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Development of new chiral *P*,*N* ligands and their applications in enantioselective 1,4-conjugate additions of diethylzinc to chalcones

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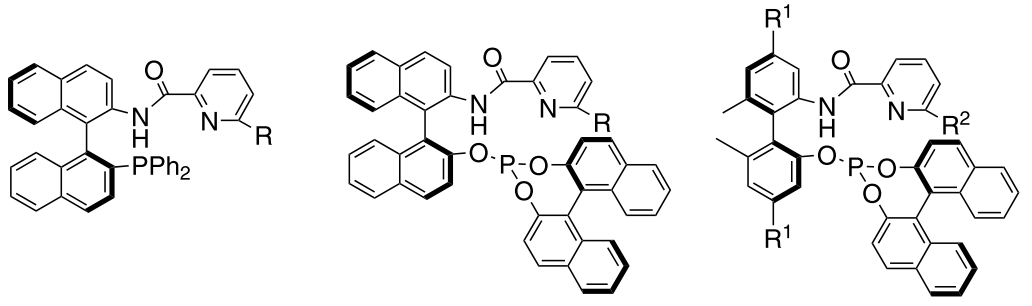
Abstract—Examples of a new type of chiral phosphine-pyridine ligand have been synthesized from (*R*)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl and (*R*)-2-amino-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl in six steps and successfully employed in Cu(I)-catalysed conjugate additions of diethylzinc to chalcones. Up to 96.1% ee and high activities were achieved.

1. Introduction

The development of new chiral ligands plays an important role for catalytic asymmetric reactions.[1] Over the past decade, chiral ligands derived from 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN[2]), especially, those from 2-amino-2′-diphenylphosphino-1,1′-binaphthyl (MAP[3]), have exhibited good asymmetric induction. Among those chiral ligands derived from MAP, Zhang's phosphine–pyridine ligand **I** (Fig. 1)[3f] showed excellent enantioselectivities in the 1,4-conjugate additions of diethylzinc to enones. Although many efficient chiral copper catalytic systems have been developed for the 1,4-conjugate additions of diorganozinc to various types of enones,[4–9] only a few copper complexes coordinated with chiral *P*,*N* ligands have proven to be efficient when chalcone was used as the enone substrate.[2a,3f,9c] On the basis of our latest report[10] on the



Ia: R = H
Ib: R = CH_3

IIa: R = H
IIb: R = CH_3

IIIa: R^1 = H, R^2 = H
IIIb: R^1 = H, R^2 = CH_3
IIIc: R^1 = CH_3, R^2 = H
IIId: R^1 = CH_3, R^2 = CH_3

Figure 1.

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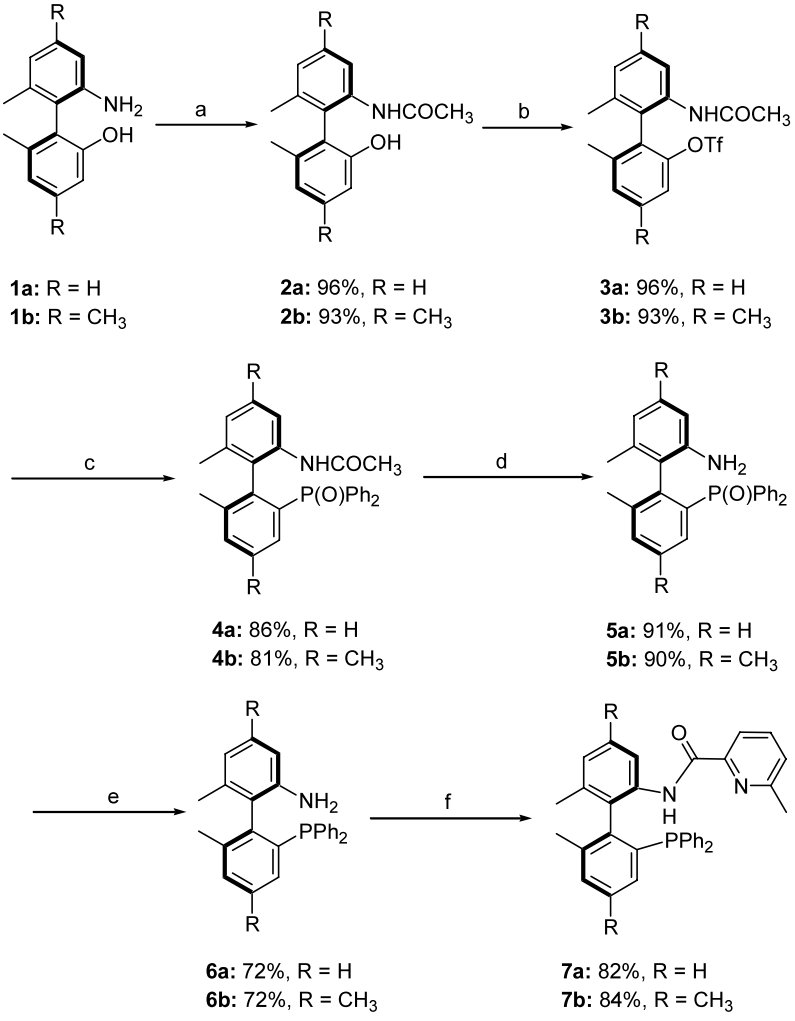
Cu(I)-catalysed 1,4-conjugate addition with phosphite–pyridine ligands **III** (Fig. 1) derived from the electron-rich chiral biphenyl backbone,[11] where the electronic property of the ligands played a very important role in obtaining high ee, compared to the phosphite–pyridine ligands **II** (Fig. 1) from the NOBIN backbone, we are interested in synthesizing MAP-type ligands **7** (Scheme 1) from the new chiral biphenyl backbone **1** to compare to Zhang's phosphine–pyridine ligands **I** (Fig. 1) in the applications of Cu(I)-catalysed 1,4-conjugate additions of diethylzinc to chalcones.

2. Results and discussions

Phosphine–pyridine ligand **7a** was synthesized from the chiral biphenyl backbone **1a** in six steps (Scheme 1). Acetylation of **1a** with excess acetyl chloride gave the *N*,*O*-diacetate, followed by selective hydrolysis of the OAc group with 1% aqueous NaOH to afford the hydroxy amide **2a** in 96% yield. Treatment of **2a** with trifluoromethanesulfonic anhydride (Tf_2O) at 0°C afforded the triflate **3a** in 96% yield. Phosphinoylation of **3a** with $Ph_2P(O)H$ to form the phosphine oxide **4a** under Pd-catalysis proceeded smoothly in DMSO at 120°C in 86% yield. Aminophosphine **6a** could then be obtained by direct reduction of **4a** with trichlorosilane, but was usually accompanied by the *N*-ethyl by-product,[3g] which could be avoided by the deacetylation of **4a**, followed by reduction with trichlorosilane.[3e] The deacetylation of **4a** with HCl under similar conditions did not work well, but we found it was a convenient process to perform this deacetylation when **4a** was refluxed in KOH–ethanol solution for 12 h, giving the aminophosphine oxide **5a** which was obtained as a white solid in 91% yield. Reduction of **5a** with trichlorosilane then produced aminophosphine **6a** in 72% yield. The amidation of **6a** with 6-methyl-2-picolinic acid in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[12] proceeded smoothly to afford the phosphine–pyridine ligand **7a** in 82% yield. Using the same procedure, the phosphine–pyridine ligand **7b** was also prepared from the chiral biphenyl backbone **1b**, with the yields of every step listed in Scheme 1.



Scheme 1. *Reagents and conditions*: (a) i. CH_3COCl, Et_3N, CH_2Cl_2, 0°C; ii. NaOH, $MeOH/H_2O$; (b) Tf_2O, pyridine, CH_2Cl_2, 0°C; (c) $Ph_2P(O)H$, $Pd(OAc)_2$, dppb, $EtN(i\text{-}Pr)_2$, DMSO, 120°C; (d) KOH, $EtOH/H_2O$, reflux; (e) Cl_3SiH, xylene, reflux; (f) 6-methylpicolinic acid, DMTMM, THF, rt.

As racemization can occur relatively easily for biphenyl backbones under some of the critical reaction conditions,[13] e.g. at high temperatures and strong base, it was worth studying the enantiomeric purities of compounds **4a**, **5a** and **6a** during the synthesis. We prepared these racemic compounds from racemic **1a** using the same procedure as described previously. It was found that chiral HPLC analysis with Daicel Chiralcel OD-H and Chiralpak AD columns could separate the enantiomers of these racemic biphenyl compounds. HPLC results showed no racemization during the preparation of homochiral compounds **4a**, **5a** and **6a** (>99.5% ee).

We chose chalcone as the substrate and the phosphine–pyridine ligand **7a** as the ligand to optimize the reaction conditions for the Cu-catalysed asymmetric 1,4-conjugate additions (Table 1). $[Cu(CH_3CN)_4]BF_4$ was selected as the copper precursor.[2a,3f,14] The conjugate addition of Et_2Zn to chalcone was conducted in the presence of 1 mol% of $[Cu(CH_3CN)_4]BF_4$ and 2.5 mol% of ligand **7a**. The catalyst was prepared via treatment of ligand **7a** with $[Cu(CH_3CN)_4]BF_4$ in toluene (25°C) and removal of the coordinated acetonitrile via stripping the solvent in vacuo.[3f] Enantioselective 1,4-conjugate addition of Et_2Zn to chalcone gave better yields and enantioselectivity in toluene than in dichloroethane, mixed solvents also achieved good yields and enantioselectivity (entries 1–4). Interestingly, on increasing the proportion of dichloroethane, the isolated yield of the addition product had a decreasing trend. The influence of temperature on the reaction was also examined (entries 4–8) with the optimal reaction temperature for obtaining high enantioselectivity being −10°C (entry 4). The reaction time from 3–12 h had only a marginal effect on the enantioselectivity and yield (entries 4, 9–11).

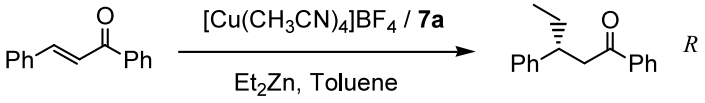
Under the optimal reaction conditions for enantioselective 1,4-conjugate additions, various chalcones were successfully converted into the corresponding chiral ketones using ligands **7a** and **7b** (Table 2). As can be seen in Table 2, ligand **7a** provides all chalcones into chiral ketone products in 90–95% ee, although ligand **7b** provides the best ee (96.1%). 4-Methoxychalcone proved to be the best substrate to give high enantioselectivity with either **7a** or **7b** as the ligand for the 1,4-conjugate addition (entries 4).

From Table 2, our new chiral *P*,*N* ligands **7** showed high catalytic activity with good to excellent ee's for various *para*-substituted chalcones compared with Zhang's *P*,*N* ligands based on NOBIN, which provided the best ees in the 1,4-conjugate addition of Et_2Zn to chalcones to date but with relatively lower catalytic activity.[3f] A possible reason was that the electron-rich phosphine, which was donated by the methyl substituted phenyl ring in the backbone, could result in a highly active Cu(I) catalytic species in the 1,4-conjugate addition.

3. Conclusion

In conclusion, we have successfully synthesized a new type of chiral phosphine–pyridine ligand **7** from (*R*)-2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl **1a** and (*R*)-2-amino-2′-hydroxy-4,4′,6,6′-tetra-methyl-1,1′-biphenyl **1b** in six steps and employed them in Cu-catalysed 1,4-conjugate additions of Et_2Zn to chalcones. Excellent enantioselectivities (up to 96.1% ee) have been obtained. Future studies will focus on the development of new chiral *P*,*N* ligands derived from MAP-type compound **6** and their applications in other catalytic asymmetric reactions.

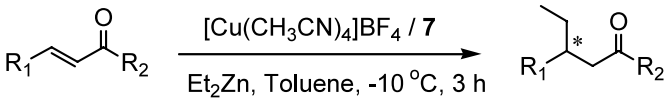
Table 1. Cu-catalyzed enantioselective 1,4-conjugate addition of Et_2Zn to chalcone[a]



Entry	Solvent	*T* (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	Toluene/$Cl(CH_2)_2Cl$ (2/1)	−10	12	75.2	93.4
2	Toluene/$Cl(CH_2)_2Cl$ (1/1)	−10	12	62.4	93.6
3	$Cl(CH_2)_2Cl$	−10	12	30.1	90.3
4	Toluene	−10	12	80.4	93.1
5	Toluene	10	12	71.8	89.0
6	Toluene	0	12	78.2	91.0
7	Toluene	−20	12	57.9	89.6
8	Toluene	−30	12	32.3	86.8
9	Toluene	−10	9	80.3	91.9
10	Toluene	−10	6	81.0	91.6
11	Toluene	−10	3	76.4	92.6

[a] The reaction was carried out in 3 ml of solvent, chalcone (0.5 mmol)/$[Cu(CH_3CN)_4]BF_4$/ligand **7a** = 1/0.01/0.025.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a Daicel Chiralpak-AD column.

Table 2. Cu-catalyzed enantioselective 1,4-conjugate addition of Et_2Zn to chalcones[a]



Entry	R_1	R_2	7a		7b		(Config.)[d]
			Yield[b] (%)	E.e.[c] (%)	Yield[b] (%)	Ee[c] (%)	
1	Ph	Ph	78.7	92.1	84.0	91.4	*R*
2	4-Me-C_6H_4	Ph	83.5	94.1	81.6	93.1	–[e]
3	Ph	4-Me-C_6H_4	74.8	93.6	71.2	92.5	–[e]
4	4-MeO-C_6H_4	Ph	75.8	95.3	81.2	96.1	*R*
5	Ph	4-MeO-C_6H_4	38.2	93.1	46.7	94.9	+[e]
6	4-Cl-C_6H_4	Ph	79.2	90.1	69.8	88.8	–[e]
7	Ph	4-Cl-C_6H_4	83.5	94.1	76.2	86.8	+[e]

[a] The reaction was carried out at −10°C for 3 h in 3 ml of toluene, substrate (0.5 mmol)/$[Cu(CH_3CN)_4]BF_4$/ligand 7 = 1/0.01/0.025.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a Daicel Chiralpak-AD column.
[d] The absolute configuration was assigned by the comparison of the specific rotation with the reported data.
[e] Sign of the specific rotation of the addition product.

4. Experimental

4.1. General methods

Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). Optical rotations were measured on a JASCO 1200 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 system with TMS as an internal reference. ^{31}P NMR spectra were recorded with 85% phosphoric acid as the external standard. High resolution mass spectra were recorded on Mat 95 (EI: 70 eV) for **2a**–**6a** and on ABMS 5303 (ESI) for **7a**, **2b**–7**b**. Enantiomeric excesses (ee) were determined by HPLC analysis (Agilent 1100 series). All experiments were carried out under an argon atmosphere. All solvents were dried with standard procedures before use.

4.2. (*R*)-(−)-2-(Acetamido)-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl 2a

Acetyl chloride (2.2 g, 28.0 mmol) was slowly added to a solution of **1a** (2.0 g, 9.4 mmol) in 80 ml of dry dichloromethane and 5 ml of pyridine at 0°C, with the resulting mixture then stirred at room temperature for 2 h. The solvent was evaporated and the residue purified by silica gel column with dichloromethane to give 2-(acetamido)-2′-acetate-6,6′-dimethyl-1,1′-biphenyl (diacetate): ^1H NMR ($CDCl_3$) δ 1.87 (s, 3H), 1.91 (s, 3H), 1.94 (s, 3H), 1.95 (s, 3H), 6.98–7.00 (m, 2H), 7.05 (d, J = 7.2 Hz, 1H), 7.23–7.29 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.90 (d, J = 7.2 Hz, 1H). The diacetate was dissolved in 100 ml of methanol, after which 15 ml of 1% aqueous NaOH was added. The mixture was stirred at room temperature for 2 h. The solvent was then evaporated under reduced pressure and the residue extracted with dichloromethane (3×30 ml). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, purified by silica gel column with a 1:1 petroleum ether–ethyl acetate as eluent to give 2.3 g of **2a** (96%) as a white solid: mp 150–152°C; $[\alpha]_D^{23} = -7.9$ (c 0.5, THF); ^1H NMR (DMSO-d_6) δ 1.82 (s, 6H), 1.90 (s, 3H), 6.77–6.82 (m, 2H), 7.06–7.13 (m, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.99 (s, 1H), 9.10 (s, 1H); ^{13}C NMR δ 19.33, 19.70, 23.63, 113.20, 120.78, 121.11, 123.07, 125.72, 126.81, 128.45, 130.24, 136.05, 136.81, 137.46, 154.72, 168.20; HRMS (m/z): M^+ calcd for $C_{16}H_{17}NO_2$ 255.1259; found, 255.1261.

4.3. (*R*)-(−)-2-(Acetamido)-2′-hydroxy-4,4′,6,6′-tetramethyl-1,1′-biphenyl 2b

Following the same method for the synthesis of **2a**, **2b** (2.5 g) was obtained from **1b** (2.4 g, 10 mmol) in 93% yield as a white solid: mp 159–161°C; $[\alpha]_D^{23} = -7.6$ (c 0.5, THF); ^1H NMR ($CDCl_3$) δ 1.89 (s, 3H), 1.93 (s, 3H), 1.95 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 5.58 (br, 1H), 6.71 (s, 1H), 6.73 (s, 1H), 6.83 (s, 1H), 6.93 (s, 1H), 8.03 (s, 1H). ^{13}C NMR δ 19.38, 19.71, 21.34, 21.55, 21.62, 113.92, 118.38, 119.39, 120.94, 123.49, 127.28, 136.38, 137.73, 138.06, 139.21, 139.81, 153.13, 168.80; HRMS (m/z): $(M+1)^+$ calcd for $C_{18}H_{22}NO_2$ 284.1655; found, 284.1645.

4.4. (*R*)-(−)-2-(Acetamido)-2′-(trifluoromethylsulfonyloxy)-6,6′-dimethyl-1,1′-biphenyl 3a

Tf_2O (2.7 g, 8.4 mmol) was slowly added to a solution of **2a** (2.0 g, 7.8 mmol) and 2 ml of pyridine in 35 ml of dichloromethane at 0°C, and the mixture was stirred for 3 h. The mixture was then diluted with 30 ml of dichloromethane and washed with 5% HCl (2×20 ml), 20 ml of saturated $NaHCO_3$ and 20 ml of water. The organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column with 5:1 petroleum ether–ethyl acetate as eluent to give 2.9 g of **3a** (96%) as a white solid: mp 62–64°C; $[\alpha]_D^{23} = -36.3$ (c 0.5, THF); ^1H NMR (DMSO-d_6) δ 1.76 (s, 3H), 1.92 (s, 3H), 2.03 (s, 3H), 7.16 (d,

$J=7.0$ Hz, 1H), 7.29–7.31 (m, 2H), 7.46–7.49 (m, 3H), 8.55 (s, 1H); ^{13}C NMR δ 19.29, 19.40, 23.06, 116.12, 118.31, 119.31, 123.03, 126.67, 127.81, 128.46, 129.57, 130.26, 136.35, 136.82, 140.98, 146.86, 168.16; HRMS (m/z): M^+ calcd for $C_{17}H_{16}F_3NO_4S$ 387.0753; found, 387.0752.

4.5. (*R*)-(−)-2-(Acetamido)-2′-(trifluoromethylsulfonyloxy)-4,4′,6,6′-tetramethyl-1,1′-biphenyl 3b

Following the same method for the synthesis of **3a**, **3b** (3.3 g) was obtained from **2b** (2.3 g, 8.5 mmol) in 93% yield as a yellow oil: $[\alpha]_D^{23}=-38.4$ (c 0.5, THF); ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 1.94 (s, 3H), 1.99 (s, 3H), 2.37 (s, 3H), 2.43 (s, 3H), 6.78 (s, 1H), 6.94 (s, 1H), 7.04 (s, 1H), 7.20 (s, 1H), 7.28 (s, 1H), 7.77 (s, 1H); ^{13}C NMR δ 19.45, 19.66, 21.03, 21.34, 24.19, 116.58, 119.58, 119.76, 121.16, 122.04, 127.24, 131.32, 135.49, 136.64, 138.98, 140.29, 140.70, 147.27, 168.30; HRMS (m/z): $(M+1)^+$ calcd for $C_{19}H_{21}F_3NO_4S$ 416.1151; found, 416.1138.

4.6. (*R*)-(−)-2-(Acetamido)-2′-(diphenylphosphinyl)-6,6′-dimethyl-1,1′-biphenyl 4a

To a mixture of **3a** (1.0 g, 2.6 mmol), diphenylphosphine oxide (1.0 g, 4.9 mmol), palladium(II) acetate (112 mg, 0.5 mmol), and 1,4-bis(diphenylphosphino)butane (dppb, 213 mg, 0.5 mmol) was added 50 ml of DMSO and 1.5 ml of diisopropylethylamine with the resulting mixture stirred at 120°C for 4 h. After cooling to room temperature, the reaction mixture was poured into 300 ml of 5% HCl with the product extracted with dichloromethane (3×50 ml). The combined extracts were washed with 1% HCl and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column with 1:1 petroleum ether–ethyl acetate as eluent to give 1.0 g of **4a** (86%) as a white solid: mp 166–168°C; $[\alpha]_D^{23}=-130.4$ (c 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.41 (s, 3H), 1.73 (s, 3H), 1.76 (s, 3H), 6.56 (d, $J=7.6$ Hz, 1H), 7.04 (t, $J=7.6$ Hz, 1H), 7.16–7.30 (m, 4H), 7.39–7.48 (m, 4H), 7.55–7.62 (m, 4H), 7.86–7.90 (m, 2H), 9.03 (s, 1H); ^{13}C NMR δ 19.34, 19.67, 23.36, 124.32, 126.57, 127.56, 127.70, 127.80, 127.99, 128.11, 128.61, 128.72, 130.29, 130.38, 130.58, 130.99, 131.09, 131.31, 131.68, 131.77, 132.00, 133.59, 134.36, 136.05, 136.57, 138.47, 138.57, 141.10, 141.18, 167.71; ^{31}P NMR δ 29.13; HRMS (m/z): M^+ calcd for $C_{28}H_{26}NO_2P$ 439.1701; found, 439.1706; >99.5% ee. HPLC analysis condition for racemic **4a**: Chiralcel OD-H, 90/10 hexanes/*i*-PrOH, 0.7 ml/min, 25°C, retention time: $t_S=12.76$ min; $t_R=16.40$ min.

4.7. (*R*)-(−)-2-(Acetamido)-2′-(diphenylphosphinyl)-4,4′,6,6′-tetramethyl-1,1′-biphenyl 4b

Following the same method for the synthesis of **4a**, **4b** (1.0 g) was obtained from **3b** (1.1 g, 2.7 mmol) in 81% yield as a white solid: mp 180–182°C; $[\alpha]_D^{23}=-94.3$ (c 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 3H), 1.74 (s, 3H), 1.75 (s, 3H), 2.17 (s, 3H), 2.24 (s, 3H), 6.35 (s, 1H), 6.97–7.03 (m, 2H), 7.29–7.87 (m, 11H), 8.98 (s, 1H); ^{13}C NMR δ 19.31, 19.66, 20.54, 20.75, 23.42, 124.65, 127.31, 127.73, 127.85, 128.48, 128.59, 130.16, 130.25, 130.51, 130.76, 130.87, 131.07, 131.33, 131.63, 131.71, 131.86, 132.11, 132.34, 134.95, 135.97, 136.37, 136.49, 136.74, 138.31, 138.39, 138.50, 138.60, 167.56; ^{31}P NMR δ 28.99; HRMS (m/z): $(M+1)^+$ calcd for $C_{30}H_{31}NO_2P$ 468.2108; found, 468.2087.

4.8. (*R*)-(−)-2-Amino-2′-(diphenylphosphinyl)-6,6′-dimethyl-1,1′-biphenyl 5a

To a solution of **4a** (2.6 g, 5.9 mmol) in 50 ml of ethanol was added 50 ml of 50% aqueous KOH, the reaction mixture was stirred under reflux for 12 h. After cooling to room temperature, most of the ethanol was removed under reduced pressure. 40 ml of water was then added to the residue. The crude product was extracted with dichloromethane (3×30 ml). The combined extracts were washed with water (2×30 ml), then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column with 1:1 petroleum ether–ethyl acetate as eluent to give 2.2 g of **5a** (91%) as a white solid: mp 216–218°C; $[\alpha]_D^{23}=-87.9$ (c 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.54 (s, 3H), 1.84 (s, 3H), 3.92 (s, 2H), 6.18-6.22 (m, 2H), 6.69 (t, $J=7.6$ Hz, 1H), 7.18–7.24 (m, 1H), 7.32–7.36 (m, 3H), 7.40–7.52 (m, 4H), 7.55–7.66 (m, 5H); ^{13}C NMR δ 19.07, 20.07, 112.47, 117.98, 123.64, 127.00, 127.13, 127.82, 127.93, 128.03, 128.15, 131.00, 131.17, 131.28, 131.36, 132.19, 132.34, 132.79, 133.21, 133.35, 133.80, 133.98, 136.03, 138.67, 138.77, 142.04, 142.12, 145.22; ^{31}P NMR δ 26.96; HRMS (m/z): M^+ calcd for $C_{26}H_{24}NOP$ 397.1596; found, 397.1585; >99.5% ee. HPLC analysis condition for racemic **5a**: Chiralpak AD, 80/20 hexanes/*i*-PrOH, 0.7 ml/min, 25°C, retention time: $t_R=9.84$ min; $t_S=11.98$ min.

4.9. (*R*)-(−)-2-Amino-2′-(diphenylphosphinyl)-4,4′,6,6′-tetramethyl-1,1′-biphenyl 5b

Following the same method for the synthesis of **5a**, **5b** (0.9 g) was obtained from **4b** (1.1 g, 2.4 mmol) in 90% yield as a white solid: mp 60–64°C; $[\alpha]_D^{23}=-78.7$ (c 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.52 (s, 3H), 1.81 (s, 3H), 2.00 (s, 3H), 2.23 (s, 3H), 3.82 (s, 2H), 5.92 (s, 1H), 5.99 (s, 1H), 7.04 (d, $J=13.8$ Hz, 1H), 7.30–7.66 (m, 11H); ^{13}C NMR δ 19.10, 20.05, 20.81, 113.08, 119.04, 120.87, 127.57, 127.68, 127.93, 128.05, 130.65, 130.80, 130.89, 131.06, 131.26, 131.34, 131.71, 131.83, 132.24, 132.59, 133.11, 133.26, 134.69, 135.88, 136.36, 138.68, 138.79, 139.10, 145.11; ^{31}P NMR δ 27.15; HRMS (m/z): $(M+1)^+$ calcd for $C_{28}H_{29}NOP$ 426.1956; found, 426.1981.

4.10. (*R*)-(−)-2-Amino-2′-(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl 6a

Trichlorosilane (3.0 g, 22.2 mmol) was added to a mixture of **5a** (870 mg, 2.2 mmol) and 4 ml of triethylamine in 40 ml of xylene at 0°C, with the resulting mixture heated to 120°C and stirred for 5 h. After cooling to room temperature, the mixture was diluted with dichloromethane and quenched with saturated

$NaHCO_3$. The resulting suspension was filtered through Celite and the solid washed with dichloromethane. The combined organic filtrates were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column with 5:1 petroleum ether–ethyl acetate as eluent to give 600 mg of **6a** (72%) as a white solid: mp 122–124°C; $[\alpha]_D^{23} = -83.9$ (*c* 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.45 (s, 3H), 1.90 (s, 3H), 6.41 (d, $J = 7.2$ Hz, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 6.92–6.96 (m, 2H), 7.10–7.14 (m, 4H), 7.28–7.38 (m, 8H); ^{13}C NMR δ 19.35, 19.57, 112.22, 117.92, 124.43, 124.50, 127.64, 127.82, 128.10, 128.39, 128.62, 131.17, 131.96, 132.58, 132.78, 133.44, 133.64, 135.76, 136.78, 136.92, 137.09, 137.14, 137.49, 137.58, 138.16, 138.30, 143.36, 143.69, 144.67; ^{31}P NMR δ –12.97; HRMS (*m*/*z*): M^+ calcd for $C_{26}H_{24}NP$ 381.1647; found, 381.1629; >99.5% ee. HPLC analysis condition for racemic **6a**: Chiralpak AD, 80/20 hexanes/*i*-PrOH, 0.7 ml/min, 25°C, retention time: $t_R = 5.20$ min; $t_S = 6.40$ min.

4.11. (*R*)-(−)-2-Amino-2′-(diphenylphosphino)-4,4′,6,6′-tetramethyl-1,1′-biphenyl 6b

Following the same method for the synthesis of **6a**, **6b** (534 mg) was obtained from **5b** (770 mg, 1.8 mmol) in 72% yield as a white solid: mp 58–62°C; $[\alpha]_D^{23} = -78.4$ (*c* 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.43 (s, 3H), 1.86 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 3.92 (s, 2H), 6.23 (s, 1H), 6.36 (s, 1H), 6.78 (s, 1H), 7.12–7.17 (m, 5H), 7.29–7.32 (m, 6H); ^{13}C NMR δ 19.37, 19.59, 20.83, 21.04, 112.81, 119.03, 121.84, 121.91, 128.01, 128.33, 132.13, 132.35, 132.57, 132.77, 133.35, 133.55, 135.74, 136.31, 137.12, 137.20, 137.41, 137.51, 138.42, 138.57, 140.70, 141.04, 144.71; ^{31}P NMR δ –13.22; HRMS (*m*/*z*): $(M+1)^+$ calcd for $C_{28}H_{29}NP$ 410.2027; found, 410.2032.

4.12. (*R*)-(−)-2-(6-Methyl-2-pyridinylcarboxamido)-2′-(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl 7a

A mixture of 6-methylpicolinic acid (345 mg, 2.5 mmol) and **6a** (800 mg, 2.1 mmol) in 10 ml of THF was stirred at room temperature for 10 min. DMTMM (700 mg, 2.5 mmol) was added to the mixture and stirred at room temperature. After the reaction was complete (detected by TLC), 10 ml of water was added into the reaction mixture. After separating the layers, the aqueous layer was extracted with diethyl ether (3×20 ml), the combined organic layers successively washed with saturated $NaHCO_3$, brine, 5% HCl and brine, then dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The residue was purified by silica gel column with 10:1 petroleum ether–ethyl acetate as eluent to give 861 mg of **7a** (82%) as a white solid: mp 104–106°C; $[\alpha]_D^{23} = -176.6$ (*c* 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.76 (s, 3H), 1.89 (s, 3H), 2.18 (s, 3H), 6.85–6.91 (m, 4H), 7.03–7.11 (m, 5H), 7.33–7.37 (m, 4H), 7.44–7.51 (m, 3H), 7.82–7.90 (m, 2H), 8.36 (d, $J = 8.0$ Hz, 1H), 9.73 (s, 1H); ^{13}C NMR δ 19.35, 19.70, 23.37, 115.66, 118.58, 124.94, 126.21, 127.79, 127.85, 128.29, 128.59, 128.77, 129.00, 129.07, 131.45, 131.98, 132.81, 133.01, 133.26, 133.46, 135.27, 136.11, 136.23, 136.34, 137.09, 137.14, 138.01, 138.12, 138.27, 140.90, 141.22, 148.18, 156.51, 160.46; ^{31}P NMR δ –12.51; HRMS (*m*/*z*): $(M+1)^+$ calcd for $C_{33}H_{30}N_2OP$ 501.2075; found, 501.2090.

4.13. (*R*)-(−)-2-(6-Methyl-2-pyridinylcarboxamido)-2′-(diphenylphosphino)-4,4′,6,6′-tetramethyl-1,1′-biphenyl 7b

Following the same method for the synthesis of **7a**, **7b** (326 mg) was obtained from **6b** (330 mg, 0.73 mmol) in 84% yield as a white solid: mp 158–160°C; $[\alpha]_D^{23} = -180.9$ (*c* 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 1.73 (s, 3H), 1.84 (s, 3H), 2.16 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 6.82–6.92 (m, 6H), 7.03–7.12 (m, 3H), 7.32–7.37 (m, 4H), 7.45 (d, $J = 7.6$ Hz, 1H), 7.80–7.82 (m, 1H), 7.90 (t, $J = 7.6$ Hz, 1H), 8.21 (s, 1H), 9.74 (s, 1H); ^{13}C NMR δ 19.39, 19.68, 20.87, 21.32, 23.06, 116.13, 118.54, 125.67, 126.24, 127.76, 128.20, 128.60, 128.74, 132.36, 132.51, 132.67, 132.87, 133.24, 133.44, 135.32, 136.13, 136.47, 136.58, 137.13, 137.54, 137.88, 137.99, 138.20, 138.36, 138.52, 148.24, 156.46, 160.33; ^{31}P NMR δ –12.65; HRMS (*m*/*z*): $(M+1)^+$ calcd for $C_{35}H_{34}N_2OP$ 529.2427; found, 529.2403.

4.14. General procedure for asymmetric 1,4-conjugate additions

Preparation of catalyst. **7a** (50.2 mg, 0.10 mmol), $[Cu(CH_3CN)_4]BF_4$ (12.6 mg, 0.04 mmol), and 8 ml of toluene were added to a 25 ml flame-dried Schlenk tube under an argon atmosphere. After 30 min of stirring at room temperature, the solvent was stripped off *in vacuo* 8 ml of CH_2Cl_2 was then added to the flask and the catalyst solution used for four separated conjugate addition reactions. **Asymmetric 1,4-conjugate addition**. The chalcone substrate (1 mmol) and 1 ml of the above prepared catalyst solution were added to a flame-dried Schlenk tube under an argon atmosphere. After the solvent had been stripped off, 3 ml of toluene was added. The slurry was stirred at room temperature for 10 min and then cooled to the desired temperature. After the slurry had been stirred for 15 min, 0.7 ml of Et_2Zn (1.1 M in toluene, 1.5 equiv.) was added slowly. The resulting mixture was stirred at that temperature for 3 h. 4 ml of 5% hydrochloric acid was added to quench the reaction. The mixture was then allowed to warm to room temperature after which 15 ml of diethyl ether was added. The organic layer was washed with 5 ml of saturated $NaHCO_3$ and 5 ml of brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by silica gel column and eluted with EtOAc/hexanes (1/40–1/20) to afford the addition product. The enantiomeric excesses (ees) were determined by HPLC with a Chiral Daicel Chiralpak AD column. The detailed analytical conditions are given in the Supporting Information of reference **2a**.

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