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Research paper

Biaryl diphosphine ligands and their ruthenium complexes: Preparation and use for catalytic hydrogenation of ketones

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ABSTRACT

Procedures for the preparation of the nucleophilic diphosphine ligands (*R*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) ((*R*)-Ph-Garphos, **2a**) and (*S*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) ((*S*)-Ph-Garphos, **2b**) were described. The ligands were used to prepare the ruthenium(II) Ph-Garphos complexes, chloro(*p*-cymene)(*R*)-(4,4′,6,6′-tetraamethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)ruthenium(II) chloride ([RuCl(*p*-cymene)(*R*)-Ph-Garphos]Cl (**3**)) and chloro(*p*-cymene)(*S*)-(4,4′,6,6′-tetraamethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)ruthenium(II) chloride ([RuCl(*p*-cymene)(*S*)-Ph-Garphos]Cl (**4**)). In the presence of the chiral diamine co-ligands (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (*R*,*R*-DPEN) and (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (*S*,*S*-DPEN), complexes **3** and **4** were found to be catalyst precursors for the enantioselective reduction of aryl ketones under mild conditions (room temperature and 3–4 atm of H_2). The chiral alcohols were isolated in moderate to good yields and with enantioselectivities of up to 93%. The ruthenium complexes chloro(*p*-cymene)(*R*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(bis(3,5-dimethylphenyl)-phosphine)ruthenium(II) chloride ([RuCl(*p*-cymene)(*R*)-Xyl-Garphos]Cl (**5**)) and chloro(*p*-cymene)(*S*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(bis(3,5-dimethylphenyl)-phosphine)ruthenium(II) chloride ([RuCl(*p*-cymene)(*S*)-Xyl-Garphos]Cl (**6**)) were also prepared and used as catalyst precursors for the hydrogenation of aryl ketones in the presence of (*R*,*R*)-DPEN and (*S*,*S*)-DPEN. Significant improvements in the enantioselectivities of the alcohols (up to 98% ee.) were afforded. A combination of **6** and (*S*,*S*)-DPEN afforded (*R*)-1-(3-methoxyphenyl)ethanol in 89% yield and with 95% ee which was shown to be a suitable precursor for the preparation of (*S*)-rivastigmine.

1. Introduction

The enantioselective reduction of carbonyl and iminocarbonyl compounds is one of the most efficient methods for the preparation of chiral alcohols and amines which are common substructures in many pharmaceutical products [1-3]. One such example is (*R*)-1-(3-methoxyphenyl)ethanol which serves as a precursor to the drug (*S*)-rivastigmine (Scheme 1). (*S*)-Rivastigmine, (*S*)-3-[1-(dimethylamino)ethyl] phenyl ethyl (methyl) carbamate, represents one of the most potent drugs for the treatment of mild-to-moderate dementia of the Alzheimer's type, Parkinson's disease and Lewy bodies [4,5]. Consequently, several catalytic systems which afford high efficiency and enantioselectivity for the preparation of such chiral pharmachores have been explored (Fig. 1).

One of the most efficient catalysts for the asymmetric hydrogenation of ketones is the *trans*-$RuCl_2$(BINAP)(diamine) system which was developed by Noyori and co-workers [6-10]. It is believed that the high efficiency of Noyori's ternary catalyst originated from the donor–acceptor bifunctionality, and that basic (and reductive) conditions facilitated the formation of the active ruthenium dihydride catalytic species [7,8,11-14]. Since then, ruthenium complexes of the type $RuCl_2$(diphosphine)(diamine) are recognized as some of the most effective catalysts for the asymmetric hydrogenation of aromatic, heteroaromatic and α,β-unsaturated ketones [15-26]. Over the years, diphosphines such as Phanephos [27,28], P-Phos [29], and C_n-TunePhos [30] have demonstrated similar efficiency, or exceeded, that of BINAP. The spiro diphosphine SDP ligands have also demonstrated high efficiency in the asymmetric hydrogenation of racemic α-arylcyclohexanones, α-arylaldehydes and α,β-unsaturated acids [31,32]. The Sunphos class of ligands are effective for the reduction of α- and β-

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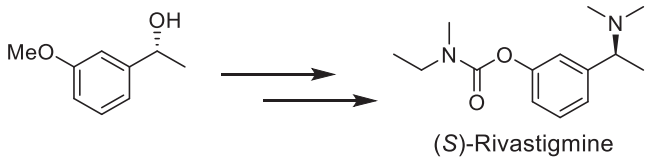


Scheme 1.

ketoesters, β-ketosulfones, polyfunctionalized ketones, aryl-pyridyl ketones and substituted ferrocenyl ketones [33,34]. Despite the recent successes however, improvements in asymmetric hydrogenations include access to more selective ligand systems, lower hydrogen pressure, and expanding the range of substrates [35-43].

To this end, we explore the use of the diphosphine ligands (*R*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) ((*R*)-Ph-Garphos, **2a**) and (*S*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis (diphenylphosphine) ((*S*)-Ph-Garphos, **2b**) as chiral auxiliaries, and the ruthenium(II) Ph-Garphos complexes ([RuCl(*p*-cymene)(*R*)-Ph-Garphos]Cl (**3**) and RuCl(*p*-cymene)(*S*)-Ph-Garphos]Cl (**4**)) as air-stable catalyst precursors for the asymmetric hydrogenation of ketones. Neutral $RuCl_2$(diphosphine)(diamine) complexes have been extensively reviewed in the literature. However the use of cationic ruthenium(II) complexes of the type ([RuCl(*p*-cymene)(diphosphine)]Cl has scarcely received any attention. We believe these readily accessible cationic ruthenium(II) complexes, in combination with the diamine ligands, (*R*,*R*)-DPEN and (*S*,*S*)-DPEN, should lead to highly efficient catalytic systems for practical applications. Furthermore, ruthenium complexes containing the 3,5-dimethylphenyl-substituted ligands such as $RuCl_2$-[(*S*)-Xyl-BINAP][(*S*)-DAIPEN] and its *R*,*R* isomer [44-48], $RuCl_2$-[(*R*)-Xyl-PhanePhos][(*S*,*S*)-DPEN] [27], $RuCl_2$-[(*S*)-Xyl-P-Phos][(*R*,*R*)-DPEN] [29], $RuCl_2$-[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] [49], amongst others [50,51], have demonstrated remarkable activity and enantioselectivity for the asymmetric hydrogenation of ketones. As such, the activity of the analogous [RuCl(*p*-cymene)(*R*)-Xyl-Garphos]Cl (**5**) /(*R*,*R*)-DPEN) and [RuCl(*p*-cymene)(*S*)-Xyl-Garphos]Cl (**6**) /(*S*,*S*)-DPEN systems, was compared to complexes **3** and **4**.

2. Experimental

All manipulations involving air- and moisture-sensitive materials were performed under an inert, dry atmosphere of nitrogen or argon. The solvents were purified using standard procedures [52] and, where necessary, were distilled under argon or nitrogen atmosphere using the appropriate drying agent. The $[RuCl_2(p\text{-cymene})]_2$ metal precursor, (*R*)- and (*S*)-Xyl-Garphos ligands, and the 1,2-diamine co-ligands, TsDPEN and DPEN, were obtained from Kamal Pharmachem Inc. The ketone substrates were obtained from commercial suppliers and used without further purification. GC analysis was carried out on a Hewlett-Packard 6890 gas chromatograph equipped with a 5973 MSD detector and β-DEX 120 chiral capillary column (30 m × 0.25 mm; Supelco., USA). HPLC analysis was done using a Agilent Technologies 1200 Series HPLC. ^{1}H- and ^{13}C NMR analysis were performed on a Bruker ACE 200, a Bruker 400 or Bruker 500 MHz Fourier Transform (FT) spectrometer and referenced to the residual protons in the deuterated solvents. Chemical shifts are reported in parts per million (δ or ppm) relative to tetramethylsilane (TMS). Optical rotation measurements were performed on an Anton Parr MCP 300 polarimeter, using a sodium lamp with a wavelength of 589 nm at 20 °C. All measurements were conducted using a cell of path length 0.5 dm using dichloromethane or chloroform as solvent and the average of 5 readings.

2.1. Preparation of Ph-Garphos ligands

Preparation of (3,5-dimethoxyphenyl)diphenylphosphine oxide (1a): 1-Bromo-3,5-dimethoxybenzene (10 g, 46.1 mmol) in THF (60 mL) was added to a Schlenk flask (250 mL) with magnesium (1.2 g, 49.9 mmol), I_2 (10 mg) and THF (40 mL). The mixture was refluxed for 2 h and then cooled to room temperature. The resulting light brown solution was transferred to another flask (250 mL) and then cooled to −78 °C. Chlorodiphenylphosphine (11 g, 49.9 mmol) in THF (30 mL) was added at −78 °C. The mixture was stirred at −78 °C for 1 h, then it was slowly warmed up to room temperature and stirred at room temperature for 1 h. Water (50 mL) was added to the reaction mixture, then H_2O_2 (30%, 13 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed thoroughly with $NaHSO_3$ (20%, 100 mL × 3) and brine (100 mL × 2) and dried over $MgSO_4$. It was filtered and the solvent was removed to give a viscous oil which was purified with crystallization (CH_2Cl_2/hexane = 1/20) to give the product as a colorless solid (15.2 g, Yield: 97.5%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.72–7.64 (m, 4H), 7.60–7.54 (m, 2H), 7.52–7.45 (m, 4H), 6.79 (dd, 2H, ^1J = 2.1 Hz, ^2J = 13.2 Hz), 6.64 (t, 1H, J = 2.1 Hz), 3.77 (s, 6H). ^{31}P NMR (121.5 MHz, CD_2Cl_2) δ: 29.03. ^{13}C (75 MHz, CD_2Cl_2) δ: 161.18 (d, J = 17.6 Hz), 135.17 (d, J = 102 Hz), 132.99 (d, J = 103 Hz), 132.12 (d, J = 2.9 Hz), 132.11 (d, J = 9.8 Hz), 109.87 (d, J = 10.9 Hz), 103.91 (d, J = 2.3 Hz), 55.74.

Preparation of (2-bromo-3,5-dimethoxyphenyl)diphenylphosphine oxide (1b): *N*-bromosuccinimide (NBS) (6.7 g, 37.6 mmol) was added to a solution of (3,5-dimethoxyphenyl)diphenylphosphine oxide (12.3 g, 36.4 mmol) in CH_2Cl_2 (140 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 1 h. Na_2CO_3 (saturated, 40 mL) was added to quench the reactions. It was stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (40 mL × 2). The combined organic layer was washed with brine and dried over $MgSO_4$. It was filtered and the solvent was removed to give the crude product as a pale yellow solid (14.3 g, 94% yield). It was sufficiently pure for the next step. The pure sample was obtained by recrystallization from CH_2Cl_2/hexane (1/15). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.73–7.67 (m, 4H), 7.62–7.56 (m, 2H), 7.53–7.46 (m, 4H), 6.69 (d, 1H, J = 3 Hz), 6.57 (dd, 1H, ^1J = 3 Hz, ^2J = 14.1 Hz), 3.89 (s, 3H), 3.68 (s, 3H). ^{31}P NMR (121.5 MHz, CD_2Cl_2) δ: 30.72.

Preparation of (*R*,*S*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl) bis(diphenylphosphine oxide) (1c): Copper powder (5.81 g, 91.5 mmol) was added to a solution of (2-bromo-3,5-dimethoxyphenyl) diphenylphosphine oxide (12.7 g, 30.5 mmol) in DMF (50 mL). Iodine (100 mg) was then added. The resulting suspension was stirred at 140 °C for 2 h after which, DMF was removed under vacuum. To the residues, $CHCl_3$ (200 mL) was added, and the mixture stirred for an additional 30 min. The solid was filtered and washed with $CHCl_3$ (20 mL). The combined filtrate was washed with aqueous ammonia (5%, 200 mL × 2), brine (20%, 200 mL × 1) and dried over $MgSO_4$. The solid was filtered and washed with $CHCl_3$ (20 mL). The solvent was removed from the filtrate to give the crude product as an off-white solid which was purified by recrystallization from CH_2Cl_2/ether (10/200) to give the pure product as a colorless solid (6.2 g, 60.3% yield).

Resolution of (*R*,*S*)-(4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl) bis(diphenylphosphine oxide) (*rac*-1c): L-(-)-DBTA monohydrate (3.49 g, 9.28 mmol) in Et_2O (30 mL) was added to a solution of (4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) (6.2 g, 9.2 mmol) in CH_2Cl_2 (30 mL). Another portion of Et_2O (120 mL) was added to the mixture. The resulting suspension was stirred for 30 min. The solid was filtered, washed with ether (20 mL) and dried to give the product as a colorless, crystalline solid which was stirred with CH_2Cl_2/ether (100 mL/150 mL) for 1 h. The white crystalline solid was filtered and then stirred with another portion of CH_2Cl_2/ether (80 mL/120 mL) for 1 h. The colorless crystalline solid was filtered and washed with ether (20 mL) and dried under vacuum to give a colorless solid which was dissolved in CH_2Cl_2 (150 mL) and washed with $NaHCO_3$ (saturated, 100 mL × 2). The organic layer was

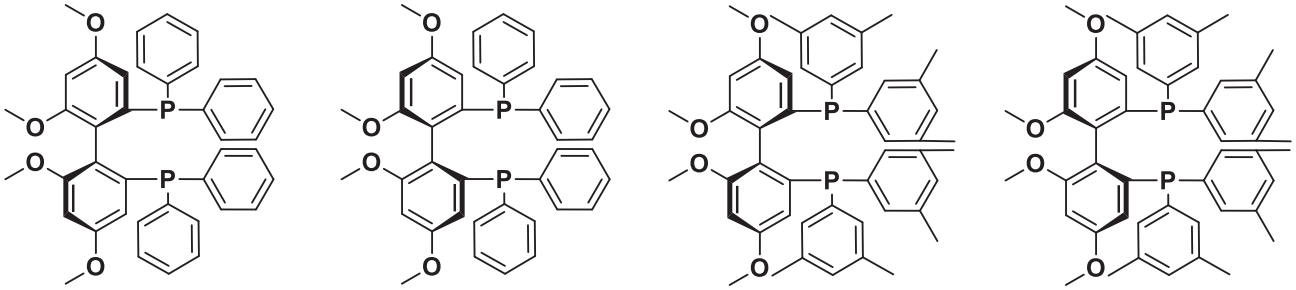


Fig. 1. Chiral Garphos ligands.

dried over $MgSO_4$. It was filtered and the solvent was removed from the filtrate to give (*S*)-Garphos oxide as a colorless solid (2.3 g, 74.2%, 99.5% ee) $[\alpha]_D^{25} - 115.2^\circ$ (*c* 0.95, CH_2Cl_2). The combined mother liquor was neutralized with $NaHCO_3$ to give the (*R*)-enriched phosphine oxide (3.9 g) which was resolved with D-(+)-DBTA (2.1 g). The enantiopure product was freed with $NaHCO_3$ to give the (*R*)-form enantiomer as a colorless crystalline solid (2.7 g, 87.1% yield, 99.9% ee). $[\alpha]_D^{25} + 114.6^\circ$ (*c* 0.99, CH_2Cl_2). (HPLC: Chiralpak IA column 0.46 cm × 25 cm. 2-PrOH/hexane = 40/60, 1 mL/min, 25 °C, 254 nm. (*S*)-form = 9.55 min, (*R*)-form = 5.88 min.

Preparation of (*R*)-4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl-bis (diphenylphosphine) (2a): $HSiCl_3$ (0.2 mL, 268 mg, 1.98 mmol) was added to a suspension of (*R*)-4,4′,6,6′-tetramethoxy-biphenyl-2,2′-diyl-bis(diphenylphosphineoxide) (50 mg, 0.074 mmol) in toluene (6 mL). The resulting mixture was refluxed for 20 h under Ar. It was cooled to room temperature and NaOH (2 N, 30 mL) was added and the resulting mixture was stirred at 50 °C for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. It was filtered through a silica gel pad. The solvent was removed to give the product as a white solid (40 mg, 84%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.35–7.24 (m, 16H), 7.18–7.11 (m, 4H), 6.33 (d, J = 2.1 Hz, 2H), 6.24–6.21 (m, 2H), 3.62 (s, 6H), 3.15 (s, 6H). ^{31}P NMR (121.1 MHz, CD_2Cl_2) δ: −12.32.

Preparation of (*S*)-4,4′,6,6′-tetramethoxybiphenyl-2,2′-diyl-bis (diphenylphosphine) (2b): (*S*)-4,4′,6,6′-tetramethoxy-biphenyl-2,2′-diyl-bis(diphenylphosphine) was prepared from (*S*)–4,4′,6,6′-tetramethoxy-biphenyl-2,2′-diyl-bis(diphenylphosphineoxide) using the procedure outlined above. The product was isolated as a white solid (44 mg, 92%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.34–7.25 (m, 16H), 7.18–7.12 (m, 4H), 6.32 (d, J = 2.1 Hz, 2H), 6.23–6.21 (m, 2H), 3.61 (s, 6H), 3.14 (s, 6H). ^{31}P NMR (121.1 MHz, CD_2Cl_2) δ: −12.34.

2.2. Preparation of ruthenium(II) Ph-Garphos complexes

A mixture of Ph-Garphos ligand (658 mg, 1.02 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (306 mg, 0.5 mmol) was dissolved in methanol (5 mL) under an atmosphere of nitrogen. The mixture was then heated at 55 °C for 1 h in a preheated water bath. At the end of the reaction, the solvent was removed under vacuum and the residue was re-dissolved in dried CH_2Cl_2 (5 mL). The mixture was slowly added to hexane (25 mL) to precipitate a yellow to yellow-green solid which was then filtered and dried under vacuum.

[RuCl(*p*-cymene)((*R*)-Ph-Garphos)] Cl (3). Yield: 920 mg, 98%; mp. 170 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (m, 2H, aryl-H), 7.96 (m, 4H, aryl-H), 7.79 (m, 2H, aryl-H), 7.78–7.74 (dd, 4H, aryl-H), 7.60–7.50 (m, 10*H*, aryl-H), 7.43–7.39 (m, 3H, aryl-H), 7.29 (m, 3H, aryl-H), 7.00 (d, 1H, ^3J = 5.8 Hz, CH), 6.62 (dd, 1H, $^3J_{HP}$ = 11.5 Hz, CH), 6.55 (dd, 1H, $^3J_{HP}$ = 11.5 Hz, CH), 6.14 (d, 2H, ^4J = 1.0 Hz, CH), 5.95 (d, 1H, ^3J = 7 Hz, CH), 5.79 (d, 1H, ^4J = 2.2 Hz, CH), 4.62 (s, 1H, CH), 4.27 (d, 1H, ^3J = 7 Hz, CH), 3.65 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.07 (septet, 1H), 2.01 (s, 3H, CH_3), 1.37 (d, 3H, ^3J = 7 Hz, CH_3), 0.10 (d, 3H, ^3J = 6.5 Hz, CH_3). ^{31}P{^{1}H} NMR (500 MHz, $CDCl_3$): δ 41.4 (J_{PP} = 63.7 Hz) and 27.0 (J_{PP} = 61.7 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 159.5, 159.4, 159.0, 157.9, 136.8, 135.8, 135.3, 134.7, 131.3, 131.1, 131.0, 130.6, 129.9, 129.3, 129.2, 128.1, 128.0, 127.8, 126.6, 125.2, 124.8, 121.7, 117.0, 112.0, 110.9, 110.5, 109.1, 105.3, 104.3, 100.9, 99.9, 96.6, 84.7, 55.9 (OCH_3), 54.9 (OCH_3), 54.6 (OCH_3), 54.2 (OCH_3), 30.0 (CH_3), 23.1 (CH_3), 21.4 (CH_3), 19.1 (CH_3). $[\alpha]_D^{20} + 247.2^\circ$ (*c* 0.1, $CHCl_3$).

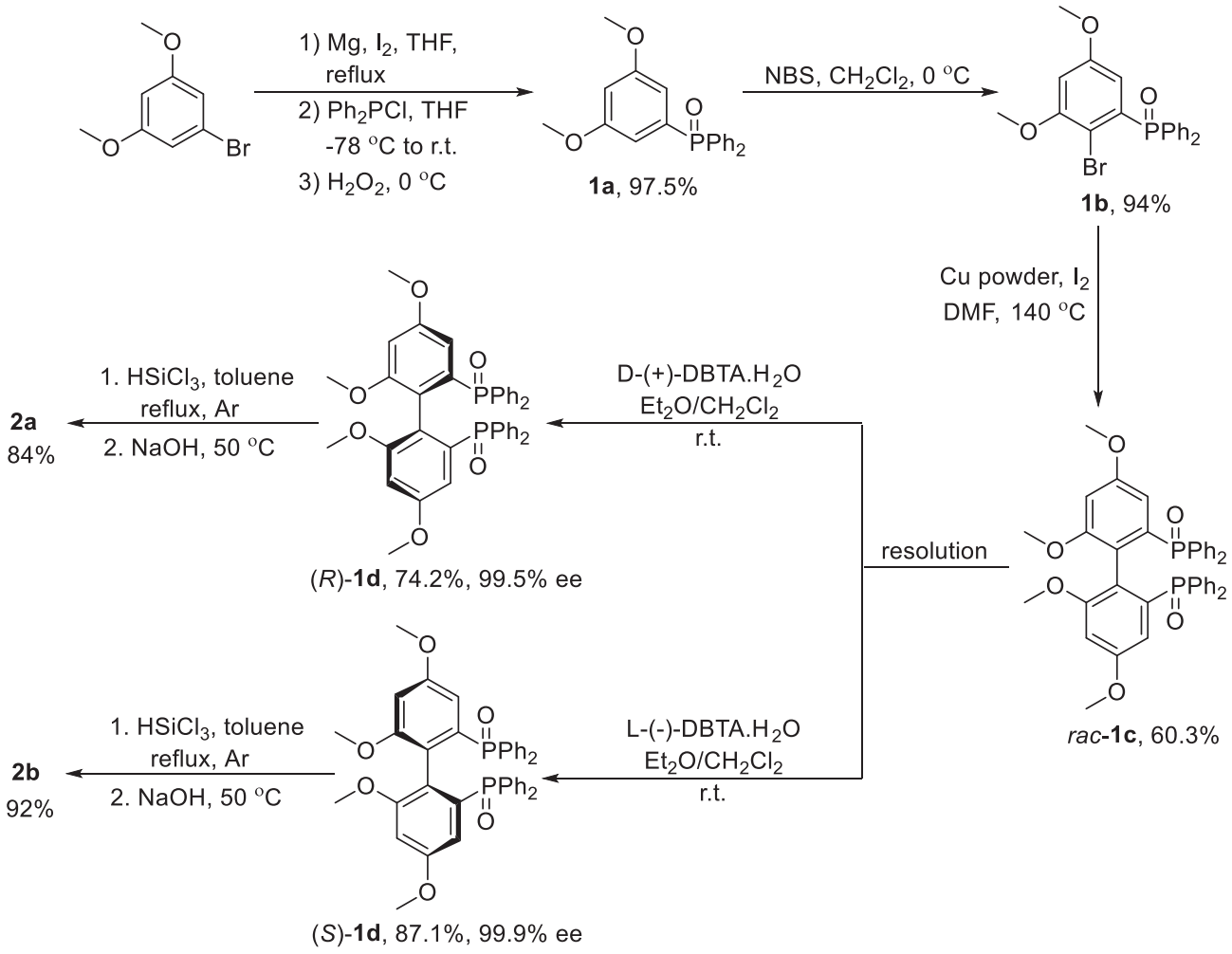
[RuCl(*p*-cymene)((*S*)-Ph-Garphos)] Cl (4). Yield: 953 mg, 98%; mp. 170 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (m, 2H, aryl-H), 7.76 (m, 2H, aryl-H), 7.61 – 7.36 (m, 14H, aryl-H), 7.00 (d, 1H, ^3J = 5.8 Hz, CH]), 6.57 (t, 1H, $^4J_{HP}$ = 2.0 Hz, CH), 6.51 (dd, 1H, $^3J_{HP}$ = 11.5 Hz, CH), 6.13 (d, 1H, ^4J = 1.0 Hz, CH), 5.94 (d, 1H, ^3J = 7.6 Hz, CH), 5.78 (d, 1H, ^4J = 2.2 Hz, CH), 4.62 (s, 1H, CH), 4.26 (d, 1H, ^3J = 7 Hz, CH), 3.63 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 3.06 (septet, 1H), 2.00 (s, 3H, CH_3), 1.35 (d, 3H, ^3J = 7 Hz, CH_3), 0.10 (d, 3H, ^3J = 6.8 Hz, CH_3). ^{31}P{^{1}H} NMR (500 MHz, $CDCl_3$): δ 41.4 (J_{PP} = 74.7 Hz) and 27.0 (J_{PP} = 68.8 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 159.9, 159.5, 159.2, 158.9, 158.1, 157.8, 137.1, 136.2, 135.3, 134.5, 134.0, 132.4, 131.4, 131.2, 130.6, 129.4, 128.8, 128.0, 126.8, 126.2, 125.4, 124.4, 123.1, 122.9, 122.6, 121.5, 117.4, 117.2, 112.3, 110.2, 109.3, 105.2, 104.0, 100.9, 99.9, 96.8, 96.6, 85.7, 55.9, 55.0 (d, OCH_3), 30.0 (CH_3), 24.0, 23.0, 21.4 (CH_3), 19.1 (CH_3). $[\alpha]_D^{20} - 277.6^\circ$ (*c* 0.1, $CHCl_3$).

2.3. General procedure for the hydrogenation of ketones with DPEN

In a typical catalytic run, a solid sample of *t*-BuOK (0.12 mmol, 10 equiv.) was added to a 100 mL Parr pressure reactor containing a stir bar. To this, a solution of the ketone (12 mmol, 1000 equiv) dissolved in 2-propanol (5 mL) was added. The reactor was then purged 3–4 times with hydrogen gas at 30 psi. This was followed by the addition of a mixture of Ru(II)-Garphos (1 equiv., 0.1 mol%) and the co-ligand DPEN (0.012 mmol, 1 equiv.) dissolved in 2-propanol (5 mL). The reactor was then purged 3–4 times with hydrogen gas at 30 psi then pressurized with hydrogen gas at 50–60 psi. At the end of the reaction, the mixture was filtered through a short pad of silica gel, transferred and made up in a volumetric flask prior to injection on the GC column. The pure product was isolated upon removal of the solvent by vacuum distillation and purification of the residue by silica gel chromatography using hexane/ethyl acetate (5/1) as eluent.

2.4. Preparation of (S)-Rivastigmine

Preparation of (*R*)-1-(3-methoxyphenyl)ethanol (8e): A solution



Scheme 2. Synthesis of Ph-Garphos ligands.

of 1-(3-methoxyphenyl)ethanone (1.0 g, 6.7 mmol) dissolved in 2-propanol (5 mL) was added to *t*–BuOK (7 mg, 0.06 mmol) in a 100 mL Parr pressure reactor containing a stir bar. The mixture was purged 4 times with hydrogen gas at 30 psi. A mixture of **6** (7 mg, 0.007 mmol) and (*S*,*S*)-DPEN (1.4 mg, 0.007 mmol) in 2-propanol (5 mL) was added and the mixture was then purged 4 times with hydrogen gas at 30 psi then pressurized with hydrogen gas at 60 psi. The mixture was stirred for 6 h at room temperature. It was then transferred to a round bottom flask and the solvent was removed under reduced pressure. Hexanes was added and the solution was filtered through a short pad of silica gel to remove the catalyst residue. The solvent was evaporated under reduced pressure to give the product as a colorless oil. Yield = 1.06 g (99%); 95% ee.

Preparation of (*S*)-1-(3-methoxyphenyl)-*N*,*N*-dimethylethanamine (9e): Triethylamine (1.0 g, 10 mmol) was added to a solution of (*R*)-1-(3-methoxyphenyl)ethanol (1.0 g, 6.6 mmol) in THF (10 mL) under argon. The mixture was cooled to 0 °C and methanesulfonyl chloride (1.14 g, 10 mmol) was added dropwise. The resulting suspension was stirred for 3 h at room temperature. All the volatiles were then removed under vacuum, then dimethylamine solution (20 mL of a 2.0 M in THF) was added and the mixture stirred at room temperature for 12 h. Another portion of dimethylamine solution (20 mL) was added and the mixture stirred for another 12 h. The mixture was then evaporated under vacuum and water (10 mL) was added to the residue, followed by sodium hydroxide solution (1.0 M) until the mixture was basic. Ethyl acetate (10 mL) was then added and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to give the product as a pale yellow oil. Yield: 1.07 g; 91%. The NMR results are consistent with those reported in the literature [53].

Preparation of (*S*)-3-(1-(dimethylamino)ethyl)phenol (10e): Hydrogen bromide (5 mL of a 48% aqueous solution) was added to (*S*)-1-(3-methoxyphenyl)-*N*,*N*-dimethylethanamine (1.0 g, 5.6 mmol) in a Teflon-stoppered Schlenk flask and the mixture was heated for 12 h at 100 °C. It was cooled to room temperature and quenched with K_2CO_3 solution until the mixture was basic. The mixture was extracted with ethyl acetate (3 × 25 mL) and the organic layers were combined and dried over $MgSO_4$. It was filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography to give the product as a white solid. Yield: 0.87 g (94%). The NMR results are consistent with those reported in the literature [53].

Preparation of (*S*)-3-(1-(dimethylamino)ethyl)phenyl ethyl (methyl)carbamate (11e): Ethyl acetate (10 mL) was added to a mixture of (*S*)-3-(1-dimethylaminoethyl)phenol (0.80 g, 4.8 mmol), K_2CO_3 (1.00 g, 7.3 mmol) and *N*-ethyl-*N*-methyl carbamoyl chloride (0.65 g, 5.3 mmol) under argon and the mixture refluxed for 6 h. It was cooled to room temperature and water (10 mL) was added and the phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give the product as a pale yellow oil. Yield: 1.15 g (95%). The NMR results are consistent

with those reported in the literature [53].

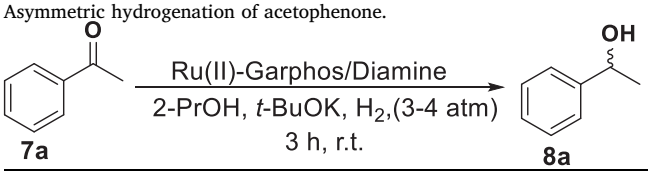
3. Results and discussion

It has been shown that the incorporation of small substituents such as methyl and methoxy groups at the 6- and 6′-positions of biaryl diphosphine ligands confer atropisomerism [54-57]. Variations of these biaryl diphosphines containing alkoxy substituents include (*R*)- and (*S*)-(6,6′-dimethoxy(1,1′-diphenyl)-2,2′-diyl)bis(diarylphosphine), (*R*)- and (*S*)-(5,5′,6,6′-tetramethoxy(1,1′-diphenyl)-2,2′-diyl)bis(diarylphosphine), or (*R*)- and (*S*)-(4,4′,5,5′,6,6′-hexamethoxy(1,1′-diphenyl)-2,2′-diyl)bis(diarylphosphine) [58]. The preparation of these biaryl diphosphine ligands was originally based on copper-catalyzed Ullmann coupling of halophosphonate intermediates, which were subsequently reduced to the respective biaryl diphospines [58]. The halophosphonate intermediates were prepared by the *ortho*-lithiation of phosphine oxide precursors followed by halogenation with molecular I_2, Br_2, ICl or IBr [58]. However, attempts to prepare the halophosphonate intermediates for the preparation of (*R*)- and (*S*)-(4,4′,6,6′-tetramethoxy-(1,1′-diphenyl)-2,2′-diyl)bis(diarylphosphine) using similar *ortho*-lithiation and halogenation procedures were unsuccessful due to the *ortho*-directing property of the alkoxy groups, resulting in polyhalogenated species. It was later discovered that the desired halophosphonate intermediates can be readily prepared in high yields from the reaction of the phosphonate ester and *N*–bromosuccinimide (NBS).

The Ph-Garphos ligands were prepared from a readily accessible and inexpensive starting material, 1-bromo-3,5-dimethoxybenzene, using a similar procedure as reported in US Patent 20130184479A1 [59]. As outlined in Scheme 2, the derived monophosphonate (**1a**) was treated with NBS to yield the desired bromophosphonate (**1b**). Ullmann coupling of the bromophosphonate (**1b**) in the presence of copper powder activated with iodine at 140 °C produced a racemic mixture of the desired bis(phosphine oxides) (*rac*-**1c**). Subsequent resolution with D-(+)-DBTA·H_2O or L-(-)-DBTA·H_2O, followed by reduction with trichlorosilane yielded the desired Ph-Garphos ligands, (*R*)-Ph-Garphos (**2a**) and (*S*)-Ph-Garphos (**2b**) in moderate yields and high chiral purity. The methoxy substituents in the 4,4′-substituents are expected to enhance the enantioselectivity of the phosphine ligands [44,60] (Scheme 3).

In order to evaluate the activity of the Ph-Garphos ligands, the ruthenium(II) complexes, **3** and **4**, were prepared from the reaction of the dichloro(*p*-cymene)ruthenium(II) dimer (1 equiv.) with either the (*R*)- or (*S*)-Ph-Garphos ligand (2 equiv.) in methanol at 55 °C for 1 h, under inert atmosphere. Following removal of the solvent, the residue was dissolved in the minimum amount of dichloromethane and slowly added to hexane with stirring. The desired product precipitated, and was isolated upon vacuum filtration as a moderately air-stable, pale yellow to green solid. Complexes **3** ([RuCl(*p*-cymene)(*R*)-Ph-Garphos]Cl) and **4** ([RuCl(*p*-cymene)(*S*)-Ph-Garphos]Cl) were isolated in yields of 87% and 91%, respectively. The ruthenium Xyl-Garphos complexes **5** ([RuCl(*p*-cymene)(*R*)-Xyl-Garphos]Cl) and **6** ([RuCl(*p*-cymene)(*S*)-Xyl-Garphos]Cl) were synthesized according to the procedure outlined and were isolated in 52% yields.

Table 1
Asymmetric hydrogenation of acetophenone.



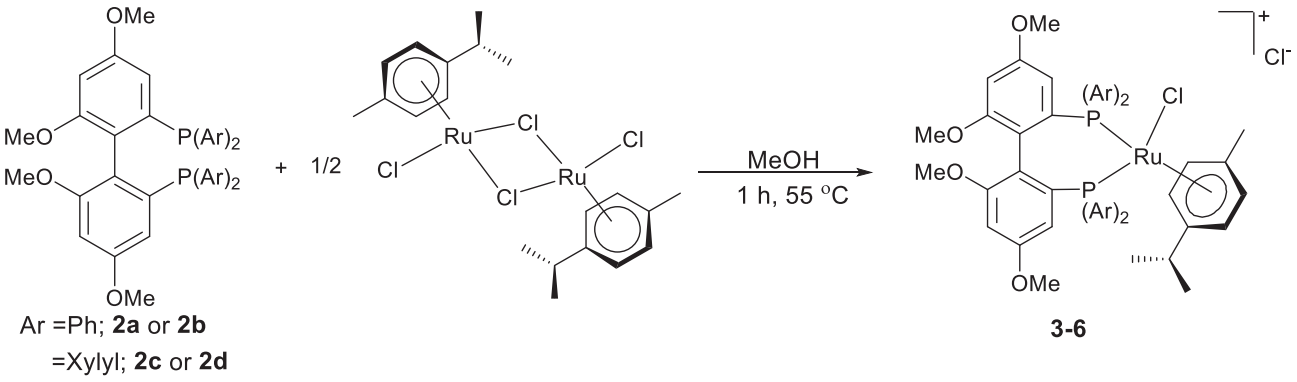
Entry	Complex	1,2-Diamine	Conv.[a] (%)	Yield[b] (%)	ee[c] (%)[conf.][d]
1	**3**	*R*,*R*-DPEN	> 99	80	90 [*S*]
2	**3**	*S*,*S*-DPEN	> 99	80	28 [*R*]
3	**3**	none	20	–	38 [*S*]
4[e]	–	*R*,*R*-DPEN	< 5	–	–
5[f]	–	*R*,*R*-DPEN	< 10	–	–
6	**5**	*R*,*R*-DPEN	> 99	88	97 [*S*]
7	**6**	*S*,*S*-DPEN	> 99	98	95 [*R*]

Reaction conditions: Ketone (12 mmol), *t*-BuOK (0.12 mmol), and catalyst (0.012 mmol). S:C ratio = 1000. [a]Conversions determined by GC analysis. [b]Isolated yields were obtained upon silica gel chromatography. [c]ee values determined by GC using a chiral Supelco β-DEX 120 column. [d]Absolute configuration was determined by comparison of elution order with literature data. [16,62] [e]In situ reaction with [Ru(*p*-cymene)Cl_2]$_2$/(*R*)-Ph-Garphos/(*R*,*R*)-DPEN. [f]In situ reaction using [Ru(*p*-cymene)Cl_2]$_2$/(*R*,*R*)-DPEN in the absence of ligand.

The ^{1}H NMR and ^{31}P{^{1}H} spectra suggested that the ruthenium(II) complexes are unsymmetrical. In complexes **3** and **4**, the methoxy protons resonated as four sharp singlets at chemical shifts of 3.30, 3.41, 3.61 and 3.65 ppm. Owing to the non-equivalence of the phosphorus atoms, two pairs of doublets were also observed at 27 and 41 ppm (J_{PP} = 62.8 Hz).

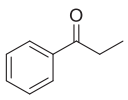
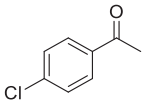
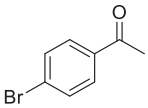
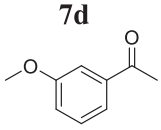
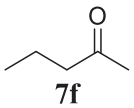
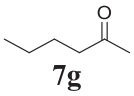
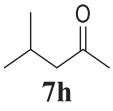
3.1. Asymmetric hydrogenation of ketones

The model substrate, acetophenone, was used to assess the catalytic capability of the ruthenium(II) Garphos complexes, **3–6**, for the asymmetric hydrogenation of ketones. The chiral diamine DPEN was selected as a suitable co-ligand due to its accessibility and low cost. Complete conversion (> 99%) of acetophenone to 1-phenylethanol (**7a**) was achieved under ambient conditions and within 3 h (Table 1). The **3**/(*R*,*R*)-DPEN combination afforded the (*S*)-1-phenylethanol in 80% yield and with 90% ee (entry 1). The corresponding **3**/(*S*,*S*)-DPEN system afforded the (*R*)-1-phenylethanol with similarly high conversions, but lower enantioselectivity (28%, entry 2). In the absence of the 1,2-diamine co-ligand, only 20% conversion was achieved and the *S*-alcohol formed in 38% ee (entry 3). This finding highlights the importance of



Scheme 3. Synthesis of the ruthenium(II) complexes.

Table 2
Ru(II)-catalyzed asymmetric hydrogenation of ketones **7b**-**7 h.**

Entry	Ketone	Pre-Cat.	Time (h)	Conv.[a] (%)	Yield[b] (%)	ee[c] (%)[conf.][d]
1	 **7b**	**3**/(*R*,*R*)-DPEN	6	98	66	90 [*S*]
2		**3**/(*S*,*S*)-DPEN	9	94	50	40 [*R*]
3[e]		**5**/(*R*,*R*)-DPEN	24	> 99	98	95 [*S*]
4[e]		**6**/(*S*,*S*)-DPEN	24	99	91	95 [*R*]
5	 **7c**	**3**/(*R*,*R*)-DPEN	2	99	88	77 [*S*]
6		**3**/(*S*,*S*)-DPEN	2	96	64	41 [*R*]
7		**5**/(*R*,*R*)-DPEN	2	> 99	94	98 [*S*]
8		**6**/(*S*,*S*)-DPEN	2	> 99	96	98 [*R*]
9	 **7d**	**3**/(*R*,*R*)-DPEN	3	> 99	80	72 [*S*]
10		**3**/(*S*,*S*)-DPEN	4	> 99	80	39 [*R*]
11		**5**/(*R*,*R*)-DPEN	3	> 99	78	97 [*S*]
12		**6**/(*S*,*S*)-DPEN	3	> 99	81	96 [*R*]
13	 **7e**	**3**/(*R*,*R*)-DPEN	2	> 99	94	93 [*S*]
14		**3**/(*S*,*S*)-DPEN	3	97	77	24 [*R*]
15[f]		**5**/(*R*,*R*)-DPEN	24	> 99	88	98 [*S*]
16		**6**/(*S*,*S*)-DPEN	6	> 99	89	95 [*R*]
17	 **7f**	**3**/(*R*,*R*)-DPEN	8	90	–	rac
18		**3**/(*S*,*S*)-DPEN	12	97	–	21
19	 **7g**	**3**/(*R*,*R*)-DPEN	4	80	–	8
20		**3**/(*S*,*S*)-DPEN	4	83		12
21	 **7h**	**3**/(*R*,*R*)-DPEN	24	99	34	11
22		**3**/(*S*,*S*)-DPEN	24	93		16

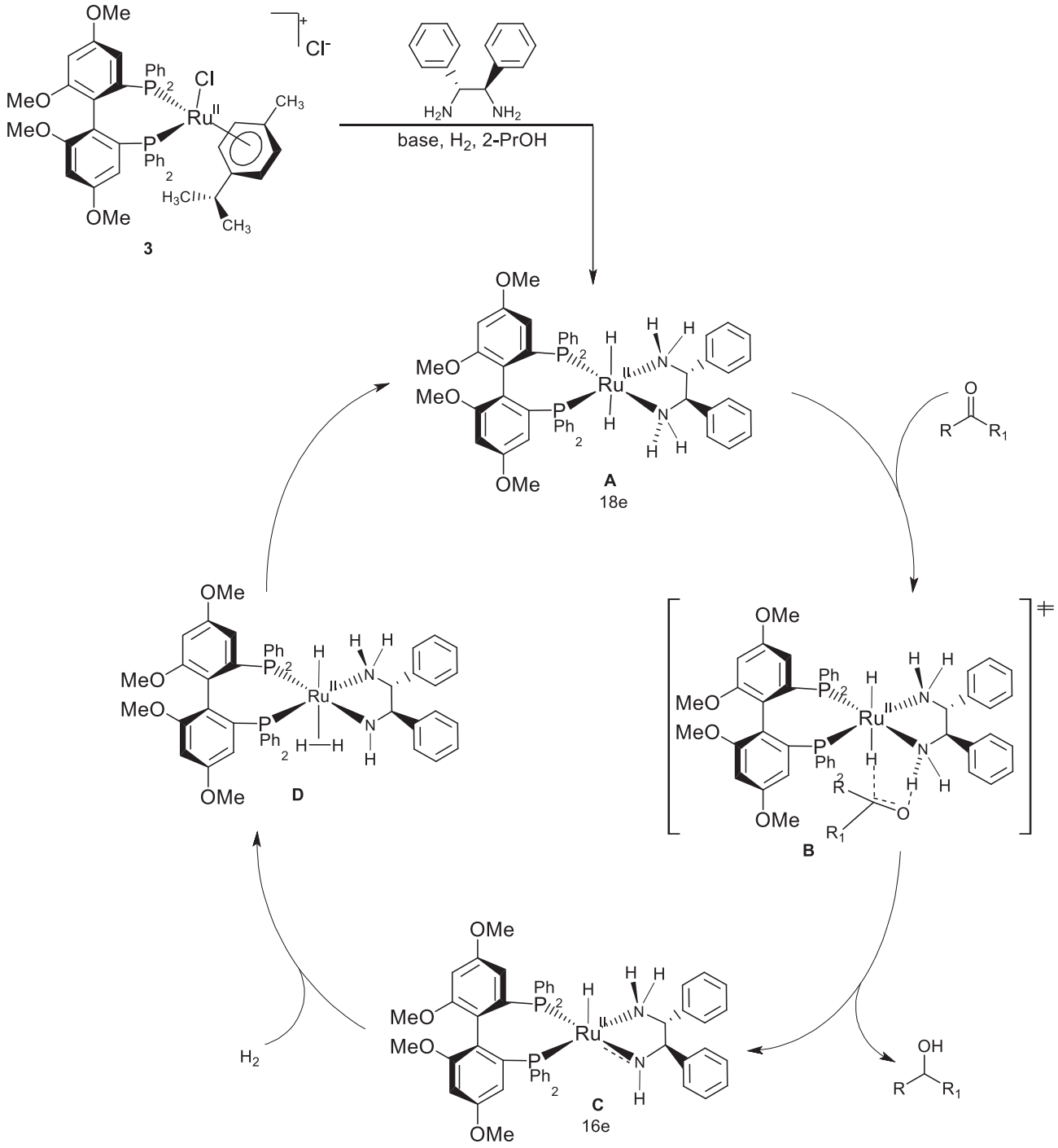
Reaction conditions: Ketone (12 mmol), *t*-BuOK (0.12 mmol), and catalyst (0.012 mmol. S:C ratio = 1000. [a]Conversions were determined by NMR spectroscopy. [b]ee values were determined by GC using a chiral Supelco β-DEX 120 column. [d]Absolute configuration was determined by comparison of elution order with literature data. [e]Hydrogenations conducted at a S:C ratio of 500 and 50 °C. [f]Reaction time unoptimized.

the 1,2-diamine co-ligand in improving the activity and enantioselectivity. This is made possible through the coordination of the diamine to the ruthenium, and the resulting complex effectively controls the stereochemical outcome and, enhances the rate of the reaction [7,61]. Matched combinations of the ruthenium (*R*)-Ph-Garphos complex and (*R*,*R*)-DPEN afforded higher enantioselectivities. Furthermore, exploratory in situ hydrogenations of acetophenone using a combination of [Ru(*p*-cymene)Cl_2]$_2$ dimer/(*R*)-Ph-Garphos/(*R*,*R*)-DPEN and [Ru(*p*-cymene)Cl_2]$_2$ dimer/(*R*,*R*)-DPEN produced significantly lower conversions (entries 4 and 5).

The **5**/(*R*,*R*)-DPEN and **6**/(*S*,*S*)-DPEN combinations were also investigated for the hydrogenation of acetophenone (entries 6 and 7). Excellent catalytic activity, and more interestingly, high enantioselectivities of up to 97% were observed. The enhanced enantioselectivity is believed to arise from a more rigid chiral pocket, allowing for improved interaction between substrate and catalyst. It has been reported that increased enantioselectivity relies on the repulsive interactions between the aryl group of the aromatic ketone and the bulky substituents on the 4,4′-positions of the diphosphine in the disfavoured transition state [29,32,44,49]. Nonetheless, the improved enantioselectivities afforded by the Xyl-Garphos ligands is expected, as similar results have been observed with other diphosphines possessing the bis(xylyl)phosphine moieties [31,44,63].

In general, the (*S*)- and (*R*)-configured alcohols were obtained in good yields and with high enantioselectivities from the matched ruthenium/(*R*-diphosphine)(*R*,*R*-diamine) and ruthenium/(*S*-diphosphine)(*S*,*S*-diamine) combinations, respectively. The 'mismatched' ([RuCl(*p*-cymene)(*R*)-Ph-Garphos]Cl)/(*S*,*S*)-DPEN system afforded the (*R*)-configured alcohol with low ee values (28%). Subsequently, the Ru(II)-catalyzed hydrogenation was expanded to include other ketone substrates **7b-7 h**. The results are summarized in Table 2.

In most cases, complete reduction of the aryl ketones **7b-7e** was achieved under ambient conditions, to give the corresponding chiral alcohols in moderate to good yields and enantioselectivities (Table 2, entries 1–16). Higher enantioselectivities were achieved with the matched ruthenium(diphosphine)(diamine) combinations than the corresponding mismatched combinations. Even so, the **5**/(*R*,*R*)-DPEN and **6**/(*S*,*S*)-DPEN combinations afforded the chiral alcohols with significantly higher ee values than the analogous **3**/DPEN combinations. This difference was more noticeable in the enantioselective reductions of the *para*-substituted ketones 4-chloroacetopheone (**7c**) and 4-bromoacetophenone (**7d**). Enantioselectivites of 77% (**7c**) and 72% (**7d**) were achieved when **3**/(*R*,*R*)-DPEN was employed (entries 5 and 9). This is in contrast to the **5**/(*R*,*R*)-DPEN and **6**/(*S*,*S*)-DPEN systems which provided the *para*-substituted alcohols with ee's of 96–98% (entries 7–8 and 11–12). Trabesinger et al. [64] suggested that the 3,5-dialkyl *meta*-effect might be substrate dependent which could explain the vast differences in enantioselectivity for some substrates. The chiral alcohol (*R*)-1-(3-methoxyphenyl)ethanol (**7e**) is of industrial interest because it is a precursor for the preparation of the acetylcholinesterase inhibitor Rivastigmine. This alcohol was prepared in 95% ee using **6**/(*S*,*S*)-DPEN

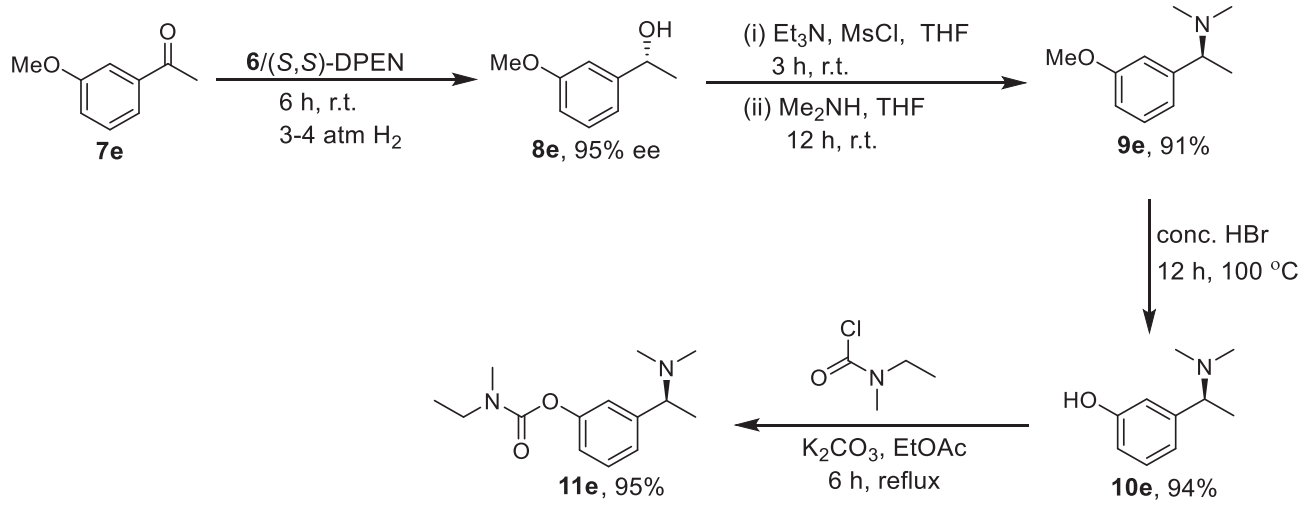


Scheme 4. Proposed mechanism for the ruthenium-mediated hydrogenation of ketones with **3**/DPEN.

(entry 16). Even though the reaction was not optimized using **5**/(*R*,*R*)-DPEN, the (*S*)-1-(3-methoxyphenyl)ethanol was afforded in 88% yield and 98% ee within 24 h. The aliphatic ketones (**7f-h**) required longer reaction times to effect high conversions with low enantioselectivities (entries 17–22).

3.2. Mechanism for the hydrogenation of ketones with 1/DPEN

We anticipate that the true catalyst formed from the reaction of the ruthenium(II) Garphos complex and DPEN, in the presence of hydrogen gas and base, is a ruthenium(II) dihydride species, **A**. This is similar to the mechanism reported for the well-established $RuCl_2$(BINAP)(diamine)-catalyzed asymmetric hydrogenation of ketones [61,65-67]. Scheme 4 highlights the proposed bifunctional mechanism in which the polarized $H^{\delta-}Ru^{\delta+}–N^{\delta-}–H^{\delta+}$ quadrupole of **A** interacts with the polar C═O dipole of the ketone substrate [14]. The hydride of the Ru-H bond and the amine proton are concomitantly transferred to the C═O atoms via a pericyclic six-membered transition state **B**, to give the chiral alcohol [68]. Following the elimination of the alcohol, a molecule of H_2 coordinates to the unsaturated 16e ruthenium-diphosphine-amido-amine [8] intermediate **C** to form species **D**. Abbel et al. [66] suggested that the heterolytic splitting of a η^2-dihydrogen across the ruthenium-amido bond is the turnover rate determining step of the catalytic cycle. The weakly coordinated η^2-dihydrogen subsequently cleaves, facilitating regeneration of the active catalytic species **A** (Scheme 4).



Scheme 5. Synthesis of (*S*)-Rivastigmine.

3.3. Application to drug synthesis

Rivastigmine (**11e**) is the first USFDA approved drug for the treatment of mild-to-moderate dementia which can be administered in the form of capsules or patches, [5,69]. However, only the (*S*)-enantiomer exhibits the desired cholinesterase inhibition [70]. Therefore, access to optically active intermediates (synthons) in high yields and enantioselectivities is critical for the preparation of enantiopure target molecules [71]. Herein, we report that (*S*)-Rivastigmine can be obtained in high yields starting with (*R*)-1-(3-methoxyphenyl)ethanol, followed by amination, then amidoesterification.

Scheme 5 outlines a facile four step protocol to achieve the target molecule in high yields. Following the asymmetric reduction of 3-methoxyacetopheone to provide the desired (*R*)-1-(3-methoxyphenyl) ethanol (**8e**) in 95% ee, the alcohol is treated with methanesulfonyl chloride followed by dimethylamine to produce (*S*)-1-(3-methoxyphenyl)-*N*,*N*-dimethyl ethanamine (**9e**) in 91% yield. Demethylation of the methoxy group of **9e** using concentrated HBr solution affords (*S*)-3-(1-(dimethylamino)ethyl)phenol (**10e**) in 94% yield. Subsequent addition of *N*-ethyl-*N*-methyl carbamoyl chloride, in the presence of a strong base and at reflux, results in the amidoesterification of the aminophenol **10e** to give (*S*)-Rivastigmine (**11e**) in 95% yield.

4. Conclusion

The (*R*)-Ph-Garphos ligand demonstrated exceptional catalytic efficiency in the asymmetric hydrogenation of aryl ketones with the [RuCl(*p*-cymene)((*R*)-Ph-Garphos)]Cl complex (**1**) and the (*R,R*)-DPEN co-ligand. Excellent conversions with moderate to high enantiomeric excesses were achieved in short reaction times. The combination of **3** and (*S,S*)-DPEN gave excellent conversions with much lower ee values. Substitution of the pendant phenyl ring with the bulkier 3,5-dimethylphenyl moiety dramatically increased the enantioselectivities. The 3,5-dimethyl substituted Xyl-Garphos, and their ruthenium(II) complexes, **5** and **6**, gave conversions of > 99% of the chiral alcohols with enantioselectivities of up to 98%. The (*S*)- and (*R*)-alcohols were the predominant isomers with the matched ruthenium(II)/(*R*)-diphosphine/(*R,R*)-DPEN and mismatched ruthenium(II)/(*R*)-diphosphine/(*S,S*)-DPEN combinations, respectively. (*R*)-1-(3-methoxyphenyl) ethanol was used for the preparation of (*S*)-Rivastigmine in high yields.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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