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Diastereoselectivity and catalytic activity in ruthenium complexes chiral at the metal centre

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ABSTRACT

Cis-$RuCl_2$(diphosphine)(CAMPY) complexes, chiral at the metal centre with matching or mismatching chiralities between diphosphine and CAMPY were prepared and the configuration at the metal was determined *in solution* by a complete set of NMR investigations; CAMPY is (*R*)-(−) or (*S*)-(+)-8-amino-5,6,7,8-tetrahydroquinoline. The complexes were used in ATH reactions of different aryl ketones with 2-propanol as hydrogen source. The effects of the chirality at the metal were studied and enantiomeric excesses up to 99% were obtained.

Introduction

The enantioselective reduction of C=O double bonds is a key synthetic transformation proved as fundamental for the preparation of fine chemicals [1,2], mainly drugs, fragrances and insecticides [3–7]; the reaction has been largely reviewed and a huge bibliography exists. The ketones' reduction can be realized by asymmetric transfer hydrogenation (ATH) based on the use of hydrogen donors, usually secondary alcohols or formic acid, or with molecular H_2 as reducing agent (asymmetric hydrogenation, AH) [8–10].

The most outstanding results have been obtained by Noyori's group who discovered and developed the catalyst [$RuCl_2$(diphospine)(diamine)] [11] in which the ruthenium complexes in *trans* geometry [12,13].

The action mechanism of these catalysts has been studied in details and elucidated by several research groups, first of all by Noyori's one [14,15] and deeply in all its aspects by Morris's one [16–18].

Metal-catalysed hydrogenation of ketones and imines [19] has a great attraction because it replaces the use of stoichiometric hydrides, usually difficult to handle and with amounts of basic by-products to be disposed off; one of the few counter-indications of this technique is the high pressure vessels necessary.

On the contrary ATH is simpler and it avoids handling H_2 gas. The ATH has been studied in details and a great number of catalytic systems have been developed; the most advanced and used are those based on η^6-arene Ru bis-amido and on η^6-arene Ru H aminoamido; these complexes are devoid of phosphine ligands and the chiral information is located on an aminoalcohol or a diamine [8,20].

The very active catalysts generated by the addition of diamines to $RuCl_2$ phosphines in 2-propanol in presence of a base have been essentially studied as hydrogenation catalysts but they have received less attention as catalysts for ATH [21].

An improvement in ATH with this type of complexes was realized by Rigo using *cis*-Ru(II) complexes, [$RuCl_2$(PP)(NN)] [22,23], where NN is the 2-(aminomethyl)pyridine. Many strategies have been developed to increase the level of enantioselectivity, particularly by exploring the matching combination between two different chiral ligands but when complexes are in a *cis* arrangement the role of the chirality at the metal centre must be taken in consideration.

Experimental

General considerations

Commercially reagent grade solvents were dried according to standard procedure and freshly distilled under nitrogen before

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using. All synthesis of ruthenium complexes were carried out under nitrogen atmosphere using standard Schlenk techniques. Unless otherwise stated, materials are obtained from commercial source and used without further purification; optically pure (*R*)-(−) and (*S*)-(+)-8-amino-5,6,7,8-tetrahydroquinoline (CAMPY) were obtained as described previously [24], $[RuCl_2(PPh_3)_3]$ [25](**1**), $[RuHCl(PPh_3)_3]$ [26] (**4**) and (2*R*,5*R*)-(−)-2,5-bis-Diphenilphosphin-3-exene (ZEDPHOS) [27] were synthesized according to literature procedures.

HPLC analysis were performed with Merck-Hitachi L-7100 equipped with Detector UV6000LP and Chiralpak AD. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on Bruker DRX Advance 300 MHz equipped with a non-reverse probe or Bruker DRX Avance 400 MHz. Chemical shifts (in ppm) were referenced to residual solvent proton/carbon peak or using external standard 85% H_3PO_4 for ^{31}P NMR. Signal multiplicity was assigned as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet).

Polarimetry analyses were carried out on Perkin Elmer 343 Plus equipped with Na/Hal lamp. Uv–Vis were recorded on Jasco V-530 UV/Vis Spectrophotometer and CD spectra on a Jasco J500 Spectrophotometer.

Catalytic activity was monitored by GC, Carlo Erba HRGC 5160 mega series using a capillary chiral column, (MEGA DMT β, 25 m, internal diameter 0.35 mm).

Synthesis of ruthenium complexes

In order to simplify the comprehension of ^1H NMR spectra the following labels were used: the phosphorous *trans* to the pyridine nitrogen is defined as P_α, the *cis* one as P_β; in chelating diphosphine ligands the labels were split in P_α and P_β considering the symmetry plane of the molecule perpendicular to the P–Ru–P plane; all the protons belonging to the diamine ligand were labelled with a superscripted N.

*t,c -[RuCl$_2$((S)-CAMPY)(PPh$_3$)$_2$] (**2**)*

$[RuCl_2(PPh_3)_3]$ (640 mg, 0.67 mmol) was dissolved in CH_2Cl_2 (10 ml), and (*S*)-CAMPY was added to the solution (100 mg, 0.67 mmol), dissolved in CH_2Cl_2 (5 ml), the colour immediately changes to orange. The solution was stirred at room temperature for 30 min. Solvent was partially evaporated to about 5 ml then diluted with 20 ml of degassed hexane to give the product as an orange powder (401 mg; yield 71%). ^{31}P NMR (121.5 MHz, $CDCl_3$, 298 K): δ ppm 43.1 (d, $J = 31.5$ Hz, 1P, P_β), 39.2 (d, $J = 31$ Hz, 1P, P_α).^1H NMR (400.1 MHz, $CDCl_3$, 298 K): δ ppm 8.46 (dd, $J = 3.4$ Hz, 1H, H^{2N}), 7.58 (m, 6H, $Ph^{P\beta}$), 7.47 (t, $J = 8.5$ Hz, 6H, $Ph^{P\alpha}$), 7.35–7.08 (m, 19H, $Ph^{P\alpha/\beta}$, H^{4N}), 6.57 (dd, $J = 7.4$ Hz, 1H, H^{3N}), 5.12 (m, 1H, H^{8N}), 3.38 (m, 1H, NH_2^N), 3.10 (m, 1H, NH_2^N), 2.76 (d, $J = 6.7$ Hz, 2H, CH_2^N), 1.88 (m, 4H, CH_2^N). ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ ppm 155.9, 136–127 (aromatic carbon), 56.5, 33.2, 27.7, 21.2. $C_{45}H_{42}Cl_2N_2P_2Ru$, PM 844, calc. C 63.98 H 5.01 N 3.32; found C 64.09 H 5.32 N 3.15.

*c,c-[RuCl$_2$((S)-CAMPY)(PPh$_3$)$_2$] (**3**)*

Complex **2** (50 mg, 0.059 mmol) was dissolved dichloromethane (10 ml), the solution was sealed in a vial purged with nitrogen and stirred at room temperature for 5–7 days. Solvent was partially evaporated under reduced pressure to 2 ml and hexane (10 ml) was added to obtain yellow solid (43.3 mg; yield 87%). ^{31}P NMR (121.5 MHz, $CDCl_3$, 298 K): δ ppm 50.1 (d, $J = 33.0$ Hz, 1P, P_β), 42.9 (d, $J = 33.4$ Hz, 1P, P_α). ^1H NMR (400.1 MHz, $CDCl_3$, 298 K): δ ppm 9.19 (m, 1H, H^{2N}), 7.66 (m, 5H, $Ph^{P\alpha}$), 7.36 (m, 6H, $Ph^{P\beta}$, H^{4N}), 7.21 (m, 15H, $Ph^{P\alpha/\beta}$), 7.04 (m, 5H, $Ph^{P\beta}$), 6.93 (m, 1H, H^{3N}), 3.32 (m, 1H, NH_2^N), 2.92 (m, 1H, H^{8N}), 2.67 (m, 2H, CH_2^N), 1.82 (m, 1H, CH_2^N), 1.62 (m, 2H, CH_2^N, NH_2^N), 1.28 (m, 1H, CH_2^N), 0.92 (m, 1H, CH_2^N); ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ ppm 149.3, 135.9–128.1 (aromatic carbon), 59.0, 32.7, 27.2, 21.7. $C_{45}H_{42}Cl_2N_2P_2Ru$, PM 844, calc. C 63.98 H 5.01 N 3.32; found C 63.51 H 5.40 N 3.01.

*t,c-[RuHCl ((S)-CAMPY)(PPh$_3$)$_2$] (**5**)*

$[RuHCl(PPh_3)_3]$ (57.8 mg, 0.062 mmol) was dissolved in benzene-d_6 (2 ml), and (*S*)-CAMPY (10 mg, 0.067 mmol) dissolved in benzene-d_6 (1 ml) was added into the solution, the colour change immediately to orange. The solution was stirred at room temperature for 1 h before NMR analysis. ^{31}P NMR (121.5 MHz, $CDCl_3$, 298 K): δ ppm 74.3 (d, $J = 37.0$ Hz, 1P, P_α), 69.6 (d, $J = 37.0$ Hz, 1P, P_β);^1H NMR (400.1 MHz, $CDCl_3$, 298 K): δ ppm 8.62 (d, $J = 5.5$ Hz, 1H, H^{2N}), 8.24–8.08 (m, 10H, $Ph^{P\alpha/\beta}$), 7.11–7.03 (m, 10H, $Ph^{P\alpha}$), 7.02–6.93 (m, 10H, $Ph^{P\beta}$), 6.41 (d, $J = 7.7$ Hz, 1H, H^{4N}), 6.05 (dd, $J = 7.7$, 5.5 Hz, 1H, H3^N), 4.03 (m, 1H, H^{8N}), 3.11 (m, 1H, NH_2^N), 2.38 (m, 1H, NH_2^N), 2.01–1.91 (m, 2H, CH_2^N), 1.17–1.07 (m, 2H, CH_2^N), 1.02–0.9 (m, 2H, CH_2^N), −16.7 (dd, $J = 29.6$, 23.1 Hz, iH).

*c-[RuCl$_2$((S)-CAMPY) ((2R,4R)-(−)-2,4-bis-(diphenylphosphine) pentane)] ((**S**),(**R**,**R**)-**8**)*

Complex **3** (50 mg, 0.059 mmol) was added into a solution of ((2*R*,4*R*)-(−)-2,4-Bis-(diphenylphosphine)pentane) (BDPP) in dichloromethane (0.059 mmol in 8 ml). After stirring at room temperature for 30 min, solvent was evaporated under reduced pressure. Toluene (8 ml) was added to the solid and the yellow solution was heated to 110 °C for 24 h. A yellow solid was obtained upon partially elimination of the solvent under reduced pressure to about 2 ml and by adding 10 ml of degassed hexane (40 mg; yield 88%). ^{31}P NMR (121.5 MHz, $CDCl_3$, 298 K): δ ppm 65.05 (d, $J = 44.5$ Hz, 1P, P_β), 45.30 (d, $J = 44.5$ Hz, 1P, P_α). ^1H NMR (400.1 MHz, $CDCl_3$, 298 K): δ ppm 8.71 (m, 1H, H^{2N}), 7.69 (m, 5H, $Ph^{P\alpha}$), 7.60–7.49 (m, 5H, $Ph^{P\alpha}$), 7.47–7.37 (m, 5H, $Ph^{P\beta}$), 7.18 (t, $J = 7.90$ Hz, 1H, H^{4N}), 7.12–7.04 (m, 5H, $Ph^{P\beta}$), 6.74 (t, $J = 6.60$ Hz, 1H, H^{3N}), 3.74 (t, $J = 10.8$ Hz, 1H, NH_2^N), 3.50–3.34 (m, 1H, $CH^{P\beta}$), 3.16–3.01 (m, 1H, $CH^{P\alpha}$), 2.91–2.78 (m, 1H, H^{8N}), 2.66–2.59 (m, 2H, CH_2^N), 2.30–2.26 (m, 1H, CH_2^P), 1.83–1.74 (m, 2H, CH_2^N, CH_2^P), 1.60–1.50 (m, 2H, CH_2^N),1.30–1.25 (m, 2H, CH_2^N, NH_2^N), 1.19 (dd, $J = 13.6$, 7.2 Hz, 3H, $CH_3^{P\alpha}$), 0.83 (dd, $J = 11.6$, 7.0 Hz, 3H, $CH_3^{P\beta}$). ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ ppm 148.8, 136.2–123.9 (aromatic carbons), 59.6, 38.3, 34, 27.57, 22.1, 20.5, 19.3, 18.2. $C_{38}H_{42}Cl_2N_2P_2Ru$, PM 760, calc. C 60.00H 5.57 N 3.68; found C 59.87 H 5.52 N 3.60.

*c-[RuCl$_2$((S)-CAMPY) ((2S,4S)-(−)-2,4-bis-(diphenylphosphine) pentane)] ((**S**),(**S**,**S**)-**8**)*

Complex ((***S***),(***S***,***S***)-**8**) was synthesized as described for ((***S***),(***R***,***R***)-**8**), using (*S*)-CAMPY as diamine (36 mg; yield 80%). ^{31}P NMR (121.5 MHz, $CDCl_3$, 298 K): δ ppm 67.13 (d, $J = 44.3$ Hz, P_β, P_β), 44.14 (d, $J = 44.3$ Hz, 1P, P_α). ^1H NMR (400.1 MHz, $CDCl_3$, 298 K): δ ppm 8.29–8.23 (m, 1H, H^{2N}), 7.79–7.66 (m, 5H, $Ph^{P\alpha}$), 7.52–7.50 (m, 2H, $Ph^{P\beta}$), 7.49–7.41 (m, 5H $Ph^{P\alpha}$), 7.22–7.08 (m, 4H, $Ph^{P\beta}$, H^{4N}), 6.98–6.81 (m, 5H, $Ph^{P\beta}$), 6.53 (t, 1H, H^{3N}), 4.69–4.56 (m, 1H, H^{8N}), 3.47–3.33 (m, 1H, $CH^{P\beta}$), 3.10–2.98 (m, 1H, $CH^{P\alpha}$), 2.67–2.48 (m, 3H, NH_2^N, CH_2^N), 2.19–2.05 (m, 1H, CH_2^P), 1.94–1.81 (m, 2H, CH_2^P, CH_2^N), 1.78–1.69 (m, 2H, CH_2^N), 1.17 (dd, $J = 13.3$, 7.2 Hz, 3H, $CH_3^{P\alpha}$), 1.02–0.84 (m, 2H, NH_2^N, CH_2^N), 0.77 (dd, $J = 11.6$, 7.0 Hz, 3H, $CH_3^{P\beta}$). ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ ppm 147.5, 137.2–123.2 (aromatic carbons), 56.68, 38.07, 33.54, 33.28, 32.38, 26.96, 21.32, 18.88, 18.17. $C_{38}H_{42}Cl_2N_2P_2Ru$, PM 760, calc. C 60.00H 5.57 N 3.68; found C 60.23 H 5.63 N 3.53.

*c-[RuCl$_2$((S)-CAMPY) ((2R,5R)-(−)-2,5-bis-diphenilphosphin-3-hexene)] ((**S**),(**R**,**R**)-**9**)*

Complex ((***S***),(***R***,***R***)-**9**) was synthesized as described for ((***S***),(***R***,***R***)-**8**), using (*cis*-(2*R*,4*R*)-(−)-2,5-bis-Diphenilphosphin-3-hexene) (ZEDPHOS) as chelating diphosphine and refluxing for 24 h in 2-propanol instead of toluene (yield 38 mg; 83%). ^{31}P NMR

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(121.5 MHz, $CDCl_3$, 298 K): δ ppm 56 (d, $J = 32.8$ Hz, 1P, P_β), 47.2 (d, $J = 32.8$ Hz, 1P, P_α). ^{1}H NMR (400.1 MHz, $CDCl_3$, 298 K): δ ppm 8.71 (m, 1H, H^{2N}), 7.5 (m, 10H, $Ph^{P\alpha}$), 7.3–7.15 (m, 10H, $Ph^{P\beta}$),7.07(m, 1H, H^{4N}), 6.65 (t, 1H, H^{3N}), 6.45 (m, 1H, C=$CH^{P\beta}$),4.9 (m, 1H, $CH^{P\beta}$), 4.30 (m, 1H, C=$CH^{P\alpha}$), 3.25 (m, 2H, $CH^{P\alpha}$, NH_2^N), 2.75 (m, 1H, H^{8N}), 2.5 (m, 2H, CH_2^N), 1.65 (m, 2H, CH_2^N), 1.48 (m, 2H, CH_2^N), 1.42 (dd, $J = 14.5$, 7.3 Hz, 3H, $CH_3^{P\alpha}$),1.25(m, 1H, NH_2^N), 1.12 (dd, $J = 13.0$, 6.7 Hz, 3H, $CH_3^{P\beta}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 149.12, 141.13–123.80 (aromatic carbon), 59.79, 40.65, 33.94, 33.00, 27.41, 21.96, 18.67, 18.57, 16.40. $C_{39}H_{42}Cl_2N_2P_2Ru$, PM 772.70, calc. C 60.62 H 5.48 N 3.63; found. C 60.32 H 5.75 N 3.61.

*[$RuCl_2$((R)-CAMPY) ((2R,5R)-(−)-2,5-bis-diphenilphosphin-3-hexene)] (**(R),(R,R)-9**)*

Complex (**(R),(R,R)-9**) was synthesized as described for (**(S),(R,R)-8**), using (*R*)-CAMPY as diamine. ^{31}P NMR (121 MHz, $CDCl_3$) δ ppm 58.47 (d, $J = 32.4$ Hz, 34%P), 57.54 (d, $J = 31.1$ Hz, 4%P), 50.66 (d, $J = 31.3$ Hz, 11%P), 47.94 (d, $J = 31.2$ Hz, 7%P), 46.47 (d, $J = 32.5$ Hz, 41%P), 42.38 (d, $J = 31.1$ Hz, 3%P). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.22, 136.01–123.53 (aromatic carbon), 57.23, 54.00, 40.75, 33.29, 32.71, 27.33, 21.73, 18.68, 16.37, 13.87. $C_{39}H_{42}Cl_2N_2P_2Ru$, PM 772.70, calc. C 60.62 H 5.48 N 3.63; found. C 60.32 H 5.75 N 3.61.

General procedure for hydrogen transfer reaction

In a Schlenk tube sealed with a rubber septum under argon atmosphere the base (potassium tert-butoxide, 0.04 mmol) was added to a solution of precatalyst **4**–**7** (0.8 μmol) in 4 ml of 2-propanol and the system thermostated at 40 °C or 82 °C; then the ketone (0.8 mmol in 1 ml of 2-propanol) was added in one portion ([sub] = 0.16 M). GC analysis was performed taking 0.3 ml of reaction mixture, the sample was treated with ammonium chloride.

Results and discussion

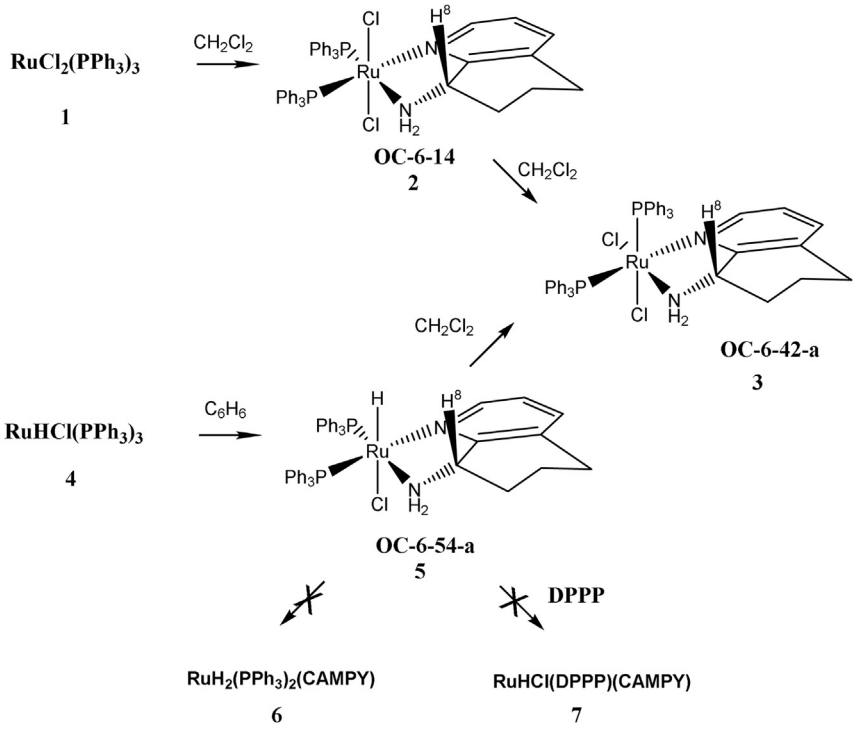
We recently reported that Ru complexes with a chiral-5,6,7,8-tetrahydro-8-amino-quinoline, (*R*)- or (*S*)-CAMPY were able to reduce ketones in 2-propanol with good enantioselectivities [24]. This C_1 chiral di-nitrogen ligand has a pyridine connected to a primary amino group which is crucial for the catalytic activity and the two nitrogen donors are fused in a rigid cyclohexane ring. Upon coordination the NH_2 group is forced into an equatorial position. When CAMPY was the only source of chirality, complex **3** [$RuCl_2$(-CAMPY)(PPh_3)$_2$] reduced acetophenone up to 55% e.e. and up to 90% e.e. when triphenylphosphine was replaced by an achiral chelating diphenylphosphinopropane, DPPP. We expected that the C_1 symmetry and the conformational rigidity of CAMPY would generate cases of matching and mismatching when the two PPh_3 ligands were replaced by a chiral chelating ligand. The unique feature of CAMPY and CAMPY-like ligands would let us to determine the stereochemistry of the complexes *in solution*.

Synthesis and characterization of trans and cis complexes

The complexes with CAMPY and chiral diphosphines were prepared either with (*R*) or (*S*) ligand; the chirality is indicated only when stereochemistry of the complexes is discussed.

The structures of *trans* and *cis* complexes were clarified by a series of 2D-NMR experiments, based also on an unexpected J^4 coupling between the proton α to the pyridine nitrogen and the phosphorus atom *trans* [24] to the pyridine itself. These complexes were investigated also by CD-spectroscopy in the region of the ligand field transitions (400–700 nm) in which chiral diphosphines and CAMPYs do not show any CD effect [28,29].

(*S*)-CAMPY reacts rapidly with [$RuCl_2(PPh_3)_3$] **1** in CH_2Cl_2 at room temperature to give the kinetic favoured **OC-6-14**, **2** [30], [*t*,*c*-[$RuCl_2$((*S*)-CAMPY)(PPh_3)$_2$]) which in turn evolvs to the ***chiral-at-metal*** optically pure **OC-6-42-C**, **(S)-3** [*c*,*c*,-[$RuCl_2$((*S*)-CAMPY)(PPh_3)$_2$] (Scheme 1).



Scheme 1.

Fig. 1a shows the CD-spectra of **(*S*)-2** (*t*,*c*-[$RuCl_2$((*S*)-CAMPY)(PPh_3)$_2$]), **(*S*)-3** *c*,*c*-[$RuCl_2$((*S*)-CAMPY)(PPh_3)$_2$] and **(*S*)-5** *t*,*c*-[RuHCl((*S*)-CAMPY)(PPh_3)$_2$] (vide infra); as expected the CD spectra of **(*R*)-2**, **(*R*)-3** and **(*R*)-5** show a complete mirror image shape (omitted for clarity).

Fig. 1b shows the CD evolution of the kinetically favoured **(*S*)-2** into the thermodynamically more stable **(*S*)-3**; the direct transformation from **2** to homochiral **3** is supported by the presence of two isodichroic [31] points at 358 nm and 478 nm and it confirms previous NMR observations that the reaction proceeds completely stereoselective.

(*S*)-CAMPY reacts with [RuHCl(PPh_3)$_3$], **4** to give [RuHCl((*S*)-CAMPY)(PPh_3)$_2$], **5** almost quantitatively in 30 min. The monohydride **5** had been characterised by 2D-NMR experiments; **5** presents hydrogen and chloride mutually *trans*, the hydridic proton resonates at −16.62 ppm as a doublet of doublets ($J(H-P) = 29.57$, 23.12 Hz). There is a second doublet of doublets at −16.21 ppm ($J(H-P) = 26.8$, 21.9 Hz) less than 1% of the major one. The ^{31}P NMR shows an intense AB system at 74.30 and 69.65 ppm ($J = 36.9$ Hz) and a second AB system, less than 1% of the former, at 67.01 ppm being the second doublet hidden by the doublet at 69.65 ppm.

The unambiguous identification of the phosphorous *trans* to the pyridine nitrogen by the J^4 coupling, the strong NOE between NH_2 and the aryl protons on phosphorus *trans* to the pyridine, the strong NOE between the H* on the stereogenic carbon and the Ru hydride indicate that **5** (*t*,*c*-[RuHCl((*S*)-CAMPY)(PPh_3)$_2$]) is the diastereomer **OC-6-54-a**, 99% optically pure at the metal centre .

In spite of a small hypsochromic shift, the CD spectra of **(*S*)-5** shows a positive CD band at 410 nm and **(*S*)-2** (*t*,*c*-[$RuCl_2$((*S*)-CAMPY)(PPh_3)$_2$]) evinces an analogous CD positive band at 420 nm. CD active transition in this region is obvious for **5** in which the metallic chromophore is chiral not racemic but it should be true also for **(*S*)-2**; X-ray structures of analogous dichloride complexes always show a distorted octahedral geometry [32,33] and it is likely that this distortion should be the origin of the CD active transitions in the LF range.

The **(*S*)-5**, dissolved in chlorinated solvents (CH_2Cl_2 or $CHCl_3$), gives the optically pure **OC-6-42-c**, **(*S*)-3** for which the CD spectrum is completely superimposable to that of **(*S*)-3**, directly obtained from **1** (Scheme 1).

Any attempt to transform **5** into the dihydride **6** and to synthesize **7** by exchange of PPh_3 with a chelating diphosphine failed.

As the ATH is usually performed at temperatures higher than room temperature and in 2-propanol which strongly accelerates the isomerization from **2** to **3**, we focused our attention on matching and mismatching and their effects on enantioselectivities only for *cis* complexes **3** (Scheme 2).

(*S*)-CAMPY reacts with [$RuCl_2$(PPh_3)$_3$] **1** and (*R*,*R*)-BDPP ((*R*,*R*)-2,4-bisdiphenylphosphinopentane) in refluxing toluene to give **8** almost quantitatively; the ^{31}P NMR shows an AB system at 65.05 and 45.30 ppm ($J = 44.6$ Hz). There is a second AB system at 59.78 ppm and 43.28 ppm ($J = 49.7$ Hz) less than 1%, presumably belonging to *trans* intermediate that rapidly disappears by adding few drops of 2-propanol.

In 2D-NMR experiments the J^4 correlation between the pyridine α-proton with the phosphorus signal at 45.30 ppm indicates that phosphorus and pyridine nitrogen are mutually *trans*; furthermore COSY cross peaks among the aryl phosphine protons at 7.36 and 7.09 ppm with the phosphorus atom at 65.05 ppm and a strong NOE between the aforementioned aryl protons and H* on the chiral carbon of (*S*)-CAMPY at 2.85 ppm, indicate that the stereochemistry of **(*S*),(*R*,*R*)-8** is **Δ-OC-6-42-a** (Fig. 2).

Similarly (*S*)-CAMPY reacts with [$RuCl_2$(PPh_3)$_3$] **1** and (*S*,*S*)-BDPP in refluxing toluene to give **8**; in a complete set of 2D-NMR experiments the J^4 correlation between the pyridine α-proton with the phosphorus signal at 44.14 ppm indicates that this phosphorus is *trans* to the pyridine; furthermore the presence of COSY cross peaks among the aryl phosphine protons at 7.13 and 6.93 ppm with the phosphorus at 67.13 ppm and *the lack* of the NOE between the aforementioned aryl protons and the hydrogen on the chiral carbon of (*S*)-CAMPY at 4.63 ppm, indicate that the stereochemistry of **(*S*),(*S*,*S*)-8** is **Λ-OC-6-42-a** (Fig. 2). Fig. 3 shows the CD spectra of **(*S*),(*R*,*R*)-8** and **(*S*),(*S*,*S*)-8** complexes in the LF region; the spectra of **(*S*),(*R*,*R*)-8** is almost the mirror image of **(*S*),(*S*,*S*)-8** indicating a local enantiomeric relationship between the metallic ruthenium

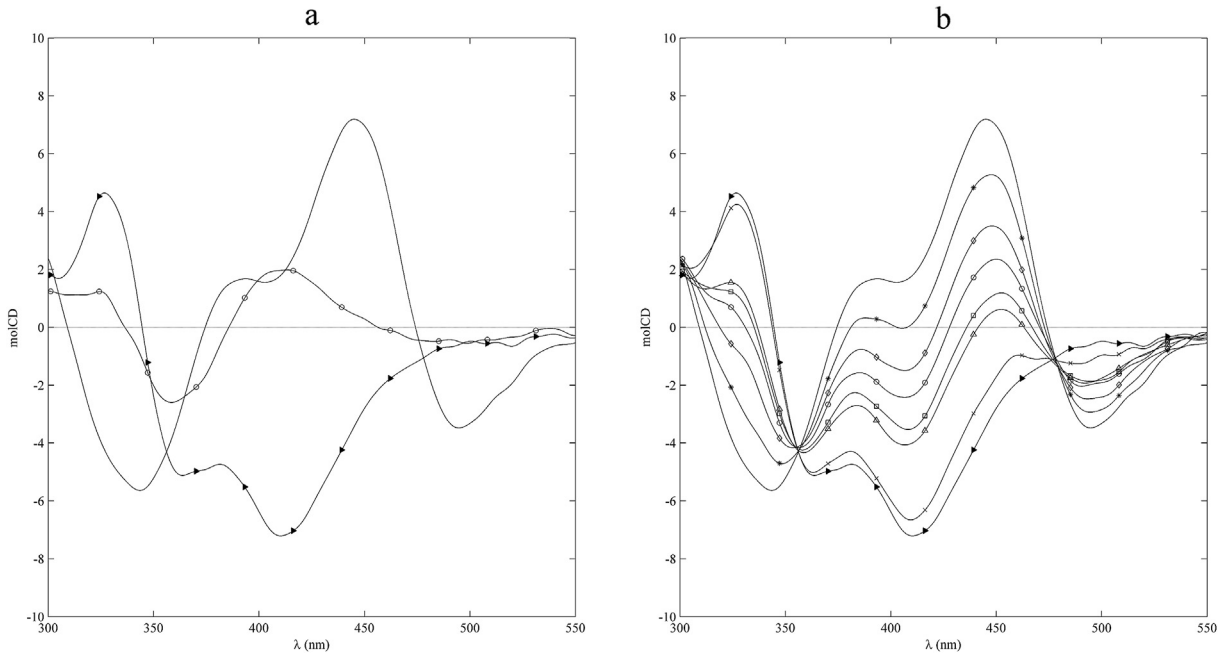


Fig. 1. a) CD spectra of complexes: **2** (—), **3**(-►-) and **5** (-o-). b) Isomerisation of complex **2**(—) to complex **3**(-►-) followed via CD spectroscopy: 1 h (*), 2 h (◊), 3 h(○), 4 h(□), 5 h(Δ) and 3 days (x) .

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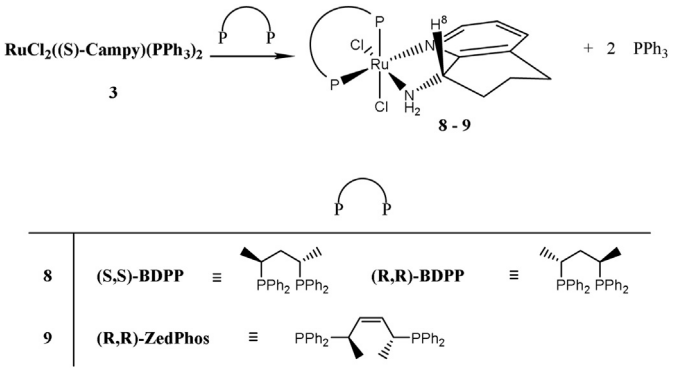


Scheme 2.

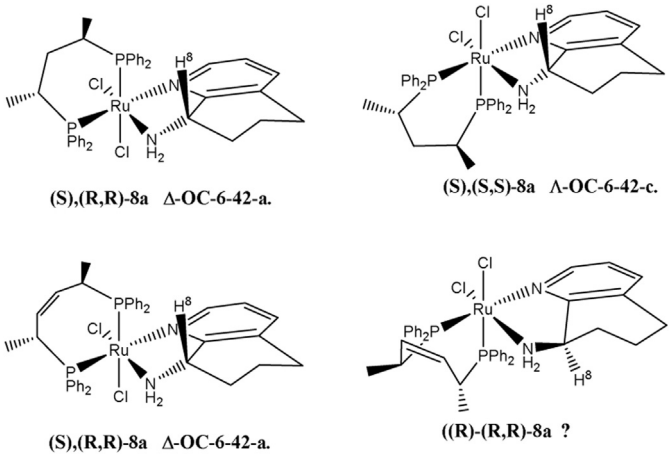


Fig. 2. Complexes configuration assigned by NMR spectroscopy.

cromofores, in spite of the complexes are distereoisomers. This behaviour implies that the chirality at the metal atom is dictated essentially by the chelating phosphine; as confirmed by the almost superimposable CD spectra of **(*S*),(*S*,*S*)-8** and **(*R*)-(*S*,*S*)-8**.

Cis-(*R*,*R*)-2,5 bis(diphenylphosphino)-3-hexene, (*R*,*R*)-ZEDPHOS [27], is a ligand that combines the easiness of synthesis of ligands based on stereogenic sp^3 carbon atoms with the tendency to chelate metal in an octahedral geometry, typical of the aromatic di-aryl and diheteroaryl diphosphines [34,35] with C_2 axial chirality. As expected (*R*,*R*)-ZEDPHOS is flexible enough to evolve to *cis* complexes. This ligand was used to reduce the precursor of 4-acetoxy-2-azetidinone with good enantioselectivity [36].

(*S*)-CAMPY reacts with $[RuCl_2(PPh_3)_3]$ **1** and (*R*,*R*)-ZEDPHOS in refluxing toluene to give **(*S*)-(*R*,*R*)-9** as a single diastereomer; the ^{31}P NMR shows only an intense AB system at 56.00 and 47.20 ppm ($J = 32.8$ Hz). $^{13}C-^{1}H$ HSQC, $^{1}H-^{31}P$ HMBC, and NOE between the H* at 2.75 ppm and the aryl proton at 7.35 ppm (phosphorus *trans* to a chloride atom), unambiguously indicate that **(*S*)-(*R*,*R*)-9** is **Δ-OC-6-42-a** (Fig. 2).

On the contrary the reaction of (*R*)-CAMPY with **1** and (*R*,*R*)-ZEDPHOS leads to the formation of a mixture of complexes; in ^{31}P NMR spectra there are three AB systems at 58.38 and 46.38 ppm ($J = 32.4$ Hz) (ca. 75%), 50.57 and 47.85 ppm ($J = 31.2$ Hz) (ca. 20%) and 57.45 and 42.29 ppm($J = 31.1$ Hz)(ca. 5%). The 7.5:2:0.5 ratio does not change even after prolonged reflux in 2-propanol. The complexity of ^{1}H and ^{13}C spectra does not allow a certain appointment of the stereochemistry. Fig. 3 shows the CD spectra of **(*S*)-(*R*,*R*)-9** and **(*R*)-(*R*,*R*)-9**; **(*S*)-(*R*,*R*)-9** (or **Δ-OC-6-42-a**) presents a strong negative CD at 370 nm while the thermodynamic mixture of **(*R*)-(*R*,*R*)-9** gives an almost flat CD confirming that it is a mixture of distereoisomers of opposite configuration at the metal.

Asymmetric transfer hydrogenation (ATH)

The results of ATH of different aryl ketones are summarized in Table 1; generally (*S*) chirality of CAMPY and diphosphines in (*R*,*R*) configuration gives the better matching; (*R*) and (*R*,*R*) chiralities give rise to a more or less pronounced mismatching .

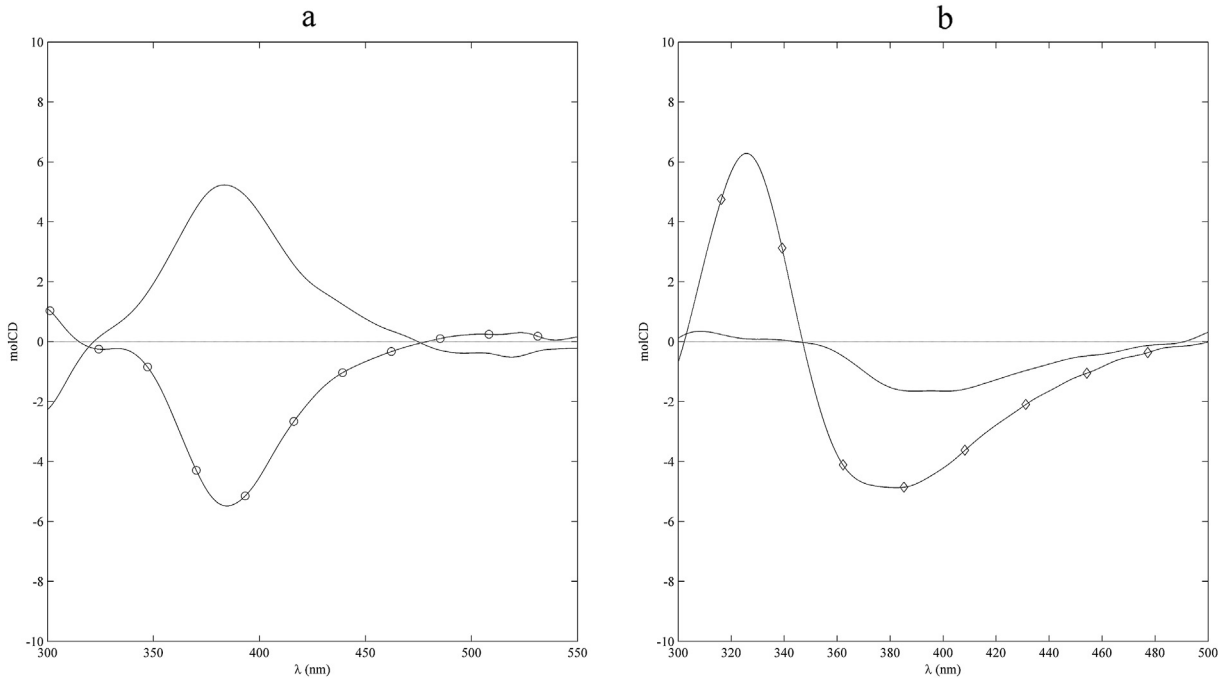


Fig. 3. a) CD spectra of complexes **(*S*),(*R*,*R*)-8** (-·-) and **(*S*),(*S*,*S*)-8** (—). b) CD spectra of complexes **(*S*)-(*R*,*R*)-9** (-◇-) and **(*R*)-(*R*,*R*)-9** (—).

(*R*,*R*)-BDPP gives a single diastereomeric precatalyst either with (*S*) or (*R*)-CAMPY and the precatalyst composition reflects the catalytic activity: **(*S*),(*R*,*R*)-8** reduces acetophenone 10a to (*R*)-1-phenylethanol **11a** in 90% e.e.(entry 1); **(*R*),(*R*,*R*)-8** gives (*R*)-1-phenylethanol **11a** in 88% e.e.(entry 3). At 82 °C (refluxing 2-propanol) **(*S*),(*R*,*R*)-8** maintains almost the same stereoselectivity (88%); **(*R*),(*R*,*R*)-8** gives also (*R*)-**11a** but in 76% e.e. (entries 1,3 vs 2,4). The same matching/mismatching operates also in the reduction of *o*-tolylacetophenone **10a**; **(*S*),(*R*;*R*)-8** gives *o*-tolyl-1-ethanol **11b** in 97% e.e. while **(*R*),(*R*,*R*)-8** gives (*R*)-**11b** in 40% e.e. (entries 11 and 12).

The different stereoselectivities are connected also to the different catalytic activities: **(*S*),(*R*,*R*)-8** reduces **10a** an **10b** with TOF 19,000 and 1600 respectively, the mismatched **(*R*),(*R*,*R*)-8** reduces the same substrates with TOF 3300 and 400.

(*S*),(*R*,*R*)-8 reduces 3,5-threfluoromethylacetophenone **10c** to (*R*)-**11c** in 83% e.e. (entry 16) and *m*-methoxyacetophenone **10d** to the corresponding alcohol (*R*)-**11d** with a stereoselectivity higher than 99% (entry 21).

The effects of matching/mismatching are dramatically enhanced with (*R*,*R*)-ZEDPHOS as co-ligand. **(*S*),(*R*,*R*)-9** reduces acetophenone **10a** to (*R*)-**11a** in 97% e.e. at 40 °C and in 94% e.e. at 82 °C; **(*R*),(*R*,*R*)-9** gives (*R*)-**11a** with a modest 9% e.e. at 82 °C but gives the opposite (*S*)-**11a** enantiomer in 63% e.e. at 40 °C and in 76% e.e. at 10 °C (entries 6–10).

(*S*),(*R*,*R*)-9 reduces **10b** to (*R*)-**11b** with stereoselectivity higher than 99% (entry 13), it reduces **10c** and **10d** to (*R*)-**11c** and (*R*)-**11d** in 96 and 98% e.e. respectively (entries 18 and 19). The mismatched **(*R*),(*R*,*R*)-9** reduces **10b** to (*S*)-**11b** and **10c** to (*S*)-**11c** in 22 and 28% e.e. respectively (entries 15 and 20).

The 7.5:2:0.5 diastereomeric composition of **(*R*),(*R*,*R*)-9** *precatalyst* does not change with the temperature. The decrease or even the inversion of configuration with the **(*R*),(*R*,*R*)-9** *precatalyst* could be due to the variation of the composition of the hydridic intermediates or to a different influence of the temperature on the ATH rates of the different hydrides.

It should be noted that **(*S*),(*R*,*R*)-9** is always twenty times more reactive than **(*R*),(*R*,*R*)-9**; TOF changes from 8100 to 500 in the reduction of **10a** (entry 6 and 9) at 40 °C, from 6400 to 300 for **10b** (entry 13 and 15) and from 6000 to 150 for **10c** (entry 18 and 20).

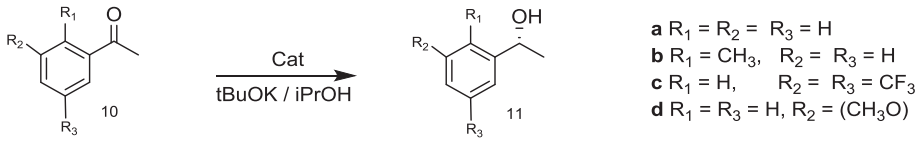
Noyori and co-workers proposed a well-defined metal-ligand bifunctional catalytic mechanism which operates in hydrogenation with H_2 but that is supposed to operate also when organic hydrogen donors like 2-propanol replace H_2 gas. The mechanism was clarified in detail for *trans*-[Ru(Binap)(diamine)H_2]; in this work we deal with *cis*-[Ru(diphesphine)(diamine)Cl_2] complexes with definite stereochemistry and diastereomeric composition that it represents the thermodynamic fate in the synthesis of the precatalysts.

Notwithstanding we were unable to prepare the dihydrides of matching/mismatching complexes *c*-**8** and *c*-**9**.

The hydride **OC-6-54-a (S)-5** reduces **10a** to (*R*)-**11a** in 45% e.e. with a TOF of about 11,000. An excess of *t*-BuOK is essential, otherwise the monohydride is unreactive also under H_2 atmospheres. The structure *in solution*, determined by NMR shows a strong NOE between H* and the hydride, one of the hydrogens on the NH_2 must be forced into an equatorial position, rather far from the hydride and thus inactive; as a consequence the axial proton must overlook a chloride atom. Under these conditions a base is necessary to convert the chloride into an hydride.

The precatalysts **(*S*),(*R*,*R*)-8**, **(*R*),(*R*,*R*)-8**, **(*S*),(*R*,*R*)-9** are composed by single diastereomer, the negative CD band around 400 nm (positive for **(*R*)-(*S*,*S*)-8**) indicates that the complexes are chiral not racemic at the metal centre; on the contrary the

Table 1
Catalytic asymmetric transfer hydrogenation of ketones.



Substrate	Complex	Entry	Temperature	Conv.% (min.)[a]	TOF (h^{-1})[b]	e.e.% (conf.)[a]
10a	**(*S*),(*R*,*R*)-8**	**1**	40 °C	92 (20)	$1.9\cdot10^4$	90 (*R*)
		2	82 °C	94 (2)	$5.3\cdot10^4$	88 (*R*)
	(*R*),(*R*,*R*)-8	**3**	40 °C	84 (20)	$3.3\cdot10^3$	88 (*R*)
		4	82 °C	85 (20)	$9.5\cdot10^3$	76 (*R*)
	(*S*)-(*R*,*R*)-9	**5**	10 °C	50 (300)		96 (*R*)
		6	40 °C	94 (10)	$8.1\cdot10^3$	97 (*R*)
		7	82 °C	95 (3)	$3.6\cdot10^4$	94(*R*)
	(*R*)-(*R*,*R*)-9	**8**	10 °C	16 (300)		76 (*S*)
		9	40 °C	52 (60)	500	63 (*S*)
		10	82 °C	57 (60)	600	9 (*R*)
10b	**(*S*),(*R*,*R*)-8**	**11**	40 °C	85 (60)	$1.6\cdot10^3$	97 (*R*)
	(*R*),(*R*,*R*)-8	**12**	40 °C	40 (60)	400	40 (*R*)
	(*S*)-(*R*,*R*)-9	**13**	40 °C	98 (40)	$6.4\cdot10^3$	>99 (*R*)
		14	82 °C	78 (20)	$1.6\cdot10^4$	93 (*R*)
	(*R*)-(*R*,*R*)-9	**15**	40 °C	37 (120)	300	22 (*S*)
10c	**(*S*),(*R*,*R*)-8**	**16**	40 °C	>99 (40)	$2.5\cdot10^3$	83 (*R*)
		17	82 °C	>99 (3)	$1.8\cdot10^4$	82 (*R*)
	(*S*)-(*R*,*R*)-9	**18**	40 °C	>99 (10)	$6\cdot10^3$	96 (*R*)
		19	82 °C	>99 (0.9)	$6\cdot10^4$	92 (*R*)
	(*R*)-(*R*,*R*)-9	**20**	40 °C	14 (120)	150	28 (*S*)
10d	**(*S*),(*R*,*R*)-8**	**21**	40 °C	96 (200)	500	>99 (*R*)
		22	82 °C	>99 (20)	$5.3\cdot10^3$	86 (*R*)
	(*S*)-(*R*,*R*)-9	**23**	40 °C	93 (10)	$1\cdot10^4$	98 (*R*)
		24	82 °C	94 (3)	$5.5\cdot10^4$	93 (*R*)

Conditions: reaction carried out at 40 or 82 °C, ketone solution 0.16 M in 2-propanol, sub/base/cat = 1000:50:1.
[a] Determined by GC analysis.
[b] TOF = turn over frequency at 50% of conversion (mmol of product on mmol of catalyst per hour).

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mismatching in (***R***),(***R***,***R***)**-9** gives rise to a mixture of diastereomers and to an almost flat CD spectrum. *If the catalysts maintain the cis configuration during the catalytic cycle, hypothesis not conflicting with the outer sphere mechanism* [14] only the chlorine *trans* to the phosphorus and closed to the axial proton of NH_2 could give a catalytically active hydride but in any case the complex is chiral at the metal centre. Asymmetric catalysis remains however a kinetic phenomenon and differences in stereoselectivity should be explained by the different reaction rates between a chiral configurationally stable hydride and the prochiral face of the substrate.

Conclusion

We were able to obtain diastereomer, enantiomers at metal centre, in steterochemically pure form using BDPP and CAMPY. In the matching combination, (*S*)-CAMPY/(*R*,*R*)-BDPP, the precatalysts gave enantioselectivities from 82 to more than 99% e.e. depending on the substrate, while in mismatching one the catalyst gave lower enantioselectivities and the reactivity is more than twenty time lower in respect to the matching one. With (*R*,*R*)-ZEDPHOS the matching combination with (*S*)-CAMPY gave enantioselectivities from 93 to 99% e.e., whereas in the mismatching we obtained a diastereomeric mixture which gave lower enantioselectivities and even opposite stereochemistry. It is likely that, with this kind of catalyst in which the outer sphere mechanism is operating, the stereoselectivity depends on the reaction rates between active specie and substrate but also, and perhaps to a greater extent, on a configurationally stable chiral metal centre. We are aware that an answer will probably arrive only from a computational study. Work is in progress towards this direction.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2014.06.016.

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