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Development of new chiral phosphine-salen type ligands and their application in the Cu(I)-catalyzed enantioselective Henry reaction

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Abstract—Chiral phosphine-salen type ligand **L4** prepared from (*R*)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine was found to be a fairly effective chiral ligand for Cu(I)-promoted enantioselective Henry reactions of arylaldehydes with nitromethane to give the corresponding adducts in moderate enantioselectivities and moderate to good yields.

1. Introduction

Among the various C–C bond forming reactions, the nitroaldol (Henry) reaction is one of the classical named reactions in organic synthesis,[1] affording efficient access to valuable functionalized structural motifs, such as 1,2-amino alcohols and α-hydroxy carboxylic acids.[2] The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.[3] Since then, many interesting reports have been continuously appearing in the literature.[4] Among the most outstanding examples, an aldehyde is usually treated with a nitroalkane (nitromethane) in the presence of a chiral metal complex and other additives to give the corresponding adducts in good to excellent enantioselectivities. Recently, Schiff base-type (salen-type) chiral ligands have attracted much attention because they can coordinate with a variety of transition-metal ions to afford the corresponding stable chiral metal complexes in good yields and these chiral metal complexes are in general quite efficient in many asymmetric reactions including the asymmetric Henry reaction. For example, Yamada et al. employed commercially available cobalt salen complexes for the enantioselective Henry reaction to give the adducts in good yields and good ees under mild reaction conditions.[5] Moreover, chiral copper Schiff base complexes for the asymmetric Henry reaction were developed by Zhou last year.[6]

These results prompted us to explore new chiral phosphine-salen type ligands for asymmetric reactions, since we envisioned that these chiral ligands can also coordinate with a variety of metal ions under mild conditions. In this paper we wish to report the preparation of these new chiral phosphine-salen type ligands and their application as fairly effective ligands in the Cu(I)-promoted enantioselective Henry reaction.

2. Results and discussion

Chiral phosphine-salen type ligands **L1**–**L6**[7] as well as their derivatives **L7**–**L10** were synthesized from the reaction of salicylaldehydes as well as its analogues with (*R*)-(−)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine[8] in absolute ethanol at reflux for 12 h, respectively (Scheme 1). Initial examinations using 4-nitrobenzaldehyde **1c** and nitromethane as substrates in the presence of chiral phosphine-salen type ligand **L1** and various copper salts were aimed at determining the optimal reaction conditions; the results of these experiments are summarized in Table 1. We found that using CH_3OH as a solvent and 4 Å MS (10 mg) as an additive, the corresponding Henry reaction product **2c** was obtained in moderate to good yields with a variety of copper salts (10 mol %) in the presence of **L1** (10 mol %) at

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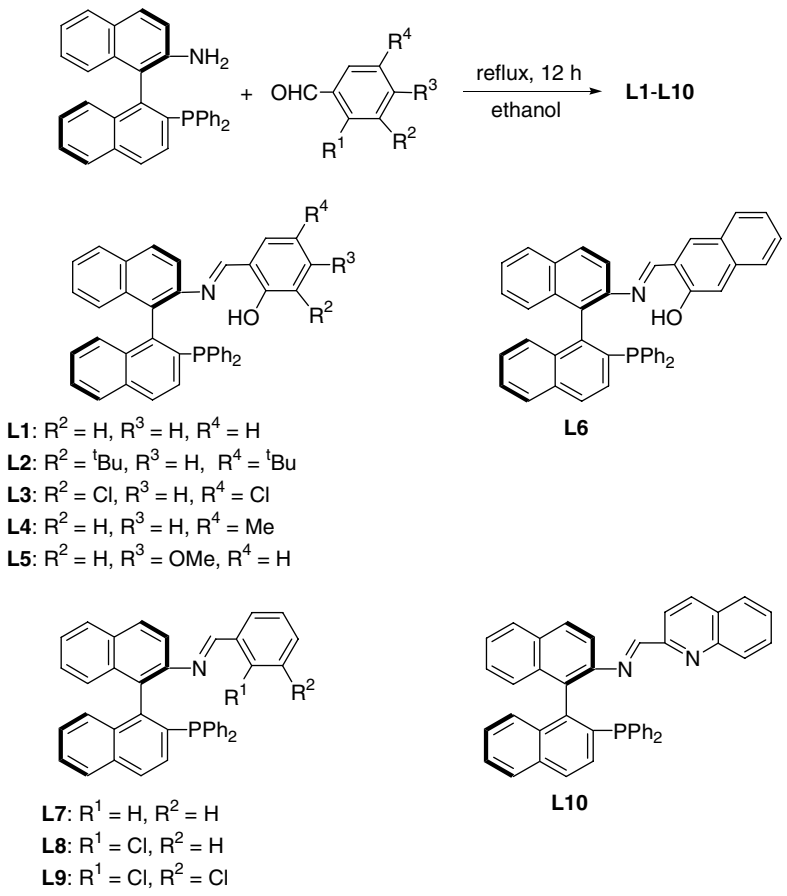


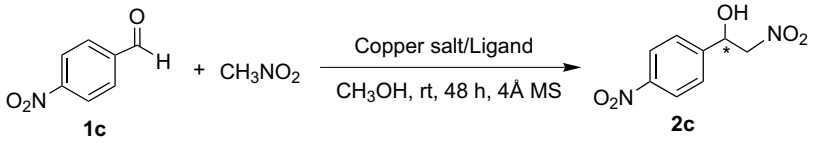
Scheme 1. Preparation of phosphine-salen type ligands **L1**–**L10**.

room temperature with up to 68% ee being achieved using $(CuOTf)_2{\cdot}C_6H_6$ as a metal catalyst (Table 1, entries 1–6). Molecular sieves 4 Å were crucial for this enantioselective Henry reaction since in the absence of MS 4 Å, the reaction became sluggish and no ee could be observed under identical conditions (Table 1, entry 15). When using 100 mg of MS 4 Å as additives, no significant improvement could be realized (Table 1, entry 16). The effect of MS 4 Å remains unclear at this present stage. However, on the basis of previous investigation, it may be attributed to the ability of molecular sieves to serve as a Brønsted base and to improve the catalyst stability.[9] By screening chiral phosphine-salen ligands **L1**–**L6**, we found that **L4** was the best chiral phosphine-salen type ligand for this enantioselective Henry reaction using $(CuOTf)_2{\cdot}C_6H_6$ as a metal catalyst, affording the corresponding adduct **2c** in 73% ee and 87% yield at room temperature (Table 1, entry 9). It should be noted that chiral phosphine-salen type ligand **L3**, bearing an electron-withdrawing group on the benzene ring, gave the corresponding adduct **2c** in 7% ee and 94% yield under identical conditions (Table 1, entry 8). In addition, an electron-donating group on the benzene ring, such as chiral phosphine-salen type ligands **L2**, **L5**, and **L6**, gave adduct **2c** in moderate ees (55–71%) and good yields (Table 1, entries 7, 10, and 11). These results suggested that the substituent on the benzene ring in the chiral phosphine-salen type ligands played an important role in the chiral induction of this enantioselective Henry reaction. We also found that factors such as the catalyst loading, ratio of ligand to $(CuOTf)_2{\cdot}C_6H_6$ and reaction temperature had little effect on the improvement of enantioselectivity (Table 1, entries 12–14).

Using chiral phosphine-salen type ligand **L2** under standard conditions, we examined the solvent effect in this asymmetric reaction with ethanol, acetonitrile, dichloroethane, and so on. The results are summarized in Table 2. We found that methanol was the best solvent for this asymmetric Henry reaction (Table 2, entry 1).

With the optimized conditions in hand, we next attempted to improve further the enantioselectivity using Et_3N (10 mol %) as a base. We found that when using $(CuOTf)_2{\cdot}C_6H_6$ as a catalyst and Et_3N (10 mol %) as base, the adduct **2c** could be obtained in moderate to good yields (71% and 90%) and 54% ee in methanol and THF at room temperature in the presence of **L2** (Table 3, entries 1 and 2). At −20 °C in THF, **2c** was formed in 87% yield and 63% ee (Table 3, entry 3). Another chiral phosphine-salen type ligand **L4** produced **2c** in good yields and 40% and 67% ee under similar conditions (Table 3, entries 4 and 5). Therefore, using Et_3N (10 mol %) as a base did not improve the enantioselectivity in this reaction. The best reaction conditions were to carry out the reaction in methanol using $(CuOTf)_2{\cdot}C_6H_6$ (5 mol %) as a catalyst and 4 Å MS (10 mg) as an additive in the presence of chiral phosphine-salen type **L4** (10 mol %) at room temperature.

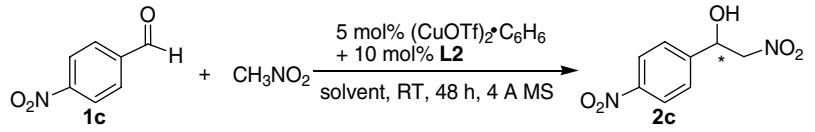
Table 1. Optimization of the reaction conditions in the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane



Entry[a]	Ligand (10 mol %)	Copper salt (10 mol %)	Yield[b] (%)	ee[c] (%)
1	**L1**	CuI	68	0
2	**L1**	CuCl	78	13
3[d]	**L1**	$Cu(OTf)_2$	49	37
4	**L1**	$Cu(OAc)_2{\cdot}H_2O$	75	24
5	**L1**	$(CuOTf)_2{\cdot}C_6H_6$	99	68
6	**L1**	$Cu(CH_3CN)_4ClO_4$	71	39
7	**L2**	$(CuOTf)_2{\cdot}C_6H_6$	94	71
8	**L3**	$(CuOTf)_2{\cdot}C_6H_6$	94	7
9	**L4**	$(CuOTf)_2{\cdot}C_6H_6$	87	73
10	**L5**	$(CuOTf)_2{\cdot}C_6H_6$	99	63
11	**L6**	$(CuOTf)_2{\cdot}C_6H_6$	64	55
12[e]	**L2**	$(CuOTf)_2{\cdot}C_6H_6$	38	50
13[f]	**L2**	$(CuOTf)_2{\cdot}C_6H_6$	71	69
14[g]	**L4**	$(CuOTf)_2{\cdot}C_6H_6$	92	73
15[h]	**L4**	$(CuOTf)_2{\cdot}C_6H_6$	40	0
16[i]	**L4**	$(CuOTf)_2{\cdot}C_6H_6$	94	60

[a] All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde in 0.8 mL of methanol and 0.6 mL of nitromethane in the presence of 10 mg of 4 Å MS.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The reaction was performed at 45 °C for 4 days.
[e] The reaction was performed at 0 °C.
[f] 15 mol % of **L2** was used.
[g] 20 mol % of **L4** and 10 mol % of $(CuOTf)_2{\cdot}C_6H_6$ were used.
[h] In the absence of 4 Å MS.
[i] 4 Å MS (100 mg) was added.

Table 2. Optimization of the reaction conditions in the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane

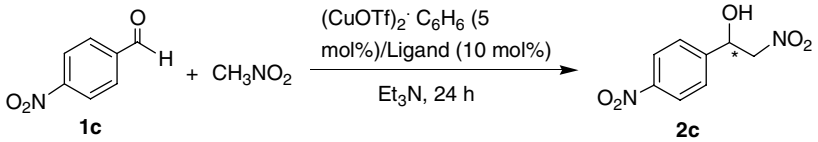


Entry[a]	Solvent	Yield[b] (%)	ee[c] (%)
1	Methanol	94	71
2	Ethanol	99	17
3	Acetonitrile	73	0
4	Dichloroethane	40	5
5	Toluene	14	2
6	Diethyl ether	71	7
7	THF	47	35
8	*tert*-Amyl alcohol	52	15
9	Nitromethane	75	0

[a] All reactions were performed on a 0.2 mmol scale 4-nitrobenzaldehyde and 0.6 mL of nitromethane in 0.8 mL of solvent.
[b] Isolated yields.

We next examined this asymmetric Henry reaction using a variety of arylaldehydes **1** with nitromethane under optimal conditions. The results are shown in Table 4. As can be seen from Table 4, moderate to good yields and moderate enantioselectivities could be achieved for various arylaldehydes **1** bearing an electron-withdrawing group on the benzene ring as well as the naphthyl group substituted aromatic aldehyde (Table 4, entries 2–5 and 7). The highest ee was achieved when using benzaldehyde **1a** as the substrate; in this case the corresponding adduct **2a** was obtained in 63% yield and 80% ee (Table 4, entry 1). Using 4-methylbenzaldehyde **1f** as the substrate, the corresponding adduct **2f** was obtained in 28% yield and 75% ee (Table 4, entry 6).

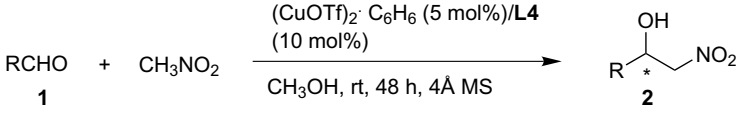
Table 3. Optimization of the reaction conditions in the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane



Entry[a]	Ligand	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	**L2**	Methanol	rt	71	54
2	**L2**	THF	rt	90	54
3	**L2**	THF	−20	87	63
4	**L4**	Methanol	−20	85	67
5	**L4**	THF	−20	92	40

[a] All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde in 0.8 mL of solvent and 0.6 mL of nitromethane in the presence of Et_3N (10 mol %).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.

Table 4. Asymmetric Henry reaction of arylaldehydes with nitromethane under optimal conditions

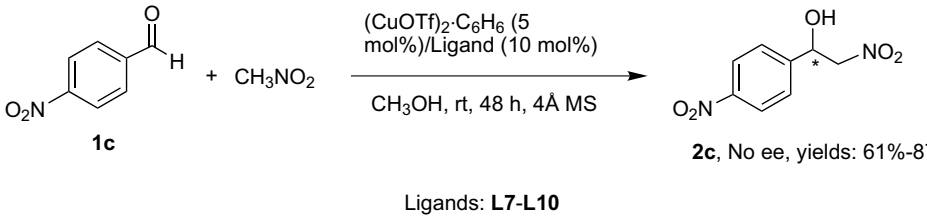


Entry[a]	Arylaldehyde	Yield[b] (%)	ee[c] (%)
1	Benzaldehyde (**1a**)	**2a**, 63	80 (*S*)
2	3-Nitrobenzaldehyde (**1b**)	**2b**, 87	67 (+)
3	4-Nitrobenzaldehyde (**1c**)	**2c**, 87	73 (*S*)
4	2-Chlorobenzaldehyde (**1d**)	**2d**, 70	75 (*S*)
5	4-Chlorobenzaldehyde (**1e**)	**2e**, 82	74 (*S*)
6	4-Methylbenzaldehyde (**1f**)	**2f**, 28	75 (*S*)
7	1-Naphthylaldehyde (**1g**)	**2g**, 74	65 (*S*)

[a] Reactions were performed on a 0.2 mmol scale of aldehyde in 0.8 mL of methanol and 0.6 mL of nitromethane in the presence of 10 mg of 4 Å MS.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis. The absolute configuration of adducts was assigned by comparison with literature compounds.

The phenol group in chiral ligands **L1**–**L6** is crucial for this catalytic asymmetric Henry reaction because similar chiral ligands **L7**–**L10** showed no enantioselectivity for this asymmetric reaction under identical conditions (Scheme 2).

Although the real active species is not yet fully understood in this catalytic asymmetric Henry reaction, we believe that these chiral phosphine-salen type ligands **L1**–**L6** are bidentate or tridentate ligands in this type of asymmetric reaction. To obtain evidence of the coordination pattern with N, O, and P atoms to Cu(I), ^1H NMR, and ^{31}P NMR spectroscopic studies of a 1/1 mixture of **L4** and $(CuOTf)_2$·C_6H_6 in $CDCl_3$ at room temperature were carried out. In the absence of $(CuOTf)_2$·C_6H_6, the signals of the hydrogen atoms in the imino and phenol group of **L4** appeared at δ 8.24 and 11.55 ppm, respectively. However, the corresponding signal of the hydrogen atom in imino group appeared at δ 9.24 ppm while that of the phenol group disappeared in the presence of $(CuOTf)_2$·C_6H_6, respectively, suggesting that nitrogen atom of imino group and oxygen atom of phenol might coordinate to Cu(I) center. In addition, the signal of the phosphorus atom in **L4** appeared at δ −12.52 ppm in the absence of $(CuOTf)_2$·C_6H_6, while it shifted to δ 6.54 ppm in the presence of $(CuOTf)_2$·C_6H_6,



Scheme 2. Asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane in the presence of $(CuOTf)_2$·C_6H_6 (5 mol %) and chiral ligands **L7**–**L10** (10 mol %).

indicating the coordination of phosphorus atom and Cu(I) center. These results may suggest that Cu(I) can be potentially coordinated by the N, O, and P atoms in ligand **L4**.

3. Conclusion

In conclusion, chiral phosphine-salen type ligand **L4** prepared from (*R*)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine was found to be a fairly effective chiral ligand for Cu(I)-promoted enantioselective Henry reactions to give the corresponding adducts in moderate enantioselectivities and moderate to good yields under mild conditions. These results have prompted us to design and synthesize more new effective chiral phosphine-salen type ligands for asymmetric reactions. Efforts are currently underway to elucidate the mechanistic details of this asymmetric Henry reaction and to disclose the exact structure of the active species in this catalytic system.

4. Experimental

4.1. General methods

Melting points were obtained with a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were determined in a solution of $CHCl_3$ or CH_2Cl_2 at 20 °C by using a Perkin–Elmer-241 MC polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Infra-red spectra were measured on a spectrometer. ^{1}H NMR spectra were recorded for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; ^{31}P NMR spectra were recorded at 121 MHz for a solution in $CDCl_3$ with 85% H_3PO_4 as the external reference. *J*-Values are in Hertz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. The organic solvents used, were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai 60F_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. All Henry reactions were performed under argon using standard Schlenk techniques. The enantiomeric purities of adducts were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel AD and OD) while the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.

4.2. General procedure for the preparation of chiral phosphine-salen type ligands L1–L6 and their derivatives L7–L10

To a solution of (*R*)-(−)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine (227 mg, 0.5 mmol) in absolute ethanol (4.0 mL) then added salicylaldehyde (68 mg, 0.5 mmol) at room temperature and the reaction mixture was stirred at reflux for 12 h. After cooling to room temperature, a yellow solid precipitated, which was then filtered to give the corresponding phosphine-salen type ligand **L1** as a yellow solid (208 mg, 75% yield).

4.2.1. (*R*)-(+)-2-((2-(Diphenylphosphino)-1,1′-binaphthyl-2′-ylimino)methyl)phenol L1. Yield: (208 mg, 75%). A yellow solid. Mp: 161–163 °C; IR (CH_2Cl_2) *v* 3437, 3044, 1607, 1553, 1433, 1282, 1146, 814, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.70 (d, $J = 8.4$ Hz, 1H, Ar), 6.77 (*t*, $J = 7.8$ Hz, 1H, Ar), 6.85 (*t*, $J = 8.1$ Hz, 2H, Ar), 6.92–7.50 (m, 18H, Ar), 7.94 (d, $J = 8.4$ Hz, 3H, Ar), 8.06 (d, $J = 9$ Hz, 1H, Ar), 8.29 (s, 1H, CH=N), 11.77 (s, 1H, OH); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.58; MS (ESI) *m/e* 558 (M^++1, 100); HRMS (ESI) calcd for $C_{39}H_{28}NOP$ ($M+H^+$): 558.1987, found: 558.1982; $[\alpha]_D^{20} = +224.6$ (*c* 0.45, $CHCl_3$).

4.2.2. (*R*)-(+)-2,4-Di-*tert*-butyl-6-((2-(diphenylphosphino)-1,1′-binaphthyl-2′-ylimino)methylphenol L2. Yield: (137 mg, 41%). A yellow solid. Mp: 108–110 °C; IR (CH_2Cl_2) *v* 3452, 3059, 2963, 2852, 1610, 1580, 1434, 1171, 815 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.22 (s, 9H, $3CH_3$), 1.26 (s, 9H, $3CH_3$), 6.83–7.58 (m, 20H, Ar), 7.88–7.91 (m, 3H, Ar), 8.05 (d, $J = 8.7$ Hz, 1H, Ar), 8.39 (s, 1H, CH=N), 12.64 (s, 1H, OH); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.32; MS (ESI) *m/e* 670 (M^++1, 100); HRMS (ESI) calcd for $C_{47}H_{44}NOP$ ($M+H^+$): 670.3239, found: 670.3239; $[\alpha]_D^{20} = +27$ (*c* 0.25, $CHCl_3$).

4.2.3. (*R*)-(+)-2,4-Dichloro-6-((2-(diphenylphosphino)-1,1′-binaphthyl-2′-ylimino)methyl)phenol L3. Yield: (230 mg, 74%). A red solid. Mp: 156–158 °C; IR (CH_2Cl_2) *v* 3459, 3044, 1606, 1449, 1433, 1177, 815, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.85–7.54 (m, 20H, Ar), 7.94 (d, $J = 8.4$ Hz, 3H, Ar), 8.07 (d, $J = 9.3$ Hz, 1H, Ar), 8.15 (s, 1H, CH=N), 12.48 (s, 1H, OH); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.90; MS (ESI) *m/e* 626 (M^++1, 100); HRMS (ESI) calcd for $C_{39}H_{26}Cl_2NOP$ ($M+H^+$): 626.1207, found: 626.1207; $[\alpha]_D^{20} = +163$ (*c* 0.25, $CHCl_3$).

4.2.4. (*R*)-(+)-2-((2-(Diphenylphosphino)-1,1′-binaphthyl-2′-ylimino)methyl)-4-methylphenol L4. Yield: (200 mg, 70%). A yellow solid. Mp: 128–130 °C; IR (CH_2Cl_2) *v* 2985, 1736, 1276, 1260, 1155, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.23 (s, 3H, CH_3), 6.68 (d, $J = 8.4$ Hz, 1H, Ar), 6.82–7.52 (m, 20H, Ar), 7.94–7.96 (m, 3H, Ar), 8.06 (d, $J = 9$ Hz, 1H, Ar), 8.24 (s, 1H, CH=N), 11.55 (s, 1H, OH); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.52; MS (ESI) *m/e* 572 (M^++1, 100); HRMS (ESI) calcd for $C_{40}H_{30}NOP$ ($M+H^+$): 572.2143, found: 572.2136; $[\alpha]_D^{20} = +178$ (*c* 0.25, $CHCl_3$).

4.2.5. (*R*)-(+)-2-((2-(Diphenylphosphino)-1,1′-binaphthyl-2′-ylimino)methyl)-5-methoxyphenol L5. Yield: (190 mg, 65%). A yellow solid. Mp: 90–92 °C; IR (CH_2Cl_2) *v* 3052, 1712, 1624, 1606, 1207, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 3.74 (s, 3H, CH_3), 6.21 (s, 1H, Ar), 6.34 (d, $J = 8.4$ Hz, 1H, Ar), 6.89–7.28 (m, 15H, Ar), 7.38–7.51 (m, 4H, Ar), 7.91–7.95 (m, 3H, Ar), 8.05 (d, $J = 8.7$ Hz, 1H, Ar), 8.21 (s, 1H, CH=N), 12.30 (s, 1H, OH); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.59; MS (ESI) *m/e* 588 (M^++1, 100); HRMS (ESI) calcd for $C_{40}H_{30}NO_2P$ ($M+H^+$): 588.2092, found: 588.2094; $[\alpha]_D^{20} = +136$ (*c* 0.35, $CHCl_3$).

4.2.6. (*R*)-(+)-1-((2-(Diphenylphosphino)-1,1′-binaphthyl-2′-ylimino)methyl)naphthalen-2-ol L6. Yield: (210 mg, 69%). A brown solid. Mp: 100–102 °C; IR (CH_2Cl_2) ν 3052, 1712, 1622, 1605, 1563, 1323, 1180, 980, 820 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.60 (t, $J = 7.2$ Hz, 1H, Ar), 6.75 (t, $J = 7.2$ Hz, 2H, Ar), 6.89 (d, $J = 9$ Hz, 1H, Ar), 7.00–7.31 (m, 12H, Ar), 7.43–7.53 (m, 4H, Ar), 7.62–7.73 (m, 4H, Ar), 7.97–8.10 (m, 3H, Ar), 8.12 (d, $J = 9$ Hz, 1H, Ar), 8.95 (s, 1H, CH=N), 13.93 (s, 1H, OH); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.74; MS (ESI) *m/e* 608 (M^++1, 100); HRMS (ESI) calcd for $C_{43}H_{30}NOP$ ($M+H^+$): 608.2143, found: 608.2151; $[\alpha]_D^{20} = +309$ (*c* 0.2, $CHCl_3$).

4.2.7. (*R*)-(+)-*N*-Benzylidene-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine L7. Yield: (108 mg, 20%). A yellow solid. Mp: 88–90 °C; IR (CH_2Cl_2) ν 3378, 3053, 1712, 1620, 1433, 1359, 1220, 815, 743 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.67 (d, $J = 8.1$ Hz, 1H, Ar), 6.93–7.56 (m, 21H, Ar), 7.74 (d, $J = 7.8$ Hz, 1H, Ar), 7.80 (d, $J = 8.7$ Hz, 1H, Ar), 7.87–7.90 (m, 3H, Ar), 8.16 (s, 1H, CH=N); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.81; MS (ESI) *m/e* 542 (M^++1, 100); HRMS (ESI) calcd for $C_{39}H_{28}NP$ ($M+H^+$): 542.2038, found: 542.2032; $[\alpha]_D^{20} = +191$ (*c* 0.25, $CHCl_3$).

4.2.8. (*R*)-(+)-*N*-(2-Chlorobenzylidene)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine L8. Yield: (160 mg, 56%). A yellow solid. Mp: 100–102 °C; IR (CH_2Cl_2) ν 3052, 1712, 1612, 1586, 1433, 814, 743 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.90–7.53 (m, 21H, Ar), 7.72–7.91 (m, 4H, Ar), 8.02 (d, $J = 8.7$ Hz, 1H, Ar), 8.52 (s, 1H, CH=N); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.89; MS (ESI) *m/e* 576 (M^++1, 100); HRMS (ESI) calcd for $C_{39}H_{27}ClNP$ ($M+H^+$): 576.1648, found: 576.1631; $[\alpha]_D^{20} = +335$ (*c* 0.25, $CHCl_3$).

4.2.9. (*R*)-(+)-*N*-(2,3-Dichlorobenzylidene)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine L9. Yield: (100 mg, 41%). A yellow solid. Mp: 105–107 °C; IR (CH_2Cl_2) ν 3053, 1713, 1608, 1433, 1414, 1220, 1181 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.92–7.51 (m, 19H, Ar), 7.69–7.93 (m, 5H, Ar), 8.04 (d, $J = 8.7$ Hz, 1H, Ar), 8.50 (s, 1H, CH=N); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.95; MS (ESI) *m/e* 610 (M^++1, 100); HRMS (ESI) calcd for $C_{39}H_{26}Cl_2NP$ ($M+H^+$): 610.1258, found: 610.1226; $[\alpha]_D^{20} = +392$ (*c* 0.2, $CHCl_3$).

4.2.10. (*R*)-(+)-2-(Diphenylphosphino)-*N*-(quinolin-2-ylmethylene)-1,1′-binaphthyl-2′-amine L10. Yield: (156 mg, 53%). A yellow solid. Mp: 95–97 °C; IR (CH_2Cl_2) ν 3052, 2925, 1595, 1503, 1433, 1197, 1145, 1090, 964 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.85 (s, 2H, Ar), 7.01–8.09 (m, 26H, Ar), 8.60 (s, 1H, CH=N); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ −12.84; MS (ESI) *m/e* 593 (M^++1, 100); HRMS (ESI) calcd for $C_{42}H_{29}N_2P$ ($M+H^+$): 593.2147, found: 593.2140; $[\alpha]_D^{20} = +230$ (*c* 0.25, $CHCl_3$).

4.3. Typical reaction procedure

Chiral ligand **L4** (11.4 mg, 0.02 mmol), 4 Å molecular sieves (10 mg), and $(CuOTf)_2{\cdot}C_6H_6$ (5.0 mg, 0.01 mmol) were added to methanol (0.8 mL) at room temperature. The reaction mixture was stirred for 30 min and then 4-nitrobenzaldehyde **1c** (30.2 mg, 0.2 mmol) and nitromethane (0.6 mL) were added to the resulting purple solution. The mixture was stirred for 48 h at room temperature and then concentrated in vacuo to give a glutinous phase residue. Next, CH_2Cl_2 (2.0 mL) and aqueous HCl solution (1.0 M, 5 mL) were added into the residue and the mixture stirred until the green color disappeared. After extraction with CH_2Cl_2 (3×10 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: PE/EtOAc = 8/1) to furnish adduct **2c** as an off-white solid.

4.3.1. (*S*)-2-Nitro-1-phenylethanol 2a. Yield: (21 mg, 63%). A yellow oil. ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.68 (br, 1H, OH), 4.52 (dd, $J = 13.2$, 3.3 Hz, 1H, CH), 4.62 (dd, $J = 13.2$, 9.3 Hz, 1H, CH), 5.48 (dd, $J = 9.3$, 3.3 Hz, 1H, CH), 7.36–7.42 (m, 5H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/*i*-PrOH = 95/5, 0.5 mL/min, 230 nm, $t_{minor} = 65.38$ min, $t_{major} = 83.53$ min; $[\alpha]_D^{20} = +28.0$ (*c* 0.95, CH_2Cl_2), 80% ee.

4.3.2. (+)-2-Nitro-1-(3-nitrophenyl)ethanol 2b. Yield: (37 mg, 87%). An off-white solid. ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 3.13 (s, 1H, OH), 4.57–4.68 (m, 2H, CH_2), 5.59–5.63 (m, 1H, CH), 7.62 (t, $J = 8.1$ Hz, 1H, Ar), 7.78 (d, $J = 7.8$ Hz, 1H, Ar), 8.24 (d, $J = 9.6$ Hz, 1H, Ar), 8.34 (s, 1H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/*i*-PrOH = 90/10, 1 mL/min, 230 nm, $t_{minor} = 26.04$ min, $t_{major} = 29.54$ min; $[\alpha]_D^{20} = +24.0$ (*c* 1.65, CH_2Cl_2), 67% ee.

4.3.3. (*S*)-2-Nitro-1-(4-nitrophenyl)ethanol 2c. Yield: (37 mg, 87%). An off-white solid. ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 3.20 (d, $J = 4.2$ Hz, 1H, OH), 4.57–4.60 (m, 2H, CH_2), 5.58–5.64 (m, 1H, CH), 7.63 (d, $J = 8.4$ Hz, 2H, Ar), 8.28 (d, $J = 8.4$ Hz, 2H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/*i*-PrOH = 65/35, 0.7 mL/min, 230 nm, $t_{minor} = 5.98$ min, $t_{major} = 7.38$ min; $[\alpha]_D^{20} = +25.8$ (*c* 1.3, CH_2Cl_2), 73% ee.

4.3.4. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol (2d). Yield: (28 mg, 70%). A yellow oil. ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 3.03 (d, $J = 3.6$ Hz, 1H, OH), 4.45 (dd, $J = 13.8$, 9.6 Hz, 1H, CH), 4.68 (dd, $J = 13.8$, 2.1 Hz, 1H, CH), 5.85 (d, $J = 9.6$ Hz, 1H, CH), 7.28–7.40 (m, 3H, Ar), 7.67 (d, $J = 7.2$ Hz, 1H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/*i*-PrOH = 98/2, 0.7 mL/min, 215 nm, $t_{minor} =$ 28.96, $t_{major} = 31.54$ min; $[\alpha]_D^{20} = +33.9$ (*c* 0.9, CH_2Cl_2), 75% ee.

4.3.5. (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 2e. Yield: (33 mg, 82%). A yellow oil. ^1H NMR ($CDCl_3$, TMS,

300 MHz) δ 2.82 (br, 1H, OH), 4.49 (dd, $J = 13.5$, 3.3 Hz, 1H, CH), 4.58 (dd, $J = 13.5$, 9.3 Hz, 1H, CH), 5.46 (dd, $J = 9.3$, 3.3 Hz, 1H, CH), 7.33–7.40 (m, 4H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/*i*-PrOH = 80/20, 0.8 mL/min, 230 nm, $t_{minor} = 8.42$ min, $t_{major} = 9.47$ min; $[\alpha]_D^{20} = +26.4$ (*c* 1.30, CH_2Cl_2), 74% ee.

4.3.6. (*S*)-2-Nitro-1-*p*-tolylethanol 2f. Yield: (10 mg, 28%). A yellow oil. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.36 (s, 3H, CH_3), 2.71 (br, 1H, OH), 4.48 (dd, $J = 13.2$, 2.7 Hz, 1H, CH), 4.60 (dd, $J = 13.2$, 9.3 Hz, 1H, CH), 5.42 (dd, $J = 9.3$, 2.7 Hz, 1H, CH), 7.21 (d, $J = 8.1$ Hz, 2H, Ar), 7.28 (d, $J = 8.1$ Hz, 2H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/*i*-PrOH = 90/10, 0.5 mL/min, 230 nm, $t_{minor} = 22.97$ min, $t_{major} = 28.85$ min; $[\alpha]_D^{20} = +20.2$ (*c* 0.85, CH_2Cl_2), 75% ee.

4.3.7. (*S*)-1-(Naphthalen-1-yl)-2-nitroethanol 2g. Yield: (32 mg, 74%). A yellow oil. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.91 (br, 1H, OH), 4.66–4.69 (m, 2H, CH_2), 6.28 (dd, $J = 8.4$, 4.2 Hz, 1H, CH), 7.50–7.63 (m, 3H, Ar), 7.78 (d, $J = 7.5$ Hz, 1H, Ar), 7.87 (d, $J = 8.4$ Hz, 1H, Ar), 7.92 (d, $J = 7.8$ Hz, 1H, Ar), 8.04 (d, $J = 8.4$ Hz, 1H, Ar); Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/*i*-PrOH = 95/5, 0.4 mL/min, 230 nm, $t_{minor} = 19.12$ min, $t_{major} = 15.46$ min; $[\alpha]_D^{20} = +15.4$ (*c* 1.40, CH_2Cl_2), 65% ee.

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