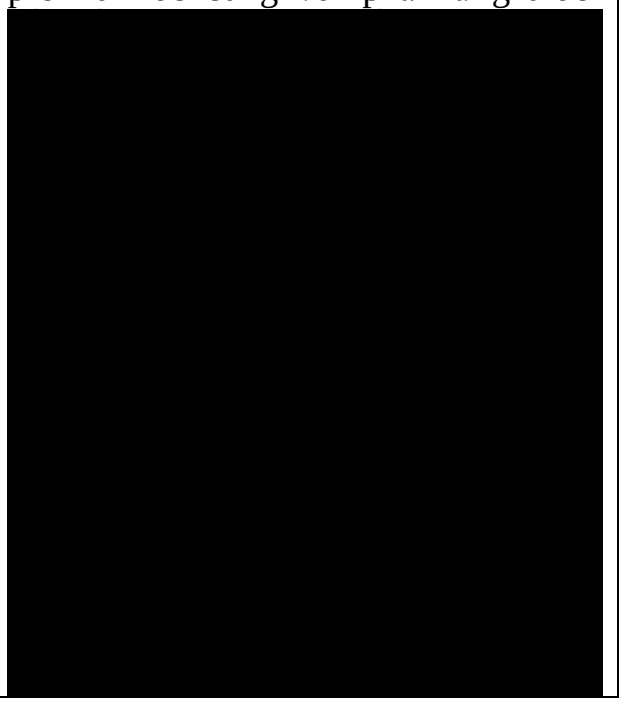
Proline-threonine dipeptide as an organocatalyst for the direct asymmetric aldol reaction 7h 13	Proline-threonine dipeptide với vai trò là chất xúc tác hữu cơ cho phản ứng aldol bất đối xứng trực tiếp
1. Introduction	1.Giới thiệu
L-Proline and several derivatives of this small amino acid have proven to be useful organocatalyst for metal-free	Người ta đã chứng minh rằng L-Proline và một số dẫn xuất của axit amin nhỏ này là chất xúc tác hữu cơ có ích cho

aldol reactions.1-3 For the proline-catalyzed reaction, the acidic proton of the carboxylic acid group is crucial for the stereoselectivity and reactivity. Based on transition state model studies most of the proline derivatives, for example, triazoles, tetrazoles, and sulfonamides, developed have been holding this acidic proton.3 However, in simple L-prolinamide, the acidic nature of the -CONH proton is less, therefore it is ineffective catalyst for the aldol rection.1c To overcome this problem various prolinamide derivatives including di- and tri-peptides have been developed.4 Particularly, prolina- mides with a terminal hydroxyl group have received significant interest compared to other derivatives due to the improved hydrogen bond donor character of the hydroxyl group. However, prolinamide derivatives containing a free carboxyl group (C-terminal) are less explored for asymmetric direct aldol reactions.5 Therefore, in continuation of our interest in organocatalysis,3a6 we became interested in a dipeptide prolinamide with a terminal carboxylic acid group catalyzed asymmetric aldol reaction. For this purpose, we chose a dipeptide derived from proline and threonine. We envisaged that the free -OH and -COOH groups on threonine after peptidation with proline would provide an additional push in the catalytic aldol process. Earlier attempts were made using a pro- line-threonine catalyst with free hydroxyl group while blocking the carboxylic acid as an ester for aldol reaction.7 We were interested in preparing the dipeptide with silyl protection on the hydroxyl group while keeping free the -COOH group as in natural proline, thus deriving the dual

các phản ứng aldol không có kim loại.1-3 Đối với phản ứng xúc tác bằng proline, proton axit của nhóm axit cacboxylic quyết định tính chọn lọc lập thể và mức độ phản ứng. Dựa trên các nghiên cứu về mô hình trạng thái chuyển tiếp, đa số các dẫn xuất proline được sản xuất, ví dụ, triazoles, tetrazoles, và sulfonamides đều giữ proton axit này.3 Tuy nhiên, trong L-prolinamide đơn giản, bản chất axit của proton –CONH ít, do đó nó không phải là chất xúc tác hiệu quả cho phản ứng aldol.1c Để khắc phục vấn đề này, người ta đã điều chế các dẫn xuất prolinamide khác nhau bao gồm di- và tri-peptide. 4 Đặc biệt, các prolina-mide với nhóm hydroxyl (ở một đầu cuối) rất được chú trọng hơn so với các dẫn xuất khác do khả năng cho liên kết hydro tốt hơn của nhóm hydroxyl. Tuy nhiên, các dẫn xuất prolinamide chứa nhóm carboxyl tự do (đầu C) ít được khai thác cho các phản ứng aldol trực tiếp bất đối xứng.5 Do đó, để tiếp nối hướng nghiên cứu về chất xúc tác hữu cơ, 3a6 chúng ta xét dipeptide prolinamide cùng với phản ứng aldol



advantages of selectivity and reactivity.8 Hence, herein we report prolinamide with terminal carbox- ylic acid group (H-Pro-Thr-OH), derived from proline and threonine, catalyzed asymmetric direct aldol reaction of various aldehydes with acetone (Scheme 1).

Scheme 1. Direct asymmetric aldol reaction catalyzed by proline-threonine dipeptide (H-Pro-Thr-OH) 1.

2. Results and discussion

The dipeptide catalyst 1 chosen for the asymmetric aldol reaction was synthesized in five steps starting from proline (Scheme 2). The coupling of Cbz-protected proline9 3 with threonine benzyl ester85 4 was achieved under standard EDCI, HOBt coupling conditions. After obtaining the dipeptide 5, the free hydroxyl group was protected as TBS ether 6 followed by hydrogenolysis to afford the required prolinamide-based dipeptide 1 with a terminal free car- boxylic acid group.

Initially, the aldol reaction of 4-nitro benzaldehyde 7a with acetone 8a was investigated using the above dipeptide catalyst 1 (20 mol %) at room temperature. The reaction was complete in 1 h and provided the expected product 9a in 70% yield with 75% ee (Table 1, entry 1). To check the effect of various solvents for better yield and selectivities, the same reaction was tested in different solvents and the

results are summarized in Table 1. Among the solvents screened, CHCl3 was found to be the best solvent, giving the product in 91% yield with 82% enantiomeric excess (Table 1, entry 9). Much improvement is not there in either the yield or the enantioselectivity when decreasing the reaction temperature to 0 °C (Table 1, entry 10). The enantioselectivity of this substrate in the case of known catalyst prolinamide with free terminal hydroxyl group (H-Pro-Thr-OMe) was 69%.7 Encouraged by this result, we planned to expand the generality of this dipeptide catalyst with a free terminal acid group (H-Pro-Thr-OH) 1 using the reaction of various aldehydes with acetone.

Table 1
Effect of solvents
a Isolated yields after column chromatography. b Reactions performed at 0 ”C. c ee% calculated by using chiral HPLC.

Accordingly, the reaction of acetone 8a (aldol donor) with a variety of aldehydes including aromatic and aliphatic ones was investigated using organocatalyst 1 under optimal conditions. The results are summarized in Table 2. All the reactions proceeded smoothly with 20 mol% of catalyst in good yields (72-91%) with high enantioselectivities regardless of the nature of the aldehyde.

3. Conclusions

In conclusion, we have developed a proline-threonine dipeptide catalyst with a free terminal acid group (H-Pro-Thr-

Scheme 2. Synthesis of proline-threonine dipeptide 1.

OH) for the direct asymmetric aldol reaction of acetone with various aldehydes. The yields are typically good and the enantioselectivities are high in almost all the cases examined, including those with aromatic and aliphatic aldehydes. The synthetic utility of this dipeptide as an organocatalyst in organic synthesis will be explored to other reactions.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60-120 mesh. IR spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer. Optical rotations were obtained on Perkin Elmer digital polarimeter. 1H and 13C NMR spectra were recorded in CDCl3 and DMSO-d6 solution on a Varian Gemini 200 and Bruc- ker Avance 300. Chemical shifts were reported in parts per million (PPM) with respect to internal TMS. Coupling constants (J) are quoted in hertz. Mass spectra were obtained on an Agilent Technologies SHIMADZU GC/MS, 6510 Q-TOF LC/MS. HPLC was performed on SHIMADZU HPLC using chiral pak IA and eurocel IA columns with isopropyl alcohol and hexane as eluants.

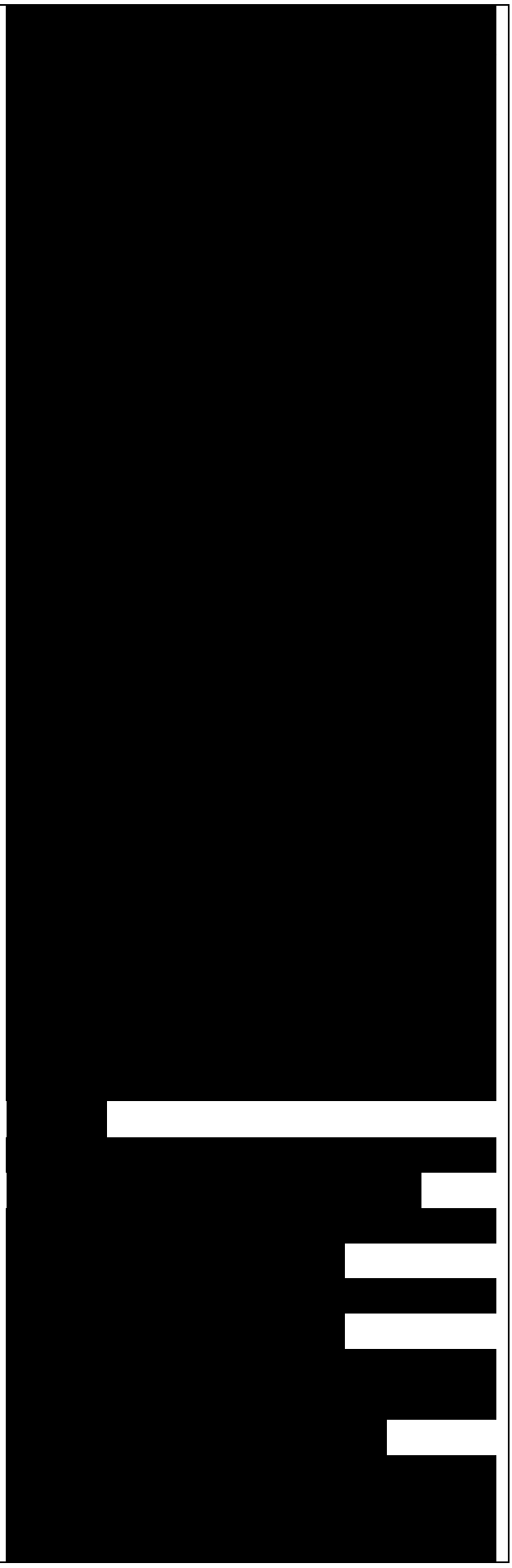
4.1.1. (S)-Benzyl 2-((2R,3S)-1-(benzyloxy)-3-hydroxy-1- oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 5

N-Benzyloxycarbonyl-protected proline 3 (2 g, 7.9 mmol) was dissolved in dry (khô, khan) dichloromethane (10 mL),

after which HOBt (1.28 g, 9.48 mmol) was added and the reaction mixture was stirred for 15 min. The solution was cooled to 0 °C and EDCI (3.02 g, 15.8 mmol) was added. To this solution was added a solution of benzyl ester of threonine 4 (2.55 g, 7.9 mmol) and DIEPA (7.9 mmol, 1.10 mL) dissolved in dry dichloromethane (10 mL) and the mixture was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), water (20 mL) was added, and the two layers were separated. The organic layer was washed with aq ammonium chloride (10 mL) and sodium bicarbonate (15 mL) simultaneously, dried over sodium sulfate, and evaporated in vacuo. The crude product was purified by column chromatography (EtOAc/hexanes, 30:70) to yield the pure dipeptide 5 as a white solid (3.07 g, 92% yield). [a]D5 = -53 (c 1, CHCl3); mp: 175-176 °C; IR (KBr): v 3385, 3319, 2954, 1728, 1662 cm-1; 1H NMR (DMSO-d6, 300 MHz): d 1.02 (dd, J = 37.7, 6.2 Hz, 3H), 1.68-1.88 (m, 1H), 2.06-2.16 (m, 3H), 3.43 (m, 2H), 4.14-4.24 (1H, m), 4.29-4.49 (m, 3H), 4.91-5.19 (m, 6H), 7.21-7.41 (m, 10H), 8.06 (t, J= 8.3 Hz, 1H); 13C NMR (CDCl3, 75 MHz): d 172.8, 172.5,153.9, 153.8, 137.0, 136.9, 135.9, 128.3, 128.3, 128.2, 127.9, 127.7,127.5, 127.4, 126.9, 66.3, 66.1, 65.9, 65.8, 65.9, 65.8, 65.7, 59.3, 58.8, 57.9, 57.8, 47.1, 46.5, 31.1, 29.8, 23.7, 29.8, 23.7, 22.8,

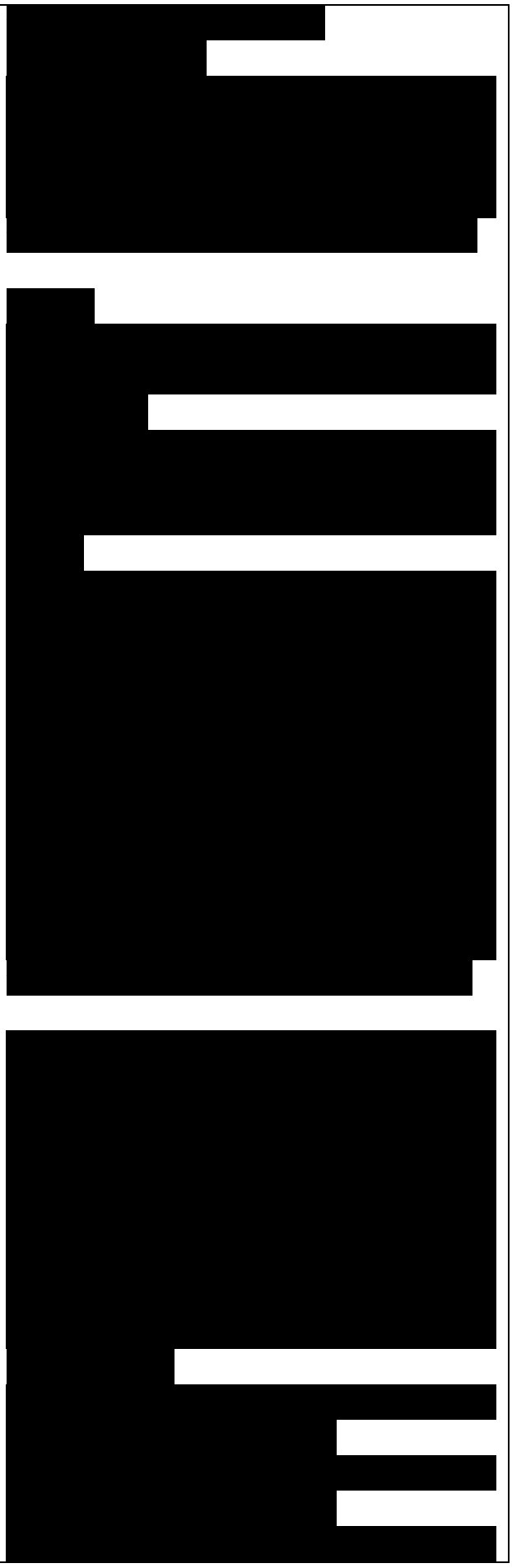
20.1. 20.0; ESIMS (m/z) 441 (M+); HRMS calcd for C24H28N2O6Na 463.1845, found 463.1841.

4.1.2. (S)-Benzyl 2-((2R,3S)-1-(benzyloxy)-3-(tert-butyldimethylsilyloxy)-1-oxobutan-2-



ylcarbamoyl)pyrrolidine-
1- carboxylate 6
To dipeptide 5 (100 mg, 0.23 mmol), dissolved in dry dichloro- methane (2 mL), was added dry dimethyl formamide dropwise until the solution became clear. tert-Butyldimethylsilyl chloride
Table 2
Proline-threonine dipeptide 1 catalyzed aldol reaction of aldehydes with acetone

a Isolated yields after column chromatography. b Reactions performed at 4 °C c ee% calculated by using chiral HPLC.
(44.41 mg, 0.29 mmol) and imidazole (31.3 mg, 0.46 mmol) were then added simultaneously at 0 °C. The solution was stirred for 24 h at room temperature. After completion of the reaction (monitored by TLC), water (2 mL) was added, the two layers were separated, and the aqueous layer was extracted twice with dichloromethane (2 x 3 mL). The combined organic layers were dried over sodium sulfate, concentrated, and the crude product was purified by column chromatography (EtOAc/hexanes: 10/90) to give the product as colorless viscous oil (98 mg, 78%). [a]D5 = -30.4 (c 1, CHCl3); IR (neat): v 2953, 1747, 1691 cm-1; 1H NMR (CDCl3, 300 MHz): d -0.09 to 0.03 (m, 3H), 0.08 (s, 9H), 1.02 (dd, J = 37.9, 6.0 Hz, 3H), 1.72-2.17 (m, 4H), 3.40 (m, 2H), 4.27-4.58 (m, 3H), 4.90-5.17 (m, 4H), 7.26-7.41 (s, 10H), 7.73-7.85 (m, 1H);
13C NMR (CDCl3, 75 MHz): d 172.6, 172.1, 169.9, 154.1, 153.8,
153.6,136.8, 135.4, 128.3, 128.0, 127.9, 127.6, 127.4, 127.3,
126.9,68.1, 66.1, 65.9, 65.8, 65.6, 59.3,



58.7, 57.5, 57.5, 47.0,
46.4, 31.0, 29.4, 25.4,23.7, 22.7, 20.1,19.9,17.5, -4.5, -5.4; ESIMS: (m/z) 555 (M+); HRMS calcd for C30H42N2O6SiNa 577.2709, found 577.2721.

4.1.3. (2R,3S)-3-(tert-Butyldimethylsilyloxy)-2-(S)-pyrrolidine- 2-carboxamido)butanoic acid 1

The TBS-protected peptide 6 (500 mg, 0.90 mmol) was dissolved in methanol (5 mL), after which 20% Pd(OH)2/C (50 mg) was added and the reaction mixture was stirred for 24 h at room temperature under a hydrogen atmosphere. The reaction mass was filtered through Celite, washed with methanol (2 x 3 mL), and evaporated in vacuo. The crude product was recrystallized from ether to obtain the dipeptide organocatalyst 1 (74% yield, 218 mg);

[a] D5 = —21.1 (c 0.5, MeOH); mp: 227-228 °C; IR (KBr, thinfilm): v 3430, 3271, 2933, 1679, 1586, 1389 cm-1; 1H NMR (CD3OD, 300 MHz): d 0.07 (s, 6H), 0.74 (s, 9H), 1.01 (d, J = 6.2 Hz, 3H), 1.791.96 (m, 2H), 1.94-2.07 (m, 1H), 2.30-2.24 (m, 1H), 3.07-3.24 (m, 3H), 4.07-4.11 (d, J = 2.2 Hz, 1H), 4.18-4.24 (dd, J= 8.4, 6.4 Hz, 1h), 4.32-4.40 (m, 1H). 13C NMR (CD3OD, 75 MHz): d 175.7, 175.5,
170.7,70.7, 61.7, 61.2, 47.5, 31.1, 26.4, 26.2, 25.3, 22.0, 19.0, -3.56, -4.37, -4.47, -5.69; ESIMS: (m/z) 331 (M+); HRMS calcd for 331.2053 C15H31N2O4SiNa, found 331.2068.

4.1.4. Representative procedure for the aldol reaction

To a stirred solution of catalyst 1 (20

mol %) in chloroform (2 mL), was added acetone (4 mmol) and then stirred for 15 min. After this time, aldehyde (1 mmol) was added and stirring was continued for a given time (Table 2) at room temperature. After completion of the reaction, (monitored by TLC), water was added and extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over sodium sulfate and evaporated in vacuo. The crude product was purified by silicagel column chromatography to afford the pure product.

4.1.4.1. (R)-4-(2-Fluorophenyl)-4-hydroxybutan-2-one 9f. Colorless oil, [a]D5 = +65.9 (c 1, CHCl3); IR (neat): v 3417, 2923, 1636, 769 cm-1; 1H NMR (CDCl3, 300 MHz): d 2.19 (s, 3H), 2.83-2.89 (m, 2H), 3.69 (d, J = 3.7 Hz, 1H), 5.39-5.46 (m, 1H), 6.96-7.04 (1H, m), 7.12-7.18 (m, 1H), 7.21-7.29 (m, 1H), 7.497.56 (m, 1H); 13C NMR (CDCl3, 75 MHz): d 30.4, 50.3, 63.9, 114.8,115.1, 124.2, 127.1, 127.2, 128.7, 128.8, 129.5, 129.7,

157.5,160.7, 208.9; ESIMS: (m/z) 205 (M+Na+); HRMS calcd for 182.0743 C10H11FO2, found 182.0740. Enantiomeric excess: 80%, determined by HPLC analysis using chiral pak 250 x 4.61, column (isopropanol/hexanes 05:95), UV , 210 nm, flow rate 1.0ml/min, , major isomer tR 7.39 min, tR minor isomer 8.23; IR, 1H, 13C NMR and mass spectral data of the known products 9a and 9b,6c 9c to 9e,4f 9g,10 9h,6c 9i to 9k4f were identical with the reported data.

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~~Chiral phosphinothiourea organocatalyst in the enantioselective Morita- Baylis-Hillman reactions of aromatic aldehydes with methyl vinyl ketone~~ Đã dịch trong song ngữ 2 (bị trùng)

The Morita-Baylis-Hillman (MBH) reaction is a powerful tool for the atom-economic construction of densely functionlized a- methylene-p-hydroxycarbonyl derivatives which serve as valuable building blocks in organic synthesis.1 The development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years.2 Various chiral organocatalysts including quinidine-derived p-isocupreidine,3 BINOL-derived Brensted acid,4 and bifunctional aminothiourea5 have been notably developed for the asymmetric MBH reaction to achieve high enantiomeric excesses. Bis(thio)ureas derived from chiral trans-1,2-diaminocyclo- hexane, isophorone-diamine (IPDA), and H8-BINAM were also proven to be efficient organocatalysts for the asymmetric MBH reactions of various aldehydes with 2-cyclohexen-1-one as described by Nagasawa, Berkessel and Shi, respectively.6 However, Morita-Baylis-Hillman reactions involving methyl vinyl ketone (MVK) as reaction partner usually afforded the corresponding products in moderate enantioselectivities.2,7 To the best of our knowledge, the highest enantioselectivity of this kind of MBH reaction was 83% ee using chiral tertiary amine/proline cocatalysts.7d
Cyclohexane-based aminothiourea has been extensively studied in recent years as a bifunctional organocatalyst for

asymmetric catalysis.8 In 2004, Yudin and co-workers reported cyclohexane-based iminophosphines derived from the ring-opening of aziridine for transition metal catalysis.9 Due to the structural analogy between aminothiourea and iminophosphine, we envisioned that the overlapped structure, that is, phosphinothiourea (Fig. 1), could serve as a new class of bifunctional organocatalysts for enantiose- lective catalysis. As tertiary phosphines are effective catalysts for the MBH reaction, it is conceivable that the phosphinothiourea could catalyze this reaction in an enantioselective fashion.

The bifunctional phosphinothiourea was not documented before for asymmetric catalysis until recently Shi and Shi10 reported the BINOL-derived phosphinothioureas as organocatalysts in the

Figure 1. Overlap approach to design new catalyst.

presence of carboxylic acid as co-catalyst for the asymmetric aza-Morita-Baylis-Hillman reaction. However, the reaction usually takes a long time. Herein, we report a new class of phosphinothiourea organocatalysts, derived from trans-2-amino- 1-(diphenylphosphino)cyclohexane (1),11 which are fairly effective bifunctional organocatalysts for the enantioselective MBH reaction of arylaldehydes with MVK to give the corresponding adducts in up to 94% ee and good to excellent yields.

The organocatalysts 2a-f12 are easily prepared by condensation of (R,R)-2-amino-1-(diphenylphosphino)cyclohexane (1) with 1.1 equiv of the corresponding

iso(thio)cyanate or isocyanate under mild conditions (Fig. 2, see Supplementary data).

We initially chose the reaction of MVK with p-nitrobenzalde- hyde to screen the phosphinothioureas as bifunctional organocat- alysts for the MBH reaction. To our delight, when using CH2Cl2 as solvent, the reaction completed in 45 min with catalyst 2a to provide the desired MBH product in 71% yield and 85% ee (Table 1, entry 3). Longer reaction time afforded lower chemical yield due

Table 1
Screening of the catalysts for the reaction of MVK and 4-nitrobenzaldehydea

a Unless stated otherwise, the reactions were conducted with 10 mol % of organocatalyst, 5 equiv of MVK in CH2Cl2 (0.2 M) at 13 °C.

b Isolated yields. c Determined by chiral HPLC. d 5 mol % 2a was used. e Not determined.

to the over reaction with MVK (entries 4 and 5 vs 3). The thiourea moiety proved to be critical for the MBH reaction in terms of both yield and enantioselectivity. Urea derivative 2b was ineffective under identical conditions (entry 7). Surprisingly, catalyst 2c gave poor enantioselectivity, albeit with high yield (entry 8). Substitution at the 4-position of phenyl has no obvious effect on the enanti- oselectivity (entries 3, 9, and 10). Bearing an alkyl group, the phosphinothiourea 2f afforded good level of enantioselectivity, but low yield (entry 11).

Further optimization including various solvents, temperature, and substrate concentration in the presence of catalyst

2a led to the optimal reaction conditions (see Supplementary data): using 2a as catalyst, the reaction of 5 equiv of MVK with 0.3 M of p-nitro- benzaldehyde in $CHCl_3$ completed in 15 min at 13 °C to provide the desired product in 75% yield and 94% ee.

Under the optimized conditions, the substrate scope in terms of aromatic aldehydes was first investigated. As indicated in Table 2, reaction of MVK with strong electron-deficient aldehydes usually proceeded very quickly (within 1 h) to provide the desired

Table 2

MBH reactions of MVK with aromatic aldehydes catalyzed by 2aa

c The ee was determined by chiral HPLC, and the absolute configuration was determined by comparison of optical rotation with that of literature report.7c,13

Figure 3. Proposed transition state.

products in very good yields and excellent enantioselectivities (90-94% ee, entries 1-5). Both mono- and di-halogen substituted arylaldehydes are tolerated to generate the products in high enantioselectivities (87-92% ee) albeit with moderate yields (entries 6-9). The reactions with non-substituted benzaldehyde and 2-naphthylaldehyde proceeded slowly to afford the product in high enantioselecitvity (90% ee), but low yields (entries 10 and

11) . As a general trend, the reaction with electron-rich arylalde- hyde proved to be difficult and complex mixture was observed.

The observed absolute configuration could be explained by the plausible transition state illustrated in Figure 3. The thiourea moiety forms hydrogen-bond with the aldehyde carbonyl. The

cyclo- hexyl scaffold forces the phosphinoyl associated enolate to attack the activated carbonyl from the si-face to generate the R configuration. In summary, we have developed a highly enantioselective Mori- ta-Baylis-Hillman reaction involving the addition of MVK to aromatic aldehydes catalyzed by a phosphinothiourea organocata- lyst derived from trans-2-amino-1-(diphenylphosphino)cyclohex- ane. The reaction proceeds under very mild conditions to afford the desired product in a short time period in good to excellent yields with generally excellent enantiomeric excesses (87-94% ee). Further efforts are underway with a focus on improving the catalyst activity and the scope of substrate as well as the mechanism of the asymmetric MBH reaction.	