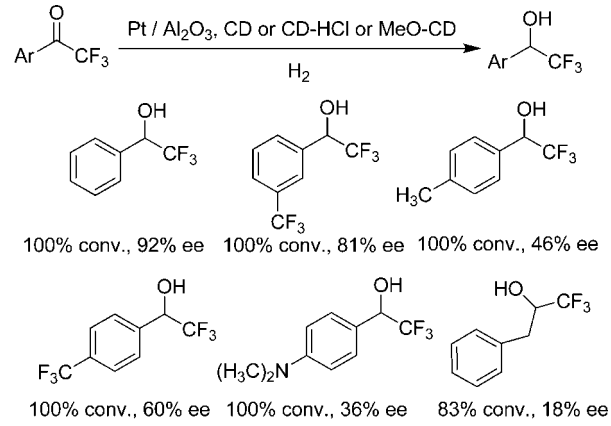
R	arene	ligand	S/C	time, h	ee, %
C_6H_{13}	mesitylene	**110a**	200	2	94
$BnCH_2$	mesitylene	**110a**	200	2	96
c-C_6H_{11}	mesitylene	**110c**	200	2	66
Ph	*p*-cymene	**110a**	200	2	38
C_6F_5	mesitylene	**110a**	200	<0.5	0
Bn	*p*-cymene	**110a**	2000	20	97
	mesitylene	**110a**	200	2	99
	mesitylene	**110a**	200	8	99/84 (dr 78:22)
	*p*-cymene	**110b**	200	8	98
	mesitylene	**110a**	25	4	98
	*p*-cymene	**110b**	200	6	96



as additive or a readily available enzyme to give the target chiral alcohol in ≥95% yield with ≥98% ee. Actually, more than three dozen commercial enzymes could be used to promote this reduction reaction (Scheme 62).

Under transfer hydrogenation conditions, Šterk, Stephan, and Mohar further extended the study of asymmetric reduction of various classes of fluoroalkyl ketones.[304] In the presence of 0.05−0.5 mol % of [Ru(η^6-arene)((*S*,*S*)-R_2NSO_2DPEN(**110**))], a variety of chiral α-trifluoromethyl alcohols and their perfluoroalkyl higher homologues were obtained in highly isolated yields (85−98%) with excellent enantioselectivities (up to 100% ee) (Table 57). This asymmetric approach allowed easy isolation of the chiral fluoro-

Scheme 63



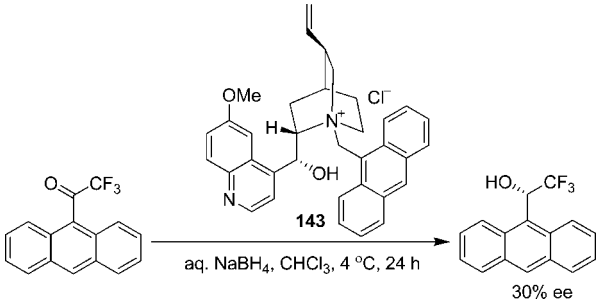
alkyl alcohols in both enantiomeric forms and may provide new opportunities for industrial synthetic application. Unfortunately, 2,2,2-trifluoroacetophenone only gave rise to 38% ee because the CF_3 group behaves as a smaller group compared to the phenyl moiety.

Stereoselective heterogeneous catalysis combines several advantages such as easy separation, efficient recycling, improved handling and process control, and overall low costs as well.[225] However, while a lot of homogeneous chiral metal catalysts afford excellent enantioselectivity in the hydrogenation of ketones, the heterogeneous catalysis is so far unsatisfactory. As a particularly attractive approach, Baiker and co-workers studied the hydrogenation of 2,2,2-trifluoromethyl ketones over Pt/Al_2O_3 modified by cinchonidine, its hydrochloride, or *O*-methyl cinchonidine; 18−92% ee could be obtained (Scheme 63). The highest 92% ee was achieved in the hydrogenation of 2,2,2-trifluoroacetophenone by using Pt/Al_2O_3-CD as catalyst in toluene and TFA, and it is the best enantioselectivity so far for this reaction.[305] Compared with this system, polyvinylpyrrolidone-stabilized platinum nanoclusters modified with cinchonidine exhibited only 20% ee in the hydrogenation of the same substrate.[306] Baiker and co-workers used Pt/Al_2O_3 modified by cinchonidine with sonochemical pretreatments in the hydrogenation of 2,2,2-trifluoroacetophenone; however, only 49% ee was measured at room temperature under 10 bar in 1,2-dichlorobenzene.[307]

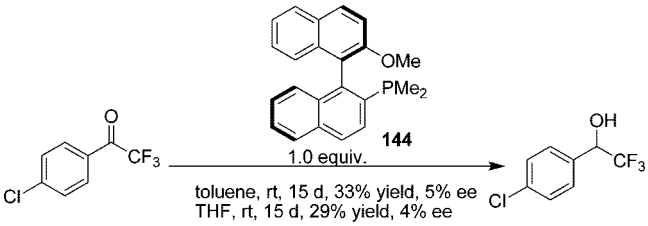
5.1.1.5. Organocatalytic Reductions. Asymmetric phase-transfer catalysis (PTC) is successfully applied in many types of organic reactions; however, application of PTC in the reduction of trifluoromethyl ketones is still unsatisfactory. Pochapsky and co-workers studied the borohydride reduction of 9-anthryl trifluoromethyl ketone in the presence of chiral PTC **143**; the reaction afforded low enantioselectivity (30% ee) (Scheme 64).[308] They also studied the NMR structure of ion pairs derived from quinine. These data provided structural information and permitted building up a model for further rational design of PTC.

In 2007, Shi and co-workers conducted reduction reactions of 2,2,2-trifluoro-1-arylethanones in the presence of 1 equiv of alkyl phosphine, such as trimethylphosphine or tributylphosphine, at room temperature in various solvents to give the corresponding alcohols in good yields. This process involved a hydrogen transfer from alkyl phosphine to the carbonyl group. However, the asymmetric version of this reaction was not successful. When chiral phosphine **144** was used, the reaction was carried out in toluene for 15 days to give only 5% ee (Scheme 65).[309]

Scheme 64



Scheme 65



5.1.2. 1,2-Addition Reactions

Asymmetric 1,2-addition reaction of trifluoromethyl ketones provides direct access to the formation of quaternary carbon centers. Therefore, there is continuing interest in the development of asymmetric syntheses of organofluorine compounds through 1,2-addition reactions. Although the formation of quaternary carbon centers via the addition of carbon nucleophiles to ketones constitutes a major challenge in synthetic chemistry, a few successful examples with trifluoromethyl ketones have been reported.

5.1.2.1. Alkynylation Reactions. The asymmetric nucleophilic alkynylation of carbonyl compounds is of considerable importance in synthetic chemistry. The enantioselective alkynylation of aldehydes with chiral amino alcohols as ligands has gained impressive progress over the past decades, whereas enantioselective nucleophilic alkynylation of prochiral trifluoromethyl ketones is suffering from very limited success. Interestingly, the emergence of Efavirenz has greatly stimulated investigation on alkynylation of prochiral trifluoromethyl ketones. Efavirenz is a potent nonnucleoside HIV reverse transcriptase inhibitor, which is used for the treatment of AIDS.[310] Stereocontrolled nucleophilic addition to carbonyl compounds is a direct and facile synthetic method for the key intermediate **146** in the synthesis of Efavirenz. In 1995, researchers at Merck laboratories developed a highly enantioselective acetylide addition to trifluoromethyl ketone **145** in the presence of *N*-pyrrolidinylnorephedrine (Scheme 66).[311] The reaction proceeded at low temperature (−60 °C) to provide **146** in 98% ee, but it required the use of 2.2 equiv of lithium cyclopropylacetylide and 2.2 equiv of (1*R*, 2*S*)-*N*-pyrrolidinylnorephedrine alkoxide as chiral controller. Upon crystallization from toluene−hexane, the trifluoromethyl alcohol **146** could be obtained in 93% yield with >99.5% ee.[17]

By using ^{13}C and ^{6}Li NMR, IR, X-ray crystallography, and MNDO semiempirical computations, researchers at Merck had further investigated the mechanism of lithium acetylide addition to trifluoromethyl ketones and obtained some important insights. The stereodetermining step involves the formation of the C_2 symmetric 2:2 tetramer of lithium ephedrate and lithium acetylide. The reaction of the 2:2 tetramer with the trifluoromethyl ketone at low temperature resulted in the rapid transfer of one acetylide via β-selective transition structure to give a much less reactive product complex containing two ephedrates, one product alkoxide, and one acetylide. The 1,2-addition is fast as compared to the slow aggregate equilibration. Steric interaction between the aromatic ring and the chiral ligand is the dominant element responsible for the observed selectivity (Scheme 67).[312,313]

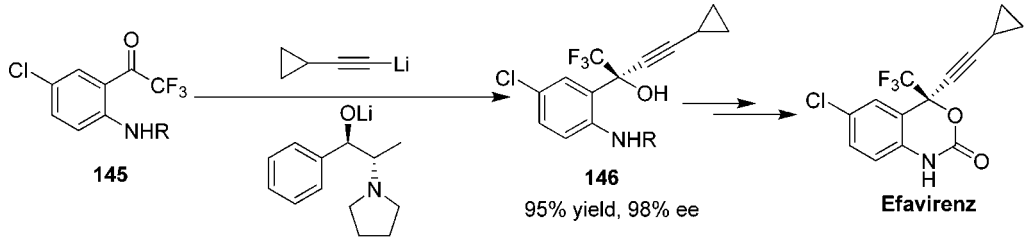
Although the above-mentioned addition reaction proceeded with >98% ee, it required the use of 2.2 equiv of lithium cyclopropylacetylide and 2.2 equiv of (1*R*, 2*S*)-*N*-pyrrolidinylnorephedrine alkoxide as chiral controller. Moreover, an additional protection/deprotection sequence was necessary. Obviously, the direct enantioselective alkynylation of the unprotected ketoaniline would be the most straightforward and efficient asymmetric synthesis of Efavirenz. However, the addition of lithium cyclopropylacetylide to the unprotected ketoaniline by the reported method suffered from low conversion and low enantioselectivity. Tan and co-workers reasoned that the complex of a zinc alkoxide $Zn(OR)_2$ with chloromagnesium acetylide would lower the strong basicity of the lithium reagent and maintain the nucleophilicity of the acetylide. Moreover, a chiral alkoxide could serve as a mediator for asymmetric induction. This conceptually simple approach proved to be highly effective for the asymmetric alkynylation of the unprotected ketoaniline (Scheme 68).[314] The zinc reagent was treated with chloromagnesium cyclopropylacetylide to generate the zincate, which reacted with trifluoromethyl ketone to afford the desired product in high yield with up to 99.2% ee. The reaction could be carried out successfully and reliably on a multikilogram scale and is now the cornerstone of the most efficient synthesis of Efavirenz. The reaction is applicable to other acetylenes and ketoaniline, which gave the corresponding products in high yields and enantioselectivities. It was noteworthy that the presence of an unprotected aniline group adjacent to the carbonyl group of the substrate is important for the reactivity (probably not for selectivity).

In 2002, Jiang and Feng studied the same asymmetric reaction by using C_2-symmetric diamino diols **147** instead of (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine as chiral auxiliary. The nucleophilic addition of a variety of lithium acetylides (2 equiv) to trifluoromethyl ketone **145** was carried out in toluene in the presence of 1 equiv of the chiral auxiliary (**147**). When cyclopropylacetylene was used, the target product **146** could be obtained in 80% yield with 99% ee (Table 58).[315]

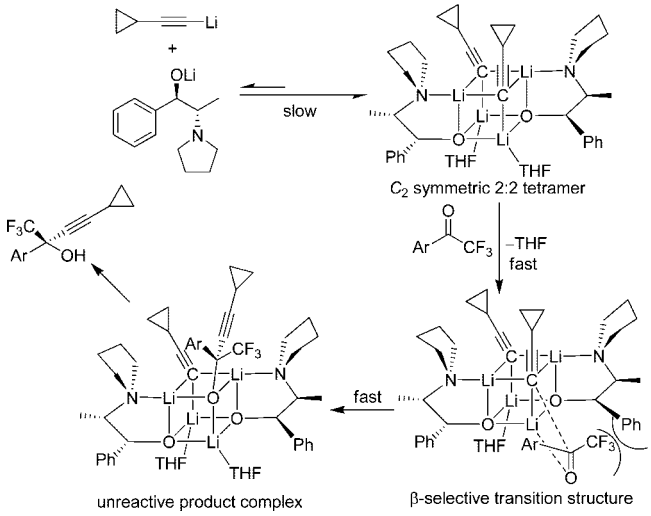
Recently, Kanai, Shibasaki, and co-workers developed a catalytic asymmetric alkynylation of trifluoromethyl ketones for the enantioselective synthesis of CF_3-substituted tertiary propargyl alcohols by using the copper−diphosphine (**148** or **149**) or copper−PyBox (**150**) complex as chiral catalyst. Although enantioselectivity was generally moderate (up to 52% ee), this direct catalytic enantioselective alkynylation of trifluoromethyl ketones opened up a new entry for the construction of enantiomerically enriched tertiary CF_3-substituted propargyl alcohols (Table 59).[316,317]

5.1.2.2. Alkylation and Alkenylation Reactions. Yearick and Wolf reported the asymmetric nucleophilic addition of diethylzinc to trifluoromethyl ketones (Table 60).[318] Sixteen chiral ligands including chiral diamines and bisoxazolines were screened, and ^{t}BuBOX was determined as the best ligand. The asymmetric nucleophilic additions were conducted in the presence of 10 mol % ^{t}BuBOX **151** in

Scheme 66



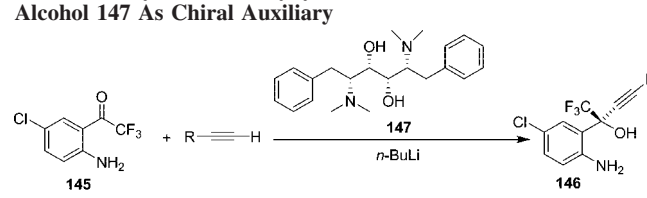
Scheme 67



hexanes/toluene (3/1 v/v) to give the corresponding 2-aryl-1,1,1-trifluorobutan-2-ols in 71−99% yield with 0−63% ee. The reaction has very low tolerance to the R group of trifluoromethyl ketones. 2,2,2-Trifluoroacetophenone and its methoxy, methylthio, methyl, and *tert*-butyl analogues gave tertiary alcohols with moderate enantioselectivities (51−63% ee). However, significantly low ee values were obtained when halides, nitriles, esters, and nitro aryl-substituent groups were present. The reaction of aliphatic substrates was more difficult and needed stoichiometric ligand amounts.

Kanai, Shibasaki, and co-workers also used CuF-DTBM-SEGPHOS (**149**) complex as a chiral catalyst in

Table 58. Asymmetric Alkynylation Reaction with Amino Alcohol 147 As Chiral Auxiliary

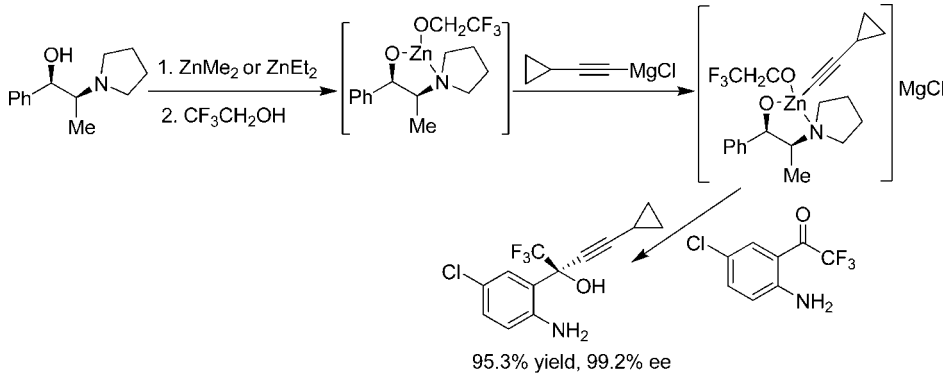


R	yield, %	ee, %
c-C_3H_5	80	99
Ph	82	75
n-C_4H_9	78	53
$TBDMSOCH_2$	75	49
t-Bu	75	11

the catalytic enantioselective alkenylation and phenylation of trifluoromethyl ketones, in which air-stable alkenylsilanes and phenylsilane were used as nucleophiles.[316] The reaction of aryl trifluoromethyl ketones with alkenylsilanes was carried out in toluene at 70 °C using 5−10 mol % Cu-complex to produce the tertiary alcohols in 80−84% ee (Table 61). This is the first example of catalytic enantioselective alkenylation of trifluoromethyl ketones. Compared with alkenylation, the phenylation of trifluoromethyl ketones proceeded with high yields but in moderate enantioselectivities (49% and 67% ee). The products containing a trifluoromethyl-substituted tertiary alcohol moiety are versatile chiral building blocks for pharmaceuticals and agrochemicals and also could be transformed into other useful molecules such as trifluoromethyl-substituted hydroxy carboxylic acid and β-hydroxy carboxylic acid derivatives (Scheme 69).

5.1.2.3. Arylation Reactions. The asymmetric addition of aryl nucleophiles to trifluoromethyl ketones is a facile

Scheme 68



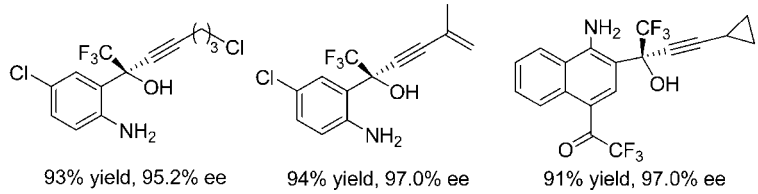
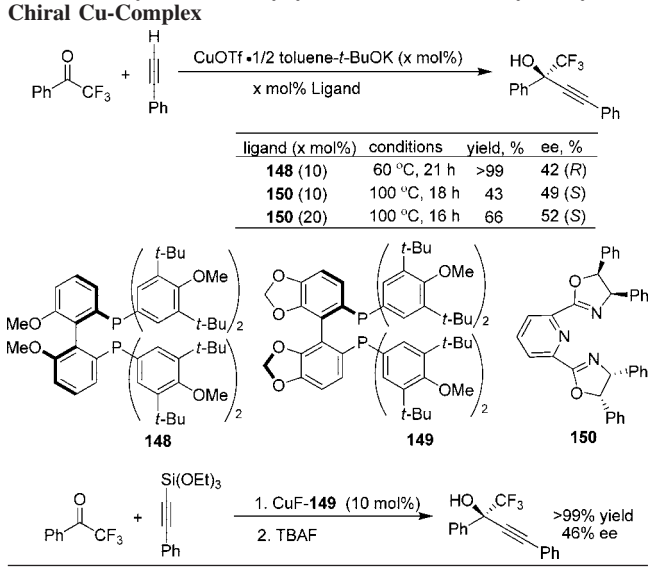
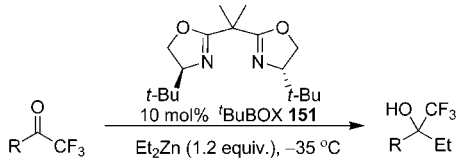


Table 59. Asymmetric Alkynylation Reaction Catalyzed by Chiral Cu-Complex



ligand (x mol%)	conditions	yield, %	ee, %
148 (10)	60 °C, 21 h	>99	42 (*R*)
150 (10)	100 °C, 18 h	43	49 (*S*)
150 (20)	100 °C, 16 h	66	52 (*S*)

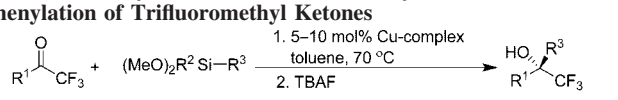
Table 60. ^{t}BuBOX-Catalyzed Addition of Et_2Zn to Trifluoromethyl Ketones



R	yield, %	ee, %	R	yield, %	ee, %
Ph	85	63	3-MeC_6H_4	99	54
4-BrC_6H_4	99	38	3-$NO_2C_6H_4$	83	7
4-ClC_6H_4	74	41	2-ClC_6H_4	99	12
4-$MeOC_6H_4$	83	56	*c*-C_6H_{11}[a]	78	2
4-$MeSC_6H_4$	99	52	*c*-$C_6H_{11}CH_2$[a]	76	0
4-^{t}BuC_6H_4	75	60			
4-CNC_6H_4	71	16			
4-$EtO_2CC_6H_4$	92	25			

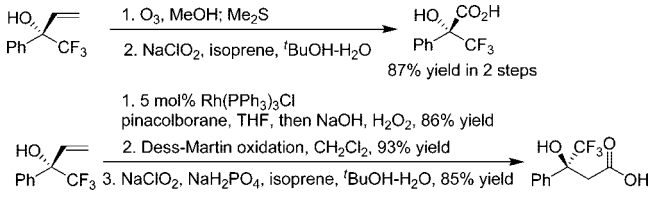
[a] 50 mol% of ^{t}BuBOX at 25 °C

Table 61. Catalytic Enantioselective Alkenylation and Phenylation of Trifluoromethyl Ketones



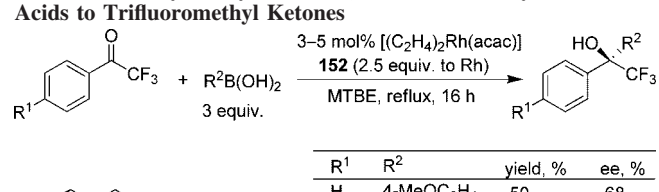
R^1	R^2	R^3	cat., mol%	time (h)	yield, %	ee, %
Ph	Me	-CH=CH_2	5	39	100	84
4-ClC_6H_4	Me	-CH=CH_2	10	43	77	84
4-BrC_6H_4	Me	-CH=CH_2	10	41	92	82
4-MeC_6H_4	Me	-CH=CH_2	10	18	100	83
Ph	MeO	(*E*)-CH=CH$(CH_2)_3CH_3$	10	17	75	80
4-MeC_6H_4	MeO	(*E*)-CH=CH$(CH_2)_3CH_3$	10	45	75	80
4-MeC_6H_4	Ph	Ph	10	10	80	67
2-naphthyl	Ph	Ph	10	37	91	49

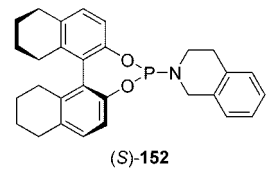
Scheme 69



access to trifluoromethyl-substituted tertiary alcohols. The above-mentioned results (see Table 61, lines 7 and 8) were improved by Feringa and co-workers, who reported the catalytic enantioselective 1,2-addition of a series of arylboronic acids to 2,2,2-trifluoroacetophenones in high

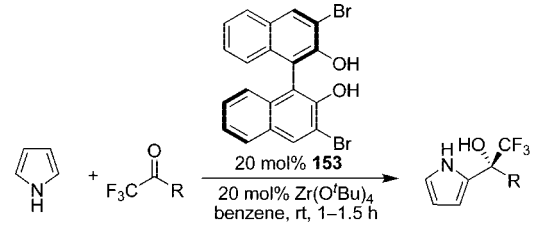
Table 62. Catalytic Asymmetric 1,2-Addition of Arylboronic Acids to Trifluoromethyl Ketones





R^1	R^2	yield, %	ee, %
H	4-$MeOC_6H_4$	50	68
H	4-ClC_6H_4	28	72
Cl	4-$MeOC_6H_4$	96	68
Cl	4-MeC_6H_4	91	83
Cl	Ph	90	79
Cl	3-$MeOC_6H_4$	94	71
Cl	3-MeC_6H_4	91	76
Cl	3-ClC_6H_4	52	83
Cl	2-MeC_6H_4	40	50
Cl	2-naphthyl	69	76

Table 63. Enantioselective Friedel–Crafts Reaction of Pyrrole with Trifluoromethyl Ketones



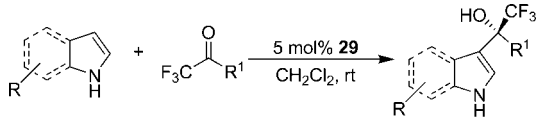
R	yield, %	ee, %	R	yield, %	ee, %
Ph	97	90	4-CNC_6H_4	94	72
4-MeC_6H_4	98	87	3-MeC_6H_4	93	85
4-EtC_6H_4	95	87	3-$MeOC_6H_4$	96	86
4-$MeOC_6H_4$	99	86	3-FC_6H_4	94	80
4-$MeSC_6H_4$	84	93	3,4-$F_2C_6H_3$	96	63
4-FC_6H_4	98	85	3,4-$Cl_2C_6H_3$	96	68
4-ClC_6H_4	99	88	Et	92	21
4-BrC_6H_4	99	77			

isolated yields (up to 96%) and good enantioselectivities (up to 83% ee) using a rhodium(I)/phosphoramidite catalyst. This catalyst was generated in situ from 5 mol % of $[(C_2H_4)_2$-Rh(acac)] and 12.5 mol % of phosphoramidite **152**. The reaction is rather sensitive to electronic effects both in substrate and arylboronic acid (Table 62).[319] Electron-donating substituents on the aryl group of the boronic acid increased the rate of the reaction, whereas the presence of electron-withdrawing substituents has a retarding effect. For example, addition of the less nucleophilic *para*-chlorophenylboronic acid gave the corresponding tertiary alcohol in low yield. In addition, *ortho*-substituted arylboronic acid did not proceed to full conversion, and lower enantioselectivity was observed.

The catalytic enantioselective arylation of a variety of 2,2,2-trifluoroacetophenones with unprotected pyrrole to afford pyrrole derivatives with a trifluoromethyl-substituted tertiary alcohol moiety at the quaternary stereogenic center was reported by Pedro and co-workers.[320] With respect to the trifluoromethyl ketone, an excess of pyrrole (5 equiv) was used to avoid the formation of dialkylated products. The reaction of aromatic trifluoromethyl ketones proceeded in the presence of a zirconium(IV)/3,3′-dibromo-BINOL (**153**) complex at room temperature to give the expected products in 84–99% yield with 63–93% ee. Unfortunately, the reaction with aliphatic trifluoromethyl ethyl ketone took place in good 92% yield, but with a poor 21% ee (Table 63).

In 2009, Ma and co-workers developed the first chiral Brønsted acid-catalyzed direct enantioselective arylation

Table 64. Chiral Brønsted Acid-Catalyzed Direct Enantioselective Arylation of Trifluoromethyl Ketones



Indole or pyrrole	R^1	time (h)	yield, %	ee, %
Indole	Ph	72	99	92
5-MeO-indole	Ph	48	99	92
5-F-indole	Ph	48	99	92
5-Cl-indole	Ph	48	99	90
5-Br-indole	Ph	96	52	92
5-MeO2C-indole	Ph	48	93	90
6-Cl-indole	Ph	48	96	92
7-Me-indole	Ph	48	99	95
7-Et-indole	Ph	48	99	98
Indole	4-$MeOC_6H_4$	48	99	87
Indole	4-MeC_6H_4	36	99	91
Indole	2-MeC_6H_4	96	81	86
Indole	3,5-$Me_2C_6H_3$	48	99	85
Indole	Biphenyl	48	99	90
Indole	3,5-$(CF_3)_2C_6H_3$	36	99	90
Indole	3,4,5-$F_3C_6H_2$	36	91	85
Indole	4-FC_6H_4	36	99	89
Indole	4-ClC_6H_4	36	99	99
Indole	4-BrC_6H_4	36	99	87
Indole	2-Thiophene	72	84	86
Indole	$PhCH_2$	72	86	76
2-Et-pyrrole	Ph	10	99	65

of trifluoromethyl ketones.[321] BINOL-derived phosphoric acids **29**, which have emerged as some of the most successful catalysts in various asymmetric transformations of imines and enamides with high enantioselectivities,[157,322] were used as organic catalysts in this direct arylation. In the presence of 5 mol % phosphoric acid **29**, the reactions were carried out in dichloromethane at room temperature to provide the corresponding trifluoromethyl-substituted tertiary alcohols (Table 64). All kinds of functional groups, including electron-withdrawing, electron-donating, and neutral groups on the aromatic rings of both substrates, are tolerable. In most cases, respectable 81−99% yield and 85−99% ee were obtained. The combination of several advantages including operational simplicity, mild reaction conditions, low catalyst loading, and high yields and enantioselectivities makes this reaction a useful and attractive protocol for the synthesis of chiral trifluoromethyl-substituted tertiary alcohols.

5.1.3. Cycloaddition Reactions

Chiral *N*-heterocyclic carbenes (NHCs) are one kind of organocatalyst, and they have been successfully utilized in a variety of asymmetric reactions.[323,324] Very recently, Ye and co-workers reported a new NHC-catalyzed ketene−ketone cycloaddition reaction.[325] The NHC precursor **154**, derived from L-pyroglutamic acid, was used in this reaction. A wide variety of aryl(alkyl)ketenes reacted with trifluoromethyl ketones to give the corresponding β-trifluoromethyl-β-lactones in good to high yields. The major products, *trans*-lactones **155**, were obtained with up to 99% ee (Table 65). Ketenes with methyl, ethyl, *n*-propyl, and *n*-butyl substituents worked well. However, ketenes with a sterically bulky substituent, such as 2-chlorophenyl and isopropyl, gave no β-lactones. A plausible catalytic cycle was proposed in which the *N*-heterocyclic carbene attacks the α-carbon of the ketene to give a triazolium enolate. Then, the nucleophilic addition of enolate to trifluoromethyl ketone furnishes triazolium ketolate, which collapses to afford the desired lactone and regenerate NHC catalyst.

5.1.4. Aldol Reactions

Asymmetric aldol condensations of trifluoromethyl ketones with suitable nucleophiles provide an alternative and convenient way for the synthesis of optically active trifluoromethyl-substituted tertiary alcohols. Researchers at Boehringer Ingelheim Pharmaceuticals reported a chiral auxiliary-controlled asymmetric aldol reaction of a trifluoromethyl ketone with acetate ester **156**.[326] The reaction of the chiral lithium enolate of **156** with trifluoromethyl ketone **157** afforded the aldol adduct **158** in 95% yield with 78:22 dr. By crystallization, the major isomer was isolated in 45% yield with >98.7:1.3 dr (Scheme 70). The reaction can be carried out on a multikilogram scale and is a practical method for the preparation of drug candidates. On a separate approach, the Lewis acid-catalyzed reactions between silyl ketene acetals and trifluoromethyl ketone **157** failed to give the desired aldol adducts.

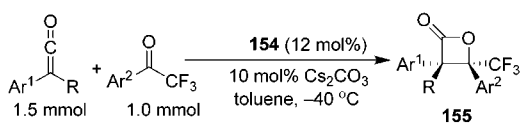
These researchers described another chiral auxiliary-controlled procedure for the one-pot synthesis of product **159**, an intermediate toward glucocorticoid receptor ligands. The process involved the diastereoselective addition of the lithium anion of 1-methyl-4-(methylsulfinyl)benzene to trifluoromethyl ketone **157** to install the chiral alcohol center in **159**. In this reaction, the trifluoromethyl tertiary alcohol was obtained with a diastereomeric ratio of 4:1. Simple recrystallization through a combination of *n*-propanol/EtOAc afforded the desired product **159** in 48% overall yield with >99% de (Scheme 71).[327]

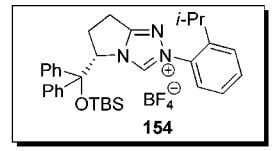
The synthesis of β-hydroxy-β-trifluoromethyl imines was achieved by Liu and co-workers via the aldol condensation of chiral ketimines with a number of trifluoromethylated ketones.[328] In the presence of LDA, a series of *N*-*tert*-butanesulfinyl ketimines were reacted with trifluoromethyl ketones in THF at low temperature (−78 °C) to give β-hydroxy-β-trifluoromethyl imines in good to high yields with diastereomeric ratios ranging from 50:50 to 85:15 (Table 66). For most of the transformations, the major and minor diastereomers were separated by column chromatography. The absolute configuration of the major diastereomer (R^1 = Ph, R = Me^2) was established by X-ray structural analysis, and the stereochemical outcome was rationalized by the chelated transition state. In addition, hydrolysis of the aldol product (R^1 = Ph, R = Me^2) with aqueous HCl and MeOH gave the enantiomerically pure β-hydroxy-β-trifluoromethyl ketone.

Nitroaldol condensation, known as the Henry reaction, is one of the most important C−C bond-forming reactions. The enantioenriched nitroaldol compounds are very useful building blocks for pharmaceuticals and agrochemicals. Jørgensen and co-workers discovered in 2002 a new reaction in which nitrones react with carbonyl compounds in an aldol-type reaction to afford functionalized β-hydroxynitrones.[329] Of interest for our review is the reaction of trifluoroacetophenone with nitrone. This aldol-type reaction can be catalyzed by secondary amines. Among the tested amines, L-proline and the dipeptide L-Pro-L-Leu are the best chiral catalysts. However, the optically active product was only obtained in up to 30% ee (Table 67).

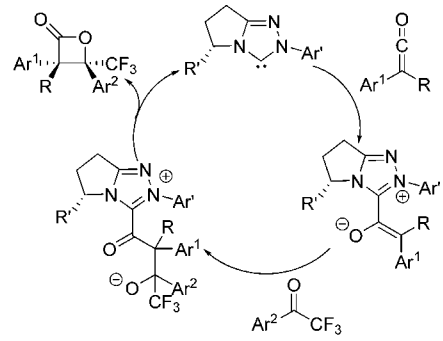
In 2007, the direct catalytic enantioselective nitroaldol (Henry) reaction of simple α-trifluoromethyl ketones was developed by Tur and Saá.[330] In the presence of 25 mol %

Table 65. Chiral NHC-Catalyzed Ketene−Ketone Cycloaddition Reaction

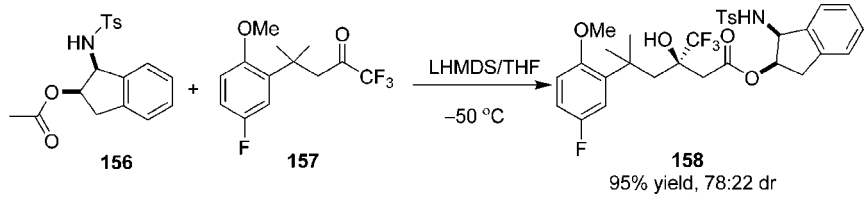




Ar^1	R	Ar^2	yield, %	dr	ee, %
Ph	Et	Ph	81	6:1	97
4-MeC_6H_4	Et	Ph	86	7:1	95
4-$MeOC_6H_4$	Et	Ph	90	7:1	93
Ph	Me	Ph	76	23:1	99
4-MeC_6H_4	Me	Ph	84	17:1	99
Ph	Et	4-ClC_6H_4	89	9:1	98
4-MeC_6H_4	Et	4-ClC_6H_4	93	11:1	99
4-$MeOC_6H_4$	Et	4-ClC_6H_4	95	11:1	97
4-ClC_6H_4	Et	4-ClC_6H_4	90	16:1	93
4-BrC_6H_4	Et	4-ClC_6H_4	83	16:1	93
4-MeC_6H_4	Me	4-ClC_6H_4	96	12:1	99
Ph	Et	4-MeC_6H_4	56	7:1	96
Bn	Et	4-$MeOC_6H_4$	99	1:1	91



Scheme 70



Scheme 71

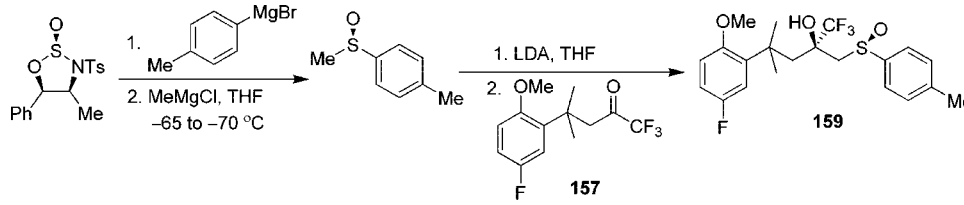
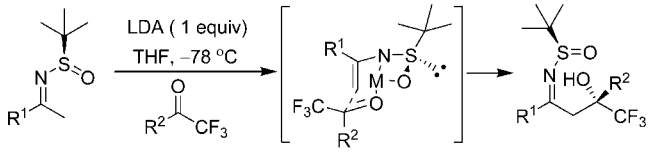


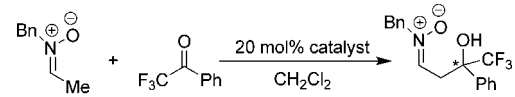
Table 66. Nucleophilic Addition of Chiral Sulfinimine Anions to Trifluoromethyl Ketones



R^1	R^2	yield (%) [a]	dr
Ph	Me	99	85:15
4-$MeOC_6H_4$	Me	72	78:22
4-FC_6H_4	Me	88	82:18
4-ClC_6H_4	Me	81	84:16
4-$NO_2C_6H_4$	Me	62	85:15
t-Bu [b, c]	Me	98	64:36
i-Pr [b]	Me	76	50:50
Ph	Ph	81	59:41
4-FC_6H_4	Ph	84	63:37
4-ClC_6H_4	Ph	82	63:37
t-Bu [c]	Ph	62	71:29
i-Pr	Ph	53	50:50

[a] Isolated total yield of two diastereomers. [b] $MgBr_2$ was added. [c] The diastereomers could not be separated by column chromatography.

Table 67. Enantioselective Nitrone−Aldol Reaction Catalyzed by Chiral Secondary Amines

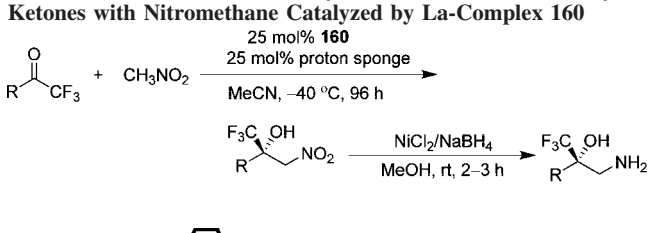


catalyst	yield, %	ee, %
L-Proline	50	30
L-Pro-L-Leu	46	29
L-Pro-L-Phe	22	9
L-Pro-L-Gly	86	21
L-Pro-Ala	81	20

of chiral monometallic lanthanum(III) complex **160** and 25 mol % proton sponge, 1 equiv of trifluoromethyl ketones reacted with 10 equiv of nitromethane in dry CH_3CN at −40 °C to produce the α-trifluoromethyl tertiary alcohols in 50−93% yield with 67−98% ee (Table 68). It was noteworthy that 2,2,2-trifluoro-1-(3-(trifluoromethyl)phenyl)ethanone gave moderate enantioselectivity (67% ee). Probably, the extra 3-CF_3 moiety on the benzene ring might be interfering with the $-COCF_3$ unit in ligating a key center on the catalyst. The nitroaldol adducts are versatile chiral building blocks and may be transformed into β-amino-α-trifluoromethyl tertiary alcohols without loss of enantiomeric purity by using $NiCl_2/NaBH_4$ reduction. This methodology opened up a new entry toward the trifluoromethyl alcohols with quaternary center.

One year later, Bandini and co-workers developed a mild organocatalyzed nitroaldol condensation of fluoromethyl ketones by using cinchona catalysts.[331] It was found that the electronic fine-tuning of the functionalization at the C9-position of cinchona catalysts could strengthen the substrate−

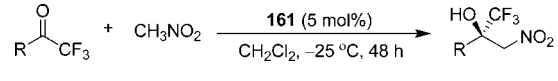
Table 68. Enantioselective Henry Reaction of Trifluoromethyl Ketones with Nitromethane Catalyzed by La-Complex 160

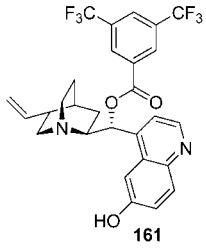


160

R	yield, %	ee, %
Et	55	85
Bn	93	92
Ph	78	96
3-$CF_3C_6H_4$	55	67
4-FC_6H_4	68	97
4-*t*-BuC_6H_4	50	98
Ph−C≡C	82	80

Table 69. Enantioselective Henry Reaction of α-Trifluoromethyl Ketones Catalyzed by 161





161

R	yield, %	ee, %
Bn	70	92
4-ClC_6H_4	80	92
3-$CF_3C_6H_4$	86	96
4-PhC_6H_4	99	97
Ph	85	99
4-FC_6H_4	85	95
4-MeC_6H_4	85	90
4-BrC_6H_4	95	90
Thienyl	79	76
Et	67	93

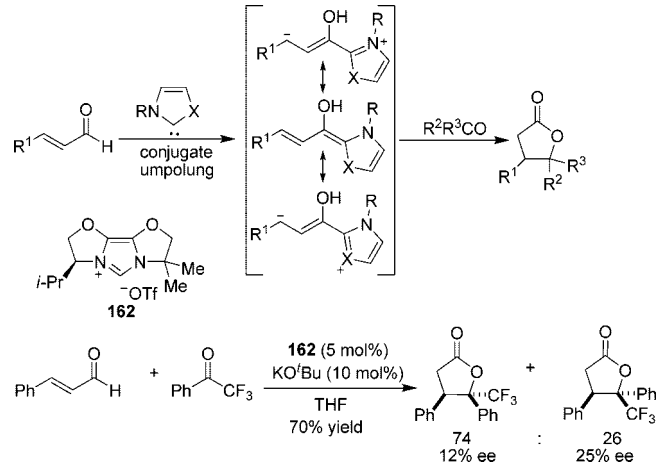
catalyst interactions, with consequent enhancement of the stereodiscrimination. The readily available, soluble, and stable C9-3,5-$(CF_3)_2$-benzoyl substituted catalyst **161** proved to be the optimal catalyst for this reaction. Under mild conditions, trifluoromethyl ketones could undertake the condensation to provide the corresponding products in 67−99% yield with 76−99% ee (Table 69). It was worth noting that both aromatic and aliphatic substrates worked very well. Moreover, the reaction showed high tolerance toward substituents at the different positions of the aromatic ring.

In 2008, Byrstein and Glorius reported a sterically demanding imidazolium- and thiazolium-derived *N*-heterocyclic carbene-catalyzed conjugated umpolung of α,β-unsaturated aldehydes for the selective formation of fluorinated γ-butyrolactone. Under optimal reaction conditions, a number of differently substituted trifluoromethyl ketones reacted with cinnamaldehyde derivatives (Scheme 72). This methodology provides a versatile and powerful tool to synthesize a series of substituted γ-lactones. Interestingly, in the presence of chiral imidazolium salt **162** (5 mol %), the reaction of cinnamyl aldehyde with phenyl trifluoromethyl ketone gave the corresponding product in 70% yield, albeit with low diastereo- and enantioselectivities (*trans*/*cis*: 74/26, 12% ee/25% ee, respectively).[332]

5.1.5. Hydrocyanation Reactions

To prepare (*R*)- and (*S*)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid, which are intermediates for the synthesis

Scheme 72



Scheme 73

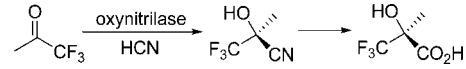
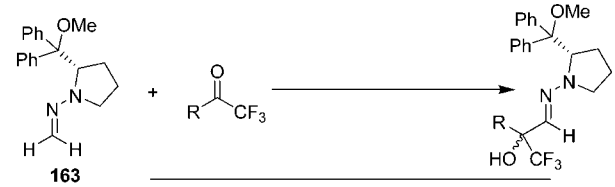
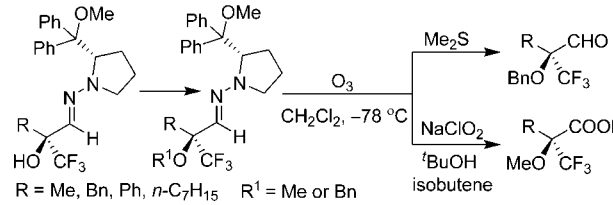


Table 70. Diastereoselective Nucleophilic 1,2-Addition of Formaldehyde Dialkylhydrazone 163 to Trifluoromethyl Ketones



163

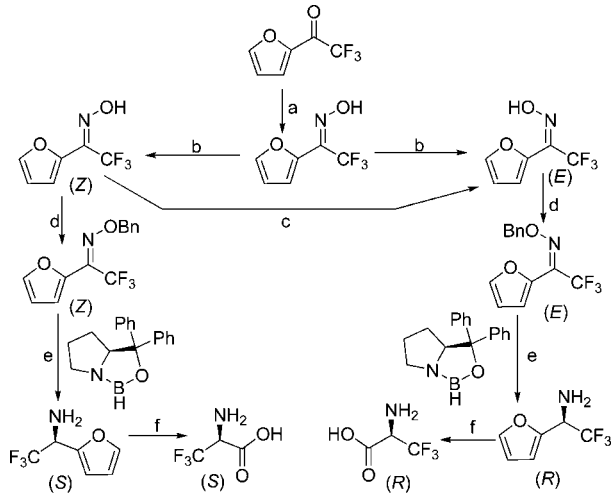
R	solvent	yield, %	dr
Me	toluene	90	70:30
Bn	cyclohexane	91	81:19
Ph	neat	90	58:42
n-C_7C_{15}	neat	85	62:38
thiophen-2-yl	neat	82	51:49



of a number of potential pharmaceuticals including ATP-sensitive potassium channel openers for the treatment of incontinence and inhibitors of pyruvate dehydrogenase kinase for the treatment of diabetes, the researchers at Lonza AG attempted to use the biocatalyzed enantioselective hydrocyanation reaction of trifluoroacetone. Screening for enantioselective oxynitrilases and enantiospecific nitrilases had been started but given up finally because another synthetic route was found to be successful (Scheme 73).[333] However, this direct hydrocyanation certainly deserves further attention.

Using formaldehyde dialkylhydrazones as a new class of neutral formyl anion and cyanide equivalents, Lassaletta and co-workers developed the diastereoselective nucleophilic 1,2-addition reaction of formaldehyde dialkylhydrazone **163** to trifluoromethyl ketones to afford α-hydroxy-α-trifluoromethylhydrazones (Table 70). The chiral formaldehyde hydrazones reacted easily with a variety of trifluoromethyl ketones in the absence of any catalyst or promoter, giving rise to the expected α-hydroxy-α-trifluoromethylhydrazones in 82−91% yield with moderate

Scheme 74



diastereoselectivity. Fortunately, both (*S*,*S*)- and (*R*,*S*)-diastereoisomers could be easily separated by simple flash chromatography. These products could be decorated to give enantiomerically pure α-alkoxy-α-trifluoromethyl aldehydes and carboxylic acids.[334]

5.2. From Nitrogen-Containg Derivatives of Trifluoromethyl Ketones

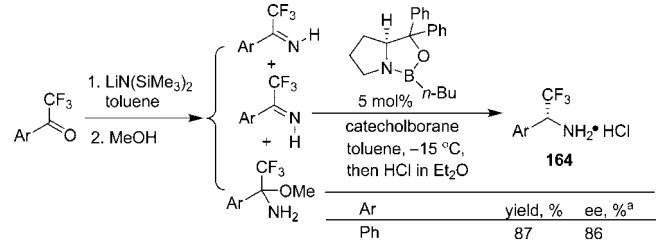
Many kinds of nitrogen-containing materials, derived from trifluoromethyl ketones, have been used for the preparation of amines, amine alcohols, amino acids, and other products. These derivatives can be easily generated in situ or beforehand. Because of high activity and diverse structures, these nitrogen-containing derivatives of trifluoromethyl ketones are very attractive substrates for the synthesis of various chiral trifluoromethyl compounds.

5.2.1. Reduction Reactions

Direct reduction of trifluoromethyl ketimines and analogues allows for efficient syntheses of trifluoromethylated amines with high degrees of stereocontrol. Demir and co-workers described an asymmetric synthesis of both enantiomers of 2,2,2-trifluoro-1-furan-2-yl-ethylamine and 3,3,3-trifluoroalanine from 2,2,2-trifluoro-1-furan-2-yl-ethanone.[335] First, 2,2,2-trifluoro-1-furan-2-yl-ethanone was selectively converted into its (*E*)- and (*Z*)-oximes and further oxime ethers in good yields. Subsequently, enantioselective reduction of the corresponding *O*-benzyl oxime ethers was achieved with BH_3 in the presence of oxazaborolidine complexes to afford both enantiomers of 2,2,2-trifluoro-1-furan-2-yl-ethylamine in good yields with up to 88% ee (Scheme 74). Finally, oxidation of the furan ring with ozone gave both enantiomers of 3,3,3-trifluoroalanine in 91−93% yields. The chirality of the amine products is controlled by the appropriate choice of geometrical isomer of the *O*-benzyloxime.

Gosselin and co-workers developed a one-pot reductive amination reaction for the preparation of perfluoroalkylamines by using CBS catalyst.[336] Addition of lithium bis(trimethylsilyl)amide to perfluorinated ketones gave (*E*)-*N*-TMS−ketimines, and subsequent solvolysis in MeOH led to the formation of bench-stable N−H imines (*Z*/*E* isomers)

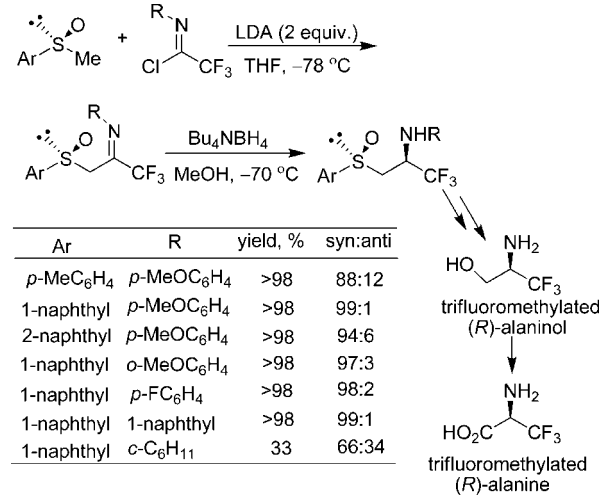
Table 71. Reductive Amination Catalyzed by CBS Catalyst



Ar	yield, %	ee, %[a]
Ph	87	86
3-BrC_6H_4	72	86 (91)
4-C_6H_4	95	91
2-$MeSC_6H_4$	93	88 (99)
3-$MeSC_6H_4$	84	85
2-PhC_6H_4	88	98 (99)
2-naphthyl	86	75
9-phenanthryl	84	97 (99)

[a] % ee of crude free amine, values in parentheses for isolated hydrochloride salts.

Table 72. Reduction of Fluorinated β-Sulfinylimines and Subsequent Synthetic Transformations



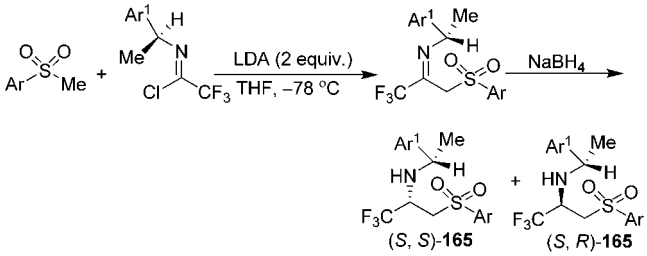
Ar	R	yield, %	syn:anti
p-MeC_6H_4	*p*-$MeOC_6H_4$	>98	88:12
1-naphthyl	*p*-$MeOC_6H_4$	>98	99:1
2-naphthyl	*p*-$MeOC_6H_4$	>98	94:6
1-naphthyl	*o*-$MeOC_6H_4$	>98	97:3
1-naphthyl	*p*-FC_6H_4	>98	98:2
1-naphthyl	1-naphthyl	>98	99:1
1-naphthyl	*c*-C_6H_{11}	33	66:34

along with the methanol adduct. In the presence of CBS catalyst, enantioselective reduction of these three-component mixtures afforded the trifluoromethylated amines **164** in 72−95% yield with 75−98% ee (Table 71).

Fluorinated β-sulfinylimines, available from imidoyl chloride and chiral sulfoxide, are suitable starting materials for the synthesis of trifluoromethylated alaninol and alanine.[337] A highly efficient hydride reduction of fluorinated β-sulfinylimines was realized in the presence of Bu_4NBH_4 in pure methanol or THF/methanol at −70 °C. Nearly quantitative yields of β-sulfinylamines were obtained with high diastereoselectivities (up to 99:1). (The similar products were also diastereoselectively formed in the reaction of chiral α-lithiated alkyl-*p*-tolysulfoxide with trifluoromethylaldimines;[104] see section 2.4.1.) However, the imine derived from cyclohexylamine gave low yield and stereoselection (Table 72). These enantiopure β-sulfinylamines were readily converted into trifluoromethylated alaninol and alanine in several steps with respectable yields.

Similarly, the diastereoselective reduction of β-imino sulfones, derived from trifluoromethylated chiral imidol chloride, provided a simple and direct way to the synthesis of fluorinated β-amino sulfones **165**.[338] In this reaction, the use of $NaBH_4$ as reducing agent and ethanol or THF/methanol as solvent gave the best diastereocontrol. In addition, the observed selectivity was affected by the size of the aromatic substitutents, particularly those on the imino

Table 73. Diastereoselective Reduction of Chiral β-Imino Sulfones



Ar	Ar[1]	reduction conditions	yield, %	(S, S):(S, R)
Ph	Ph	EtOH, 40 h, 25 °C	>99	70:30
Ph	Ph	EtOH, 48 h, −20 °C	>99	73:27
p-MeC$_6$H$_4$	Ph	THF/MeOH, 72 h, 25 °C	>99	76:24
p-MeC$_6$H$_4$	Ph	THF/MeOH, 96 h, −20 °C	>99	77:23
2-naphthyl	Ph	THF/MeOH, 72 h, 25 °C	>99	77:23
2-naphthyl	Ph	EtOH, 96 h, −20 °C	>99	79:21
Ph	1-naphthyl	THF/MeOH, 72 h, 25 °C	>99	83:17
2-naphthyl	1-naphthyl	THF/MeOH, 72 h, 25 °C	>99	82:18
2-naphthyl	1-naphthyl	EtOH, 96 h, −20 °C	93	85:15
1-naphthyl	1-naphthyl	EtOH, 48 h, 25 °C	>99	89:11
1-naphthyl	1-naphthyl	EtOH, 72 h, −20 °C	94	93:7
1-naphthyl	1-naphthyl	EtOH, 240 h, −40 °C	>99	96:4

nitrogen moiety. The larger naphthyl group provided higher diastereocontrol than the smaller phenyl group (Table 73).

Török and Prakash described an efficient palladium-catalyzed diastereoselective heterogeneous hydrogenation reaction for the synthesis of chiral 2,2,2-trifluoro-1-phenylethylamines.[339] This one-pot process involved the diastereoselective hydrogenation of chiral imines and subsequent hydrogenolysis. The hydrogenation of (*R*)-imine led to the formation of (*R*,*R*)-secondary amine as the major product (Scheme 75). In the process of hydrogenolysis, advantageous secondary kinetic resolution was observed. The (*R*,*R*)-diastereomer proceeded with a significantly higher reaction rate than the (*R*,*S*)-diastereomer. As a result, the diastereomeric excess of the starting material (73% de) was gradually increased. Finally, the desired trifluoromethyl (*R*)-amine was obtained in 50−55% yield with 90−93% ee. Likewise, the trifluoromethyl (*S*)-amine was prepared using (*S*)-imine.

In 2007, Hughes, Devine, and co-workers reported another diastereoselective reduction of trifluoromethylketimines, which were prepared in a K_2CO_3-mediated condensation of 2,2,2-trifluoroacetophenones with chiral α-amino esters.[340] As shown in Table 74, by choosing $NaBH_4$ or $Zn(BH_4)_2$ as the reducing agent, they found that the reaction allowed for the stereoselective access to either the (*R*,*S*)- or (*S*,*S*)-diastereomer of 1-aryl-2,2,2-trifluoroethyl-substituted amino acids **166** in moderate to excellent yields. The diastereoselective ratio could be up to 46:1 or 1:21. Preliminary mechanistic studies showed that the hydride (generated from nonchelating reductant $NaBH_4$) attacks the *Si*-face of the imine, whereas a chelating reductant $Zn(BH_4)_2$ allowed for the attack at the *Re*-face. The reversal in selectivity was observed upon switching from $NaBH_4$ to $Zn(BH_4)_2$. The simplicity and flexibility of this methodology, along with the availability of a wide variety of 2,2,2-trifluoroacetophenones and α-amino esters, make it an appealing protocol for the synthesis of fluorinated α-amino acids.

The asymmetric 1,2-reduction of chiral trifluoromethyl α,β-unsaturated *N*-*tert*-butanesulfinyl ketoimines was reported by Liu and Liu (Table 75).[341] (R_S,*R*)-allylic amines were obtained in high yields with excellent diastereoselectivities when DIBALH was employed as the metal hydride reagent. Interestingly, L-Selectride gave (R_S,*S*)-allylic amines as the major products with hexamethylphosphoramide (HMPA) as a cosolvent. The stereochemical outcome was rationalized by using a cyclic transition state for the DIBALH reductions and an open transition state for the L-Selectride reactions. The probable role of HMPA in the reaction system is to coordinate with lithium(I) ion and disrupts the chelation of Li(I) with sulfinyl oxygen.

5.2.2. Transamination Reactions

[1,3]-Proton shift reaction (PSR), a reducing agent-free biomimetic reductive amination, has been developed as a simple, convenient, and useful protocol for the preparation of various fluorine-containing amino compounds. Soloshonok and co-workers have extensively explored the application of PSR in the preparation of all kinds of fluorine-containing amino molecules (see also section 4.2.1).[342,343] In general, asymmetric PSR was realized through a chiral amine substrate-control isomerization and allowed for preparing enantiomerically pure fluorinated amines from alkyl fluoroalkyl and aryl fluoroalkyl ketones. As indicated in Table 76, *N*-(α-phenylethyl)imine can be readily prepared from chiral α-phenylethylamine under Dean−Stark conditions in excellent yields (>90%). In the presence of the strong base DBU, the clean and complete isomerization of imine to Schiff base produced the desired products in 74−95% yield with 87−97% ee.[344] DBU not only plays a role of the catalyst but also works as a unique reaction medium facilitating the isomerization. To avoid racemization and dehydrofluorination, Soloshonok's group explored continuous-flow reaction for this reductive amination of fluorinated carbonyl compounds to amines, using silica-adsorbed DBU as catalyst for on-column process. Compared with in-flask reactions, these continuous-flow reactions could give improved yield or enantioselectivity in most of the cases. For example, in the case of phenyl trifluoromethyl ketone, the amine product was obtained with the same yield but with increased enantioselectivity from 87 to 93% ee.[345]

Besides the stoichiometric asymmetric version, Soloshonok's group also disclosed the catalytic asymmetric synthesis of α-(trifluoromethyl)benzylamine via biomimetic transamination by using chiral base as catalyst. Achiral imine was isomerized to Schiff base in the presence of 50 mol % of cinchonidine in chloroform at room temperature.[346] The product (*R*)-imine was obtained in 35% ee as sole compound without any byproducts. The catalyst cinchonidine can be recovered (>95%) by adding *n*-hexane to the reaction mixture and a simple filtration. However, the reaction was extremely slow; 19% and 79% conversion of the starting imine required 8 and 52 days, respectively (Scheme 76).

5.2.3. Strecker-Type Reactions

In 2006, Huguenot and Brigaud reported Strecker-type reactions of chiral CF_3-containing imines or oxazolidines to prepare diastereomerically pure α-trifluoromethyl α-amino nitriles.[100] In all cases, the Strecker-type reaction with trimethylsilylcyanide (TMSCN) was very efficiently promoted in mild conditions with a catalytic amount of $Yb(OTf)_3$ or 1.5 equiv of $BF_3 \cdot OEt_2$. The expected amino nitriles were obtained in 75−97% yield, albeit with low to moderate diastereoselectivities (Scheme 77). Interestingly,

Scheme 75

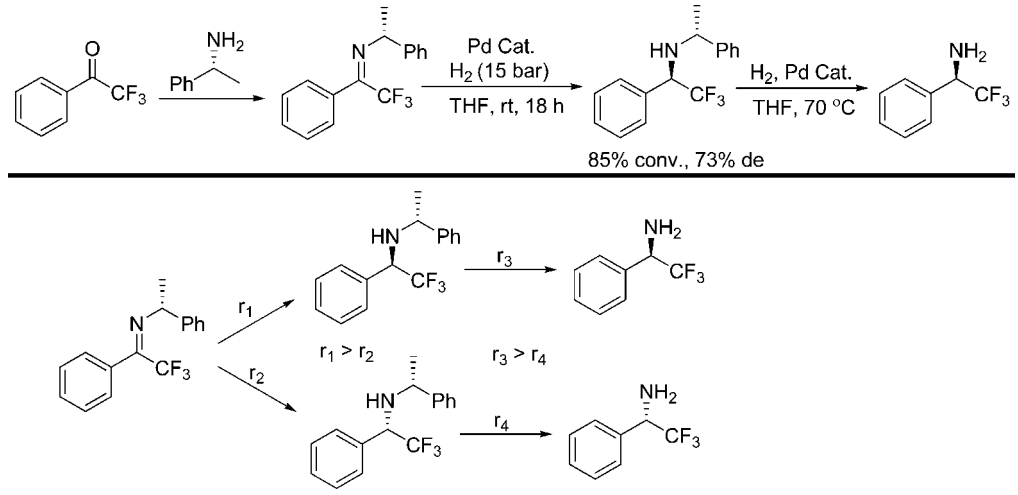
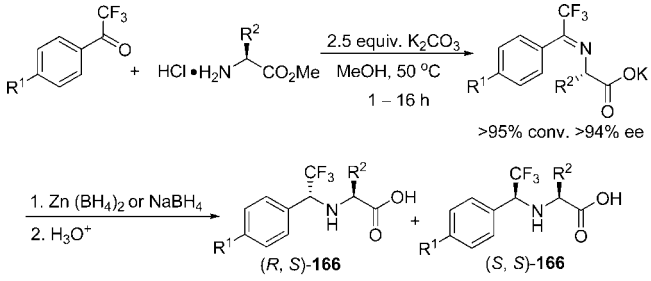
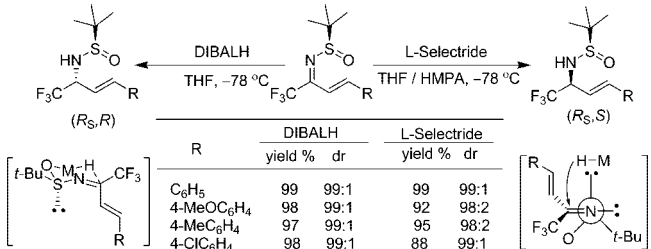


Table 74. Diastereoselective Reduction of Trifluoromethylketimines



R^1	R^2	$NaBH_4$		$Zn(BH_4)_2$	
		yield, %	(*R*,*S*):(*S*,*S*)	yield, %	(*R*,*S*):(*S*,*S*)
H	Me	58	10:1	45	1:15
H	*i*-Bu	79	19:1	90	1:13
H	*i*-Pr	86	25:1	92	1:21
Br	Me	46	4:1	46	1:8
Br	*i*-Bu	76	17:1	76	1:12
Br	*i*-Pr	91	46:1	80	1:12
MeO	Me	53	4:1	48	1:8
MeO	*i*-Bu	79	19:1	76	1:16
MeO	*i*-Pr	75	33:1	72	1:13

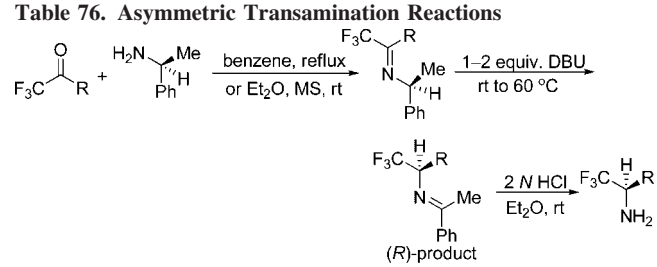
Table 75. Reduction of Trifluoromethyl Ketoimines with DIBALH and L-Selectride



R	DIBALH		L-Selectride	
	yield %	dr	yield %	dr
C_6H_5	99	99:1	99	99:1
4-$MeOC_6H_4$	98	99:1	92	98:2
4-MeC_6H_4	97	99:1	95	98:2
4-ClC_6H_4	98	99:1	88	99:1
4-BrC_6H_4	97	99:1	96	98:2
2-$MeOC_6H_4$	97	99:1	96	97:3
3-BrC_6H_4	93	97:3	90	99:1
1-Naphthyl	96	99:1	94	99:1
2-Furyl	94	98:2	97	98:2
$C_6H_5C{\equiv}C$	93	96:4	81	95:5
n-C_6H_{17}	87	99:1	60	96:4
$C_6H_4(CH_2)_3$	81	99:1	62	99:1

by assistance of the (*R*)-phenylglycinol side chain, each diastereomer could be efficiently obtained in diastereomerically pure form after silica gel separation. More importantly, chiral α-trifluoromethyl α-amino nitriles proved to be versatile intermediates, and could easily be transformed into enantiopure α-trifluoromethyl alanine, diamines, and amino

Table 76. Asymmetric Transamination Reactions



R	In-flask reaction		Continuous-flow reaction	
	yield, %	ee, %	yield, %	ee, %
Ph	95	87	95	93
Bn	86	88	93	91
Me	94	93	95	93
Et	90	87	92	91

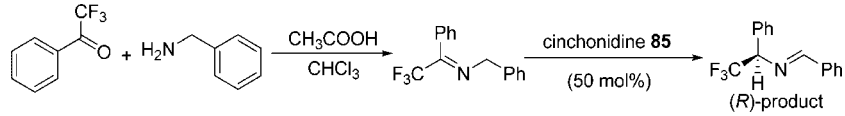
alcohols, which are valuable fluorinated synthons and potential ligands for organometallic chemistry.

The synthesis of α-trifluoromethyl α-amino acids from trifluoromethylated *N*-*tert*-butanesulfinyl ketimines through the asymmetric Strecker reaction was achieved by Lu and co-workers (Table 77).[347] A variety of aromatic and aliphatic ketimines were evaluated to afford the corresponding adducts in good to high yields and diastereoselectivities. Notably, the reaction in hexane gave (R_S,*S*)-adducts under the optimized conditions, while DMF provided the opposite (R_S,*R*)-diastereomer. On the basis of the diastereoselectivity observed, a possible mechanism was proposed. The Strecker reaction in hexane could proceed via the six-membered chairlike models where the sulfinyl group activates the TMSCN and the equatorial position of the CF_3 moiety minimizes electrostatic repulsion, providing (R_S,*S*)-product. In DMF, an open transition state was proposed where the Lewis basic DMF can activate TMSCN instead of the sulfinyl group to give the diastereomer with (R_S,*R*) configuration. Additionally, it was found that the reaction of *N*-*tert*-butanesulfinyl ketimines without a CF_3 substituent cannot proceed under these conditions. Hydrolysis of one of the adducts (R = Ph) gave (*S*)-2-amino-2-phenyl-1,1,1-trifluoropropanoic acid in 80% yield.

5.2.4. Cyclopropanation Reactions

Considerable attention has been placed in the chemistry of donor/acceptor-substituted rhodium carbenoids, which have demonstrated great efficiency in a wide range of highly

Scheme 76



Scheme 77

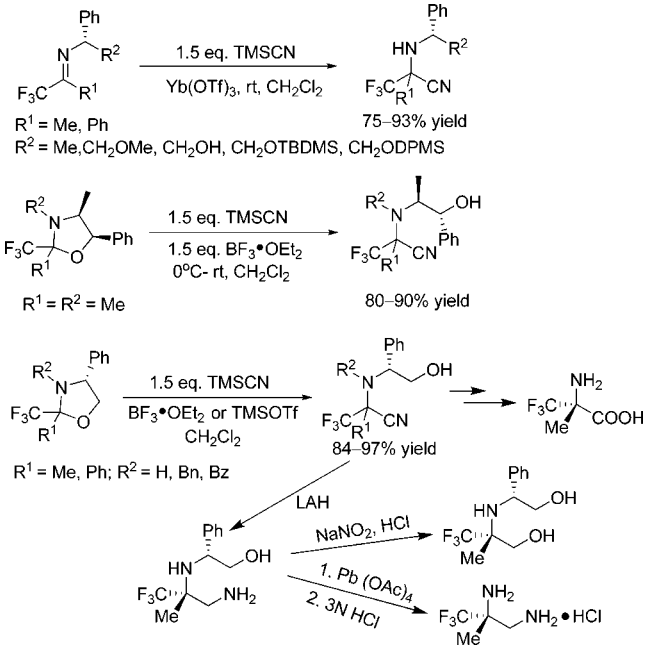
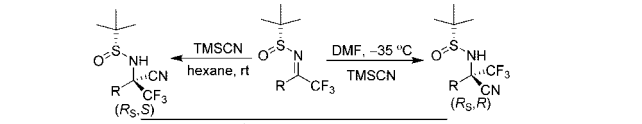
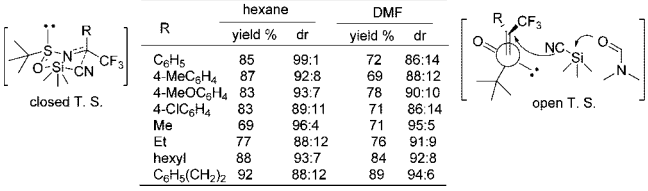


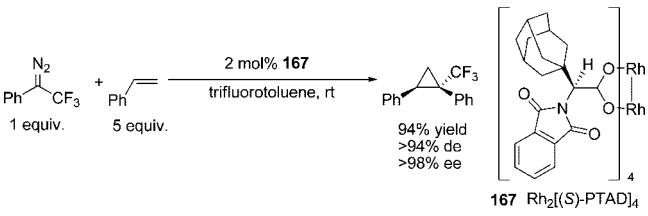
Table 77. Addition of TMSCN to Trifluoromethylated *N-tert*-Butanesulfinyl Ketimines



R	hexane yield %	hexane dr	DMF yield %	DMF dr
C_6H_5	85	99:1	72	86:14
4-MeC_6H_4	87	92:8	69	88:12
4-$MeOC_6H_4$	83	93:7	78	90:10
4-ClC_6H_4	83	89:11	71	86:14
Me	69	96:4	71	95:5
Et	77	88:12	76	91:9
hexyl	88	93:7	84	92:8
$C_6H_5(CH_2)_2$	92	88:12	89	94:6

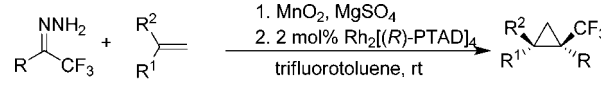


Scheme 78



selective reactions. In 2007, Davies and co-workers explored the cyclopropanation chemistry of trifluoromethyl ketoimines by using these rhodium carbenoids (Scheme 78).[348] To avoid isolation of the diazo compound, the reactions were conducted through a two-step sequence. Oxidation of the hydrazone with MnO_2 generated the diazo compound in situ, which was then exposed to cyclopropanation conditions to give the corresponding cyclopropanation products. The process is effective with a range of styrene derivatives and trifluoromethyl ketones. In the presence of Rh_2-[(*R*)-PTAD)]$_4$ (*R*-**167**), the reaction of 1-aryl-2,2,2-trifluorodiazoethanes with alkenes afforded trifluoromethyl-substituted cyclopropanes with high diastereoselectivities (>94%) and enantioselectivities (88−98%) (Table 78). These studies further broaden the range of donor/acceptor-substituted rhodium carbenoids that are capable of highly stereoselective transformations.

Table 78. Rh-Catalyzed Asymmetric Cyclopropanation of Trifluoromethyl Hydrazone Derivatives



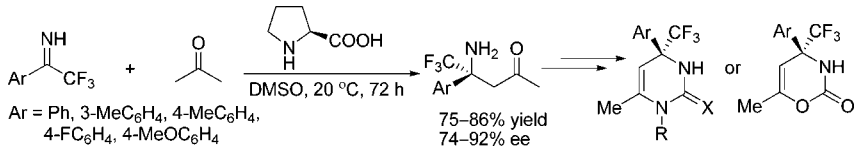
R	R^1	R^2	yield, %	de, %	ee, %
Ph	Ph	H	71	>94	>98
Ph	4-MeC_6H_4	H	72	>94	90
Ph	4-$MeOC_6H_4$	H	76	>94	88
Ph	4-ClC_6H_4	H	64	>94	90
Ph	4-$CF_3C_6H_4$	H	61	>94	>94
Ph	2-naphthyl	H	75	>94	89
4-MeC_6H_4	Ph	H	75	>94	>98
4-FC_6H_4	Ph	H	78	>94	97
4-BrC_6H_4	Ph	H	77	>94	98
4-BrC_6H_4	4-BrC_6H_4	H	78	>94	>98
4-BrC_6H_4	4-$NO_2C_6H_4$	H	75	>94	>98
4-BrC_6H_4	2-naphthyl	H	80	>94	98
4-BrC_6H_4	Ph	Ph	75	-	>98

5.2.5. Mannich Reactions

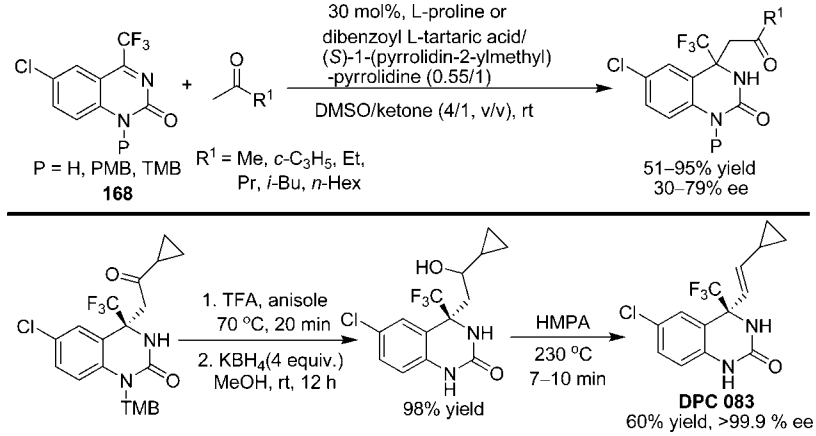
The asymmetric Mannich reaction of ketimines is a well-studied addition process. However, the use of trifluoromethyl ketimines as electrophiles has not been well developed. Vovk and co-workers reported a L-proline-catalyzed asymmetric Mannich reaction of aryl trifluoromethyl ketimines with acetone.[349] In the presence of 10 mol % L-proline, trifluoromethyl ketimines reacted with 5 equiv of acetone in dimethylsulfoxide (DMSO) at room temperature within 3 days to furnish β-trifluoromethyl-β-aminoketones in high yields with 74−92% ee (Scheme 79). The resulting products could be further transformed into trifluoromethyl substituted 1,3-aminoalcohols and 1,3-diamines. In addition, these β-trifluoromethyl-β-aminoketones have been successfully applied in the synthesis of optically active heterocycles containing a quaternary endocyclic chiral center, e.g., 4-trifluoromethyl-substituted 3,4-dihydropyrimidin-2(1H)-(thi)ones and 3,4-dihydro-1,3-oxazin-2-ones.[350]

The same year, Jiang and co-workers presented a diamine−Brønsted acid-catalyzed regio- and enantioselective Mannich reaction for the construction of trifluoromethyl-substituted dihydroquinazoline with a quaternary carbon center.[351] In the reaction of 4-trifluoromethyldihydroquinazoline **168** with diverse methyl ketones, high regioselectivities were observed in most cases. The dihydroquinazoline was regioselectively attacked by methyl ketones to give the β-amino ketone as the sole product. Although the combination of diamine and Brønsted acid resulted in 51−95% yield with 30−79% ee (Scheme 80, top), the ee values of the Mannich adducts can be easily improved up to >99% by a single recrystallization thanks to the precipitation of the heterochiral hydrogen-bonded dimers. A rapid and

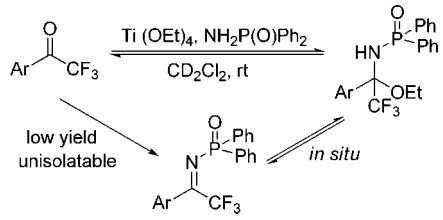
Scheme 79



Scheme 80



Scheme 81



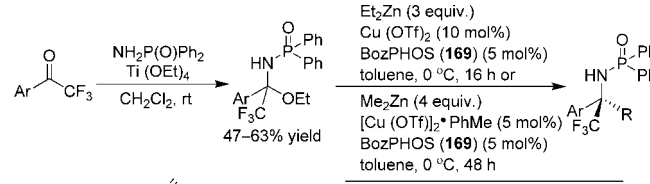
facile access to enantipure non-nucleoside reverse transcriptase inhibitor DPC 083 (>99.9% ee) has been described (Scheme 80, bottom).

5.2.6. Alkylation and Alkynylation Reactions

Because of lower reactivity of ketimines (compared to aldimines) toward nucleophilic addition, the number of methods for asymmetric construction of trifluoromethylated tertiary amines by this approach is very limited. Lauzon and Charette designed a copper-catalyzed asymmetric addition of diorganozinc reagents to *N*-phosphinoylimines for the synthesis of chiral α,α,α-trifluoromethylamines.[352] Direct synthesis of the trifluoromethyl ketimines was not successful. As a result, various trifluoromethyl ketones were treated with *P*,*P*-diphenyl phosphinamide in the presence of Lewis acid $Ti(OEt)_4$ to give the corresponding stable hemiaminals in 47−63% yield, which could be used to generate the corresponding trifluoromethylimines in situ in the presence of dialkylzinc (Scheme 81). Therefore, the hemiaminals were treated with 3.0 equiv of Et_2Zn or 4.0 equiv of Me_2Zn, copper salt (10 mol %), and (*R*,*R*)-BozPHOS (**169**) (5 mol %) to provide the desired products in 71−89% yield with 91−99% ee. Both diethylzinc and less-reactive dimethylzinc proceeded very well (Table 79).

Recently, Hoveyda and co-workers disclosed Zr-catalyzed enantioselective alkylations of trifluoromethyl ketimines with dialkylzinc reagents to furnish *N*-substituted quaternary carbon by using inexpensive dipeptides **170** as chiral ligands.[353] A series of trifluoromethyl ketimines could be catalytically alkylated in 66−96% yield with 96−98% ee (Table 80). However, there are some substrates for which the addition reaction is difficult. For example, the ketimine with diminished electrophilicity and the steric hindrance of an *o*-methoxy substituent could not undertake alkylation even at 60 °C for 48 h. The *o*-methoxy group of the *N*-activating unit and the two amino acid moieties of the chiral ligand play an important role in the catalytic process. A working model was proposed in which the amine group of the chiral

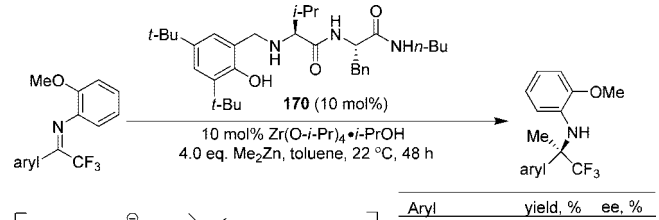
Table 79. Copper-Catalyzed Asymmetric Addition of Dialkylzinc Reagents to *N*-Phosphinoylimines

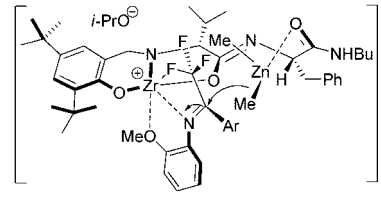


(*R*, *R*)-BozPHOS
169

Ar	R	yield, %	ee, %
Ph	Et	83	91
Ph	Me	85	99
4-BrC_6H_4	Et	71	95
4-BrC_6H_4	Me	89	97
3-MeC_6H_4	Et	78	95
3-MeC_6H_4	Me	84	99
4-MeC_6H_4	Et	77	97
2-Naphthyl	Et	73	94
4-ClC_6H_4	Et	71	93

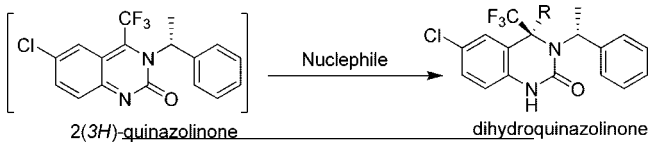
Table 80. Zr-Catalyzed Enantioselective Alkylations of Trifluoromethyl Ketimines





Aryl	yield, %	ee, %
Ph	93	>98
4-BrC_6H_4	92	>98
4-$CO_2MeC_6H_4$	70	96
4-$MeOC_6H_4$	66	>98
2-$MeOC_6H_4$	<2	-
	96	98

Table 81. 1,4-Addition of Nucleophiles to Chiral CF_3-Substituted 2(3*H*)-Quinazolinones



2(3*H*)-quinazolinone dihydroquinazolinone

nucleophile	Temp, °C	con. %	de %
CPAMgCl [a]	–60	95	92
CPAMgCl [a]	–10	97	80
CPALi [a]	–70	95	85
CH_3OH	–5	97	80
$CH_2{=}CH_2MgBr$	–60	88	95
$CH_2{=}CH_2MgBr$	0	90	70
PhMgCl	–60	35	95
PhLi	–20	40	40
$PhCH_2MgCl$	–60	93	10
CH_3MgI	–60	90	55
CH_3ZnCl	–5	94	85
Li(*t*-BuO)$_3$AlH	–60	94	85
	–60	89	95

[a] CPA = cyclopropylacetylene

ligand allows for the formation of a Zr−N bond, stabilizing a Lewis acidic cationic metal center and resulting in a favorable complex caused by the dissociation of a sterically demanding isopropoxide ligand. In addition, the reactive complex could involve chelation of a fluoride atom with the Lewis acidic Zr center.

Magnus and co-workers described a practical 1,4-addition of nucleophiles to chiral CF_3-substituted 2(3*H*)-quinazolinones.[354,355] The hydrate hydrochloride ketoaniline reacted with (*R*)-(+)-α-methylbenzyl isocyanate in THF containing 1N HCl to give the hemiaminal as a mixture of diastereomers in a ratio of 93:7. The hemiaminal was treated with thionyl chloride in a mixture of toluene and triethylamine at 0 °C in situ to generate chiral CF_3-substituted 2(3*H*)-quinazolinones, which were trapped by a series of nucleophiles to give the dihydroquinazolinone with diastereoselectivities ranging from 10 to 95% (Table 81). This methodology was applied for the synthesis of the important second-generation nonnucleoside reverse transcriptase inhibitors DPC 961. Exposure of the desired dihydroquinazolinone to wet TFA at 18 °C caused complete deprotection within 1 h, affording an 80% yield of DPC 961. Warm formic acid also induced ionization of the phenethyl group to transform the dihydroquinazolinone into DPC 961 in 85% yield. Therefore, DPC 961 was obtained in three steps with >55% overall yield from the hydrate hydrochloride ketoaniline (Scheme 82).

In the synthesis of the nonnucleoside reverse transcriptase inhibitors DPC 963, however, this methodology did not provide the desired 1,4-adduct. Accordingly, Nugent and co-workers developed an alternative approach to DPC 963 based on the enantioselective addition of lithium cyclopropylacetylide to ketimine by using chiral amino alcohol **171** (Scheme 83).[356] In this system, lithium bis(trimethylsilyl)amide proved superior to butyllithium or other lithium amides as the strong base. In addition, a 3:1 ratio of chiral amino alcohol **171** to ketimine proved optimal in terms of both yield and enantioselectivity. Under these conditions, the desired product was obtained in 94% ee. Further purification could be improved to 99.6% ee through a single crystallization from heptane. Chiral amino alcohol **171** could be recovered in 92% yield by basification of the citric acid extracts.

By using chloramphenicol-derived ligands, Jiang and Si presented another efficient enantioselective alkynylation of trifluoromethylated cyclic ketimines **168**.[357] In the presence of chiral ligand **172**, a series of trifluoromethyl substituted 3,4-dihydroquinazolin-2(1H)-ones were obtained in 60−96% yield with excellent enantioselectivities (>98.2% ee) at room temperature (Table 82). The chiral ligand could be recovered and reused without decreased enantioselectivity and chemical yield. This reaction provides an efficient approach for the synthesis of DPC 961.

5.3. From α,β-Unsaturated Trifluoromethyl Ketones

It is well-documented that α,β-unsaturated ketones behave as excellent Michael acceptors and undergo 1,4-addition reaction with various nucleophiles. On the other hand, α,β-unsaturated ketones also act as reactive substrates for 1,2-nucleophilic addition reactions. A practical addition reaction requires excellent regioselectivity when α,β-unsaturated ketones are used as substrates. However, two reaction sites existing in one molecule also provide the great chance to develop tandem reactions for the construction of multifunctionalized compounds.

5.3.1. Aldol Reactions

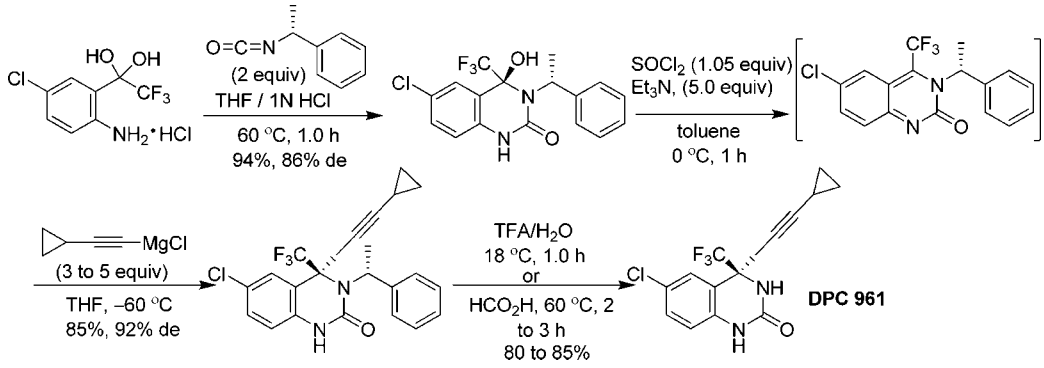
Liu and co-workers explored the aldol reaction of acetone and α,β-unsaturated trifluoromethyl ketones by using the combination of proline-derived *N*-sulfonylamide and trifluoroacetic acid as cocatalyst.[358] Under optimized conditions, the corresponding α-trifluoromethyl tertiary alcohols were obtained in 76−99% yield with 81−95% ee (Table 83). The reaction tolerated both electron-rich and electron-deficient phenyl-substituted unsaturated ketones. Even unsaturated ketones with alkynyl, alkenyl, or alkyl substituents at the β-position proceeded well. The role of TFA as additive not only favored the formation of the enamine intermediate but also served to decrease the electron density of the carbonyl group of unsaturated ketones.

Simultaneously to this research work, Zhang and Yuan reported a similar direct asymmetric aldol reaction by using 4-hydroxyproline derivative **174**, preferentially, as chiral catalyst.[359] A series of substrates reacted quite well with acetone giving 49−97% yield and 79−91% ee. No significant substituent effect was observed in this reaction. However, compared with the above-mentioned Liu's catalyst **173**, catalyst **174** gave slightly lower enantioselectivities and required longer reaction time (Table 84).

5.3.2. Hetero-Diels−Alder Reactions

After the aldol reaction of acetone with α,β-unsaturated trifluoromethyl ketones was found, Liu and co-workers examined the addition reaction of aldehydes to α,β-unsaturated trifluoromethyl ketones.[360] Surprisingly, no anticipated product was obtained in the reaction of propanal and unsaturated ketone in the presence of pyrrolidine, *p*-fluorophenol, and silica gel. The spectroscopic analysis revealed that the product is a cyclic compound, which came from the inverse-electron-demand hetero-Diels−Alder (HDA) reaction of aldehydes and α,β-unsaturated trifluoromethyl ketones (Scheme 84). The HDA products could be further oxidized to give the corresponding lactone derivatives, followed by elimination with methanesulfonyl chloride and

Scheme 82



Scheme 83

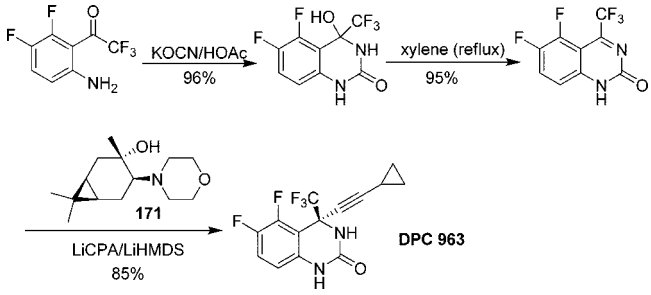
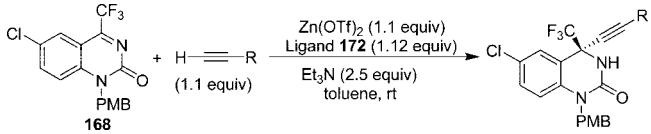
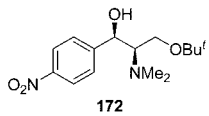


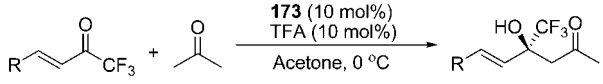
Table 82. Enantioselective Alkynylation of Trifluoromethylated Cyclic Ketimine

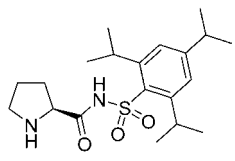




R	time, h	yield, %	ee, %
c-Pr	6	96	99.1
Ph	8	88	98.2
t-Bu	15	63	98.5
n-Bu	6	92	99.5
TMS	8	87	99.5
c-PenCH$_2$	6	86	99.5

Table 83. Enantioselective Aldol Reaction of Acetone and α,β-Unsaturated Trifluoromethyl Ketones

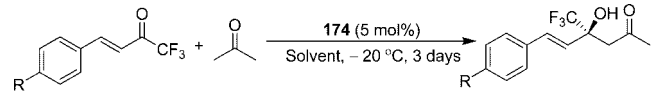


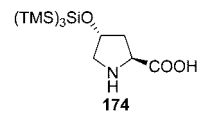


R	time, h	yield, %	ee, %
Ph	6	93	92
4-ClC$_6$H$_4$	10	92	94
4-BrC$_6$H4	14	98	95
4-MeOC$_6$H4	24	94	94
4-MeC$_6$H$_4$	20	99	89
1-Naphthyl	22	85	92
2-furyl	12	87	86
Ph—≡	22	99	81
Ph-CH=CH	31	76	87
Ph(CH$_2$)$_3$	28	86	88

triethylamine to afford dihydropyranones with high diastereoselectivities. Under the optimized conditions, a variety of 6-trifluoromethyl-3,4-dihydropyan-2-ones were obtained in 50−76% yield in three steps with high enantioselectivities (up to 97% ee). It is worth mentioning that the combination of *p*-fluorophenol and silica gel along with catalyst was necessary; otherwise, the reaction proceeded very slowly in poor yield.

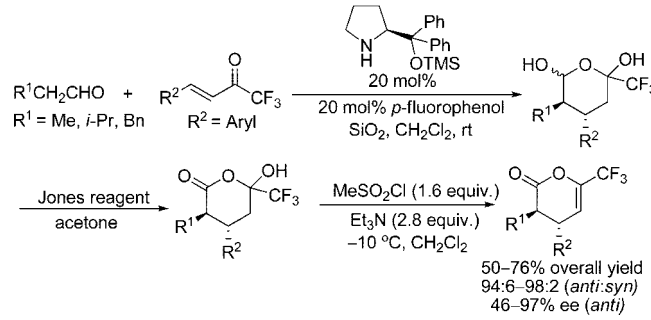
Table 84. Organocatalyzed Aldol Reaction of Acetone and α,β-Unsaturated Trifluoromethyl Ketones





R	Solvent	yield, %	ee, %
H	CH_2Cl_2/DMF	92	83
Me	CH_2Cl_2/DMF	91	85
OMe	DMF	92	87
NMe_2	CH_2Cl_2	49	91
F	CH_2Cl_2	94	87
Cl	CH_2Cl_2	96	80
CN	CH_2Cl_2	97	80
p-NO_2	CH_2Cl_2	92	79
m-NO_2	CH_2Cl_2	89	82
Br	CH_2Cl_2	90	91

Scheme 84



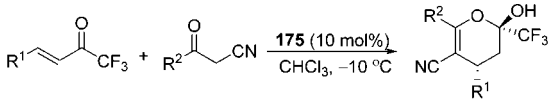
5.3.3. Michael Additions

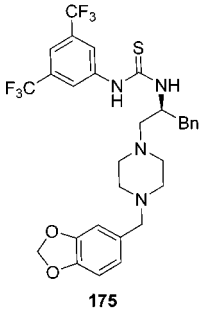
With the rapid development of chiral organocatalysts, many asymmetric organocatalytic reactions have been applied to the synthesis of optically active CF_3-containing compounds. Zhu and co-workers reported an enantioselective Michael addition of α-cyanoketones to α,β-unsaturated trifluoromethyl ketones by using piperazine−thiourea catalyst **175**.[361] The reaction of various α,β-unsaturated trifluoromethyl ketones with α-cyanoketones afforded α-trifluoromethyldihydropyrans in good to high yields with high enantioselectivity (87−95% ee) and excellent diastereoselectivity (>19: 1) (Table 85). Moreover, the highly enantioenriched adducts could be readily converted into useful CF_3-substituted dihydropyridines without loss of stereochemical information.

5.3.4. Reduction Reactions

In 1998, Resnati and co-workers reported the stereoselective reduction of 1,1,1-trifluoro-4-phenyl-3-buten-2-one by using some growing microorganisms.[362] In the presence of *Geotrichum candidum*, (*E*,*S*)-1,1,1-trifluoro-4-phenylbut-3-

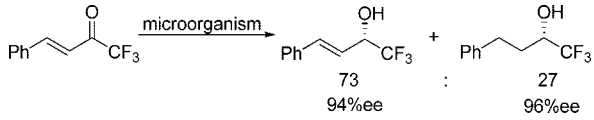
Table 85. Chiral Thiourea-Catalyzed Asymmetric Reaction of α,β-Unsaturated Trifluoromethyl Ketones with α-Cyanoketones



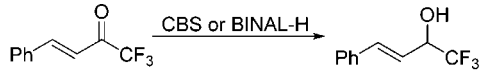


R^1	R^2	yield, %	dr	ee, %
Ph	Ph	99	>19:1	93
4-$MeOC_6H_4$	Ph	99	>19:1	91
4-MeC_6H_4	Ph	99	>19:1	92
3-$MeOC_6H_4$	Ph	99	>19:1	93
2-$MeOC_6H_4$	Ph	98	6:1	95
2-thienyl	Ph	99	>19:1	88
n-octyl	Ph	99	>19:1	87
3-$MeOC_6H_4$	4-$MeOC_6H_4$	99	>19:1	92
3-MeC_6H_4	4-$MeOC_6H_4$	99	>19:1	92
Ph	4-FC_6H_4	98	>19:1	92
Ph	4-BrC_6H_4	99	>19:1	92
4-MeC_6H_4	4-BrC_6H_4	99	>19:1	91
4-BrC_6H_4	4-BrC_6H_4	97	>19:1	94
Ph	*t*-Bu	62	>19:1	92

Scheme 85



Scheme 86



(*S*)-BINAL-H (3 equiv.) 94% yield, 71% ee (S)
(*R*)-*B*-Me-CBS, catecholborane 90% yield, 75% ee (*S*)
(*S*)-*B*-*n*-Bu-CBS, catecholborane 85% yield, 85% ee (*R*)

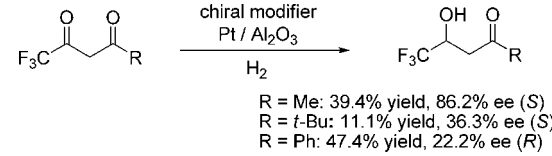
en-2-ol and (*S*)-1,1,1-trifluoro-4-phenylbutan-2-ol were obtained with high enantioselectivities (94% and 96% ee, respectively) (Scheme 85). The ratio of the butenol to butanol was 73:27. Actually, in the above-mentioned Nakamura's work (see section 5.1.1.3), the alcohol dehydrogenase from the *Geotrichum candidum* was also used in the reduction of simple trifluoromethyl ketones to afford good to excellent enantioselectivity.[291]

In an additional example, Prakash and co-workers disclosed the enantioselective reduction reaction of 1,1,1-trifluoro-4-phenyl-3-buten-2-one by means of either the CBS system or BINAL-H.[274] As shown in Scheme 86, the combination of (*S*)-*B*-*n*-Bu-CBS and catecholborane provided (*E*,*R*)-1,1,1-trifluoro-4-phenylbut-3-en-2-ol in 85% yield with 85% ee. (*S*)-B-Me-CBS and BINAL-H exhibited lower enantioselectivities. Fortunately, no saturated alcohol was observed along with the desired allylic alcohol.

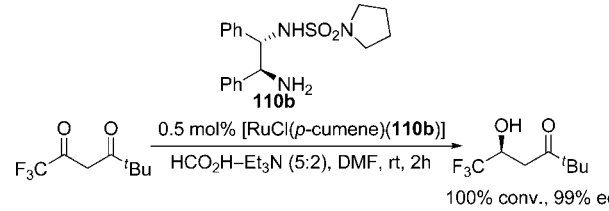
5.4. From Trifluoromethyl β-Diketones

Trifluoromethyl β-diketones are interesting substrates for selective reduction to provide chiral β-hydroxy ketones, which are useful building blocks. Several catalytic systems have been developed for the reduction of these prochiral substrates. For example, in 2004 Baiker and co-workers reported the heterogeneous regio- and enantioselective hydrogenation of 1,1,1-trifluoro-2,4-diketones over Pt/Al_2O_3 modified by various chiral 1,2-aminoalcohols and amines to afford the corresponding chiral alcohols (Scheme 87).[363] The best chiral modifiers cinchonidine and *O*-methyl cinchonidine (MeOCD) could enhance the chemoselectivity up to 99%.

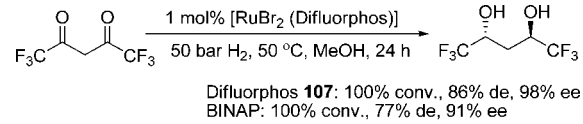
Scheme 87



Scheme 88



Scheme 89



Depending on the steric hindrance around the nonactivated carbonyl group of the substrate, the ee's varied in the range 22−86%. The ee dropped from 86% to 36% and 22%, when the methyl group of 1,1,1-trifluoro-2,4-diketone was replaced by *tert*-butyl and phenyl groups, respectively. A reversal of enantioselectivity was observed in the case of the substrate having a phenyl group; however, this was not commented.

By means of homogeneous Ru(II)-R_2NSO_2DPEN (**110b**) complex, Mohar and co-workers reported the regioselective catalytic enantioselective transfer hydrogenation of 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione with the sole reduction of the trifluoromethylcarbonyl group to the corresponding chiral alcohol in 100% conversion with excellent enantioselectivity (99% ee) (Scheme 88).[304]

In 2004, Genêt and co-workers applied the difluorphos ligand **107** to the hydrogenation of 1,1,1,5,5,5-hexafluoropentane-2,4-dione. (*R*,*R*)-1,1,1,5,5,5-Hexafluoro-2,3-pentandiol was obtained in 100% conversion with high diastereo- and enantioselectivity (86% de and 98% ee) (Scheme 89).[220] Compared with other diphosphanes such as BINAP (77% de, 91% ee), *p*-TolBinap (70% de, 70% ee), MeO-Biphep (71% de, 87% ee), Synphos (67% de, 85% ee), and Segphos (71% de, 88% ee), the difluorphos provided the best diastereoselectivity and enantioselectivity. The superiority of difluorphos over other diphosphane ligands in ruthenium-mediated hydrogenation revealed that the typical combination of a narrow dihedral angle and a stronger electrodeficiency could be crucial for high levels of enantioselectivity.

6. Asymmetric Reactions of Prochiral Trifluoromethyl Olefins and Derivatives

Among the prochiral trifluoromethyl substrates, trifluoromethyl olefins and derivatives (Figure 13) are readily available, attractive, and diverse precursors for various

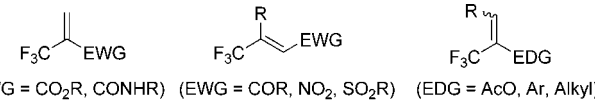


Figure 13. Prochiral trifluoromethyl olefins and derivatives.

asymmetric transformations. Trifluoromethyl olefins can be classified as either electron-deficient alkenes (**P** and **Q**) or electron-rich alkenes (**R**) according to their structure. Over the past decades, these prochiral trifluoromethyl olefin species have been extensively investigated.

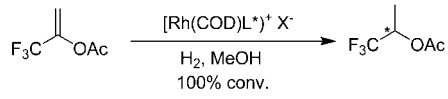
6.1. Hydrogenation and Reduction Reactions

The reduction reaction of olefins is a prominent transformation in organic synthesis. The intense study of asymmetric reduction methodologies has provided organic chemists with the tools necessary to synthesize a variety of chiral products. In the field of organofluorine chemistry, lots of reports about asymmetric hydrogenation and reduction reactions of trifluoromethyl olefins and derivatives have been included in the literature. In 1980, chemists at Monsanto Company gave the first example of asymmetric hydrogenation of prochiral trifluoromethyl olefins by using chiral Rh-complexes. In the presence of (*R*,*R*)-DIPAMP **176**, 2-acetoxy-1,1,1-trifluoro-2-propene was enantioselectively hydrogenated in 100% conversion with up to 77% ee (Table 86).[364] Subsequently, the great improvement of enantioselectivity was achieved for the reduction of the same substrate by using (*S*,*S*)-Duphos **177** (94% ee) and (*R*,*R*)-Et-BPE **178** (95% ee) as chiral ligands (Table 86).[365]

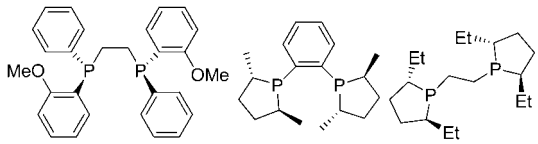
Iseki and co-workers further enlarged the scope of functionalized trifluoromethyl olefins in enantioselective hydrogenation reaction.[366] Hydrogenation of (*E*)-2-(trifluoromethyl)alk-2-en-1-ols **179** catalyzed by (*R*)-BINAP-Ru complex was carried out with moderate to good enantiomeric excess (42−83% ee). Interestingly, the hydrogenation of a mixture of stereomeric *E* and *Z* enols (R = *n*-C_8H_{17}, *E*/*Z* = 45:55) led to a recovery of 56% of the starting material in a ratio of 14:86 (*E*/*Z*), indicating (*E*)-enol to be hydrogenated faster than (*Z*)-enol (Table 87).[367]

In 2000, the same group employed similar ruthenium complexes as chiral catalysts for the asymmetric hydrogenation of (*Z*)-1,1,1-trifluoroalkan-2-one enol acetates **180**.[368] A series of enol acetates with alkyl chains gave the hydrogenated products in 77−100% yield with 89−99% ee (Table 88). However, the attachment of a phenyl group at the olefinic carbon (R^2 = Ph) failed to produce the hydrogenation product under the same conditions. Notably,

Table 86. Enantioselective Hydrogenation of 2-Acetoxy-1,1,1-trifluoro-2-propene



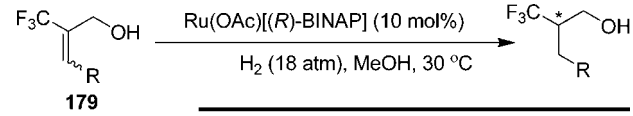
Catal. (mol%)	P, atm	temp. °C	ee, %
[Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$ (1.2)	3.5	50	77 (*S*)
[Rh(COD)((*S*,*S*)-DuPhos)]$^+OTf^-$ (0.1)	2	20 – 25	94 (*S*)
[Rh(COD)((*R*,*R*)-Et-BPE)]$^+OTf^-$ (0.1)	2	20 – 25	>95 (*R*)



(*R*,*R*)-DIPAMP (*S*,*S*)-Me-DuPhos (*R*,*R*)-Et-BPE

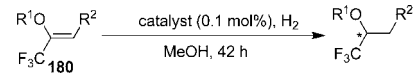
176 **177** **178**

Table 87. Catalytic Enantioselective Hydrogenation of 2-(Trifluoromethyl)alk-2-en-1-ols



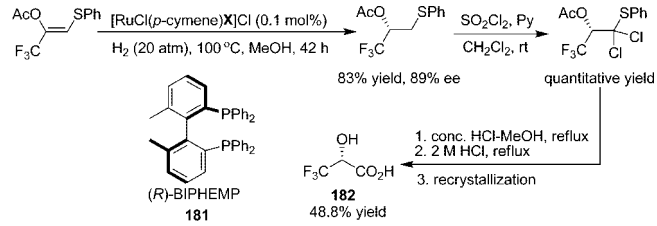
R	time, h	yield, %	ee, %
Ph	240	13	42
C_2H_4Ph	240	40	71
n-C_8H_{17} (*E*)	240	85	83
n-C_8H_{17} (*Z*)	48	16	15
n-C_8H_{17} (*E*/*Z*)	72	40	68

Table 88. Enantioselective Hydrogenation of (*Z*)-1,1,1-Trifluoroalkan-2-one Enol Acetates



R^1	R^2	catalyst	P, atm	temp, °C	yield, %	ee, %
Ac	$(CH_2)_3CH_3$	$RuCl_2$((*S*)-BINAP)	10	100	94	98 (*S*)
Ac	$(CH_2)_6CH_3$	$RuCl_2$((*S*)-BINAP)	10	100	94	98 (*S*)
Ac	$CH_2CH(CH_3)_2$	[RuCl((*R*)-BINAP)(*p*-cymene)]Cl	4	50	100	>99
Ac	*c*-C_6H_{11}	[RuCl((*R*)-BINAP)(*p*-cymene)]Cl	4	50	81	95
Ac	$(CH_2)_2CO_2Et$	[RuCl((*R*)-BINAP)(*p*-cymene)]Cl	4	50	71	>99 (*R*)
Bz	$(CH_2)_8CH_3$	[RuCl((*R*)-BINAP)(*p*-cymene)]Cl	4	50	99	99 (*R*)

Scheme 90

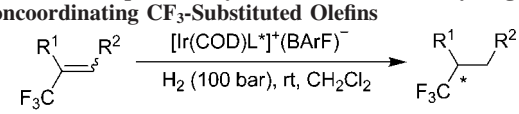


in the presence of (*R*)-BIPHEMP **181**, the enol acetate bearing a phenylthio moiety at the olefinic carbon was hydrogenated to yield the corresponding product, which was further transformed into the optically active trifluorolactic acid **182** (Scheme 90).

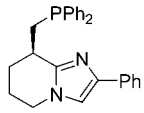
More recently, Andersson's group presented the Ir-catalyzed asymmetric hydrogenation of noncoordinating CF_3-substituted olefins.[369] In most cases these trifluoromethyl olefins without additional functionality were hydrogenated by iridium catalysts with N,P ligands (**183** and **184**) to give the fluoroalkanes in high conversion with up to 96% ee. Interestingly, the hydrogenation of an isomeric mixture (*Z*/*E*) of olefins gave almost the same ee, identical to that obtained in the hydrogenation of the pure *Z* isomer (Table 89). In addition, ^1H NMR detection supported that (*Z*)-olefin reacted much faster than *E* isomer.

For CF_3-substituted α,β-unsaturated carbonyl compounds, a few examples of enantioselective hydrogenation and reduction of these prochiral substrates have been reported (Scheme 91). With Iseki's catalytic system, 2-(trifluoromethyl)acrylic acid was hydrogenated in the presence of a ruthenium complex, followed by derivatization to give (*S*)-3,3,3-trifluoro-2-methylpropan-1-ol with 80% ee (Scheme 91a).[367] Sodeoka and co-workers presented the catalytic asymmetric conjugate reduction of β-CF_3-enone using ethanol as a hydride source. In the presence of a chiral Pd complex, the desired product was obtained in 85% yield with

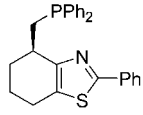
Table 89. Ir-Complex-Catalyzed Enantioselective Hydrogenation of Noncoordinating CF_3-Substituted Olefins



L*	R^1,	R^2	conv., %	ee, %
184	(*Z*), Ph,	Me	94	95
184	(*Z*), Ph,	Pr	87	92
184	(*Z*), Ph,	Pentyl	88	96
184	(*Z*), Ph,	Octyl	85	95
183	(*Z*), Ph,	CH_2CH_2Ph	21	90
183	(*Z*), 4-F-C_6H_4,	Pentyl	84	81
183	(*Z*), 4-Tol-C_6H_4,	Octyl	92	84
184	(*E*), Cy,	Ph	96	74
183	(*E*), $Ph_2(O)PO$,	Ph	99	96
183	(*E*), Ph,	Pentyl	4	0
183	(*Z*), Ph,	Pentyl	95	87
183	(*E*/*Z* = 1/1), Ph,	Pentyl	95	87



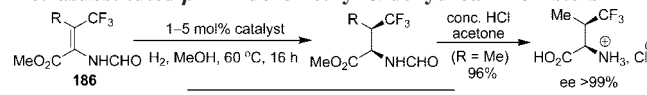
183

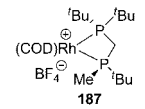


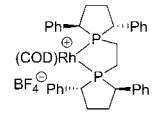
184

84% ee (Scheme 91b).[370] Alternatively, Szöllösi's group reported the hydrogenation of CF_3-substituted prochiral α,β-unsaturated carboxylic acids with cinchonidine-modified palladium heterogeneous catalysts. Only 43% ee value was obtained in the hydrogenation of 4,4,4-trifluoro-3-methyl-2-butenoic acid with benzylamine as additive (Scheme 91c).[371] These three examples present some drawbacks, such as insufficient level of enantioselectivity, low catalytic efficiency, and limited scope of the substrates. Improved results were recently described by Alimardanov and co-workers. The asymmetric hydrogenation of (*E*)-3-(3,5-difluorophenyl)-4,4,4-trifluorobut-2-enoic acid by using the combination of $Rh(nbd)_2BF_4$ and Walphos 8-1 **185** was

Table 90. Catalytic Enantioselective Hydrogenation of Tetrasubstituted β-Trifluoromethyl-α-dehydroamino Esters







R	catalyst	conv., %	ee, %
Et	**187**[a]	100	>99
Et	**188**[a]	100	60
CH_2Ph	**187**[a]	100	99
CH_2Ph	**188**[a]	0	
CF_3	**187**[a]	100	86
Ph	**187**[b]	78	50
Ph	**188**[b]	100	93
p-ClPh	**187**[b]	14	50
p-ClPh	**188**[b]	100	91
p-MeOPh	**187**[b]	65	39
p-MeOPh	**188**[b]	100	90

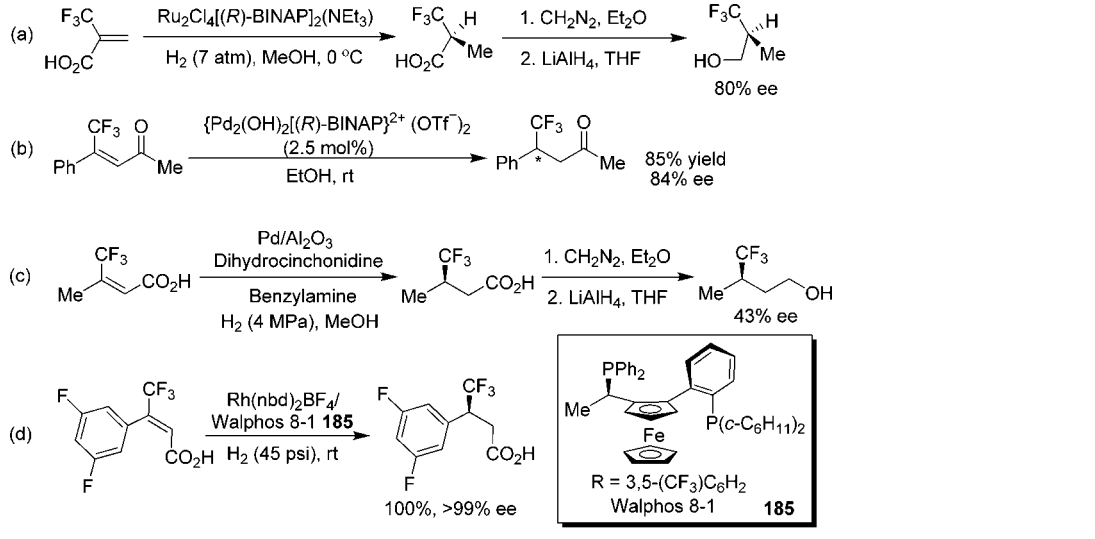
[a] at 70 psi of H_2 with S/C 100
[b] at 250 psi of H_2 with S/C 20.

conducted at room temperature under 45 psi H_2 using a 200:1 substrate-to-catalyst ratio to afford the desired product in quantitative yield with excellent enantioselectivity (99% ee) (Scheme 91d).[372]

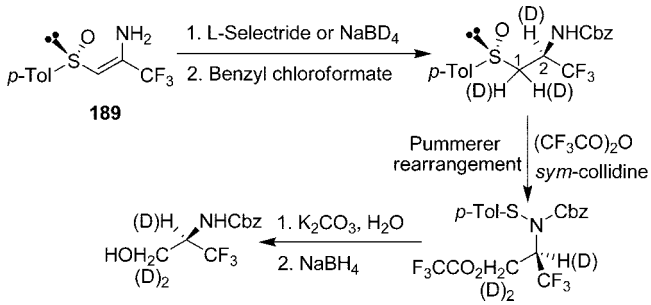
Benhaim and co-workers developed a convenient Rh-complex-catalyzed enantioselective hydrogenation reaction of a series of sterically demanding tetrasubstituted β-trifluoromethyl-α-dehydroamino esters **186** for which variable conversions and enantioselectivities were observed (Table 90).[373] (*R*)-Trichickenfootphos-Rh complex **187** required a methylene group installed at the β-position of substrates to access high enantioselectivity and/or conversion, whereas (*R*)-Ph-BPE-Rh complex **188** was better suited for substrates with the aryl group directly attached at the same β-position, giving excellent conversions and ~90% ee. During the hydrogenation of all tetrasubstituted alkenes **186**, only the formation of a single diastereoisomer was observed. Finally, a simple treatment with concentrated HCl in acetone afforded optically active fluorinated valine in 96% yield without any loss of enantioselectivity.

Some diastereoselective reductions with hydride donors or hydrogenation reactions were also reported through diastereocontrol of a chiral substrate bearing or not a temporary chiral auxiliary. For example, diastereoselective reduction of CF_3-substituted (R_S)-β-enaminosulfoxide **189** with L-Selectride or $NaBD_4$, and subsequent protection with benzyl chloroformate, gave (un)labeled (R_S,2*S*)-β-aminosulfoxides in quantitative yields with high diastereoselectivities (dr 90/10 in CH_2Cl_2 and 93/7 in THF) (Scheme 92).[374,375]

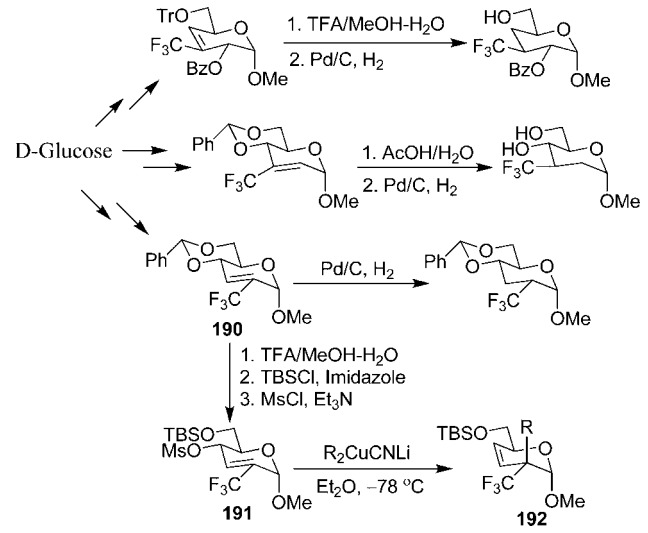
Scheme 91



Scheme 92



Scheme 93

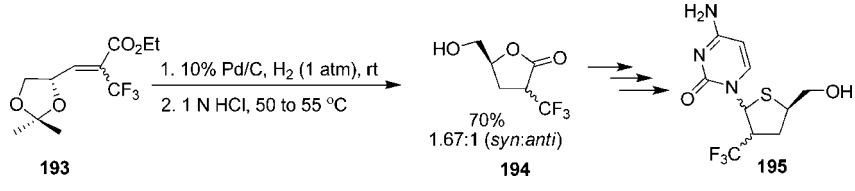


Then, (*R*)-trifluoroalaninols were obtained in one pot with 85% yield, upon treatment with trifluoroacetic anhydride/*sym*-collidine and reduction with $NaBH_4$ of the sulfonamide formed in the Pummerer rearrangement.[376]

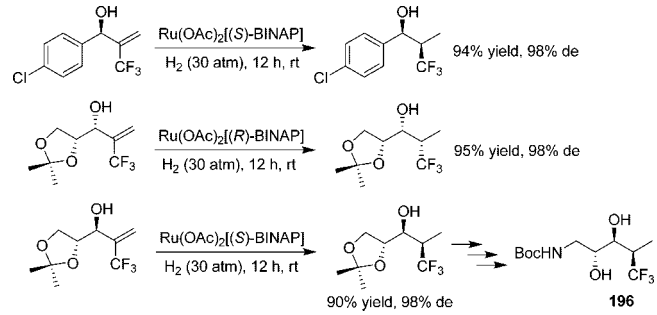
D-Glucose is a very cheap starting material, which can be readily converted into derivatives possessing a trifluoromethylated alkene moiety. The hydrogenation of these alkenes took place in a highly diastereoselective manner; a series of CF_3-containing glucose derivatives were obtained in optically pure form.[377,378] In addition, the trifluoromethylated alkene **190** was transformed into γ-trifluoromethylated allylic mesylate **191**, which was subjected to the S_N2' reaction with higher-ordered cuprates to afford the highly functionalized product **192** with a quaternary carbon center (Scheme 93).[379]

In the presence of palladium on activated carbon, the asymmetric hydrogenation of trifluoromethyl acrylic ester **193**, derived from 1-(*R*)-glyceraldehyde acetonide, followed by deprotection and ring closure, provided the corresponding lactones as a mixture of C-2 epimers (*syn*/*anti* = 1.67:1). Further protection of hydroxyl group of the lactone with *tert*-butyldimethylsilyl chloride (TBDMSCl) and separation by column chromatography gave the two useful intermediates **194**. Then, four potential L-2′,3′-dideoxy-2′-trifluoromethyl-4′-thionucleosides **195** were synthesized through multistep transformations (Scheme 94).[380]

Scheme 94



Scheme 95



Chen and Qing also reported a doubly stereocontrolled hydrogenation of nonracemic 2-(trifluoromethyl)allylic alcohols catalyzed by chiral BINAP-Ru(II) diacetate complexes.[381] The corresponding products were obtained in high yields (90−95%) with excellent diastereoselectivities (98% de). Accordingly, the treatment of one of the hydrogenated intermediates provided the optically active CF_3-amino diol **196** in 36% yield over five steps (Scheme 95).

In recent years, trifluoromethyl analogues of proteinogenic amino acids have attracted a great deal of attention in protein structural biology owing to their isosteric compatibility with their natural counterparts.[382] Asymmetric synthesis of chiral trifluoromethyl-substituted amino acid has been an attractive subject in organic chemistry.[383] For example, Qiu and Qing presented convenient procedures for the synthesis of 4-trifluoromethyl-L-proline derivatives (Scheme 96). Starting from *trans*-4-hydroxy-L-proline, the corresponding trifluoromethylated 1,2-dihydropyrrole and 3,4-dihydropyrrole were obtained in high yields. The stereoselective hydrogenation of 4-trifluoromethyl-3,4-dihydropyrrole gave *cis*-4-trifluoromethyl-L-proline **197** in optically pure form. Additionally, amine protection followed by the ruthenium-catalyzed oxidation and deprotection by CF_3CO_2H furnished *cis*-4-trifluoromethyl-L-glutamide **198**.[384,385] From 4-trifluoromethyl-1,2-dihydropyrrole, the stereoselective hydrogenation and the subsequent desilylation under hydrogen atmosphere in the presence of a catalytic amount of Pd/C led to the formation of the *cis*-4-trifluoromethylprolinol, which can easily be oxidized into *cis*-4-trifluoromethyl-L-proline **197**. On the other hand, the desilylation of 4-trifluoromethyl-1,2-dihydropyrrole followed by the stereoselective hydrogenation in the presence of $[Ir(cod)(py)PCy_3]$ and oxidation afforded the optically pure *trans*-4-trifluoromethyl-L-proline **198**.[386]

Molinski and co-workers described a flexible approach for the preparation of (2*S*,3*S*)-4,4,4-trifluorovaline **199a** and (2*S*,4*S*)-5,5,5-trifluoroleucine **199b** through several simple transformations: conversion of chiral acids into the oxazolines, oxidative rearrangement of oxazolines to dihydro-2*H*-oxazinones, and face-selective hydrogenation of the C=N bond, followed by hydrogenolysis-hydrolysis (Figure 14).[387] For this purpose, (*S*)-4,4,4-trifluoro-3-methylbutanoic acid

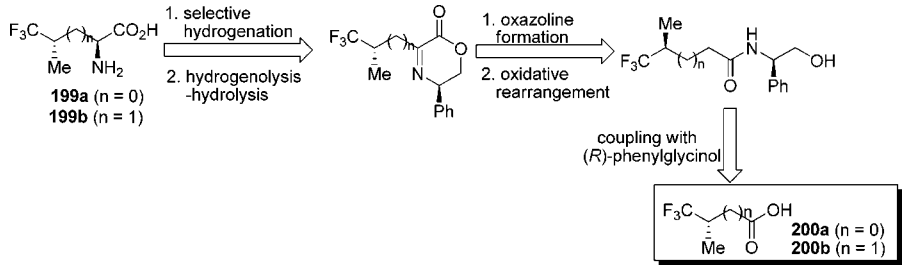
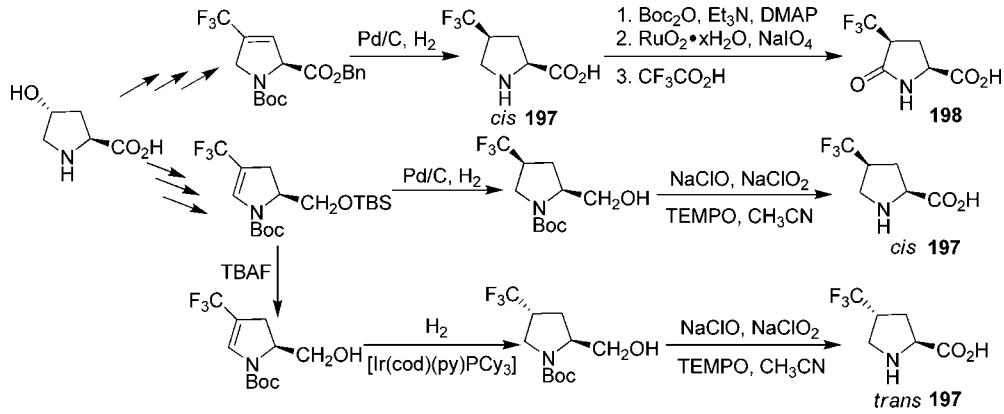
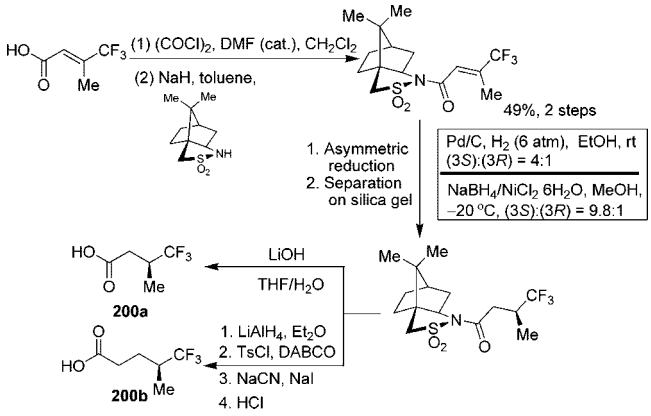


Figure 14. Retrosynthetic analysis of fluorinated valine and leucine.

Scheme 96



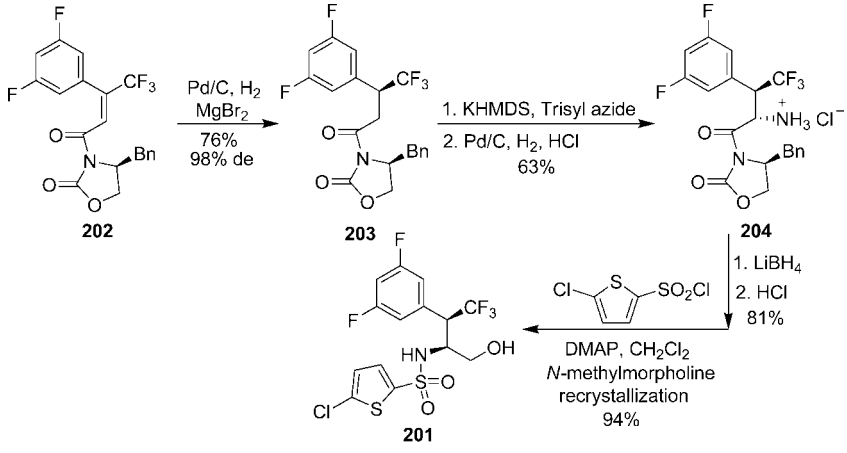
Scheme 97



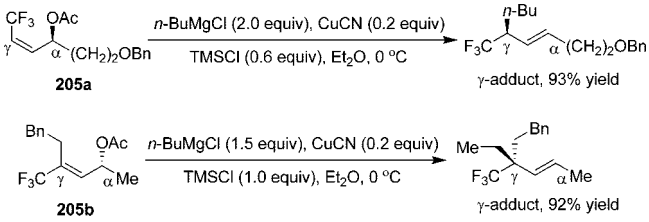
200a and (*S*)-5,5,5-trifluoro-4-methylpentanoic acid **200b** are the required starting materials. Starting from commercially available (*E*)-4,4,4-trifluoro-3-methylbut-2-enoic acid, *N*-acyl sultam was obtained in 49% yield. Then, the β-stereocenter was controlled by diastereoselective heterogeneous catalytic hydrogenation over Pd/C giving moderate diastereoselectivity, whereas enhanced selectivity was achieved by reduction with "nickel boride" generated in situ from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$, albeit with difficult separation under practical preparative conditions (Scheme 97).

To control both stereocenters at α- and β-positions of the carbonyl function and to avoid the need for the expensive chiral catalyst in the synthesis of the optically active amino alcohol-containing pharmaceutical ingredient **201**, Alimardanov and co-workers presented a more practical asymmetric hydrogenation of (*S*,*E*)-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **202**.[372] The reduction was carried out at 60−65 psi H_2 and 45−50 °C in THF in the presence of 1.2 equiv of $MgBr_2$ and Pd/C catalyst, followed by crystallization from ^{i}PrOH−H_2O, to afford the key intermediate **203** typically in 76% yield with >98% de (Scheme 98). Subsequent transformations involved low-temperature enolization, trisyl azide addition, and reduction to give β-trifluoromethyl α-amino

Scheme 98



Scheme 99



acid derivative **204** in 63% yield. Finally, reduction and sulfonylation gave the desired chiral product **201** in respectable yields.

The reductive elimination of optically active γ-trifluoromethylated allylic acetates and sulfonates provides an important and efficient access to chiral CF_3-containing compounds. For example, in the presence of a catalytic amount of CuCN and TMSCl, the reaction of chiral (*Z*)-γ-trifluoromethylated allylic acetates **205** with various Grignard reagents furnished the corresponding γ-adducts in a highly regioselective manner. Furthermore, a complete chirality transmission was observed (Scheme 99).[388,389] The coordination of TMSCl to copper could decrease the transition state energy barrier of the reductive elimination, resulting in the smooth reductive elimination to give the corresponding γ-adducts. This synthetic methodology can be successfully extended to the highly stereoselective construction of a quaternary carbon center bearing a CF_3 group.[390]

Konno and co-workers developed an interesting palladium-catalyzed formate reduction of γ-trifluoromethylated allylic mesylate.[391] Indeed, the reductive elimination of γ-trifluoromethyl allylic mesylate **206**, derived from β-trifluoromethylated α,β-unsaturated ketone, with HCO_2H-Et_3N in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ and PPh_3 in DMF at 80 °C afforded the corresponding γ-adduct in high yield with excellent regioselectivity. Nevertheless, a slight loss of chiral information was observed during the reductive elimination (Scheme 100).

6.2. Dihydroxylation Reactions

The Sharpless asymmetric dihydroxylation (AD) of olefins is a powerful methodology for the preparation of chiral 1,2-diols with high levels of enantioselectivity and has been widely applied in both industrial and academic laboratories.[392] In the field of organofluorine chemistry, asymmetric dihydroxylation of prochiral trifluoromethyl olefins and derivatives can provide a variety of useful trifluoromethylated chiral synthons. One example involved a short synthesis of the Mosher's acid (MTPA), which is a valuable derivatizing agent for enantiomeric excess determination of alcohols and amines. In the presence of $(DHQD)_2DPP$ **207**, asymmetric dihydroxylation of α-trifluoromethyl styrene gave the chiral diol in high yield with 91% ee. After oxidation and recrystallization, α-hydroxy-α-trifluoromethyl phenylacetic acid **208**, a precursor to Mosher's acid, was obtained in optically pure form (Scheme 101).[393]

3,3,3-Trifluoropropene was dihydroxylated to give (*S*)-3,3,3-trifluoropropane-1,2-diol **209** with 63% ee, which was

Scheme 101

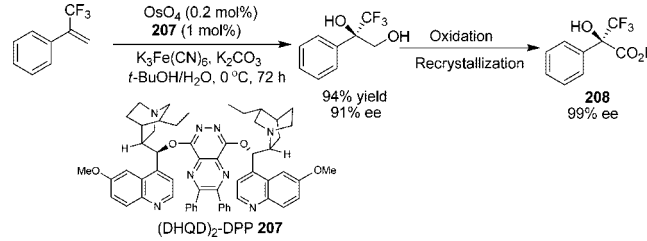
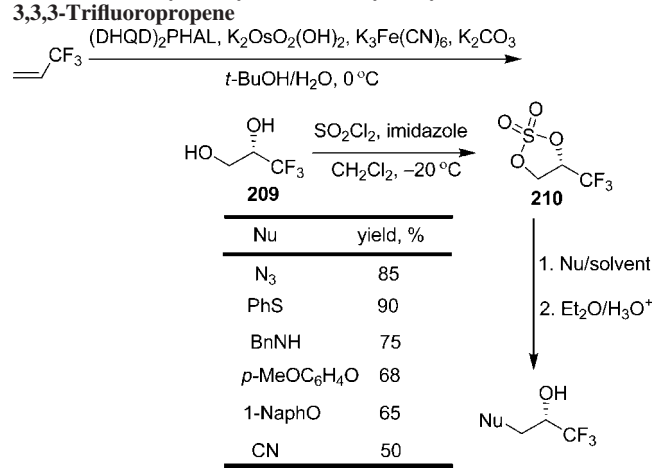


Table 91. Catalytic Asymmetric Dihydroxylation of 3,3,3-Trifluoropropene



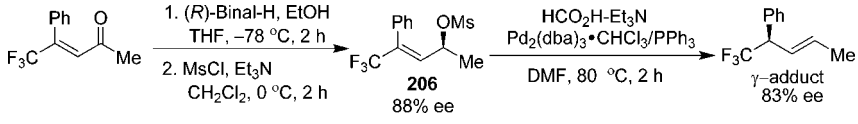
Nu	yield, %
N_3	85
PhS	90
BnNH	75
p-$MeOC_6H_4O$	68
1-NaphO	65
CN	50

raised to enantiopurity by a single recrystallization. Treatment of diol with sulfuryl chloride afforded the crystalline cyclic sulfate **210** in 82% yield. As an attractive synthetic equivalent of (trifluoromethyl)oxirane, cyclic sulfate could be readily converted into many important chiral building blocks with a series of nucleophiles. In all cases, nucleophilic opening took place exclusively at the terminal carbon atom in moderate to high yields (Table 91).[394]

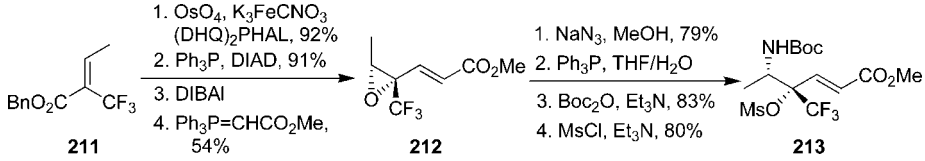
Benzyl (*Z*)-2-(trifluoromethyl)but-2-enoate **211** was subjected to the Sharpless asymmetric dihydroxylation, and the resulting diol was obtained in 73% ee and converted into the epoxide under Mitsunobu conditions. Reduction of the ester function into aldehyde and Wittig chain extension gave (trifluoromethyl)oxirane **212**. After azide-mediated ring-opening, Staudinger reduction of the azide, and protections, the trifluoromethylated chiral amino alcohol **213** was isolated in good overall yield (Scheme 102).[395]

Fluorinated analogues and derivatives of naturally occurring compounds have proved to be of fundamental interest because the introduction of fluorinated functionalities into bioactive targets often leads to significant changes in the physical, chemical, and biological properties of the parent compounds. Avenoza and co-workers described a useful method to obtain enantiomerically pure α-CF_3-isoserine through a catalytic asymmetric dihydroxylation reaction. Two derivatives of commercially available 2-(trifluoromethyl)acrylic acid were subjected to Sharpless dihydroxylation conditions using $(DHQD)_2PHAL$ to give the (*S*)-diols **214** in good yields (87% from ester and 90% from amide). Further transformation involved the synthesis of sulfamidates

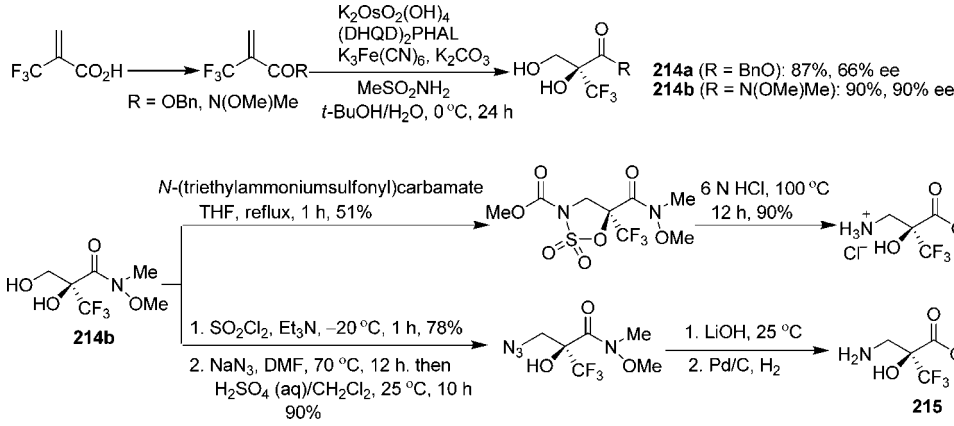
Scheme 100



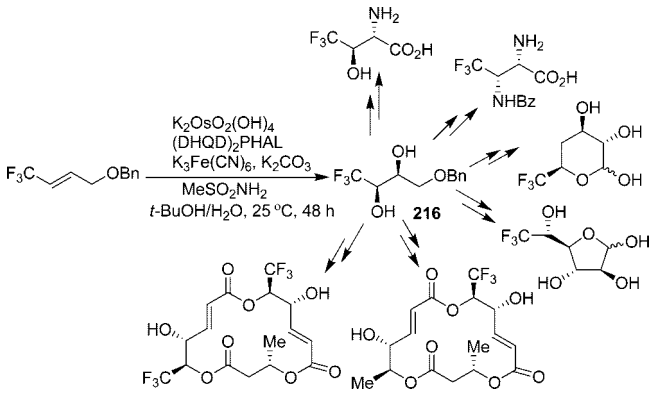
Scheme 102



Scheme 103



Scheme 104



(using Burgess reagent) or five-membered cyclic sulfates (using sulfuryl chloride) from chiral diol **214b**. Finally, (*S*)-α-CF_3-isoserine **215** was obtained by two routes in total yields of 34% (four steps) and 51% (seven steps), respectively (Scheme 103).[396]

Making use of the Sharpless asymmetric dihydroxylation, the Qing group reported the preparation of highly enantioenriched 1-benzyloxy-4,4,4-trifluoro-2,3-butanediol **216**.[397] Possibly owing to the strong electron-withdrawing effect of the trifluoromethyl group, the Sharpless asymmetric dihydroxylation of (*E*)-1-benzyloxy-4,4,4-trifluorobut-2-ene proceeded quite slowly under standard asymmetric dihydroxylation conditions. Interestingly, a dramatic increase of the reaction rate can be achieved by doubling the amount of both OsO_4 and chiral ligand. Both enantiomers of 1-benzyloxy-4,4,4-trifluoro-2,3-butanediol were obtained on a large scale in high yields with excellent enantioselectivities (96% yield and 99.4% ee for (2*S*,3*R*), 93% yield and 97.5% ee for (2*R*,3*S*)). Starting from this versatile chiral intermediate (**216**), several trifluoromethylated analogues of naturally occurring compounds, such as *anti*-threonine,[397] *syn*-isoserine,[398] β-L-fucofuranose, β-L-4,6-dideoxyxylohexopyranose,[399] and macrosphelide A,[25] were efficiently synthesized via a series of highly stereoselective transformations (Scheme 104).

6.3. Conjugate Additions

Asymmetric conjugate additions of nucleophiles to α,β-unsaturated compounds and subsequent transformation of the products is an extensively studied procedure and is applied to the preparation of a variety of optically active compounds.[400,401] A new stereogenic center is formed in the asymmetric conjugate addition to CF_3-substituted α,β-unsaturated carbonyl compounds or sulfur derivatives with a variety of nucleophiles. For example, β-trifluoromethyl vinyl sulfoxides, sulfones, and sulfonamides are versatile prochiral reactants in asymmetric synthesis. Treatment of chiral β-trifluoromethyl vinyl sulfoxides with various lithium enolates afforded the corresponding adducts in high yields with excellent diastereoselectivities (Scheme 105).[402,403] The reaction occurred via an eight-membered ring transition state, in which a *p*-Tol group preferentially occupies a pseudoequatorial position, thus avoiding a large repulsion with R^3 group and leading to the corresponding *R*-isomer. However, further synthetic transformation of these adducts through Pummerer rearrangement led to complete racemization in the presence of even weak base. The oxidative cleavage of the diol, which was prepared via conjugate

Scheme 105

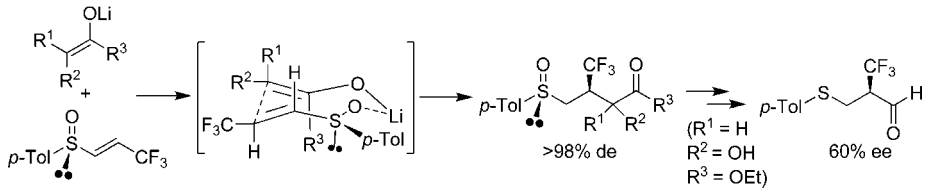
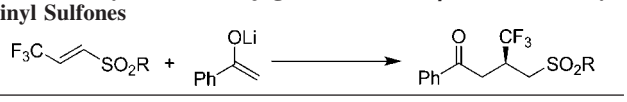


Table 92. Asymmetric Conjugate Addition to β-Trifluoromethyl Vinyl Sulfones



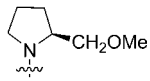
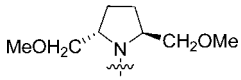
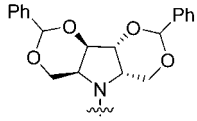
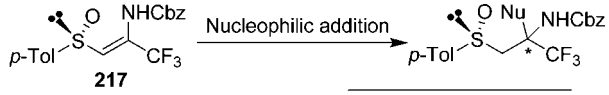
R	de, %
	20
	46
	98

Table 93. Diastereoselective Nucleophilic Addition to Chiral Enamine 217



Nu	yield, %	dr
MeO	81	1:1
NH_2	90	1:1
CH_2NO_2	80	1:1
CN	90	1.9:1

addition of the lithium enolate derived from α-alkoxyacetate, gave α-trifluoromethylaldehyde with only 60% enantiomeric excess.[404]

Eguchi and co-workers reported a conjugate addition of lithium 1-phenylethenolate to chiral β-trifluoromethyl vinyl sulfonamides.[405] Only moderate diastereoselectivities were observed except with the α,β-unsaturated sulfonamide prepared from D-mannitol, for which the corresponding adduct was obtained in high diastereoselectivity (Table 92).

Under mild conditions, (*Z*)-α-(trifluoromethyl)-*N*-Cbz-β-sulfinyl enamine **217** reacted efficiently with methanol, ammonia, and nitromethane. Concerning the diastereoselectivity, almost equimolar mixtures of addition products were obtained.[406] Similarly, the treatment with KCN in a mixture of THF/H_2O (4:1) was carried out to form *N*-Cbz-α-aminonitrile in 90% yield, albeit with a modest diastereoselectivity (1.9:1 dr) (Table 93).[407] In addition, when **217** reacted with a sulfur nucleophile such as thiophenol, the desired adduct was not observed.

Concerning the asymmetric conjugate addition to prochiral CF_3-substituted unsaturated carbonyl compounds, there are more examples in the literature with often high stereoselectivity. α-(Trifluoromethyl)acrylic acid represents an attractive fluorinated building block for the preparation of chiral compounds featuring the CF_3 group at the α-position of this carbonyl function. In 1991, Ojima and Jameison described the preparation of fluorinated captopril analogues by conjugate addition of thiolacetic acid to the Michael acceptor **218** derived from α-(trifluoromethyl)acrylic acid and L-proline *t*-butyl ester (Scheme 106).[408] A 1:2 ($R,S_{pro}/S,S_{pro}$) diasteromeric mixture of adducts was obtained and separated on silica gel. Removal of *tert*-butyl and thioacetyl groups with iodotrimethylsilane and methanolic ammonia, followed by treatment with sodium borohydride, resulted in the formation of (R,S_{pro})- and (S,S_{pro})-trifluoromethyl captopril. It was found that the (R,S_{pro})-isomer exhibited higher inhibitory activity of angiotensin-converting enzyme than the (S,S_{pro})-isomer. Moreover, (R,S_{pro})-isomer is more potent than captopril. Stereoelectronic and conformational effects attributed to trifluoromethyl incorporation served to explain the enhanced inhibitory activity.

The asymmetric aza-Michael reaction has emerged as a very powerful tool for the creation of carbon−nitrogen bonds, owing to its simplicity and atom economy. Recently, chiral auxiliary-controlled asymmetric aza-Michael addition of nosyloxycarbamates to 2-(trifluoromethyl)acrylates was reported.[409] Two kinds of chrial adducts could be obtained by using different inorganic bases. Calcium oxide promoted aza-Michael 1,4-addition to give *N,N′*-disubstituted α-(trifluoromethyl)-β-amino esters **219**, whereas in the presence of sodium hydride an aza-Michael-initiated ring-closure reaction yielded aziridines **220** in high yields. While the use of (−)-8-phenylmenthol induced a low diastereoselectivity, more satisfactory results were obtained by using the bulkier auxiliary derived from (+)-camphor (Table 94).

The use of peptides in drug development is limited due to their rapid degradation in vivo and poor bioavailability. Peptide backbone modification is an attractive strategy for overcoming these disadvantages, while retaining specific and potent bioactivity. The groups of Fustero in Spain and Zanda in Italy presented a methodology for the synthesis of partially modified retro (PMR) Ψ[$NHCH_2$] peptide mimetics **221** containing a chemically stable and stereodefined $CH_2CH(CF_3)CO$ unit. The key reaction is an aza-Michael addition of α-amino esters to *N*-(2′-trifluoromethyl)acryloyl α-amino acids, which takes place in a stereoselective manner. The reaction features an unusual high 1,4-asymmetric induction, which is strongly dependent on several experimental factors, such as solvent, catalytic base, R and R^1 chains, and relative stereochemistry of the reaction partners. The R′ and R^3 ester groups had a minor influence on the stereoselectivity. The highest 1,4-asymmetric induction (up to 33:1 dr) was observed in apolar solvents (such as CCl_4), together with

Scheme 106

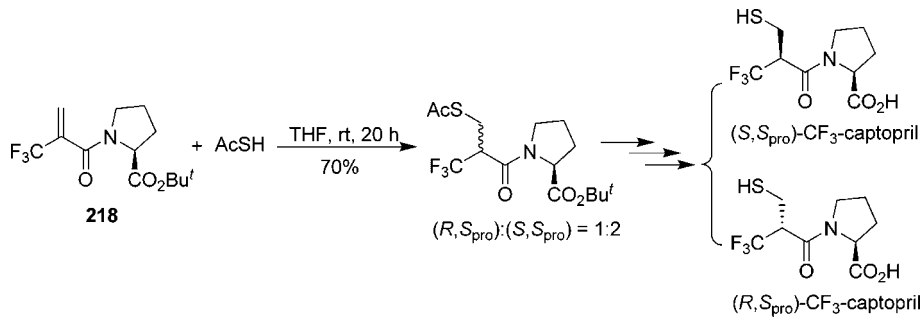
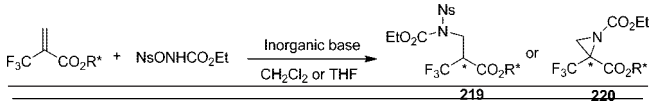


Table 94. Asymmetric Aza-Michael Addition of Nosyloxycarbamates to 2-(Trifluoromethyl)acrylates



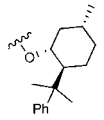
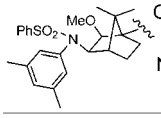
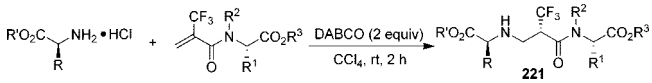
			219		220	
R*	base	solvent	yield, %	de, %	yield, %	de, %
	CaO	CH_2Cl_2	70	12		
	NaH	THF			90	19
	CaO	CH_2Cl_2	81	70		
	NaH	THF			96	72

Table 95. Asymmetric Aza-Michael Addition of α-Amino Esters to *N*-Trifluorometacryloyl α-Amino Esters



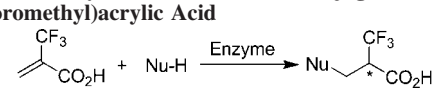
R	R′	R^1	R^2	R^3	yield, %	dr
H	Et	^{i}Pr	H	Bn	98	7:1
^{t}Bu	Bn	^{i}Pr	H	Bn	80	11:1
Bn	Me	^{i}Pr	H	Bn	85	13:1
^{s}Bu	Me	^{i}Pr	H	Bn	80	23:1
^{i}Pr	^{t}Bu	^{i}Pr	H	^{t}Bu	90	33:1
Bn	Me	-(CH$_2$)$_3$-		Bn	84	12:1
Me	Me	-(CH$_2$)$_3$-		Bn	85	24:1
^{s}Bu	Me	-(CH$_2$)$_3$-		Bn	83	29:1
Bn	Bn	Bn	H	Bn	70	6:1
^{i}Pr	Bn	Me	H	^{t}Bu	71	29:1
Me	^{t}Bu	Me	H	^{t}Bu	76	17:1
Bn	Me	H	H	Bn	85	2:1
^{s}Bu	Me	H	H	Bn	82	3:1
^{i}Pr	Bn	H	H	Bn	89	6:1

the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalytic base and bulky R and R^1 side-chains (such as isopropyl and isobutyl groups) (Table 95).[410]

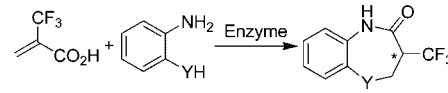
These researchers also developed stereocontrolled solid- and fluorous-phase syntheses of partially modified retropeptides by using Wang resin-bound *N*-(2′-trifluoromethyl)acryloyl α-amino esters **222**[411] and fluorous (trimethylsilyl)ethyl-tagged Michael acceptors **223**,[412] respectively (Figure 15). Thus, the preparation of large arrays of PMR peptides makes possible high-throughput biological screening.

A mechanistic investigation revealed that this reaction is a two-step process. The aza-Michael addition of α-amino esters to α-trifluoromethyl acrylamide acceptors afforded an amide enol intermediate, followed by its tautomerization to the adduct, which is the actual stereoselective step.[413] The use of different amines as Michael donors extended further this addition reaction to the synthesis of other families of peptidomimetics, such as dipeptides, tripeptides, and structures containing two units of α-trifluoromethyl-β^2-alanine or a urea moiety. With the aid of X-ray analysis and NMR

Table 96. Biocatalytic Enantioselective Conjugate Addition to α-(Trifluoromethyl)acrylic Acid

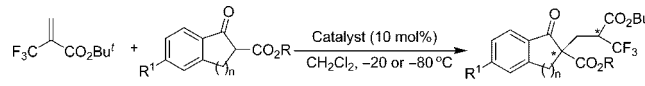


Nu-H	enzyme	yield, %	ee, %
H_2O	*Candida cylindracea*	48	70
H_2O	Pig liver esterase	54	60
Et_2NH	*Candida cylindracea*	47	71
Et_2NH	Pig liver esterase	39	69
$PhNH_2$	*Candida cylindracea*	76	39
PhSH	Pig liver esterase	64	50



Y = O, NH, S 52–94% yield, 25–67% ee

Table 97. Cinchona Alkaloid-Catalyzed Enantioselective Michael Addition

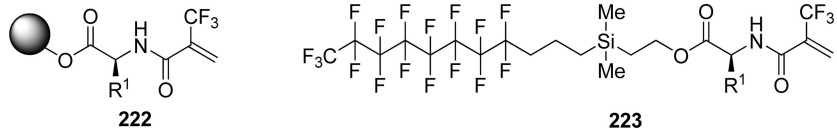


Catalyst	R	R^1	n	yield, %	dr	ee, %
Cinchonine	*t*-Bu	H	1	91	75:25	97 (+)
Cinchonine	Me	H	1	91	84:16	93 (+)
Cinchonine	*i*-Pr	H	1	88	86:14	94 (+)
Cinchonine	cyclohexyl	H	1	42	82:18	90 (+)
Cinchonine	*t*-Bu	OMe	1	93	75:25	87 (+)
Cinchonine	*t*-Bu	H	2	75	67:33	40 (+)
Cinchonine	Me	H	2	55	69:31	57 (+)
Cinchonidine	*t*-Bu	H	1	91	74:26	86 (−)

techniques, conformational studies on several of the newly synthesized peptidomimetics revealed a β-turn-like conformation for the structures both in the solid state and in solution.[40]

The catalytic enantioselective Michael addition has clear advantages over the substrate and/or auxiliary-controlled approach because a catalytic amount of chiral material can produce large quantities of enantiomerically enriched or enantiopure products. In 1986, Kitazume and co-workers reported biocatalytic enantioselective conjugate additions of a series of nucleophiles to α-(trifluoromethyl)acrylic acid.[414] The nucleophiles, which include water, diethylamine, aniline, thiophenol, and aminophenols, gave the adducts with moderate enantioselectivities. For *o*-substituted anilines, the heterocycles were obtained in good yields (Table 96).

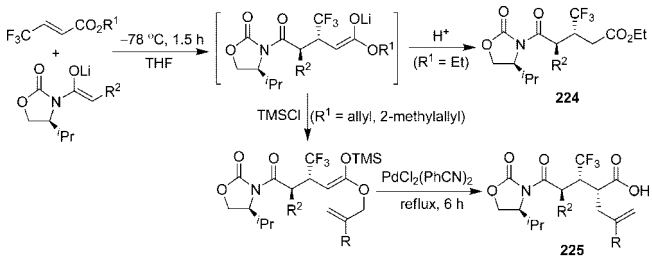
The first chemical enantioselective Michael addition of β-ketoesters to *tert*-butyl α-(trifluoromethyl)acrylate in the presence of cinchona alkaloid catalysts was disclosed recently by Shibata and co-workers (Table 97).[415] In the presence of a catalytic amount of cinchonine, the Michael addition of several indanone and tetralone carboxylates afforded trifluoromethylated diesters in which two nonadjacent stereocenters are formed with moderate to high diastereocontrol and enantiocontrol up to 97% ee. The opposite stereochemistry of the major diastereomer was obtained by the use of



222 **223**

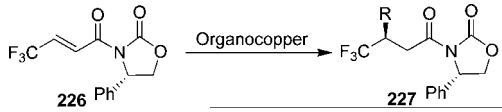
Figure 15. Supported and fluorous reactants.

Table 98. Asymmetric Conjugate Addition of Chiral Oxazolidinone Enolates to 4,4,4-Trifluorocrotonates



		224		225	
R^2	R	yield, %	de, %	yield, %	de, %
Me		88	>98%		
Et		52	>98%		
^{i}Pr		97	>98%		
BnO		36	>98%		
Me	H			65	>98%
Et	H			63	>98%
^{i}Pr	H			60	>98%
Me	Me			65	>98%
Et	Me			74	>98%
^{i}Pr	Me			62	>98%

Table 99. Asymmetric Conjugate Addition of RCu to 4,4,4-Trifluorocrotonimide 226



Organocopper reagent	yield, %	de, %
p-$MeOC_6H_4MgBr/CuBr\cdot SMe_2$	100	90
$C_6H_4MgBr/CuBr\cdot SMe_2$	100	72
$MeMgBr/CuBr\cdot SMe_2$	92	60
$VinylMgBr/CuBr\cdot SMe_2$	80	98
MeCu/LiI	68	98
n-BuCu/Li	65	87

the pseudoenantiomeric cinchonidine catalyst. However, this methodology has some limitations with β-ketoester generality.

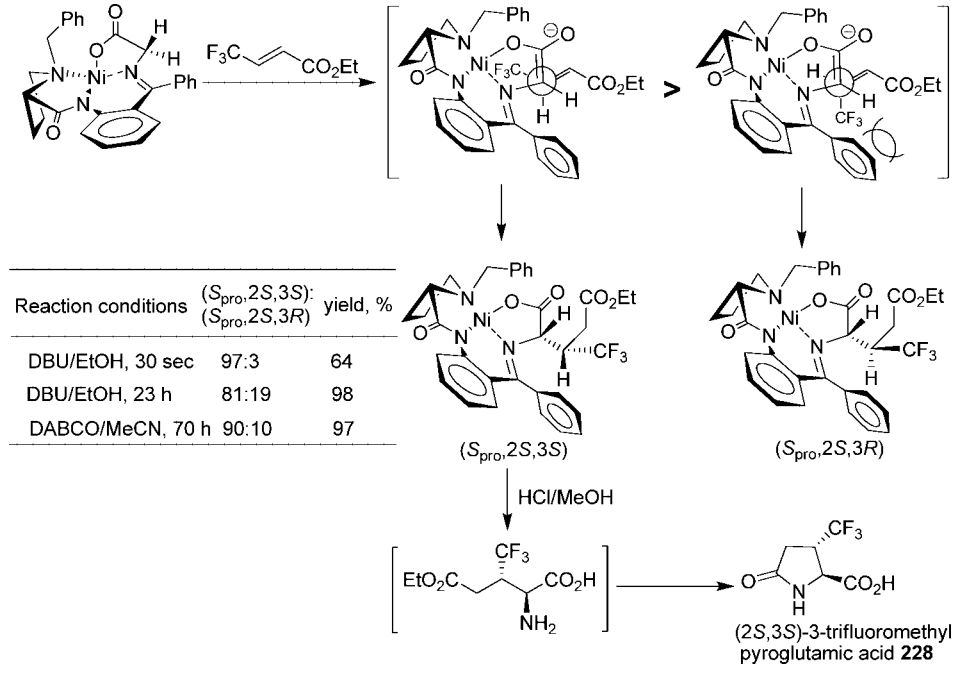
4,4,4-Trifluorocrotonates and derivatives are another kind of prochiral building block for the synthesis of optically active fluorinated products. In particular, they allow the preparation of carbonyl compounds featuring a CF_3 moiety at the β-position. Yamazaki and co-workers disclosed a conjugate addition of chiral oxazolidinone enolates to 4,4,4-trifluorocrotonates for the synthesis of optically active CF_3-containing compounds with two or three consecutive stereogenic centers (Table 98).[416] A series of lithium enolates reacted with ethyl 4,4,4-trifluorocrotonate to give the corresponding adducts **224** in excellent diastereoselectivities (>98% de). Interestingly, the Michael intermediates, generated from allyl 4,4,4-trifluorocrotonate, were trapped with TMSCl and heated in the presence of a palladium complex to furnish the Ireland−Claisen rearranged products **225** as a single stereoisomer in moderate yields.[417]

Subsequently, the same group employed chiral 4,4,4-trifluorocrotonimides **226** as Michael acceptors with a series of organocopper reagents. The reactions proceeded smoothly to afford the corresponding adducts **227** in 65−100% yields with 60−98% de (Table 99). The stereochemical outcome of the reaction showed that organocopper could approach the β-position of the Michael acceptor from the *Si*-face of metal-chelated α,β-unsaturated imide.[418]

The conjugate addition of Ni(II) complex of chiral Shiff base to ethyl 4,4,4-trifluorocrotonate has been developed for the synthesis of optically active 3-trifluoromethylpyroglutamic acid (Scheme 107).[419] It was noteworthy that the reaction time influences the diastereoselectivity in the presence of DBU. In the favorable transition state, steric repulsions between CF_3 and phenyl groups are avoided, and an attractive electrostatic interaction between the electron-rich CF_3 group and the partially positively charged Ni(II) atom are worth mentioning. The decomplexation of the major diastereomer (S_{pro},2*S*,3*S*) was readily accomplished with HCl/MeOH to afford the enantiopure (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid **228**.

The conjugate additions of optically active *N*-sulfinyl nitroamines toward methyl 4,4,4-trifluorocrotonate have been used for the direct synthesis of pharmaceutically interesting γ-trifluoromethyl piperidones (Scheme 108).[420] The 6-methylpiperidin-2-one was obtained in 50% yield with 82% de

Scheme 107



Scheme 108

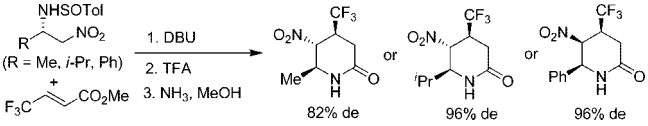
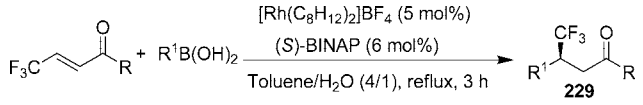


Table 100. Rhodium-Catalyzed Conjugate Addition of Organoboronic Acids onto β-Fluoroalkylated Electron-Deficient Olefins

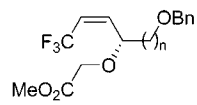
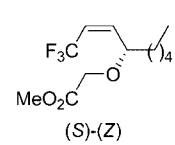


R	R^1	yield, %	ee, %
Ph	Ph	90	90
Ph	*p*-$CH_3C_6H_4$	91	92
Ph	*p*-$CH_3OC_6H_4$	89	92
Ph	*p*-ClC_6H_4	94	94
Ph	*m*-ClC_6H_4	81	91
Ph	*p*-FC_6H_4	80	90
Ph	*p*-$CH_3(O)CC_6H_4$	95	93
Ph	*p*-$EtO_2CC_6H_4$	80	92
Ph		64	90
Ph		51	70
Ph		70	40
Ph	*n*-Bu	11	
NMe_2	Ph	46	92

after chromatographic purification (through a column of strong cation-exchange resin), whereas 6-isopropyl and 6-phenyl piperidin-2-ones were formed in 96% de. The stereochemistry of 6-phenylpiperidin-2-one (all groups are in a *cis*-arrangement) is different from that of 6-methyl and 6-isopropyl piperidin-2-ones, which is probably related to the thermodynamic stability of the epimers at C-5.

Chiral rhodium-catalyzed conjugate additions of organoboronic acids to α,β-unsaturated carbonyl compounds provide an excellent approach for the enantioselective catalytic introduction of aryl and alkenyl groups at the β-position of electron-deficient olefins. Konno and co-workers described the rhodium-catalyzed conjugate addition reaction of aryl and alkenylboronic acids to trifluoromethyl-containing α,β-unsaturated ketones as well as one amide.[421] A series of arylboronic acids could participate nicely in the conjugate addition to give the corresponding adducts **229** in good to high yields (64−95%) with high enantioselectivities (90−94% ee). However, the use of 1-naphthyl and alkenylboronic acids led to a significant decrease of the chemical yield and the enantioselectivity

Table 101. [2,3]-Wittig Rearrangement of (*Z*)-2-[(3′-Trifluoromethyl)allyloxy]acetates

Substrate	Product yield, %	*anti*:*syn*	ee, %
 (*R*)-(*Z*) (n = 1)	73	>99:1	>98% ee (*anti*)
(*R*)-(*Z*) (n = 2)	78	>99:1	>98% ee (*anti*)
 (*S*)-(*Z*)	64	>99:1	>98% ee (*anti*)

(Table 100). It has been observed that the rhodium complex with BINAP catalyzed the isomerization of (*Z*)-trifluoromethyl-containing α,β-unsaturated ketone much more rapidly than the conjugate addition of organoboronic acids. Thus, the use of either (*E*)- or (*Z*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one provided the Michael adduct with the same absolute configuration.

6.4. Rearrangement Reactions

Sigmatropic rearrangement is an atom-economic tool for the construction of a new carbon−carbon bond, and indeed, a stereoselective version with CF_3-containing reactants has been reported. In 1997, Konno and co-workers found that Johnson− or Eschenmoser−Claisen rearrangements of chiral (*E*)- and (*Z*)-γ-trifluoromethylated allylic alcohols proceeded very smoothly at 100−130 °C. The corresponding rearranged (*S*)- and (*R*)-products were obtained in 50−96% yield with a complete chirality transfer (Scheme 109).[422]

Konno and Kitazume also developed the [2,3]-Wittig and [3,3]-Ireland−Claisen rearrangements of ester enolates for the stereoselective synthesis of chiral trifluoromethylated compounds.[423] Treatment of chiral methyl 2-[(3′-trifluoromethyl)allyloxy]acetates or (3′-trifluoromethyl)allyl 2-methoxyacetates with lithium bis(trimethylsilyl)amide (LHMDS) and TMSCl (or $ZnCl_2$) at −78 °C to room temperature in THF gave the corresponding chiral isomers in a stereospecific way. Interestingly, [2,3]-Wittig rearrangement of methyl (*Z*)-2-[(3′-trifluoromethyl)allyloxy]acetates proceeded to afford *anti*-isomers with *E* configuration at a newly created olefinic bond via complete chirality transfer (Table 101), whereas (*E*)-substrates showed relatively low stereoselectivities resulting in mixtures of *syn*- and *anti*-products.[424] Investigation of (*E*)-(3′-trifluoromethyl)allyl 2-methoxyacetates and 2-aminoacetates as substrates in [3,3]-Ireland−Claisen rearrangement gave *syn*-products, while (*Z*)-substrates were efficiently transformed into *anti*-products.[425−427]

Scheme 109

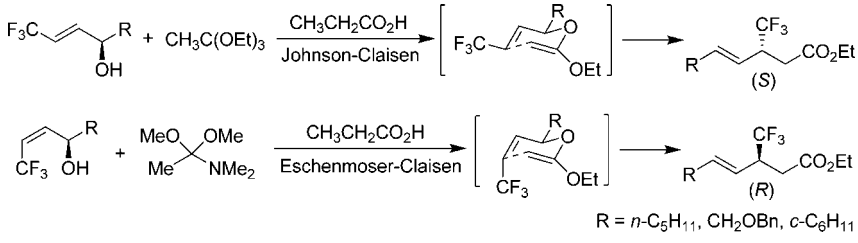
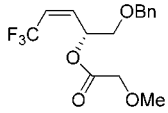
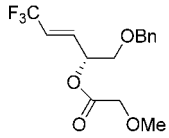
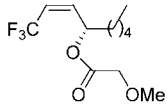
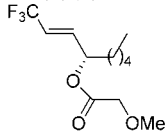
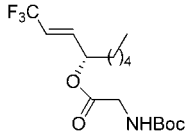


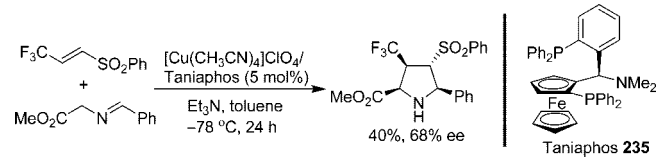
Table 102. [3,3]-Ireland−Claisen Rearrangement of (3′-Trifluoromethyl)allyl 2-Methoxyacetates or 2-Aminoacetates

Substrate	Product yield, %	*anti*:*syn*	ee, %
			
(*R*)-(*Z*)	68	97:3	>98% ee (*anti*)
			
(*R*)-(*E*)	59	1:99	>98% ee (*syn*)
			
(*S*)-(*Z*)	75	96:4	>98% ee (*syn*)
			
(*S*)-(*E*)	67	1:99	>98% ee (*syn*)
			
(*S*)-(*E*)	82	0:100	>98% ee (*syn*)

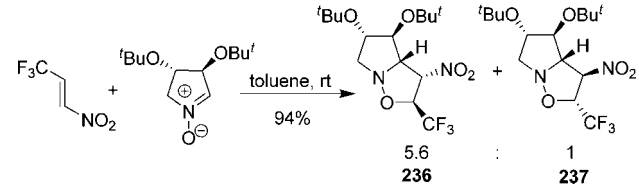
In these reactions, complete chirality transfers were observed. The two complementary methods provided facile access to highly functionalized trifluoromethyl-containing molecules with a high degree of stereocontrol (Table 102).[424]

In view of their unique biological properties, many fluorinated steroids have been synthesized. Jiang and co-workers presented a practical stereocontrolled pathway for the synthesis of trifluoromethylated analogues of naturally occurring crinosterol and typhasterol. Hydroxycholic acid **230** was readily converted into the trifluoromethylated (22*S*,23*E*)-allylic alcohol **231**, which was heated with triethyl *ortho*-propionate in xylene at 130 °C for 5 h, through Johnson−Claisen rearrangement, to predominantly give the *syn*-rearrangement product **232** (*syn*/*anti* = 96:4). This key intermediate was transformed into the trifluoromethylated crinosterol **233** and typhasterol **234** via multistep reactions (Scheme 110).[428]

Scheme 111



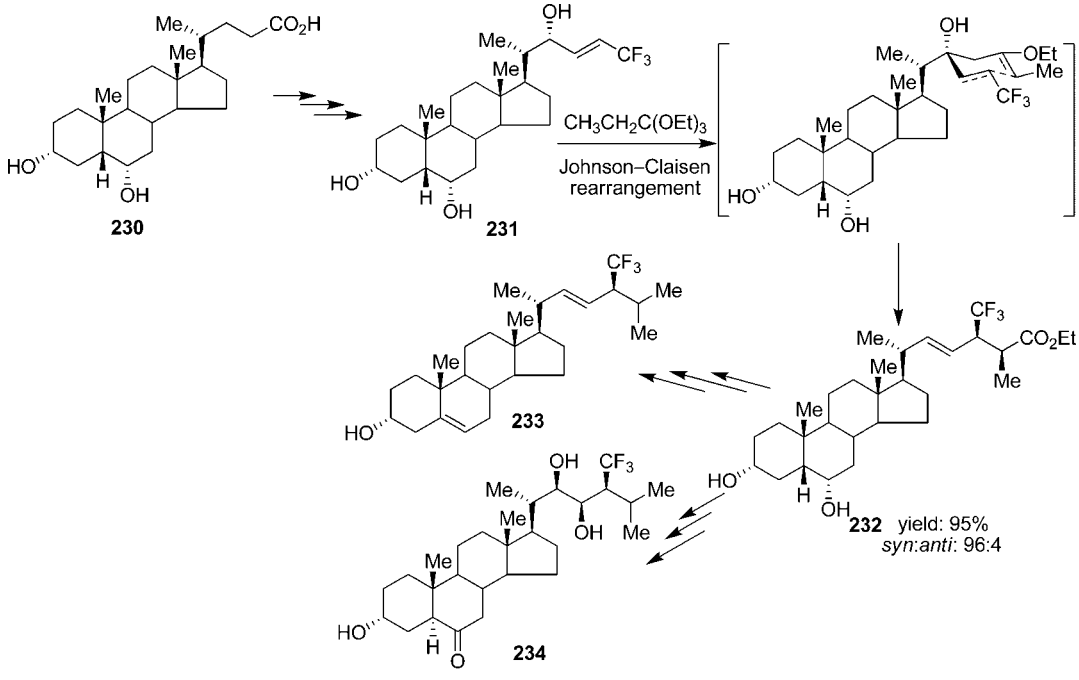
Scheme 112



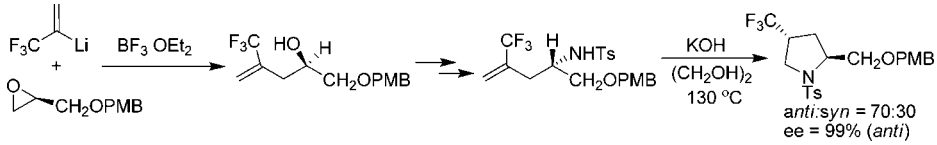
6.5. Cycloaddition and Cyclization Reactions

Fluorinated heterocyclic compounds have been widely studied in pharmaceutical and agrochemical chemistry because of their ability to penetrate the cell membrane barriers and their potential biological activity.[429] An asymmetric 1,3-dipolar cycloaddition reaction provides efficient access to chiral five-membered heterocyclic compounds.[430−432] One example involved the enantioselective 1,3-dipolar cycloaddition for the synthesis of trifluoromethylated proline derivative.[433] Thus, the reaction of β-trifluoromethylated vinyl sulfone with *N*-benzylidene glycine ester in the presence of

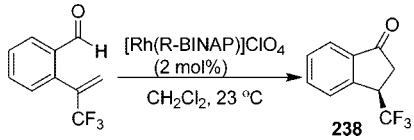
Scheme 110



Scheme 113



Scheme 114



copper(I)−Taniaphos (**235**) complex in toluene at −78 °C furnished the corresponding adduct in 40% yield with 68% ee. A high *exo*-selectivity was observed (Scheme 111).

Zanda and co-workers reported another example of 1,3-dipolar cycloaddition for the asymmetric synthesis of chiral trifluoromethylated isoxazolidines. In this context, the reaction of (*E*)-3,3,3-trifluoro-1-nitroprop-1-ene with enantiomerically pure nitrone proceeded well in high yield and with good diastereocontrol, essentially providing two diastereomeric cycloadducts with a quite large predominance of **236** over **237** (Scheme 112).[434]

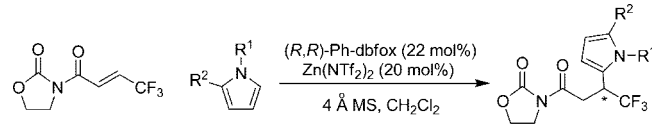
Ichikawa and co-workers developed a divergent chemical synthesis of 4-trifluoromethylproline derivatives by using 2-bromo-3,3,3-trifluoropropene.[435] The reaction of the epoxide with 1-(trifluoromethyl)vinyllithium in the presence of $BF_3 \cdot OEt_2$ gave the corresponding ring-opening product, which can be converted into the tosylamine in two steps. The cyclization of tosylamine with an excess amount of KOH in ethylene glycol afforded the *anti*-prolinol with excellent enantioselectivity (99% ee) (Scheme 113).

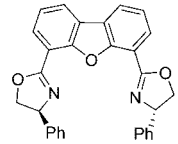
Morehead and co-workers developed a rhodium(I)-catalyzed intramolecular hydroacylation for the synthesis of CF_3-containing carbocycles (Scheme 114).[436] In this reaction, treatment of 2-(1-trifluoromethylvinyl)benzaldehyde with a catalytic amount of [Rh(*R*-BINAP)]ClO_4 afforded the corresponding 3-(trifluoromethyl)-1-indanone in 90% yield with 99% ee. The synthesis gave access to chiral nonracemic 3-CF_3 indanone **238** that is otherwise difficult to obtain.

6.6. Allylation Reactions

Allylation of carbonyl compounds and derivatives with various allylating reagents is one of the most fundamental reactions in organic synthesis. The asymmetric version offers a convenient approach to create optically active products.[437] (*E*)-4-Bromo-1,1,1-trifluoro-2-butene, derived from commercially available ethyl 4,4,4-trifluoro-3-oxobutanoate, has been used as an allylating reagent for the construction of trifluoromethylated molecules.[438] Qing and co-workers developed an efficient indium-mediated allylation of (*R*)- and (*S*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine with (*E*)-4-bromo-1,1,1-trifluoro-2-butene.[439] The *syn*-amines were obtained through S_N2' reaction in good yields with high diastereoselectivities (>95% de). Furthermore, the homoallylic amines can be readily transformed into (2*R*,3*S*)-4,4,4-trifluorovaline and (2*R*,3*S*)- and (2*S*,3*R*)-4,4,4-trifluoroisoleucines (Scheme 115). However, under the same reaction conditions, (*R*)-2,3-*O*-isopropylideneglyceraldehyde gave a mixture of homoallylic alcohols with low diastereoselectivity (dr = 1.5:1).

Table 103. Lewis Acid-Catalyzed Enantioselective Friedel−Crafts Reaction of Pyrroles



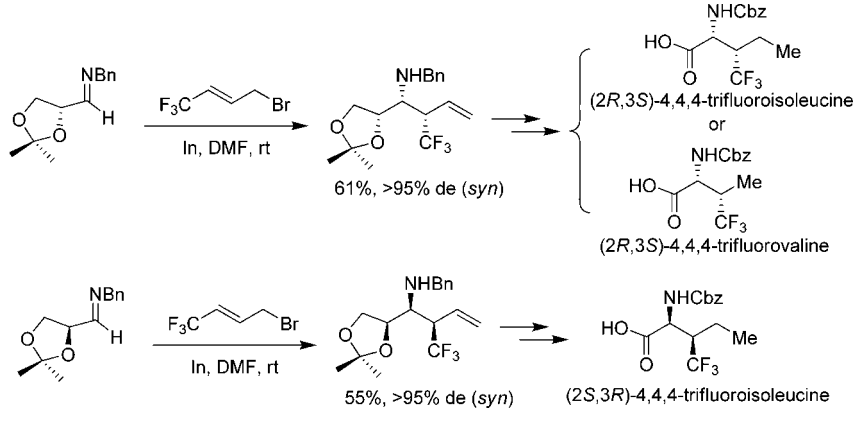


R^1	R^2	yield, %	ee, %	R^1	R^2	yield, %	ee, %
H	H	97	99	allyl	H	90	95
H	Me	96	97	Bn	H	93	85
H	Et	98	92	Ph	H	94	88
Et	H	96	96	Me	Me	97	94
n-Pr	H	96	95	Me	Et	99	88
n-Bu	H	95	93	Me	Bn	95	76

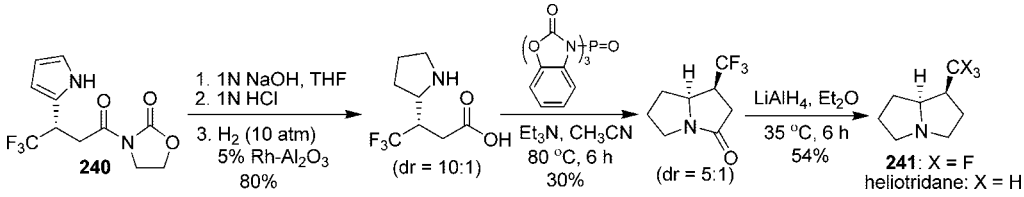
6.7. Friedel−Crafts Reactions

Asymmetric Friedel−Crafts reactions have gained particular attention and made much progress in recent years. As mentioned above, several prochiral substrates, such as trifluoroacetaldehyde, trifluoropyruvates, trifluoromethyl ketones, and their derivatives, have been widely applied in asymmetric Friedel−Crafts reactions. However, the use of trifluoromethyl olefins as the Friedel−Crafts acceptors is relatively rare. Recently, Shibata and co-workers reported a chiral Lewis acid-catalyzed asymmetric Friedel−Crafts reaction of pyrroles and indoles with

Scheme 115



Scheme 116



β-trifluoromethyl acrylates.[440] In the presence of 20 mol % Zn(NTf)$_2$-Ph-dbfox (**239**) complex, the reaction of (*E*)-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one with a series of pyrroles afforded the corresponding adducts in excellent yields (90−99%) with good to high enantioselectivities (76−99% ee) (Table 103). Notably, this simple catalytic asymmetric Friedel−Crafts reaction has been extended to indole and 4,7-dihydroindole to access trifluoromethylated 3- and 2-substituted indoles in high yields with 99% and 75% ee, respectively. Adduct **240** could be converted into trifluorinated heliotridane **241** through several convenient synthetic transformations (Scheme 116).

7. Asymmetric Reactions of Other Prochiral Trifluoromethyl Substrates

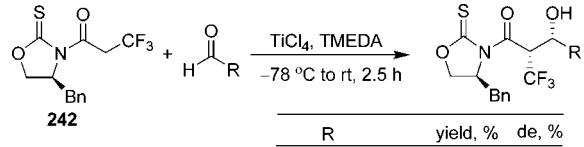
Some novel prochiral trifluoromethyl materials, such as 2,2,2-trifluorodiazoethane, 3,3,3-trifluoropropanates, and relative derivatives, have emerged in recent years. Asymmetric transformations of these prochiral substrates involve different bond-forming processes and open new pathways to chemically and/or biologically interesting chiral CF_3-containing compounds.

7.1. Aldol Reactions with 3,3,3-Trifluoropropionic Acid Derivatives

Although the reactions of α-CF_3 enolates could provide convenient access to the synthesis of CF_3-containing compounds, facile defluorination in the generation of α-CF_3 enolates has limited its utility. Following Mikami and co-workers' pioneering work on the titanium enolate of α-CF_3 ketone,[441] Figadére and co-workers examined the aldol reaction of chiral α-CF_3 titanium enolate with various aldehydes.[442] Thus, treatment of (*S*)-*N*-3,3,3-trifluoropropionyl-4-benzyloxazolidine-2-thione **242** with $TiCl_4$ and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at −78 °C, followed by the addition of various aldehydes, afforded a series of *syn*-aldols in good yields with excellent diastereoselectivities (>96%) (Table 104). When using diisopropylethylamine as base, only poor yields were obtained. The reaction proceeded through a *Z*-$TiCl_3$-enolate to provide the *syn*-Evans aldol via a cyclic six-membered transition state involving a stronger interaction of Ti for the sulfur atom than for the fluorine.

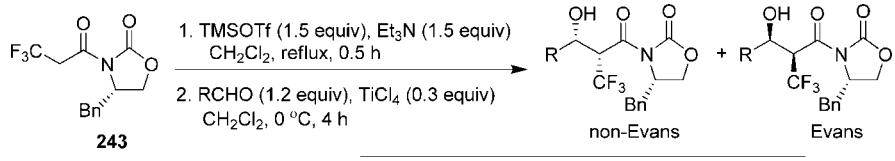
Simultaneously, Ishihara's group developed $TiCl_4$-catalyzed aldol reactions of aldehydes optically active 3,3,3-trifluoropropanoic imide **243** featuring a chiral oxazolidinone.[443] The chiral silyl enol ether, generated from 3,3,3-trifluoropropanoic imide and TMSOTf in the presence of Et_3N, was treated with $TiCl_4$ and aldehydes to afford *syn*-products in moderate yields with high diastereoselectivities.

Table 104. Aldol Reaction of Chiral Oxazolidinone Titanium Enolate with Aldehydes



R	yield, %	de, %
4-$NO_2C_6H_4$	72	>96
Ph	86	>96
4-$MeOC_6H_4$	85	>96
$(CH_2)_4CH_3$	63	>96
$CH{=}CH(CH_2)_5CH_3$	64	>96

Table 105. Aldol Reaction of (*S*)-4-Benzyl-3-(3,3,3-trifluoropropanoyl)oxazolidin-2-one with Aldehydes



R	yield, %	*syn* (non-Evans:Evans) : *anti*
Ph	59	97 (99:1) : 3
p-MeC_6H_4	54	84 (95:5) : 16
p-$MeOC_6H_4$	60	89 (96:4) : 11
p-ClC_6H_4	59	92 (99:1) : 8
p-FC_6H_4	56	89 (99:1) : 11
n-Pr	38	91 (99:1) : 9
i-Pr	11	90 (99:1) : 10
MeCH=CH	56	93 (99:1) : 7

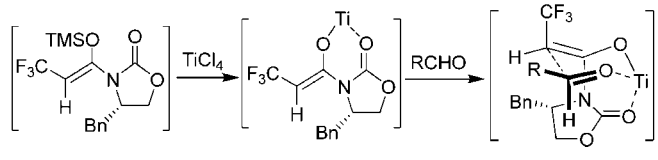
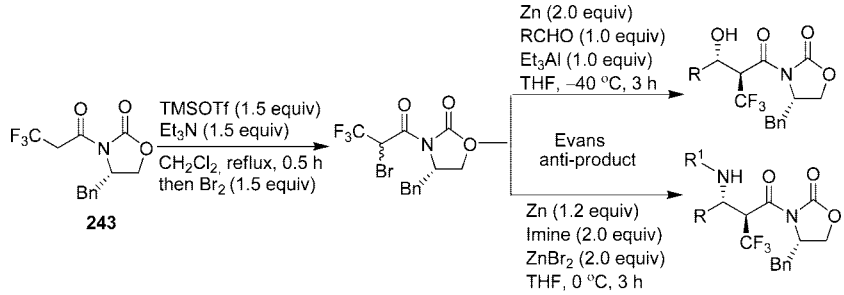
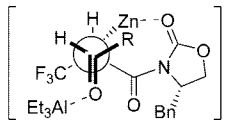
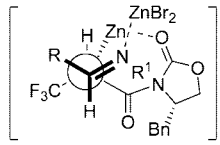


Table 106. Reformatsky-Type Reactions with a Series of Aldehydes and Imines

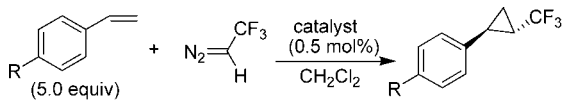




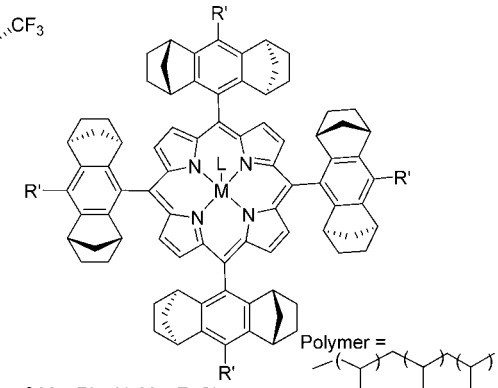


R	R^1	yield, %	*anti* (Evans:non-Evans)	:	*syn*
Ph		86	96 (98:2)	:	4
p-MeC_6H_4		81	93 (98:2)	:	7
p-$MeOC_6H_4$		85	91 (97:3)	:	9
p-ClC_6H_4		65	92 (97:3)	:	8
n-Pr		76	75 (73:27)	:	25
i-Pr		79	67 (66:34)	:	33
MeCH=CH		82	86 (96:4)	:	14
Ph	Boc	92	100 (>99:1)	:	0
p-MeC_6H_4	Boc	85	100 (>99:1)	:	0
p-$MeOC_6H_4$	Boc	80	100 (>99:1)	:	0
p-ClC_6H_4	Boc	84	100 (>99:1)	:	0
p-$CF_3C_6H_4$	Boc	90	100 (>99:1)	:	0
Ph	Cbz	80	100 (94:6)	:	0
p-MeC_6H_4	Cbz	90	100 (93:7)	:	0
p-$MeOC_6H_4$	Cbz	88	100 (96:4)	:	0

Table 107. Catalytic Asymmetric Cyclopropanation of Styrenes with Trifluorodiazoethane



R	Catalyst	yield, %	trans:cis	ee, %
H	**244a**	40	99:1	67
OMe	**244a**	42	99:1	69
Br	**244a**	43	99:1	67
H	**244b**	32	98:2	58
OMe	**244b**	35	99:1	30
Br	**244b**	24	99:1	50
H	**244c**	52	97:3	56
OMe	**244c**	51	96:4	17
Br	**244c**	42	97:3	37
H	**244d**	33	99:1	61
OMe	**244d**	35	94:6	25
Br	**244d**	31	96:4	39

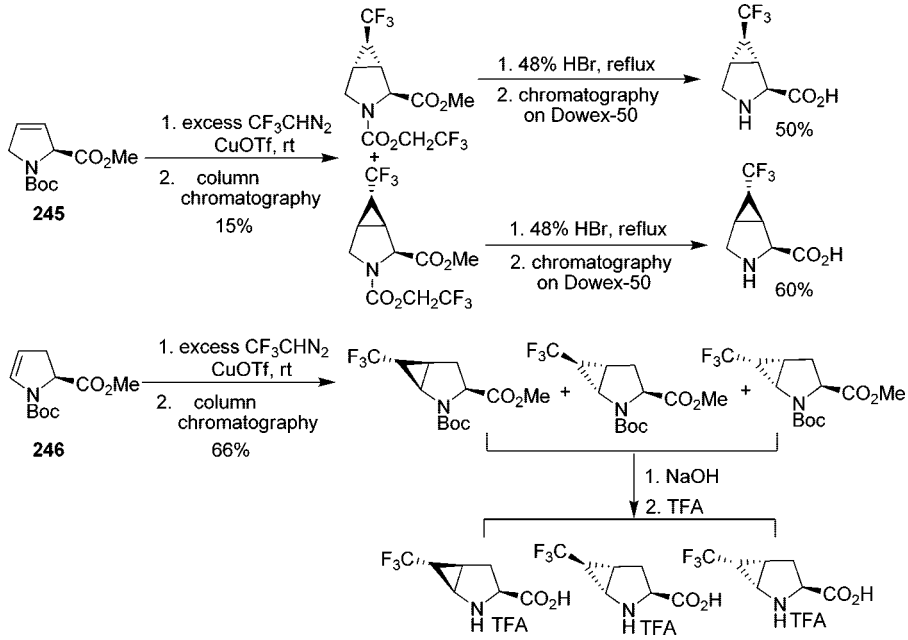


244a, R' = H, M = FeCl
244b, R' = H, M = RuCO
244c, R' = Polymer, M = FeCl
244d, R' = Polymer, M = RuCO

However, the reaction of isobutyraldehyde proceeded reluctantly to give the aldol in low yield, while the stereoselection was high (Table 105). The reaction mechanism could involve the transmetalation of silyl enolate with $TiCl_4$ to generate titanium enolate. An aldehyde would approach the titanium enolate from the less-hindered *Re*-face with simultaneous coordination of the titanium atom to the carbonyl oxygen of the aldehyde, leading to a six-membered chairlike chairlike transition state, for which the substituent R occupies the equatorial position to minimize a 1,3-diaxial repulsion. Consequently, the non-Evans *syn*-product was produced preferentially.

Subsequently, the same group presented a convenient route to the Evans *anti*-products via the highly stereoselective Reformatsky-type reaction of chiral 3-(2-bromo-3,3,3-trifluoropropanoyl)-4-benzyl-2-oxazolidinone with various aldehydes and imines (Table 106).[443,444] In the presence of Et_3Al, treatment of chiral 3-(2-bromo-3,3,3-trifluoropropanoyl)-4-benzyl-2-oxazolidinone with zinc dust and aldehydes gave α-trifluoromethyl-β-hydroxypropanoic imides in good yields. On the other hand, α-trifluoromethyl-β-amino acid derivatives were also obtained in high yields when $ZnBr_2$ was employed as Lewis acid. High stereoselection in Reformatsky-type reaction has been explained on the basis of the open-chain transition state. Thus, Lewis acid-activated electrophiles approach the reactive carbon of Reformatsky reagents from the side opposite to that occupied by the zinc atom. Because of a large steric repulsion between electrophiles and the benzyl substituent of the oxazolidinone ring, the reaction proceeds preferentially via open-chain transition state, in which there is less steric gauche repulsion, giving the Evans *anti*-isomers.

Scheme 117



7.2. Cyclopropanation Reactions by Means of 2,2,2-Trifluorodiazoethane

As a reactive reagent, 2,2,2-trifluorodiazoethane provides efficient access to valuable cyclopropanes upon reaction with olefins. Simonneaux and co-workers developed a simple method for the synthesis of optically active trifluoromethylcyclopropanes by using chiral metalloporphyrins.[445] In the presence of chiral Fe− and Ru−porphyrin complexes **244**, the reaction of 2,2,2-trifluorodiazoethane with three styrenes afforded the cyclopropanes in 24−50% yields with excellent diastereoselectivities (*trans*/*cis* > 98:2), albeit with moderate enantioselectivities (30−69% ee). Interestingly, under heterogeneous conditions with metalloporphyrin supported on polymers, the yield was maintained but the stereoselectivity decreased (Table 107). In this process, troublesome 2,2,2-trifluorodiazoethane has to be prepared beforehand. Recently, Morandi and Carreira disclosed the generation of 2,2,2-trifluorodiazoethane in situ with catalysts and olefins in aqueous media. However, the enantioselectivity was not discussed at this stage.[446]

In 2008, Komarov and co-workers realized several studies on cyclopropanation reaction for the synthesis of ^{19}F NMR labeled prolines. The optically pure 3,4-dehydro and 4,5-dehydroproline derivatives (**245** and **246**) were treated with an excess amount of 2,2,2-trifluorodiazoethane in the presence of a copper salt to afford CF_3-containing cyclopropane proline derivatives in 15% and 66% yields, respectively. The diastereomers were deprotected under standard conditions and separated by ion-exchange column chromatography to give a series of trifluoromethyl-substituted prolines in optically pure forms (Scheme 117).[447]

8. Concluding Remarks

As illustrated in this review, efficient asymmetric reactions of diverse prochiral trifluoromethyl substrates have emerged as attractive and powerful synthetic tools that nicely complement recently established methods for direct nucleophilic, electrophilic, and radical trifluoromethylations. Nevertheless, it is clear that methods developed for nonfluorinated substrates are often not appropriate for CF_3-containing molecules, and a reinvestigation of the condition reactions, nature of catalyst, and so forth is required for success in this chemistry. Yet, a great number of elegant approaches allow convenient preparation of a broad range of optically active trifluoromethyl products from readily available starting materials. Given the potential of chiral fluorinated compounds and the high demand in organic synthesis, medicinal and agrochemical chemistry, and material science, there is an increasing need for additional research in this area. Among future research of great interest are de novo design of prochiral trifluoromethyl substrates and the development of novel catalytic systems that could be employed in new and/or challenging asymmetric reactions for the construction of enantiopure fluorinated molecules with wide structural and functional diversities.

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10. References

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