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4-Aminothiourea Prolinol *tert*-Butyldiphenylsilyl Ether: A Chiral Secondary Amine-Thiourea as Organocatalyst for Enantioselective *anti*-Mannich Reactions

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Abstract: *anti*-Selective Mannich reactions of *N*-*p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate with unmodified aldehydes or ketones were effectively catalyzed by 4-aminothiourea prolinol *tert*-butyldiphenylsilyl ether. The reactions led to chiral β-amino carbonyl compounds in high yields (up to 94%), excellent diastereo- and enantioselectivities (up to 98% *de* and >99% *ee*). The study demonstrated for the first time that direct Mannich-type reactions of unmodified aldehydes or ketones to α-iminoglyoxylate can be promoted by secondary amine-thiourea chiral organocatalyst.

Keywords: β-amino carbonyl compounds; 4-aminothiourea prolinol *tert*-butyldiphenylsilyl ether; asymmetric *anti*-Mannich reactions; secondary amine-thiourea organocatalyst

Direct catalytic asymmetric Mannich reactions are highly effective carbon-carbon bond forming reactions,[1] to build β-amino acids, amino alcohols, amino carbonyls, and their derivatives that contain two adjacent stereocenters. Due to the wide utility of these synthons, especially in pure *syn*- or *anti*-form, it is highly desirable to develop stereoselective methods. In this respect, the catalytic asymmetric Mannich-type reaction has recently been the subject of intense research,[2–8] and tremendous efforts have been focused on the development of an organocatalytic asymmetric version of the reaction. Great success has been achieved in the development of *syn*-selective direct organocatalytic asymmetric Mannich-type reactions[3,4] wile *anti*-selective Mannich reactions are considerably more challenging and only a limited number of reports were documented.[5–8] In this context, pyrrolidine-based derivatives were found to be generally more effective catalysts, as demonstrated by the work of the Barbas group: pyrrolidine derivatives (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid and 3-pyrrolidinecarboxylic acid as effective catalysts for *anti*-selective Mannich-type reactions with unmodified aldehydes and ketones as nucleophiles;[5b–d] Blanchet's group has developed 3-trifluoromethanesulfonamidopyrrolidine[5g] and Maruoka's group has discovered that chiral cyclic amines were effective catalysts with high diastereoselectivity and enantioselectivity;[5h–l] Good results were also achieved by using other organocatalysts, including acyclic primary amino acids,[6] chiral Brønsted acids[7] and primary amine-thioureas[8] in direct *anti*-selective Mannich reactions. In these catalytic systems, solvents such as DMSO and DMF were often chosen as the reaction media, because most of the catalysts, especially chiral amino acids and some chiral amino sulfonamides were hardly soluble in less polar solvents. Although these reactions are highly enantioselective, removal of such high boiling-point solvents has engendered inconveniency, especially in practical synthesis.

Thiourea-based organocatalysts have been widely used in asymmetric catalysis due to their strong activation efficiency through double hydrogen-bonding.[9] Among them, Chen's group has successfully used chiral secondary amine-thiourea to the catalyze asymmetric nitro-Mannich reaction.[9x] However, studies of these catalysts in direct asymmetric Mannich reactions are limited. To the best of our knowledge, only one example was shown in which chiral primary amine-thioureas were developed as the catalysts in direct *anti*-selective asymmetric Mannich reactions.[8] No report has been found on the reaction catalyzed by chiral secondary amine-thiourea for either *anti*- or *syn*-Mannich products.

Interested in developing new and broadly useful chiral organocatalysts for asymmetric synthesis, we have previously designed and synthesized a series of

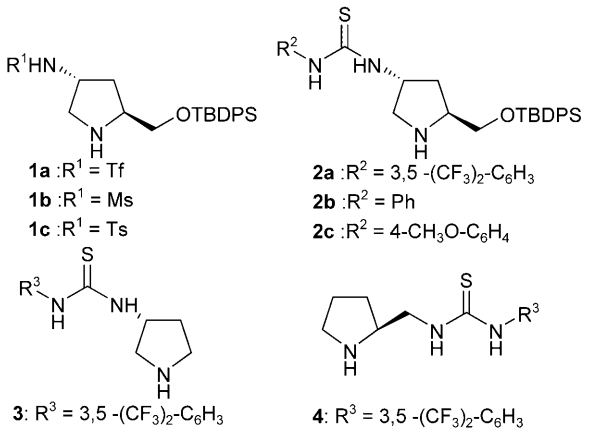


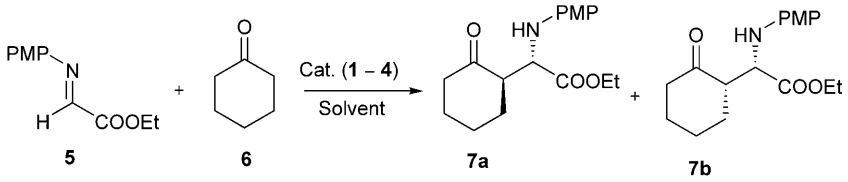
Figure 1. Pyrrolidine-based chiral organocatalysts.

catalysts **1a**–**2c**, which bear diverse proton donors at the 4-position to activate electrophiles and a -CH_2OTBDPS group at the α-position of the pyrrolidine nitrogen atom (Figure 1). These catalysts have shown excellent performance in the catalytic asymmetric Michael addition of ketones and aldehydes to nitroolefins.[10] The results have encouraged us to explore their utility in other asymmetric catalysis reactions, especially, the direct Mannich reaction. Our studies may provide examples of chiral secondary amine-thiourea catalysts in Mannich reactions, as well as their roles in *anti*-selective Mannich reactions.

Herein we report for the first time that chiral secondary amine-thiourea **2a** catalyzed simple Mannich-type addition of unmodified aldehydes and ketones to *N*-*p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate to afford *anti*-Mannich products with high diastereoselectivities (up to 98% *de*) and excellent enantioselectivities (up to >99% *ee*).

We selected the Mannich-type reaction of *N*-*p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate (**5**) with cyclohexanone (**6**) as the model reaction to evaluate the catalytic efficiency of the catalysts **1**–**4** (Table 1). Good yields (86%) and enantioselectivities (94% *ee* for *syn* and 98% *ee* for *anti*) were achieved

Table 1. Catalytic asymmetric *anti*-Mannich-type reactions of α-imino ester (**5**) with cyclohexanone (**6**) under various conditions.[a]



Entry	Cat. (%)	Solvent	Temp. [°C]	Time [h]	Yield[b] [%]	*anti*:*syn*[c]	*ee*% *anti* (*syn*)[c]
1	**1a** (10)	CH_3CN	0	4	86	33:67	98 (94)
2	**1b** (10)	CH_3CN	0	6	67	37:63	5 (3)
3	**1c** (10)	CH_3CN	0	24	49	66:34	24 (20)
4	**2a** (10)	CH_3CN	0	4	79	93:7	97 (–)
5	**2b** (10)	CH_3CN	0	11	79	34:66	3 (0)
6	**2c** (10)	CH_3CN	0	24	0	–	– (–)
7	**3** (10)	CH_3CN	0	16	67	52:48	99 (82)
8	**4** (10)	CH_3CN	r.t.	24	0	–	– (–)
9	**2a** (10)	THF	0	15	80	89:11	96 (66)
10	**2a** (10)	Tol	0	11	75	89:11	96 (78)
11	**2a** (10)	Et_2O	0	4	80	92:8	96 (–)
12	**2a** (10)	CH_2Cl_2	0	4	80	91:9	96 (–)
13	**2a** (10)	*i*-PrOH	0	24	79	89:11	94 (69)
14	**2a** (10)	$CHCl_3$	0	11	78	90:10	96 (–)
15	**2a** (10)	DMF	0	24	69	76:24	90 (79)
16	**2a** (10)	$Cl(CH_2)_2Cl$	0	7	82	92:8	99 (–)
17	**2a** (10)	$Cl(CH_2)_2Cl$	20	4	80	92:8	95 (–)
18	**2a** (10)	$Cl(CH_2)_2Cl$	-20	12	87	98:2	>99 (–)
19	**2a** (5)	$Cl(CH_2)_2Cl$	-20	12	82	92:8	99 (–)
20	**2a** (2)	$Cl(CH_2)_2Cl$	-20	24	80	92:8	98 (–)
21	**2a** (1)	$Cl(CH_2)_2Cl$	-20	24	78	90:10	96 (–)

[a] Unless specified, reactions conducted on a 0.2 mmol scale α-imino ester (**5**) in solvent (1.5 mL) with cyclohexanone (**6**) (2.0 mmol) in the presence of catalyst.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

when the reaction was catalyzed by **1a**. However, the diastereoselectivity was moderate (*anti*:*syn* = 33:67) and the predominant product was the *syn*-isomer (Table 1, entry 1). When **1b** or **1c** was used as the catalyst, the reactivity and enantioselectivity decreased dramatically. Only 67% yield after 6 h or 49% yield after 24 h was achieved. In either case, enantioselectivity was lower than 24% *ee* (Table 1, entries 2 and 3). Almost racemic mixtures were obtained when catalyzed by **1b** (Table 1, entry 2). As supposed in our previous work,[10] the decrease in reactivity and enantioselectivity may be caused by the decrease in the hydrogen-bond donating ability of the sulfonamide proton. Hydrogen-bond donating ability is closely linked to acidity, and is governed by the electronic and steric nature of the R^1 group. As the acidity and hydrogen-bond donating ability of the sulfonamide proton in **1a** are much higher than those in **1b** and **1c**, the catalytic performance of **1a** is better than that of **1b** and **1c** (Table 1xtabr1 >, entries 1–3). We further screened chiral secondary amine-thiourea **2**–**4** for catalytic performance. To our delight, the predominantly formed product was the *anti*-isomer with excellent enantioselectivity (97% *ee*) and diasteroselectivity (86% *dr*) when catalyzed by **2a** (Table 1, entry 4). Compound **2b** gave the similar results to those catalyzed by **1b**: *syn*-product as the major product with moderate diastereoselectivity and almost no enantioselectivity (Table 1, entries 2 and 5). Compound **2c** showed no catalytic activity (Table 1, entry 6). In catalyst **2a**, with two electron-withdrawing groups (CF_3) on the phenyl ring, both the hydrogen-bond donating ability and the acidity of the thiourea hydrogen were stronger than those of **2b** or **2c**, and thus the catalytic reactivity of **2a** is stronger than that of **2b** or **2c**. Under the catalysis of **3**, which lacks the -CH_2OTBDPS group in comparison with **2a**, good enantioselectivities were obtained (99% *ee* for *anti* and 82% *ee* for *syn*), but the diastereoselectivity was very low (only 4% *de*) (Table 1, entry 7). This result indicated that the -CH_2OTBDPS group in **2a** plays an important role to control the diastereoselectivity. We further changed the thiourea group from the 3-position to 2-position and replaced the catalyst **3** with **4**,[9y] but no product was observed (Table 1, entry 8). This demonstrated that the proper position of the thiourea group in the catalyst is also very important to maintain the catalytic reactivity.

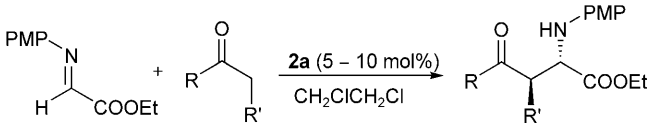
A solvent screening was then performed to identify the best reaction conditions (Table 1, entries 4, 9–16). Among the various organic solvents tested, CH_3CN and CH_2ClCH_2Cl were slightly better in terms of both the diastereoselectivity and enantioselectivity, with 97% *ee* and 99% *ee* in enantioselectivity, respectively (Table 1, entries 4 and 16). When the reaction proceeded in THF, toluene, Et_2O, CH_2Cl_2, *i*-PrOH and $CHCl_3$ (Table 1, entries 9–14), the diastereoselectivities or enantioselectivities were slightly inferior to the results obtained in CH_2ClCH_2Cl. In DMF the desired product was formed in 69% yield with moderate diastereoselectivity (Table 1, entry 15). CH_2ClCH_2Cl was then selected as the solvent in the study of the influence of temperature and catalyst loading (Table 1, entries 16–21). The diastereoselectivity increased greatly (from 84% *de* to 96% *de*) and the enantioselectivity remained higher than 99% *ee* when the reaction temperature was lowered from 0 °C to −20 °C, however, reaction time had to be prolonged from 7 h to 12 h for completion of the reaction (Table 1, entries 16 and 18). When the catalyst load was reduced from 10% to 5%, the yield and diastereoselectivity decreased slightly, affording 82% yield and 84% *de* after 12 h (Table 1, entries 18 and 19), however, 5% catalyst load was enough for good reactivity, diastereoselectivity, and enantioselectivity. Further reduction of the catalyst load to 2 mol% or 1 mol% led to a decline of reactivity, but little change in enantioselectivity and diastereoselectivity (Table 1, entries 20 and 21). For operational perspectives, we decided to use 5 mol% or 10 mol% of catalyst **2a** to explore the scope of the reaction.

With the optimal reaction conditions, we screened some unmodified aldehydes or ketones that could participate in the *anti*-Mannich-type reaction with α-imino ester. As shown in Table 2, all the aldehydes gave high yields (84–94%), excellent diastereoselectivity (86–98% *de*), and enantioselectivity (> 96% *ee*) (Table 2, entries 1–7) at −20 °C and in a short reaction time, except for cyclohexanecarboxaldehyde (Table 2, entry 8). Even the hindered isovaleraldehyde reacted rapidly at the same conditions (Table 2, entry 7). However, the reaction time for isobutyraldehyde had to be prolonged to 19.5 h at −20 °C (Table 2, entry 2).

When cyclic ketones were used as substrates to react with α-imino ester, moderate to good yields were obtained except cyclopentanone (Table 2, entries 9–13). In the case of cyclopentanone, only little of the desired product was observed after 3 d (Table 2, entry 10). Cyclohexanone gave the desired product with excellent diastereoselectivity (96% *de*) and enantioselectivity (> 99% *ee*) at −20 °C after 12 h (Table 2, entry 9). Other cyclic ketones gave moderate yields, moderate to excellent diastereoselectivity and enantioselectivity at 0 °C or room temperature (Table 2, entries 11–13).

In the cases of unsymmetrical ketone substrates, such as methyl ethyl ketone and methyl propyl ketone, the reaction occurred predominantly at the more substituted α-position of the ketones (Table 2, entries 14 and 15). Methyl ethyl ketone gave products **8a** and **8b** with good regioselectivity (9:1) and excellent enantioselectivity(*anti* up to 98% *ee*), while methyl propyl ketone gave products **9a** and **9b** with

Table 2. Scope of the *anti*-Mannich-type reaction of unmodified aldehydes or ketones catalyzed by **2a**.



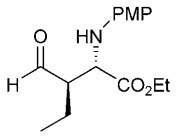
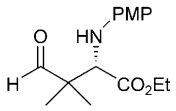
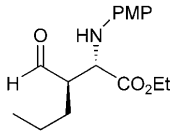
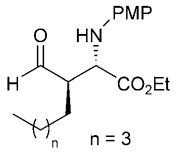
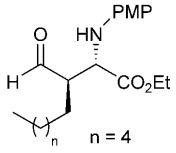
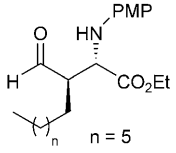
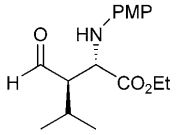
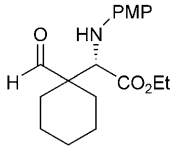
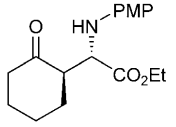
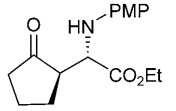
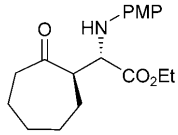
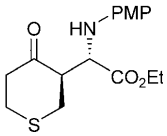
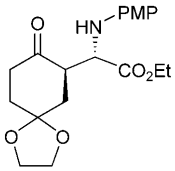
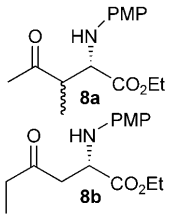
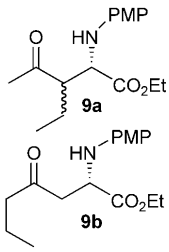
Entry[a]	Product	Temp. [°C]	Time	Yield[b] [%]	*anti*:*syn*[c]	*ee*% (*anti*)[c]
1		−20	2 h	93	96/4	>99
2		−20	19.5 h	85	–	96
3		−20	20 min	84	93/7	>99
4		−20	20 min	87	97/3	>99
5		-20	20 min	93	>99/1	>99
6		−20	8 min	93	95/5	>99
7[d]		−20	30 min	94	93/7	>99
8		0	48 h	66	–	96
9		−20	12 h	87	98/2	>99
10		14	72 h	nd		
11		14	24 h	63	3/1	94 (*anti*), 43 (*syn*)

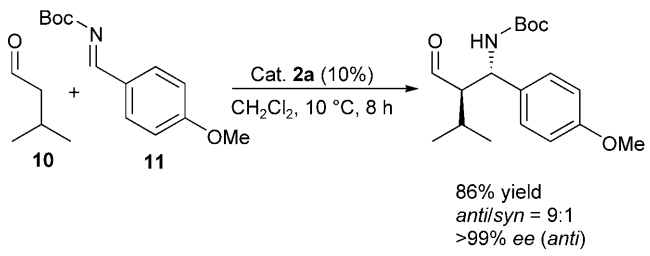
Table 2. (Continued)

Entry[a]	Product	Temp. [°C]	Time	Yield[b] [%]	*anti*:*syn*[c]	*ee*% (*anti*)[c]
12		0	24 h	70	96/4	97
13		0	72 h	75	91/9	81.5
14[e]		0	18 h	78	*dr* = 55/45, *rr* = 9/1, (**8a**:**8b**)	98 (*anti*), 97 (*syn*)
15[e]		0	23 h	75	*dr* = 62/38, *rr* = 77/23, (**9a**:**9b**)	97 (*anti*), 93 (*syn*)

[a] Unless specified, reactions conducted on a 0.2-mmol scale α-imino ester in CH_2ClCH_2Cl (1.5 mL) with aldehyde (1.0 mmol, 5 equiv.) or ketone (2.0 mmol, 10 equiv.) in the presence of 5 mol% or 10 mol% **2a**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] When the isovaleraldehyde was reduced to 0.50 mmol (2.0 equiv.), the product was obtained in 82% yield with the same diastereoselectivity and enantioselectivity after 4 h.
[e] The *rr* value was determined by ^{1}H NMR and chiral HPLC analysis.

modest regioselectivity (77:23) and high enantioselectivities (*anti* up to 97% *ee*).

The asymmetric Mannich reaction between isovaleraldehyde (**10**) and *N*-Boc-protected imine (**11**) using **2a** as catalyst was also investigated. As shown in Scheme 1, the *anti*-Mannich adduct was obtained in 86% yield with good diastereoselectivity (*anti*/*syn* = 9:1) and excellent enantioselectivity (>99% *ee* for *anti*).



Scheme 1.

The achievement of high stereoselectivity may be explained by the transition state model originally proposed by Barbas.[5b] As shown in Figure 2, the bulky group (-CH_2OTBDPS) should effectively shield the *re*-face of an enamine double bond, and make the *si*-face available for attack to give the observed major enantiomer. The hydrogen bonding between the both thiourea protons and the imine nitrogen may serve to activate the imine effectively and stabilize the transition state.

In conclusion, for the first time a chiral secondary amine-thiourea organocatalyst, 4-aminothiourea prolinol *tert*-butyldiphenylsilyl ether, has been applied successfully to the *anti*-selective direct asymmetric Mannich reaction of unmodified aldehydes or ketones to the α-imino ester. The reaction gave the corresponding products in moderate to high yields (up to 94%), excellent diastereoselectivity (up to >98% *de*) and enantioselectivities (up to >99% *ee*). Further applications of the present bifunctional thiourea catalysts in

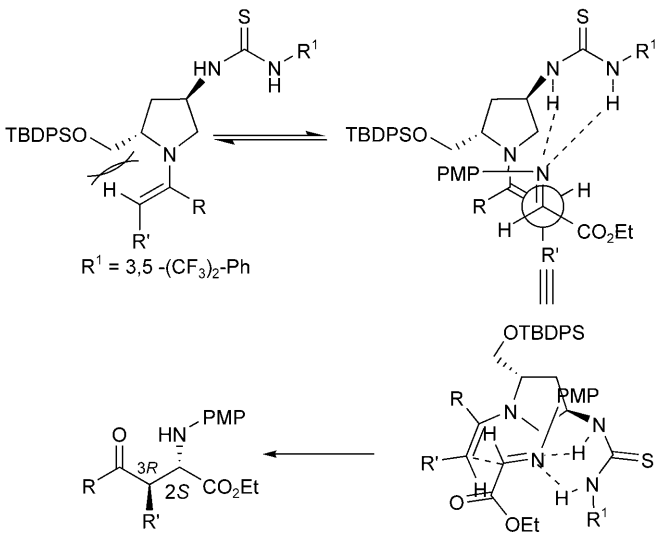


Figure 2. Proposed transition state model.

other catalytic asymmetric reactions are ongoing in our laboratory.

Experimental Section

General Procedure for the Mannich-Type Reactions between *N*-PMP Protected α-Imino Ethylglyoxylate and Aldehydes or Ketones Donors Catalyzed by 2a

N-PMP-protected α-imino ethyl glyoxylate (0.2 mmol, 1 equiv.) was dissolved in anhydrous CH_2ClCH_2Cl (1.5 mL) and an aldehyde (1.0 mmol, 5 equiv.) or a ketone (2.0 mmol, 10 equiv.) was added, followed by catalyst **2a** (0.01 mmol, 0.05 equiv. or 0.02 mmol, 0.10 equiv.). The mixture was stirred at a given temperature for a given time (see Table 2); Disappearance of the imine in the reaction mixture was monitored by TLC. At the end of the reaction, the mixture was quenched with aqueous saturated ammonium chloride solution and extracted with AcOEt (three or four times). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography (5–10% AcOEt/PE) to afford the corresponding Mannich addition product. The *ee* and *dr* of all products were determined by chiral-phase HPLC analysis.

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