doi:10.2533/chimia.2011.894 Chimia 65 (2011) 894–901

The Recent Development of Organofluorine Chemistry in China: Asymmetric Construction of Stereogenic Trifluoromethyl-substituted Carbon Centers

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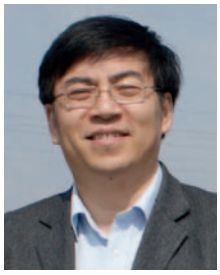
Abstract: The stereospecific incorporation of the trifluoromethyl group into an organic compound has attracted considerable attention and significant progress has been achieved in the past decade. Scholars from China have also contributed greatly to this field, which is the subject of the current review.

Keywords: Asymmetric catalysis · Stereogenic trifluoromethyl-substituted carbon center · Trifluoromethyl-containing building blocks



Long Lu was born in 1964 in Nanjing, Jiangsu Province, China. He received his B.Sc. Degree in Chemistry in 1986 from Nanjing University, China and his Ph.D. in 1991 from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS) under the supervision of Professor Weiyuan Huang. After about four years' postdoctoral studies in DuPont CR&D and University of Iowa, he joined the faculty team of SIOC from October 1996 and was appointed as Professor in October, 1997. His research interests are focused on organo-fluorine chemistry, fluoropolymers and crop protection *etc*.

1. Introduction

In recent years, organofluorine compounds have attracted great attention from academia and the pharmaceutical and agrochemical industry, mainly due to the beneficial changes in chemical, physical and biological activities after incorporation of fluorine into these compounds.[1] Consequently, the introduction of fluorine atom(s) into candidate scaffolds has become a regular method in every novel product discovery and development stage in the crop protection and pharmaceutical industries.[2] In particular, trifluoromethylated molecules that exhibit high metabolic stabilities and increased lipophilicities are of special interest and have been targets for many synthetic chemists. More specifically, the asymmetric introduction of the trifluoromethyl group into biologically active molecules remains a challenge and has been the subject of intense world-wide research over the past decade (Fig. 1).[3]

In general, two approaches have been developed for the construction of trifluoromethyl-substituted chiral carbon centers. In the first approach, trifluoromethylated reagents such as nucleophilic Ruppert-Prakash reagent (Me_3SiCF_3), electrophilic Umemoto and Togni's reagents, and radical precursor (CF_3I) were reacted with non-fluorinated substrates to give the desired chiral trifluoromethylation products in the presence of asymmetric catalysts. However, despite the recent progress by MacMillan at Princeton University, generally, it is still quite difficult to control the enantioselectivity by this approach. Alternatively, in the second strategy, trifluorinated building blocks that are

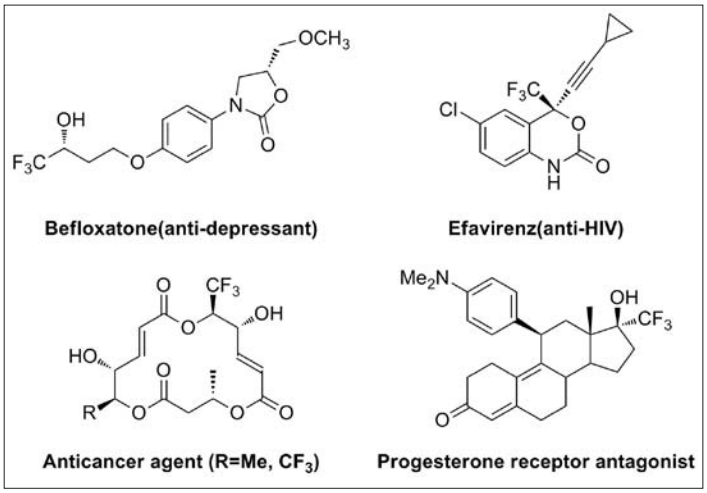


Fig. 1. Some drugs with trifluoromethyl substituted chiral carbon centers.

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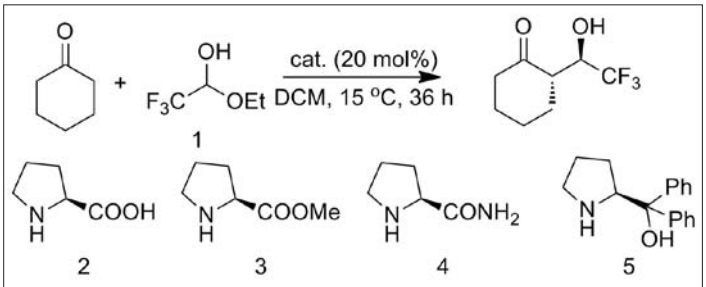
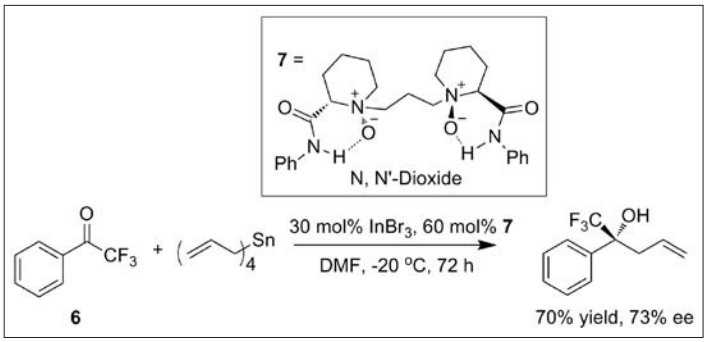
Table 1. Organocatalytic aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with cyclohexanone



entry	catalyst	Yield (%)	anti/syn	ee (anti/syn)
1	2	57	66:34	35:10
2	3	95	21:79	12:13
3	4	92	90:10	88:56
4	5	<1	/	/



Scheme 1. Chiral indium complex catalytic allylation of 2,2,2-trifluoroacetophenone.

either commercial available or could be prepared readily in a few steps were utilized in the presence of chiral transition-metal catalysts or organocatalysts to generate the desired enantiomer-enriched trifluoromethylated products highly selectively. Not surprisingly, many efficient methodologies for the construction of stereogenic trifluoromethyl-substituted carbon centers have been developed by chemists all over the world. Chemists from China have contributed significantly to this specific field and that is the subject of this article.

2. Construction of Chiral Trifluoromethyl-Substituted Alcohols

The optically active trifluoromethyl-substituted tertiary and quaternary alcohols are important structural motifs in many newly discovered pharmaceutical drugs. In general, this family of trifluoromethylated compounds were prepared from trifluoroacetaldehyde and its derivatives,[4] trifluoromethyl substituted ketones[5] and 3,3,3-trifluoropyruvates[6] through asymmetric reduction, aldol reaction, ene reaction, or Friedel-Crafts reaction.

Trifluoroacetaldehyde is a highly active electrophile but is difficult to handle. Trifluoroacetaldehyde hemiacetal was therefore developed as a synthetic surrogate of trifluoroacetaldehyde. In 2007, Gong and co-workers described an organocatalytic stereoselective aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with cyclohexanone. After the screening of four L-proline-derived catalysts, the best result was observed with L-prolinamide **4** as catalyst (Table 1).[4g]

Trifluoromethylated ketones are good electrophiles for construction of stereogenic trifluoromethyl-substituted quaternary carbon centers. Several examples of asymmetric1,2-addition reactions of trifluoromethyl ketones have been reported. In 2007, Feng's group at Sichuan University reported asymmetric allylation of 2,2,2-trifluoroacetophenone catalyzed by chiral indium complexes from indium (III) bromide and (*S*)-pipecolic acid-derived N,N'-dioxides. Under the optimized conditions, the desired products were obtained with moderate yields and stereoselectivities (70% yield, 73% *ee*) (Scheme 1).[7]

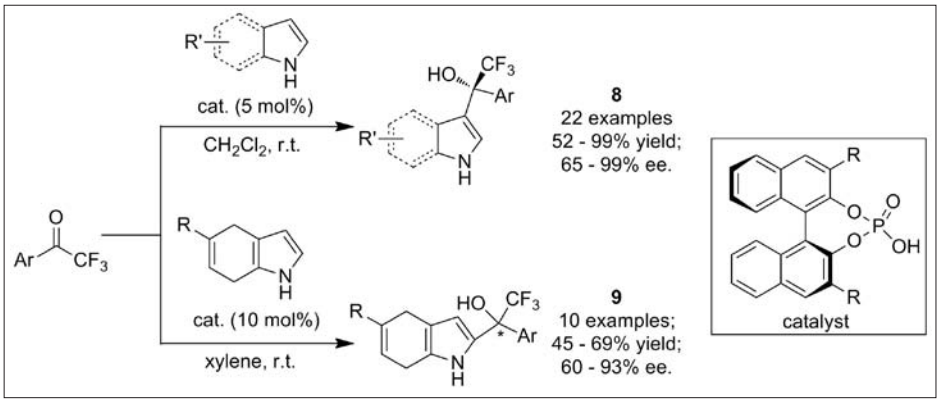
More recently, Ma and co-workers at Tianjin University described two catalytic stereoselective Friedel-Crafts reactions of electron-rich arenes with trifluoromethyl ketones catalyzed by BINOL-derived phosphoric acids. In the presence of 5–10 mol% of chiral phosphoric acids, electron-rich arenes such as indoles, pyrroles and 4,7-dihydroindoles reacted with trifluromethylated ketone to give the target products **8** in good to excellent yields (up to 99% yield) and high enantioselectivities (up to 99% *ee*) (Scheme 2).[8,9]

In 2008, Cheng and co-workers at Nankai University described a chiral primary-tertiary diamine-catalyzed enantioselective aldol reactions of 2,2,2-trifluoroacetophenone. However, the desired aldol product was obtained in only moderate stereoselectivity (Scheme 3).[10]

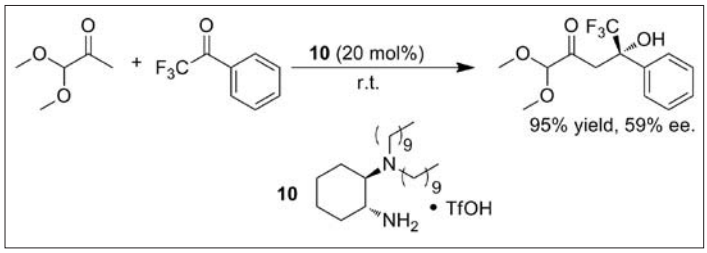
The asymmetric nucleophilic alkynylation of prochiral trifluoromethyl ketones has received much attention in the past few decades, mainly because the desired adducts were key intermediates for the preparation of Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) and part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1.

Jiang's group at Shanghai Institute of Organic Chemistry (SIOC) reported a highly enantioselective lithium acetylide addition to trifluoromethyl ketone in which the C_2-symmetric diamino diols was employed as chiral auxiliary. Reaction of cyclopropylacetylene occurred with good yield and excellent enantioselectivity (80% yield, 99% *ee*) (Scheme 4).[11]

Very recently, Ye's group at the Institute of Chemistry, Chinese Academy of Science (ICCAS) developed a chiral *N*-heterocyclic carbenes (NHCs) catalyzed [2+2] cycloaddition of ketene-ketone. A variety of ketenes and trifluoromethyl ketones were used as substrates to give the desired β-trifluoromethyl-β-lactone



Scheme 2. Asymmetric catalytic Friedel-Crafts reaction of various arenes with trifluoromethyl ketones.



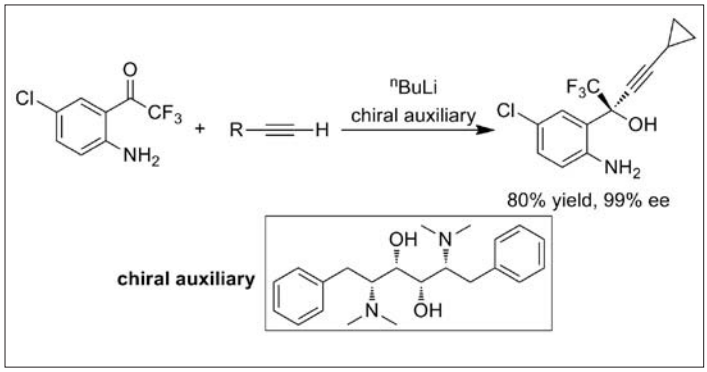
Scheme 3. Organocatalytic enantioselective aldol reaction with pyruvate to 2,2,2-trifluoro-acetophenone.

derivatives in good to excellent yields (up to 99% yield) and moderate to high diastereoselectivities (up to 23:1 dr) and excellent enantioselectivities for major diastereomer (up to 99% *ee*) (Scheme 5).[12]

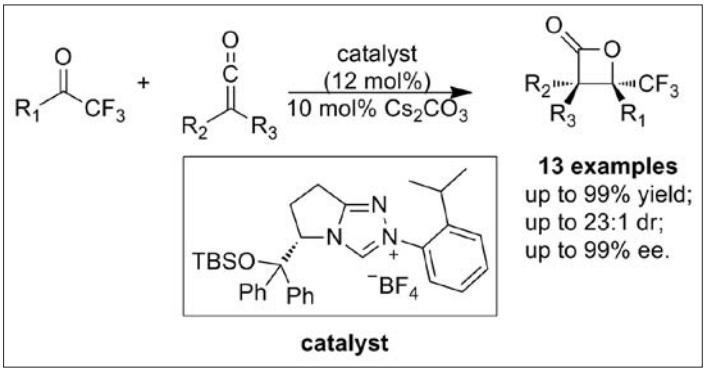
Vinyl trifluoromethyl ketones, one of specific trifluoromethyl ketones, were good electrophiles and have been studied extensively in asymmetric reactions. Recently, Liu and co-workers at SIOC disclosed an Aldol reaction of acetone and α,β-unsaturated trifluoromethyl ketones in the presence of proline-derived N-sulfonylamide **11** and trifluoroacetic acid as cocatalyst. The corresponding trifluoromethylated tertiary alcohols were obtained with good to excellent yields and stereoselectivities (76–99% yield, 81–95% *ee*).[13] Shortly after, Yuan and co-workers at SIOC also described a similar reaction by using 4-hydroxyproline derivative **12** as the catalyst with good yields and enantioselectivities (up to 97% yield, up to 91% *ee*)(Scheme 6).[14]

Liu's group subsequently developed an organocatalytic hetero-Diels-Alder (HDA) reaction of aldehydes with vinyl trifluoromethyl ketones. The resulting products could be readily converted into trifluoromethylated dihydropyranones with good to high yields through oxidation and elimination steps (Scheme 7).[15]

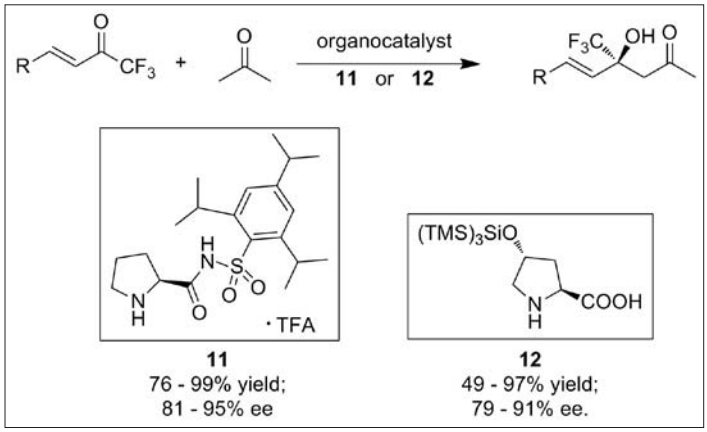
In 2009, Zhu and co-workers at SIOC developed an asymmetric sequential Michael/Aldol reaction of α-cyanoketones to α,β-unsaturated trifluoromethyl ketones catalyzed by bifunctional amine-thiourea organocatalyst. The corresponding α-trifluoromethyldihydropyrans were produced in good to high enantioselectivities, yields and distereoselectivities (up to 95% *ee*, 99% yield, >19:1 dr). Moreover,



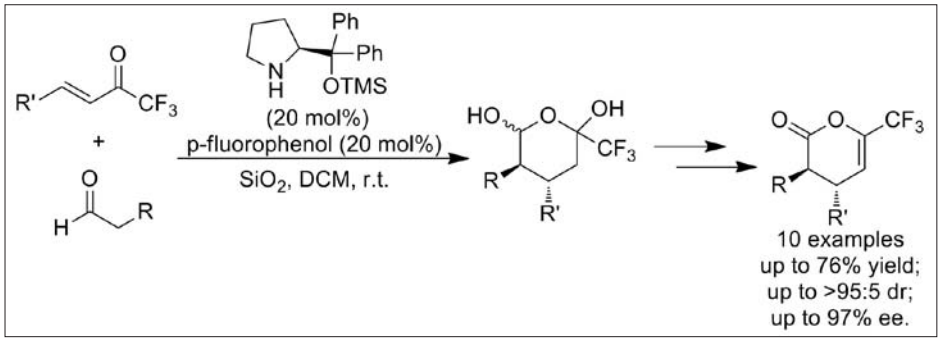
Scheme 4.



Scheme 5.



Scheme 6.



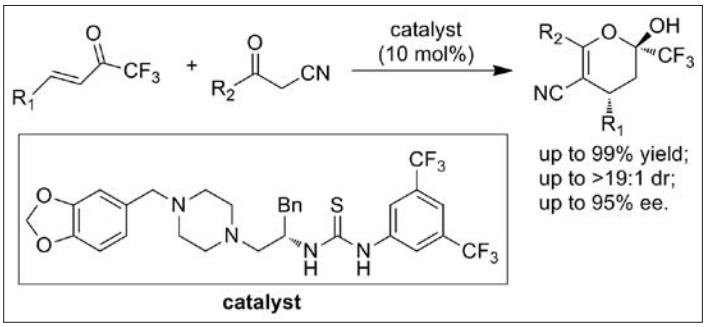
Scheme 7.

the products could be easily converted into trifluoromethylated dihydropyridines without loss of diastereoselectivities and stereoselectivities (Scheme 8).[16]

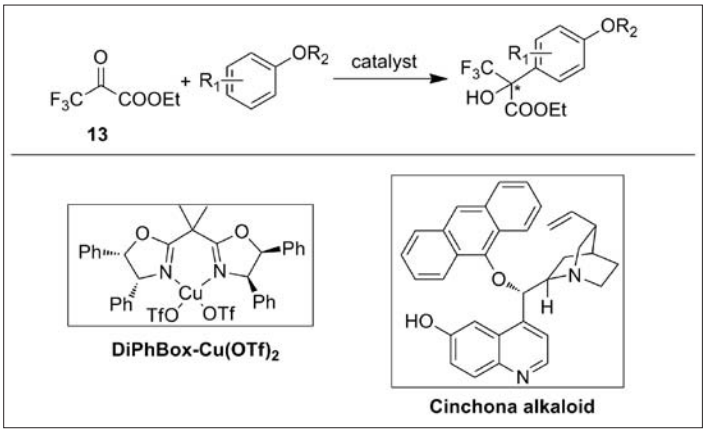
Among all the prochiral CF_3-containing building blocks, 3,3,3-trifluoropyruvates are a class of important substrates because of their excellent electrophilicity. As a result, the asymmetric reaction of trifluoropyruvates and derivatives have been studied by many research groups.[6]

In 2006, Liu and co-workers described an enantioselective Friedel-Crafts alkylation of phenol analogues with trifluoropyruvates using the combination of copper(II) trifluoromethanesulfonate and DiPhBox as the catalyst. A variety of Friedel-Crafts adducts were obtained in high stereoselectivities under solvent-free conditions. More recently, the same group reported that cinchona alkaloid derivatives could also catalyze the same reaction to give the desired products in moderate to excellent yields and stereoselectivities (58–96% yield, 71–94% *ee*) (Scheme 9).[17,18]

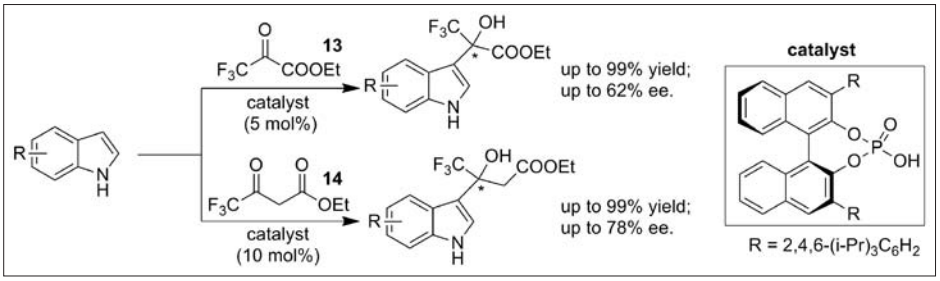
Independently, Ma's group at Tianjin University developed an enantioselective Friedel-Crafts reaction of indole derivatives



Scheme 8.



Scheme 9.



Scheme 10.

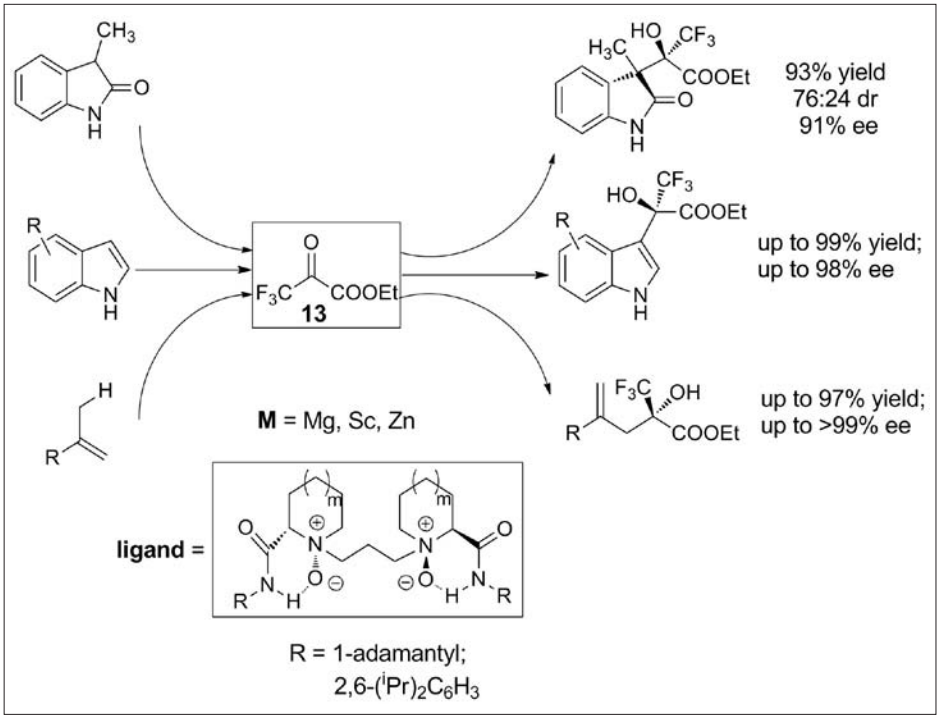
with ethyl trifluoropyruvate by using chiral phosphoric acids as the catalyst. In most cases, the desired adducts were obtained with excellent yields (91–99% yield), albeit in low to moderate stereoselectivities (20–62% *ee*). In addition, the same group also investigated the reaction of indoles with ethyl 4,4,4-trifluoroacetoacetate and it was found that the corresponded chiral trifluoromethylated alcohols were obtained with moderate to good yields and high enantioselectivities (up to 99% yield, up to 78% *ee*) (Scheme 10).[19]

Very recently, as a continuing investigation of asymmetric reactions using the C_2-symmetrical *N*,*N*'-dioxide that was developed in their own group, Feng and co-workers at Sichuan University developed a series of highly enantioselective reactions of ethyl trifluoropyruvate with different substrates. For example, in the presence of 5 mol% Sc(III)-*N*,*N*'-dioxide complex, a highly enantioselective aldol reaction of 3-methyloxindole with ethyl trifluoropyruvate was reported in 2010. The reaction proceeded smoothly to give the chiral tertiary alcohols in good yields and enantioselectivites (91% *ee*, 76:24 dr, 93% yield). In another example, a highly stereoselective ketone-ene reaction of trifluoropyruvate in the presence of N,N'-dioxide-Mg(II) complex as catalyst with 10 mol% loading was reported by the same group. The reaction typically occurred under solvent-free conditions to give the products of trifluoromethyl substituted chiral tertiary alcohols in excellent enantioselectivities (Scheme 11).[20–22]

Trifluoropyruvate could also be employed in the asymmetric Henry reaction. Du and co-workers at Peking University reported the enantioselective Henry reaction of ethyl trifluoropyruvate with nitromethane promoted by bis(oxazoline)-Cu(II) complex or bis(thiazoline)-Cu(II) complex, respectively. However, the stereoselectivities and yields of adducts were only low or moderate (Scheme 12).[23,24]

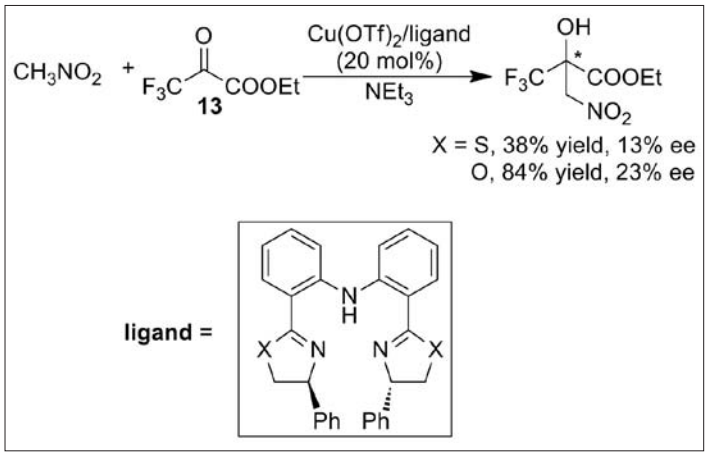
3. Construction of Chiral Trifluoromethyl-substituted Amines

Trifluoromethyl-substituted amines have emerged as key building blocks in the synthesis of pharmaceuticals and agrochemicals. Prakash was the first to recognize the potential of chiral sulfinimines as auxiliary to control the regioselective nucleophilic addition of trifluoromethylated substrates and subsequently developed a few methods for the preparation of optically pure trifluoromethyl-substituted amines.[25] In 2006, Lu and co-workers at SIOC adopted the same strategy and developed

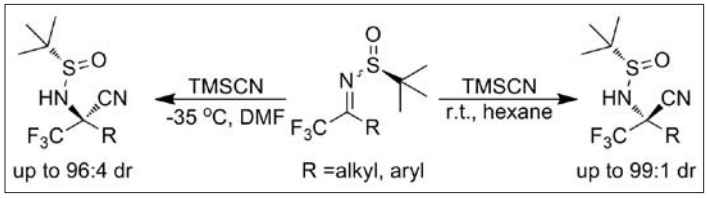


Scheme 11.

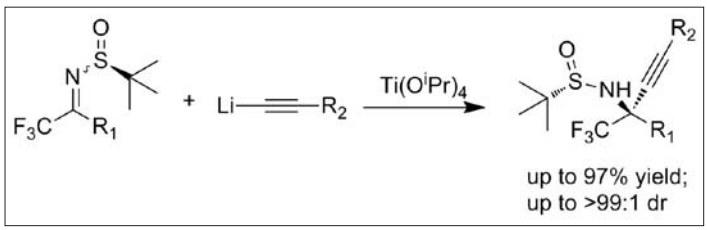
Scheme 12.



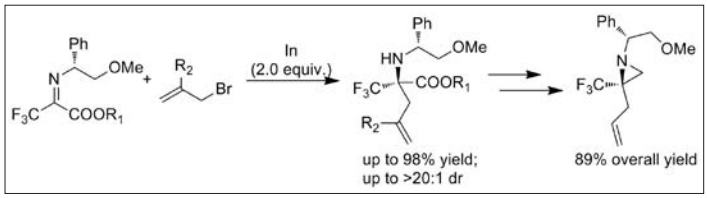
Scheme 13.



Scheme 14.



Scheme 15.



a highly enantioselective Strecker reaction of trifluoromethylated (R)-N-*tert*-butylsufinylketoimines (Tfm-NBSKIs). Interestingly, reactions conducted in DMF produced predominantly (S,R_s)-isomer, whereas in hexane, the major product was obtained as (R,R_s)-configuration. Furthermore, the application of this method was demonstrated by converting to the optically active α-trifluoromethylated α-amino acids (α-Tfm AAs), which are potentially useful in biochemistry and pharmacology (Scheme 13).[26]

Similarly, Huang, Qing and co-workers at SIOC reported an asymmetric addition of acetylide with chiral CF_3-substituted N-*tert*-butanesulfinyl ketimines when $Ti(O^iPr)_4$ was used as the catalyst. In most cases, the corresponding adducts were produced in moderate to high yields (56–97%) and excellent distereoselectivities (>99:1) (Scheme 14).[27]

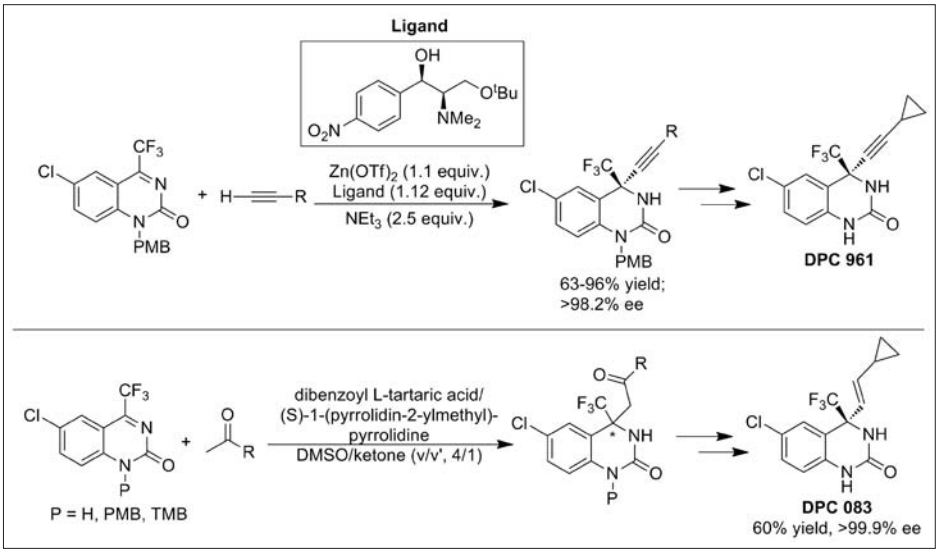
In addition to the chiral sulfinimines, other chiral imine could also be used to direct the selectivity of the nucleophilic addition reaction. In 2010, Zhang and co-workers at SIOC disclosed a protocol for the preparation of quaternary α-Tfm-AAs *via* indium-mediated allylation of (*R*)-phenylglycinol methyl ether based imines of trifluoropyruvate with good yields and excellent diastereoselectivities. As an application of this method, 2-allyl-2-(trifluoromethyl) azirideine could be readily prepared (Scheme 15).[28]

The methods mentioned above for the preparation of chiral trifluoromethylated amines typically require stoichiometric amounts of auxiliary and additional steps to install and remove the auxiliary. In contrast, catalytic asymmetric addition of nucleophiles to imines only requires catalytic amount of catalyst and thus shows advantages over the substrate-controlled reaction.

In 2004, Jiang and co-workers developed an efficient enantioselective alkynylation of trifluoromethylated cyclic ketimines by using chiral aminoalcohol derived from chloramphenicol as the ligand. Under the optimized reaction conditions, a variety of desired trifluoromethylated 3,4-dihydroquinazolin-2(1H)-ones were obtained in good yields with excellent stereoselectivities (60–90% yield, >98.2% *ee*). Based on this reaction, DPC 961, a potential HIV inhibitor was synthesized in high enantioselectivity (Scheme 16, top).

When a combination of diamine-Brønsted acid was used as the catalyst instead of the aminoalcohol, the same group discovered an asymmetric Mannich reaction of trifluoromethyl imine with methyl aryl ketone. In most cases, the Mannich adducts were obtained with low to good enantioselectivities and moderate to excellent yields (30–79% *ee*, 51–95% yield). Enantipure non-nucleoside reverse transcriptase inhibitor DPC 083 (>99.9% *ee*) could be readily prepared after reduction of the carbonyl group, dehydration and single recrystallization from chloroform and hexane (Scheme 16, bottom).[29]

In 2008, a highly enantioselective chiral phosphoric acid-catalyzed Friedel-Crafts



Scheme 16.

reaction of indoles with trifluoromethyl substituted imines *in situ* generated from trifluoroacetaldehyde hemiacetal and aniline was achieved by Ma's group. This three-component reaction occurred with excellent yields and enantioselectivities (up to 99% yield, up to 98% *ee*) and represents one of the green chemistry protocols for the synthesis of 2,2,2-trifluoro-1-(1*H*-indol-3-yl)ethyanamine (Scheme 17).[30]

Very recently, Shi and co-workers at SIOC developed a highly regio- and enantioselective asymmetric vinylogous Mannich reaction of readily available trifluoromethyl-substituted aldimines with siloxyfurans catalyzed by a combination of Ag(I) and chiral phosphine-oxazoline ligand. Trifluoromethylated γ-butenolides or γ-lactones were obtained with high yields, high diastereoselectivities and excellent enantioselectivities (Scheme 18).[31]

In addition to the asymmetric addition reactions, asymmetric reduction of trifluoromethyl substituted imines with stoichiometric reduction reagent or transition-metal catalyzed hydrogenation were also investigated.

In 2008, Liu and co-workers reported substrate-controlled diastereoselective reduction of trifluoromethyl-substituted α,β-unsaturated *N*-tert-butanesulfinyl ketoimines. Under the optimized conditions, the reaction proceeded smoothly to afforded either diastereomer of the corresponding trifluoromethyl-substituted allylic amines by using appropriate reducing agent, respectively (Scheme 19).[32]

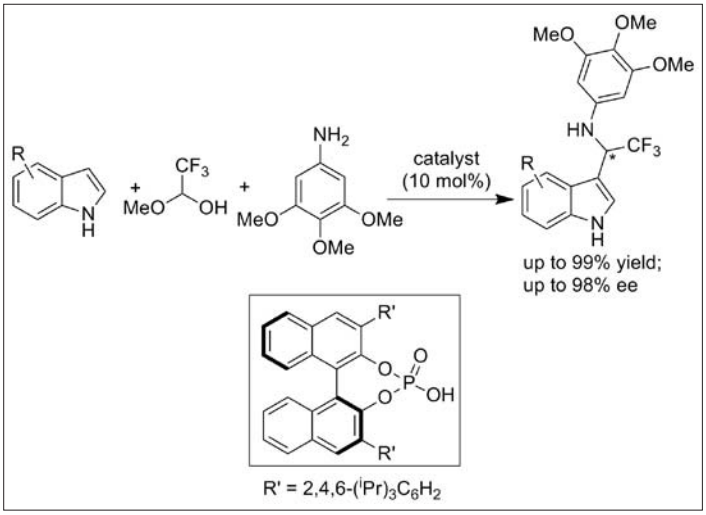
More recently, Zhou and co-workers at Dalian Institute of Chemical Physics described a catalytic asymmetric hydrogenation of trifluoromethylated imines by using Pd-(*R*)-Cl-MeO-BIPHEP complexes as the catalyst. The desired CF_3-containing amines were isolated in high yields (up to 99% yield) with good to excellent enantioselectivities (up to 94% *ee*) (Scheme 20).[33]

4. Construction of Trifluoromethyl-substituted All-C Tertiary Chiral Carbon Centers

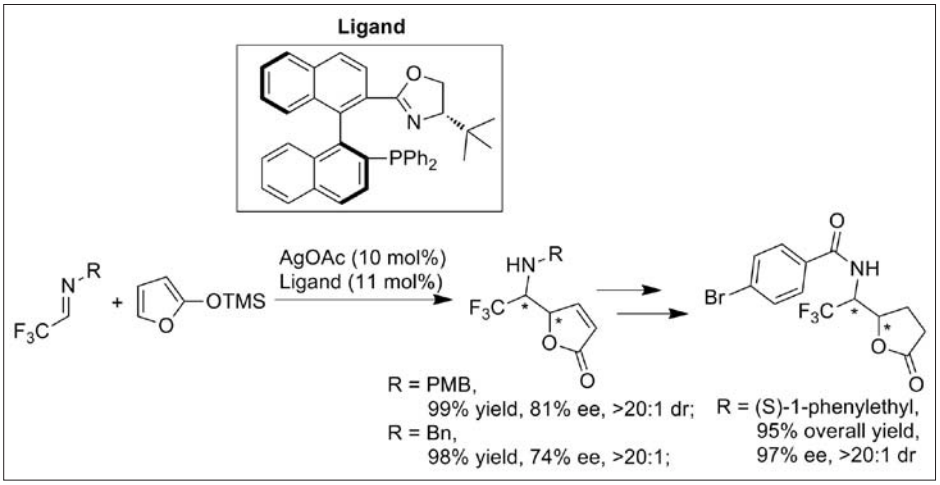
Compared to numerous asymmetric methodologies for the preparation of chiral trifluoromethyl substituted alcohols and amines, the development of general catalytic methods for the construction of stereogenic tertiary carbon centers bearing a trifluoromethyl group without any heteroatom substituent is a challenge for synthetic organic chemists. Few such reactions have been reported in the literature.

In 2010, Lu and co-workers at SIOC reported a highly enantioselective asymmetric Michael addition of aldehydes to trifluoroethylidene malonates, a powerful Michael acceptor. The reactions utilized easily available prolinol silyl ether as organocatalyst to give the corresponding adducts in high yields, good diastereoselectivities and excellent enantioselectivities. Furthermore, the optically pure trifluoromethyl-substituted δ-lactones could be readily synthesized through reduction of the aldehyde and intramolecular esterification (Scheme 21, top).[34a]

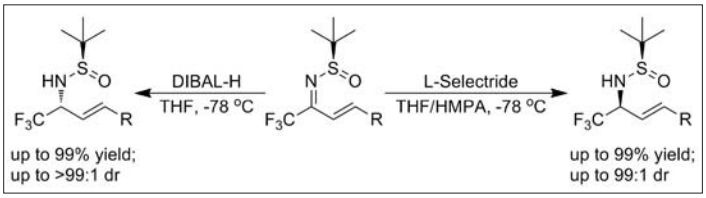
More recently, the same group reported a protocol for asymmetric Friedel-Crafts reaction of indoles with trifluoroethylidene malonates by using ^{i}Pr-BOX-Cu(II) complex as catalyst. Various indoles bearing electron-donating and electron-withdrawing substituents were studied and the desired chiral trifluoromethyl-substituted indole derivatives could be obtained with good to excellent enantioselectivities and high yields (75–96% *ee*, 84–99% yield). Interestingly, low enantioselectivities were observed for the reactions of pyrrole with trifluoroethylidene malonates or indole with β-trifluoromethylated acrylamide and β-CF_3-α,β-unsaturated ketone under



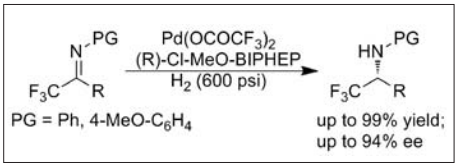
Scheme 17.



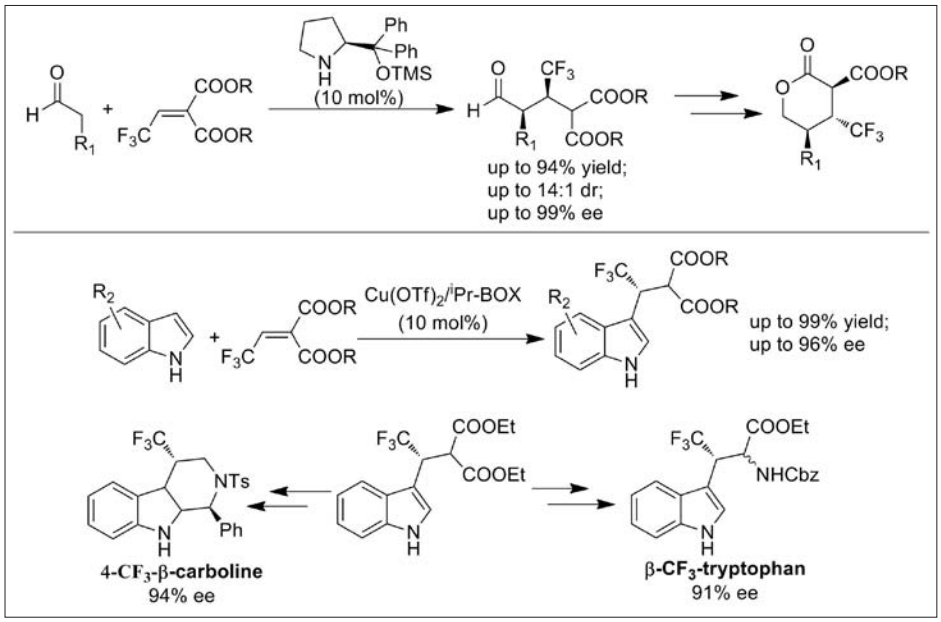
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

the same conditions. The products could be converted to some enantiomerically enriched trifluoromethyl-containing alkylated indole derivatives with potentially interesting bioactivities (Scheme 21, bottom).[34b]

In 2011, Feng's group reported a highly stereoselective Friedel-Crafts alkylation of β-trifluoromethyl-α,β-enones catalyzed by *N*,*N*'-dioxide-Y(III) complexes. The reaction occurred in high yields and excellent enantioselectivities (up to 99% yield and 96% *ee*) (Scheme 22).[35]

During our preparation of this manuscript, Wang and co-workers at Wuhan University reported the first asymmetric thio-Michael addition of thiols to (*Z*)-4,4,4-trifluorocrotonates by using 1 mol% of chiral amine-thiourea bifunctional organocatalyst. Good to excellent yields and high enantioselectivities were achieved under these conditions. In addition, optically pure thiochroman-4-one and (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate which are the key intermediates of the potent inhibitor of MMP-3, were prepared through Friedel-Crafts reactions or oxidation (Scheme 23).[36]

5. Conclusion and Outlook

In the past decade, significant progress has been made by scholars from China in the field of diastereoselective and enantioselective construction of trifluoromethyl-substituted chiral carbon centers. High enantioselectivity has been achieved in the transition-metal or organocatalyst-catalyzed nucleophilic addition of trifluoromethyl-substituted ketones. Likewise, high diastereoselective formation of trifluoromethylated amines was obtained when chiral sulfinimines or other chiral amines were used as the auxiliary. And a few highly selective catalytic enantioselective nucleophilic addition or reduction reactions were developed as well. In contrast, the development of general catalytic methods for the construction of stereogenic tertiary carbon center bearing a trifluoromethyl group without any heteroatom substituent is still in the early stage and remains a challenge. Nevertheless, several catalytic reactions for this important transformation have appeared in the past few years and more asymmetric reactions are expected to be published in the near future.

Despite the remarkable advancements in asymmetric introduction of trifluoromethyl group into organic molecules, further developments are necessary for chiral nonracemic trifluoromethylated molecules to be increasingly used in pharmaceutical and agrochemical industry.

Received: September 25, 2011

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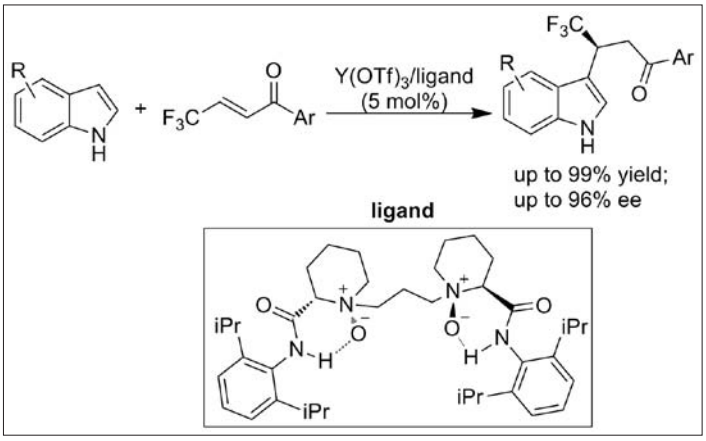
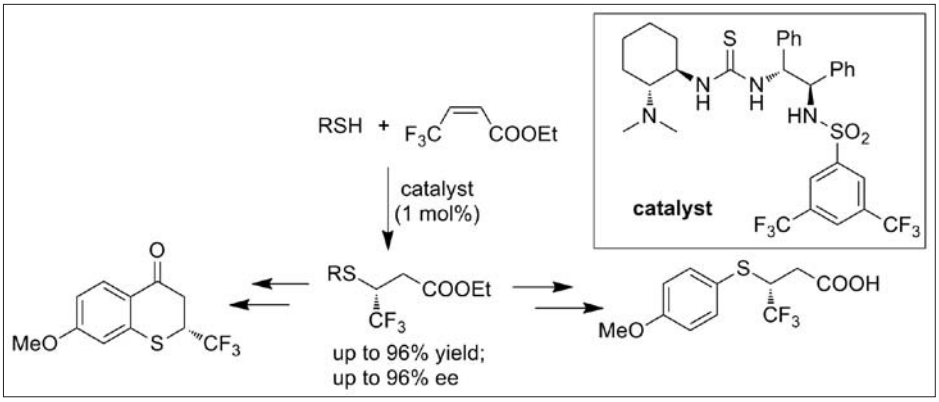


Scheme 22.



Scheme 23.

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