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Chiral Thiophosphoramidate-Catalyzed Asymmetric Michael Addition of Ketones to Nitro Olefins

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A novel type of pyrrolidine-based chiral (thio)phosphoramidates was synthesized. Among them, compound (*S*,a*R*)-**3d** was proven to be an effective bifunctional organocatalyst for the asymmetric Michael addition of ketones to nitro olefins. The corresponding adducts were obtained in good to excellent chemical yields with high levels of diastereo- and enantioselectivities (up to >99:1 *dr* and 99 % *ee*).

Introduction

The Michael reaction of carbon-centered nucleophiles to nitro olefins represents a direct and most appealing approach to nitroalkanes, which are versatile synthetic intermediates owing to the various possible transformations of the nitro group into other useful functional groups. The development of organocatalytic asymmetric versions of such processes has been extensively investigated in recent years.[1] Among them, the direct Michael addition of ketones to nitroalkenes offers particularly attractive access to synthetically valuable γ-nitro ketones in an atom-economical manner. Inspired by the pioneering work of List and Barbas at the beginning of this century,[2] a great number of pyrrolidine-type organocatalysts have been reported for this type of transformation.[3] The cyclic five-membered secondary amine structure of these compounds is now regarded as one of the "privileged" backbones for asymmetric organocatalysis. Among them, organocatalysts that consist of an appropriate combination of a hydrogen-bonding donor moiety and the "privileged" pyrrolidine unit have been proven to be effective in the Michael addition of ketones to nitro olefins, which is due to their strong activation of the nitro groups through efficient hydrogen-bonding interactions.[3c,3d,3g,3i,3k,3y,3z,4] Notably, *N*-triflyl phosphoramides, which contain an acidic hydrogen, also represent a novel fine-tuning class of strong Brønsted acid organocatalysts for organic transformations.[5] Therefore, it is anticipated that the acidic hydrogen of simple (thio)phosphoramides can also function as a hydrogen-bonding donor, and the combination of the *N*-(thio)phosphoramide moiety with the "privileged" pyrrolidine unit could result in a potential bifunctional organocatalyst. In this type of catalyst, the pyrrolidine backbone can serve as a catalytic site and the (thio)phosphoramide moiety can function as a hydrogen-bonding donor to activate the nitro olefins. Generally, very subtle changes in the catalyst structure can often lead to large and unpredictable differences in the performance of the catalyst, especially in terms of enantioselectivity. The great advantage of this type of organocatalyst is that the diversity of phosphorus compounds offers an opportunity to finely tune the catalytic activity by changing the substituents on the phosphorus atom. Herein, we report the asymmetric organocatalytic Michael addition of cyclic ketones to nitro olefins, which is promoted by a simple bifunctional organocatalyst bearing a simple amino thiophosphoramide.

Results and Discussion

The trifluoroacetic acid salts of newly designed pyrrolidine–(thio)phosphoramidates **3** were easily prepared by the coupling of (*S*)-*tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (**1**)[3w] with the corresponding phosphoryl chlorides **2** as shown in Scheme 1.

In control reactions, it was found that the in situ generated catalyst gave results that were comparable to those of the free-base catalyst (Table 1, Entry 2 vs. 1). So we kept these catalysts in their trifluoroacetate form and employed the in situ generated free base as the catalyst with the addition of an equivalent of organic base, such as triethylamine. Then, rough examination of the effect of the substituents on the phosphorus atom of **3** was carried out by employing the reaction of β-nitrostyrene (**4a**) with cyclohexanone as a model. As shown in Table 1, it is noteworthy that not only the steric demand of the substituents but also their electronic nature had a prominent effect on both the catalytic activity and the stereoselectivity. When *O*,*O*-diethyl

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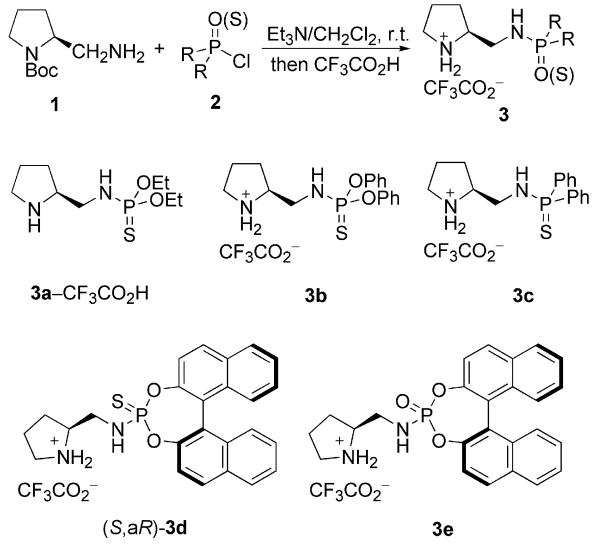
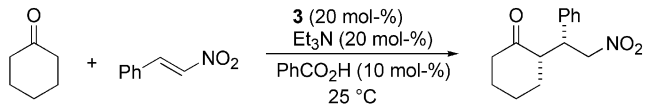


Scheme 1. Synthesis of catalysts.

Table 1. Catalyst screening.[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][d]
1	**3a**/CF_3CO_2H	6	95	99:1	77
2	**3a**	8	92	94:6	79
3	**3b**	72	48	78:22	77
4	**3c**	12	88	98:2	81
5	(*S*,a*R*)-**3d**	1	>99	99:1	90
6	(*S*,a*S*)-**3d**	48	82	91:9	63
7	**3e**	20	95	92:8	74

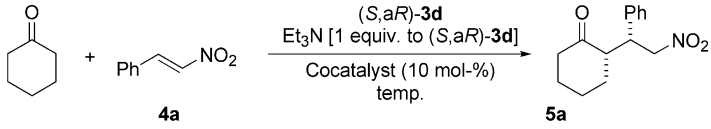
[a] All reactions were carried out by using cyclohexanone (226 mg, 2.3 mol) and **4a** (0.23 mmol) in the presence of catalyst **3**. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

thiophosphoramidate **3a** was employed as the catalyst, the reaction was complete in 8 h, and the corresponding adduct was obtained with excellent diastereoselectivity (*syn*/*anti* = 94:6) and good enantioselectivity (79%*ee*), whereas catalyst **3b** with phenoxy groups proved to be poor in terms of turnover frequency and diastereoselectivity (Table 1, Entry 2 vs. 3). An improvement in both the catalytic activity and the stereoselectivity was observed when the phenoxy groups (**3b**) were replaced with phenyl groups (**3c**) (Table 1, Entry 3 vs. 4). With respect to selectivity, the best result was obtained with bulky catalyst (*S*,a*R*)-**3d** bearing an (*R*)-binaphthyl skeleton (Table 1, Entry 5; 99:1 *dr*, 90%*ee*). However, much lower catalytic activity and stereocontrol were observed for the corresponding oxo analogue **3e**. This may be attributed to the decrease in the acidity of the hydrogen upon substitution of the sulfur in the P=S bond with oxygen.[6] Under otherwise identical conditions, bifunctional thiophosphoramidate (*S*,a*S*)-**3d** derived from (*S*)-binaphthol demonstrated much lower catalytic activity. The reaction became quite sluggish, and a decreased yield of 82% was attained at a prolonged reaction time. Moreover, a dramatic decrease in both the diastereoselectivity and the enantioselectivity were recorded (Table 1, Entry 6 vs. 5). This indicates that the (*R*)-configuration of binaphthol matched (*S*)-2-(aminomethyl)pyrrolidine to enhance the catalytic activity of the catalyst.

Having identified bulky (*S*,a*R*)-**3d** to be the best catalyst for the reaction, other factors influencing the reaction were further thoroughly investigated. The results are summarized in Table 2. A survey of six acidic cocatalysts revealed that the acidic cocatalyst has an important influence on the reaction. The addition of 10 mol-% of carboxylic acid as cocatalyst significantly accelerated the reaction rate and enhanced the selectivity relative to that with the catalyst in the absence of an acidic cocatalyst (Table 2, Entries 2–7 vs. entry 1). In terms of enantioselectivity, a variety of carboxylic acid cocatalysts were tolerated by this Michael addition reaction. Almost the same level of enantioselectivity was observed for benzoic acid (Table 2, Entry 4; 90%*ee*), bulky pivalic acid (Table 2, Entry 5; 89%*ee*), and chiral mandelic acid [Table 2, Entries 6 and 7; 90%*ee* for (*S*)-enantiomer and 89%*ee* for (*R*)-enantiomer]. Considering both the reaction rate and diastereoselectivity, benzoic acid is the best choice. The reaction was complete within only 1 h with excellent diastereoselectivity (Table 2, Entry 4). Moreover, the reaction temperature was found to be an essential factor to the enantioselectivity of this reaction. The stereoselectivity gradually increased with a decrease in the reaction temperature from 25 to –30 °C (Table 2, Entries 4, 9, 10, and 11; 90–96%*ee*). Although the same excellent selectivity was obtained upon lowering the temperature further to –40 °C, the reaction became quite sluggish to afford the product in rather low yield even with a prolonged reaction time (Table 1, Entry 12). In addition, reducing the amount of (*S*,a*R*)-**3d** from 20 mol-% to 10 mol-% resulted in an obvious decrease in both the turnover frequency and the stereoselectivity (Table 2, entry 8).

With optimized reaction conditions in hand, a variety of nitro olefins with different structures were investigated, and the results are summarized in Table 3. Various styrene-type nitro olefins reacted smoothly with cyclohexanone to provide the corresponding adducts in good to excellent yields with excellent diastereoselectivities and enantioselectivities (Table 3, Entries 1–12). Generally, the nature of the substituent on the benzene ring exhibited a slight influence on the reaction. Nitrostyrene bearing either electron-withdrawing or electron-donating substituents on the benzene ring provided high *syn* selectivity (up to >99:1) as well as enantioselectivity (up to >99%*ee*). The excellent enantioselectivity achieved for heteroaryl nitro olefin **4l** (Table 3, Entry 12) indicates that it is also a good Michael acceptor for cyclohexanone. Furthermore, alkenyl-substituted nitro olefin **4m** can also be employed, albeit with a slight decrease in diastereo- and enantioselectivity (Table 3, Entry 13). Notably, aliphatic aldehyde derived nitro olefin **4n** also appeared to

Table 2. Optimization of reaction conditions.[a]

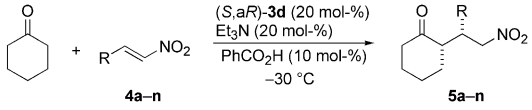


Entry	(*S*,a*R*)-**3d** [mol-%]	Cocatalyst [10 mol-%]	Temp. [°C]	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][d]
1	20	–	25	48	43	76:24	37
2	20	CH_3CO_2H	25	2	92	97:3	79
3	20	$PrCO_2H$	25	2	98	86:14	82
4	20	$PhCO_2H$	25	1	>99	99:1	90
5	20	$tBuCO_2H$	25	4.5	>99	98:2	89
6	20	(*S*)-mandelic acid	25	4.5	91	98:2	90
7	20	(*R*)-mandelic acid	25	1	92	98:2	89
8	10	$PhCO_2H$	25	9	>99	90:10	85
9	20	$PhCO_2H$	0	4	96	97:3	92
10	20	$PhCO_2H$	–15	10	95	>99:1	93
11	20	$PhCO_2H$	–30	22	96	>99:1	96
12	20	$PhCO_2H$	–40	63	60	>99:1	96

[a] All reactions were carried out by using cyclohexanone (226 mg, 2.3 mol) and **4a** (0.23 mmol) in the presence of catalyst **3**. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

be a good candidate at an elevated temperature (Table 3, Entry 14; *syn*/*anti* = 73:27, 91%*ee* for *syn* isomer), which clearly demonstrated the broad generality of this asymmetric Michael addition reaction.

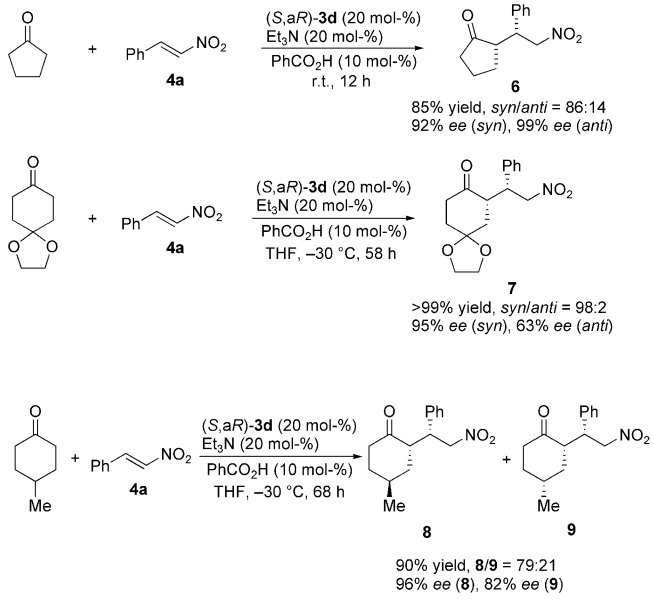
Table 3. Substrate scope of (*S*,a*R*)-**3d**-catalyzed asymmetric Michael addition of cyclohexanone to nitro olefins.[a]



Entry	R	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][d]
1	Ph (**a**)	22	>99	>99:1	96
2	3-$CF_3C_6H_4$ (**b**)	21	85	98:2	96
3	4-$CF_3C_6H_4$ (**c**)	23	87	>99:1	99
4	4-FC_6H_4 (**d**)	19	95	99:1	97
5	4-ClC_6H_4 (**e**)	21	85	98:2	98
6	2-BrC_6H_4 (**f**)	21	98	>99:1	97
7	4-BrC_6H_4 (**g**)	21	83	>99:1	98
8	2-$MeOC_6H_4$ (**h**)	19	77	99:1	96
9	4-MeC_6H_4 (**i**)	19	>99	99:1	97
10	benzo[*d*][1,3]dioxol-5-yl (**j**)	40	82	>99:1	98
11	1-naphthyl (**k**)	19	97	>99:1	97
12	2-furyl (**l**)	16	>99	98:2	95
13	(*E*)-cinnamyl (**m**)	17[e]	92	93:7	89
14	phenylethyl (**n**)	4[e]	89	73:27	91

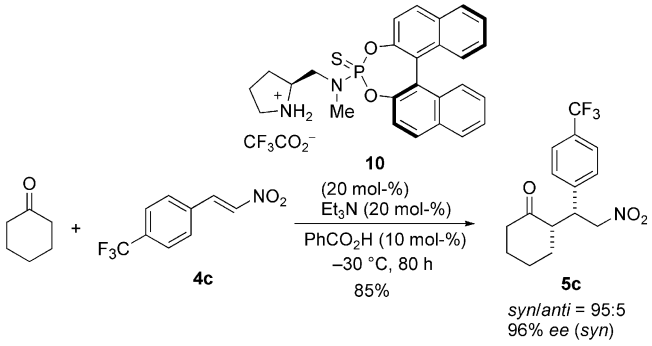
[a] All reactions were carried out by using cyclohexanone (226 mg, 2.3 mol) and **4a** (0.23 mmol) in the presence of catalyst **3**. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out at room temperature (25 °C).

The asymmetric additions of other ketones to nitrostyrene (**4a**) with the use of (*S*,a*R*)-**3d** as a catalyst were also preliminarily investigated. As shown in Scheme 2, challenging cyclopentanone worked well to provide desired product **6** in 85% yield with excellent enantioselectivity (*syn*/*anti* = 86:14, 92%*ee* for *syn*-**6** and 99%*ee* for *anti*-**6**) at room temperature. Other cyclic ketones such as cyclohexane-1,4-dione monoethylene acetal also reacted smoothly with **4a** in THF at –30 °C and excellent stereoselectivities were maintained. Moreover, the desymmetrization of prochiral 4-methylcyclohexanone could also be realized under identical conditions to give the desired Michael adducts bearing three carbon stereocenters. In this case, the reaction went to completion in 68 h, affording 90% yield, 79:21 *dr*, and 96%*ee* for the major isomer.



Scheme 2. Reaction of other ketones.

We envisioned that the acidic hydrogen of the (thio)phosphoramide can function as a hydrogen-bonding donor in the reaction. To testify to this hypothesis, the corresponding *N*-methylated compound **10** of catalyst (*S*,a*R*)-**3d** was synthesized and examined under the same conditions for the Michael addition of cyclohexanone to the best suitable nitro olefin **4c** (Scheme 3). As shown in Scheme 3, obvious decreases in both the diastereo- and enantioselectivity were observed in this case; especially, it is worth noting that the use of *N*-methylated catalyst **10** led to a dramatic decrease in the reaction rate (reaction time: 23 vs. 80 h; only 25% conversion of **4c** was achieved after stirring for 23 h). In comparison to the results of catalyst **10**, the observed significant rate acceleration for catalyst (*S*,a*R*)-**3d** may be attributed to the capability of the acidic hydrogen to form a hydrogen bond with the nitro group of the nitro olefin.



Scheme 3. Michael addition catalyzed by catalyst **10**.

On the basis of the experimental results, a possible transition state for this reaction was proposed to account for the observed high diastereo- and enantioselectivity. As shown in Figure 1, the free base of (*S*,a*R*)-**3d** functioned as a bifunctional catalyst. The pyrrolidine ring will first react with a carbonyl compound to form an enamine with the aid of an acidic cocatalyst. Subsequently, the acidic hydrogen as well as the Brønsted acid additive will orientate the nitro group through hydrogen-bonding interaction so that the enamine will act as a nucleophile and attack the nitro olefin from the *Re* face to give the highly enantio- and diastereoselective product. This explanation is consistent with the experimental results.

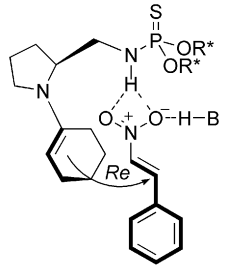


Figure 1. Possible transition state of the present reaction.

Conclusions

In conclusion, we have developed a novel pyrrolidine-based thiophosphoramidate catalyst, which worked well as a bifunctional organocatalyst to promote the asymmetric Michael reaction of ketones to nitro olefins. In the presence of the newly prepared catalyst, the reaction takes place smoothly with excellent diastereo- (up to >99:1 *dr*) and enantioselectivity (up to 99% *ee*), which may provide a potentially useful method for the preparation of enantiomerically enriched γ-nitro ketones. Further investigations on the application of this catalyst in asymmetric catalysis are in progress.

Experimental Section

General Procedure for Asymmetric Michael Addition of Ketones to Nitro Olefins Catalyzed by (*S*,a*R*)-3d: A mixture of catalyst (*S*,a*R*)-**3d** (0.046 mmol) and triethylamine (0.046 mmol) in cyclohexanone (226 mg, 2.3 mmol) was stirred at room temperature for 30 min. Then, benzoic acid (2.8 mg, 0.023 mmol) was added, and the reaction mixture was stirred for 15 min. To the resulting mixture was added nitro olefin (0.23 mmol) at the required temperature. After the reaction was complete (monitored by TLC), the mixture was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/EtOAc, 1:5) to afford the product.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of the prepared compounds, copies of the NMR spectra, chiral HPLC spectra of the Michael addition products.

Acknowledgments

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