Journal of Molecular Structure 1200 (2020) 127146

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Imine containing C_2-Symmetric chiral half sandwich η^6-*p*-cymene-Ru(II)- phosphinite complexes: Investigation of their catalytic activity in the asymmetric transfer hydrogenation of ketones

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ARTICLE INFO

Article history:
Received 17 April 2019
Received in revised form
26 September 2019
Accepted 27 September 2019
Available online 27 September 2019

Keywords:
Phosphinite
Chiral
Catalysis
Asymmetric transfer hydrogenation
Ruthenium

ABSTRACT

New chiral C_2-symmetric bis(phosphinite) ligands containing imine group were synthesized from 1-({[(1*R*,2*R*)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]- imino}methyl)- naphthalen-2-ol and two equivalents of Ph_2PCl, $(i\text{-}Pr)_2PCl$ or $(Cy)_2PCl$, in high yields. Binuclear C_2-symmetric half sandwich η^6-*p*-cymene-Ru(II) complexes of the chiral phosphinite ligands were synthesized by treating of $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-}Cl)Cl]_2$ with the phosphinites in 1:1 M ratio in CH_2Cl_2. Their catalytic activities in asymmetric transfer hydrogenation (ATH) were investigated for the reaction of acetophenone derivatives with isopropyl alcohol. The corresponding optically active secondary alcohols were obtained in excellent levels of conversion (96–99%) and moderate enantioselectivity (up to 60% *ee*). Among three complexes investigated, complex **4** was the most efficient one.

1. Introduction

The development of well-designed catalytic systems is an important field of modern synthetic chemistry for attaining suitable building blocks of all kind of chemicals [1,2]. A great deal of chiral compounds such as aminoalcohols [3], diamines [4], S-donor ligands [5], P-donor ligands [6–12], heterocyclic ligands [13] and ferrocene based ligands [14] have been designed, synthesized and applied successfully in a numerous of catalytic reactions. Over the years, among the above named ligands, P-donor ligands are used as homogeneous catalysts in various catalytic reactions. Complexes including these types of ligands are of considerable interest because of their potential use in many organic processes such as C–H activation [15], allylic substitution [16], C–C cross coupling arylation [17] and alkylation and transfer hydrogenation [18] processes to name a few. It has been shown that the steric and electronic properties of the ligands play a crucial role in the efficiencies of catalyst [19]. Morris et al. reported both steric and electronic effect of R substituents on P atom on the catalytic activity in terms of TOF and ee values in the reduction of acetophenone catalyzed by iron phosphine complexes (P–NH–N–P') in details [20].

Among the synthetic intermediates, chiral alcohols have an important place in many fields such as pharmaceutical industry and organic synthesis [21]. ATH (asymmetric transfer hydrogenation) is an important method to obtain chiral alcohols because its fractional yields of side products are lower and product yields and enantiomeric excess are higher [22]. Furthermore, its reaction conditions are milder and lower cost owing to its operational simplicity [23,24]. Therefore, development of new chiral catalysts tailored to the transfer hydrogenation of prochiral ketones has been widely studied [25]. Among the different transition metals, transfer hydrogenation is usually promoted by Rh, Ru, or Ir metal catalysts [26,27].

In our laboratory we have been engaged in developing chiral phosphinite ruthenium (II) complex catalysts for the asymmetric reduction of a variety of aromatic ketones [28–30]. However, to the best of our knowledge, there are only few reports on the use of imine containing bis(phosphinite) ligands in transfer

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https://doi.org/10.1016/j.molstruc.2019.127146
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hydrogenation reaction [6]. Inspired by these studies, herein, synthesis and characterization of three new imine based binuclear C_2-symmetric chiral phosphinite-Ru(II)-η^6-*p*-cymene half sandwich complexes are reported. For this aim, phosphinite ligands, **1**–**3**, were synthesized by hydrogen abstraction from synthesized precursor of 1-({[(1*R*,2*R*)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl)naphthalene-2-ol, by a reaction of two equivalents of Ph_2PCl, $(i\text{-Pr})_2PCl$ or Cy_2PCl, respectively. The binuclear ruthenium complexes **4**–**6** were synthesized by treatment of $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$ with phosphinites **1**–**3** in 1:1 M ratio. Herein, we also present that binuclear phosphinite-Ru(II)-η^6-*p*-cymene half sandwich complexes **4**–**6** are efficient catalysts for the ATH of acetophenone derivatives with 2-propanol under optimized conditions.

2. Experimental

2.1. Materials and methods

All reactions were performed under an inert atmosphere using conventional Schlenk glassware. All chemicals were purchased commercially (Sigma-Aldrich, Merck, Fluka and Alfa Aesar) and used as received. All solvents were dried and distilled under inert atmosphere immediately prior to use according to the established procedures. 1-({[(1*R*,2*R*)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl)naphthalene-2-ol was prepared according to the literature [31]. NMR spectra were recorded on a Bruker AV400 spectrometer (^{1}H NMR at 400.1 MHz, ^{13}C NMR at 100.6 MHz, ^{31}P-{^{1}H} NMR at 162.0 MHz). A PerkinElmer Spectrum 100 spectrometer was used for FTIR-ATR spectra. A PerkinElmer 341 model polarimeter was used for specific rotations. Elemental analysis was carried out on a Costech ECS 4010 instrument. Melting points were recorded by a Gallenkamp Model apparatus with open capillaries.

2.1.1. GC analyses

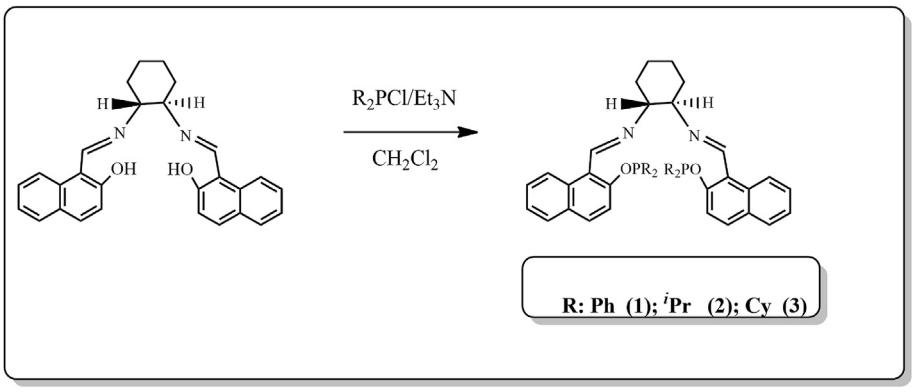
Shimadzu GC 2010 Plus Gas Chromatograph equipped with a cyclodex-B (Agilent) capillary column (30 m × 0.32 mm I.D. x 0.25 μm film thickness) was used for performed of GC analyses. Racemic samples of alcohols were obtained by reduction of the corresponding ketones with $NaBH_4$ and used as the authentic samples for % *ee* determination. The GC parameters used for the product analysis in our one of previous studies were applied to product analysis done for the current study [32].

2.1.2. Synthesis

2.1.2.1. General procedure for the synthesis of bis(phosphinite) ligands (1–3). The new chiral C_2-symmetric bis(phosphinite) ligands were prepared according to the our recent publications [33]. To a solution of 1-({[(1*R*,2*R*)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl)- naphthalen-2-ol (1.5 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (3.0 mmol) and the mixture was stirred for 10 min under argon atmosphere. To this solution was added dropwise Ph_2PCl (3.0 mmol), $(i\text{-Pr})_2PCl$ (3.0 mmol) or $(Cy)_2PCl$ (3.0 mmol). The mixture was then stirred at room temperature until the reactions were completed. A white precipitate of triethylamine hydrochloride was removed by filtration under argon and the remaining organic phase was evaporated under reduced pressure to produce a yellow oily product. The progress of these reactions was followed by ^{31}P–{^{1}H} NMR spectroscopy.

2.1.2.1.1. 1-({[(1R,2R)-2-[({2-[(diphenylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino] cyclohexyl]imino}methyl)naphthalen-2-yl diphenylphosphinite (1). Yield: 100 mg, (84%). ^{1}H NMR ($CDCl_3$, ppm): δ 9.07 (s, 2H, −N=C**H**) 6.88–7.84 (m, 32H, protons of naphthyl + OP**Ph**$_2$), 3.78 (br, 2H, C**H** of Cy), 1.87 (br, 4H, -C**H$_2$** of Cy), 1.31–1.37 (m, 4H, -C**H$_2$** of Cy). ^{13}C NMR ($CDCl_3$, ppm): δ 158.08 (d, J = 44.3 Hz, *ipso* carbon of OP**Ph**$_2$), 157.86 (-N=**C**H), 135.32 (d, J = 20.2 Hz, *ortho* carbon of OP**Ph**$_2$), 130.95 (*para* carbon of OP**Ph**$_2$), 130.57 (d, J = 10.1 Hz *meta* carbon of OP**Ph**$_2$), 176.02, 136.91, 133.97, 128.58, 127.83, 127.49, 124.51, 122.46, 118.77, 106.46 (carbons of naphthyl), 68.00 (-**C**H of Cy), 32.26 (-**C**H$_2$ of Cy), 24.64 (-**C**H$_2$ of Cy). ^{31}P-{^{1}H} NMR ($CDCl_3$, ppm): δ 114.09 (s, O**P**Ph$_2$). IR (KBr pellet in cm^{-1}): υ 3068, 3028 (Aromatic C–H), 2922, 2862 (Aliphatic C–H), 1436 (P-Ph), 1020 (O–P). Anal. calcd. for $C_{52}H_{44}N_2O_2P_2$ (790.884 g/mol): C, 78.97; H, 5.61; N, 3.54, found: C, 78.71; H, 5.52; N, 3.38%. $[\alpha]_D^{20} = +7.0°$ (c = 1.0, $CHCl_3$).

2.1.2.1.2. 1-({[(1R,2R)-2-{[(2-{[bis(propan-2-yl)phosphanyl]oxy} naphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl) naphthalen-2-ylbis(propan-2-yl)phosphinite (2). Yield: 85 mg, (87%). ^{1}H NMR ($CDCl_3$, ppm): δ 9.02 (s, 2H, −N=C**H**), 6.95–7.82 (m, 12H, protons of naphthyl), 3.76 (s, 2H, C**H** of Cy), 1.85–1.87 (m, 2H, -C**H**$(CH_3)_2$ of OP^{i}Pr), 0.90–1.42 (m, 32H, CH(C**H**$_3)_2$ of OP^{i}Pr + -C**H**$_2$ of Cys). ^{13}C NMR ($CDCl_3$, ppm): δ 172.31, 136.79, 133.18, 129.00, 127.78, 126.60, 122.80, 122.74, 118.39, 107.17 (carbons of naphthyl), 159.22 (-N=**C**H), 67.98 (-**C**H of Cy), 32.71 (-**C**H$_2$ of Cy), 29.71 (-**C**H$(CH_3)_2$ of OP^{i}Pr), 24.70 (-**C**H$_2$ of Cy), 17.53, 17.35, (-CH(**C**H$_3)_2$) of OP^{i}Pr). ^{31}P-{^{1}H} NMR ($CDCl_3$, ppm): δ 150.62 (s, O**P**CH$(CH_3)_2$). IR (KBr pellet in cm^{-1}): υ 2963, 2870 (Aliphatic C–H), 1454 (P-^{i}Pr), 1039 (O–P). Anal. calcd. for $C_{40}H_{52}N_2O_2P_2$ (654.816 g/mol): C, 73.37; H, 8.01; N, 4.28, found: C, 73.17; H, 7.90; N, 4.08%, $[\alpha]_D^{20} = -4.2°$ (c = 2, $CHCl_3$).



Scheme 1. Synthesis of C_2-symmetric bis(phosphinite) ligands (**1**–**3**).

2.1.2.1.3. 1-({[(1R,2R)-2-[({2-[(dicyclohexylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino] cyclohexyl]imino}methyl)naphthalen-2-yl dicyclohexylphosphinite (3). Yield: 110 mg, (90%). ^{1}H NMR ($CDCl_3$, ppm): δ 9.19 (s, 2H, −N═C**H**), 7.05−7.82 (m, 12H, protons of naphthyl), 3.75−3.78 (m, 2H, -C**H** of Cy), 1.87−1.97 (m, 4H, C**H$_2$** of Cy), 1.22−1.78 (m, 48H, protons of OP**Cy$_2$** + -C**H$_2$** of Cy). ^{13}C NMR ($CDCl_3$, ppm): δ 172.22, 136.42, 133.39, 128.84, 127.78, 126.53, 123.36, 122.82, 118.62, 107.16 (carbons of naphthyl), 157.89 (-N═**C**H), 67.98 (-**C**H of Cy), 32.71 (-**C**H$_2$ of Cy), 24.95 (**C**H$_2$ of Cy), 37.02, 26.23, 26.40, 26.52, 26.75, 26.97, 29.71 (carbons of OP**Cy$_2$**). ^{31}P-{^{1}H} NMR ($CDCl_3$, ppm): δ 146.75 (s, O**P**(Cy)$_2$). IR (KBr pellet in cm^{-1}): υ 2963, 2870 (Aliphatic C−H), 1454 (P-Cy), 1039 (O−P). Anal. calcd. for $C_{52}H_{68}N_2O_2P_2$ (815.076 g/mol): C, 76.63; H, 8.41; N, 3.44, found: C, 76.47; H, 8.29; N, 3.32%, $[\alpha]_D^{20} = +2.0^{\circ}$ (c = 0.65, $CHCl_3$).

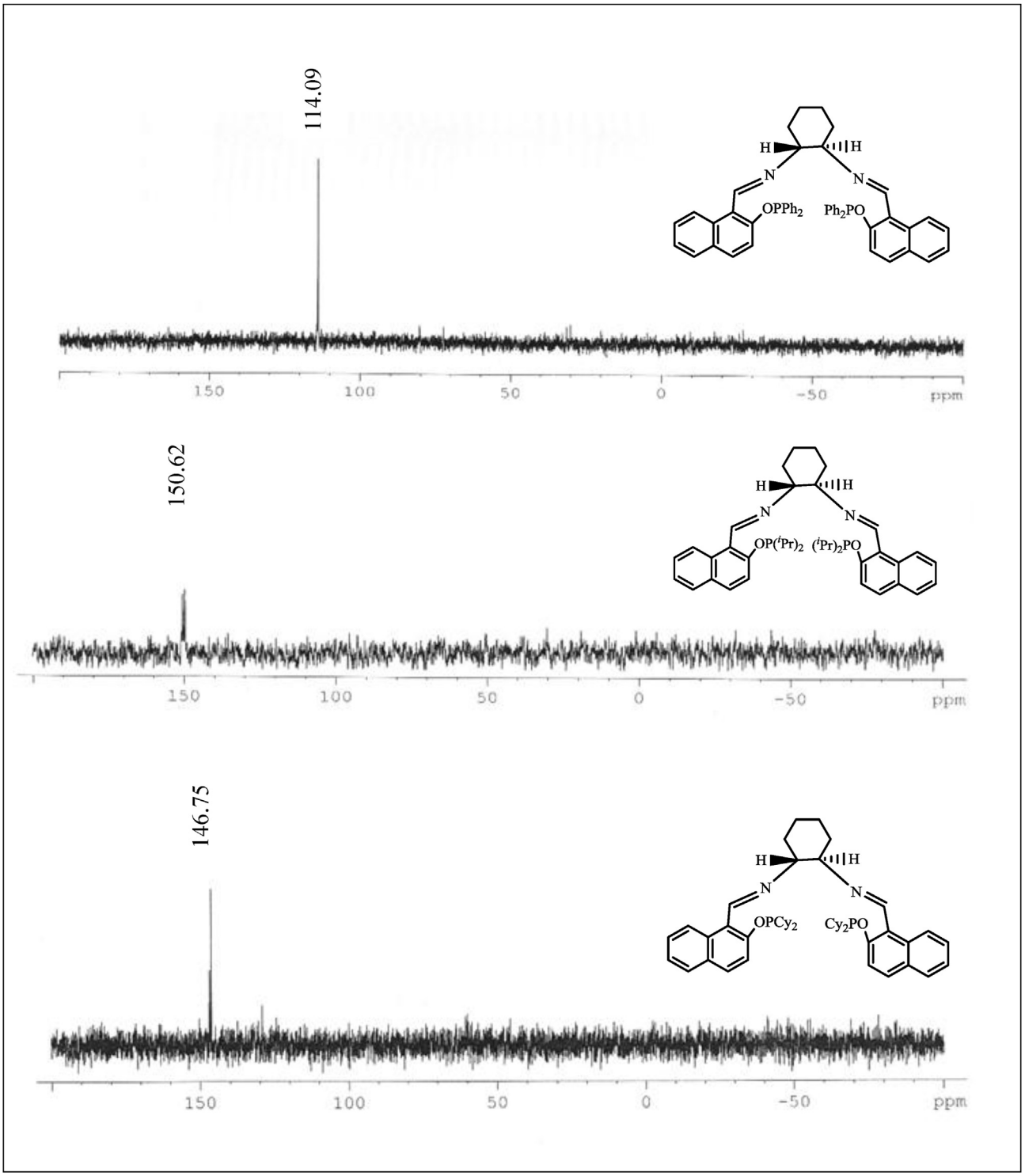


Fig. 1. ^{31}P-{^{1}H} NMR spectra of C_2-symmetric bis(phosphinite) ligands (**1**−**3**).

2.1.2.2. General procedure for synthesis of the C_2-symmetric η^6-p-cymene-Ru(II)-phosphinite complexes, 4-6. The binuclear half sandwich Ru(II) complexes **4**–**6** were synthesized by reacting equimolar amounts of the phosphinite ligands, **1**–**3** and {[Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$ in 30 mL of CH_2Cl_2 under argon atmosphere. General procedure for the synthesis of Ru(II) complexes **4**–**6** can be found in our recent publications [1,32,34].

2.1.2.2.1. 1-({[(1R,2R)-2-[({2-[(diphenylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino] cyclohexyl]imino}methyl)naphthalen-2-yldiphenylphosphinite(bis(dichloro-η^6-p-cymeneruthenium(II))(4). Yield: 180 mg (86%), m.p: 120–122 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 9.16 (br, 2H, −N=C**H**), 7.27–8.03 (m, 32H, protons of naphthyl + OP**Ph**$_2$), 5.06–5.41 (m, 8H, aromatic protons of *p*-cymene), 3.10 (br, 2H, -C**H** of Cy), 2.47 (m, 2H, -C**H**$(CH_3)_2$ of *p*-cymene), 1.81 (br, 4H, -C**H$_2$** of Cy), 1.66 (s, 6H, -C**H**$_3$ of *p*-cymene), 1.32 (br, 4H, -C**H$_2$** of Cy), 0.85–0.87 (m, 12H, −CH(C**H$_3$**)$_2$). ^{13}C NMR ($CDCl_3$, ppm): δ 171.11, 136.94, 133.78, 128.65, 128.27, 128.17, 124.36, 122.72, 121.37, 110.41 (carbons of naphthyl), 158.87 (-N=**C**H), (not observed *ipso* carbon of OP**Ph**$_2$), 135.17, 132.07, 129.81 (*ortho, para, meta* carbons of OP**Ph**$_2$), 111.62, 96.72 (*ipso* carbons of *p*-cymene), 87.47, 87.54, 92.02, 92.07 (aromatic carbons of *p*-cymene), 66.95 (**C**H of Cy), 30.16 (-**C**H$(CH_3)_2$ of *p*-cymene), 29.82 (-**C**H$_2$ of Cy), 24.24 (-**C**H$_2$ of Cy), 21.31 (-CH(**C**H$_3$)$_2$ of *p*-cymene), 17.36 (-**C**H$_3$ of *p*-cymene). ^{31}P-{^{1}H} NMR ($CDCl_3$, ppm): δ 118.18 (s, O**P**Ph$_2$). IR (KBr pellet in cm^{-1}): υ 3054, 3015 (Aromatic C–H), 2907, 2855 (Aliphatic C–H), 1426 (P-Ph), 1008 (O–P). Anal. Calc. for [$C_{72}H_{72}N_2O_2P_2Ru_2Cl_4$] (1403.274 g/mol): C 61.63, H 5.17, N 2.00; found: C 61.49, H 4.98, N 1.92%, $[\alpha]_D^{20} = +8.3°$ (c = 1, $CHCl_3$).

2.1.2.2.2. 1-({[(1R,2R)-2-{[(2-{[bis(propan-2-yl)phosphanyl]oxy}naphthalen-1-yl)methylidene] amino}cyclohexyl]imino}methyl)naphthalen-2-ylbis(propan-2-yl)phosphinite (bis(dichloro-η^6-p-cymeneruthenium(II)) (5). Yield: 170 mg (90%), m.p: 120–122 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 9.28 (s, 2H, −N=C**H**), 7.28–7.78 (m, 12H, protons of naphthyl), 5.31–5.54 (m, 8H, aromatic protons of *p*-cymene), 3.82 (s, 2H, -C**H** of Cy), 2.06–2.30 (m, 2H, -C**H**$(CH_3)_2$ of *p*-cymene), 1.84–1.98 (m, 2H, -C**H**$(CH_3)_2$ of OP^{i}Pr), 1.72 (s, 6H, -C**H**$_3$ of *p*-cymene), 1.11–1.45 (m, 32H, −CH(C**H**$_3$)$_2$ of OP^{i}Pr + -C**H$_2$** of Cy), 0.85–0.89 (m, 12H, −CH(C**H**$_3$)$_2$ of *p*-cymene).^{13}C NMR ($CDCl_3$, ppm): δ 173.30, 137.20, 133.61, 129.50, 127.81, 126.73, 124.54, 122.60, 118.66, 111.63 (carbons of naphthyl), 160.13 (-N=**C**H), 111.31, 99.51 (*ipso* carbons of *p*-cymene), 88.79, 88.74, 86.50, 85.64 (aromatic carbons of *p*-cymene), 68.05 (-**C**H of Cy), 32.07 (-**C**H$_2$ of Cy), 30.44 (-**C**H$(CH_3)_2$ of *p*-cymene), 29.79 (-**C**H$(CH_3)_2$ of OP^{i}Pr), 24.74 (-**C**H$_2$ of Cy), 22.11 (-CH(**C**H$_3$)$_2$ of *p*-cymene), 18.20, 18.51 (-CH(**C**H$_3$)$_2$ of OP^{i}Pr), 17.42 (-**C**H$_3$ of *p*-cymene). ^{31}P-{^{1}H} NMR ($CDCl_3$, ppm): δ 160.84 (s, O**P**CH$(CH_3)_2$). IR (KBr pellet in cm^{-1}): υ 3054, 3015 (Aromatic C–H), 2907, 2855 (Aliphatic C–H), 1426 (P-^{i}Pr), 1008 (O–P). Anal. Calc. for [$C_{60}H_{80}N_2O_2P_2Ru_2Cl_4$] (1267.206 g/mol): C 56.87, H 6.36, N 2.21; found: C 56.72, H 6.22, N 2.09%, $[\alpha]_D^{20} = -10.3°$ (c = 1, $CHCl_3$).

2.1.2.2.3. 1-({[(1R,2R)-2-[({2-[(dicyclohexylphosphanyl)oxy]naphthalen-1-yl}methylidene)amino] cyclohexyl]imino}methyl)naphthalen-2-yldicyclohexylphosphinite(bis(dichloro-η^6-p-cymeneruthenium(II)) (6). Yield: 190 mg (89%), m.p: 120–122 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 9.16 (s, 2H, −N=C**H**), 7.10–7.81 (m, 12H, protons of naphthyl), 5.29–5.55 (m, 8H, aromatic protons of *p*-cymene), 3.80–3.85 (m, 2H, C**H** of Cy), 2.10–2.30 (m, 2H, -C**H**$(CH_3)_2$ of *p*-cymene), 1.96–2.06 (m, 4H, -C**H$_2$** of Cy), 1.82 (s, 6H, -C**H**$_3$ of *p*-cymene), 1.24–1.80 (m, 48H, protons of OP**Cy$_2$** + -C**H**$_2$ of Cy) 0.80–0.92 (m, 12H, −CH(C**H**$_3$)$_2$ of *p*-cymene). ^{13}C NMR ($CDCl_3$, ppm): δ 172.10, 136.62, 133.40, 128.28, 127.80, 126.55, 123.30, 122.80, 118.50, 107.20 (carbons of naphthyl), 158.03 (-N=**C**H), 110.98, 97.51 (*ipso* carbons of *p*-cymene), 88.70, 87.98, 87.74, 86.48 (aromatic carbons of *p*-cymene), 68.00 (**C**H of Cy)), 30.35 (-**C**H$(CH_3)_2$ of *p*-cymene), 37.10, 29.73, 26.96, 26.70, 26.55, 26.35, 26.21 (-**C**H$_2$ of Cys + -**C**H$_2$ of OPCy$_2$), 22.15 (-CH(**C**H$_3$)$_2$ of *p*-cymene), 17.44 (-**C**H$_3$ of *p*-cymene). ^{31}P-{^{1}H} NMR ($CDCl_3$, ppm): δ 155.42 (s, O**P**(Cy)$_2$). IR (KBr pellet in cm^{-1}): υ 3073, 3053 (Aromatic C–H), 2960, 2823 (Aliphatic C–H): 1436 (P-Cy), 1024 (O–P). Anal. Calc. for [$C_{72}H_{96}N_2O_2P_2Ru_2Cl_4$] (1427.466 g/mol): C 60.58, H 6.78, N 1.96; found: C 60.35, H 6.49, N 1.53%, $[\alpha]_D^{20} = +9.0°$ (c = 0.65, $CHCl_3$).

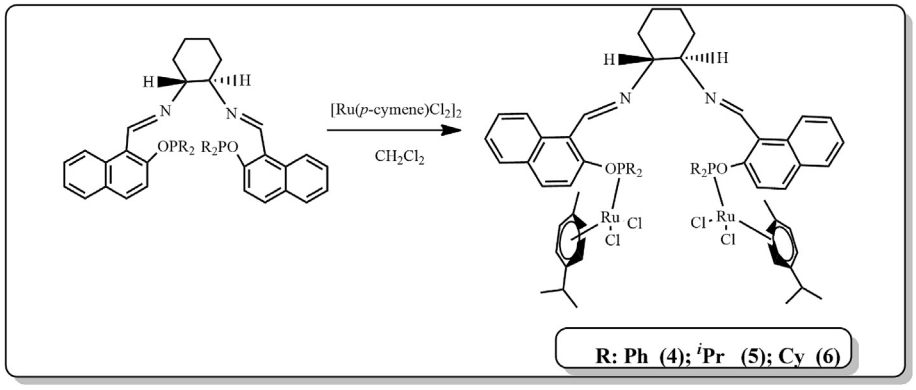
2.1.3. General procedure for the asymmetric transfer hydrogenation of ketones

The details of the procedure used for the catalytic asymmetric transfer hydrogenation of ketones and the methods for product analysis can be found in our recent publications [34,35].

3. Results and discussion

3.1. Synthesis and characterization of the bis(phosphinite) ligands (1–3) and their binuclear half sandwich η^6-p-cymene-Ru(II) complexes

In the present work, firstly, 1-({[(1R,2R)-2-{[(2-hydroxynaphthalen-1-yl)methylidene] amino}cyclohexyl]imino} methyl)naphthalen-2-ol was synthesized as precursors for phosphinites. Then, new chiral C_2-symmetric bis(phosphinite) ligands were prepared from the reaction of above mentioned corresponding alcohol with two equivalents of Ph_2PCl, (*i*-Pr)$_2$PCl or (Cy)$_2$PCl (Scheme 1). ^{31}P-{^{1}H} NMR spectroscopy was used to follow the progress of these reactions. Resonances of the starting materials disappeared and new singlets obtained in downfield corresponding



Scheme 2. Synthesis of C_2-symmetric half sandwich η^6-*p*-cymene-Ru(II) complexes (**4**–**6**) from the bis(phosphinite) ligands (**1**–**3**).

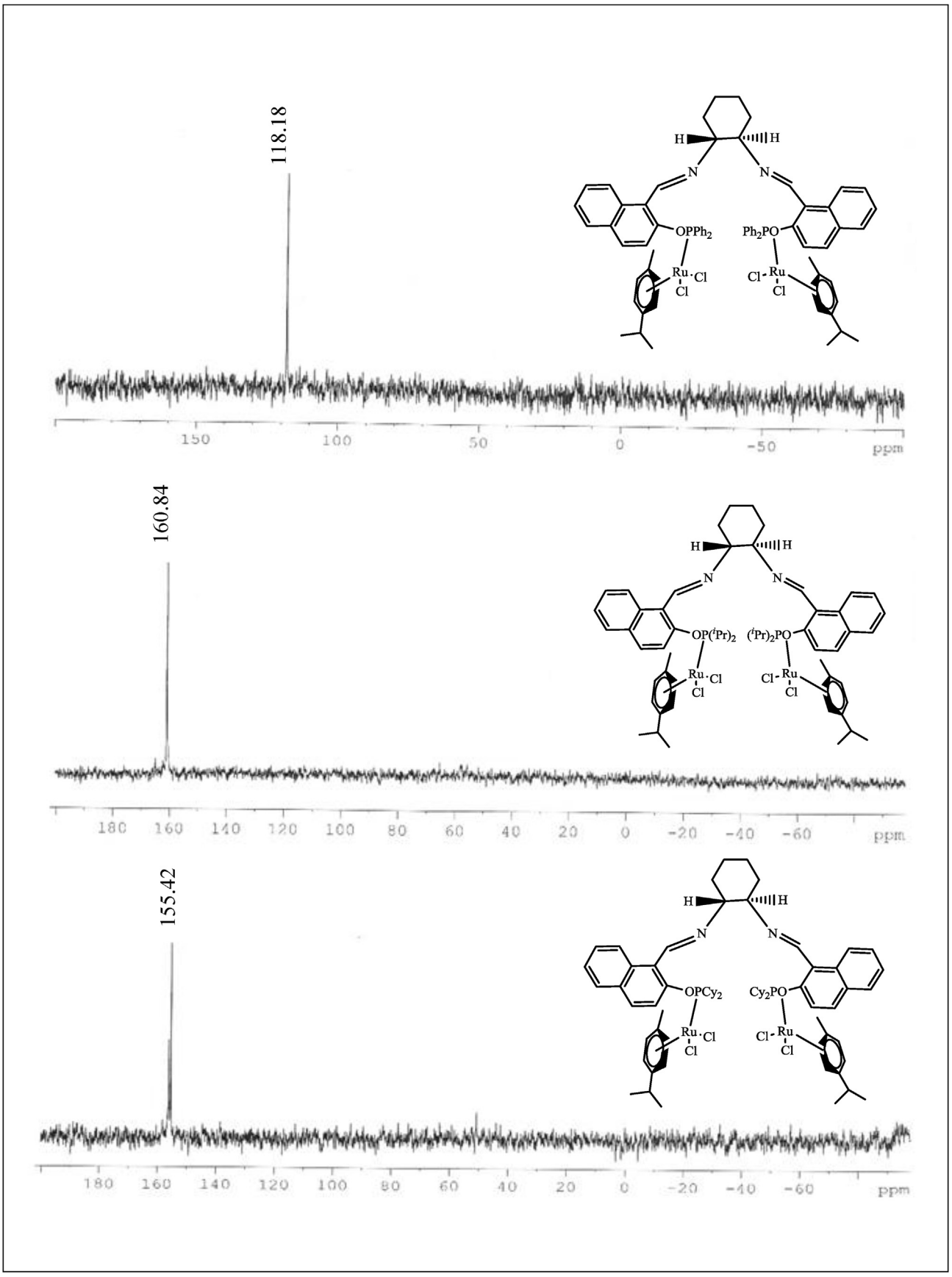


Fig. 2. ^{31}P-{^{1}H} NMR spectra of C_2-symmetric half sandwich η^6-*p*-cymene-Ru(II) complexes (**4**–**6**).

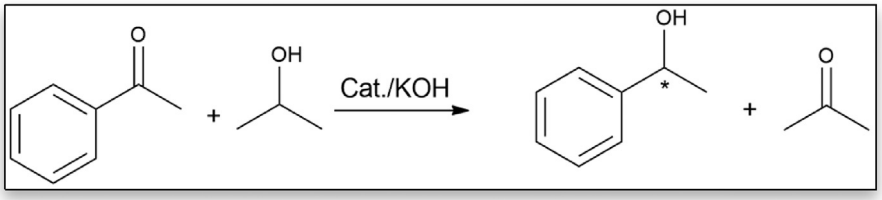
to the phosphinites at δ 114.09, 150.62, 146.24 ppm for compounds **1**, **2** and **3** (Fig. 1), respectively, in accord with the values previously observed for similar compounds [36–38]. Additionally, ^{1}H NMR, ^{13}C-{^{1}H} NMR, IR spectra and C, H, N elemental analyses were in agreement with the proposed structures for the new phosphinite ligands.

The binuclear half sandwich Ru(II) complexes were synthesized by reacting equimolar amounts of the phosphinite ligands, **1**–**3** and {[Ru(η^6-*p*-cymene)(μ-Cl)Cl]$_2$ under argon atmosphere (Scheme 2). They were obtained as orange-red crystalline solids in good yields. Singlet resonances were observed in the ^{31}P-{H} NMR spectra at δ 118.18, 160.84 and 155.42 ppm for **4**–**6** (Fig. 2.), respectively. The observed downfield shifts compared to free ligands were attributed to formation of the complexes [36–38]. The ^{1}H, ^{13}C-{^{1}H} NMR, IR spectroscopic data and the elemental analysis data of the complexes were in agreement with the expected compounds. We tried to obtain single crystal suitable for X-ray in different solvent systems or media several times but we failed.

3.2. Transfer hydrogenation studies

Ruthenium complexes **4**–**6** were applied to asymmetric transfer hydrogenation of aromatic ketones using 2-propanol as a source of hydrogen in the presence of base. The asymmetric transfer hydrogenation reaction conditions were optimized using acetophenone as a model substrate (Table 1). As expected, complexes catalyzed the reduction of acetophenone to 1-phenylethanol in high conversions, preferring the (*R*) enantiomer. In a typical experiment, 0.005 mmol of the Ru(II) complex and 0.5 mmol of acetophenone were added to a solution of KOH in 2-propanol (0.025 mmol of KOH in 5 mL 2-propanol), refluxed at 82 °C and the progress of the reaction was monitored by gas chromatography at regular intervals. The catalytic activity of the catalyst was investigated in four temperature protocols (25, 40, 60 and 82 °C). At room temperature,

Table 1
Transfer hydrogenation of acetophenone with 2-propanol catalyzed by C_2-symmetric half sandwich η^6-*p*-cymene-Ru(II) complexes (**4**, **5** and **6**).



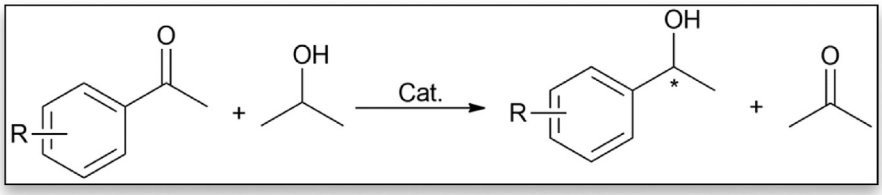
Entry	Cat.	Subs./Cat/KOH	Time(h)	Conv.(%)[f]	ee (%)[b]	Config.	TOF (h^{-1})[g]
1	**4**[a]	100:1:5	1	98	44	*R*	98
2	**5**[a]	100:1:5	4	97	22	*R*	25
3	**6**[a]	100:1:5	3	99	24	*R*	34
4	**4**[b]	100:1	24	trace	–	-	–
5	**5**[b]	100:1	24	trace	–	-	–
6	**6**[b]	100:1	24	trace	–	-	–
7	**4**[c]	100:1:5	72	<10	60	*R*	–
8	**5**[c]	100:1:5	72	<10	34	*R*	–
9	**6**[c]	100:1:5	72	<10	37	*R*	–
10	**4**[d]	100:1:5	2	96	40	*R*	48
11	**5**[d]	100:1:5	6	98	25	*R*	16
12	**6**[d]	100:1:5	5	95	28	*R*	19
13	**4**[e]	500:1:5	20	97	38	*R*	<10
14	**5**[e]	500:1:5	24	98	17	*R*	<10
15	**6**[e]	500:1:5	24	96	19	*R*	<10
16	**4**[h]	100:1:5	1	95	42	*R*	95
17	**4**[i]	100:1:5	1	91	41	*R*	91
18	**4**[j]	100:1:5	1	98	37	*R*	98
19	**4**[k]	100:1:5	1	96	38	*R*	96
20	**4**[l]	100:1:5	1	97	35	*R*	97
21	**4**[m]	100:1:5	5	95	34	*R*	20
22	**4**[n]	100:1:5	3	93	31	*R*	31
23	**4**[o]	100:1:5	1	6	23	*R*	<10

Reaction conditions.
[a] Refluxing in *iso*-PrOH; acetophenone/Ru/KOH, 100:1:5.
[b] Refluxing in *iso*-PrOH; acetophenone/Ru, 100:1, in the absence of base.
[c] At room temperature; acetophenone/Ru/KOH, 100:1:5.
[d] Refluxing the reaction in air.
[e] Refluxing in *iso*-PrOH; acetophenone/Ru/KOH, 500:1:5.
[f] Determined by GC (three independent catalytic experiments).
[g] Referred at the reaction time indicated in column; TOF= (mol product/mol Ru(II)Cat.)x h^{-1}.
[h] Refluxing in *iso*-PrOH; acetophenone/Ru/NaOH, 100:1:5.
[i] Refluxing in *iso*-PrOH; acetophenone/Ru/^{t}BuOK, 100:1:5.
[j] Refluxing in *iso*-PrOH; acetophenone/Ru/KO*i*Pr, 100:1:5.
[k] Refluxing in *iso*-PrOH; acetophenone/Ru/^{t}BuONa, 100:1:5.
[l] Refluxing in *iso*-PrOH; acetophenone/Ru/NaO*i*Pr, 100:1:5.
[m] At 40 °C; acetophenone/Ru/KOH.
[n] At 60 °C; acetophenone/Ru/KOH.
[o] Refluxing in ethanol; acetophenone/Ru/KOH, 100:1:5.

transfer hydrogenation of acetophenone occurred considerably sluggishly and its conversion was too low (<10% after 72 h, Table 1, entries 7–9) with all catalysts. A survey of the reactions at 40 °C and 60 °C (Table 1, entries 21–22) reveals that overall reduction is faster than that at rt while *ee* values were lower than those obtained at rt. However, when the temperature was increased to 82 °C, the conversion of acetophenone to 1-phenylethanol became satisfactory. During the reaction, the colour of the reaction solution altered from orange to deep red. When the base was added, the reaction began instantly without any induction time. A blank experiment was performed to demonstrate that the presence of a base is necessary for conversion in transfer hydrogenation (Table 1, entries 4–6). The optimization of acetophenone/Cat/KOH molar ratio and reaction temperature were essential to achieve high enantioselectivity or conversion. So, in a series of experiments, the optimal conditions were investigated, such as molar ratios of both substrate to catalyst and base to catalyst (Table 1). The optimization studies exhibited that good catalytic activity was gained with a base/cat. ratio of 5:1. Table 1, entries 1 and 16–20 shows the effect of different bases on the asymmetric transfer hydrogenation reactions. Various bases such as KOH, NaOH, *t*BuOK, KO*i*Pr, *t*BuONa, NaO*i*Pr were employed under the same conditions. Among the bases used, KOH showed the highest activity with 98% conversion and 44% ee. (Table 1, entry 1). It should be noted that without base no significant conversion was observed (Table 1, entries 4–6). The optimized molar ratio of the acetophenone/Cat/KOH was found to be 100:1:5. Asymmetric transfer hydrogenation of acetophenone at 82 °C catalyzed by complex **4** in the presence of ethanol as sole solvent gave (*R*)-1-phenylethanol in 23% *ee* and 6% conversion after 1 h (Table 1, entry 23). From Table 1, it can be seen that all complexes catalyze almost quantitatively (%97 to 99) the transfer hydrogenation of acetophenone within a period of 4 h. Furthermore, complex **4** showed higher enantioselectivity than those of the ruthenium complexes **5** and **6**. As Morris et al. showed catalytic activity (conversion) is concerned with cone angle (θ) of the PR_2 group. PPh_2 moiety with θ: 141° angle exhibits the highest catalytic activity [20]. Therefore, in this study, the catalytic activity in terms of conversion in the reduction of acetophenone catalyzed by complex **4** (PR_2; R:Ph) was higher than those of complexes **5** (PR_2; R: *i*-Pr) and **6** (PR_2; R: Cy).

Encouraged by the good enantioselectivities attained in these initial studies, we next extended our researches to involve asymmetric hydrogenation of substituted acetophenone derivatives. The findings summarized in Table 2 demonstrate that a variety of acetophenone derivatives can be hydrogenated with moderate to good enantioselectivities. Thus, the reaction of several aromatic ketones with different electronic and steric variations on the substrate backbone was investigated and found that the position and

Table 2
Asymmetric transfer hydrogenation results for substituted acetophenones catalyzed by C_2-symmetric half sandwich η^6-*p*-cymene-Ru(II) complexes (**4, 5 and 6**).3



Entry	Cat.	R	Time	Conv.(%)[b]	*ee*(%)[c]	TOF (h^{-1})[d]	Conf.[e]
1	**4**	**2-F**	30 min	99	45	198	*R*
2	**5**		2 h	99	21	50	*R*
3	**6**		3 h	98	22	33	*R*
4	**4**	**4-F**	30 min	97	54	194	*R*
5	**5**		2 h	98	23	49	*R*
6	**6**		3 h	96	24	32	*R*
7	**4**	**4-Cl**	30 min	97	49	194	*R*
8	**5**		2 h	97	24	49	*R*
9	**6**		3 h	96	23	32	*R*
10	**4**	**2-Br**	45 min	98	48	130	*R*
11	**5**		2 h	98	19	46	*R*
12	**6**		3 h	96	25	32	*R*
13	**4**	**4-Br**	45 min	97	42	129	*R*
14	**5**		2 h	96	21	48	*R*
15	**6**		3 h	94	20	31	*R*
16	**4**	**4-NO_2**	3 h	98	59	33	*R*
17	**5**		5 h	99	22	20	*R*
18	**6**		5 h	90	21	18	*R*
19	**4**	**2-MeO**	3 h	98	60	33	*R*
20	**5**		3 h	92	32	31	*R*
21	**6**		3 h	92	28	31	*R*
22	**4**	**4-MeO**	2 h	96	57	48	*R*
23	**5**		3 h	96	29	32	*R*
24	**6**		3 h	90	25	30	*R*

Reaction conditions.
a Catalyst (0.005 mmol), substrate (0.5 mmol), *iso*-PrOH (5 mL), KOH (0.025 mmol %), 82 °C, respectively, the concentration of acetophenone derivatives is 0.1 M.
[b] Purity of compounds is checked by NMR and GC (three independent catalytic experiments), yields are based on methyl aryl ketone.
[c] TOF = (mol product/mol Cat.) x h^{-1}.

electronic property of the substituents present in the substrates influenced hydrogenation results. As expected, we observed that the introduction of electron withdrawing substituents, such as F, Cl and Br to the *o*- or *p*-position of the aryl ring of the ketone increased the electron deficiency in the carbonyl group so that the activity was enhanced leading to easier hydrogenation. An electron-withdrawing group such as fluoro or nitro group to the *p*-position of the aryl ring of the ketone was useful to achieve excellent conversion and moderate enantioselectivity (up to 54% *ee*, Table 2). On the other hand, the introducing electron donating substituent such as methoxy to the *o*- or *p*-position make the ketone substrate more electron rich and thus, it needs longer time to obtain higher conversion. However, methoxy substituent at *o*-position of the phenyl ring increases the rate and improves the enantioselectivity (Table 2).

The best result was acquired in the reduction of 2-methoxyacetophenone among all selected ketones affording 60% *ee* (Table 2, entry 19). The data in Table 2 clearly displayed that strong electron-withdrawing substituents, such as fluoro, chloro, bromo were able to cause higher conversion but with slightly lower enantiomeric purity. On the contrary, the most electron donating substituent (-OCH_3) resulted in higher conversion and higher *ee* (Table 2, entry 19 and 22).

4. Conclusions

In summary, three new C_2-symmetric bis(phosphinite) ligands containing different groups on phosphorus atom (**1**–**3**) and their binuclear Ru(II)($_\eta^6$-*p*-cymene) complexes (**4**–**6**) were synthesized, characterized and studied in the asymmetric transfer hydrogenation of ketones under optimized conditions. All complexes were found to be active catalyst precursors displaying quantitative conversions and good to moderate enantioselectivities. Additionally, complex **4** prepared from ligand **1,** having a phenyl group on phosphorus atom, gives higher enantioselectivity than those of the ruthenium complexes **5** and **6**.

Acknowledgements

This work was supported by the Research Fund of Dicle University (DUBAP- FEN.15.023, DUBAP-FEN.16.008).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molstruc.2019.127146.

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