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Authors: Gang Zhao, Lijun Xu, Changwu Zheng, and Hongyu Wang

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Enantioselective Mannich-type Reactions to Construct CF_3S-containing Tetrasubstituted Carbon Stereocenters via Asymmetric Dual-Reagent Catalysis

Lijun Xu,[a] Hongyu Wang,[a] Changwu Zheng,[a] Gang Zhao[a]*

[a] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China.
[E-mail: zhaog@sioc.ac.cn]

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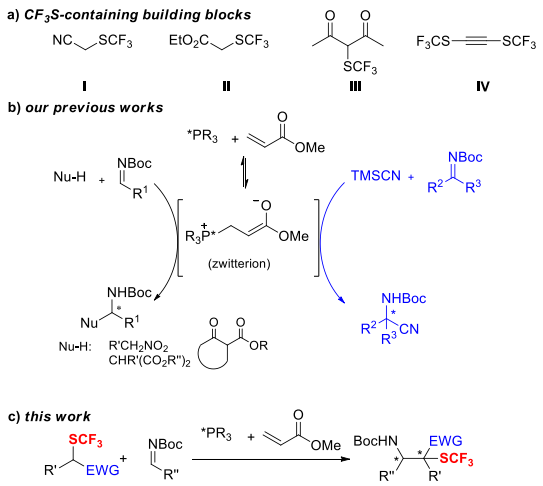
Abstract: An approach to construct tetrasubstituted carbon stereocenters bearing both a SCF3 group and a cyano group has been realized, through asymmetric organophosphine-catalyzed Mannich-type reactions. The products were obtained in high yields and moderate to high enantioselectivities. Two diastereoisomers could be isolated from each reaction (25 overall examples), rendering this approach a viable opportunity for molecular diversity generation and improvement of the bioactivity of related drug candidates.

Keywords: CF_3S-containing building blocks; Mannich-type reactions; Nucleophilic phosphines; The dual-reagent catalysis

Introduction

The incorporation of fluorine-containing groups into organic molecules often modifies their chemical and physicochemical properties.[1] Trifluoromethylthio (SCF_3) containing compounds are frequently found in pharmaceuticals and agrochemicals because of the high lipophilicity and electron-withdrawing character of the SCF_3 moiety.[2] Recently, tremendous progress for the introduction of SCF_3 group into organic compounds using nucleophilic or electrophilic SCF_3 transfer reagents has been achieved.[3] Alternatively, strategies for the formation of trifluoromethylthiolated compounds through the transformation from SCF_3-containing building blocks have drawn attention due to their high atom economy. So far, several examples related to CF_3S-containing building blocks of type **I-IV** (Scheme 1, eq. a) have been independently reported by Ponticello and Wakselman for the synthesis of heteroaryl trifluoromethyl sulfides.[4] Other than these methods, very recently, an enantioselective trifluoromethylthiolation of β-ketoesters has been developed by Rueping,[5] Shen[6] and Tan[7] using cinchona alkaloid as the catalyst. Zhao and co-workers also revealed an efficient approach for enantioselective trifluoromethylthiolating lactonization catalyzed by an indane-based chiral sulfide.[8] However, until now, no reports for the construction of stereogenic centers using CF_3S-containing building blocks have been reported.

Asymmetric catalysis with nucleophilic phosphines has captured considerable interest due to the effectivity for the synthesis of chiral organic molecules.[9] Recently, we have developed novel asymmetric dual-reagent catalysis to expand the application of the asymmetric nucleophilic phosphine to Mannich-type reactions between *N*-Boc imines and nucleophilic reagents such as dimethyl 2-fluoro-mal-



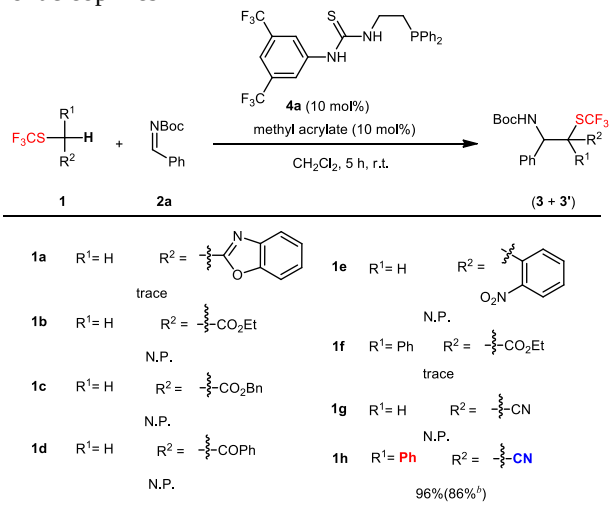
Scheme 1. a) Reported CF_3S-containing building blocks. b) Asymmetric dual-reagent catalysis. c) Enantioselective Mannich-type reactions involving CF_3S-pronucleophiles.

onate, nitroalkanes and β-ketoesters (Scheme 1, eq. b).[10] Besides, the zwitterion generated in situ could also serve as an efficient Lewis base catalyst for the asymmetric cyanation of ketimines derived from isatins (Scheme 1, eq. b). [11] Inspired by the above-mentioned process, we envisaged that an appropriate CF_3S-containing pro-nucleophile could be utilized in the asymmetric dual-reagent catalysis. Herein, we report an enantioselective Mannich-type reaction between *N*-Boc imines and CF_3S-containing building blocks. This transformation offers an expeditious approach to enantioenriched CF_3S-containing tetrasubstituted carbon stereocenters (Scheme 1, eq. c).

Results and Discussion

The initial stages of the study revolved around finding an appropriate CF_3S-containing building block for the Mannich-type reaction with *N*-Boc imine (**2a**) to get the desired product in acceptable yield. Unfortunately, under previously used conditions, no products were observed with a variety of CF_3S-containing pro-nucleophiles (Figure 1, **1a**–**1g**) (for details, see the Supporting Information). To our delight, the more reactive pronucleophile **1h** provided the desired product bearing a tetrasubstituted carbon stereocenters as a mixture of two diastereomers (**3a** + **3a′**) in 96% yield, as determined by ^{19}F NMR spectroscopy (Figure 1). In contrast, compound **1f**, which differs from **1h** by containing an ester group instead of the cyano group, produced traces of the product, indicating that the cyano group is quite important for reaction efficiency. It is worth mentioning that nitriles are ubiquitous in organic synthesis and aryl nitriles are present in num-

Figure 1. Screening of CF_3S-containing building blocks as pronucleophiles

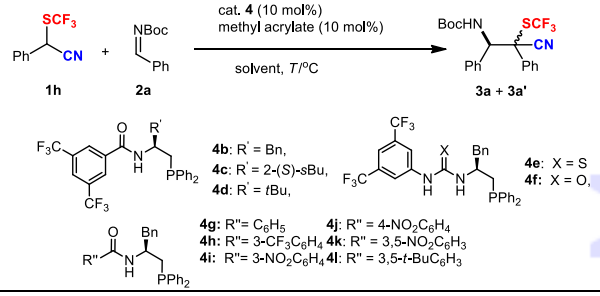


[a] Unless otherwise noted, all reactions were carried out with **1** (0.05 mmol), **2a** (0.10 mmol), **4a** (10 mol%), methyl acrylate (10 mol%) in CH_2Cl_2 (0.5 mL) at r.t. for 5 h and monitored by ^{19}F NMR spectroscopy. [b] Reaction was stirred for 0.5 h. Yield of the isolated products.

erous natural products and marketed drugs.[12] The acidity of the proton alpha to the nitrile group may play a key role in favoring the deprotonation of **1h**, even if other factors such as steric and/or solvent effects could be relevant for the success of the reaction (for details, see the Supporting Information).[13]

Encouraged by this result, a series of chiral bifunctional catalysts derived from amino acids were synthesized and evaluated. The reaction was first performed in DCM at room temperature without methyl acrylate (MA) in the presence of **4b** to give trace of product. On the other hand, when MA was added to the reaction mixture, the yield and enantioselectivity drastically improved to 85% and 65%/33% ee for the two diastereomers, respectively (Table 1, entries 1 and 2). Various reaction temperatures were then investigated and it was found that the reaction was much more enantioselective at low temperature without the need for extending reaction time (Table 1, entries 3 and 4).

Table 1. Optimization of chiral catalysts[a]



Entry	Catalyst	Solvent	*T*/°C	Yield (%)[b]	*dr*[c] (3a : 3a′)	*ee*(%)[c] (3a/3a′)
1[d]	**4b**	CH_2Cl_2	r.t.	trace	—	—
2	**4b**	CH_2Cl_2	r.t.	85	59:41	65(33)
3	**4b**	CH_2Cl_2	-30	83	62:38	75(44)
4	**4b**	CH_2Cl_2	-72	82	70:30	86(63)
5	**4c**	CH_2Cl_2	-72	80	57:43	31(-21)
6	**4d**	CH_2Cl_2	-72	82	58:42	32(-6)
7	**4e**	CH_2Cl_2	-72	85	67:33	37(-17)
8	**4f**	CH_2Cl_2	-72	81	59:41	46(-49)
9	**4g**	CH_2Cl_2	-30	83	57:43	18(0)
10	**4h**	CH_2Cl_2	-72	82	68:32	62(14)
11	**4i**	CH_2Cl_2	-72	82	72:28	66(13)
12	**4j**	CH_2Cl_2	-72	82	69:31	59(19)
13	**4k**	CH_2Cl_2	-72	82	78:22	90(73)
14	**4l**	CH_2Cl_2	-72	81	74:26	66(45)
15	**4k**	Toluene	-72	81	66:34	43(68)
16	**4k**	EtOAc	-72	48	55:45	82(52)
17[e]	**4k**	CH_2Cl_2	-72	82	64:36	76(81)

[a] Unless otherwise noted, the reactions were performed with **1h** (0.05 mmol), **2a** (0.10 mmol) and methyl acrylate (10 mol%) in the presence of chiral phosphine **4** (10 mol%) in solvent (0.5 mL) for 0.5 h. [b] Total isolated yields of **3a** and **3a′**. [c] The *dr* values were determined by chiral HPLC analysis and the *ee* values of the minor diastereomer **3a′** were shown in parentheses. [d] The reaction was performed without methyl acrylate. [e] The reaction was performed with **4k** (5 mol%) and methyl acrylate (5 mol%).

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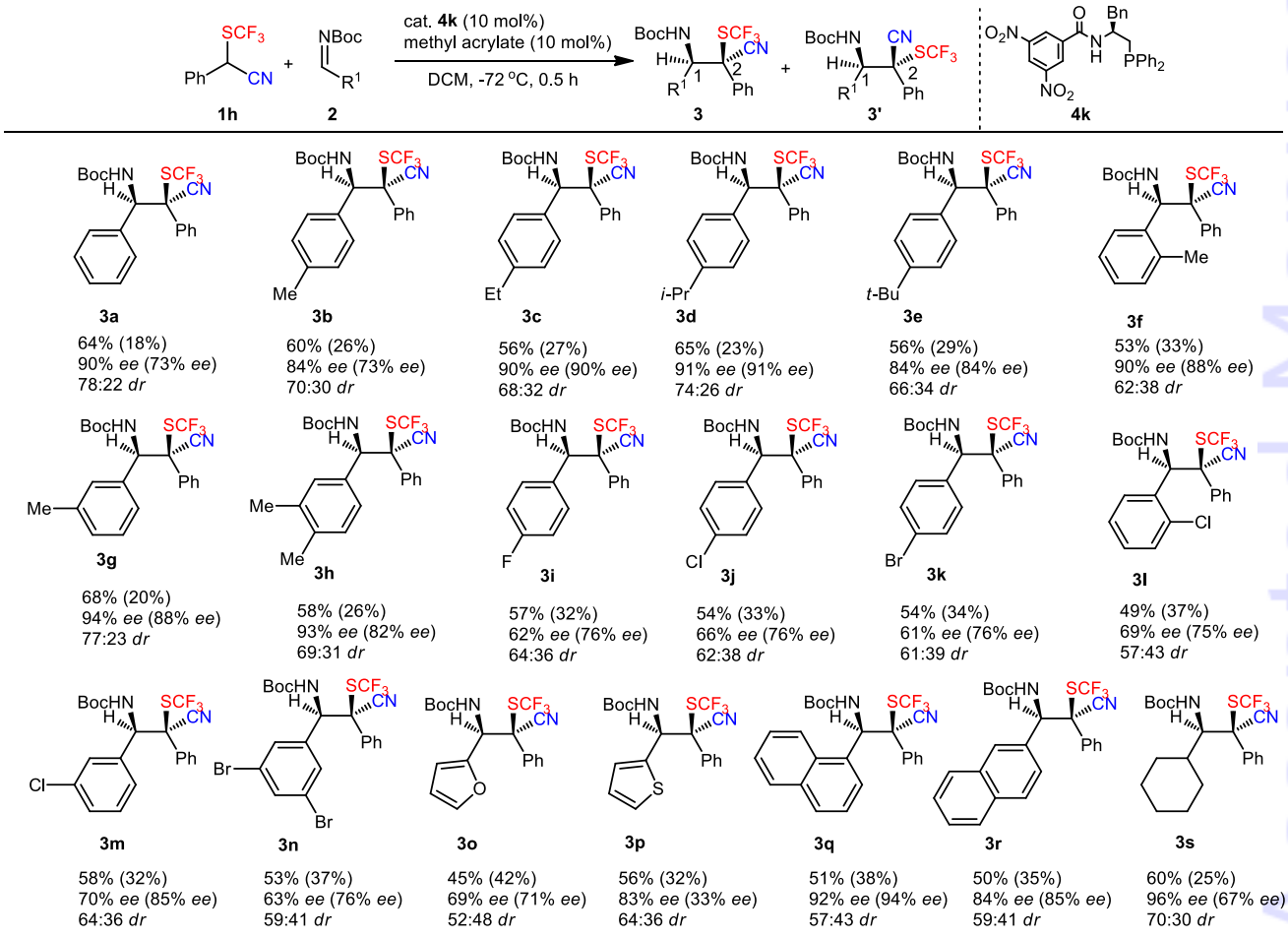
Among the several catalysts screened, the chiral skeleton derived from L-phenylalanine performed best in terms of enantioselectivity and diastereoselectivity (Table 1, entry 4 versus 5 and 6). The acyl group of bifunctional chiral phosphine catalysts seemed crucial for the enantiocontrol. Replacement of this moiety with thiourea (**4e**) or urea (**4f**) led to inferior results (Table 1, entries 7 and 8). Further investigations indicated that the electronic effect of different substitutent groups of the acyl moiety were also crucial to the enantioselectivity (Table 1, entries 9 to 14). Catalyst **4k**, which contains strongly electron-withdrawing nitro-groups, turned out to be the best under the same reaction conditions providing products with 82% isolated yield and higher enantioselectivity (90% *ee* and 73% *ee*, for the two diastereomers, respectively) (Table 1, entry 13). We also investigated the effect of various solvents on the Mannich-type reaction, however no improvement in enantioselectivity was found (Table 1, entries 15 and 16). Additionally, reducing the catalyst loading to 5 mol% led to a loss of stereoselectivity (Table 1, entry 17).

After optimized reaction conditions were found, we next turned our attention to exploring the CF_3S-containing building block (**1h**) and various *N*-Boc imines (**2**) in this Mannich-type reaction. As summarized in Table 2, all of the *N*-Boc imines examined provided the corresponding products in high isolated yields within 0.5 hour regardless of the electronic nature and the steric effect of substituents on the aryl ring of imines. In general, substituted aromatic imines bearing electron-donating groups (such as Me, Et, *i*-Pr, and *t*-Bu) afforded the major diastereomer products with high levels of enantiose-

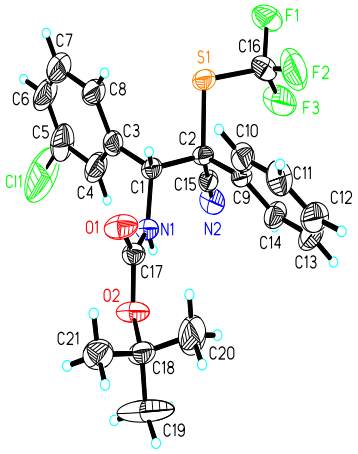
Table 2. Scope of the Mannich-type reaction catalyzed by the dual-reagent catalysis[a]



[a] Isolated yields of the major diastereomer **3** on a 0.1 mmol scale. Isolated yields and the *ee* values of the minor diastereomer **3´** were shown in parentheses. The *dr* values were determined by chiral HPLC analysis. The *dr* value of **3n** and **3n′** was determined by ^{1}H NMR spectroscopic analysis of the crude product.

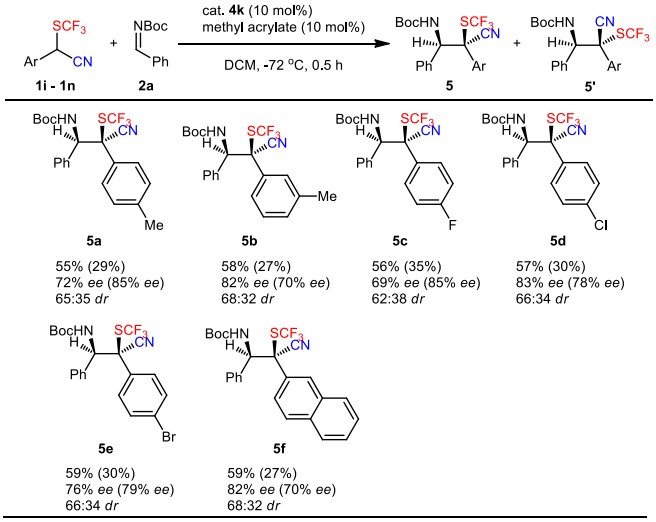
lectivity and moderate levels of diastereoselectivity (**3a**–**3h**). Particularly, imine bearing *meta*-methyl group on the aryl ring reacted efficiently, producing **3g** in 94% *ee*. Aromatic imines with electron-withdrawing groups (such as F, Cl and Br) provided the addition products **3i**–**3n** with moderate stereoselectivity. Additionally, heteroaryl and poly-cyclic aromatic imines also worked under the reaction conditions, furnishing the products **3o**–**3r** in moderate to good enantioselectivities. Moreover, the cyclohexyl containing imine afforded the corresponding product in 96% *ee* (**3s**). The absolute configuration of **3m** was confirmed by X-ray crystallographic analysis after recrystallization

(Figure 2); additionally, the absolute configuration of the minor diastereomer (**3n′**) was also determined, supporting the notion that the diastereoisomeric couples **3**/**3′** are epimeric at C2 (see the Supporting Information for details). [14]



Figur 2. X-ray crystal structure of **3m**

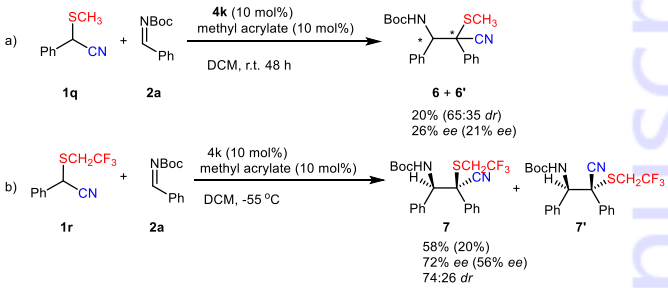
Table 3. Substrate Scope of the CF_3S-containing buildings[a]



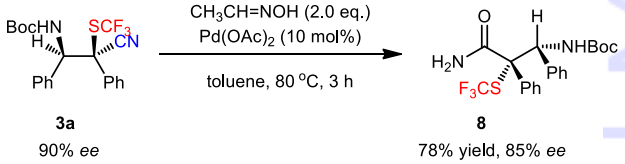
[a] Isolated yields of the major diastereomers **5** on a 0.1 mmol scale; Isolated yields and the *ee* values of the minor diastereomer **5′** were shown in parentheses. The *dr* values were determined by chiral HPLC analysis. The *dr* value of **5e** and **5e′** was determined by ^{1}H NMR spectroscopic analysis of the crude product.

We next examined the scope of the CF_3S-containing reagent (**1**) in the reaction to show the variety of tolerated pronucleophiles (Table 3). In general, good isolated yields (of the two diastereomers) were obtained with a range of aryl containing pronucleophiles **(5a–5f)**. Electronic effects and steric effects on the aryl ring of 2-(trifluoromethylthio) phenylacetonitrile **1** showed a negative influence on the enantioselectivity compared to **3a**. Reactions afforded the products with moderate to high enantioselectivities.

Changing the protecting group of the imine to *p*-toluenesulfonyl, 1,1-diphe-nylmethenyl, *p*-methoxy-phenyl and diphenylphos-phinyl did not furnish the desired products while *N*-Cbz imine could provide the the corresponding major diastereomeric product in 53% *ee* (see the SI). We also investigated substituents other than a trifluoromethyl group on the sulfide, as shown in scheme 2. With the electron-donating methyl group (**1q**), the reaction also worked under the similar conditions at ambient temperature, although extended time was required. However, the yield and enantioselectivity were low. To our delight, the reaction proceeded smoothly with the trifluoroethyl substituted sulfide (**1r**) to give the the major diastereomeric product **7** in 58% yield and 72% ee (20% yield and 56% ee for the minor diastereomer). The trifluoroethylthio group (-SCH_2CF_3) has been proved to be an important moiety in several agrochemical and pharmaceutical compounds.[15]



Scheme 2. Related R_3CS-building blocks in the Mannich-type reaction



Scheme 3. The representative transformation of **3a**

To demonstrate the utility of the products, compound **3a** (90% *ee*) was converted to the useful amide **8** (85% *ee*) under the condition of $Pd(OAc)_2$ and acetaldoxime (Scheme 3).[16]

A possible mechanism for the reaction is shown in Figure 3. First, the chiral phosphine adds to the methyl acrylate, forming phosphonium enolate **A**, which was confirmed by ESI-MS (m/z for $(M + H)^+$: 600.2). This zwitterion, which acts a mild Brønsted base, deprotonates **1h** to generate the ion-pair **B**. This ion-pair can then react with imine **2a** to form intermediates **D** (via transition state **C**). A proton exchange then occurs to produce the product (**3a** + **3a′**) and regenerate the ion-pair **B**. A possible transition state **C** can be considered to control the stereoselectivity. The *N*-Boc imine is activated by the amide moiety of the catalyst through hydrogen bonding and the pronucleophile seems to be controlled via the ion pair generated in situ. Further mechanistic studies to elucidate the reaction mechanism will be explored.

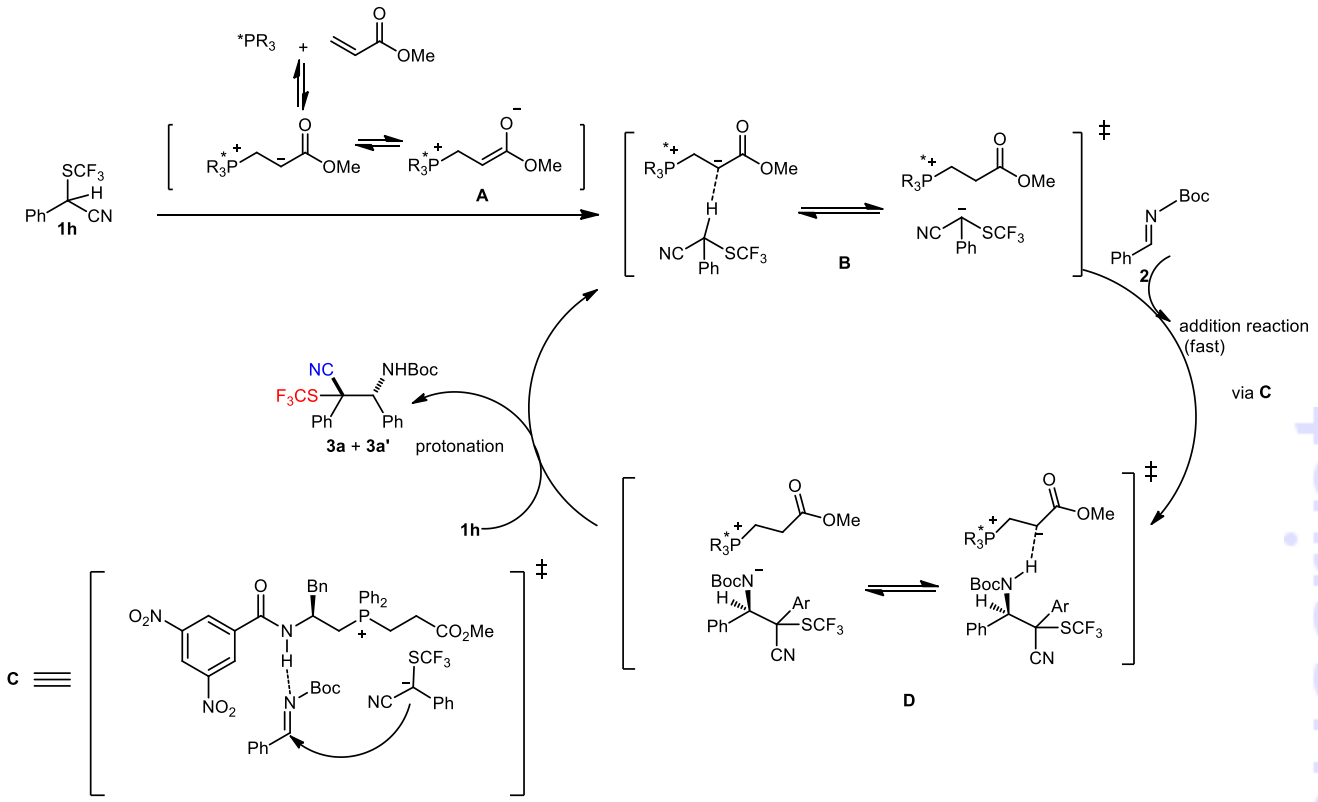


Figure 3. Possible reaction mechanism and transition state

Conclusion

In summary, we have developed the enantio-selective Mannich-type reaction of the CF_3S-containing building blocks via a dual-reagent catalysis system consisting of a bifunctional phosphine derived from an amino acid and methyl acrylate as the additive. This catalyst system can offer an efficient approach to construct the chiral stereocenters bearing a SCF_3 group and a cyano group in good yields and moderate to high enantioselectivities. These moieties might modulate the physicochemical properties of some drug candidates by enhancing the lipophilicity. Our future research is directed at exploring the bioactivity of these unique molecules. Additionally, the full potential of this asymmetric dual-reagent catalysis will be further explored.

Experimental Section

General procedure for the symmetric dual-reagent catalyzed Mannich-type reactions: To a solution of the catalyst **4k** (10 mol %) in DCM (1 mL) was added methylacrylate (10 mol %), and the mixture was stirred at room temperature for 10 min, and then the CF_3S-containing building blocks **1** (0.10 mmol) was added. The resulting mixture was vigorously stirred for 10 min at room temperature, and then cooled to -72 ºC before the imine **2** (0.20 mmol) was introduced. When the reaction was finished (determined by TLC analysis), the crude mixture was warmed to the room temperature and quenched by water (2 mL). The aqueous phase was extracted with DCM (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by PTLC to afford two diastereomers. The diastereomer ratio was determined by HPLC, ^{1}H NMR and ^{19}F NMR at this stage. The major isomer and the minor isomer were isolated with PTLC for data collection.

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FULL PAPER

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Lijun Xu,[a] Hongyu Wang,[a] Changwu Zheng,[a] Gang Zhao[a]*