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Ruthenium(II)-assisted asymmetric hydrogen transfer reduction of acetophenone using chiral tridentate phosphorus-containing ligands derived from (1*R*, 2*R*)-1,2-diaminocyclohexane

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Abstract

Several chiral and unsymmetrical tridentate [NNP]-type ligands with sp^2-N and sp^3-N were synthesized from monosulfonamide of (1*R*, 2*R*)-1,2-diaminocyclohexane and 2-(diphenylphosphino)benzaldehyde. Their ruthenium(II) complexes have been used in the enantioselective asymmetric hydrogen transfer reduction of acetophenone in 2-propanol with selectivities in the range 14–99% e.e. The good enantioselectivity with the ligands with sp^2-N and sp^3-N is believed to be due to formation of hexacoordinated complexes with a 2:1 ligand to metal ratio.

Keywords: Asymmetric; Ruthenium(II); Transfer; Hydrogenation; Schiff base

1. Introduction

Bidentate and tetradentate ligands derived from chiral 1,2-diaminocyclohexane with C_2 symmetry exhibit very rich coordination chemistry and serve as powerful stereodirecting ligands in asymmetric synthesis [1–7]. Tetradentate salen ligands of the [ONNO]-type developed by Jacobsen and Katsuki from chiral 1,2-diaminocyclohexane have found a plethora of application in asymmetric synthesis, including epoxidation, cycloaddition, aziridination, oxidation of sulfide to sulfoxide [8–12], cyanohydration of carbonyl [13], regioselective ring opening of epoxides [14,15] and addition of cyanide to imines [16–18]. As an extension of this application Bu and Nguyen have independently synthesized a number of unsymmetrical Schiff base ligands derived from chiral 1,2-diaminocyclohexane as potential substitutes for Jacobsen's symmetrical catalyst [19–21]. Similar tetradentate ligands of the [NNNN]-type with 1,2-diaminocyclohexane backbone containing oxazolines have been synthesized by Zhu and coworkers; interestingly, the catalytic application of these ligands have not yet been explored [22]. Tetradentate salen ligands in which the hard oxygen donor atom is replaced by a soft phosphorus donor atom of the type [OPNNPO], [SPNNPS] [23], [PNNP], [PNHNHP] bearing C_2 symmetry, and [$PNHNHNR_2$]-type of ligands, have also been extensively studied as catalysts with metals such as titanium [23a], iridium [23b], ruthenium [24–26], rhodium [23b], molybdenum [27,28] and palladium [29,30].

Noyori and co-workers have demonstrated the use of C_2-diphosphine/diimine and diphosphine/diamine ligands *N*,*N*-(*S*,*S*)-bis[*o*-(diphenylphosphino)-benzylidine]cyclohexane-1,2-diamine and *N*,*N*-(*S*,*S*)-bis[*o*-(diphenylphosphino)-benzyl]cyclohexane-1,2-diamine with ruthenium(II) as catalysts in the asymmetric reduction of ketones. In their work they also showed the remarkable difference in activity between sp^2-N and sp^3-N ligands [24–26,31]. In an attempt to mimic enzymes, Liese and coworkers [32] have bound the above ligands to a polymer and have demonstrated that it could behave like enzymes in the asymmetric hydrogen transfer reduction of acetophenone. Interestingly, in their work the synthetic Schiff base intermediate derived from chiral 1,2-diaminocyclohexane and 2-(diphenylphosphino)benzaldehyde and its reduced form was not tested for catalytic activity. Although with most

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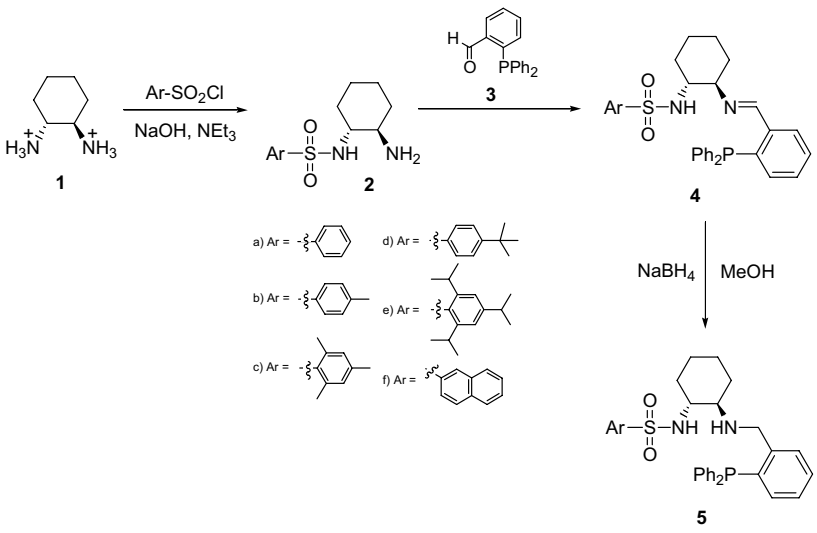


Scheme 1.

ligands, ruthenium(II) has been the metal of choice, Gao and coworkers [33] have shown that cationic rhodium complexes of [PNNP] ligands are equally good in the hydrogen transfer reduction of acetophenone. Following this, Zhang and coworkers [34], and Sablong and Osborn [35] independently developed tridentate chiral [NPN] and [PNP] ligands not bearing the 1,2-diaminocyclohexane backbone and used them effectively in hydrogen transfer reduction.

Our goal in this work was to design similar unsymmetrical tridentate chiral ligands of the [NNP]-type with the (1*R*,2*R*)-1,2-diaminocyclohexane backbone, thus permitting to tune the electronic properties from one side and the steric effects from the other side simultaneously to maximize the performance of the ligand in the ruthenium-catalyzed asymmetric hydrogen transfer reaction. To meet these requirements we selected *trans* (1*R*,2*R*)-1,2-diaminocyclohexane as the backbone in designing our ligands. This diamine with two chiral centers would permit the introduction of different substituents on the nitrogens that could be sterically and electronically fine-tuned. Our intention was to attach a sulfonamide group to one nitrogen, thus making it harder, and at the same time giving the opportunity to alter the steric factor on the aryl sulfonamide ring. In addition, introducing a soft phosphorus atom and a Schiff base on the other nitrogen would lead to a tridentate ligand with hard and soft centers for coordination with ruthenium.

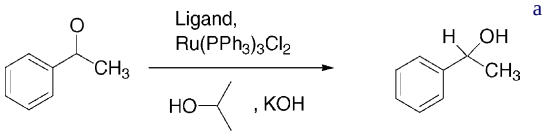
2. Results and discussion

Walsh and coworkers [36,37] have developed an efficient method for making chiral mono-substituted sulfonamide ligands from 1,2-diaminocyclohexane. Reacting these readily available ligands **2** with 2-(diphenylphosphino)benzaldehyde (**3**) gave a series of phosphine-amino-imine ligands **4**. Reduction of the imine bond with sodium borohydride gave the phosphine-diamine ligands **5** readily (Scheme 1).

Having synthesized these tridentate ligands, our goal was to explore their use in the asymmetric hydrogen transfer reduction of acetophenone. The ligands **4** were combined with $Ru(PPh_3)_3Cl_2$ to generate the chiral intermediate in situ, which then reacted with acetophenone, isopropanol and potassium hydroxide at room temperature. The final alcohol was obtained in low yields but with good enantioselectivity (73–99% e.e.) (Table 1, entries 1–3).

Since Noyori and coworkers [24] have established that ligands with sp^3-N provide better enantioselectivity than sp^2-N containing ligands in the hydrogen transfer reduction, we turned our attention to sp^3-N-containing ligands by reducing Schiff base ligands **4** with $NaBH_4$ to give the ligands **5** in good yields. Using these reduced sp^3-N-containing ligands with $Ru(PPh_3)_3Cl_2$ as catalyst led to reduction of

Table 1
Ruthenium-assisted asymmetric hydrogen transfer reduction of acetophenone



[a]

Entry	Ligand	e.e. (%)[b]	Absolute configuration
1	4c (*R*,*R*)	73	(*R*)
2	4e (*R*,*R*)	84	(*R*)
3	4f (*R*,*R*)	99	(*R*)
4	5a (*R*,*R*)	14	(*R*)
5	5b (*R*,*R*)	54	(*R*)
6	5c (*R*,*R*)	77	(*R*)
7	5f (*R*,*R*)	99	(*R*)
8	7a (*R*)	48	(*R*)
9	7b (*R*)	26	(*R*)
10	8b (*R*)	21	(*R*)

[a] All reactions were performed with ligand:$Ru(PPh_3)_3Cl_2$ (2:1) in 20 mol%. Average yield was 15–20%. Each e.e. is the result of three runs.
[b] Enantioselectivities were determined as described in Section 3.

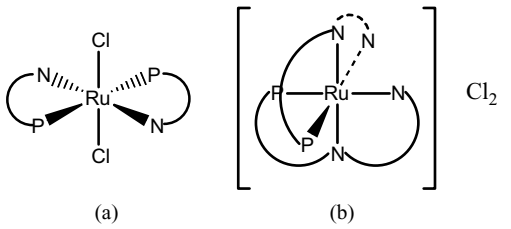


Fig. 1. Possible structures for intermediate complexes in a bidentate (a), or tridentate (b) coordination of the ligand.

acetophenone to alcohol with 14–99% enantioselectivity (Table 1, entries 4–7).

The good enantioselectivities observed with the sp^3-N ligands **4**, and sp^2-N ligands **5** (Table 1) led us to believe that both would form hexacoordinated complexes with a 2:1 ligand to metal ratio. However, ligands **4** probably bind to ruthenium metal in a bidentate fashion resembling the salen-like chelation [25] (Fig. 1a), while ligands **5**, with the imine reduced form [NNHCP], bind in a tridentate fashion leading to a ruthenium intermediate like that proposed by Kwong and coworkers [38] (Fig. 1b).

Interestingly, in both types of ligands increasing the size of substituents on the benzene ring of the sulfonamide fragment (Table 1, entries 1–7) led to higher enantioselectivities, suggesting that steric crowding around the Ru(II) metal center probably enhances enantioselectivity.

Encouraged by these results, we repeated Gimeno and coworkers' [26] synthesis of ligands, but with chiral amines to generate the chiral Schiff bases. The aldehyde **3** was reacted with chiral amines **6** to give the Schiff bases **7**, reduction of which with sodium borohydride led to the corresponding amines **8** (Scheme 2).

These Schiff bases and their corresponding reduced form of ligands **7** and **8** were used with $Ru(PPh_3)_3Cl_2$ as catalysts in the asymmetric hydrogen transfer reaction (Table 1). Results indicated a similar trend in the enantioselectivity between sp^2-N and sp^3-N ligands. Ligands **7a** and **7b** (entries 8, 9) gave slightly better enantioselectivity compared to the ligand **8b** (entry 10). However, the overall enantioselectivity observed for both types of ligands was much lower compared to the monosulfonamide derived ligands **4** and **5**. This result suggests that the aryl substituent containing the sulfonamide probably plays a role in increasing the steric crowding around the ruthenium metal in the transition state, thus enhancing the enantioselectivity of the acetophenone reduction.

3. Experimental

All experiments were carried out under nitrogen atmosphere with standard Schlenk techniques in oven-dried flasks. Solvents were dried and purified according to standard methods. All commercially available reagents were used as received. The monosulfonamides **2** were synthesized by a previously reported method [36,37].

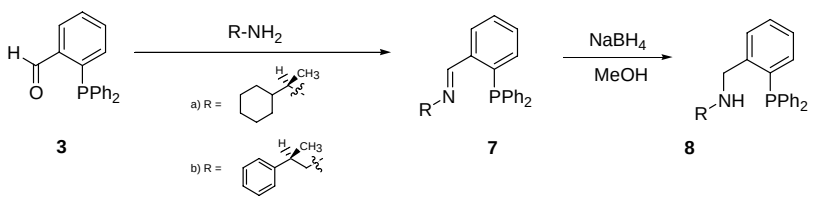
3.1. Preparation of the sulfonamide-iminophosphines:

*3.1.1. N-[2-(2-Diphenylphosphanyl-benzylidene-amino)-cyclohexyl]-benzenesulfonamide (**4a**)*

A mixture of *N*-[(1*R*,2*R*)-2-aminocyclohexyl]-benzenesulfonamide (**1a**) (0.13 g, 0.51 mmol) and 2-(diphenylphosphino)benzaldehyde (**3**) (0.15 g, 0.51 mmol) in mixture 3:1 (v/v) of $MeOH/CH_2Cl_2$ (30 ml) was stirred for 72 h under Ar. The progress of the reaction was monitored by TLC and IR spectroscopy. The solution was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to obtain **4a**. Yellow solid; 0.24 g, 73% yield; mp 73–75 °C; $[\alpha]_D^{25} = -21.0°$ ($c = 0.0021$, CH_2Cl_2); IR (KBr) 3057, 2932, 2859, 1638, 1438, 1159, 749, 649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (1H, d, $J_{PH} = 4.0$ Hz), 7.76–7.93 (3H, m), 7.17–7.72 (14H, m), 6.86–6.89 (2H, m), 2.83-2.86 (1H, m), 2.24-2.26 (1H, m), 1.61-1.66 (4H, m), 1.21-1.35 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.18 ($J_{PC} = 19.3$ Hz), 138.81 ($J_{PC} = 16.3$ Hz), 137.6 ($J_{PC} = 19.3$ Hz), 136.60 ($J_{PC} = 16.5$ Hz), 136.14 ($J_{PC} = 10.0$ Hz), 134.28 ($J_{PC} = 20.0$ Hz), 134.09 ($J_{PC} = 28.1$ Hz), 133.56, 132.34, 130.60, 129.12 ($J_{PC} = 13.1$ Hz), 128.86 ($J_{PC} = 3.3$ Hz), 128.80 ($J_{PC} = 3.0$ Hz), 127.40, 72.58, 58.40, 33.21, 32.51, 24.69, 24.16 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −15.2 ppm; HRMS-FAB (*m/z*): $[M + H]^+$ calculated for $C_{31}H_{32}N_2O_2PS$, 527.1922; found, 527.1927.

*3.1.2. (R,R)-N-[2-(2-Diphenylphosphanyl-benzylidene-amino)-cyclohexyl]-4-methyl-benzenesulfonamide (**4b**)*

White solid; 0.18 g, 88% yield; mp 144–146 °C; $[\alpha]_D^{25} = +7.1°$ ($c = 0.0021$, CH_2Cl_2); IR (KBr) 3055, 2931, 2859, 1639, 1435, 1157, 1029, 741, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.70 (1H, d, $J_{PH} = 4.8$ Hz), 7.68 (2H, d, $J = 8.0$ Hz), 7.31 (2H, d, $J = 8.0$ Hz), 7.08-7.29 (14H, m), 2.61 (1H, m), 2.42 (3H, s), 2.32 (1H, m), 1.62-1.94 (4H, m), 1.01-1.30 (4H, m) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.24 ($J_{PC} = 19.4$ Hz), 143.02, 139.12 ($J_{PC} = 16.0$ Hz),



Scheme 2.

138.21, 137.86 (J_{PC} = 19.4 Hz), 136.9 (J_{PC} = 10.0 Hz), 136.82 (J_{PC} = 8.0 Hz), 134.43 (J_{PC} = 9.5 Hz), 134.04 (J_{PC} = 9.5 Hz), 133.63, 129.68, 129.18 (J_{PC} = 6.0 Hz), 128.91 (J_{PC} = 7.0 Hz), 128.87 (J_{PC} = 7.3 Hz), 128.44 (J_{PC} = 4.0 Hz), 72.59, 58.27, 33.16, 32.48, 24.63, 24.11, 21.65 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −14.50 ppm; HRMS-FAB (*m/z*): $[M+H]^+$ calculated for $C_{32}H_{34}N_2O_2PS$, 541.207; found, 541.2060.

3.1.3. (R,R)-N-[2-(2-Diphenylphosphanyl-benzylidene-amino)-cyclohexyl]-2,4,6-trimethyl-benzenesulfonamide (**4c**)

Yellow solid; 0.41 g, 71% yield; mp 78–80 °C; $[\alpha]_D^{25}$ = +15.6° (*c* = 0.0042, CH_2Cl_2); IR (KBr) 3049, 2929, 2859, 1636, 1440, 1153, 1065, 747, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (1H, d, J_{PH} = 5.0 Hz), 6.85-7.66 (14H, m), 6.82 (2H, s), 2.66 (6H, s), 2.58 (1H, m), 2.34 (1H, m), 2.29 (3H, s), 1.85-1.95 (2H, m), 1.6-1.7 (2H, m), 1.0-1.25 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.13 (J_{PC} = 23.0 Hz), 141.73, 139.03 (J_{PC} = 17.0 Hz), 139.02, 137.71 (J_{PC} = 19.0 Hz), 136.69 (J_{PC} = 10.0 Hz), 136.41 (J_{PC} = 9.2 Hz), 134.28 (J_{PC} = 9.5 Hz), 134.12 (J_{PC} = 9.6 Hz), 130.65, 129.28, 129.00 (J_{PC} = 12.0 Hz), 128.86 (J_{PC} = 9.0 Hz), 128.80 (J_{PC} = 7.0 Hz), 127.90 (J_{PC} = 2.0 Hz), 72.64, 58.16, 33.41, 32.46, 24.74, 24.17, 23.30, 21.18 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −15.99 ppm; HRMS-FAB (*m/z*): $[M + H]^+$ calculated for $C_{34}H_{38}N_2O_2PS$, 569.2392; found, 569.2411.

3.1.4. (R,R)-4-tert-Butyl-N-[2-(2-diphenylphosphanyl-benzylidene-amino)-cyclohexyl]-benzenesulfonamide (**4d**)

Yellow solid; 0.34 g, 92% yield; mp 69–71 °C; $[\alpha]_D^{25}$ = −12.8° (*c* = 0.0020, CH_2Cl_2); IR (KBr) 3057, 2934, 2863, 1640, 1438, 1161, 1089, 739, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.68 (1H, d, J_{PH} = 4.2 Hz), 7.74 (2H, d, *J* = 8.6 Hz), 7.50 (2H, m), 6.86-7.41 (14H, m), 2.5-2.69 (1H, m), 2.36 (1H, td, *J* = 6.5, 6.0 Hz), 1.8-1.93 (2H, m), 1.8-1.93 (2H, m), 1.61 (2H, s), 1.34 (9H, s), 1.26 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.26 (J_{PC} = 17.0 Hz), 156.05, 139.00 (J_{PC} = 17.0 Hz), 137.93 (J_{PC} = 20.20 Hz), 137.70, 137.06 (J_{PC} = 11.1 Hz), 136.98 (J_{PC} = 7.0 Hz), 134.37 (J_{PC} = 20.0 Hz), 133.88 (J_{PC} = 19.7 Hz), 133.75, 130.53, 128.91 (J_{PC} = 22.0 Hz), 128.74 (J_{PC} = 7.5 Hz), 127.45, 125.93, 72.58, 58.34, 35.21, 33.16, 32.12, 31.29, 24.61, 24.21 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −14.01 ppm; HRMS-FAB (*m/z*): $[M + H]^+$ calculated for $C_{35}H_{40}N_2O_2PS$, 583.2548; found, 583.2531.

3.1.5. (R,R)-N-[2-(2-Diphenylphosphanyl-benzylidene-amino)-cyclohexyl]-2,4,6-triisopropyl-benzenesulfonamide (**4e**)

Yellow solid; 0.09 g, 85% yield; mp 61–63 °C; $[\alpha]_D^{25}$ = −26.4° (*c* = 0.0020, CH_2Cl_2); IR (KBr) 3055, 2956, 2868, 1598, 1441, 1162, 1116, 724, 659 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.84 (1H, d, J_{PH} = 4.8 Hz), 7.15-7.86 (14H, m), 7.11 (2H, s), 2.89 (1H, m), 2.84 (1H, td, *J* = 10.5, 3.5 Hz), 1.9-2.0 (2H, m), 1.6-1.7 (2H, m), 1.3-1.6 (3H, m), 1.29 (6H, d, *J* = 7.0 Hz), 1.27 (6H, d, *J* = 7.0 Hz), 1.25 (6H, d, *J* = 7.0 Hz), 1.20-1.23 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.46 (J_{PC} = 20.0 Hz), 150.10, 139.48 (J_{PC} = 18.0 Hz), 137.49 (J_{PC} = 19.0 Hz), 136.97 (J_{PC} = 9.4 Hz), 136.76 (J_{PC} = 7.5 Hz), 133.47, 129.32, 134.32 (J_{PC} = 6.3 Hz), 134.21 (J_{PC} = 6.6 Hz), 134.11 (J_{PC} = 7.4 Hz), 129.03 (J_{PC} = 13.0 Hz), 128.88 (J_{PC} = 6.0 Hz), 128.76 (J_{PC} = 9.0 Hz), 123.89, 72.37, 58.13, 34.27, 33.13, 31.42, 29.82, 25.13, 24.94, 24.54, 24.13, 23.82, 23.78 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −15.49 ppm; HRMS-FAB (*m/z*): $[M + H]^+$ calculated for $C_{40}H_{50}N_2O_2PS$, 653.3331; found, 653.3354.

3.1.6. (R,R)-{2-[(2-Diphenylphosphanyl-benzylidene-amino)-cyclohexyl]}-naphtalenesulfonamide (**4f**)

Yellow solid; 0.23 g, 78% yield; mp 72–74 °C; $[\alpha]_D^{25}$ = −59.8° (*c* = 0.0011, CH_2Cl_2); IR (KBr) 3057, 2932, 2859, 1638, 1438, 1163, 735, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.88 (1H d, J_{PH} = 5.0 Hz,), 8.68 (1H, m), 8.25-8.30 (1H, m), 8.06 (1H, d, *J* = 8.5 Hz), 7.94-8.01 (1H, m), 7.84-7.92 (14H, m), 7.69-7.82 (1H, m), 7.54 (1H, dd, *J* = 8.0, 7.5 Hz), 2.60 (1H, m), 2.33 (1H, td, *J* = 10.0, 4.0 Hz), 1.8-1.9 (1H, m), 1.6-1.7 (1H, m), 1.53-1.6 (1H, m), 1.45-1.52 (1H, m), 0.8-1.2 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.18 (J_{PC} = 20.0 Hz), 138.92 (J_{PC} = 17.0 Hz), 136.37 (J_{PC} = 16.0 Hz), 134.37 (J_{PC} = 11.0 Hz), 134.25, 134.11 (J_{PC} = 11.0 Hz), 134.09, 132.16 (J_{PC} = 10.0 Hz), 132.12 (J_{PC} = 10.0 Hz), 130.42, 129.37, 128.98 (J_{PC} = 9.2 Hz), 128.83 (J_{PC} = 10.3 Hz), 128.78 (J_{PC} = 10.0 Hz), 128.81, 128.76 (J_{PC} = 7.2 Hz), 128.18, 126.77, 124.85, 124.31, 72.26, 58.66, 33.23, 32.12, 24.66 24.11 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −14.73 ppm; HRMS-FAB (*m/z*): $[M + H]^+$ calculated for $C_{35}H_{34}N_2O_2PS$, 577.2079; found, 577.2101.

3.2. Preparation of sulfonamide-aminophosphines [39]

3.2.1. (R,R)-N-[2-(2-Diphenylphosphanyl-benzylamino)-cyclohexyl]-benzenesulfonamide (**5a**)

A solution of compound (*R,R*)-*N*-[2-(2-Diphenylphosphanyl-benzylidene-amino]-cyclohexyl]-benzenesulfonamide (4a) (0.24 g, 0.46 mmol) and $NaBH_4$ (0.16 g, 4.14 mmol) in methanol was stirred at room temperature for 12 h and water (10 ml) added to destroy excess $NaBH_4$. The mixture was extracted with CH_2Cl_2 (20 ml × 3). The combined extract was washed with 10% aqueous NH_4Cl (10 ml × 2) and H_2O (10 ml × 2). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give **5a**. White solid; 0.11 g, 44% yield; mp 89–92 °C; $[\alpha]_D^{25}$ = −23.0° (*c* = 0.003, CH_2Cl_2); IR (KBr) 3260, 3057, 2930, 2861, 1638, 2360, 1596, 1437, 1327, 1160, 1093, 814, 747, 665, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.0 Hz), 7.60-7.20 (17H, m), 5.80 (1H, brs), 3.95 (1H, d, *J* = 12.9 Hz), 3.62 (1H, d, *J* = 12.9 Hz), 2.48 (1H, m), 2.20 (2H, m), 2.05 (1H, m), 1.60 (2H, m), 1.5

(4H, m) ppm; $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 134.39 (J_{PC} = 11.0 Hz), 134.00 (J_{PC} = 11.0 Hz), 133.65, 132.46, 129.30 (J_{PC} = 6.9 Hz), 129.16 (J_{PC} = 6.9 Hz), 129.00, 128.90 (J_{PC} = 8.0 Hz), 128.81 (J_{PC} = 8.0 Hz), 127.65, 127.49, 127.20, 60.27, 58.12, 48.99, 33.03, 31.55, 24.85, 24.54 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −16.62 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{31}H_{33}N_2O_2PS$, 528.2000; found, 528.1982.

*3.2.2. (R,R)-N-[2-(2-Diphenylphosphanyl-benzylamino)-cyclohexyl]-4-methyl-benzenesulfonamide (**5b**)*

White solid; 0.05 g, 65% yield; mp 94–97 °C; $[\alpha]_D^{25}$ = −20.3° (*c* = 0.003, CH_2Cl_2); IR (KBr) 3263, 3055, 2930, 2857, 1597, 1435, 1327, 1161, 1093, 901, 815, 746, 697, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.0 Hz), 7.40-7.10 (14H, m), 7.15 (2H, d, *J* = 8.0 Hz), 5.65 (1H, brs), 3.90 (1H, dd, *J* = 13.0, 1.3 Hz), 3.68 (1H, dt, *J* = 13.0, 1.3 Hz), 2.58 (1H, dt, *J* = 9.7, 3.7 Hz), 2.36 (3H s), 2.14 (1H, dt, *J* = 10.6, 3.8 Hz), 1.60 (2H, m), 1.42 (2H, m), 1.1 (4H, m) ppm; $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 143.90, 142.91, 137.39, 134.12 (J_{PC} = 20.0 Hz), 133.88 (J_{PC} = 19.9 Hz), 132.42, 129.41 (J_{PC} = 6.9 Hz), 129.19 (J_{PC} = 5.8 Hz), 129.01 (J_{PC} = 12.20 Hz), 128.89, 128.89 (J_{PC} = 9.4 Hz), 128.63 (J_{PC} = 9.4 Hz), 127.46, 127.33, 60.11, 57.86, 48.98 (J_{PC} = 20.0 Hz), 32.88, 31.34, 24.66, 24.38, 21.51 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −16.58 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{32}H_{35}N_2O_2PS$, 542.2157; found, 542.2140.

*3.2.3. (R,R)-N-[2-(2-Diphenylphosphanyl-benzylamino)-cyclohexyl]-2,4,6-trimethyl-benzenesulfonamide (**5c**)*

Yellow solid; 0.17 g, 69% yield; mp 72–75 °C; $[\alpha]_D^{25}$ = −35.20° (*c* = 0.0021, CH_2Cl_2); IR (KBr) 3285, 3050, 2931, 2857, 1599, 1437, 1324, 1155, 1089, 1056, 853, 747, 697, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.17-7.55 (1H, m), 6.86-6.93 (16H, m), 5.67 (1H, brs), 2.66 (6H, s), 2.57 (1H, m), 2.34 (1H, m), 2.28 (3H, s), 1.80-1.92 (2H, m), 1.6-1.7 (2H, M), 1.09-1.26 (4H, m) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 142.02, 141.92 (J_{PC} = 10.3 Hz), 139.11, 139.05, 138.92, 136.57, 134.23 (J_{PC} = 12.2 Hz), 134.05 (J_{PC} = 7.0 Hz), 132.01 (J_{PC} = 7.3 Hz), 129.72, 129.29, 128.84 (J_{PC} = 6.8 Hz), 128.65, 127.68, 127.49, 60.11, 56.41, 54.78, 35.77, 32.57, 24.74, 24.17, 23.30, 21.18 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −17.22 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{34}H_{39}N_2SO_2P$, 570.2470; found, 570.2489.

*3.2.4. (R,R)-4-tert-Butyl-N-[2-(2-diphenylphosphanyl-benzylamino)-cyclohexyl]-benzenesulfonamide (**5d**)*

Pale brown solid; 0.31 g, 93% yield; mp 86–89 °C; $[\alpha]_D^{25}$ = −20.0° (*c* = 0.0040, CH_2Cl_2); IR (KBr) 3258, 3056, 2933, 2860, 1594, 1435, 1327, 1163, 1113, 1027, 836, 738, 697, 630, 580 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 8.8 Hz), 7.49 (16H, m), 6.85 (1H, dd, *J* = 7.7, 4.8 Hz), 5.68 (1H, brs), 3.88 (1H, dd, *J* = 12.8, 1.8 Hz), 3.68 (1H, dd, *J* = 12.0, 1.8 Hz), 2.60 (1H, dt, *J* = 10.4, 4.3 Hz), 2.18 (1H, dt, *J* = 6.7, 3.6 Hz), 1.26 (2H, m), 1.25 (9H, s), 1.12 (4H, m) ppm; $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 155.96, 143.90, 137.36, 134.16 (J_{PC} = 20.0 Hz), 133.90 (J_{PC} = 19.7 Hz), 132.42, 129.25 (J_{PC} = 4.8 Hz), 129.02 (J_{PC} = 14.7 Hz), 128.86, 128.69 (J_{PC} = 9.7 Hz), 128.63 (J_{PC} = 9.3 Hz), 127.47, 127.15, 125.75, 60.09, 57.85, 48.49 (J_{PC} = 20.0 Hz), 35.08, 32.90, 31.11, 24.69, 24.35 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −17.05 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{35}H_{41}N_2O_2PS$, 584.2626; found, 584.2616.

*3.2.5. (R,R)-N-[2-2-Diphenylphosphonyl-benzylamino-cyclohexyl]-2,4,6-triisopropyl-benzenesulfonamide (**5e**)*

Pale yellow oil; 0.15 g, 70% yield; $[\alpha]_D^{25}$ = −48.23° (*c* = 0.0017 CH_2Cl_2); IR(KBr) 3212, 3054, 2929, 2866, 1599, 1434, 1324, 1164, 1070, 1041, 883, 744, 697, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.59 (1H, m), 7.10 (1H, s), 3.80 (2H, m), 3.16 (3H, m), 2.80 (2H, m), 1.52-1.66 (4H, m), 1.44 (4H, m), 1.20 (18H, m) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 151.6, 145.0, 142.4 (J_{PC} = 12.0 Hz), 137.0 (J_{PC} = 20.0 Hz), 133.5 (J_{PC} = 9.0 Hz), 132.2, 128.5 (J_{PC} = 7.0 Hz), 128.8 (J_{PC} = 7.0 Hz), 128.0 (J_{PC} = 7.0 Hz), 121.6, 54.0, 48.30, 47.20, 32.3, 28.8, 27.5, 24.5, 22.3, 22.6 ppm. ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −15.5 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{40}H_{51}N_2O_2SP$, 654.3409; found, 654.3437.

*3.2.6. (R,R)-{2-[(2-Diphenylphosphanyl-benzylamino)-cyclohexyl]}-naphthalenesulfonamide (**5f**)*

Pale brown solid; 0.1 g, 64% yield; mp 87–90 °C; $[\alpha]_D^{25}$ = −61.0° (*c* = 0.0025, CH_2Cl_2); IR (KBr) 3250, 3057, 2932, 2858, 1592, 1437, 1324, 1162, 1130, 902, 804, 722, 696, 676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (1H, s), 7.60-7.95 (6H, m), 7.20-7.50 (14H, m), 3.80 (2H, m), 2.80 (2H, m), 1.50-1.65 (4H, m), 1.40 (4H, m) ppm; $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 142 (J_{PC} = 12.0 Hz), 137.6 (J_{PC} = 20.0 Hz), 137.0 (J_{PC} = 19.9 Hz), 136.0, 133 (J_{PC} = 9.0 Hz), 128.8 (J_{PC} = 7.0 Hz), 128.0, 126.0, 123.0, 54.0, 48.0, 47.0, 28.0, 27.0, 22.0 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −17.2 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{35}H_{35}N_2SO_2P$, 578.2157; found, 578.2186.

3.3. Preparation of iminophosphines

The iminophosphines **7** were synthesized with the procedure described for the synthesis of the compounds **4**.

*3.3.1. (R)-(1-Cyclohexyl-ethyl)-(2-diphenylphosphanyl-benzylidene)-amine (**7a**)*

Yellow oil; 0.74 g, 53% yield; $[\alpha]_D^{25}$ = −30° (*c* = 0.0024, CH_2Cl_2); IR (KBr) 3327, 2918, 2849, 1572, 1486, 1439, 1367, 1118, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.78 (1H, d, J_{PH} = 6.6 Hz), 7.96 (1H, m), 7.31 (12H, m), 6.84 (1H, m), 2.86 (1H, qnt, *J* = 13.2, 6.4 Hz), 1.36 (10H, m), 1.0 (3H, d, *J* = 6.4 Hz) ppm; $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 157.64 (J_{PC} = 21.4 Hz), 136.81 (J_{PC} = 9.9 Hz),

134.38 (J_{PC} = 19.8 Hz), 133.18, 130.09, 129.03, 128.87, 128.73, 127.99 (J_{PC} = 16.8 Hz), 72.06, 43.66, 29.82, 26.66, 26.51, 26.34, 19.82 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −15.41 ppm; HRMS-FAB (*m/z*): $[M + H]^+$ calculated for $C_{27}H_{31}NP$, 400.2194; found, 400.2216.

3.3.2. (R)-(2-Diphenylphosphanyl-benzylidene)-(2-phenyl-propyl)-amine (**7b**)

Yellow oil; 0.15 g, 50% yield; $[\alpha]_D^{25} = 7.1^\circ$ (c = 0.0091, CH_2Cl_2); IR (KBr) 3418, 3056, 2960, 2916, 1637, 1586, 1437, 1185, 1106, 1027, 997, 722, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.80 (1H, d, J_{PH} = 4.8 Hz), 7.95 (2H, d, J = 8.4 Hz), 7.27 (17H, m), 3.56 (2H, m), 2.83 (1H, m), 1.07 (3H, d, J = 12.8 Hz) ppm; ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 160.58, 160.15, 145.68, 136.86, 136.67, 134.39 (J_{PC} = 3.4 Hz), 133.99 (J_{PC} = 3.4 Hz), 133.53, 133.27, 132.50, 132.24, 132.08, 130.32, 129.07, 128.99, 128.84, 128.70, 128.46, 127.44, 126.30, 40.98, 39.65, 19.18 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ −15.92 ppm; HRMS-FAB (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{27}NP$, 408.1881; found, 408.1899.

3.4. Preparation of aminophosphines

The aminophosphine **8** was synthesized with the procedure described for the synthesis of the compounds 5.

3.4.1. (R)-(2-Diphenylphosphanyl-benzyl)-(2-phenyl-propyl)-amine (**8b**)

Yellow oil; yield: 75% (0.15 g); $[\alpha]_D$ = +6.7° (c = 0.009, CH_2Cl_2); IR (KBr) 3311, 3056, 2961, 2917, 1590, 1437, 1183, 1118, 1027, 998, 757, 719 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (17H, m), 7.02 (2H, m), 3.97 (2H, s), 3.68 (2H, dd, J = 14.2, 7.2 Hz), 3.00 (sext, J = 7.0 Hz), 1.24 (3H, d, J = 6.8 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.83, 142.81, 133.77 (J_{PC} = 12.97 Hz), 132.67, 132.33 (J_{PC} = 3.0 Hz), 132.14 (J_{PC} = 2.3 Hz), 131.95 (J_{PC} = 2.3 Hz), 131.38, 128.95, 128.67 (J_{PC} = 3.4 Hz), 127.37, 126.55, 55.76, 52.06 (J_{PC} = 11.6 Hz), 39.25, 19.80 ppm; ^{31}P NMR (80.95 MHz, $CDCl_3$) δ 32.4 ppm; HRMS-FAB (*m/z*): $[M]^+$ calculated for $C_{28}H_{28}NP$, 409.1959; found, 409.1979.

3.5. General method for reduction of acetophenone [40]

A mixture of $Ru(PPh_3)_3Cl_2$ (0.03 mmol) and the chiral ligand (0.06 mmol) was placed in a oven-dried Schlenk flask in distilled propan-2-ol (10 ml). The solution was stirred at 80 °C for 30 min under nitrogen. After being cooled to room temperature, additional propan-2-ol (10 ml) and solid KOH (16.8 mg) was added, followed by acetophenone (3 mmol) in propan-2-ol (10 ml). The mixture was stirred at room temperature for 16 h. The final mixture was filtered through a plug of silica gel and concentrated under reduced pressure to give an oily residue. The residue containing the alcohol was derivatized using acetic anhydride (2 ml). Enantiomeric excesses were determined by GC using a Hewlett-Packard 5890 apparatus using chiral β-DEX^{TM} 120, 30 m × 0.25 mm × 0.25 μm column. The GC conditions were: oven temperature 110 °C, flow rate 1.33 ml/min. The retention time for (*S*) acetate is 18.5 min and for (*R*) acetate is 19.7 min.

4. Conclusion

In conclusion we have synthesized a series of ligands derived from chiral (1*R*, 2*R*)-1,2-diaminocyclohexane containing phosphorus. These ligands are readily prepared from a mono-sulfonamide of 1,2-diaminocyclohexane and commercially available 2-(diphenyphosphino)benzaldehyde and are stable. These phosphine-based ligands along $Ru(PPh_3)_3Cl_2$ assists in the transfer hydrogenation of acetophenone, giving alcohols in 14–99%, enantioselectively. From our results it appears that steric bulkiness on the arysulfonamide fragment could behave as flexible chiral pickets to induce chiral recognition during catalytic proton transfer reduction. The high enantioselectivity and low yields (compared to the catalyst loading) suggests that the reaction may not be truly catalytic. Conditions to optimize the yields are currently underway. The potential application of these ligands as metal complexes in other asymmetric chemical transformations is also currently under study in our laboratory.

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