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Aminohydroxy phosphine oxide ligands in ruthenium-catalysed asymmetric transfer hydrogenation reactions

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Abstract—A class of aminohydroxy phosphine oxide ligands was derived from optically active amino alcohols, containing stereogenic centres at phosphorus and at carbon. Their activities and selectivities in the asymmetric transfer hydrogenation reaction were assessed, including match and mismatch of chiralities. Enantioselectivities of more than 92% were achieved in the reduction of acetophenone and propiophenone under mild reaction conditions.

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1. Introduction

Previously, we reported the synthesis and coordination of a class of aminophosphine **1** (PNH) and diphosphine **2** (PNP) ligands to ruthenium complexes (Fig. 1), and their comparative catalytic activity in transfer hydrogenation reactions of aryl ketones.[1,2] In subsequent attempts to achieve asymmetric catalysis, we prepared a range of chiral aminodiphenylphosphine (PNH) ligands from optically active amines, and established that the catalyst activity of ruthenium catalysts generated from these ligands (both phosphines and phosphine oxides) can be enhanced by the incorporation of an extra hydroxy group. From this study, the norephedrine-derived P–N–O ligand **3a** was found to induce good enantioselectivities in the reduction of acetophenone and propiophenone, affording products with up to 93% ee (Scheme 1).[3]

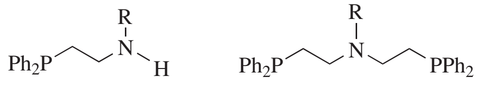
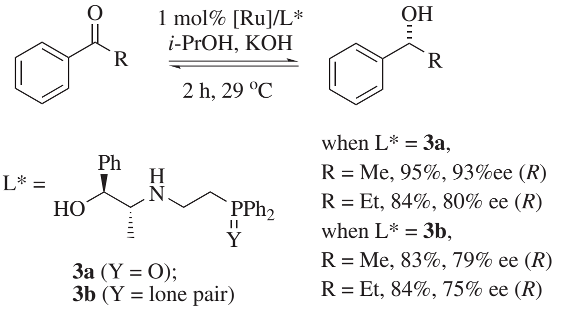

1 (PNH) **2** (PNP)

Figure 1.



3a (Y = O);
3b (Y = lone pair)

when L* = **3a**,
R = Me, 95%, 93%ee (*R*)
R = Et, 84%, 80% ee (*R*)
when L* = **3b**,
R = Me, 83%, 79% ee (*R*)
R = Et, 84%, 75% ee (*R*)

Scheme 1. Asymmetric ruthenium-catalysed transfer hydrogenation of ketones by PNO ligands.

Prior and concurrent to our investigation, Pietrusiewicz et al. reported the synthesis of β-aminophosphine oxides of type **4** (Fig. 2) as ligands in ruthenium-catalysed asymmetric transfer hydrogenation of aryl ketones,

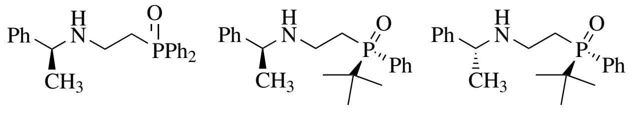

4a **4b** **4c**

Figure 2. Pietrusiewicz's ligands **4a**–**c**.

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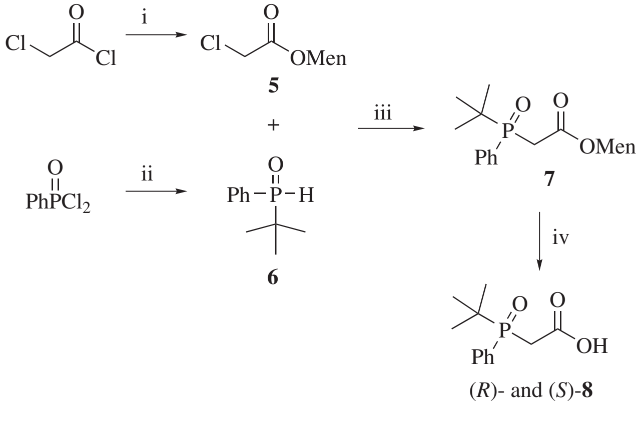
producing optically active alcohols with up to 84% ee.[4,5] The authors observed that the aminophosphine oxides generally induced much higher rates of turnover than the corresponding aminophosphines. They also noted an enhancement in the catalytic activities of the phosphine oxide ligands by the presence of a bulky alkyl substituent at the phosphorus **4b** and **4c**. Interestingly, the configuration of the hydrogenation product appeared to be independent of the stereochemistry at the phosphorus donor atom.

With the above findings, we initiated a project to examine the activity of aminophosphine oxide ligands, combining the bulky stereogenic phosphorus moiety with an OH donor; two key structural features identified in earlier systems to promote fast catalytic turnover.

2. Results and discussion

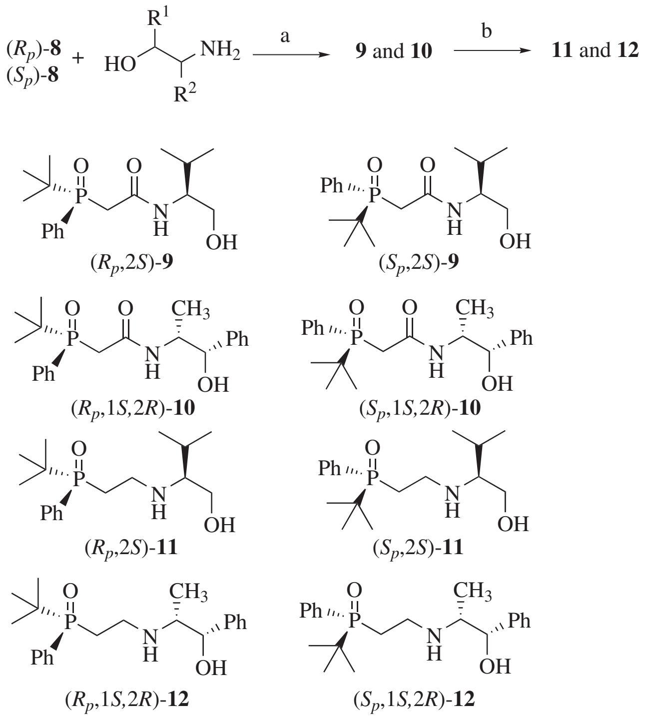
2.1. Preparation of *P*-chirogenic amido and aminophosphine ligands

By modifying literature procedures, menthyl(*tert*-butylphenylphosphinoyl)acetate **7** was obtained by the nucleophilic substitution of (−)-menthyl chloroacetate **5** with the anion generated from *tert*-butylphenylphosphine oxide **6** (Scheme 2). The resultant product was purified by fractional crystallisation, affording 20% and 26% of the enantiomerically pure (R_p)- and (S_p)-diastereomers of **7**, respectively.



Scheme 2. Preparation of optically active (*tert*-butylphenylphosphinoyl)acetic acid **8**. Reagents and conditions: (i) (−)-menthol, *N*,*N*-dimethylaniline, CH_2Cl_2, 0–30 °C; (ii) *tert*-BuMgCl (5 equiv), Et_2O, reflux, 40 h; (iii) NaH, THF, 0 °C, fractional crystallisation; (iv) KOH, MeOH.

Following hydrolysis under mild conditions, the resultant phosphinoacetic acids **8** were coupled with (*S*)-valinol and (−)-norephedrine to furnish diastereomeric pairs of amido ligands **9** and **10** (Scheme 3) as highly crystalline solids. Thus, the stereochemistry of (S_p,1*S*,2*R*)-**10** can be determined unequivocally by single-crystal X-ray crystallography (Fig. 3).[6] Finally, using borane as a reducing agent, amino hydroxyl phosphine oxides **11** and **12** can be obtained from **9** and **10**, respectively.



Scheme 3. Amide coupling to give PNO ligands. Reagents and conditions: (a) EDC, DMAP (cat); (b) i. BH_3–THF; ii. NaOH, MeOH.

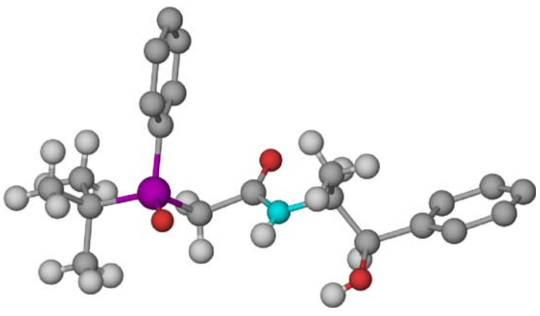
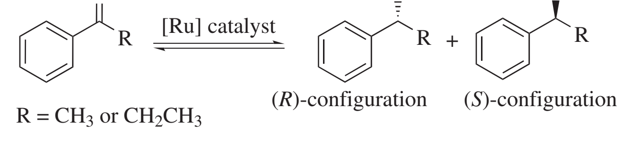


Figure 3. Crystal structure of **10**, showing the requisite S_p, 1*S*,2*R* stereochemistry (aromatic hydrogens omitted for clarity).

2.2. Catalytic results

Using reaction conditions previously optimised for P–N–O ligands **3a** and **3b**, the asymmetric transfer hydrogenation reactions of aryl ketones (acetophenone and propiophenone) were carried out using isopropanol as the hydrogen source (Scheme 4).



Scheme 4. Asymmetric transfer hydrogenation of ketones.

2.2.1. Amido phosphine oxide ligands 9 and 10. The presence of a lone pair of electrons on the nitrogen was once again found to be crucial for catalyst activity. The amidophosphine oxide ligands (R_p,2*S*)-**9**, (S_p,2*S*)-**9**, (R_p,1*S*,2*R*)-**10** and (S_p,1*S*,2*R*)-**10** gave uniformly low conversions in the reduction of acetophenone (12%, 15%, 6% and 6%, respectively). As a result, these ligands were not investigated further for this catalytic reaction.

2.2.2. Amino hydroxy phosphine oxides 11 and 12.

Reduction of the amido functionality to ligands **11** and **12** led to much more impressive turnovers. For the purpose of comparison, norephedrine and the previously prepared aminodiphenylphosphine oxide ligand **3a** were included in this part of the study.

Without the phosphine moiety, the amino alcohol norephedrine gave good conversions under these catalytic conditions, offering an ee of 85% for the reduction of acetophenone (Table 1, entry 1). The incorporation of a diphenylphosphine oxide moiety improved the enantioselectivity of this process to 93% (entry 2).

In comparison, the valinol-derived ligand (R_p,2*S*)-**11** showed fast catalytic turnover, but low enantioselectivity (entry 3). Its (S_p,2*S*)-diastereomer displayed a lower conversion rate and ee (entry 4), suggesting a cooperative effect between the two stereogenic centres on the reaction outcome. In both cases, the configuration of the product alcohol was found to be predominantly *S*.

In contrast, both diastereomers of ligand **12** displayed comparable conversions, but with dramatically different enantioselectivities (entries 5 and 6). (R_p,1*S*,2*R*)-**12** facilitated the formation of the alcohol with 93% ee, whereas the opposite diastereomer afforded only 41% ee. Once again, the stereogenic centres associated with the amino alcohol dictated stereoinduction—favouring the (*R*)-configuration in both cases.

The enantioselectivity of the asymmetric hydrogenation of aryl ketones is often very sensitive to the steric bulk of the substrate. When the acetophenone is substituted by propiophenone, a drop in product ee from 85% to 65% was observed when norephedrine was used as the ligand (entry 1 vs 7), and 93% to 80% whilst employing ligand **3a** (entries 2 vs 8). In the case of ligand **11**, there is a dramatic reduction in catalytic turnover, falling to just 11%, suggesting a significant steric effect exerted by the isopropyl substituent.

In light of the above observations, it is rather surprising to find that the ligand (R_p,1*S*,2*R*)-**12** does not seem to suffer any decline in yield or selectivity in the reduction of the more sterically demanding substrate (entries 5 and 11); a high ee of 92% was achieved for the reduction of propiophenone under the same catalytic conditions, making it one of the most selective for this particular substrate. Once again, changing the chirality at the phosphorus moiety had a detrimental effect on the activity and selectivity of the catalyst (entry 12). The stereoinduction remained unchanged, with the (*R*)-alcohol as the major product in both cases.

3. Conclusions

A class of asymmetric aminohydroxy phosphine oxide ligands was prepared. The ligands derived from norephedrine were found to afford high activities and selectivities in ruthenium-catalysed transfer hydrogenation of aryl ketones. Unusually, high enantioselectivities of greater than 90% can be achieved with ligand (R_p,1*S*,2*R*)-**12** for the reduction of acetophenone and propiophenone. The studies demonstrate the existence of highly synergistic effects between the donor groups and the stereogenic centres, working in concert to determine the course of these reactions. However, the optical activity of the product is dictated only by the chirality of the amino alcohol.

4. Experimental

4.1. General procedure

All reactions were carried out under an inert atmosphere of nitrogen using standard Schlenk line techniques. Solvents were purified by standard procedures.

Table 1. Asymmetric ruthenium-catalysed transfer hydrogenation of ketones[a]

Entry	Ligand	Substrate	% Conversion[b]	% Ee[c] (*R*/*S*)
1	Norephedrine	**A**	94	85 (*R*)
2	**3a**	**A**	91	93 (*R*)
3	(R_p,2*S*)-**11**	**A**	98	34 (*S*)
4	(S_p,2*S*)-**11**	**A**	76	29 (*S*)
5	(R_p,1*S*,2*R*)-**12**	**A**	95	93 (*R*)
6	(S_p,1*S*,2*R*)-**12**	**A**	98	41 (*R*)
7	Norephedrine	**B**	96	65 (*R*)
8	**3a**	**B**	84	80 (*R*)
9	(R_p,2*S*)-**11**	**B**	11	—[d]
10	(S_p,2*S*)-**11**	**B**	11	—[d]
11	(R_p,1*S*,2*R*)-**12**	**B**	99	92 (*R*)
12	(S_p,1*S*,2*R*)-**12**	**B**	80	86 (*R*)

[a] General reaction conditions: $[RuCl_2(cymene)]_2$ (0.5 mol%), ligand (1.0 mol%), KOH (1.3 mol%) and the aryl ketone substrate (1 mmol) in isopropanol (10 mL) at 29 °C for 2 h. **A**: acetophenone, **B**: propiophenone.

[b] Determined by ^1H NMR.

[c] Determined by chiral HPLC using a Chiralcel OD-H column.

[d] Not determined.

$[RuCl_2(\eta^6\text{-}p\text{-}MeC_6H_4CHMe_2)]_2$[7] was prepared following reported procedures. Unless otherwise stated, all other reagents were obtained from Avocado, Lancaster or Aldrich chemical companies and used as received. ^{31}P, ^{1}H and ^{13}C NMR spectra were recorded using Bruker Avance 360, 400 or 500 MHz instruments with TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P) as external standards. Mass spectrometry facilities were performed at London Metropolitan University. HPLC were performed on a Gilson instrument. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FTIR spectrometer.

4.2. Ligand synthesis

4.2.1. (−)-Menthyl chloroacetate 5.[8] (−)-Menthol (40 g, 256 mmol) was slowly added to a cooled (ice bath) mixture of chloroacetic chloride (20 mL, 256 mmol) and *N*,*N*-dimethylaniline (32.6 mL, 256 mmol) in CH_2Cl_2 (30 mL) over 20 min, during which the reaction temperature was maintained at <30 °C. The reaction mixture was stirred at room temperature for 1 h, before it was cooled in an ice-water bath. H_2O (3 mL) was added and the mixture stirred for another 10 min, before it was extracted using hexane (120 mL). The organic extract was washed with cold 10% H_2SO_4 until the aqueous layer, made alkaline with NaOH, was no longer cloudy. The organic layer was then washed with brine (20 mL), saturated aq $NaHCO_3$ (20 mL), brine (10 mL) and dried over Na_2SO_4. The solution was filtered and concentrated, then fractionally distilled to afford a colourless liquid. Yield: 52.7 g, 81%. Bp 98–99 °C (3 mmHg). $[\alpha]_D^{25} = -84.9$ (*c* 1.24, EtOH) lit.[8] -86.2 (*c* 1.0, EtOH). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.78 (d, 3H, $J = 7.0$ Hz), 0.79–1.18 (m, 10H), 1.30–1.61 (m, 2H), 1.65–1.73 (m, 2H), 1.83–1.93 (m, 1H), 4.05 (s, 2H), 4.78 (dt, 1H, $J = 4.4, 10.9$ Hz). ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 16.6, 21.1, 22.3, 23.7, 26.5, 31.7, 34.6, 40.9, 41.5, 47.2, 76.9, 167.3. IR (cm^{-1}, thin film, NaCl discs) ν: 2956, 1758, 1735, 1456, 1188, 983.

4.2.2. *tert*-Butylphenylphosphine oxide 6. A solution of *tert*-butyl chloride (60.9 mL, 560 mmol) in Et_2O (50 mL) was added slowly to a suspension of Mg turnings (15.0 g, 625 mmol) in Et_2O (280 mL), such that the reaction mixture was maintained under slow reflux. After the addition, the reaction mixture was refluxed for 3 h. After cooling to room temperature, the mixture was filtered by using a cannula. The filtrate was brought to reflux, whereupon a solution of phenyl phosphonic dichloride (20.0 g, 102.6 mmol) in Et_2O (40 mL) was added dropwise. The reaction mixture was refluxed for another 40 h during which precipitation of a yellow solid occurred. After cooling to 0 °C, 10% aq HCl (200 mL) was added dropwise. The layers were separated, and the aqueous layer extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and fractionally distilled to afford a colourless liquid. Yield 0.86 g, 46%. Bp 100–104 °C (0.1 mmHg). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.77 (d, 9H, $J = 16.6$ Hz), 7.04 (d, $J = 453$ Hz), 7.06–7.73 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +48.7. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 23.8 (d, $J = 2$ Hz), 32.4 (d, $J = 69$ Hz), 129.0 (d, $J = 12$ Hz), 130.0 (d, $J = 92$ Hz), 131.0 (d, $J = 10$ Hz), 133.0 (d, $J = 3$ Hz). IR (cm^{-1}, thin film, NaCl discs) ν: 3442, 2963, 2307, 1591, 1175.

4.2.3. *tert*-Butylphenylphosphinoyl acetic acid menthyl ester 7.[9] (−)-Menthyl chloroacetate **5** (10.1 g, 43.3 mmol) was added dropwise to a mixture of butylphenylphosphine oxide **6** (9.0 g, 43.3 mmol) and NaH (1.4 g, 60.6 mmol) in THF (80 mL) at 0 °C under nitrogen. After stirring overnight at room temperature, satd NH_4Cl (30 mL) was added, followed by extraction with hexane (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give a syrup, which was dissolved in hexane (40 mL). The solution was kept at 5 °C to give a crystalline solid (12.2 g). The solid was dissolved in hexane (240 mL) and cooled to −7 °C, whereupon white crystal needles formed, which were filtered off and recrystallised in hexane (180 mL) to give (*R*$_p$)-**7**. The combined mother liquid was concentrated and dissolved in hexane (50 mL) and kept at 5 °C for 3 days, to give a crystalline solid. The mixture was warmed to 30 °C and filtered. The residue was then recrystallised from hexane (30 mL) to give (*S*$_p$)-**7**. (*R*$_p$)-**7**: Yield 3.8 g, 20%. Mp 75–76 °C (lit.[8] 75–76 °C). $[\alpha]_D^{25} = -80.0$ (*c* 1.0, CH_3OH) lit.[8] -85.7 (*c* 1.0, CH_3OH). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.65 (d, 3H, $J = 6.9$ Hz), 1.16 (d, 9H, $J = 15.3$ Hz), 0.67–1.18 (m, 15H), 3.18–3.32 (m, 2H), 4.60 (dt, 1H, $J = 4.4, 10.9$ Hz), 7.45–7.82 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +44.9. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 16.1, 21.2, 22.2, 23.2, 24.7, 25.8, 31.6, 33.5 (d, $J_{PC} = 51$ Hz), 34.1 (d, $J_{PC} = 63$ Hz), 34.4, 40.6, 46.8, 75.9, 128.4 (d, $J_{PC} = 12$ Hz), 129.7 (d, $J = 92$ Hz), 132.1 (d, $J = 3$ Hz), 132.4 (d, $J = 9.0$ Hz), 166.7 (d, $J = 7$ Hz). IR (cm^{-1}, Nujol, NaCl discs) ν: 3053, 2921, 1721, 1464, 1265, 1171, 727. (*S*$_p$)-**7**: Yield 5.1 g, 26%. Mp 116–117 °C (lit.[8] 116.5–117.5 °C). $[\alpha]_D^{25} = +7.8$ (*c* 1.0, CH_3OH), lit.[8] +9.4 (*c* 1.0, CH_3OH). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.43 (d, 3H, $J = 7.0$ Hz), 1.16 (d, 9H, $J = 15.3$ Hz), 0.60–1.80 (m, 15H), 3.10–3.32 (m, 2H), 4.54 (dt, 1H, $J = 4.3, 10.9$ Hz), 7.46–7.81 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +44.9. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 15.9, 21.1, 22.3, 23.2, 24.6, 25.8, 31.6, 33.5 (d, $J = 42$ Hz), 34.1 (d, $J = 61$ Hz), 34.4, 40.6, 46.8, 76.1, 128.3 (d, $J = 11$ Hz), 128.9 (d, $J = 91$ Hz), 132.1 (d, $J = 3$ Hz), 132.5 (d, $J = 8$ Hz), 166.6 (d, $J = 6$ Hz). IR (cm^{-1}, Nujol, NaCl discs) ν: 2924, 1731, 1723, 1462, 1377, 1170.

4.2.4. (*tert*-Butylphenylphosphinoyl)acetic acid 8. The corresponding ester **7** (3.2 g, 13.3 mmol) and KOH (1.5 g, 26.8 mmol) were stirred in CH_3OH (10 mL) at room temperature for 48 h. After removal of methanol, H_2O (10 mL) was added. The aqueous layer was washed with diethyl ether and acidified by the addition of concd HCl (3 mL). NaCl (2.0 g) was added and the mixture extracted repeatedly with $CHCl_3$ (6 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed to give the product as a white solid. Yield 2.0 g, 99%.

Mp 166–168 °C (decompose) (lit.[8] 166–168 °C). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.17 (d, 9H, $J = 15.9$ Hz), 3.17 (dd, 1H, $J = 10.1$, 14.6 Hz), 3.31 (dd, 1H, $J = 11.8$, 14.6 Hz), 7.44–7.71 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +50.7. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 24.2, 31.8 (d, $J = 52$ Hz), 33.8 (d, $J = 71$ Hz), 128.1 (d, $J = 94$ Hz), 128.8 (d, $J = 12$ Hz), 131.9 (d, $J = 8$ Hz), 132.8 (d, $J = 3$ Hz), 167.1 (d, $J = 6$ Hz). IR (cm^{-1}, Nujol, NaCl discs) ν: 3418, 2925, 2854, 2576, 1961, 1724, 1463, 1270.

(S_p)-**8**: $[\alpha]_D^{25} = -52.1$ (c 1.0, EtOH).

(R_p)-**8**: $[\alpha]_D^{20} = +51.9$ (c 1.0, EtOH).

4.2.5. General procedure for the synthesis of (R_p,1*S*,2*R*)-2-(*tert*-butylphenylphosphinoyl)-*N*-(2-hydroxyl-1-methyl-2-phenylethyl)acetamide, (R_p,1*S*,2*R*)-10. EDC (1.0 g, 5.2 mmol) was added to a solution of (R_p)-**8** (0.60 g, 2.5 mmol), L-(−)-(1*S*,2*R*)-norephedrine (0.42 g, 2.7 mmol) and DMAP (0.45 g, 3.7 mmol) in CH_2Cl_2 (12 mL) at room temperature. The reaction mixture was stirred at 40 °C overnight and then diluted with $CHCl_3$. The organic layer was washed with 1 M aq HCl (6 mL, 6 mmol), brine (6 mL), saturated sodium carbonate (3 mL) and brine (6 mL) successively, before it was dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuum to give a white powder. Yield 0.91 g, 93%. Mp 188–189 °C. Anal. Calcd for $C_{21}H_{28}NO_3P$: C, 67.54; H, 7.56; N, 3.75. Found: C, 67.66; H, 7.64; N, 3.65. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.83 (d, 3H, $J = 6.9$ Hz), 1.13 (d, 9H, $J = 15.7$ Hz), 2.95–3.17 (m, 2H), 3.99–4.09 (m, 1H), 4.43 (d, 1H, $J = 3.5$ Hz), 7.08–7.67 (m, 10H). ^{31}P NMR (145 Hz, $CDCl_3$) δ: 50.0. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 13.0, 24.4, 33.2 (d, $J = 50$ Hz), 33.7 (d, $J_{PC} = 70$ Hz), 52.1, 74.9, 126.3–141.3, 165.5 (d, $J = 5$ Hz). HRMS (FAB): exact mass calcd for $C_{21}H_{29}NO_3P$ (M^++1) 374.1874, found 374.1885. IR (cm^{-1}, Nujol, NaCl discs): ν 3165, 2921, 1636, 1539, 1463, 1377, 1166. $[\alpha]_D^{25} = -36.0$ (c 1.05, EtOH).

4.2.6. (S_p,1*S*,2*R*)-2-(*tert*-Butylphenylphosphinoyl)-*N*-(2-hydroxyl-1-methyl-2-phenylethyl)acetamide, (S_p,1*S*,2*R*)-10. This was prepared from (S_p)-**8** and L-(−)-(1*S*,2*R*)-norephedrine. Yield: 88%. Mp 166–167 °C. Anal. Calcd for $C_{21}H_{28}NO_3P$: C, 67.54; H, 7.56; N, 3.75. Found: C, 67.51; H, 7.66; N, 3.66. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.75 (d, 3H, $J = 6.8$ Hz), 1.14 (d, 9H, $J = 15.7$ Hz), 3.04 (dd, 1H, $J = 9.4$, 14.8 Hz), 3.21 (dd, 1H, $J = 12.7$, 14.8 Hz), 4.06–4.16 (m, 1H), 4.54–4.59 (br s, 1H), 4.91 (t, 1H, $J = 3.0$ Hz), 7.21–7.72 (m, 10H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: 48.8. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 13.1, 24.4, 33.6 (d, $J_{PC} = 51$ Hz), 33.8 (d, $J_{PC} = 70$ Hz), 52.0, 75.1, 126.4–141.8, 165.5 (d, $J_{PC} = 5.0$ Hz). HRMS (FAB): exact mass calcd for $C_{21}H_{29}NO_3P$ (M^++1) 374.1885, found 374.1900. IR (cm^{-1}, Nujol, NaCl discs) ν: 3267, 2917, 1659, 1529, 1463, 1163, 1103. $[\alpha]_D^{25} = +33.5$ (c 1.35, EtOH).

4.2.7. (R_p,2*S*)-2-(*tert*-Butylphenylphosphinoyl)-*N*-(1-hydroxymethyl-2-methylpropyl)acetamide, (R_p,2*S*)-9. From (R_p)-**8** and (*S*)-(+)-2-amino-3-methyl-1-butanol. Yield: 88%. Mp 159–160 °C. Anal. Calcd for $C_{17}H_{28}NO_3P$: C, 62.75; H, 8.67; N, 4.30. Found: C, 62.66; H, 8.69; N, 4.22. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.91 (d, 3H, $J = 6.8$ Hz), 0.92 (d, 3H, $J = 6.8$ Hz), 1.17 (d, 9H, $J = 15.7$ Hz), 1.78–1.89 (m, 1H), 3.04–3.23 (m, 3H, H_2), 3.27–3.39 (m, 2H), 3.52–3.60 (m, 1H), 7.06 (br d, $J = 8.6$ Hz), 7.48–7.75 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: 50.4. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 18.2, 18.9, 28.1, 31.0 (d, $J_{PC} = 51$ Hz), 32.5 (d, $J_{PC} = 70$ Hz), 57.7, 62.9, 126.9–137.9, 165.3 (d, $J_{PC} = 5$ Hz). HRMS (FAB): exact mass calcd for $C_{17}H_{29}NO_3P$ (M^++1) 326.1885, found 326.1870. IR (cm^{-1}, Nujol, NaCl discs): ν 3273, 2924, 1628, 1561, 1463, 1377, 1165. $[\alpha]_D^{25} = -61.8$ (c 1.23, EtOH).

4.2.8. (S_p,2*S*)-2-(*tert*-Butylphenylphosphinoyl)-*N*-(1-hydroxymethyl-2-methylpropyl)acetamide (S_p,2*S*)-9. From (S_p)-**8** and (*S*)-(+)-2-amino-3-methyl-1-butanol. Yield: 92%. Mp 106–107 °C. Anal. Calcd for $C_{17}H_{28}NO_3P$: C, 62.75; H, 8.67; N, 4.30. Found: C, 62.67; H, 8.77; N, 4.28. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.60 (d, 3H, $J = 6.8$ Hz), 0.63 (d, 3H, $J = 6.8$ Hz), 1.10 (d, 9H, $J = 15.5$ Hz), 1.59–1.69 (m, 1H), 3.00 (dd, 1H, $J = 8.3$, 15.1 Hz), 3.19 (dd, 1H, $J = 13.5$, 15.1 Hz), 3.37–3.41 (br s, 1H), 3.47–3.64 (m, 3H), 7.39–7.67 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: 49.4. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 15.8, 17.2, 21.9, 26.7, 30.5 (d, $J_{PC} = 51$ Hz), 31.3 (d, $J_{PC} = 70$ Hz), 55.7, 61.8, 126.1–130.2, 164.0 (d, $J_{PC} = 6$ Hz). HRMS (FAB): exact mass calcd for $C_{17}H_{29}NO_3P$ (M^++1) 326.1893, found 326.1885. IR (cm^{-1}, Nujol, NaCl discs) ν: 3291, 3162, 2925, 1654, 1557, 1463, 1161. $[\alpha]_D^{25} = +19.1$ (c 1.62, EtOH).

4.2.9. General procedure for the reduction of amide ligands and deprotection of borane for the synthesis of (R_p,1*S*,2*R*)-2-[2-(*tert*-butylphenylphosphinoyl)ethylamino]-1-phenylpropan-1-ol (R_p,1*S*,2(*R*)-12. BH_3–THF solution (1.5 M in THF, 4.0 mL, 6.0 mmol, 4 equiv) was added to a suspension of (R_P)-**10** (0.52 g, 1.4 mmol) in THF (20 mL). The mixture was stirred at room temperature for 2 h and then at 60 °C overnight. The reaction mixture was then cooled in an ice bath and CH_3OH (1 mL) added. Solvents were removed in vacuum. CH_3OH (20 mL) and 30% aqueous NaOH solution (2 mL) were added to the residue and the reaction mixture stirred at 40 °C for 1 h. The volatiles were removed in vacuo, H_2O (5 mL) and CH_2Cl_2 (20 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and purified by flash chromatography (SiO_2, isopropanol/NEt_3/chloroform: 2/1/22, $R_f = 0.36$) to give a white solid. Yield: 0.32 g, 64%. Mp 164–166 °C. Anal. Calcd for $C_{21}H_{30}NO_2P$: C, 70.17; H, 8.41; N, 3.90. Found: C, 70.26; H, 8.45; N, 3.83. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.68 (d, 3H, $J = 6.6$ Hz), 1.06 (d, 9H, $J = 14.7$ Hz), 1.60 (br s, 1H), 2.12–2.31 (m, 2H), 2.69–2.77 (m, 1H), 2.81–3.01 (m, 2H), 3.80 (br s, 1H), 4.64 (d, 1H, $J = 3.2$ Hz), 7.11–7.69 (m, 10H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: 50.9. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 14.7, 23.9 (d, $J_{PC} = 63$ Hz), 24.6, 32.1 (d, $J_{PC} = 69$ Hz), 40.6 (d, $J_{PC} = 3$ Hz), 58.7, 72.5, 126.3–142.1. HRMS (FAB): exact mass calcd for $C_{21}H_{31}NO_2P$ (M^{+}+1) 312.2092, found 312.2084. IR (cm^{-1}, Nujol, NaCl discs) *v*: 3265, 2923, 1600, 1462, 1157, 1000. $[\alpha]_D^{25} = -6.5$ (*c* 1.38, EtOH).

4.2.10. (S_p,1*S*,2*R*)-2-[2-(*tert*-Butylphenylphosphinoyl)ethylamino]-1-phenylpropan-1-ol, (S_p,1*S*,2*R*)-12 was similarly prepared from (S_p)-10. Yield 51%. Mp 143–144 °C. Anal. Calcd for $C_{21}H_{30}NO_2P$: C, 70.17; H, 8.41; N, 3.90. Found: C, 70.26; H, 8.45; N, 3.83. ^1H NMR (360 MHz, $CDCl_3$) δ: 0.69 (d, 3H, $J = 6.5$ Hz), 1.13 (d, 9H, $J = 14.2$ Hz), 1.50 (br, s, 1H), 2.45–2.48 (m, 2H), 2.77–2.85 (m, 1H), 2.86–3.10 (m, 2H), 4.20 (br s, 1H), 4.72 (d, 1H, $J = 3.6$ Hz), 7.10–7.91 (m, 10H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: 45.1. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 14.8, 23.9 (d, $J_{PC} = 63$ Hz), 24.6, 33.1 (d, $J_{PC} = 69$ Hz), 41.1 (d, $J_{PC} = 3$ Hz), 58.7, 73.1, 126.0–141.1. HRMS (FAB): exact mass calcd for $C_{21}H_{31}NO_2P$ (M^{+}+1) 360.2092, found 360.2083. IR (cm^{-1}, Nujol, NaCl discs) *v*: 3274, 2922, 1463, 1377, 983, 702. $[\alpha]_D^{25} = +19.0$ (*c* 1.15, EtOH).

4.2.11. (S_p,2*S*)-2-[2-(*tert*-Butylphenylphosphinoyl)ethylamino]-3-methylbutan-1-ol, (S_p,2*S*)-11. From (S_p)-**9**. Yield: 48%. Mp 81–82 °C. Anal. Calcd for $C_{17}H_{30}NO_2P$: C, 65.57; H, 9.71; N, 4.50. Found: C, 65.53; H, 9.73; N, 4.40. ^1H NMR (360 MHz, $CDCl_3$) δ: 0.78 (d, 3H, $J = 6.9$ Hz), 0.83 (d, 3H, $J = 6.8$ Hz), 1.07 (d, 9H, $J = 20.2$ Hz), 1.56–1.66 (m, 1H), 2.12–2.41 (m, 3H), 2.75–3.00 (m, 2H), 3.24 (dd, 1H, $J = 7.6$, 10.9 Hz), 3.52 (dd, 1H, $J = 3.8$, 10.9 Hz), 3.80 (br s, 2H), 7.41–7.80 (m, 5H). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +52.0. ^{13}C NMR (90.5 MHz, $CDCl_3$) δ: 18.9, 19.7, 23.6 (d, $J_{PC} = 64$ Hz), 24.6, 29.6, 33.1 (d, $J_{PC} = 69$ Hz), 41.7 (d, $J_{PC} = 5$ Hz), 61.4, 65.0, 128.6–132.2. HRMS (FAB): exact mass calcd for $C_{17}H_{31}NO_2P$ (MH^{+}) 312.2092, found 312.2084. IR (cm^{-1}, Nujol, NaCl discs) *v*: 3366, 2922, 1466, 1376, 1148, 1050. $[\alpha]_D^{25} = +23.9$ (*c* 1.10, EtOH).

4.2.12. (R_p,2*S*)-2-[2-(*tert*-Butylphenylphosphinoyl)ethylamino]-3-methylbutan-1-ol, (R_p,2*S*)-11. From (R_P)-**9**. Colourless liquid. Yield: 46%. Anal. Calcd for $C_{17}H_{30}NO_2P$: C, 65.57; H, 9.71; N, 4.50. Found: C, 65.46; H, 9.85; N, 4.39. ^1H NMR (360 MHz, $CDCl_3$) δ: 0.73 (d, 3H, $J = 6.7$ Hz), 0.79 (d, 3H, $J = 6.8$ Hz), 1.06 (d, 9H, $J = 14.7$ Hz), 1.40–1.60 (m, 1H), 2.19–2.40 (m, 3H), 2.76–2.92 (m, 2H), 3.21 (dd, 1H, $J = 7.5$, 11.0 Hz), 3.46 (dd, 1H, $J = 3.9$, 11.0 Hz), 7.30–7.72 (m). ^{31}P NMR (145 MHz, $CDCl_3$) δ: +51.3. ^{13}C NMR (90.5 MHz, $CDCl_3$): δ 19.1, 19.9, 24.1 (d, $J_{PC} = 63$ Hz), 24.6, 29.5, 32.7 (d, $J_{PC} = 69$ Hz), 40.8, 61.0, 65.0, 128.6–132.2. HRMS (FAB): exact mass calcd for $C_{21}H_{31}NO_2P$ (MH^{+}) 312.2092, found 312.2100. IR (cm^{-1}, thin film, NaCl discs) *v*: 3325, 2957, 1655, 1475, 1155. $[\alpha]_D^{25} = -19.2$ (*c* 1.08, EtOH).

4.3. General catalytic procedure

Ligand (0.011 mmol) and $[RuCl_2(\eta^6\text{-}p\text{-}MeC_6H_4\text{-}CHMe_2)]_2$ (0.005 mmol, 0.5 mol %) were added to a dry Schlenk tube, which was subsequently purged and filled with nitrogen successively. Anhydrous isopropanol (8 mL) was added and the mixture was left to reflux at 83 °C for 30 min. After cooling to 30 °C, acetophenone (0.12 mL, 1.0 mmol) was added. The catalytic process was initiated by the addition of a solution of KOH in isopropanol (0.013 M, 2.0 mL, 0.026 mmol). After the appropriate time, the reaction was quenched by the addition of water (0.5 mL). The solvents were evaporated and the residue was examined by ^1H NMR to determine the percentage conversion. Enantiomeric excesses were determined by HPLC with a Chiracel OD-H column: for 1-phenylethanol, 5% isopropanol in hexane, 0.5 mL/min, $t_R = 15.5$ min, $t_S = 17.7$ min; for 1-phenylpropanol, 2% isopropanol in hexane, 0.3 mL/min, $t_R = 48.7$ min, $t_S = 53.9$ min.

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