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PAPER

Enantioselective Morita–Baylis–Hillman reaction promoted by L-threonine-derived phosphine–thiourea catalysts†

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A series of bifunctional phosphine–thiourea organic catalysts based on natural amino acid scaffolds were designed and prepared. L-Threonine-derived bifunctional phosphine catalysts were found to be very efficient in promoting asymmetric Morita–Baylis–Hillman (MBH) reaction of acrylates with aromatic aldehydes, affording the desired MBH adducts with up to 90% ee. To gain mechanistic insights into the reaction, the effects of adding various additives on the MBH reaction were investigated. We propose that the hydrogen bonding interactions between the thiourea moiety of the catalyst and the enolate intermediate are crucial for the stereochemical outcome of the reaction. The method described in this report may provide a practical solution to the enantioselective MBH reaction of simple acrylates.

Introduction

Trivalent phosphines, traditionally utilized as ligands in transition metal mediated processes, have recently emerged as versatile Lewis base catalysts in synthetic organic chemistry.[1] As a significant complement to the amine-based catalysts, phosphines often display remarkable and unique properties in nucleophilic catalysis due to their weaker basicity and stronger nucleophilicity. Compared with the extensive studies carried out on phosphine-triggered organic transformations, the development of efficient and versatile chiral phosphine catalysts and their applications in enantioselective organic reactions remain a less-explored research area.[2] As part of our continuous efforts toward the evolution of amino acid-derived organic catalysts for enantioselective organic transformations,[3] we recently embarked on an exciting journey of exploring novel bifunctional chiral phosphines derived from amino acid structural scaffolds (Fig. 1). We showed that novel chiral phosphines bearing dipeptidic backbones could efficiently promote the enantioselective [3 + 2] cycloaddition of allenoates with acrylates, affording functionalized cyclopentenes in excellent chemical yields and with very high enantioselectivities.[2p] Subsequently, we demonstrated acrylamides were suitable substrates in asymmetric [3 + 2] cycloaddition.[2q] Very recently, we derived a series of phosphine–sulfonamide bifunctional catalysts and demonstrated their effectiveness in the enantioselective aza-Morita–Baylis–Hillman (MBH) reaction.[3l] It is thus highly desirable to further extend the utility of amino acid-based phosphine catalysts to other important organic reactions.

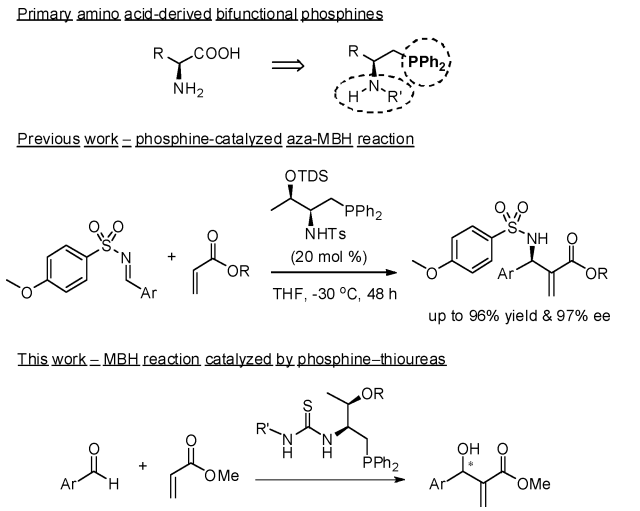

Fig. 1 Applications of amino acid-derived bifunctional phosphines in (aza)-MBH reactions.

The MBH reaction is one of the most valuable carbon–carbon bond-forming reactions, which provides easy access to heavily functionalized and synthetically useful MBH adducts from readily available activated olefins and aldehydes.[4] In the past decade, the development of enantioselective versions of MBH reactions has received increasing attention from the synthetic community. Among the activated alkenes suitable for MBH reactions, enones are most commonly employed; a number of elegant asymmetric MBH reactions between enones and aldehydes have been developed in the past few years.[5] On the other hand, examples using acrylates as a reaction partner in highly enantioselective MBH reactions are very limited.[6] In 1999, Hatakeyama and

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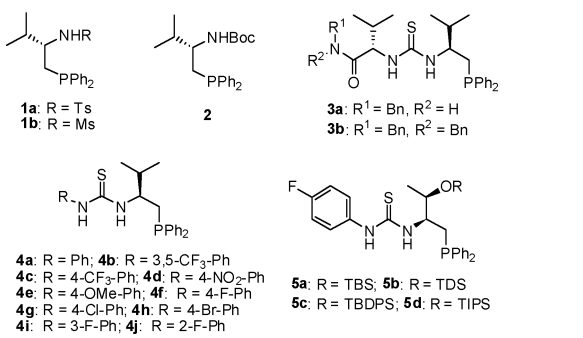
co-workers disclosed a highly enantioselective MBH reaction between hexafluoroisopropyl acrylate (HFIPA) and aldehydes, catalyzed by a novel quinine-derived β-isocupreidine (β-ICD).[7] Although HFIPA had to be employed, and the chemical yields were modest in many cases, nevertheless, the Hatakeyama method represented a breakthrough in the field; highly enantioselective MBH reaction of acrylates was shown to be feasible.[8] Recently, there have been a few reports on organocatalytic enantioselective MBH reactions between aldehydes and acrylates.[9] These methods, however, suffered from limited substrate scope, moderate yields or low enantioselectivities. There clearly exists a need for an enantioselective MBH reaction in which simple acrylates can be used directly. Herein, we describe the development of amino acid-derived phosphine–thiourea catalysts, and their applications in enantioselective MBH reaction between aromatic aldehydes and simple acrylates.

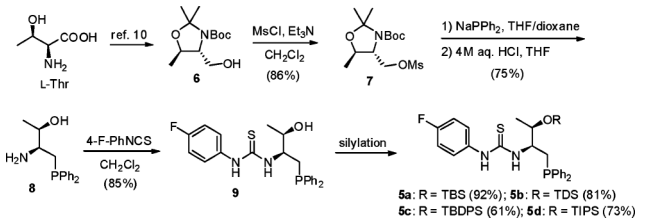
Results and discussion

Amino acids serve as an excellent starting point for derivatizing various bifunctional chiral phosphine catalysts. The phosphine group in the catalysts is derived from the carboxylic acid *via* simple functional group transformations. Moreover, the presence of a neighbouring primary alkyl carbon makes the phosphorus center highly nucleophilic, as we demonstrated in our previous reports.[2p,q,3l] By installing different Brønsted acid moieties at the amino sites, and selecting valine or threonine as the chiral backbone, a number of bifunctional phosphine catalysts were prepared (Scheme 1). We chose to prepare L-threonine-based phosphine catalysts, since the effectiveness of the threonine motif in stereochemical control has been amply demonstrated by us.[2p,q,3b–d,3g,3l] The isopropyl group in valine serves as a convenient gauge for evaluating steric effects in the asymmetric induction, and the preparation of valine-based catalysts is also more straightforward.



Scheme 1 Amino acid-derived bifunctional phosphines.

Preparation of bifunctional phosphine–thiourea catalysts from L-threonine is illustrated in Scheme 2. Following the literature procedure,[10] threonine was protected as an oxazolidine **6**. The hydroxy group was converted to a mesylate, and a substitution reaction with $NaPPh_2$ introduced the phosphine moiety into the catalyst. Acidic treatment yielded phosphine **8** with the free amino group, which smoothly reacted with thioisocyanate to afford the advanced intermediate **9**. Finally, silylation gave phosphine–thiourea catalysts **5a** to **5d**. It is noteworthy that the above phosphine catalysts and phosphorus-containing synthetic

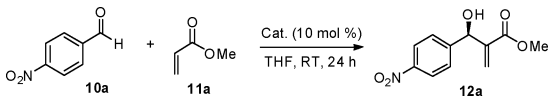


Scheme 2 Preparation of L-threonine-derived phosphine–thiourea catalysts.

intermediates are stable in the air at room temperature, and have a shelf life of at least a few months.

The MBH reaction between *p*-nitrobenzaldehyde and methyl acrylate was chosen as a model reaction to evaluate the effectiveness of our phosphine catalysts (Table 1). L-Valine-based bifunctional phosphines with different Brønsted acid moieties were tested first to establish the influence of Brønsted acids on the reaction. Phosphine–sulfonamides **1a** and **1b** displayed high reactivity, however, the enantioselectivity was disappointing (entries 1–2). Phosphine **2** containing a Boc group led to the formation of the desired product with moderate ee (entry 3). Dipeptide-derived phosphine–thioureas **3a** and **3b** turned out to be quite good catalysts, and the MBH adducts were formed in high yields and with good enantioselectivities (entries 4–5). The thiourea moieties in the catalysts seemed important in the asymmetric induction, thus, a number of phosphines bearing different aryl thioureas (catalysts **4a–4j**) were next prepared and screened (entries 6–15), and it was found the *p*-F-phenyl-thiourea moiety was most efficient in chiral induction (entry 11, 85% yield, 83% ee). Having established the importance of steric effects in

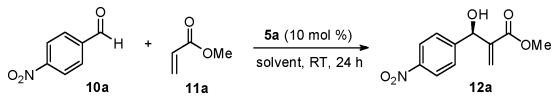
Table 1 Screening of amino acid-based bifunctional phosphines in the MBH reaction[a]



Entry	Cat.	Yield (%)[b]	ee (%)[c]
1	**1a**	88	40
2	**1b**	92	37
3	**2**	67	53
4	**3a**	85	79
5	**3b**	70	72
6	**4a**	89	80
7	**4b**	90	76
8	**4c**	83	80
9	**4d**	80	77
10	**4e**	84	77
11	**4f**	85	83
12	**4g**	88	79
13	**4h**	91	78
14	**4i**	78	77
15	**4j**	81	69
16	**5a**	90	85
17	**5b**	78	85
18	**5c**	88	84
19	**5d**	79	84

[a] The reaction was performed with **10a** (0.1 mmol), **11a** (0.15 mmol) and the catalyst (0.01 mmol) in anhydrous THF (0.2 mL) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

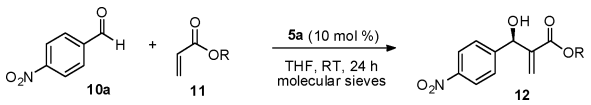
Table 2 Solvent screening for **5a**-catalyzed MBH reaction[a]



Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF	90	85
2	1,4-Dioxane	88	82
3	Toluene	49	65
4	CH_2Cl_2	45	42
5	Ether	48	61
6	CH_3CN	25	45
7	DMSO	24	45
8	DMF	32	51
9	MeOH	36	13
10	THF/H_2O (4/1)	15	39
11[d]	THF	85	87
12[e]	THF	92	87
13[f]	THF	84	86

[a] The reaction was performed with **10a** (0.1 mmol), **11a** (0.15 mmol) and **5a** (0.01 mmol) in anhydrous THF (0.2 mL) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 0.4 mL THF was used. [e] 4 Å molecular sieves were added. [f] The reaction was performed at 10 °C for 72 h.

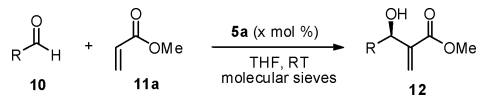
Table 3 Employment of different acrylates in the MBH reaction[a]



Entry	R	Yield (%)[b]	ee (%)[c]
1	Me	92	87
2	Et	92	85
3	Bn	94	84
4	*t*-Bu	84	82
5	Ph	*trace*	—[d]
6	1-naphthyl	32	11

[a] The reaction was performed with **10a** (0.1 mmol), **11a** (0.15 mmol) and **5a** (0.01 mmol) in anhydrous THF (0.4 mL) containing 4 Å molecular sieves (50 mg) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Not determined.

Table 4 Substrate scope of **5a**-catalyzed MBH reaction[a]



Entry	x	*t* (h)	Product (R)	Yield (%)[b]	ee (%)[c]
1	10	24	**12b** (3-NO_2-Ph)	84	85
2	10	24	**12c** (2-NO_2-Ph)	91	69
3	10	36	**12d** (4-CN-Ph)	92	87
4	10	36	**12e** (3-CN-Ph)	89	85
5	10	40	**12f** (4-CF_3-Ph)	80	87
6	10	40	**12g** (3,5-CF_3-Ph)	74	84
7	10	40	**12h** (3-NO_2-2-Cl-Ph)	89	85
8	20	60	**12i** (4-F-Ph)	72	81
9	20	60	**12j** (4-Cl-Ph)	67	84
10	20	60	**12k** (3-Cl-Ph)	63	82
11	20	60	**12l** (4-Br-Ph)	73	83
12	20	60	**12m** (3-Br-Ph)	77	84
13	20	72	**12n** (Ph)	43	80
14	20	96	**12o** (4-Me-Ph)	25	76
15	20	96	**12p** (3-Me-Ph)	27	77
16	20	72	**12q** (2-naphthyl)	53	90
17	20	72	**12r** (3-pyridine)	87	84
18	20	72	**12s** (2-thiophenyl)	52	70
19	20	96	**12t** (CH_2Ph)	—[d]	—

[a] The reaction was performed with **10** (0.1 mmol), **11a** (0.15 mmol for entries 1–7 and 0.2 mmol for entries 8–19) and **5a** in anhydrous THF (0.4 mL for entries 1–12 and 0.2 mL for entries 13–19) containing 4 Å molecular sieves under N_2 at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] No reaction.

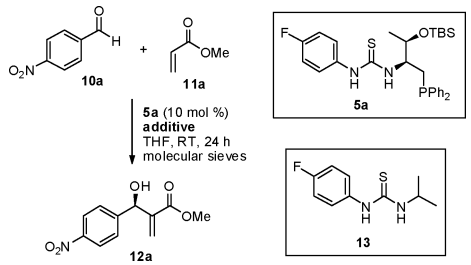
asymmetric induction with valine-derived phosphines, we then focused on derivatization of phosphine–thiourea catalysts (**5a–5d**) based on threonine backbone. Very similar reactivities and selectivities were observed with different silyloxy groups (entries 16–19); the catalyst with the TBS group (**5a**) was chosen for further studies as it gave slightly better results than the other silyloxy-containing catalysts, and its preparation was more economical.

The influence of different solvents on **5a**-catalyzed MBH reaction was next investigated, and the results are summarized in Table 2. 1,4-Dioxane was found to be a suitable solvent, offering slightly inferior results to those obtained with THF (entry 2). All the other common organic solvents were shown to be unsuitable, affording products in low yields and with poor enantioselectivities (entries 3–8). A protic solvent, *e.g.* methanol, proved to be an extremely poor medium, and the desired MBH adduct was obtained in 36% yield and with only 13% ee (entry 9). This result seemed to suggest hydrogen bonding interactions might be very important in stereochemical control, as methanol likely disrupted such key interactions. When a THF/water solvent pair was employed, a very low yield and poor enantioselectivity were observed, contrasting with the excellent results attainable using THF alone as the solvent. Under the optimized reaction conditions in which molecular sieves were added, the MBH adduct was obtained in 92% yield and 87% ee (entry 12).

With the best catalyst and the most appropriate solvent in hand, we next examined different acrylates in the **5a**-catalyzed MBH reaction (Table 3). Simple alkyl acrylates gave best results, excellent yields and enantioselectivities were attainable (entries 1–4); the enantioselectivity seemed to be dependent on the steric hindrance of the ester group, and the most sterically hindered *t*-butyl acrylate led to decreased enantioselectivity compared with less hindered acrylates. The aryl acrylates, on the other hand, were found to be unsuitable for the reaction (entries 5–6).

The substrate scope for **5a**-catalyzed MBH reactions was next investigated (Table 4). The reaction is applicable to aromatic aldehydes with various electron-withdrawing groups at different positions of the aryl ring, and high yields and enantioselectivities were generally attainable (entries 1–7). In contrast to the related examples in the literature in which virtually only electron-poor aldehydes could be utilized,[7–9] our reaction was applicable to a wide range of aryl aldehydes. The reaction worked well for the halogenated aromatic aldehydes and benzaldehyde, and consistently high enantioselectivities were achieved (entries 8–13). Moreover, electron-rich aromatic aldehydes could be employed as well, and the reactions proceeded with good enantioselectivities, even though the chemical yields were poor (entries 14–15). In addition, aromatic aldehydes bearing naphthyl or heterocyclic rings were also found to be suitable (entries 16–18). However, aliphatic

Table 5 Examination of the effects of various additives on **5a**-catalyzed MBH reaction[a]



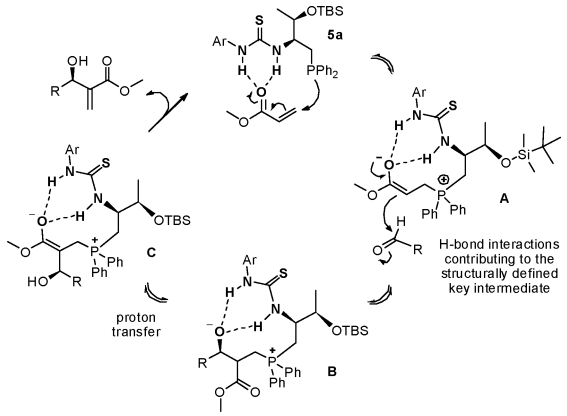
Entry	Additive	Yield (%)[b]	ee (%)[c]
1	none	92	87
2	MeOH (10 mol%)	93	84
3	**13** (10 mol%)	90	85
4	**13** (20 mol%)	89	85
5	**13** (50 mol%)	86	84
6	**13** (100 mol%)	81	83
7	PhOH (10 mol%)	84	77
8	2-Naphthol (10 mol%)	88	74
9	PhCOOH (10 mol%)	37	85
10	PhCOOH (20 mol%)	—[d]	—
11	TFA (10 mol%)	—[d]	—

[a] The reaction was performed with **10a** (0.1 mmol), **11a** (0.15 mmol) and **5a** (0.01 mmol) in anhydrous THF (0.4 mL) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] No reaction.

aldehydes could not be efficiently activated in our system. It should be noted that only the desired MBH adducts were observed in the **5a**-catalyzed MBH reactions, undesired dioxanones[11] were not observed under our reaction conditions.

Given the widespread uses of thiourea as the hydrogen bonding catalyst in asymmetric catalysis,[12] a mechanistic proposal involving hydrogen bonding interactions between the bifunctional phosphines and the substrate/intermediates seems to be plausible. We focused on the potential roles that the thiourea moiety might have played in our catalytic systems. Toward this end, the effects of adding various external proton donors on the **5a**-catalyzed MBH reaction were next investigated (Table 5). The presence of methanol slightly decreased the enantioselectivity of the reaction (entry 2). The addition of thiourea **13**, which mimics the thiourea moiety in catalyst **5a**, did not have much influence on the stereoselectivity of the reaction, even in a large excess (entries 3–6). However, the addition of a stronger hydrogen bond donor, phenol or 2-naphthol, clearly lowered the enantioselectivity of the reaction (entries 7–8). Interestingly, inclusion of a strong acid in the reaction system, *e.g.* benzoic acid, had virtually no effect on the enantioselectivity, but resulted in a dramatically decreased chemical yield (entry 9). On the other hand, adding excess benzoic acid, or a much stronger trifluoroacetic acid completely stopped the reaction (entries 10–11).

Based on the above additive studies, as well as recent elegant mechanistic investigations on (aza)-MBH reactions,[13] we propose the mechanism of **5a**-catalyzed MBH reaction to be as shown in Scheme 3. The reaction is initiated by a reversible conjugate addition of phosphine **5a** to the acrylate to generate phosphonium enolate intermediate **A**, which then undergoes aldol reaction with the aldehyde to create intermediate **B**. The subsequent proton transfer, followed by β-elimination, affords the final MBH adduct and regenerates the phosphine catalyst **5a**. We propose that the



Scheme 3 Proposed mechanism for phosphine–thiourea **5a**-promoted MBH reaction.

strong intramolecular hydrogen bonding interactions[3l,7,14] between thiourea and the enolate facilitate the formation of a structurally well-defined intermediate **A**, which reacts with the aldehyde substrate in a highly stereochemically selective manner, accounting for the high enantioselectivity observed. This proposal is supported by the results obtained with the additive studies. Relatively weak external hydrogen bond donors competed unfavourably with the intramolecular thiourea in their interactions with the enolate, and thus had no significant influence on the enantioselectivity (Table 5, entries 2–6). Stronger hydrogen bond donors disrupted thiourea–enolate interaction more, resulting in decreased enantioselectivity (Table 5, entries 7–8). The addition of carboxylic acids, such as benzoic acid or TFA, may partially/completely protonate the enolate intermediate **A**, thus leading to a marked decrease in chemical yield or a complete stop of the reaction. Had the external proton donors participated in the proton transfer step, a more dramatic decrease in enantioselectivity would be anticipated, as we had observed in a related study.[14]

Conclusions

In summary, we have designed and prepared a series of phosphine–thiourea organic catalysts based on the structural scaffolds of natural amino acids. In particular, L-threonine-derived bifunctional phosphine **5a** was prepared for the first time and found to be an effective catalyst for the enantioselective MBH reaction of acrylates with aromatic aldehydes. The desired MBH adducts were obtained with good to very good enantioselectivities. We studied the influences of various additives on the **5a**-catalyzed MBH reaction, and we propose that the hydrogen bonding interactions between the thiourea and the phosphonium enolate intermediate **A** are crucial for the high enantioselectivity observed. The reaction described in this report provides a general and practical solution to the enantioselective MBH reaction of simple acrylates, and is anticipated to find wide applications in organic synthesis in the future.

Experimental

General methods and materials

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated.

Toluene, THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. Dioxane was dried and distilled from Na prior to use. All the solvents used in reactions involving phosphorus-containing compounds were de-gassed by N_2. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040– 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by HPLC analysis on a chiral stationary phase.

A representative procedure for 5a-catalyzed Morita–Baylis–Hillman (MBH) reaction

To a flame-dried round bottom flask with a magnetic stirring bar under N_2 were added methyl acrylate **11a** (14 µl, 0.15 mmol), anhydrous THF (0.4 mL), **5a** (5.4 mg, 0.01 mmol) and 4 Å molecular sieves (50 mg). The resulting mixture was stirred for 2 min, followed by the addition of *p*-nitrobenzaldehyde **10a** (15.1 mg, 0.1 mmol). The flask was then sealed, and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered (to remove molecular sieves) and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 10 : 1 to 1 : 1) to afford **12a** (21.8 mg, 92%) as a yellow solid.

Preparation of phosphine–thiourea catalysts 5a–5d

(4*S*,5*R*)-*tert*-Butyl-2,2,5-trimethyl-4-((methylsulfonyloxy)methyl)oxazolidine-3-carboxylate (7). To a solution of alcohol **6**[10] (2.33 g, 9.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added Et_3N (3.30 mL, 23.7 mmol), followed by dropwise addition of $MeSO_2Cl$ (970 µL, 12.50 mmol) over 10 min. The reaction mixture was stirred at room temperature for 3 h. The mixture was then washed with water, and the aqueous layer was back extracted with CH_2Cl_2 several times (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography (hexanes/ethyl acetate = 10 : 1 to 5 : 1) afforded the desired product **7** as a colorless oil (2.64 g, 86% yield).

^1H NMR (500 MHz, DMSO, 50 °C) δ 4.43 (br, 1H), 4.34–4.31 (m, 1H), 4.15–4.12 (m, 1H), 3.62–3.59 (m, 1H), 3.17 (s, 3H), 1.54 (s, 3H), 1.44 (s, 9H), 1.41 (s, 3H), 1.29 (d, J = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, DMSO, 50 °C) δ 150.8, 93.3, 79.5, 78.9, 72.2, 66.6, 61.2, 36.6, 27.7, 25.6, 19.1; HRMS (ESI) m/z calcd for $C_{13}H_{26}NO_6S$ [M+H]+ = 324.1403, found = 324.1400.

(2*R*,3*S*)-3-Amino-4-(diphenylphosphino)butan-2-ol (8). To a solution of **7** (2.6 g, 8.0 mmol) in anhydrous THF (20 mL) under N_2 at 0 °C was slowly added a solution of $NaPPh_2$ in THF/dioxane (0.2 M in THF/dioxane, 52.0 mL, 10.40 mmol). The resulting mixture was stirred at 0 °C for 2 h. The reaction was then quenched by adding H_2O (25 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. A THF solution of HCl (4 M, 25 ml) was added to the residue, and the resulting mixture was stirred for 1 h. The pH value of the mixture was adjusted to 10 by slow addition of 2 M aqueous NaOH solution at 0 °C. The mixture was then extracted with ethyl acetate several times (3 × 30 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. Purification by column chromatography (hexane/ethyl acetate = 5 : 1 to 1 : 1, hexanes containing 5% Et_3N) afforded **8** as a white solid (1.7 g, 78%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.30 (m, 10H), 3.59–3.54 (m, 1H), 2.61–2.55 (m, 1H), 2.42 (t, J = 3.5 Hz, 1H), 2.40–2.25 (m, 3H), 2.05–1.99 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8 (dd), 132.7 (dd), 129.1, 128.6 (dd), 71.0 (d), 56.7 (d), 34.6 (d), 20.0; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ –22.3 (s); HRMS (ESI) m/z calcd for $C_{16}H_{21}NOP$ $[M+H]^+$ = 274.1361, found = 274.1362.

1-((2*S*,3*R*)-1-(Diphenylphosphino)-3-hydroxybutan-2-yl)-3-(4-fluorophenyl)-thiourea (9). To a solution of **8** (0.81 g, 3.0 mmol) in CH_2Cl_2 (5 mL) under N_2 was added 4-fluorophenyl isothiocyanate (0.51 g, 3.3 mmol), and the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*, and the residue was directly purified by column chromatography (hexane/ethyl acetate = 15 : 1 to 5 : 1) to afford **9** as a white solid (1.14 g, 90% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.51–7.41 (m, 4H), 7.33–7.29 (m, 6H), 7.10–6.98 (m, 4H), 6.47 (d, J = 7.7 Hz, 1H), 4.60 (br, 1H), 4.21–4.19 (m, 1H), 2.49–2.47 (m, 2H), 1.14 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 161.0 (d), 137.8 (d), 137.2 (d), 132.8 (d), 132.6 (d), 132.1, 128.8 (d), 128.6 (d), 128.5 (d), 127.1 (d), 127.1, 116.7 (d), 68.9 (d), 58.1 (d), 31.6 (d), 20.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –23.9; HRMS (ESI) m/z calcd for $C_{23}H_{25}FN_2OPS$ $[M+H]^+$ = 427.1409, found = 427.1409.

1-((2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-yl)-3-(4-fluorophenyl)thiourea (5a). To the solution of thiourea **9** (0.50 g, 1.17 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added DIPEA (0.61 mL, 3.51 mmol), followed by slow addition of TBSOTf (0.11 mL, 0.69 mmol). The resulting mixture was allowed to warm to room temperature and stirring was continued for an additional hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL), and then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane/ethyl acetate = 10 : 1) afforded **5a** (0.58 g, 92% yield) as a white solid.

^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (br, 1H), 7.70–7.64 (m, 2H), 7.40–7.35 (m, 5H), 7.29–7.23 (m, 3H), 7.15–7.09 (m, 2H), 7.07–7.02 (m, 2H), 6.37 (d, J = 8.9 Hz, 1H), 4.45 (s, 1H), 4.35 (d, J = 5.7 Hz, 1H), 2.66 (dd, J = 4.4 Hz, 8.8 Hz, 1H), 2.04–2.00 (m, 1H), 1.09 (d, J = 6.3 Hz, 3H), 0.69 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 161.4 (d), 139.1, 139.0, 137.0, 136.9, 133.2(d), 132.8, 132.7, 131.9, 128.8, 128.5, 128.5, 128.4, 128.3, 127.9 (d), 117.0 (d), 68.5 (d), –4.6, 58.6 (d), 31.9 (d), 21.5,

17.6, –4.3, –4.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ –22.60; HRMS (ESI) m/z calcd for $C_{29}H_{39}FN_2OPSSi$ $[M+H]^+$ = 541.2274, found = 541.2269.

1-((2*S*,3*R*)-3-(((2,3-Dimethylbutan-2-yl)dimethylsilyl)oxy)-1-(diphenylphosphino)butan-2-yl)-3-(4-fluorophenyl)thiourea (5b). To a solution of **9** (57.5 mg, 0.14 mmol) in THF (1 mL) at 0 °C was added NaH (22.4 mg, 0.60 mmol, 60% (w/w) in mineral oil). The mixture was stirred at 0 °C for 20 min, followed by the addition of *tert*-butyldimethylsilyl chloride (32.5 mg, 0.18 mmol). The mixture was then allowed to warm to room temperature and the stirring was continued for 2 h. The reaction was quenched by the addition of water (2 mL), and the mixture was extracted with EtOAc several times (3 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate = 10 : 1 to 5 : 1) to afford **5b** as a white solid (64.5 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (br, 1H), 7.70–7.65 (m, 2H), 7.40–7.26 (m, 8H), 7.15–7.03 (m, 4H), 6.31 (s, 1H), 4.47 (s, 1H), 4.32 (d, J = 6.0 Hz, 1H), 2.68–2.65 (m, 1H), 2.10–2.03 (m, 1H), 1.45–1.36 (m, 1H), 1.09 (d, J = 6.2 Hz, 3H), 0.69 (d, J = 6.9 Hz, 6H), 0.64 (d, J = 2.0 Hz, 6H), 0.08 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 161.0 (d), 133.3, 133.1, 132.8, 132.6, 131.9, 128.9, 128.5, 128.6, 128.4, 128.3, 128.0 (d), 117.0 (d), 68.7 (d), 58.6 (d), 33.8, 31.7 (d), 24.6, 20.1, 18.4, 18.4, 2.4, 2.2, –2.4, –2.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ –24.2; HRMS (ESI) m/z calcd for $C_{31}H_{43}FN_2OPSSi$ $[M+H]^+$ = 569.2587, found = 569.2589.

1-((2*S*,3*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1-(diphenylphosphino)butan-2-yl)-3-(4-fluorophenyl)thiourea (5c). Following the procedure described for the preparation of **5b**, catalyst **5c** (61% yield) was prepared similarly. A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br, 1H), 7.58–7.51 (m, 4H), 7.49–7.40 (m, 4H), 7.36–7.30 (m, 7H), 7.28–7.26 (m, 5H), 7.19–7.14 (m, 2H), 7.07–7.01 (m, 2H), 6.47 (d, J = 8.8 Hz, 1H), 4.49 (s, 1H), 4.28–4.23 (m, 1H), 2.66–2.60 (m, 1H), 2.17–2.10 (m, 1H), 0.96 (d, J = 4.5 Hz, 3H), 0.89 (s, 9H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 161.5 (d), 137.5, 135.9, 135.8, 134.8, 133.5, 133.3, 133.0, 132.8, 132.8, 132.6, 129.9, 129.8, 129.6, 128.8, 128.5, 128.4, 128.3, 128.3, 128.1 (d), 127.7, 127.5, 117.1 (d), 70.7 (d), 58.8 (d), 32.5 (d), 29.7, 26.9, 21.4, 19.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ –23.8; HRMS (ESI) m/z calcd for $C_{39}H_{43}FN_2OPSSi$ $[M+H]^+$ = 665.2587, found = 665.2592.

1-((2*S*,3*R*)-1-(Diphenylphosphino)-3((triisopropylsilyl)oxy)butan-2-yl)-3-(4-fluorophenyl)thiourea 5d. Following the procedure described for the preparation of **5b**, catalyst **5d** (73% yield) was prepared similarly. A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (br, 1H), 7.53–7.48 (m, 2H), 7.27–7.12 (m, 8H), 7.00–6.92 (m, 2H), 6.90–6.87 (m, 2H), 6.25 (d, J = 8.5 Hz, 1H), 4.34 (d, J = 5.7 Hz, 2H), 2.58–2.51 (m, 1H), 2.06 (t, J = 10.5 Hz, 1H), 1.01 (d, J = 6.2 Hz, 3H), 0.80 (br, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 161.5 (d), 139.0, 137.5, 137.3, 133.2, 132.9, 132.9, 132.6, 131.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.1 (d), 116.9 (d), 69.2 (d), 58.9 (d), 32.1 (d), 18.1, 18.1, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ –23.7; HRMS (ESI) m/z calcd for $C_{32}H_{45}FN_2OPSSi$ $[M+H]^+$ = 583.2665, found = 583.2746.

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