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Asymmetric Synthesis of Fluorine-containing Compounds Using Organocatalysts

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Abstract: Asymmetric synthesis of fluorine-containing compounds using organocatalysts has been extensively investigated and several important strategies have been developed in the last decade. This review focuses on the recent advances in the introduction of the fluorine atom into organic molecules by: i) electrophilic fluorination reactions; ii) the use of easily available fluorine-containing building blocks, both of interest in our research laboratory.

Keywords: Fluorine-containing compounds · Organocatalysis

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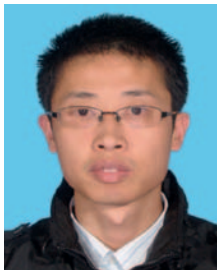

Zhengqing Ye was born in Hubei Province, China. He received a B.Sc. in chemistry from Wuhan University (2006), and a Ph.D. degree (2011) from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Prof. Gang Zhao. In September 2011 he joined the laboratory of Prof. Gang Zhao as research assistant working on the total synthesis of bioactive natural products.

1. Introduction

The introduction of a fluorine atom, the most electronegative element, would affect the basicity or acidity and dipole moment of neighboring groups, and alter sterically and electronically the properties of the whole molecule, thus greatly changing the overall reactivity and stability of the fluorinated compounds. Since the C–F bond is highly polarized and exerts a stereoelectronic influence on neighboring bonds or lone pairs of electrons, fluorine-containing compounds have many important applications in materials, medicinal, pharmaceutical and agrochemical sciences.[1] Especially, strategic fluorination is commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability, and protein–drug interactions.[2] The replacement of metabolically active hydrogen atoms with fluorine atoms increases the *in vivo* lifetime of drugs. As such, fluorine-containing compounds are ubiquitous in blockbuster drugs, such as fluoxetine (antidepressant), atorvastatin (cholesterol-lowering) and ciprofloxacin (antibacterial).

The specific incorporation of fluorine in a stereoselective manner has thus become one of the most fascinating aspects of organofluorine chemistry.[3] There are two common strategies for the introduction of the fluorine atom: direct fluorination of organic compounds with either electrophilic or nucleophilic fluorinating reagents and the use of easily available simple fluorine-containing building blocks.[4] Recently, with the rapid development of organocatalysis, organocatalytic synthesis of chiral fluorinated molecules with both strategies has received considerable attention among organic chemists.[5,6]

In this review, a personal overview of the some recent developments in this field is provided mainly based on the recent work from our research group.

2. Asymmetric Fluorination Using Electrophilic Fluorination Regents

Molecular fluorine is a versatile reagent able to perform many selective reactions, though it is indiscriminate in asymmetric synthesis.[7,8a] Thus, a wide variety of electrophilic fluorinating agents have been developed over the past few decades.[8b,c] The majority of them are prepared from molecular fluorine.

Unlike many other types of electrophilic fluorinating agents, N–F electrophilic fluorinating agents are usually stable and easy to handle. They are usually prepared

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by reacting the corresponding N–H compound with F_2, and many of these agents are now commercially available, such as Selectfluor and NFSI (Fig. 1).[9]

On the other hand, organic compounds bearing an α-fluorocarbonyl moiety present interesting biological activities, which have potential applications in medicinal chemistry and the pharmaceutical industry.[2a] In particular, they are effective mimics of α-hydroxy ketones, useful probes for various biological processes, and they can also act as enzyme inhibitors.

In this review, the use of Selectfluor or NFSI as a ready available electrophilic fluorine source in combination with the advantages of organocatalysis has marked an important milestone for the realization of asymmetric fluorination producing intriguing simple protocols for the introduction of a fluorine atom into organic compounds.

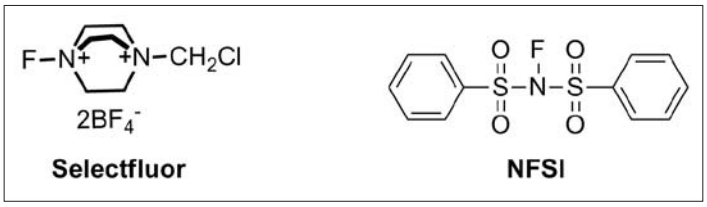


Fig. 1. Electrophilic fluorination regents.

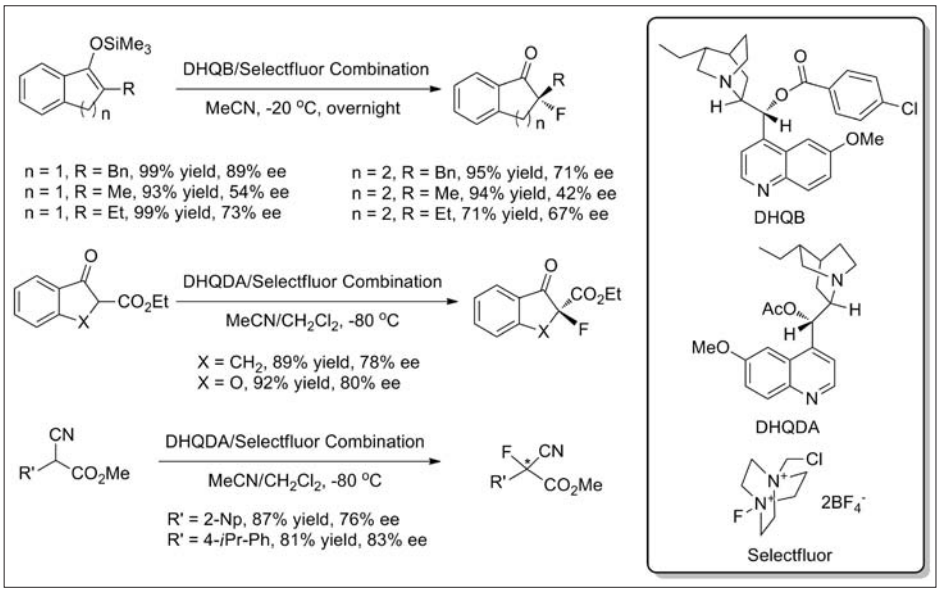
2.1 *Asymmetric Electrophilic Fluorination Reactions Using Stoichiometric Amounts of Cinchona Alkaloid Derivative*

Several routes for asymmetric introduction of a fluorine atom into a molecule such as diastereoselective fluorination of chiral organic compounds,[10] enantioselective alkylation of monofluoro-organic compounds,[11] and especially reagent-controlled enantioselective fluorination have been developed.[12,13] An important breakthrough on reagent control was made by Differding and Lang, who introduced chiral *N*-fluorocamphorsultam as the first enantioselective electrophilic fluorinating agent.[14] Later, modified *N*-fluorosultam structures,[15] saccharin-based agents[16] as well as acyclic *N*-fluoro compounds were also developed.[17] However, owing to low yield, low optical purity of the fluorinated products and relatively inaccessible reagents, more practical enantioselective fluorination reactions were sought.

In 2000, Takeuchi disclosed an enantioselective fluorination reaction based on a cinchona alkaloid derivatives/Selectfluor combination.[18] The chiral *N*-fluoro species, *N*F-DHQB·BF_4 and *N*F-DHQDA·BF_4, generated *in situ* by 'fluorine transfer' of the cinchona alkaloid by Selectfluor, have played a key role in the enantioselective fluorination of both cyclic and acyclic carbonyl compounds (Scheme 1).

Independently, Cahard described the synthesis of *N*-fluoro quaternary ammonium salts of cinchona alkaloids as enantioselective fluorinating agents,[19a] which exhibited asymmetric induction up to 61% *ee* on fluorination of enolates and silyl enol ethers of 2-methyl-1-tetralone (Scheme 2).

The advantage of these reagents is the commercial availability of both Selectfluor and cinchona alkaloids, and that a wide range of substrates including silyl enol ethers, 1,3-dicarbonyl compounds and lactones can be effectively fluorinated in an enantioselective manner. In addition, Gouverneur described regio- and enantioselective synthesis of allylic fluorides by electrophilic fluorodesilylation of allyl silanes in similarly controlled manner.[19b]



Scheme 1. Enantioselective fluorination by cinchona alkaloid derivatives/Selectfluor combination.

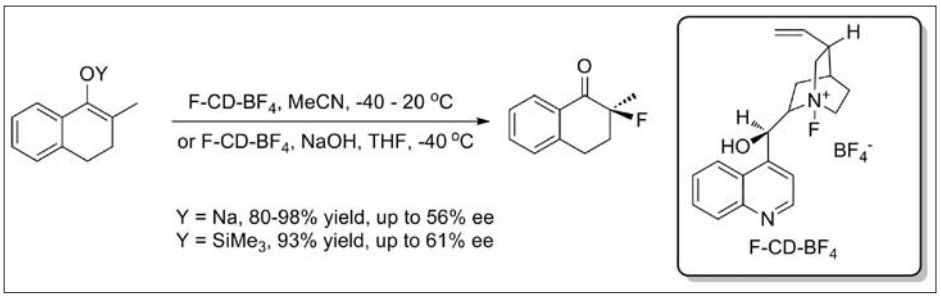
However, since this methodology requires a stoichiometric amount of the cinchona alkaloids, an efficient catalytic reaction for stereoselective fluorination affording satisfactory selectivity as well as versatility was required.

2.2 *Asymmetric Electrophilic Fluorination Reactions Using Catalytic Amounts of Cinchona Alkaloid Derivative*

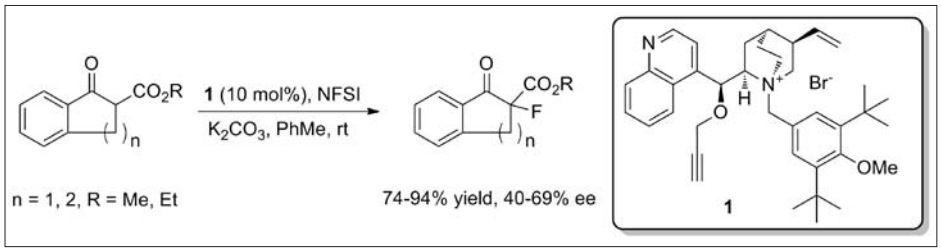
Hintermann and Togni achieved the first real breakthrough in catalytic enantioselective fluorination using a TADDOL-modified titanium complex and Selectfluor.[20] In this process, the metal Lewis acid was assumed to have played a role in activating the nucleophile and not in enhancing the electrophilicity of the coordinated carbonyl compounds, as is more common in reactions involving carbonyl compounds. This new catalytic fluorination reaction can readily compete with the highest enantioselectivity from stoichiometric reactions with chiral enantiopure *N*-fluoro compounds. Nevertheless, a new organocatalytic enantioselective fluorination process without the use of Lewis acid was desirable.

In 2002, Kim first reported catalytic enantioselective electrophilic fluorination employing quaternary ammonium salt from cinchonine as a phase-transfer catalyst. The α-fluoro β-keto esters could be obtained in excellent yields, albeit with moderate enantiomeric excesses (40–69% *ee*) (Scheme 3).[5c]

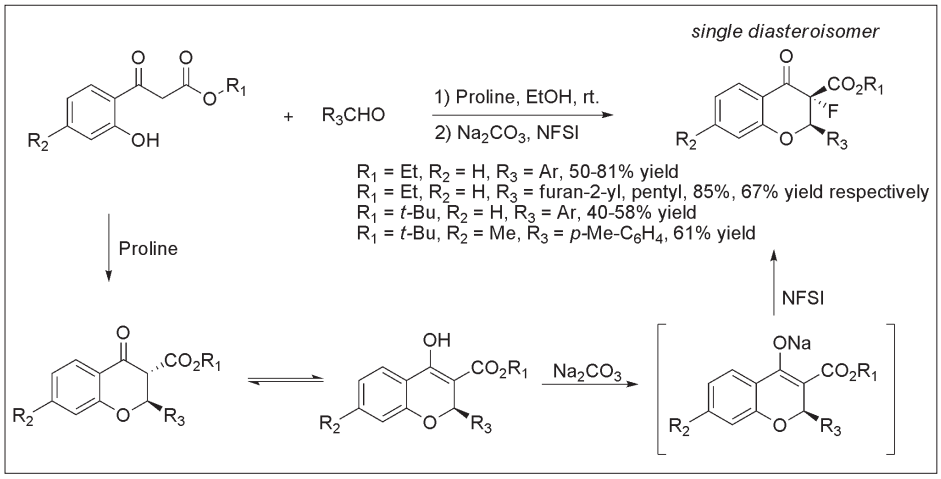
Thereafter, with the development of



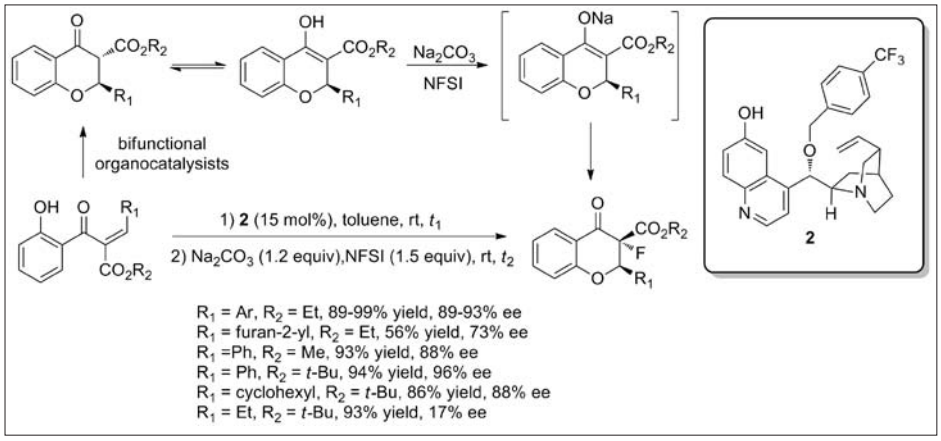
Scheme 2. Enantioselective electrophilic fluorinating agents: F-CD-BF_4.



Scheme 3. Catalytic enantioselective fluorination with phase-transfer catalyst.



Scheme 4. Stereoselective synthesis of fluorinated flavanones.



Scheme 5. Catalytic synthesis of chiral fluorinated flavanones.

organocatalysis, asymmetric electrophilic fluorination reaction using Selectfluor or NFSI as an electrophilic fluorine source has been extensively studied and several important procedures have been developed in the last decade.[5]

2.3 *Synthesis of Fluorinated Flavanone Derivatives via a One-Pot Tandem Reaction Involving Asymmetric Electrophilic Fluorination Reaction*

Flavanones represent an important structural motif occurring in many natural products with important biological activities, such as antitumor and anti-inflammatory properties.[21] However, very few methods have been developed to synthesize fluoro-containing flavanone.[22] In 2007, Ma utilized a triple cascade Knoevenagel condensation/Nazarov cyclization/electrophilic fluorination reaction of aromatic β-ketoesters and aldehydes to afford fluorinated indanones.[23] It is worth mentioning that stoichiometric Lewis acids were required in this system to effect the reaction. On the other hand, a breakthrough based on intramolecular oxa-Michael addition reaction of a phenol to chalcone in an organocatalytic way was accomplished by Scheidt *via* the use of alkylidene β-ketoesters.[24] On the basis of these studies and as a part of our continued interest in the synthesis of fluorinated heterocyclic compounds,[25] we reasoned that fluorinated flavanones could be obtained through a domino Knoevenagel condensation/Michael addition/electrophilic fluorination sequence from β-ketoesters and aldehydes.[26]

First, L-proline was found to be the optimal catalyst to effect the Knoevenagel condensation reaction. After completion of the proline-catalyzed Knoevenagel condensation of β-ketoester and benzaldehyde, Na_2CO_3 and NFSI were then added to the reaction system, respectively. Diastereoisomerically pure *trans*-monofluorinated flavanones were obtained in moderate to good yields for all the substituted benzaldehydes examined, irrespective of the electronic nature or positions of the substituents on the phenyl ring. Notably, heterocyclic furan-2-carbaldehyde and aliphatic aldehyde hexanal also proved to be suitable substrates for this transformation, giving the corresponding products in 85% and 67% yields, respectively. In addition, when β-ketoester bearing a more sterically demanding *tert*-butyl group on the ester moiety was subjected to similar reaction conditions as its ethyl counterpart, the same excellent diastereosectivity could be obtained, albeit with a decrease in the yields (Scheme 4).

On the basis of the above results, we envisaged that by using an appropriate bifunctional organocatalyst, an organocatalytic intramolecular oxa-Michael addition of the substrate would produce enantioenriched flavanone, which could then be subjected to electrophilic fluorination to yield chiral fluorinated flavanone derivatives (Scheme 5).[27]

Due to their easy availability and well-documented power as good hydrogen bonding donors, cinchona alkaloids and their derivatives have proved to be efficient bifunctional organocatalysts in a myriad of asymmetric reactions.[27b,c] Structural modifications on quinidine led to the optimal catalyst **2**, which afforded the desired product in 99% yield and 93% *ee* with 15 mol% loading of catalyst **2** in toluene at room temperature.

For substrates with different R^1 substituents, excellent yields and high *ee* values were generally obtained irrespective of the electronic nature or positions of the substituents on the arene ring, except for the heterocyclic substrate (R^1 = furan-2-yl). Notably, the reactions of substrates with electron-donating substituents generally required longer reaction times than those with electron-withdrawing groups. While changing the ester moiety (R^2) of substrate to a less bulky methyl group resulted in a slightly lower yield and *ee* value, the use of a more sterically demanding *tert*-butyl group improved the enantioselectivity to 96% *ee* and still with an excellent yield, although a longer reaction time was required. The cyclohexyl-substituted substrate with a *tert*-butyl ester group also

afforded the desired product with high enantioselectivity and yield. When R^1 was an ethyl group, the reaction still proceeded efficiently to give the desired product in excellent yield, but a sharp decrease in enantioselectivity was observed, which may be attributable to its decreased steric hindrance.

3. Asymmetric Organocatalysis Using Fluorinated Building Blocks

Besides employing electrophilic fluorination regents such as Selectfluor or NFSI to construct chiral fluorinated quaternary carbon centers, an alternative way by using simple fluorinated building blocks would also provide a class of versatile fluorinated synthons utilized in organic synthesis.[6] For examples, Lu *et al*.[6d] and Wang *et al*.[6c] independently reported asymmetric Michael and Mannich addition using racemic α-fluoro-β-keto esters as nucleophiles with good to excellent enantioselectivities; Tan *et al*. reported the construction of chiral quaternary carbon centers bearing a fluorine atom *via* enantio- and diastereoselective guanidine-catalyzed additions of fluorocarbon nucleophiles to N-alkyl maleimides or imines.[6d]

3.1 *Enantioselective Synthesis of α-Trifluoromethyldihydropyrans*

Among fluorinated molecules, tetrasubstituted α-trifluoromethyl molecules have extensively provided novel drug candidates with unusual biological activities.[28] As the emergence of drugs such as Efavirenz (anti-HIV)[29] and CJ-17493 (neurokinin 1 receptor antagonist),[3g] methods for the incorporation of a tertiary α-trifluoromethyl stereocenter into heterocycles attracted much attention but their construction in a highly enantioselective way is still a big challenge. Over the past decades, great efforts have been devoted to the development of organocatalytic synthesis of optically active CF_3-containing compounds. For example, cinchona and derivatives,[30] chiral phosphoric acid,[31] chiral guanidine catalyst,[32] and Macmillan's imidazolidinone catalyst,[33] have all been used for this purpose. As one of the most successful organocatalysts developed to date, bifunctional thiourea catalysts have been successfully applied in many reactions.[34] Since there was no report dealing with the use of thiourea catalysts in the catalytic asymmetric synthesis of CF_3-containing compounds and our group have focused on the organocatalytic asymmetric reactions of electron-deficient α,β-unsaturated carbonyl compounds,[35] the reaction of α-cyanoketones with α,β-unsaturated trifluoromethyl ketones catalyzed by chiral thioureas, which provides an easy access to a series of novel chiral α-trifluoromethyldihydropyrans, came into our mind (Scheme 6).[36]

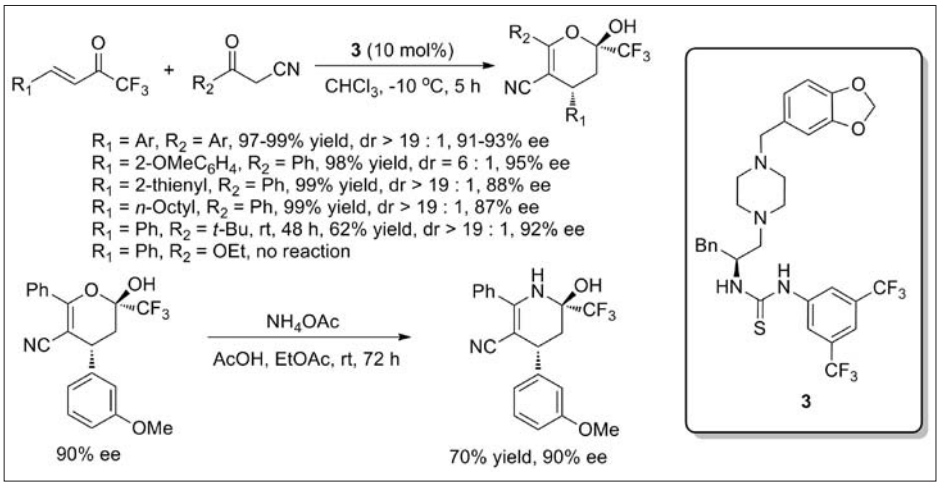
Amino-acid derived thiourea catalysts, which are efficient and have an easily fine-tuning skeleton, have been considered promising catalysts in the past few years.[37] Under the catalysis of the novel thiourea **3** derived from L-phenylalanine, the reaction proceeded very well when R^1 and R^2 were aryl groups, except for R^1 = 2-$OMeC_6H_4$, for which a poor *dr* value was obtained but still with excellent yield and *ee*. When R^1 was an alkyl group, no appreciable reduction in reactivity was observed, albeit with a slight drop in *ee*. When R^2 was an alkyl group (*t*-Bu), excellent *dr* and *ee* values could still be obtained with diminished yield although a longer reaction time was required. However, the reaction failed to take place when R^2 was an alkoxyl group (OEt). The α-trifluoromethyldihydropyran products could be converted to chiral trifluoromethyldihydropyridines in one step with no loss of enantioselectivity.

When an alkyl-substituted group was introduced into the acidic part instead of the relatively expensive aryl unit as illustrated by Cheng[38] recently, the design of an alkyl-substituted thiourea catalyst derived from amino acid is promising. Herein new advances towards the synthesis of α-trifluoromethyldihydropyrans using a chiral trifluoroethyl-substituted thiourea catalyst derived from amino acid were realized in our lab (Scheme 7).[39]

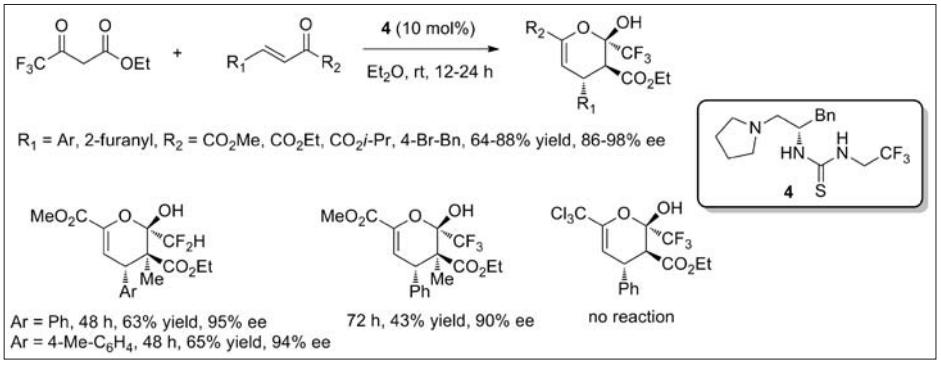
With cyclic tertiary amine derived catalyst **4**, for substrates with different substituents on the phenyl ring of R^1, good yields and *ee* values were obtained irrespective of the electronic nature and position of the substituents. Changing the R_2 group to relatively bulky substituents did not influence the *ee*s of the products. When ethyl 4,4-difluoro-3-oxobutanoate was used as a reactant, excellent *ee* values could still be obtained with diminished yield and a longer reaction time. Interestingly, α-methyl substituted ethyl 4,4,4-trifluoro-3-oxobutanoate was also a suitable reactant, giving the corresponding product as the first example of two adjacent chiral quaternary carbons containing a CF_3 group was formed, in 90% *ee* although the yield was moderate after 72 h. By comparison, the reaction did not proceed using the same protocol when R_2 was a trichloro group mainly due to steric hindrance.

3.2 *Enantioselective Synthesis of Functionalized Fluorinated Cyclohexenones*

Chiral cyclohexenones, as a common structural motif in many biologically active molecules, represent very important building blocks in organic synthesis.[40] The well-known Robinson annulation has been



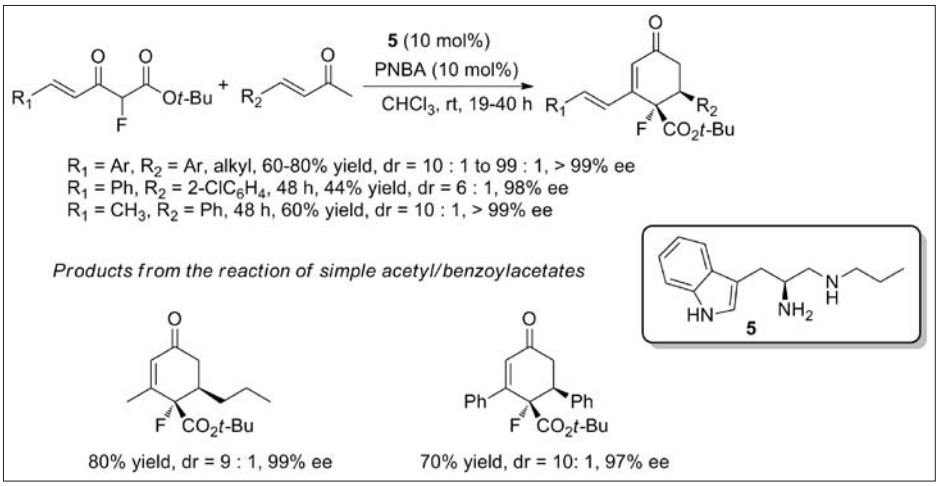
Scheme 6. Michael addition to α,β-unsaturated trifluoromethyl ketones.



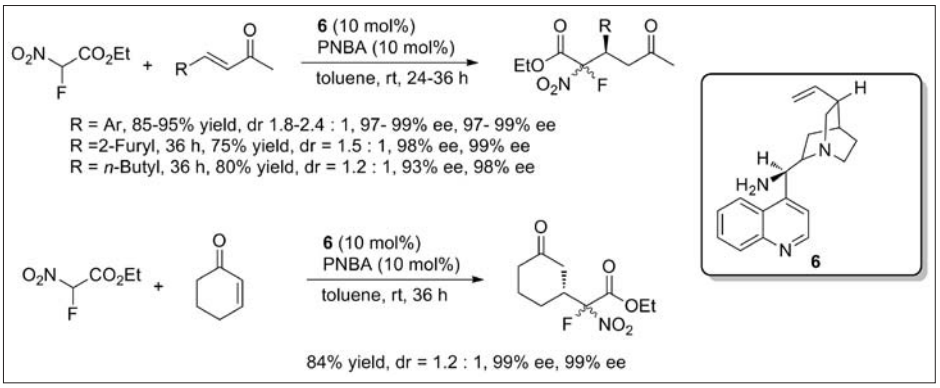
Scheme 7. Michael addition to α,β-unsaturated ketone esters.

a powerful method to construct various substituted cyclohexenones.[41] With a phenylalanine-derived imidazolidine catalyst, Jørgensen *et al.* realized a highly enantio- and diastereoselective domino Michael-aldol reaction of β-ketoesters with enones to give functionalized chiral cyclohexanes, which could be easily converted to chiral cyclohexenones, although a long reaction time was generally required (95–240 h).[42]

Recently, we have developed some primary-secondary diamine catalysts for the Michael additions of malonates to α,β-unsaturated ketones with excellent results.[43] As expected, α-fluoro-β-keto-esters were found to be suitable Michael donors in similar system. Here, the catalyst **5** in combination with 4-nitrobenzoic acid (PNBA) could catalyze the asymmetric Robinson annulation to give multiply-substituted fluorinated cyclohexenones in excellent *ee* and *dr* values (Scheme 8).[44] Actually, simple fluorinated acetylacetate and benzoylacetate were more reactive than their non-fluorinated counterparts for this transformation in that only half of the corresponding catalyst was required. This might be ascribed to an enhanced acidity of the hydrogen atom between the two carbonyl groups after the introduction of the fluorine atom, which may in turn facilitate the deprontonation step to form the actual nucleophile, namely the corresponding enolate.



Scheme 8. Asymmetric Robinson annulation of α-fluoro-β-ketoesters with α,β-unsaturated ketones.



Scheme 9. Asymmetric Michael addition of ethyl 2-fluoro-2-nitroacetate to enones.

3.3 *Catalytic Construction of Chiral Fluorinated Quaternary Carbon Centers*

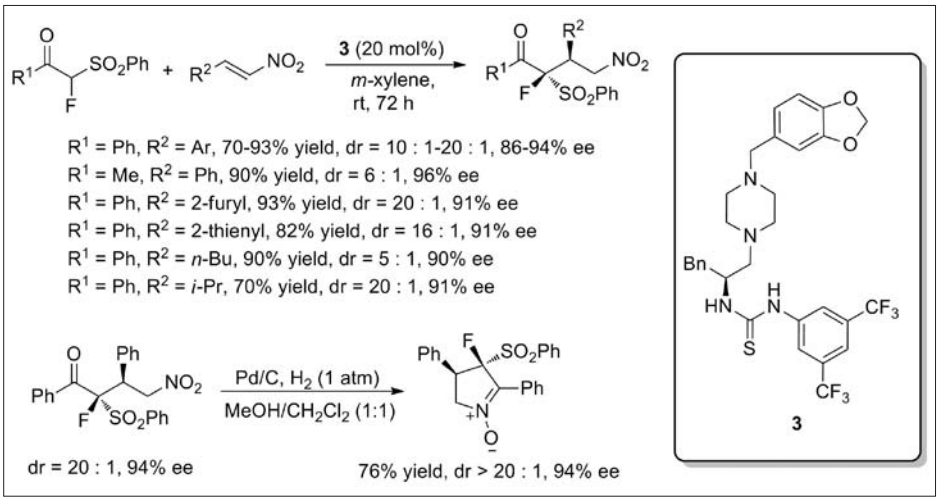
Nitro compounds are valuable synthons due to the rich chemistry of the nitro group and many of them have also shown important biological activity.[45] However, enantioselective reactions employing both the nitro group and fluorine atom are currently very limited. Togni *et al.* first reported asymmetric electrophilic fluorination of α-nitro esters with Selectfluor to synthesize chiral α-fluoro-α-nitro esters with up to 40% *ee*.[46] Alternatively, the direct use of racemic α-fluoro-α-nitro esters as nucleophiles in organocatalytic asymmetric Michael addition reactions would also yield the desired chiral α-fluoro-α-nitro esters. Lu *et al.* reported a primary amine-based Michael addition of nitro esters to enones in a highly enantioselective manner, but the conjugate addition did not proceed when catalyzed by primary amine/(+)-CSA salt when α-fluorinated nitro-acetate was used.[47] Alternatively, they prepared a chiral α-fluoro-α-nitro ester *via* electrophilic fluorination of the Michael adduct. Fortunately, in our research when other organic acids were used, an asymmetric Michael addition reaction of α-fluoro-α-nitro esters to enones catalyzed by chiral primary amine catalysts was realized,[48] giving good results.

The reaction proceeded smoothly with 10 mol% of the quinidine-derived catalyst **6** and PNBA in toluene at room temperature (Scheme 9). For substrates with different substituents on the phenyl ring (R = aryl), generally excellent *ee* values and yields with 1.8 : 1 to 2.4 : 1 *dr* values were obtained irrespective of the electronic nature or positions of the substituents. Though slightly lower yields were observed for substrates bearing electron-donating substituents. Excellent results were also obtained when R was a heterocyclic 2-furyl or an aliphatic *n*-butyl. Interestingly, besides open chain enones, the Michael addition with cyclohexenone also took place smoothly with excellent enantioselectivities.

Amazingly, it was found that the thiourea **3** was the catalyst of choice for the asymmetric Michael addition of α-fluoro-α-phenylsulfonyl ketones to nitroolefins (Scheme 10),[49] which provided an easy access to chiral fluorine-containing multifunctional molecules bearing adjoining chiral fluorine-substituted quaternary and tertiary centers. Substrates with aryl substituents (R^2) performed well in the reaction, irrespective of the substitution types of the aryl groups. When R^1 was an alkyl group like Me, the reaction still gave excellent yield and *ee* value, albeit with a drop in *dr* value. Moreover, satisfactory results were also obtained when alkyl-substituted nitroalkenes were used, except for a decreased *dr* value in the case of the less sterically hindered *n*-Bu substrate. Furthermore, the resulting product could be transformed to useful chiral cyclic nitrones with no decrease in diastereoselectivity and enantioselectivity.

4. Conclusions

In summary, asymmetric synthesis of fluorine-containing organic compounds in a regio- and stereoselective manner by organocatalysis has emerged as a powerful tool in the past decade, which makes the introduction of fluorine atom into molecules more efficient and environmently benign. Notable improvements have been achieved on asymmetric fluorination using electrophilic fluorination regents, as well as organocatalytic methods using fluorinated building blocks, comprising the two common strategies for the introduction of a fluorine atom into organic compounds. On



Scheme 10. Michael addition of α-fluoro-α-phenylsulfonyl ketones to nitroolefins.

the base of the more unique biological activities of the novel discovered fluorinated compounds and tremendous development of asymmetric organocatalysis, we will be able to design more efficient organocatalysts and make even more challenging transformations allowing more practical applications of organocatalysis in modern organic synthesis.

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