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Mixed donor aminophosphine oxide ligands in ruthenium-catalysed asymmetric transfer hydrogenation reactions

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Abstract—A number of mixed-donor aminophosphine ligands have been prepared and their activity and selectivity in asymmetric transfer hydrogenation reactions assessed. Enantioselectivities up to 93% and 80% were achieved for the reduction of acetophenone and propiophenone, respectively.

1. Introduction

Over the last few years, we have been actively engaged in developing novel nitrogen–phosphorus ligands for catalytic processes.[1–6] Previously, we reported the synthesis and coordination chemistry of a class of aminophosphine (PNH) **1** and diphosphine (PNP) **2** ligands to ruthenium complexes.[3,7] In the ensuing catalytic reduction of ketones, we observed that the PNH ligands **1** promoted higher catalytic activity than the PNP ligands **2**, and the activity of both classes of ligands is dependent on the nature of the nitrogen substituent (R) (Fig. 1).

Herein, we report a class of optically active PNH compounds, employing chiral amines as the source of chirality. The resultant aminophosphine hybrid (PNH) ligands were subsequently assessed as ligands in ruthenium-catalysed transfer hydrogenation of unsymmetrical alkyl aryl ketones.

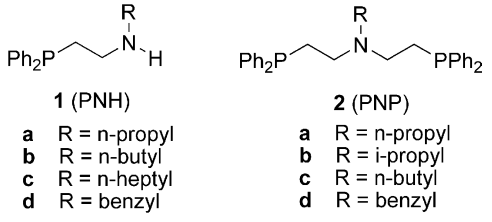

Figure 1.

2. Preparation of ligands

Six optically active primary amines were chosen for this part of our investigation: (*R*)-*sec*-butylamine, (*S*)-1-phenylethylamine, (*S*)-1-indan-amine, (*R*)-1,2,3,4-tetrahydronaphthylamine, (1*R*,2*R*)-cyclohexane diamine (to give a PNNP ligand) and, guided by the success of aminoalcohol ligands in this class of reactions, (1*R*,2*S*)-norephedrine.

The addition of optically active 1-phenylethylamine to vinyldiphenylphosphine was previously achieved by prolonged heating in toluene (48 h).[8] However, employing a procedure developed in our laboratory, the ligands were prepared in a comparative short period of time.[7] By heating a slight excess of the Michael acceptor (vinyldiphenylphosphine oxide) with the requisite amine in methanol, aminophosphine oxides may be obtained in typically 3–6 h. Subsequent acid/base work-up, followed by recrystallisation from methylcyclohexane, furnished the aminophosphine oxides **3a**–**f** in good to excellent yields (>80%). These aminophosphine oxides were then reduced in a basic trichlorosilane solution to give the phosphorus(III) analogues **4a**–**f** (Scheme 1).

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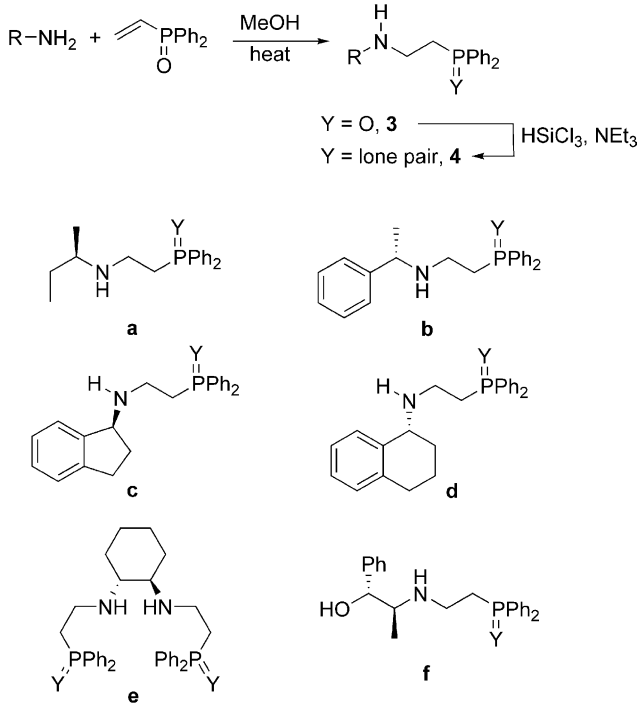
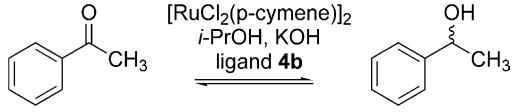


Scheme 1. Preparation of chiral PNH ligands.

3. Optimisation of catalytic conditions

3.1. Reaction temperature and catalyst/base ratios

Guided by our previous work,[9] the catalytic precursor was generated by heating to reflux a mixture of $[RuCl_2(p\text{-cymene})]_2$ and the required ligand in isopropanol for 30 min (Scheme 2).



Scheme 2. Reaction condition optimisation.

In order to establish optimal catalytic protocols, several reaction conditions known to affect the outcome of hydrogenation reactions were examined using ligand **4b**, including: temperature, catalytic loading, catalyst/ligand ratios and concentration effects (Table 1).[10]

Lowering the temperature from 60 to 29 °C led to a decrease in catalyst activity with no significant change in enantioselectivity (Table 1, entries 1–4). At temperatures lower than 25 °C, the conversions were dramatically reduced (less than 50%).

Increasing the catalytic loading from 0.4 to 1 mol % led to an expected increased conversion and a slight improvement in the selectivity (entry 5). Meanwhile, lowering the amount of KOH led to a slight improvement of the ee value at the expense of conversion (entries 5–8). In the absence of the base co-catalyst, the reaction showed no conversion (entry 9). The optimal base-to-catalyst ratio (for the highest ee) was thus found to be 5:1.

Table 1. Effect of substrate and base concentration and reaction temperature[a]

Entry	S:C[b]	B:C[c]	T/°C	%Conversion[d]	%Ee (*R*/*S*)[e]
1	250:1	15:1	60	89	26 (*R*)
2	250:1	15:1	50	83	26 (*R*)
3	250:1	15:1	40	80	28 (*R*)
4	250:1	15:1	29	70	28 (*R*)
5	100:1	15:1	29	89	30 (*R*)
6	100:1	8.5:1	29	73	32 (*R*)
7	100:1	5:1	29	62	33 (*R*)
8	100:1	2.5:1	29	10	32 (*R*)
9	100:1	0:1	29	0	— (–)

[a] Typical catalytic run carried out with 0.18M of acetophenone with 1:1 metal-to-ligand ratio for 2 h.
[b] Substrate:catalyst ratio.
[c] Base:catalyst ratio.
[d] Monitored by ^1H NMR.
[e] Determined by chiral HPLC.

3.2. Substrate concentration and metal-to-ligand ratio

Dilution effects have been reported to be important as it affects the ketone–alcohol equilibrium.[11] Thus, the reaction was repeated at different dilutions, from 180 to 25 mM (Fig. 2). The optimal concentration (90 mM of acetophenone in isopropanol) was accompanied by a concomitant improvement of the enantioselectivity to 36%. Further dilutions led to erosion of both these values.

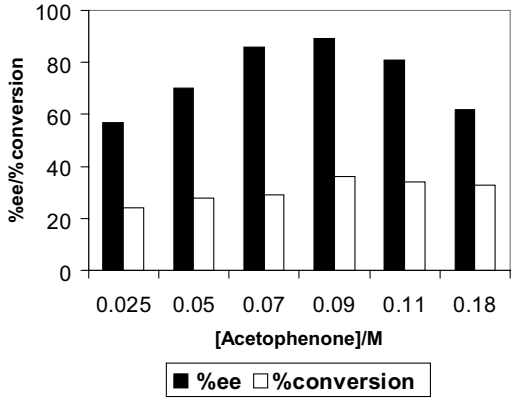


Figure 2. Effect of dilution on conversion and enantioselectivity.

Containing potentially hemilabile donor groups, it is possible that more than one ligand may coordinate to the metal centre, generating different catalytic active species.[5] The effect of metal-to-ligand ratio was thus investigated (Table 2).[12]

Between 0.5 and 4 equiv of ligand were employed in this study. Sub-stoichiometric amounts of ligand led to a dramatic decrease in activity and selectivity of the reaction (entry 1). When the ratio was increased to 2:1, the conversion decreased, although there was no change in enantioselectivity (entry 3). This implies that the catalytic active species involves the binding of just one ligand per metal. Rather interestingly, the ee increased

Table 2. Catalytic reaction optimisation[a]

Entry	Ligand-to-metal ratio	%Conversion[b]	%Ee[c]
1	0.5/1	26	26
2	1/1	66	36
3	2/1	29	36
4	4/1	24	41

[a] Reaction runs were carried out with 0.5 mol% of the catalyst, 5 mol% of KOH and 90 mM of acetophenone at 29 °C for1 h.
[b] Monitored by ^{1}H NMR.
[c] Determined by chiral HPLC, the (*R*)-configuration predominated in all cases.

to 41% when 4 equiv of ligand was employed, but the corresponding conversion was low (entry 4).

4. Catalytic activity of ligands 3 and 4

Using the optimal conditions established in the above studies, both aminophosphines and their oxides **3** and **4** were evaluated in the asymmetric reduction of acetophenone and propiophenone (Scheme 2, Table 3).

Table 3. Catalytic asymmetric transfer hydrogenation reactions[a]

Entry	R	Ligand	%Conversion[b]	%Ee[c] (*R*/*S*)
1	CH_3	**3a**	20	8 (*S*)
2	CH_2CH_3	**3a**	15	0 (−)
3	CH_3	**3b**	62	32 (*R*)
4	CH_2CH_3	**3b**	59	43 (*R*)
5	CH_3	**3c**	13	22 (*R*)
6	CH_2CH_3	**3c**	13	15 (*R*)
7	CH_3	**3d**	48	26 (*R*)
8	CH_2CH_3	**3d**	29	45 (*R*)
9	CH_3	**3e**	7	19 (*R*)
10	CH_2CH_3	**3e**	7	18 (*R*)
11	CH_3	**3f**	95	93 (*R*)
12	CH_2CH_3	**3f**	84	80 (*R*)
13	CH_3	**4a**	30	3 (*S*)
14	CH_2CH_3	**4a**	10	0 (−)
15	CH_3	**4b**	89	36 (*R*)
16	CH_2CH_3	**4b**	63	43 (*R*)
17	CH_3	**4c**	60	16 (*R*)
18	CH_2CH_3	**4c**	51	5 (*R*)
19	CH_3	**4d**	95	9 (*R*)
20	CH_2CH_3	**4d**	87	21 (*R*)
21	CH_3	**4e**	24	16 (*R*)
22	CH_2CH_3	**4e**	7	19 (*R*)
23	CH_3	**4f**	83	79 (*R*)
24	CH_2CH_3	**4f**	84	75 (*R*)
25	CH_3	(−)-Ephedrine	95	55 (*R*)

[a] Reaction conditions: $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%), ligand (1 mol%), 0.09 M of the appropriate ketone in isopropanol, KOH (5 mol%) at 29 °C for 2 h.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.

Overall, ligands derived from chiral amines exhibited low enantioselectivity in the reduction of unsymmetrical ketones (entries 1–10, 13–22), with values no more than 36% for the reduction of acetophenone (with ligand **3b**, entry 15) and 45% (with ligand **3d**, entry 8). Generally, the β-aminophosphines **4** induce higher conversions (24–89%) than the corresponding β-aminophosphine oxides **3** (7–62%) but the enantioselectivities were better with the latter. Interestingly, the stereoinduction remained the same, regardless of the oxidation state of the phosphorus donor.

By incorporation of an added donor group (OH), norephedrine-derived ligands **3f** and **4f** proved to be unique in this study, affording superior conversions and ee values (entries 11, 12, 23 and 24). The aminophosphine oxide **3f** afforded comparable, if not better conversions than the aminophosphine **4f**. The reduction of acetophenone employing ligand **3f** achieved excellent conversion and ee (95% and 93% ee, respectively, entry 11), compared to using the phosphorus(III) analogue (83% conversion, 79% ee, entry 23). Equally, propiophenone was reduced with higher enantiomeric excess in the presence of the phosphorus(V) compound **3f** (80% ee, entry 12) compared to **4f** (75% ee, entry 24), although conversions were the same in these cases.

It will perhaps be reasonable to postulate, at this juncture, that the phosphorus moiety is not involved in the catalytic process, since amino alcohols are known to be excellent ligands in these reductions.[13] However, this appears not to be the case, as (−)-norephedrine induced only 55% ee under these reaction conditions (entry 25), that is, the phosphorus moiety played an important role in the degree of enantioselection.

Previously, Pietrusiewicz and co-workers reported that β-amino diphenylphosphine oxides induced low conversions and enantioselectivities in transfer hydrogenation of ketones and the activity and selectivity of these ligands may be improved by increasing the steric bulk (and introducing an extra stereogenic element) at the phosphorus donor.[14]

In the present work, we have demonstrated that the performance of β-amino diphenylphosphine oxide ligands in these reactions may also be improved dramatically by the introduction of an additional OH group and an extra carbon centred chirality. Since amino alcohols are much more available than chirogenic phosphorus compounds, structural variations will be much easier to introduce. Further development of these PNO ligands, involving the introduction of chirogenic phosphorus donor groups, suggests that the phosphine oxide moiety is intimately involved in the catalyst activity and stereoselectivity. This work will be reported in due course.

5. Experimental

5.1. General procedure

The apparatus and general techniques were the same as in other recent papers from this laboratory.[3] (S_P)-(*tert*-butylphenylphosphinoyl)acetic acid (S_P)-4.19, (R_P)-(*tert*-butylphenylphosphinoyl)acetic acid (R_P)-4.19[15] and $[RuCl_2(\eta^6\text{-}p\text{-}MeC_6H_4CHMe_2)]_2$[16] were prepared following reported procedures. Unless otherwise stated,

all other reagents were procured from Avocado, Lancaster or Aldrich chemical companies and used as received. A Gilson system equipped with a manual injector was used for HPLC analysis. Detection was made by UV absorption at 254 nm.

5.2. Ligand synthesis

5.2.1. General procedure for the preparation of chiral aminophosphine oxides 3. The appropriate chiral amine (2.1 mmol) was added to a slight excess of vinyldiphenylphosphine oxide (0.5 g, 2.2 mmol) in methanol (1 mL) and the reaction mixture was heated at 65 °C in a sealed tube. After the appropriate reaction time (^{31}P NMR) the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether and acidified using 2 N HCl (pH ~ 2). The aqueous layer was washed with diethyl ether (50 mL). The aminophosphine oxides were recovered by cooling the aqueous layer to 0 °C and basifying it to ~pH 10 by the addition of NaOH pellets. The compound was extracted into dichloromethane (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate evaporated in vacuo to leave the required compound as a white solid, which was recrystallised from methylcyclohexane to yield analytically pure samples.

5.2.1.1. [2-(Diphenylphosphinoyl)-ethyl]-(*R*)-*sec*-butylamine 3a. Yield: 98%. $[\alpha]_D^{20} = +5.3$ (*c* 1, $CHCl_3$). Mp: 70–71 °C. Anal. Calcd for $C_{18}H_{24}NOP$: C, 71.75; H, 8.0; N, 4.65%. Found C, 71.25; H, 7.9; N, 4.50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, 3H, $J = 7$ Hz), 0.95 (d, 3H, $J = 7$ Hz), 1.18–1.46 (dm, 2H), 1.64 (br s, 1H), 2.46–2.55 (m, 3H), 2.85–2.99 (m, 2H), 7.24–7.95 (m, 10H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +32.4. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 10.5, 19.9, 29.8, 30.9 (d, $J_{PC} = 71$ Hz), 40.5 (d, $J_{PC} = 2$ Hz), 54.7, 129.0 (d, $J_{PC} = 11.7$ Hz), 131.0 (d, $J_{PC} = 11.0$ Hz), 131.1, 131.6 (d, $J_{PC} = 91$ Hz). IR (cm^{-1}, KBr disc) *v*: 1180 (P=O), 3288 (N–H).

5.2.1.2. [2-(Diphenylphosphinoyl)-ethyl]-(*S*)-1-phenylethyl-amine 3b. White solid, yield 95%. Mp: 175–177 °C (lit.[8] 176–177 °C). $[\alpha]_D^{20} = +40.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$): 1.21 (3H, d, $J = 6.8$ Hz), 1.97 (1H, br s), 2.32–2.46 (2H, m), 2.66–2.85 (2H, m), 3.62 (1H, q, $J = 6.8$ Hz), 7.08–7.26 (5H, m), 7.30–7.50 (6H, m), 7.55–7.74 (4H, m). ^{31}P NMR (145.8 MHz, CDCl3) δ: +32.9. ^{13}C NMR (90.6 MHz, CDCl3) δ: 23.3, 29.3 (d, $J_{PC} = 71$ Hz), 39.8 (d, $J_{PC} = 3$ Hz), 57.0, 125.5, 125.8, 127.4, 127.6 (d, $J_{PC} = 12$ Hz), 129.6 (d, $J_{PC} = 9$ Hz), 130.7 (d, s, $J_{PC} = 3$ Hz), 132.0 (d, $J_{PC} = 99$ Hz), 144.2. IR (cm^{-1}, KBr disc) *v*: 3316 (NH), 1173 (P=O). HRMS (FAB): exact mass calcd for $C_{22}H_{25}NOP$ (M^+) 350.1674. Found 350.1678.

5.2.1.3. [2-(Diphenylphosphinoyl)-ethyl]-(*S*)-1-indanamine 3c. Yield: 92%. $[\alpha]_D^{20} = -9.3$ (*c* 1, $CHCl_3$). Mp: 90–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.66–1.68 (m, 1H), 1.89 (br s, 1H), 2.12–2.30 (m, 1H), 2.42–2.50 (m, 2H), 2.66–2.69 (m, 1H), 2.84–2.86 (m, 1H), 2.94–3.17 (m, 2H), 4.11 (t, 1H, $J = 6.6$ Hz), 6.97–7.69 (m, 14H). ^{31}P NMR (161 MHz, $CDCl_3$) δ: +34.1. ^{13}C NMR (125 MHz, $CDCl_3$) δ: +30.7 (d, $J_{PC} = 71$ Hz), 31.4, 33.7, 40.9 (d, $J_{PC} = 2$ Hz) 63.5, 124.5–145.0 (aromatic). IR (cm^{-1}, KBr disc) *v*: 1185 (P=O), 3270 (N–H). HRMS (FAB): exact mass calcd for $C_{23}H_{25}NOP$ (MH^+) 362.1674. Found 362.1684.

5.2.1.4. [2-(Diphenylphosphinoyl)-ethyl]-(*R*)-1,2,3,4-tetrahydronaphthylamine 3d. Yield: 91%. $[\alpha]_D^{20} + 2.3$ (*c* 1, $CHCl_3$). Mp: 105–107 °C. Anal. Calcd for $C_{24}H_{26}NOP$: C, 76.78; H, 6.98; N, 3.73%. Found C, 77.05; H, 7.10; N, 3.92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58–1.81 (m, 5H), 2.44–2.48 (m, 2H), 2.61–2.68 (m, 2H), 2.92–3.05 (m, 2H), 4.63 (t, 1H, $J = 4.9$ Hz), 6.95–7.65 (m, 14H). ^{31}P NMR (161 MHz, $CDCl_3$) δ: +32.3. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.3, 28.6, 29.7, 31.3 (d, $J_{PC} = 71$ Hz), 40.7 (d, $J_{PC} = 2$ Hz), 55.8, 126.1–139.2 (aromatic). IR (cm^{-1}, KBr disc): 1185 cm^{-1} (P=O); 3280 (N–H). HRMS (FAB): exact mass calcd for $C_{24}H_{27}NOP$ (MH^+) 376.1830. Found 376.1839.

5.2.1.5. *N*,*N*-Bis-[(2-diphenylphosphinoyl)-ethyl]-(1*R*,2*R*)-cyclohexane-diamine 3e. Prepared with 4.4 mmol of vinyldiphenylphosphine oxide. Yield: 80%. $[\alpha]_D^{20} = +38.3$ (*c* 1, $CHCl_3$). Mp: 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89–0.92 (m, 2H), 1.11–1.16 (m, 2H), 1.31–1.42 (m, 2H) 1.64–1.66 (m, 2H), 1.95–2.19 (m, 4H) 2.48–2.59 (m, 4H), 2.74–2.82 (m, 2H), 3.02–3.11 (m, 2H), 7.25–7.99 (m, 20H). ^{31}P NMR (161.9 MHz, $CDCl_3$) δ: +32.1. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 25.2, 31.3 (d, $J_{PC} = 71$ Hz), 31.7, 40.3 (d, $J_{PC} = 2$ Hz), 61.6, 128.8–134.1 (aromatic). IR (cm^{-1}, KBr disc) *v*: 1185 (P=O), 3275 (N–H). HRMS (FAB): exact mass calcd for $C_{34}H_{41}N_2O_2P_2$ (MH^+) 571.2643. Found 571.2652.

5.2.1.6. [2-(Diphenylphosphinoyl)-ethyl]-(1*R*,2*S*)-norephedrine 3f. Yield: 82%. $[\alpha]_D^{20} = +2.3$ (*c* 1, $CHCl_3$). Mp: 144–146 °C. Anal. Calcd for $C_{23}H_{26}NO_2P$: C, 72.81; H, 6.91; N, 3.69%. Found: C, 73.08; H, 6.92; N, 3.95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (d, 3H, $J = 7$ Hz), 2.43–2.47 (m, 2H), 2.75–2.79 (m, 1H), 2.96–3.01 (m, 2H), 4.63 (d, 1H, $J = 4$ Hz), 7.11–7.70 (m, 15H). ^{31}P NMR (145.7 MHz, $CDCl_3$) δ: +32.7. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 14.9, 31.0 (d, $J_{PC} = 71$ Hz), 40.7 (d, $J_{PC} = 3$ Hz), 58.7, 73.3, 124.5–139.8 (aromatic). IR (cm^{-1}, KBr disc) *v*: 1181 (P=O), 3273 (N–H).

5.2.2. General procedure for the reduction of aminophosphine oxides. Triethylamine (6 mL) was added to a stirred suspension of the aminophosphine oxide (0.22 mol) in toluene (25 mL) at 0 °C. After 10 min, trichlorosilane (0.84 mL, 1.12 mol, 5 equiv) was added dropwise, and the mixture refluxed for 3.5 h. After cooling to room temperature, the solution was diluted with ether (100 mL) and a few drops of Na_2CO_3 were added to destroy the excess reducing agent. The reaction mixture was filtered under argon and evaporated to leave the product as a colourless residue, which was purified by distillation or recrystallisation as appropriate.

5.2.2.1. [2-(Diphenylphosphino)ethyl]-(*R*)-*sec*-butylamine 4a. Yield: 90%. $[\alpha]_D^{20} = +4.0$ (*c* 1, $CHCl_3$). Bp: 218–220 °C/0.04 mmHg. Anal. Calcd for $C_{18}H_{24}$ NP: C, 75.76; H, 8.48; N, 4.91. Found C, 75.75; H, 8.33; N, 4.78. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.78 (t, 3H, $J = 7$ Hz), 1.19 (d, 3H, $J = 6.5$ Hz), 1.48 (m, 1H), 1.8 (m, 1H), 2.75 (m, 2H), 2.78–2.90 (m, 4H), 7.20–7.80 (m, 10H). ^{31}P NMR (145.7 MHz; $CDCl_3$) δ: −19.2. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 9.2, 18.7, 28.1 (d, $J_{PC} = 12$ Hz), 28.4, 42.9 (d, $J_{PC} = 21$ Hz), 53.3, 127.4 (d, $J_{PC} = 7$ Hz), 127.5, 131.6 (d, $J_{PC} = 17$ Hz), 137.3 (d, $J_{PC} = 12$ Hz). IR (cm^{-1}, thin film, NaCl discs) *v*: 3412 (N–H).

5.2.2.2. [2-(Diphenylphosphino)ethyl]-(*S*)-1-phenylethylamine 4b. Yield: 80%. $[\alpha]_D^{20} = -56.4$ (*c* 2, $CHCl_3$). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.23 (3H, d, $J = 6.8$ Hz), 1.41 (1H, br s), 2.09–2.23 (2H, m), 2.48–2.63 (2H, m), 3.66 (1H, q, $J = 6.8$ Hz), 7.14–7.33 (15H, m). ^{31} P NMR (145.8 MHz, $CDCl_3$) δ: −19.6. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ: 24.3, 29.2 (d, $J_{PC} = 12$ Hz), 44.3 (d, $J_{PC} = 20$ Hz), 57.9, 126.5, 126.8, 128.3, 128.4 (d, $J_{PC} = 4$ Hz), 128.6, 132.7, 138.4 (d, $J_{PC} = 14$ Hz), 145.4. IR (cm^{-1}, thin film, NaCl discs) *v*: 3382 (NH). HRMS (FAB): exact mass calcd for $C_{22}H_{25}NP$ (MH^+) 334.1725. Found 334.1709.

5.2.2.3. [2-(Diphenylphosphino)ethyl]-(*S*)-1-indanamine 4c. Yield: 82%. $[\alpha]_D^{20} = -4.7$ (*c* 1, $CHCl_3$). Bp: 240–245 °C/0.04 mmHg. Anal. Calcd for $C_{23}H_{24}NP$: C, 79.97; H, 7.0; N, 4.06%. Found C, 80.05; H, 6.92; N, 3.95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59–1.71 (m, 2H), 2.19 (m, 2H), 2.05–2.72 (m, 1H), 2.77–2.82 (m, 2H), 2.86–2.94 (m, 1H), 4.13 (t, 1H, $J = 6.5$ Hz), 7.10–8.3 (m, 14H). ^{31} P NMR (161 MHz, $CDCl_3$) δ: −19.1. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.6 (d, $J_{PC} = 12$ Hz), 30.8, 33.9, 44.5 (d, $J_{PC} = 21$ Hz) 53.4, 124.6–145.3 (aromatic). IR (cm^{-1}, thin film, NaCl discs): 3312 (N–H).

5.2.2.4. [2-(Diphenylphosphino)-ethyl]-(*R*)-1,2,3,4-tetrahydro-naphthylamine 4d. Yield: 95%. $[\alpha]_D^{20} = +5.0$ (*c* 1, $CHCl_3$). Bp: 225–230 °C/0.04 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.56–1.97 (m, 5H), 2.30–2.34 (m, 2H), 2.56–2.90 (m, 4H), 3.78–3.85 (t, 1H, $J = 4.9$ Hz), 6.97–7.65 (m, 14H). ^{31}P NMR (161 MHz, $CDCl_3$) δ: −19.3. ^{13} C NMR (100.6 MHz, $CDCl_3$) δ: 19.4, 28.1, 28.6 (d, $J_{PC} = 12$ Hz), 29.5, 43.6 (d, $J_{PC} = 22$ Hz) 55.6, 126.3–138.0 (aromatic). IR (cm^{-1}, thin film, NaCl discs) *v*: 1185 (P═O), 3280 (N–H). HRMS (FAB): exact mass calcd for $C_{24}H_{27}NP$ (MH^+) 360.1881. Found 360.1884.

5.2.2.5. *N*,*N*-Bis-[(2-diphenylphosphino)ethyl]-(1*R*,2*R*)-cyclohexane-diamine 4e.[17] Yield: 80%. $[\alpha]_D^{20} = +33.4$ (*c* 1, $CHCl_3$). Bp: 285–28 °C/0.04 mmHg. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.80–1.17 (m, 4H), 1.75–2.02 (m, 8H), 2.14–2.27 (m, 4H), 2.45–2.58 (m, 2H), 2.73–2.83 (m, 2H), 7.25–7.99 (m, 20H). ^{31}P NMR (161 MHz, $CDCl_3$) δ: −20.1. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 25.7, 29.4 (d, $J_{PC} = 12$ Hz), 31.7, 43.4 (d, $J_{PC} = 21$ Hz), 59.6, 129.0–135.2 (aromatic). IR (thin film, NaCl discs) 3275 *v* (N–H). HRMS (FAB): exact mass calcd for $C_{34}H_{41}N_2P_2$ (MH^+) 539.2745. Found 539.2749.

5.2.2.6. [2-(Diphenylphosphino)ethyl]-(1*R*,2*S*)-norephedrine 4f. Yield: 75%. $[\alpha]_D^{20} = +5.5$ (*c* 1, $CHCl_3$). Mp: 105–110 °C. ^{1}H NMR (400.1 MHz; $CDCl_3$) δ: d 0.71 (d, 3H, $J = 7$ Hz, CH_3), 2.23–2.29 (m, 2H, CH_2P), 2.71–2.80 (m, 3H, *CHN*, CH_2N), 4.67 (d, 1H, $J = 3$ Hz, *CH*OH) 7.06–7.94 (m, 15H, *Ph*), ^{31}P NMR (145.7 MHz; $CDCl_3$) δ: −19.0. ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 13.0 (s, CH_3), 27.7 (d, $^1J_{PC} = 13$ Hz, CH_2P), 42.9 (d, $^2J_{PC} = 21$ Hz, CH_2N), 57.43 (s, *CH*N), 71.89 (s, *CH*OH), 115.3–140.1 (*aromatic*). IR (cm^{-1}, KBr disc) 3412 (N–H). HRMS: exact mass calcd for $C_{23}H_{27}NOP$ (MH^+) 364.1830. Found 364.1833.

5.3. Typical catalytic procedure

The catalytic reactions were carried out in parallel using a Radley's reaction carousel. $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and the appropriate ketone substrate was dissolved in anhydrous isopropanol under argon to create the stock solution. To each carousel tube was added an appropriate amount of the stock solution and further amounts of isopropanol. The appropriate ligand was then added to each tube and the contents were refluxed at 83 °C for 30 min, then cooled to 29 °C. A solution of KOH in isopropanol was added to initiate the reaction. The progress of the reaction was monitored by ^{1}H NMR and the enantioselectivity was determined by chiral HPLC (Chiralcel OD-H column).

5.3.1. 1-Phenylethanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (d, 3H, $J = 6.4$ Hz, CH_3), 1.96 (br s, 1H, *OH*), 4.8 (q, 1H, $J = 6.4$ Hz, *CH*), 7.25–7.35 (m, 5H, *Ph*). Chiral HPLC (hexane/isopropanol = 95/5, flow rate = 0.5 mL/min, $\lambda = 254$ nm): $t_R = 15.5$ min, $t_S = 17.7$ min.

5.3.2. 1-Phenyl-1-propanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.76 (t, 3H, $J = 7.5$ Hz, CH_3), 1.40 (m, 2H, CH_2) 2.96 (br s, 1H, *OH*), 4.35 (t, 1H, $J = 6.5$ Hz, *CH*), 7.07–7.23 (m, 5H, *Ph*). Chiral HPLC (hexane/isopropanol = 98/2, flow rate = 0.3 mL/min, $\lambda = 254$ nm): $t_R = 48.7$ min, $t_S = 53.9$ min.

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