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"In situ" Activation of Racemic Ru^{II} Complexes: Separation of *trans* and *cis* Species and Their Application in Asymmetric Reduction

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Ruthenium(II) dichlorides with racemic atropos-biaryl-based diphosphanes and optically active 1,2-diphenylethane-1,2-diamine (DPEN) as ligands have been synthesised. *trans* and *cis* isomers were formed due to the low basicity of the diphosphane ligands, in particular, with BITIANP and BIMIP. The *trans* and *cis* species were easily separated by filtration. In particular, when *rac*-BITIANP was used in combination with chiral DPEN, the asymmetric separation of optically pure complexes in *cis* and *trans* arrangements was realised and they were used as precatalysts in the asymmetric hydrogenation of ketones. Matching and mismatching combinations exhibited different performances.

Introduction

In the past, asymmetric homogeneous catalysis was based on the use of transition-metal complexes as catalysts in which the source of chirality was often only a phosphorus ligand.[1,2] Over the last two decades, Noyori and co-workers[3–8] have introduced new catalytically active Ru^{II} complexes characterised by the combination of a chiral diphosphane and a chiral chelating diamine. These two ligands cooperatively accelerate the reaction rate and also control the enantiofacial selectivity. These types of complexes are very suitable as catalysts for the asymmetric hydrogenation of acetophenone-like ketones,[9–12] the corresponding alcohols of which are important building blocks for industrial and pharmaceutical applications.

However, one drawback of this ground-breaking discovery is the expense of isolating the two chiral enantiopure ligands. One of the best methodologies for reducing costs without changing the high quality results is to use metal complexes bearing a racemic ligand in combination with non-racemic auxiliaries, which are essential for the enantiomer/diastereoisomer selective activation of the racemic Ru^{II} pre-catalysts. This strategy is based on the assumption that the interaction between the two ligands is irreversible and on the relative turnover frequencies of the diastereoisomers.[13,14]

One possibility that has been explored is the resolution of Ru^{II} pre-catalysts by using a chiral diphosphane as resolving agent starting from an achiral diamine precursor in combination with $[RuCl_2(PPh_3)_3]$.[15]

A more economic methodology for the asymmetric activation of racemic Ru^{II} complexes has successfully been realised by employing a chiral diamine in the presence of racemic diphosphanes.[14,16] This strategy has been applied to the resolution of atropoisomeric diphosphanes belonging to the BINAP family.

Atropoisomeric diphosphanes represent a class of phosphorus ligands that have been established as being extremely efficient in the asymmetric hydrogenation of a wide range of substrates, particularly aryl and heteroaryl ketones.[17–22] The classic method reported for isolating these ligands in enantiopure form involves oxidation followed by selective precipitation of the diphosphane oxides in the presence of dibenzoyltartaric acid. However, this approach is usable only in the resolution of diphosphanes of relatively low acidity and has been successfully applied to BINAP and to the more basic members of a class of diphosphanes derived from the condensation of heteroaryl rings such as Tetra-Me-BITIOP and Tetra-Me-BITIANP (Figure 1).[23–26] The technique involving the use of dibenzoyltartaric acid as resolving agent failed when applied to the oxides of less basic atropoisomeric ligands such as BITIANP, BICUMP, BISCAP and BIMIP. We therefore focused our attention on BITIANP and BIMIP and in particular on the asymmetric activation of the corresponding Ru^{II} complexes formed by these last racemic atropoisomeric diphosphane ligands, employing the resolving ability of the chiral diamine 1,2-diphenylethane-1,2-diamine (DPEN). Furthermore, we highlighted the possibility of forming the

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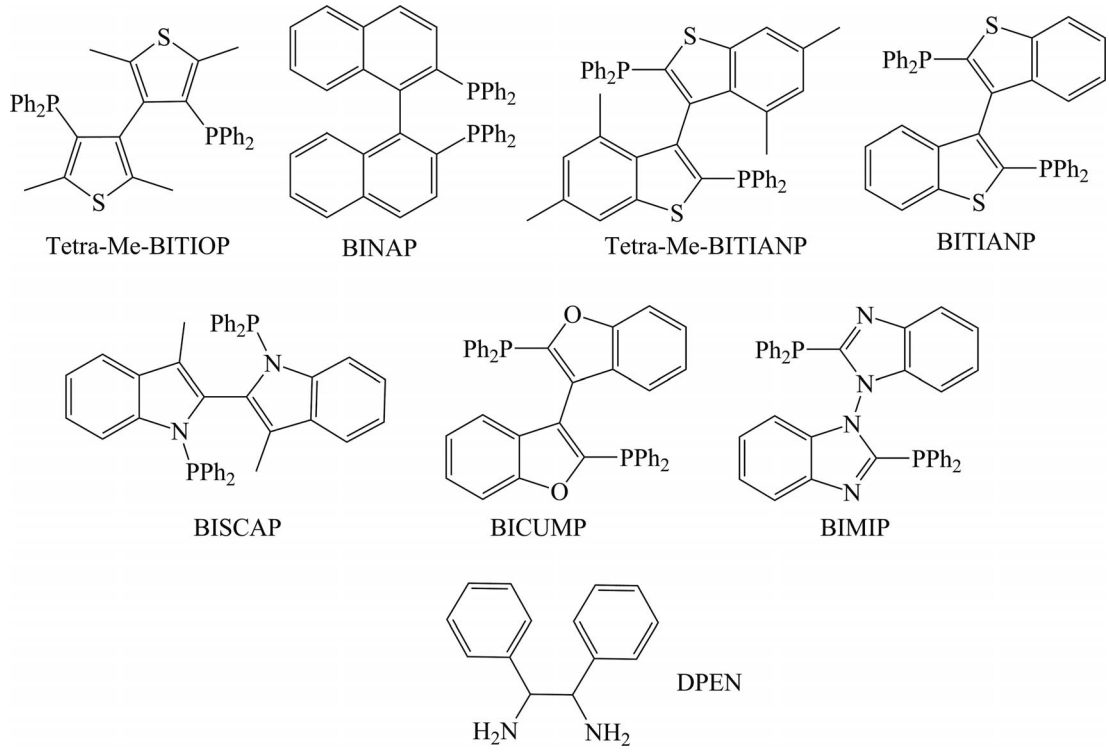


Figure 1. Atropoisomeric diphosphanes and the chiral diamine DPEN.

thermodynamically favoured *cis* isomers by exploiting the different electronic properties of these diphosphanes in combination with DPEN in analogy and/or in comparison with the studies of James[27,28] and Noyori and their co-workers.[14]

Results and Discussion

On consideration of the electronic properties of the atropoisomeric diphosphanes and on the basis of the method of Henderson and Streuli,[29,30] the basicities of the diphosphanes were evaluated by titration in nitromethane.[31] The pK_a values were determined to have an error of ±0.2 units. According to this method, the pK_a for PPh_3 is 2.7 and that of BINAP is 2.9. Table 1 reports the pK_a values of the biheteroaromatic atropoisomeric ligands, which show a linear relationship with the electrochemical oxidative potentials, previously determined in acetonitrile by voltammetry with the Ag/Ag^+ electrode as reference (Figure 2).[25]

Table 1. pK_a values of some atropoisomeric diphosphanes.[a]

Diphosphane	pK_a	$E°$ [V]
Tetra-Me-BITIOP	3.8	0.57
BINAP	2.9	0.63
Tetra-Me-BITIANP	1.2	0.76
BITIANP	1.1	0.83
BISCAP	0.7	0.90
BICUMP	–0.1	1.03
BIMIP	<–1.6	1.15

[a] Measurements realised in nitromethane at 50 °C.

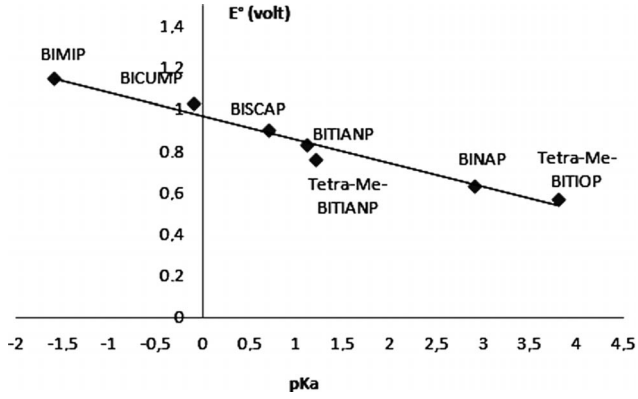


Figure 2. Linear relationship between the pK_a values and the oxidative potentials of the heteroaromatic atropisomeric diphosphanes and BINAP.

The data show that the electron-rich Tetra-Me-BITIOP has a high basic strength whereas the electron-poor BIMIP is relatively acidic (Figure 2). The same relationship was evinced by comparing the chemical shifts in the ^{31}P NMR spectra of the free ligands and the corresponding pK_a values: the chemical shift of the phosphorus atoms in the electron-rich and more basic Tetra-Me-BITIOP is at δ = –20.02 ppm, whereas the chemical shift of the phosphorus atoms in the electron-poor and less basic BIMIP is at δ = –28.08 ppm. The signal of the intermediate BITIANP is at δ = –24.06 ppm. All the ^{31}P NMR spectra were recorded in C_6D_6.

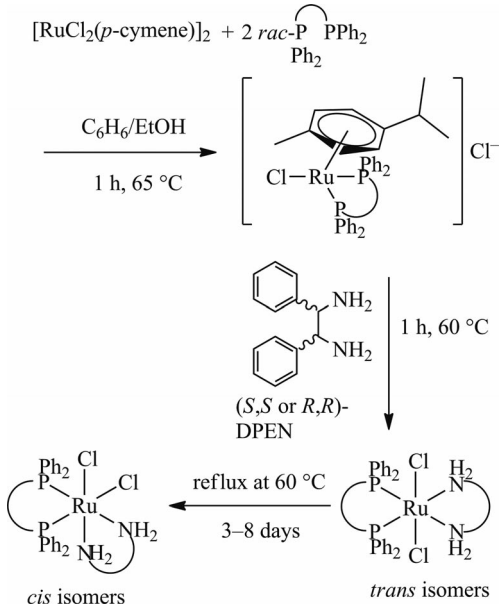
James and co-workers[27,28] observed that BINAP is able to form *cis* Ru^{II} complexes when combined with different

diamines, whereas only *trans* species were evinced with DPEN, as reported by Noyori and co-workers.[14] Thus, the possibility of forming *cis* and/or *trans* complexes from combinations of these biheteroaromatic diphosphanes and DPEN was evaluated.

We focused our attention on Tetra-Me-BITIOP and BIMIP, placed at either end of the scale above, and BITIANP, which is in the middle. This methodology was particularly interesting if applied to racemic mixtures of BIMIP and BITIANP with the aim of bypassing the problems connected with their resolution in enantiomerically pure form.

Note that the more acidic members of this family have never been resolved by the classic method, their corresponding oxides selectively forming precipitates in the presence of dibenzoyltartaric acid.

As a starting material for the synthesis of Ru^{II} complexes bearing atropoisomeric ligands and diamines, $[RuCl_2(p\text{-cymene})]_2$ was the best choice for two main reasons. The first being that the arene ligands are easily removed from the complex leading to the formation of coordinatively unsaturated species and secondly for its capacity to form the corresponding Ru^{II}–diphosphane complexes in high yields and purity.[32] The $[Ru^{II}$(diphosphane)(diamine)] complexes were synthesised as shown in Scheme 1.



Scheme 1. Synthesis of Ru^{II} complexes.

The formation of the *trans* complexes and their potential isomerisation to the thermodynamically favoured *cis* species[16] were evaluated by ^{31}P NMR spectroscopy. As expected for the more basic diphosphane, *rac*-Tetra-Me-BITIOP, only *trans* complexes were formed (two singlets at δ = 46.9 and 47.1 ppm by ^{31}P NMR) with no evidence for the formation of *cis* complexes even after heating the solution at reflux at 60 °C for several weeks.

When the least basic *rac*-BIMIP was used as the ligand, the addition of enantiopure DPEN to $[RuCl_2$(diphosphane)(*p*-cymene)] led rapidly and quantitatively to the formation of two isomers corresponding to *trans* complexes. After heating at reflux for 2 h the two *trans* isomers had partially converted into the thermodynamically favoured isomers with a *cis* arrangement of the chloride ligands.

In the ^{31}P NMR spectra of $[RuCl_2$(BIMIP)(DPEN)], the *trans* isomers are represented by two singlets (δ = 36.19 and 34.79 ppm) and the *cis* species by two pairs of doublets (δ = 49.29 and 38.51 ppm, and 48.33 and 38.38 ppm). Thus, the spectra in Figure 3 show that both *trans* isomers evolve into *cis* species in the presence of this more electron-poor ligand. After standing in solution for a week, the ratio between the two *cis* isomers reached at least 30% (Figure 3). The *cis* and *trans* species were completely separated by the slow diffusion of hexane into an ethanol-saturated solution, which led to a red precipitate. The solvent was removed by filtration to leave the *cis* isomers as a red solid and the *trans* complex was obtained as a yellow solid after concentration in vacuo.

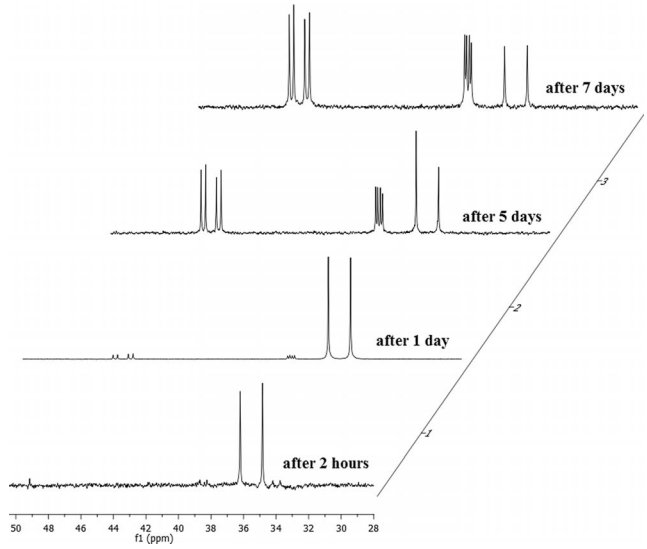


Figure 3. ^{31}P NMR spectra of $[RuCl_2$(*rac*-BIMIP)(*R*,*R*)-DPEN] from 2 h to a week.

With regard to BITIANP, this diphosphane showed intermediate behaviour compared with the other ligands in the same class, both in terms of electron properties and basicity.

Also in this case, the combination of $[RuCl_2$(*rac*-BITIANP)(*p*-cymene)] and (*R*,*R*)- or (*S*,*S*)-DPEN gave rise to the formation of *trans* isomers with signals of equal intensities in the ^{31}P NMR spectra (δ = 45.15 and 44.75 ppm). After standing in solution for 3 d at 60 °C, the *trans* isomers at δ = 44.75 ppm quantitatively converted into the *cis* species, as evinced by the presence of only one singlet at δ = 45.15 ppm and the appearance of a pair of doublets corresponding to a single *cis* isomer (δ = 59.82 and 37.76 ppm; Figure 4). The *cis* species appeared as a yellow solid precipitated in solution and thus the complete separation of the two pure isomers was easily achieved by filtration.

The assignment of the absolute configuration of the diastereopure isomer obtained with this last ligand was based

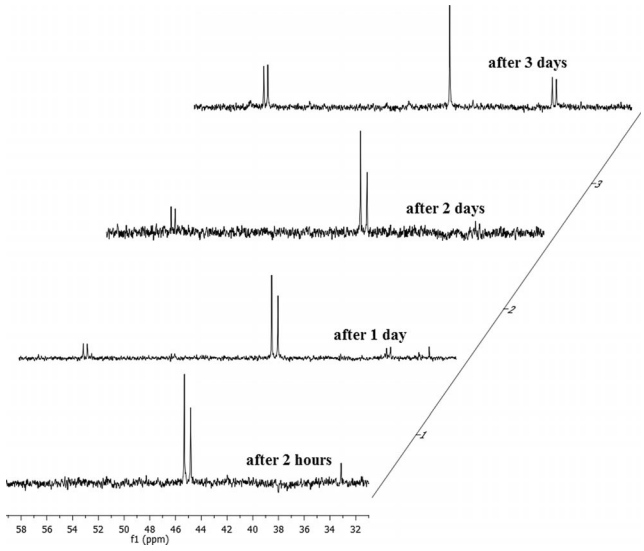


Figure 4. ^{31}P NMR spectra of [$RuCl_2$(*rac*-BITIANP)(*R*,*R*)-DPEN] from 2 h to 3 d.

on a comparison with the chiral BITIANP in the *R* configuration.

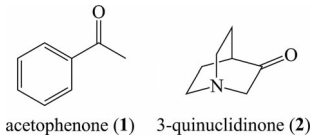
All the species obtained were utilised in the hydrogenation of a standard substrate like acetophenone **(1)** under both hydrogen transfer and asymmetric hydrogen transfer conditions. The results were comparable by both approaches in terms of enantioselectivity, although the TOFs were lower in the hydrogen transfer (3–4 h^{-1}) than in the asymmetric hydrogen transfer (40–50 h^{-1})

The results obtained for the asymmetric hydrogenation of **1** are summarised in Table 2 and are compared with the results of the hydrogenation of a pharmaceutical precursor like 3-quinuclidinone (**2**; Figure 5).[33,34]

Table 2. Asymmetric hydrogenation of **1** and **2** under hydrogen transfer conditions.[a]

	Complex	Substrate	*ee* [%][b]
1	*trans*-[$RuCl_2${(*R*,*R*)-Tetra-Me-BITIOP}{(*R*,*R*)-DPEN}]	**1**	48 (*S*)
2	*cis*-[$RuCl_2${(*R*)-BITIANP}{(*R*,*R*)-DPEN}][c]	**1**	85 (*S*)
3	*trans*-[$RuCl_2${(*S*)-BITIANP}{(*R*,*R*)-DPEN}][c]	**1**	12 (*S*)
4	*cis*/*trans*-[$RuCl_2$(*rac*-BITIANP){(*R*,*R*)-DPEN}][d]	**1**	53 (*S*)
5	*cis*-[$RuCl_2${(*R*)-BITIANP}{(*R*,*R*)-DPEN}][e]	**1**	87 (*S*)
6	*cis*-[$RuCl_2${(*R*)-BITIANP}{(*R*,*R*)-DPEN}][c]	**2**	10 (*S*)
7	*trans*-[$RuCl_2${(*S*)-BITIANP}{(*R*,*R*)-DPEN}][c]	**2**	73 (*S*)
8	*cis*-[$RuCl_2${(*R*)-BITIANP}{(*R*,*R*)-DPEN}][e]	**2**	12 (*S*)
9	*trans*-[$RuCl_2$(*rac*-BIMIP){(*R*,*R*)-DPEN}]	**1**	81 (*S*)
10	*cis*-[$RuCl_2$(*rac*-BIMIP){(*R*,*R*)-DPEN}]	**1**	80 (*S*)
11	*trans*-[$RuCl_2$(*rac*-BIMIP){(*R*,*R*)-DPEN}]	**2**	21 (*S*)
12	*cis*-[$RuCl_2$(*rac*-BIMIP){(*R*,*R*)-DPEN}]	**2**	7 (*S*)

[a] Reactions were conducted with a 0.16 M solution of the substrate (0.8 mmol) in 2-propanol in the presence of *t*BuOK (ketone/base = 1:200) at room temperature and under 10 atm of H_2 for 24 h. [b] Determined by chiral GC. [c] Pure isomer obtained by isomerisation. [d] Ratio *cis*/*trans* = 39:61. [e] Pre-catalyst containing chiral pure ligand.



acetophenone (**1**) 3-quinuclidinone (**2**)

Figure 5. Substrates used in the asymmetric hydrogenation reactions.

The asymmetric reduction of **1** with BITIANP as a ligand showed that matching and mismatching combinations of the *cis* and *trans* isomers occurred (entries 2–5). The performance of the matched and mismatched pairs markedly depends on the nature of the carbonyl substrate: in the case of the reduction of **2**, the trend was opposite to that found for **1** (entries 6–8 vs. 2 and 3).

The results obtained for the combination of *rac*-BIMIP with DPEN in the different pure forms furnished 1-phenylethanol in almost 80% *ee* in both cases (entries 9 and 10), which confirms that the interaction between the $RuCl_2$(diphosphane) complex and DPEN was almost irreversible, as in the case of TolBINAP.[9,12,14,35–37]

When 3-quinuclidinone (**2**) was reduced, the *S* configuration of 3-quinuclidinol was obtained in a modest 21% *ee* with *trans*-[$RuCl_2$(*rac*-BIMIP)(*R*,*R*)-DPEN] (entry 11) whereas the same configuration was achieved with an *ee* of 7% by using *cis*-[$RuCl_2$(*rac*-BIMIP)(*R*,*R*)-DPEN] (entry 12).

Conclusions

In accordance with the work of James and co-workers,[27] we have demonstrated that the *trans*/*cis* rearrangement of the [Ru(diphosphane)(DPEN)] is related to the electron properties and/or basicity of one of the chelating ligands.

In particular, when complexes with *rac*-BITIANP and optically pure DPEN were used, two different efficient pre-catalysts were formed, one in the *cis* and one in the *trans* arrangement of chlorides, resulting in different matching and mismatching combinations. The performances of these catalysts were studied in the hydrogenation of acetophenone (**1**) and 3-quinuclidinone (**2**) under hydrogen-transfer conditions. The effect of different substrates has been highlighted: in the reduction of **2**; matching and mismatching combinations were opposite to those observed in the reduction of **1**.

When the ligand *rac*-BIMIP was used, we achieved asymmetric activation, otherwise unrealisable by the classic method. In fact, it has been demonstrated that the less basic or more acidic ligands of this family can be resolved by using a chiral palladium complex, di(μ-chloro)bis[(*R*)-dimethyl(α-methylbenzyl)aminato-C^2N]dipalladium(II),[24] but in unacceptably low yields.

The "in situ" activation of the *cis*-Ru^{II} complexes has been achieved in the presence of two racemic heteroaromatic atropoisomeric diphosphanes with chiral DPEN. This behaviour depended on the electron properties of these ligands and differed to that of BINAP with which only *trans* isomers were formed.

Experimental Section

General: All manipulations involving air-sensitive materials were carried out in an inert atmosphere in a glovebox or by using standard Schlenk line techniques under nitrogen or argon in oven-dried glassware. All the solvents used were anhydrous. Catalytic reactions were performed in a 200 mL stainless-steel autoclave equipped with temperature control and magnetic stirrer. DPEN was obtained from commercial suppliers. Tetra-Me-BITIOP, BITIANP and BIMIP were synthesised according to literature procedures.[24,25] The ruthenium catalysts were prepared by the well-established literature procedure.[32] ^{1}H and ^{31}P NMR spectra were recorded with a Bruker DRX Avance 300 MHz spectrometer equipped with a nonreverse probe or with a Bruker DRX Avance 400 MHz spectrometer. Gas chromatography was performed with a Carlo–Erba HRGC 5160 MEGA SERIES instrument equipped with a DIMEDEB-086 chiral column (length 25 m, internal diameter 0.25 mm). MS analyses were performed with a Thermo Finnigan (MA, USA) LCQ Advantage mass spectrometer equipped with an electronspray ionisation source and an "Ion Trap" mass analyser. The MS spectra were obtained by direct infusion of a sample in MeOH/H_2O/AcOH (10:89:1) under ionisation (ESI positive).

[RuCl$_2$(*rac*-TetraMe-BITIOP){(*R*,*R*)- or (*S*,*S*)-DPEN}]: *rac*-Tetra-Me-BITIOP (11.8 mg, 0.02 mmol) was added to a solution of [RuCl$_2$(*p*-cymene)]$_2$ (6.0 mg, 0.01 mmol) in a mixture of benzene and ethanol (8 mL, 1:3) under argon and stirred for 1 h at 65 °C. (*R*,*R*)- or (*S*,*S*)-DPEN (4.26 mg, 0.02 mmol) was then added and the mixture was stirred for 1 h at 60 °C to give *trans* isomers. The solvent was removed by filtration to leave the complex as a yellow solid (17.3 mg, 89% yield). ^{31}P NMR (300 MHz, $CDCl_3$): δ = 46.99 (s), 47.10 (s) ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82–8.34 (m, 30 H, aromatic), 5.26 (m, 4 H, NH*H*CH), 4.52 (m, 2 H, NH_2CH), 4.49 (m, 2 H, NH_2CH), 3.74 (m, 2 H, N*H*HCH), 3.62 (m, 2 H, N*H*HCH), 1.88 (s, 6 H, CH_3), 1.74 (s, 6 H, CH_3) ppm. MS (ESI, +ve): calcd. for $C_{50}H_{48}N_2P_2S_2RuCl_2$ 974.12; found 938.1 [M – 2Cl]$^+$. $C_{50}H_{48}Cl_2N_2P_2RuS_2$ (974.99): calcd. C 61.59, H 4.96, N 2.87; found C 61.65, H 4.75, N 2.75.

[RuCl$_2$(*rac*-BITIANP){(*R*,*R*)- or (*S*,*S*)-DPEN}]: *rac*-BITIANP (12.68 mg, 0.02 mmol) was added to a solution of [RuCl$_2$(*p*-cymene)]$_2$ (6.0 mg, 0.01 mmol) in a mixture of benzene and ethanol (8 mL, 1:3) under argon and the mixture was stirred for 1 h at 65 °C. (*R*,*R*)- or (*S*,*S*)-DPEN (4.24 mg, 0.02 mmol) was then added and the mixture was stirred for 1 h at 60 °C. *trans* isomers were initially obtained. After 3 d at 60 °C, a solid, found to be a *cis* thermodynamically favoured species, precipitated from solution. The yellow solid *cis* species and the solution containing the *trans* isomers were separated by filtration. The *trans* complex was obtained as an orange solid after concentration in vacuo.

***cis*-[RuCl$_2${(*R*)-BITIANP}{(*R*,*R*)-DPEN}]:** Yield 7.6 mg, 38%. ^{31}P NMR (300 MHz, $CDCl_3$): δ = 59.82 (d, *J* = 38.0 Hz, *cis* isomer), 37.76 (d, *J* = 38.7 Hz, *cis* isomer) ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.74–7.89 (m, 38 H, aromatic), 4.58 (m, 2 H, NH_2CH), 3.65 (m, 2 H, NH*H*CH), 2.06 (m, 2 H, N*H*HCH) ppm..

***trans*-[RuCl$_2${(*S*)-BITIANP}{(*R*,*R*)-DPEN}]:** Yield 9.2 mg, 46%. ^{31}P NMR (300 MHz, $CDCl_3$): δ = 45.15 (s, *trans* isomer), 44.75 (s, *trans* isomer) ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76–7.93 (m, 38 H, aromatic), 4.60 (m, 2 H, NH_2CH), 3.99 (m, 2 H, NH*H*CH), 2.34 (m, 2 H, N*H*HCH) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 138.83–143.33 (C, aromatic), 121.93–134.60 (CH, aromatic), 63.25 (s, NH_2CH) ppm. MS (ESI, +ve): calcd. for $C_{54}H_{44}N_2P_2S_2RuCl_2$ 1018.08; found 983.0 [M – Cl]$^+$, 947.1 [M – 2Cl]$^+$. $C_{54}H_{44}Cl_2N_2P_2RuS_2$ (1019.00): calcd. C 63.65, H 4.35, N 2.75; found C 61.02, H 4.11, N 2.20.

[RuCl$_2$(*rac*-BIMIP){(*R*,*R*)- or *S*,*S*)-DPEN}]: *rac*-BIMIP (30.1 mg, 0.05 mmol) was added to a solution of [RuCl$_2$(*p*-cymene)]$_2$ (15.0 mg, 0.025 mmol) in a mixture of benzene and ethanol (8 mL, 1:3) under argon and stirred for 1 h at 65 °C. (*R*,*R*)- or (*S*,*S*)-DPEN (10.6 mg, 0.05 mmol) was then added and the mixture was stirred for 1 h at 60 °C. *trans* isomers were initially obtained. After a week at reflux at 60 °C, four different species were identified in the solution: two *cis* isomers and two *trans* isomers. Recrystallisation of the crude product by slow diffusion of hexane into an ethanol-saturated solution afforded a red precipitate of the *cis* species and a solution containing the *trans* isomers. The solvent was removed by filtration to leave the *cis* isomers as a red solid and the *trans* complex was obtained as a yellow solid after concentration in vacuo.

***cis*-[RuCl$_2$(*rac*-BIMIP){(*R*,*R*)-DPEN}]:** Yield 18.2 mg, 37%.^{31}P NMR (300 MHz, $CDCl_3$): δ = 49.29 (d, *J* = 34.2 Hz, *cis* isomer), 38.51 (d, *J* = 33.9 Hz, *cis* isomer), 48.33 (d, *J* = 34.3 Hz, *cis* isomer), 38.38 (d, *J* = 34.0 Hz, *cis* isomer) ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76–8.17 (m, 38 H, aromatic), 4.28 (m, 2 H, NH_2CH), 3.7(m, 2 H, NH*H*CH), 1.56 (m, 2 H, N*H*HCH) ppm.

***trans*-[RuCl$_2$(*rac*-BIMIP){(*R*,*R*)-DPEN}]:** Yield 22.19 mg, 45%. ^{31}P NMR (300 MHz, $CDCl_3$): δ = 36.19 (s, *trans* isomer), 34.79 (s, *trans* isomer) ppm. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.72–7.85 (m, 38 H, aromatic), 4.32(m, 2 H, NH_2CH), 3.99(m, 2 H, NH*H*CH), 1.71 (m, 2 H, N*H*HCH) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 133.55–140.18 (C, aromatic), 120.76–131.70 (CH, aromatic), 63.35 (s, NH_2CH) ppm. MS (ESI, +ve): calcd. for $C_{52}H_{44}N_6P_2RuCl_2$ 986.15; found 1009.2 [M + Na]$^+$, 915.3 [M – 2Cl]$^+$. $C_{52}H_{44}Cl_2N_6P_2Ru$ (986.88): calcd. C 63.29, H 4.49, N 8.52; found C 62.89, H 4.18, N 8.12.

General Procedure for the Determination of pK_a Values: The pK_a values were determined in CH_3NO_2 at 50 °C by using standard perchloric acid solutions (0.1 N) in acetic acid with a glass-calomel electrode system under an inert atmosphere. The temperature was set at 50 °C because some ligands were not completely soluble at room temperature. The relative basicities were determined through the use of $E_{1/2}$ or ΔHNP (half neutralisation potential) values.[29,30]

General Procedure for the Asymmetric Hydrogenation of Acetophenone Under Hydrogen-Transfer Conditions: Acetophenone (96 mg, 0.8 mmol) was added to the Ru complex (8×10^{-4} mmol) in a Schlenk tube sealed under argon, followed by 2-propanol (1.5 mL). Solid *t*-C_4H_9OK (4.5 mg, 0.04 mmol) and 2-propanol (3.5 mL) were then added to the Schlenk tube. The solution was stirred for 30 min and then transferred to a stainless-steel autoclave (200 mL) through a cannula. The autoclave was purged with H_2 five times, the mixture was added, then the vessel was pressurised at 25 atm, and the temperature was maintained at 25 °C. At the end of the reaction, the autoclave was opened and the mixture analysed by GC and NMR spectroscopy. GC analysis conditions: T_1 = 90 °C, rate 2 °C/min, T_2 = 120 °C for 20 min; R_t(acetophenone) = 6.47 min, R_t(*R*) = 9.05 min, R_t(*S*) = 9.3 min.

General Procedure for the Asymmetric Hydrogenation of 3-Quinuclidinone Under Hydrogen-Transfer Conditions: 3-Quinuclidinone (129 mg, 0.8 mmol) was added to the Ru complex (8×10^{-4} mmol) in a Schlenk tube sealed under argon, followed by ethanol (1.5 mL). Solid *t*-C_4H_9OK (94 mg, 0.84 mmol) and ethanol (3.5 mL) were then added to the Schlenk tube. The solution was stirred for 30 min and then transferred to a stainless-steel autoclave (200 mL) through a cannula. The autoclave, equipped with temperature control and a magnetic stirrer, was purged five times with hydrogen, after the transfer of the reaction mixture, the autoclave was pressurised at 25 atm and heated at 40 °C. At the end of the reaction, the autoclave was opened and the mixture analysed by

GC and NMR spectroscopy. GC analysis conditions: T = 120 °C for 30 min; R_t(3-quinuclidinone) = 11.31 min, R_t(R) = 22.78 min, R_t(S) = 23.56 min. ^{1}H NMR analysis of the corresponding derivatives with MPA (α-methoxyphenylacetic acid): (*S*)-(+)-MPA (1 equiv.), 4-DMAP (0.5 equiv.) and DCC (1.5 equiv.) were added to a solution of 3-quinoclidinol (1 equiv.) in $CDCl_3$ (0.75 mL).[38] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82–3.92 [m, CH, *R* configuration], 3.93–3.99 [m, CH, *S* configuration] ppm.

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