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Construction of highly substituted pyrazole derivatives with P–C bond: access to racemic and enantioselective forms by conjugate addition of diarylphosphane oxides to α,β-unsaturated pyrazolones

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ABSTRACT

The synthesis of organophosphorus compounds is of great importance to industrial, agricultural, and pharmaceutical chemistry. In this paper, we have reported the synthesis of highly substituted pyrazole derivatives through P–C bond formation under catalyst-free conditions. On the other hand, the first catalytic asymmetric version of this reaction has also been developed under catalysis by an isosteviol derived thiourea organocatalyst. The optically active phosphorus-containing compounds have been obtained in good chemical yields with moderate enantioselectivities.

1. Introduction

In recent years, organophosphorus compounds have been widely studied, because they not only serve as a valuable class of building blocks, but also play an important role in industrial, agricultural, and pharmaceutical chemistry because of their wide spectrum biological activities (Fig. 1).[1] P–C bond formations can be constructed in various methods. Among them, Michael addition reaction of trivalent and pentavalent phosphorus species to electron-poor alkenes was a straightforward and efficient strategy.[2] It was usually promoted by bases, Lewis acids and also microwave condition.[3] The direct addition of diaryl or dialkylphosphine oxides ($R_2P(O)H$) to activated alkenes was a convenient and efficient method to the synthesis of stable precursors of phosphine compounds.[4] Because of the importance of phosphines used as ligands in metal-catalysis or organocatalyst,[5] so, the development of new and efficient reaction to access this transformation is necessary. Besides, asymmetric synthesis of organophosphorus compound via Michael addition has also been well achieved by metal-catalysis[6] or organo-catalysis.[7]

Pyrazole, a five-membered heterocycle compound containing two adjacent nitrogen atoms, is a motif found in a number of small molecules that possess a wide range of agricultural and pharmaceutical activities (Fig. 1).[8] They could be achieved by Knorr reaction of hydrazine derivatives with 1,3-dicarbonyl compounds,[9] 1,3-dipolar cycloaddition,[10] and other methods.[11] Among them, the addition of nucleophile to α,β-unsaturated pyrazolones was a direct and efficient method to synthesize pyrazol-5-ol. However, there were only a few reports on this kind of transformations. In 1999, Meng et al. reported the solid-state Michael addition of indole to α,β-unsaturated pyrazolones.[12] Two years later, Khidre and co-workers reported the Michael addition of alkyl phosphites or hexamethylphosphorus triamides to α,β-unsaturated pyrazolones.[13] It should be noted that the products were obtained with 75–85% yield at 100 °C. So, we are interested in the search of new nucleophile with α,β-unsaturated pyrazolones as acceptor under mild reaction conditions. Based on our previous work on constructing carbon-heteroatom bond and the importance of molecules containing phosphines atoms, herein, we wish to report our preliminary work about the addition of diarylphosphane oxides to α,β-unsaturated pyrazolones

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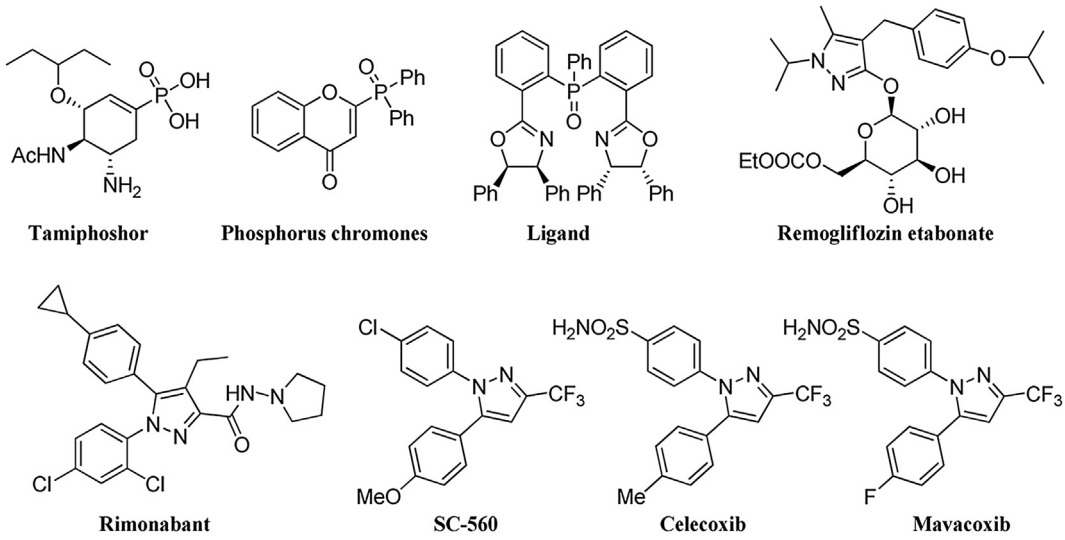


Fig. 1. Some phosphorus and pyrazole-substituted important compounds.

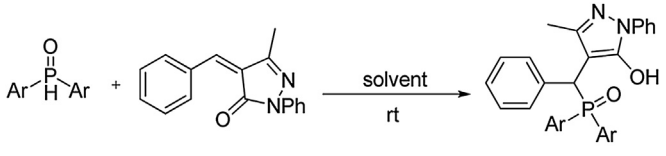
in racemic form under catalyst-free conditions and chiral form catalyzed by isosteviol derived thiourea organocatalyst developed by Tao's and our group.[14]

2. Results and discussion

Initially, we found that the Michael reaction between **1a** and **2a** was smoothly proceeded in $CHCl_3$ in the absence of catalyst to furnish the desired product **3a** in 88% yield (Table 1, entry 1). With this result in hand, the screening of solvents for Michael addition of diphenyl oxide **1a** to α,β-unsaturated pyrazolone **2a** was further carried out. As we could see from Table 1, the solvents showed great influence on the reactivity (Table 1, entries 1–8). With diethyl ether as solvent, the reaction was proceeded completely for about 15 min and the product was obtained in 96% yield (Table 1, entry 8). The molar ratio of **1a** to **2a** and diarylphosphane oxide substrates **1b** and **1c** with methyl substituents on the phenyl rings were further investigated for this transformation (Table 1, entries 9–14). Finally, the optimal reaction conditions were finally established as the reaction being performed for diphenyl oxide **1a** as nucleophile with 2:1 molar ratio of **1a** to **2a** in diethyl ether for further substrate scope.

With the optimized reaction conditions in hand, the substrate scope of this reaction was then investigated and the results were summarized in Table 2. All the reactions between **1a** and α,β-

Table 1
Optimization of the reaction conditions and diarylphosphane oxides



Ar = Ph (**1a**)
Ar = 4-MeC_6H_4 (**1b**)
Ar = 3,5-$Me_2C_6H_3$ (**1c**)

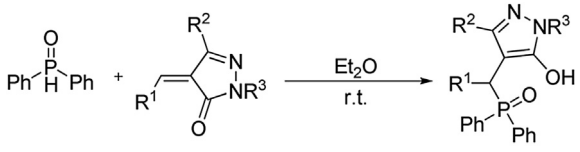
2a

3a
4a
5a

Entry[a]	**1** (mmol)	**2a** (mmol)	Solvent	Time (min)	Yield[b] (%)
1	0.3	0.1	$CHCl_3$	420	**3a**/88
2	0.3	0.1	CH_2Cl_2	270	**3a**/91
3	0.3	0.1	MeOH	100	**3a**/89
4	0.3	0.1	MeCN	60	**3a**/91
5	0.3	0.1	Toluene	45	**3a**/95
6	0.3	0.1	THF	45	**3a**/93
7	0.3	0.1	EtOAc	30	**3a**/92
8	0.3	0.1	Et_2O	15	**3a**/96
9	0.25	0.1	Et_2O	20	**3a**/95
10	0.2	0.1	Et_2O	20	**3a**/96
11	0.15	0.1	Et_2O	50	**3a**/95
12	0.11	0.1	Et_2O	90	**3a**/96
13[c]	0.2	0.1	Et_2O	60	**4a**/96
14[d]	0.2	0.1	Et_2O	60	**5a**/95

[a] Unless noted, the reactions were carried out with **1**, **2a** in Et_2O (1.0 mL) at room temperature.
[b] Isolated yield.
[c] With **1b** as substrate.
[d] With **1c** as substrate.

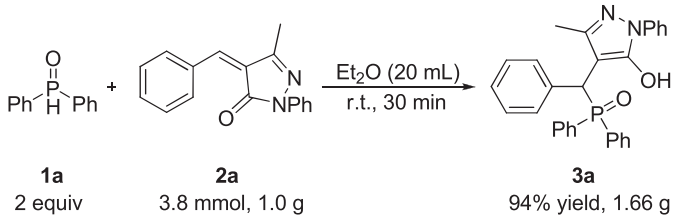
Table 2
Substrate scope



1a **2** **3**

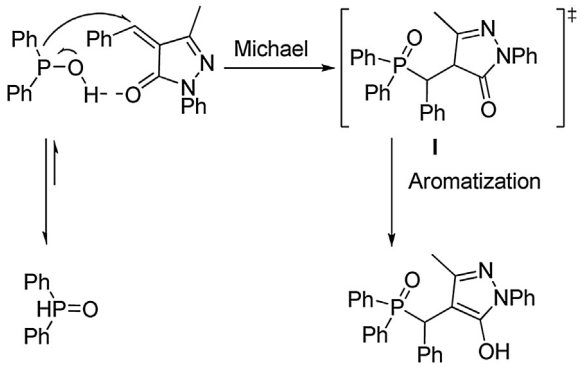
Entry[a]	$R^1/R^2/R^3$	Time (min)	Product	Yield[b] (%)
1	Ph/Me/Ph/**2a**	20	**3a**	96
2	4-ClC_6H_4/Me/Ph/**2b**	20	**3b**	97
3	4-BrC_6H_4/Me/Ph/**2c**	20	**3c**	95
4	3-ClC_6H_4/Me/Ph/**2d**	30	**3d**	98
5	2,4-$Cl_2C_6H_3$/Me/Ph/**2e**	7	**3e**	97
6	4-MeC_6H_4/Me/Ph/**2f**	120	**3f**	99
7	4-$MeOC_6H_4$/Me/Ph/**2g**	150	**3g**	97
8	4-$MeSC_6H_4$/Me/Ph/**2h**	90	**3h**	94
9	3,5-$(MeO)_2C_6H_3$/Me/Ph/**2i**	40	**3i**	96
10	3,4-$(OCH_2O)C_6H_3$/Me/Ph/**2j**	140	**3j**	98
11	2-Naphthyl/Me/Ph/**2k**	40	**3k**	95
12	2-Furyl/Me/Ph/**2l**	180	**3l**	93
13	Ph/Me/4-BrC_6H_4/**2m**	60	**3m**	93
14	Ph/CF_3/Ph/**2n**	5	**3n**	96
15	Ph/CF_3/4-BrC_6H_4/**2o**	10	**3o**	94
16	4-ClC_6H_4/Me/4-BrC_6H_4/**2p**	30	**3p**	93
17	4-BrC_6H_4/Me/4-BrC_6H_4/**2q**	35	**3q**	95
18	Ph/Me/4-ClC_6H_4/**2r**	15	**3r**	93
19	4-ClC_6H_4/Me/4-ClC_6H_4/**2s**	30	**3s**	94
20	4-BrC_6H_4/Me/4-ClC_6H_4/**2t**	35	**3t**	94

[a] Unless noted, the reactions were carried out with **1a** (0.60 mmol), **2** (0.3 mmol) in Et_2O (3.0 mL) at room temperature.
[b] Isolated yield.



Scheme 1. The addition of diphenylphosphine oxide **1a** to α,β-unsaturated pyrazolone **2a** on gram-scale.

unsaturated pyrazolones **2a**–**t** were proceeded smoothly and the products were obtained in high yields (93–99%) within 5–150 min (Table 2, entries 1–20). Generally, the reactions for α,β-unsaturated pyrazolones **2b**–**e** with electron-withdrawing groups on the aromatic rings were proceeded more fast (7–30mins) (Table 2, entries 2–5), whereas the reactions for α,β-unsaturated pyrazolones **2f**–**j** bearing electron-donating groups on the aromatic rings were carried out longer reaction time (40–150mins) to complete (Table 2, entries 6–10). The 2-naphthyl substituted α,β-unsaturated pyrazolone **2k** showed quite good performance to give the desired product **3k** in 95% yield with 40 min (Table 2, entry 11). When the substrate **2l** with 2-furyl group was used for the reaction, 93% yield was obtained, although with longest reaction time (Table 2, entry 12). In addition, more α,β-unsaturated pyrazolones **2m**–**t** with different R^2 and R^3 groups were also investigated. To our delight, all these substrates **2m**–**t** were also well tolerated for this transformation, and the corresponding products **3m**–**t** were, respectively, obtained in 93–96% yield within 35 min (Table 2, entries 13–20). To further evaluate the synthetic potential of this reaction system, gram-scale synthesis of the product **3a** was performed. As shown in Scheme 1, the product **3a** could be obtained in 94% yield in 30 min. Fortunately, the single crystals of racemic compounds **3c** and **3g** were obtained by recrystallization from $CDCl_3$, and the relative configurations of the desired compounds were unambiguously determined by X-ray analyses (Fig. 2).[15]



Scheme 2. Proposed transition state and mechanism.

Then, we turned our attention to the development of the asymmetric version of this reaction.[16] Because the background reaction could take place readily at room temperature, the model reaction of **1a** and **2a** was carried out at 0 °C with toluene as solvent in the presence of 20 mol % of chiral organocatalyst and the results were summarized in Table 3. A series of chiral organocatalysts **6a**–**o** were screened (Table 3, entries 1–15). Quinine and its derivatives **6a**–**d** were firstly tested and very low enantioselectivities were observed. (Table 3, entries 1–4). The tertiary amino-thiourea organocatalysts **6e** and **6f** also showed disappointing catalytic results (Table 3, entries 5 and 6).[17] Chiral squaramides organocatalysts **6g**–**j** could not improve the enantioselectivity of the desired products (Table 3, entries 7–10).[18] Subsequently, chiral organocatalysts **6k**–**o** were further investigated (Table 3, entries 11–15). To our delight, chiral organocatalyst **6l** gave the promising result and the product was obtained in 95% yield and 40% enantioselectivity (Table 3, entry 12).

With **6l** as the optimal chiral organocatalyst, the reaction conditions were further optimized by adjusting several reaction parameters, including reaction temperature, reaction medium,

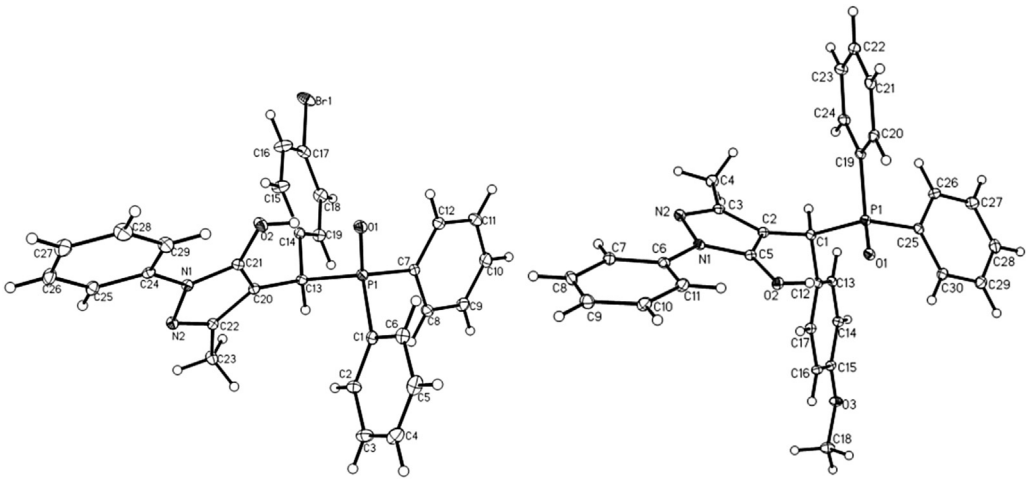
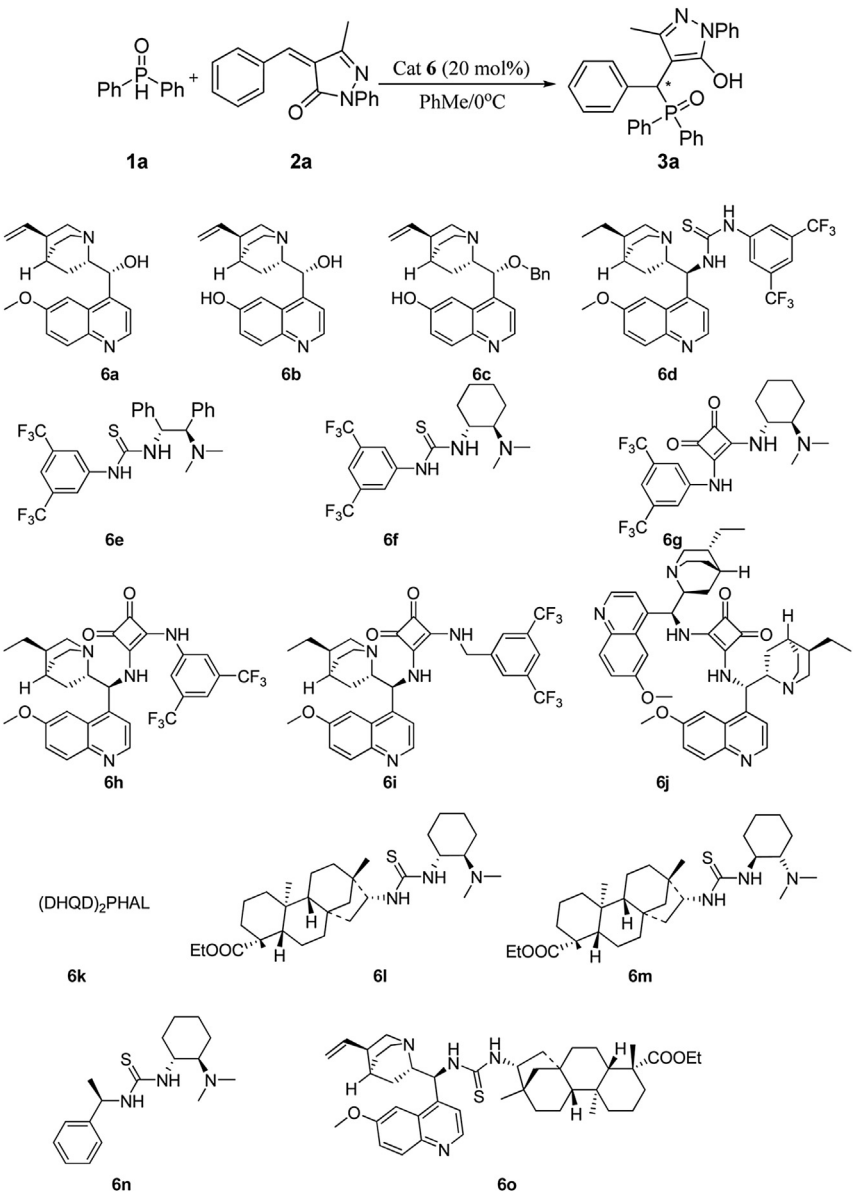


Fig. 2. X-ray crystal structures of racemic **3c** and **3g**.

Although the mechanistic detail remains ambiguous, it is presumed that the diphenylphosphine oxides firstly equilibrate with the tautomer phosphinous acids, which is the nucleophilic form. The phosphinous acids activate the α,β-unsaturated pyrazolones through the hydrogen bonding and the intramolecular Michael addition is smoothly proceeded, which provides the intermediate **I** of Michael addition. Subsequently, aromatization of intermediate **I** generates the desired products (Scheme 2).

substrate concentration, catalyst loading, additives, and diarylphosphane oxide substrates, and the results were summarized in Table 4. Firstly, some common solvents were screened for this transformation, and toluene was proved to be the best solvent (Table 4, entry 1 vs entries 2–7). When the temperature was dropped to −40 °C, the enantioselectivity of product **3a** was increased from 40% to 48% (Table 4, entry 8 vs 1). To our delight, the enantioselectivity could be further improved to 61% by adding activated 4 Å

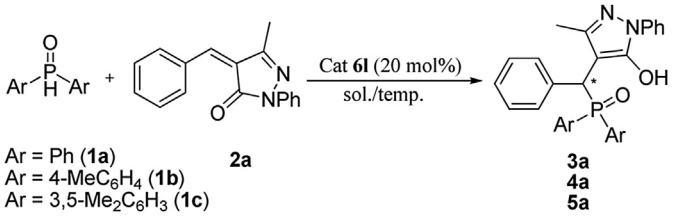
Table 3
Optimization of chiral organocatalysts



Entry[a]	Cat	Time (h)	Yield[b] (%)	ee[c] (%)
1	**6a**	12	95	17
2	**6b**	12	93	2
3	**6c**	12	91	1
4	**6d**	12	95	12
5	**6e**	12	81	2
6	**6f**	12	93	15
7	**6g**	12	86	7
8	**6h**	12	92	24
9	**6i**	12	94	14
10	**6j**	12	80	1
11	**6k**	12	87	14
12	**6l**	12	95	40
13	**6m**	12	92	30
14	**6n**	12	90	20
15	**6o**	12	88	26

[a] Unless noted, the reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol), and **6** (20 mol %) in toluene (2.0 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Table 4
Optimization of the reaction conditions



Entry[a]	Solvent	T (°C)	Concn (M)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	0	0.05	12	**3a**/95	40
2	*o*-Xylene	0	0.05	12	**3a**/95	39
3	Mesitylene	0	0.05	12	**3a**/97	39
4	PhCl	0	0.05	20	**3a**/92	34
5	CH_2Cl_2	0	0.05	40	**3a**/72	30
6	$(ClCH_2)_2$	0	0.05	40	**3a**/78	28
7	Et_2O	0	0.05	2	**3a**/95	25
8	Toluene	−40	0.05	60	**3a**/85	48
9[d]	Toluene	−40	0.05	60	**3a**/78	56
10[e]	Toluene	−40	0.05	60	**3a**/77	60
11[f]	Toluene	−40	0.05	60	**3a**/78	61
12[g,f]	Toluene	−40	0.05	60	**3a**/89	70
13[g,h]	Toluene	−40	0.025	84	**3a**/85	73
14[g,i]	Toluene	−40	0.020	84	**3a**/76	74
15[g,h,j]	Toluene	−40	0.025	96	**4a**/46	48
16[g,h,k]	Toluene	−40	0.025	96	**5a**/50	44

[a] Unless noted, the reactions were carried out with **1** (0.15 mmol), **2a** (0.1 mmol), and **6l** (20 mol %) in solvent (2.0 mL) at 0 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] With additive Na_2SO_4 200 mg.
[e] With additive $MgSO_4$ 200 mg.
[f] With additive 4 Å MS 200 mg.
[g] With 30 mol % of catalyst.
[h] With additive 4 Å MS 400 mg, in 4.0 mL toluene.
[i] With additive 4 Å MS 500 mg, in 5.0 mL toluene.
[j] With **Ib** as substrate, in 4.0 mL toluene.
[k] With **Ic** as substrate, in 4.0 mL toluene.

molecular sieves at −40 °C in toluene (Table 4, entry 11). After investigating the effects of substrate concentration, catalyst loading, and diarylphosphane oxides (Table 4, entries 13–16), the best catalytic results (85% yield, 73% ee) were obtained by using diphenyl oxide **1a** as nucleophile with the concentration of 0.025 M to **2a** and 30 mol % catalyst loading (Table 4, entry 13).

Having established the optimized reaction conditions, the scope of the substrate was then explored with thiourea **6l** (30 mol %) as the organocatalyst in toluene at −40 °C with 4 Å molecular sieves as additive and the results were summarized in Table 5. A variety of α,β-unsaturated pyrazolone derivatives **2** were examined to study the effects of electronic property and steric hindrance on enantioselectivities and reactivities. The α,β-unsaturated pyrazolone derivatives **2b**–**d** with electron-deficient or **2f**–**h** with electron-rich substituents in *m*-, or *p*-position of aromatic ring gave the desired products **3b**–**d**, **3f**–**h** in 61–91% yield and 67–75% enantioselectivity, respectively (Table 5). The substrate **2k** with moderately electron-rich 2-naphthyl system was also well tolerated, and the reaction provided the desired product **3k** in 75% yield with 76% enantioselectivity (Table 5). In addition, 92% yield and 58% ee were obtained with aromatic heterocyclic α,β-unsaturated pyrazolone **2l** (Table 5). Besides, R^3 group of α,β-unsaturated pyrazolones were also examined. With **2m** and **2r** as substrates, the products **3m** and **3r** were obtained in good yields with moderate enantioselectivities (Table 5). However, when **2p**, **2q**, **2s**, and **2t** were employed as the substrates, the products were obtained in only moderate yields and enantioselectivities. We thought that low solubility of these substrates in the toluene leaded to the relatively poor results.

3. Conclusion

In conclusion, we have developed the conjugate addition reaction of diarylphosphane oxides to α,β-unsaturated pyrazolones in high yields under catalyst-free conditions. The asymmetric version of this conjugate addition has also been realized with the isosteviol derived thiourea **6l** as an organocatalyst. A series of enantiomerically enriched phosphorus-containing compounds have been obtained in moderate to good chemical yields with moderate enantioselectivities. The development of new chiral organocatalyst to improve both the reactivity and enantioselectivity of this reaction is now in progress in our lab.

4. Experimental section

4.1. General

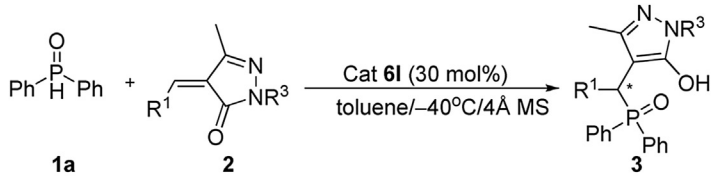
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted. Organic solutions were concentrated under reduced pressure on an EYELA N-1001 rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (0.2±0.03 mm thickness, GF-254, particle size 0.01–0.04 mm) from Yantai Chemical Industry Research Institute, P.R. China. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. Flash column chromatography was performed using silica gel (particle size 0.04–0.05 mm) from Yantai Chemical Industry Research Institute, P.R. China. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Inova (400 MHz or 300 MHz and 100 MHz or 75 MHz, respectively) spectrometer. Chemical shifts (δ ppm) are relative to the resonance of the deuterated solvent as the internal standard ($CDCl_3$, δ 7.27 ppm for proton NMR, δ 77.23 ppm for carbon NMR). ^1H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s=singlet, d=doublet, q=quartet, m=multiplet), coupling constants (J), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High-resolution mass spectra (HRMS) for all the compounds were determined on Micromass GCT-TOF mass spectrometer with ESI resource. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 Series chromatographs using a Daicel Chiralpak AD-H, OD-H column (0.46 cm×25 cm). X-ray data were recorded on a Rigaku Mercury CCD/AFC diffractometer. Optical rotations are reported as follows: $[\alpha]_D^{rt}$ (c in g per 100 mL, solvent).

4.2. General experimental procedure for conjugate addition of diarylphosphane oxides to α,β-unsaturated pyrazolones in racemic form

In an ordinary tube equipped with a magnetic stirring bar, the solution of diarylphosphane oxides **1** (0.6 mmol) in Et_2O (3.0 mL) was added α,β-unsaturated pyrazolone **2** (0.30 mmol) at room temperature. After the reaction mixture was stirred for 5–180 min at room temperature. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (eluant: petroleum ether/dichloromethane or petroleum ether/ethyl acetate) to give desired products **3**–**5**.

*4.2.1. 4-((Diphenylphosphoryl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3a**).* Yield 96%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.86 (s, 1H), 7.86 (dd, J=11.0, 7.2 Hz, 2H), 7.77 (d, J=7.6 Hz, 2H), 7.60–7.55 (m, 1H), 7.54–7.45 (m, 2H), 7.44–7.34 (m, 5H), 7.29 (dd, J=7.6, 2.8 Hz, 2H), 7.24–7.18 (m, 3H), 7.16–7.10 (m, 3H), 4.59 (d, J=11.6 Hz, 1H), 2.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.93 (d, $J_{C,P}$=4.50 Hz), 147.35 (d, $J_{C,P}$=9.75 Hz), 139.12, 136.14 (d, $J_{C,P}$=3.75 Hz), 132.73 (d, $J_{C,P}$=1.50 Hz),

Table 5
Substrate scope of asymmetric addition[a]



1a 2 3

3a
84h, 85% yield, 73% ee

3b
84h, 91% yield, 70% ee

3c
84h, 88% yield, 70% ee

3d
84h, 83% yield, 67% ee

3f
96h, 80% yield, 75% ee

3g
144h, 61% yield, 70% ee

3h
120h, 70% yield, 71% ee

3k
96h, 75% yield, 76% ee

3l[b]
84h,92% yield, 58% ee

3m
84h, 82% yield, 68% ee

3p
96h, 45% yield, 44% ee

3q
96h, 55% yield, 50% ee

3r
84h, 71% yield, 64% ee

3s
96h, 41% yield, 49% ee

3t
96h, 43% yield, 50% ee

[a]Unless noted, the reactions were carried out with **1a** (0.15 mmol), **2** (0.1 mmol), **6l** (30 mol %) and 4Å MS 400mg in toluene (4.0 mL) at –40 °C, the yield is isolated yield and the ee was determined by chiral HPLC analysis.
[b] at –20 °C.

132.35 (d, $J_{C,P}$=2.25 Hz), 131.32 (d, $J_{C,P}$=9.0 Hz), 130.99 (d, $J_{C,P}$=9.0 Hz), 129.34 (d, $J_{C,P}$=5.25 Hz), 129.16 (d, $J_{C,P}$=11.25 Hz), 128.75, 128.52, 128.37 (d, $J_{C,P}$=12.00 Hz), 127.29 (d, $J_{C,P}$=1.50 Hz), 125.61, 121.62, 95.26 (d, $J_{C,P}$=4.50 Hz), 44.25 (d, $J_{C,P}$=64.50 Hz), 12.98; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.24; IR (KBr) ν_{max}: 3447.6, 3058.2, 3029.7, 1595.5, 1523.4, 1498.1, 1451.1, 1436.9, 1137.6, 752.7, 724.8, 699.7 cm^{-1}; HRMS (ESI): m/z=487.1528 (calcd for $C_{29}H_{25}N_2O_2P+Na^+$=487.1546).

*4.2.2. 4-((4-Chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3b**).* Yield 97%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.80 (s, 1H), 7.90–7.80 (m, 2H), 7.75 (d, J=7.6 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.55–7.28 (m, 9H), 7.20 (t, J=7.2 Hz, 1H), 7.16–7.08 (m, 4H), 4.57 (d, J=11.6 Hz, 1H), 2.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.81 (d, $J_{C,P}$=5.25 Hz), 147.16 (d, $J_{C,P}$=9.00 Hz), 138.99, 134.74 (d, $J_{C,P}$=3.75 Hz), 133.21 (d, $J_{C,P}$=2.25 Hz), 132.82 (d, $J_{C,P}$=1.50 Hz), 132.56 (d, $J_{C,P}$==2.25 Hz), 131.22 (d, $J_{C,P}$=9.00 Hz), 130.86 (d, $J_{C,P}$=9.00 Hz), 130.56 (d, $J_{C,P}$=4.50 Hz), 129.17 (d, $J_{C,P}$=12.00 Hz), 128.75, 128.62, 128.45, 125.68, 121.58, 94.88 (d, $J_{C,P}$=4.50 Hz), 43.58 (d, $J_{C,P}$=64.50 Hz), 12.92; ^{31}P NMR (121 MHz, $CDCl_3$) δ 41.87; IR (KBr) ν_{max}: 3471.3, 3058.6, 1591.5, 1574.0, 1521.6, 1488.7, 1455.9, 1140.1,

879.6, 849.3, 756.1 cm^{-1}; HRMS (ESI): m/z=521.1144 (calcd for $C_{29}H_{24}ClN_2O_2P+Na^+$=521.1156).

*4.2.3. 4-((4-Bromophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3c**).* Yield 95%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.78 (s, 1H), 7.90–7.80 (m, 2H), 7.75 (d, J=8.0 Hz, 2H), 7.57 (t, J=7.2 Hz, 1H), 7.55–7.30 (m, 10H), 7.30–7.25 (m, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.06 (d, J=7.6 Hz, 2H), 4.55 (d, J=11.2 Hz, 1H), 2.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.86 (d, $J_{C,P}$=5.25 Hz), 147.18 (d, $J_{C,P}$=9.00 Hz), 139.04, 135.32 (d, $J_{C,P}$=3.75 Hz), 132.91 (d, $J_{C,P}$=2.25 Hz), 132.65 (d, $J_{C,P}$=2.25 Hz), 131.64, 131.32 (d, $J_{C,P}$=9.60 Hz), 131.00, 130.92, 129.26 (d, $J_{C,P}$=12.00 Hz), 128.82, 128.63 (d, $J_{C,P}$=12.00 Hz), 125.78, 121.69, 94.83 (d, $J_{C,P}$=4.50 Hz), 43.77 (d, $J_{C,P}$=63.75 Hz), 13.00; ^{31}P NMR (121 MHz, $CDCl_3$) δ 41.66; IR (KBr) ν_{max}: 3479.6, 3056.3, 2955.2, 1594.3, 1522.2, 1485.2, 1455.2, 1436.2, 1143.6, 868.9, 840.6 cm^{-1}; HRMS (ESI): m/z=565.0627 (calcd for $C_{29}H_{24}BrN_2O_2P+Na^+$=565.0651).

*4.2.4. 4-((3-Chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3d**).* Yield 98%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.79 (s, 1H), 7.90–7.80 (m, 2H), 7.77 (d, J=7.6 Hz, 2H), 7.65–7.55 (m, 1H), 7.55–7.45 (m, 3H), 7.43–7.30 (m, 6H), 7.20 (t, J=7.2 Hz, 1H), 7.15–7.07 (m, 3H), 7.07 (s, 1H), 4.55 (d, J=11.6 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.99 (d, $J_{C,P}$=5.25 Hz), 147.27 (d, $J_{C,P}$=9.00 Hz), 139.07, 138.14 (d, $J_{C,P}$=4.50 Hz), 134.22 (d, $J_{C,P}$=2.25 Hz), 132.96 (d, $J_{C,P}$=2.25 Hz), 132.71 (d, $J_{C,P}$=2.25 Hz), 131.35 (d, $J_{C,P}$=9.75 Hz), 131.03 (d, $J_{C,P}$=9.00 Hz), 129.80, 129.44, 129.37, 129.21, 128.83, 128.59 (d, $J_{C,P}$=9.00 Hz), 127.54, 125.79, 121.72, 94.61 (d, $J_{C,P}$=4.50 Hz), 44.13 (d, $J_{C,P}$=64.50 Hz), 13.02; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.00; IR (KBr) ν_{max}: 3472.0, 3416.1, 3053.3, 2916.9, 1593.6, 1589.4, 1525.0, 1481.9, 1438.9, 1142.0, 892.8, 763.8, 689.4 cm^{-1}; HRMS (ESI): m/z=499.1320 (calcd for $C_{29}H_{24}ClN_2O_2P+H^+$=499.1337).

*4.2.5. 4-((2,4-Dichlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3e**).* Yield 97%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.93 (s, 1H), 7.95–7.85 (m, 3H), 7.74 (d, J=8.0 Hz, 2H), 7.65–7.50 (m, 3H), 7.46 (t, J=7.2 Hz, 1H), 7.38 (t, J=7.2 Hz, 4H), 7.33–7.28 (m, 3H), 7.20 (t, J=7.2 Hz, 1H), 7.10 (s, 1H), 5.39 (d, J=12.0 Hz, 1H), 2.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.13 (d, $J_{C,P}$=4.50 Hz), 147.68 (d, $J_{C,P}$=9.00 Hz), 139.03, 133.98 (d, $J_{C,P}$=3.00 Hz), 133.63 (d, $J_{C,P}$=3.00 Hz), 133.45 (d, $J_{C,P}$=6.75 Hz), 133.13 (d, $J_{C,P}$=2.25 Hz), 132.83 (d, $J_{C,P}$=2.25 Hz), 132.61 (d, $J_{C,P}$=3.00 Hz), 131.48 (d, $J_{C,P}$=9.75 Hz), 131.17 (d, $J_{C,P}$=9.00 Hz), 129.37 (d, $J_{C,P}$=12.00 Hz), 128.85, 128.75, 128.45, 128.28, 125.86, 121.75, 94.89 (d, $J_{C,P}$=5.25 Hz), 39.19 (d, $J_{C,P}$=65.25 Hz), 13.24; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.01; IR (KBr) ν_{max}: 3476.0, 3415.1, 3058.6, 1592.6, 1573.5, 1522.7, 1476.9, 1438.0, 1138.6, 752.6, 693.6 cm^{-1}; HRMS (ESI): m/z=533.0927 (calcd for $C_{29}H_{24}Cl_2N_2O_2P+H^+$=533.0947).

*4.2.6. 4-((Diphenylphosphoryl)(p-tolyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3f**).* Yield 99%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.82 (s, 1H), 7.90–7.80 (m, 2H), 7.76 (d, J=8.0 Hz, 2H), 7.60–7.45 (m, 3H), 7.45–7.33 (m, 5H), 7.32–7.27 (m, 2H), 7.18 (t, J=7.2 Hz, 1H), 7.09 (d, J=7.2 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 6.06 (d, J=11.6 Hz, 1H), 2.24 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.89 (d, $J_{C,P}$=5.25 Hz), 147.28 (d, $J_{C,P}$=9.75 Hz), 139.16, 136.94 (d, $J_{C,P}$=3.00 Hz), 133.03 (d, $J_{C,P}$=3.75 Hz), 132.65 (d, $J_{C,P}$=2.25 Hz), 132.30 (d, $J_{C,P}$=2.25 Hz), 131.36 (d, $J_{C,P}$=9.00 Hz), 131.00, 130.89, 129.22, 129.04, 128.74, 128.37 (d, $J_{C,P}$=12.00 Hz), 125.57, 121.62, 95.46 (d, $J_{C,P}$=4.50 Hz), 43.73 (d, $J_{C,P}$=65.25 Hz), 21.11, 12.97; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.08; IR (KBr) ν_{max}: 3475.8, 3415.5, 3054.3, 2917.1, 1591.8, 1521.5, 1500.2, 1455.6, 1438.6, 1141.1, 752.9, 692.1 cm^{-1}; HRMS (ESI): m/z=501.1685 (calcd for $C_{30}H_{27}N_2O_2P+Na^+$=501.1702).

*4.2.7. 4-((Diphenylphosphoryl)(4-methoxyphenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3g**).* Yield 97%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.84 (s, 1H), 7.95–7.77 (m, 2H), 7.76 (d, J=8.0 Hz, 2H), 7.63–7.45 (m, 3H), 7.45–7.26 (m, 7H), 7.25–7.15 (m, 1H), 7.11 (d, J=7.6 Hz, 2H), 6.68 (d, J=8.0 Hz, 2H), 4.55 (d, J=11.2 Hz, 1H), 3.73 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.83, 151.89 (d, $J_{C,P}$=3.75 Hz), 147.29 (d, $J_{C,P}$=6.00 Hz), 139.20, 132.75 (d, $J_{C,P}$=1.50 Hz), 132.40, 131.45 (d, $J_{C,P}$=6.75 Hz), 131.08 (d, $J_{C,P}$=6.75 Hz), 130.45 (d, $J_{C,P}$=3.00 Hz), 129.21 (d, $J_{C,P}$=8.25 Hz), 128.83, 128.48 (d, $J_{C,P}$=9.00 Hz), 128.09 (d, $J_{C,P}$=2.25 Hz), 125.67, 121.70, 114.00, 95.59 (d, $J_{C,P}$=3.00 Hz), 55.38, 43.33 (d, $J_{C,P}$=48.75 Hz), 13.04; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.08; IR (KBr) ν_{max}: 3477.0, 3415.2, 3057.5, 2903,6, 1591.2, 1519.9, 1498.1, 1455.5, 1248.8, 1138.1, 840.1, 761.6 cm^{-1}; HRMS (ESI): m/z=495.1813 (calcd for $C_{30}H_{27}N_2O_3P+H^+$=495.1832).

*4.2.8. 4-((Diphenylphosphoryl)(4-(methylthio)phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3h**).* Yield 94%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.81 (s, 1H), 7.90–7.80 (m, 2H), 7.75 (d, J=8.0 Hz, 2H), 7.60–7.55 (m, 1H), 7.55–7.46 (m, 2H), 7.46–7.30 (m, 7H), 7.20 (t, J=7.6 Hz, 1H), 7.11 (d, J=7.2 Hz, 2H), 7.03 (d, J=8.0 Hz, 2H), 4.55 (d, J=11.6 Hz, 1H), 2.41 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.92 (d, $J_{C,P}$=5.25 Hz), 147.27 (d, $J_{C,P}$=9.00 Hz), 139.15, 137.65 (d, $J_{C,P}$=3.00 Hz), 132.90 (d, $J_{C,P}$=4.50 Hz), 132.82 (d, $J_{C,P}$=2.25 Hz), 132.51 (d, $J_{C,P}$=3.00 Hz), 131.43 (d, $J_{C,P}$=9.75 Hz), 131.04 (d, $J_{C,P}$=8.25 Hz), 129.77 (d, $J_{C,P}$=4.50 Hz), 129.24 (d, $J_{C,P}$=11.25 Hz), 128.84, 128.55 (d, $J_{C,P}$=12.00 Hz), 126.65 (d, $J_{C,P}$=0.75 Hz), 125.73, 121.72, 95.21 (d, $J_{C,P}$=4.50 Hz), 43.74 (d, $J_{C,P}$=65.25 Hz), 15.90, 13.03; ^{31}P NMR (121 MHz, $CDCl_3$) δ 41.88; IR (KBr) ν_{max}: 3478.3, 3053.7, 2923.4, 1591.1, 1521.4, 1496.6, 1437.2, 1139.9, 758.2, 691.3 cm^{-1}; HRMS (ESI): m/z=533.1404 (calcd for $C_{30}H_{27}N_2O_2PS+Na^+$=533.1423).

*4.2.9. 4-((3,5-Dimethoxyphenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3i**).* Yield 96%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.80 (s, 1H), 7.90–7.80 (m, 2H), 7.75 (d, J=8.0 Hz, 2H), 7.62–7.28 (m, 10H), 7.25–7.15 (m, 1H), 6.37 (s, 2H), 6.25 (s, 1H), 4.52 (d, J=11.6 Hz, 1H), 3.64 (s, 6H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.65, 152.03 (d, $J_{C,P}$=4.50 Hz), 147.34 (d, $J_{C,P}$=9.00 Hz), 139.15, 138.22 (d, $J_{C,P}$=3.00 Hz), 132.59 (d, $J_{C,P}$=4.50 Hz), 132.78, 132.40, 131.45 (d, $J_{C,P}$=9.75 Hz), 131.03 (d, $J_{C,P}$=9.00 Hz), 129.19 (d, $J_{C,P}$=12.00 Hz), 128.79, 128.45 (d, $J_{C,P}$=12.00 Hz), 125.68, 121.73, 107.45 (d, $J_{C,P}$=4.50 Hz), 99.68, 95.04 (d, $J_{C,P}$=5.25 Hz), 55.38, 44.52 (d, $J_{C,P}$=65.25 Hz), 13.04; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.14; IR (KBr) ν_{max}: 3477.6, 3414.9, 3067.6, 2993.3, 2955.7, 1595.4, 1455.7, 1420.1, 1204.4, 1140.1, 838.4, 764.3, 706.5 cm^{-1}; HRMS (ESI): m/z=547.1743 (calcd for $C_{31}H_{29}N_2O_4P+Na^+$=547.1757).

*4.2.10. 4-(Benzo[d][1,3]dioxol-5-yl(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3j**).* Yield 98%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.80 (s, 1H), 7.92–7.78 (m, 2H), 7.76 (d, J=7.6 Hz, 2H), 7.60–7.40 (m, 6H), 7.40–7.30 (m, 4H), 7.19 (d, J=7.6 Hz, 1H), 6.84 (s, 1H), 6.55 (s, 2H), 5.88 (d, J=14.4 Hz, 2H), 4.51 (d, J=11.6 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.78 (d, $J_{C,P}$=4.50 Hz), 147.88, 147.26 (d, $J_{C,P}$=9.00 Hz), 146.87 (d, $J_{C,P}$=2.25 Hz), 139.10, 132.74, 132.45 (d, $J_{C,P}$=1.50 Hz), 131.38 (d, $J_{C,P}$=9.00 Hz), 130.97 (d, $J_{C,P}$=9.00 Hz), 129.84 (d, $J_{C,P}$=3.75 Hz), 129.18 (d, $J_{C,P}$=11.25 Hz), 128.79, 128.49 (d, $J_{C,P}$=12.00 Hz), 128.68, 122.67 (d, $J_{C,P}$=6.00 Hz), 121.69, 109.80 (d, $J_{C,P}$=3.75 Hz), 108.07, 101.18, 95.42 (d, $J_{C,P}$=4.50 Hz), 65.99, 43.83 (d, $J_{C,P}$=65.25 Hz), 12.98; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.11; IR (KBr) ν_{max}: 3475.0, 3415.1, 3058.1, 2892.5, 1595.4, 1575.5, 1523.0, 1487.5, 1437.7, 1248.4, 1139.1, 753.6, 691.2 cm^{-1}; HRMS (ESI): m/z=531.1421 (calcd for $C_{30}H_{25}N_2O_4P+Na^+$=531.1444).

*4.2.11. 4-((Diphenylphosphoryl)(naphthalen-2-yl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3k**).* Yield 95%, ^1H NMR (400 MHz, $CDCl_3$): δ 12.94 (s, 1H), 7.95–7.85 (m, 2H), 7.79 (d, J=7.6 Hz, 2H), 7.75–7.68 (m, 1H), 7.65–7.48 (m, 6H), 7.45–7.28 (m, 8H), 7.23–7.13

(m, 3H), 4.77 (d, J=11.6 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.04 (d, $J_{C,P}$=4.50 Hz), 147.42 (d, $J_{C,P}$=9.00 Hz), 139.20, 133.63 (d, $J_{C,P}$=4.50 Hz), 133.28 (d, $J_{C,P}$=4.50 Hz), 132.81 (d, $J_{C,P}$=1.50 Hz), 132.45, 131.40 (d, $J_{C,P}$=9.75 Hz), 131.07 (d, $J_{C,P}$=8.25 Hz), 129.24 (d, $J_{C,P}$=11.25 Hz), 128.84, 128.53, 128.47, 128.37, 128.30, 127.97, 127.64, 127.22 (d, $J_{C,P}$=4.50 Hz), 126.17 (d, $J_{C,P}$=12.00 Hz), 125.71, 121.73, 95.22 (d, $J_{C,P}$=4.50 Hz), 44.43 (d, $J_{C,P}$=64.50 Hz), 13.06; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.10; IR (KBr) ν_{max}: 3475.8, 3414.8, 3057.6, 1595.1, 1522.7, 1500.9, 1436.3, 1138.5, 861.4, 748.6, 691.4 cm^{-1}; HRMS (ESI): m/z=515.1858 (calcd for $C_{33}H_{27}N_2O_2P+H^+$=515.1883).

*4.2.12. 4-((Diphenylphosphoryl)(furan-2-yl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3l**).* Yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (s, 1H), 7.90–7.70 (m, 4H), 7.68–7.46 (m, 6H), 7.45–7.30 (m, 4H), 7.25–7.15 (m, 1H), 7.12 (s, 1H), 6.40 (s, 1H), 6.23 (s, 1H), 4.82 (d, J=11.2 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.37 (d, $J_{C,P}$=3.75 Hz), 148.77 (d, $J_{C,P}$=3.00 Hz), 147.00 (d, $J_{C,P}$=0.75 Hz), 141.90, 139.07, 132.88, 132.62 (d, $J_{C,P}$=1.50 Hz), 131.27 (d, $J_{C,P}$=9.75 Hz), 130.94 (d, $J_{C,P}$=9.00 Hz), 129.16 (d, $J_{C,P}$=12.00 Hz), 128.85, 128.66 (d, $J_{C,P}$=12.00 Hz), 125.79, 121.67, 111.20, 109.33 (d, $J_{C,P}$=4.50 Hz), 93.40 (d, $J_{C,P}$=4.50 Hz), 38.16 (d, $J_{C,P}$=66.75 Hz), 12.85; ^{31}P NMR (121 MHz, $CDCl_3$) δ 40.08; IR (KBr) ν_{max}: 3477.5, 3414.7, 3058.6, 1594.1, 1525.1, 1500.5, 1456.7, 1436.6, 1140.2, 739.9 cm^{-1}; HRMS (ESI): m/z=477.1317 (calcd for $C_{27}H_{23}N_2O_3P+Na^+$=477.1339).

*4.2.13. 1-(4-Bromophenyl)-4-((diphenylphosphoryl)(phenyl)methyl)-3-methyl-1H-pyrazol-5-ol (**3m**).* Yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.04 (s, 1H), 7.86 (t, J=8.8 Hz, 2H), 7.70 (d, J=8.0 Hz, 2H), 7.60–7.55 (m, 1H), 7.55–7.45 (m, 4H), 7.45–7.40 (m, 1H), 7.40–7.32 (m, 2H), 7.32–7.26 (m, 1H), 7.20–7.10 (m, 5H), 4.57 (d, J=11.2 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.11 (d, $J_{C,P}$=5.25 Hz), 147.81 (d, $J_{C,P}$=9.00 Hz), 138.31, 135.98 (d, $J_{C,P}$=3.75 Hz), 132.82 (d, $J_{C,P}$=2.25 Hz), 132.43 (d, $J_{C,P}$=2.25 Hz), 131.72, 131.31 (d, $J_{C,P}$=9.00 Hz), 130.97 (d, $J_{C,P}$=9.00 Hz), 129.31, 129.28, 129.13, 128.57, 128.41 (d, $J_{C,P}$=12.75 Hz), 127.37 (d, $J_{C,P}$=2.25 Hz), 122.81, 118.59, 95.56 (d, $J_{C,P}$=4.50 Hz), 44.17 (d, $J_{C,P}$=64.50 Hz), 12.99; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.49; IR (KBr) ν_{max}: 3474.6, 3415.3, 3063.0, 1590.2, 1520.1, 1483.4, 1421.3, 1136.5, 832.4, 707.6, 692.8 cm^{-1}; HRMS (ESI): m/z=565.0655 (calcd for $C_{29}H_{24}BrN_2O_2P+Na^+$=565.0651).

*4.2.14. 4-((Diphenylphosphoryl)(phenyl)methyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (**3n**).* Yield 96%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.59 (s, 1H), 7.95–7.85 (m, 2H), 7.85–7.65 (m, 2H), 7.65–7.45 (m, 3H), 7.45–7.17 (m, 10H), 7.16–7.05 (m, 3H), 4.85 (d, J=11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.05 (d, $J_{C,P}$=5.25 Hz), 138.25, 135.62 (d, $J_{C,P}$=3.75 Hz), 133.10 (d, $J_{C,P}$=2.25 Hz), 132.68 (d, $J_{C,P}$=2.25 Hz), 131.40, 131.27, 131.15, 129.38, 129.31, 129.23, 128.99, 128.68, 128.63, 128.47, 127.67 (d, $J_{C,P}$=1.50 Hz), 127.29, 122.69, 95.17 (d, $J_{C,P}$=4.50 Hz), 43.33 (d, $J_{C,P}$=64.50 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.66; IR (KBr) ν_{max}: 3476.9, 3032.5, 2924.6, 1597.3, 1567.1, 1522.9, 1457.7, 1436.9, 1139.6, 755.1, 694.4 cm^{-1}; HRMS (ESI): m/z=511.1439 (calcd for $C_{29}H_{22}F_3N_2O_2P+H^+$=519.1444).

*4.2.15. 1-(4-Bromophenyl)-4-((diphenylphosphoryl)(phenyl)methyl)-3-(trifluoromethyl)-1H-pyrazol-5-ol (**3o**).* Yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.79 (s, 1H), 7.99–7.85 (m, 2H), 7.75–7.65 (m, 2H), 7.65–7.45 (m, 5H), 7.45–7.40 (m, 1H), 7.39–7.25 (m, 4H), 7.24–7.10 (m, 5H), 4.84 (d, J=11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.27 (d, $J_{C,P}$=5.25 Hz), 137.40, 135.49 (d, $J_{C,P}$=4.50 Hz), 133.16 (d, $J_{C,P}$=2.25 Hz), 132.73 (d, $J_{C,P}$=3.00 Hz), 132.02, 131.39, 131.25, 131.12, 129.42, 129.32, 129.26, 128.72, 128.71, 128.66, 128.49, 127.73 (d, $J_{C,P}$=2.25 Hz), 123.89, 120.63, 95.38 (d, $J_{C,P}$=3.75 Hz), 43.25 (d, $J_{C,P}$=63.75 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.88; IR (KBr) ν_{max}: 3475.6, 3415.4, 3058.8, 2849.6, 1588.7, 1567.6, 1524.0, 1436.9, 1166.3, 888.6, 690.5 cm^{-1}; HRMS (ESI): m/z=597.0538 (calcd for $C_{29}H_{21}BrF_3N_2O_2P+H^+$=597.0549).

*4.2.16. 1-(4-Bromophenyl)-4-((4-chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1H-pyrazol-5-ol (**3p**).* Yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.03 (s, 1H), 7.90–7.80 (m, 2H), 7.70 (d, J=8.8 Hz, 2H), 7.58–7.34 (m, 8H), 7.33–7.27 (m, 2H), 7.14–7.06 (m, 4H), 4.57 (d, J=11.6 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.06 (d, $J_{C,P}$=5.00 Hz), 147.65 (d, $J_{C,P}$=9.00 Hz), 138.19, 134.63 (d, $J_{C,P}$=4.00 Hz), 133.39 (d, $J_{C,P}$=3.00 Hz), 132.96 (d, $J_{C,P}$=2.00 Hz), 132.69 (d, $J_{C,P}$=3.00 Hz), 131.78, 131.30 (d, $J_{C,P}$=10.00 Hz), 130.93 (d, $J_{C,P}$=8.00 Hz), 130.56 (d, $J_{C,P}$=4.00 Hz), 130.27, 129.53, 129.34, 129.29, 129.22, 128.74, 128.72, 128.69, 128.57, 128.52, 122.88, 118.80, 95.24 (d, $J_{C,P}$=4.00 Hz), 43.60 (d, $J_{C,P}$=65.00 Hz), 12.93; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.14; IR (KBr) ν_{max}: 3445.8, 3061.3, 1590.9, 1520.3, 1487.3, 1453.3, 1437.1, 1182.8, 1140.3, 878.9, 795.1 cm^{-1}; HRMS (ESI): m/z=577.0430 (calcd for $C_{29}H_{23}BrClN_2O_2P+H^+$=577.0442).

*4.2.17. 1-(4-Bromophenyl)-4-((4-bromophenyl)(diphenylphosphoryl)methyl)-3-methyl-1H-pyrazol-5-ol (**3q**).* Yield 95%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.04 (s, 1H), 7.86–7.76 (m, 2H), 7.70 (d, J=8.8 Hz, 2H), 7.55–7.35 (m, 8H), 7.34–7.20 (m, 4H), 7.10–7.00 (m, 2H), 4.56 (d, J=11.6 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.10 (d, $J_{C,P}$=5.00 Hz), 147.68 (d, $J_{C,P}$=9.00 Hz), 138.22, 135.20 (d, $J_{C,P}$=4.00 Hz), 133.02 (d, $J_{C,P}$=2.00 Hz), 132.76 (d, $J_{C,P}$=3.00 Hz), 131.84, 131.75 (d, $J_{C,P}$=2.00 Hz), 131.36 (d, $J_{C,P}$=10.00 Hz), 131.04, 130.95, 130.31, 129.57, 129.35 (d, $J_{C,P}$=11.00 Hz), 129.33, 128.70 (d, $J_{C,P}$=12.00 Hz), 128.57, 122.95, 121.60 (d, $J_{C,P}$=3.00 Hz), 118.88, 95.20 (d, $J_{C,P}$=5.00 Hz), 44.25 (d, $J_{C,P}$=65.00 Hz), 13.01; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.01; IR (KBr) ν_{max}: 3442.0, 3036.5, 1636.4, 1590.7, 1570.8, 1520.9, 1486.4, 1437.0, 1182.3, 1140.3, 878.8, 792.4 cm^{-1}; HRMS (ESI): m/z=620.9920 (calcd for $C_{29}H_{23}Br_2N_2O_2P+H^+$=620.9937).

*4.2.18. 1-(4-Chlorophenyl)-4-((diphenylphosphoryl)(phenyl)methyl)-3-methyl-1H-pyrazol-5-ol (**3r**).* Yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.05 (s, 1H), 7.90–7.80 (m, 2H), 7.76 (d, J=8.8 Hz, 2H), 7.60–7.45 (m, 3H), 7.44–7.29 (m, 5H), 7.28–7.22 (m, 2H), 7.21–7.16 (m, 2H), 7.15–7.08 (m, 3H), 4.58 (d, J=11.6 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.21 (d, $J_{C,P}$=5.00 Hz), 147.79 (d, $J_{C,P}$=9.00 Hz), 137.75, 136.07 (d, $J_{C,P}$=4.00 Hz), 132.93 (d, $J_{C,P}$=3.00 Hz), 132.51 (d, $J_{C,P}$=2.00 Hz), 131.46 (d, $J_{C,P}$=9.00 Hz), 131.12 (d, $J_{C,P}$=8.00 Hz), 131.02, 129.42, 129.37, 129.26, 128.91, 128.69 (d, $J_{C,P}$=2.00 Hz), 128.56, 128.44, 127.49 (d, $J_{C,P}$=3.00 Hz), 122.73, 95.66 (d, $J_{C,P}$=5.00 Hz), 44.32 (d, $J_{C,P}$=65.00 Hz), 12.99; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.48; IR (KBr) ν_{max}: 3440.2, 3045.8, 1593.5, 1518.6, 1492.2, 1452.5, 1436.9, 1139.2, 873.9, 748.7, 693.1 cm^{-1}; HRMS (ESI): m/z=499.1347 (calcd for $C_{29}H_{24}ClN_2O_2P+H^+$=499.1337).

*4.2.19. 1-(4-Chlorophenyl)-4-((4-chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1H-pyrazol-5-ol (**3s**).* Yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.00 (s, 1H), 7.86–7.80 (m, 2H), 7.75 (d, J=8.8 Hz, 2H), 7.60–7.35 (m, 6H), 7.35–7.25 (m, 4H), 7.15–7.05 (m, 4H), 4.57 (d, J=11.2 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.07 (d, $J_{C,P}$=5.00 Hz), 147.61 (d, $J_{C,P}$=9.00 Hz), 137.70, 134.67 (d, $J_{C,P}$=4.00 Hz), 133.45 (d, $J_{C,P}$=3.00 Hz), 133.01 (d, $J_{C,P}$=3.00 Hz), 132.73 (d, $J_{C,P}$=3.00 Hz), 131.35 (d, $J_{C,P}$=10.00 Hz), 130.99 (d, $J_{C,P}$=8.00 Hz), 130.61 (d, $J_{C,P}$=5.00 Hz), 130.34, 129.61, 129.33 (d, $J_{C,P}$=12.00 Hz), 128.88, 128.78 (d, $J_{C,P}$=12.00 Hz), 128.67 (d, $J_{C,P}$=12.00 Hz), 122.66, 95.22 (d, $J_{C,P}$=4.00 Hz), 43.66 (d, $J_{C,P}$=64.00 Hz), 12.95; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.12; IR (KBr) ν_{max}: 3443.2, 3038.6, 1590.2, 1519.3, 1488.9, 1451.3, 1436.9, 1183.9, 879.4, 794.3 cm^{-1}; HRMS (ESI): m/z=533.0929 (calcd for $C_{29}H_{23}Cl_2N_2O_2P+H^+$=533.0947).

*4.2.20. 4-((4-Bromophenyl)(diphenylphosphoryl)methyl)-1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5-ol (**3t**).* Yield, ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.00 (s, 1H), 7.87–7.81 (m, 2H), 7.75 (d, J=8.8 Hz, 2H), 7.62–7.36 (m, 6H), 7.35–7.20 (m, 6H), 7.10–7.00 (m, 2H), 4.56 (d,

J=11.6 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.06 (d, $J_{C,P}$=5.00 Hz), 147.59 (d, $J_{C,P}$=9.00 Hz), 137.69, 135.21 (d, $J_{C,P}$=4.00 Hz), 133.00 (d, $J_{C,P}$=2.00 Hz), 132.74 (d, $J_{C,P}$=3.00 Hz), 131.73 (d, $J_{C,P}$=2.00 Hz), 131.35 (d, $J_{C,P}$=9.00 Hz), 131.02, 130.95, 130.93, 130.91, 130.32, 129.58, 129.33 (d, $J_{C,P}$=11.00 Hz), 128.88, 128.68 (d, $J_{C,P}$=12.00 Hz), 122.65, 121.58 (d, $J_{C,P}$=3.00 Hz), 95.14 (d, $J_{C,P}$=4.00 Hz), 43.73 (d, $J_{C,P}$=64.00 Hz), 12.95; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.98; IR (KBr) ν_{max}: 3421.8, 3062.7, 1636.3, 1590.5, 1519.4, 1488.3, 1437.1, 1140.8, 879.4, 793.4 cm^{-1}; HRMS (ESI): m/z=577.0449 (calcd for $C_{29}H_{23}BrClN_2O_2P+H^+$=577.0442).

*4.2.21. 4-((Di-p-tolylphosphoryl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**4a**).* Yield 96%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.98 (s, 1H), 7.80–7.70 (m, 4H), 7.37 (t, J=7.6 Hz, 2H), 7.32–7.12 (m, 10H), 7.10–7.02 (m, 2H), 4.53 (d, J=11.2 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.03 (d, $J_{C,P}$=5.25 Hz), 147.42 (d, $J_{C,P}$=10.50 Hz), 143.30 (d, $J_{C,P}$=3.00 Hz), 142.91 (d, $J_{C,P}$=3.00 Hz), 139.25, 136.49 (d, $J_{C,P}$=4.50 Hz), 131.44 (d, $J_{C,P}$=9.75 Hz), 131.03 (d, $J_{C,P}$=9.00 Hz), 129.94 (d, $J_{C,P}$=12.00 Hz), 129.45 (d, $J_{C,P}$=4.50 Hz), 129.15 (d, $J_{C,P}$=12.75 Hz), 128.80, 128.56, 127.25 (d, $J_{C,P}$=2.25 Hz), 125.59, 121.66, 95.55 (d, $J_{C,P}$=4.50 Hz), 44.47 (d, $J_{C,P}$=64.50 Hz), 21.75, 13.04; ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.61; IR (KBr) ν_{max}: 3476.7, 3414.6, 3056.4, 3027.5, 2918.5, 1595.3, 1522.7, 1497.9, 1452.3, 1419.2, 1118.6, 805.5, 754.0, 693.8 cm^{-1}; HRMS (ESI): m/z=515.1865 (calcd for $C_{31}H_{29}N_2O_2P+Na^+$=515.1859).

*4.2.22. 4-((Bis(3,5-dimethylphenyl)phosphoryl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**5a**).* Yield 95%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.98 (s, 1H), 7.77 (d, J=7.6 Hz, 2H), 7.45 (d, J=11.2 Hz, 2H), 7.38 (t, J=7.6 Hz, 2H), 7.25–7.10 (m, 7H), 7.02 (s, 1H), 6.87 (d, J=11.2 Hz, 2H), 4.53 (d, J=11.2 Hz, 1H), 2.36 (s, 6H), 2.17 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.05 (d, $J_{C,P}$=5.25 Hz), 147.27 (d, $J_{C,P}$=9.00 Hz), 139.18, 138.71 (d, $J_{C,P}$=12.00 Hz), 137.95 (d, $J_{C,P}$=12.75 Hz), 136.40 (d, $J_{C,P}$=4.50 Hz), 134.45 (d, $J_{C,P}$=1.50 Hz), 133.94 (d, $J_{C,P}$=2.25 Hz), 129.42 (d, $J_{C,P}$=4.50 Hz), 128.91 (d, $J_{C,P}$=9.75 Hz), 128.68, 128.56 (d, $J_{C,P}$=9.00 Hz), 128.32, 127.10 (d, $J_{C,P}$=1.50 Hz), 125.45, 121.52, 95.53 (d, $J_{C,P}$=4.50 Hz), 44.12 (d, $J_{C,P}$=64.50 Hz), 21.45, 21.14, 12.94; ^{31}P NMR (121 MHz, $CDCl_3$) δ 43.13; IR (KBr) ν_{max}: 3477.1, 3414.8, 3029.3, 2913.5, 1594.1, 1575.7, 1524.5, 1497.2, 1144.2, 903.2, 765.7, 691.4 cm^{-1}; HRMS (ESI): m/z=521.2350 (calcd for $C_{33}H_{33}N_2O_2P+H^+$=521.2352).

4.3. General experimental procedure for the enantioselective conjugate addition of diarylphosphane oxides to α,β-unsaturated pyrazolones

In an ordinary tube equipped with a magnetic stirring bar, the solution of diarylphosphane oxides **1** (0.15 mmol), 4 Å MS (400 mg), catalyst **6l** (30 mol %) in toluene (4.0 mL) was stirred at −40 °C for 30 min, and then α,β-unsaturated pyrazolone **2** (0.10 mmol) was added. After the reaction mixture was stirred for 84–144 h at −40 °C. The reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (eluant: petroleum ether/dichloromethane) to give desired products **3**–**5**.

*4.3.1. (−)-4-((Diphenylphosphoryl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3a**).* Yield 85%, 73% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R (major)=8.974, t_R(minor)=12.425]; $[\alpha]_D^{26}$ −254.6 (*c* 0.26, $CHCl_3$).

*4.3.2. (−)-4-((4-Chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3b**).* Yield 91%, 70% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=9.690, t_R(minor)=14.287]; $[\alpha]_D^{26}$ −219.8 (*c* 0.48, $CHCl_3$).

*4.3.3. (−)-4-((4-Bromophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3c**).* Yield 88%, 70% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=9.817, t_R(minor)=14.057]; $[\alpha]_D^{26}$ −215.7 (*c* 0.35, $CHCl_3$).

*4.3.4. (−)-4-((3-Chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3d**).* Yield 83%, 67% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=7.685, t_R(minor)=11.083]; $[\alpha]_D^{26}$ −140.8 (*c* 0.99, $CHCl_3$).

*4.3.5. (−)-4-((Diphenylphosphoryl)(p-tolyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3f**).* Yield 80%, 75% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=10.259, t_R(minor)=14.061]; $[\alpha]_D^{26}$ −135.4 (*c* 1.12, $CHCl_3$).

*4.3.6. (−)-4-((Diphenylphosphoryl)(4-methoxyphenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3g**).* Yield 61%, 70% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=12.335, t_R(minor)=15.128]; $[\alpha]_D^{26}$ −171.2 (*c* 0.73, $CHCl_3$).

*4.3.7. (−)-4-((Diphenylphosphoryl)(4-(methylthio)phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3h**).* Yield 70%, 71% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=12.195, t_R(minor)=16.386]; $[\alpha]_D^{26}$ −212.6 (*c* 0.87, $CHCl_3$).

*4.3.8. (−)-4-((Diphenylphosphoryl)(naphthalen-2-yl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3k**).* Yield 75%, 76% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=11.677, t_R(minor)=21.821]; $[\alpha]_D^{26}$ −127.9 (*c* 0.61, $CHCl_3$).

*4.3.9. (−)-4-((Diphenylphosphoryl)(furan-2-yl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**3l**).* Yield 92%, 58% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=12.417, t_R(minor)=17.206]; $[\alpha]_D^{26}$ −33.2 (*c* 1.32, $CHCl_3$).

*4.3.10. (−)-1-(4-Bromophenyl)-4-((diphenylphosphoryl)(phenyl)methyl)-3-methyl-1H-pyrazol-5-ol (**3m**).* Yield 82%, 68% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=9.817, t_R(minor)=14.057]; $[\alpha]_D^{26}$ −200.3 (*c* 0.63, $CHCl_3$).

*4.3.11. (−)-1-(4-Bromophenyl)-4-((4-chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1H-pyrazol-5-ol (**3p**).* Yield 45%, 44% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=8.453, t_R(minor)=9.362]; $[\alpha]_D^{26}$ −109.3 (*c* 0.55, $CHCl_3$).

*4.3.12. (−)-1-(4-Bromophenyl)-4-((4-bromophenyl)(diphenylphosphoryl)methyl)-3-methyl-1H-pyrazol-5-ol (**3q**).* Yield 55%, 50% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=8.833, t_R(minor)=9.756]; $[\alpha]_D^{26}$ −113.8 (*c* 0.94, $CHCl_3$).

*4.3.13. (−)-1-(4-Chlorophenyl)-4-((diphenylphosphoryl)(phenyl)methyl)-3-methyl-1H-pyrazol-5-ol (**3r**).* Yield 71%, 64% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=7.551, t_R(minor)=8.761]; $[\alpha]_D^{26}$ −112.5 (*c* 0.12, $CHCl_3$).

*4.3.14. (−)-1-(4-Chlorophenyl)-4-((4-chlorophenyl)(diphenylphosphoryl)methyl)-3-methyl-1H-pyrazol-5-ol (**3s**).* Yield 41%, 49% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=8.089, t_R(minor)=9.135]; $[\alpha]_D^{26}$ −93.4 (*c* 0.35, $CHCl_3$).

*4.3.15. (−)-4-((4-Bromophenyl)(diphenylphosphoryl)methyl)-1-(4-chlorophenyl)-3-methyl-1H-pyrazol-5-ol (**3t**).* Yield 43%, 50% ee [Daicel Chiralcel OD-H, hexane/*i*-PrOH (90:10), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=8.396, t_R(minor)=9.480]; $[\alpha]_D^{26}$ −105.5 (*c* 0.40, $CHCl_3$).

*4.3.16. (−)-4-((Di-p-tolylphosphoryl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**4a**).* Yield 46%, 48% ee [Daicel Chiralcel AD-

H, hexane/*i*-PrOH (80:20), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=32.263, t_R(minor)=20.327]; $[\alpha]_D^{26}$ −127.2 (*c* 0.57, $CHCl_3$).

*4.3.17. (−)-4-((Bis(3,5-dimethylphenyl)phosphoryl)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**5a**).* Yield 50%, 44% ee [Daicel Chiralcel AD-H, hexane/*i*-PrOH (70:30), flow rate: 1.0 mL min^{-1}, λ=254 nm, t_R(major)=5.014, t_R(minor)=4.304]; $[\alpha]_D^{26}$ −92.9 (*c* 0.70, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.038

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