

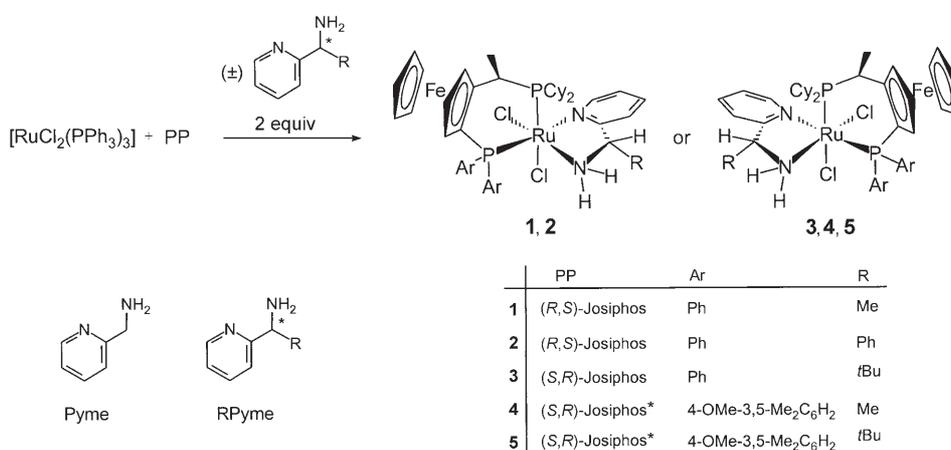
Highly Diastereoselective Formation of Ruthenium Complexes for Efficient Catalytic Asymmetric Transfer Hydrogenation**

Walter Baratta,* Giorgio Chelucci, Eberhardt Herdtweck, Santo Magnolia, Katia Siega, and Pierluigi Rigo

The development of more efficient asymmetric catalysts for organic transformations is a topic of great interest for both industrial applications and academic research.^[1] The choice of the chiral ligand for transition-metal complexes is a key factor in attaining a high level of asymmetric induction. Complexes containing two appropriate chiral ligands have been successfully employed to increase the level of enantioselectivity in catalytic reactions (the matched-ligands approach). This method is relatively tedious and requires the isolation of a library of enantiomerically pure ligands which need to be correctly assembled. A particularly successful example is the *trans*-[RuCl₂(PP)diamine] (PP = diphosphane) system in which the correct combination of chiral diphosphane and diamine ligands leads to high enantioselectivity in the catalytic hydrogenation of ketones.^[2] To overcome the problem of using two precious chiral ligands, different strategies have been developed. Efficient asymmetric catalytic systems have been obtained by reaction of a racemic metal complex, prepared from a racemic ligand, with a suitable

chiral auxiliary, leading to deactivation (chiral poisoning) or activation of one metal enantiomer species.^[3] Alternatively, efficient chiral catalysts have been prepared from a chirally flexible (tropos) ligand in combination with a rigid one.^[4]

The ligand 1-(pyridin-2-yl)methanamine (Pyme; Scheme 1) has been used in the recently developed asymmetric transfer hydrogenation and hydrogenation complexes [RuCl₂(PP)Pyme].^[5] The presence of this ligand has been proven to accelerate^[5a,6] dramatically the transfer hydrogenation^[7] of ketones relative to the most active systems



Scheme 1. Synthesis of the single ruthenium diastereomers 1–5.

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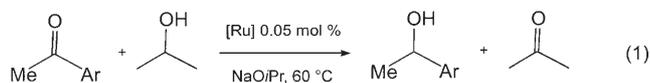
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reported to date.^[8] Therefore, fast and highly enantioselective catalytic systems are expected when chiral diphosphanes are matched with an appropriate chiral Pyme ligand. Particularly attractive are the chiral 1-substituted-1-(pyridin-2-yl)methanamines^[9] (RPyme, R = alkyl; Scheme 1) that display a stereogenic carbon center bound to the active NH₂ function.

We report herein the single-diastereomer complexes *cis*-[RuCl₂(Josiphos)RPyme], obtained by a one-pot reaction of [RuCl₂(PPh₃)₃] with a Josiphos diphosphane (1-[diarylphosphano]-2-[1-(dicyclohexylphosphano)ethyl]ferrocene) and a *racemic* mixture of RPyme (R = alkyl, Ph). These complexes catalyze the transfer hydrogenation of ketones with very high turnover frequency (TOF up to 70 000 h⁻¹) and enantioselectivity (up to 99% *ee*). To our knowledge, this is the first example in which the preparation of an efficient asymmetric catalyst with two matched chiral ligands has been greatly simplified by a step-economical synthesis that avoids the necessity of using both ligands in enantiopure form.

In situ generated *cis*-[RuCl₂((*R,S*)-Josiphos)Pyme], prepared by heating at reflux a 2-propanol solution of [RuCl₂(PPh₃)₃] and the C₁-symmetric diphosphane (*R,S*)-Josiphos (1 h) and Pyme (2 h), promotes the asymmetric transfer hydrogenation of acetophenone in basic 2-propanol at 60 °C to give (*R*)-1-phenylethanol with a high TOF (30 000 h⁻¹) and with 91 % *ee*.^[10] These results parallel those obtained with the isolated complex [Eq. (1)].



When Pyme in the above system is substituted by a racemic mixture of 1-methyl-1-(pyridin-2-yl)methanamine (MePyme; 3 equiv), complete reduction of acetophenone occurs under the same reaction conditions in 10 min, with increases in both the TOF (40 000 h⁻¹) and of the *ee* value of the *R*-alcohol (95 % *ee*) relative to the Pyme derivative. A ³¹P NMR spectroscopic control experiment reveals that the RuCl₂-(*R,S*)-Josiphos system prepared in situ reacts with (±)-MePyme (2.2 equiv) at 110 °C within 2 h, affording predominantly one set of resonances (> 95 % major isomer) attributable to the single diastereomer, *cis*-[RuCl₂((*R,S*)-Josiphos)(*S*)-MePyme] (**1**; Scheme 1).

Isolation of the thermally stable complex **1**^[11] was easily accomplished (see Experimental Section). To establish the geometry of the complex and the configuration of the coordinated MePyme ligand, an X-ray structural analysis was carried out on a single crystal of **1** (Figure 1).^[11] The ruthenium atom is in a distorted octahedral environment with the two chloride ligands *cis* relative to another, and the carbon atom C6 of the MePyme ligand has an *S* configuration. The (*S*)-MePyme ligand has a small N1-Ru-N2 angle [76.50(12)°],

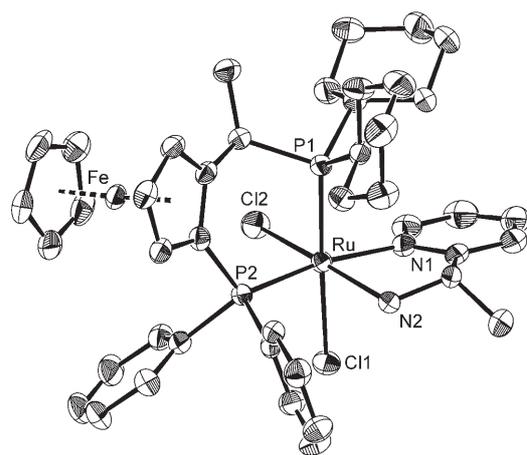


Figure 1. ORTEP drawing of **1**. Thermal ellipsoids are set at 50% probability; hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ru-Cl1 2.4868(10), Ru-Cl2 2.4453(11), Ru-P1 2.3140(10), Ru-P2 2.2854(10), Ru-N1 2.127(3), Ru-N2 2.100(3); Cl1-Ru-Cl2 89.54(3), N1-Ru-N2 76.50(12).

with the methyl substituent oriented away from the cyclohexyl groups as a result of steric hindrance.

When the RuCl₂-(*R,S*)-Josiphos system is treated with an excess of (±)-MePyme (2.5 equiv) at room temperature rather than at elevated temperature, both enantiomers of MePyme coordinate to the metal center, leading to a mixture of **1** and two [RuCl₂((*R,S*)-Josiphos)(*R*)-MePyme] diastereomers.^[12] Importantly, upon heating, these two isomeric complexes exchange the (*R*)-MePyme ligand with (*S*)-MePyme present in excess in solution, giving **1** as the sole diastereomer. This point has been established definitively using the single enantiomer (*R*)-MePyme,^[9] which reacts with the RuCl₂-(*R,S*)-Josiphos system, affording a mixture of the two diastereomers reported above. Addition of an excess of (±)-MePyme (2.5 equiv) leads to the conversion of these isomers into **1** (110 °C in 3 h), as expected. It is likely that the process of enantiomeric exchange occurring at high temperatures and leading to the thermodynamically most stable diastereomer^[5a] for the *cis* ruthenium complex **1** is due to steric effects, that is, repulsion between the methyl group of (*R*)-MePyme with a cyclohexyl substituent of the diphosphane. It should be noted that this system clearly differs from the well-known catalytic system for hydrogenation, *trans*-[RuCl₂(Tolbinap)diamine] (Tolbinap = (1,1'-binaphthalene)-2,2'-diylbis(di-*p*-tolylphosphane)), in which the coordination of the diamine is virtually irreversible and therefore the single-diastereomer complex can only be obtained using two single-enantiomer ligands.^[3e]

The complexes **2** and **3**^[11] were easily isolated in a similar fashion to **1** as single diastereomers in 81 and 71 % yield, using [RuCl₂(PPh₃)₃] in combination with (*R,S*)-Josiphos/(±)-PhPyme and (*S,R*)-Josiphos/(±)-*t*BuPyme, respectively (Scheme 1). The X-ray analysis of **2**^[11] confirms that the same arrangement observed for **1** occurs, with the phenyl group bound to a carbon in *S* configuration. Complexes **1–3** display high catalytic activity in the transfer hydrogenation of acetophenone (0.1 M; ketone/[Ru] = 2000:1) in 2-propanol in the presence of NaOiPr (2 mol %) at 60 °C, giving quantitative formation of 1-phenylethanol within a few minutes and with TOFs in the range 63 000–70 000 h⁻¹, which are among the highest values reported at this temperature (Table 1).

With compounds **1** and **2**, (*R*)-1-phenylethanol has been obtained with 96 and 95 % *ee*, respectively, whereas with **3** bearing (*S,R*)-Josiphos, the *S* enantiomer (95 % *ee*) was formed. These complexes are also efficient systems for the asymmetric reduction of other methyl aryl ketones. For example, with compound **1**, 2'-methylacetophenone and 3'-methoxyacetophenone are rapidly reduced to the *R*-alcohols with excellent enantiomeric excesses (98 and 99 % *ee*, respectively), whereas with **3**, the methyl aryl ketones having *ortho* substituents (Me, Cl, OMe) are promptly converted (TOF = 26 000–30 000 h⁻¹) into the *S* enantiomers with 97–98 % *ee* (Table 1). No decrease in enantioselectivity was observed at lower ruthenium loadings (ketone/[Ru] = 5000:1) and the *ee* value remains largely constant during the reaction and 30 min after complete conversion, suggesting that the oxidation of the chiral alcohol with the acetone formed is a slow process. It is noteworthy that complexes **1–3** can also be generated in situ using racemic RPyme ligands

Table 1: Catalytic transfer hydrogenation of methyl aryl ketones (MeCOAr) with complexes **1–5**.^[a]

| Complex | Ar | Conversion | | TOF [h ⁻¹] ^[c] | ee [%] ^[b] |
|----------|-------------------------------------|--------------------|---------|---------------------------------------|-----------------------|
| | | [%] ^[b] | t [min] | | |
| 1 | Ph | 97 | 5 | 63 000 | 96 (R) |
| 1 | 2'-MeC ₆ H ₄ | 95 | 10 | 44 000 | 98 (R) |
| 1 | 3'-MeOC ₆ H ₄ | 98 | 5 | 66 000 | 99 (R) |
| 2 | Ph | 97 | 10 | 67 000 | 95 (R) |
| 3 | Ph | 96 | 10 | 70 000 | 95 (S) |
| 3 | 2'-MeC ₆ H ₄ | 98 | 40 | 26 000 | 97 (S) |
| 3 | 2'-ClC ₆ H ₄ | 99 | 30 | 27 000 | 98 (S) |
| 3 | 2'-MeOC ₆ H ₄ | 94 | 10 | 30 000 | 97 (S) |
| 4 | Ph | 97 | 10 | 40 000 | 96 (S) |
| 5 | Ph | 97 | 10 | 34 000 | 97 (S) |
| 5 | 2'-ClC ₆ H ₄ | 99 | 30 | 24 000 | 97 (S) |
| 5 | 2'-MeOC ₆ H ₄ | 98 | 30 | 25 000 | 98 (S) |
| 5 | 3'-MeOC ₆ H ₄ | 97 | 10 | 26 000 | > 99 (S) |

[a] Conditions: MeCOAr (0.1 M), complexes **1–5** (0.05 mol%), and NaOiPr (2 mol%) in 2-propanol at 60 °C. [b] The conversion and ee values were determined by GC analysis. [c] Turnover frequency (moles of ketone converted into alcohol per mole of catalyst per hour) at 50% conversion.

and have much the same enantioselectivity as the isolated compounds. Regarding the effect of the matched/mismatched ligands in catalysis, when the single enantiomer (*R*)-MePyme is employed in combination with (*R,S*)-Josiphos, 2'-methoxyacetophenone is reduced to the *R*-alcohol with 71% ee (TOF = 15 000 h⁻¹), whereas with (*S,R*)-Josiphos, which leads to a single ruthenium diastereomer, the conversion into the *S*-alcohol occurs with both higher ee value (98%) and rate (TOF = 32 000 h⁻¹).

To extend this method to other diphosphanes, we have prepared derivatives for the asymmetric reduction of ketones containing a Josiphos ligand with bulkier aryl groups (Josiphos*). Thus, the complexes *cis*-[RuCl₂((*S,R*)-Josiphos*)(*R*)-RPyme] (R = Me (**4**), *t*Bu (**5**)),^[11] bearing 4-MeO-3,5-Me₂C₆H₂ in place of phenyl groups have been successfully isolated by treating [RuCl₂(PPh₃)₃] with (*S,R*)-Josiphos* and the corresponding (±)-RPyme (1:1.2:2.5) in dichloromethane at 20 °C, followed by heating the mixture of products to reflux in 2-propanol/heptane (1:1 in volume) overnight (Scheme 1). Preliminary results with atropis ligands show that a single ruthenium diastereomer is formed using (*R*)-MeObiphep (biphep = 6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphane)) in combination with the (±)-PhPyme ligand.^[13] Complexes **4** and **5** are found to catalyze the complete reduction of acetophenone in a few minutes under the same catalytic conditions used for **1–3**, with a high TOF (up to 40 000 h⁻¹) and a slightly higher ee value (96 and 97%) of the *S*-alcohol (Table 1). Furthermore, 2'-chloroacetophenone, and 2'- and 3'-methoxyacetophenone have been reduced to the *S* enantiomers using **5** with ee values in the range 97–99%.

It is likely that the mechanism of the transfer hydrogenation involves the [RuHX(Josiphos)RPyme] (X = H, OR') species, with β-hydrogen elimination and ketone insertion reactions,^[14] in accordance with our study on *cis*-[RuCl₂(PP)Pyme].^[15a]

In conclusion, we have described herein a practical procedure for the simple preparation of the single-diastereo-

mer catalysts *cis*-[RuCl₂(Josiphos)RPyme]—also in situ— from [RuCl₂(PPh₃)₃], Josiphos ligands, and a racemic mixture of RPyme ligands, avoiding the need for the resolution of the aminopyridine ligands. These complexes efficiently catalyze the asymmetric transfer hydrogenation of ketones with both a very high TOF (up to 70 000 h⁻¹ at 60 °C) and enantioselectivity (up to 99% ee) which is due to the correctly matched diphosphane and aminopyridine ligands. Work is in progress to extend this practical approach to other metal-catalyzed asymmetric reactions.

Experimental Section

1: Toluene (2 mL) was added to [RuCl₂(PPh₃)₃] (175 mg, 0.182 mmol) and (*R,S*)-Josiphos-C₂H₅OH (120 mg, 0.187 mmol) and the suspension was heated to reflux for 2 h. After addition of (±)-MePyme (50 mg, 0.409 mmol), the solution was heated to reflux again for a further 2 h and thereafter the solvent was evaporated. The solid was treated with 2-propanol (2 mL), and the solution was heated to reflux for 1 h, affording a yellow precipitate, which was collected by filtration and dried under reduced pressure. Yield: 89 mg (55%).

2: The synthesis of the yellow compound **2** was carried out as described for **1**, using (±)-PhPyme (75 mg, 0.407 mmol) in place of (±)-MePyme. Yield: 140 mg (81%).

3: The synthesis of **3** was carried out as described for **1**, using (*S,R*)-Josiphos-C₂H₅OH (120 mg, 0.187 mmol) and (±)-*t*BuPyme (66 mg, 0.402 mmol) in place of (±)-MePyme. The toluene solution was concentrated, and addition of pentane afforded a yellow precipitate, which was collected by filtration and dried under reduced pressure. Yield: 120 mg (71%).

4: [RuCl₂(PPh₃)₃] (50 mg, 0.052 mmol) and (*S,R*)-Josiphos* (44 mg, 0.062 mmol) were dissolved in dichloromethane (2 mL), and the solution was stirred for 2 h. After addition of (±)-MePyme (16 mg, 0.131 mmol), the solution was stirred for 1 h and the solvent was evaporated. The resulting dark oil was treated with a 2-propanol/heptane (1:1) mixture (2 mL) and the solution was heated to reflux overnight. After evaporation, the product was treated with heptane (2 mL, 1 h at reflux) to give a yellow precipitate, which was collected by filtration, washed with pentane, and dried under reduced pressure. Yield: 40 mg (77%).

5: The synthesis of the yellow compound **5** was carried out as described for **4**, using (±)-*t*BuPyme (21 mg, 0.128 mmol) in place of (±)-MePyme. Yield: 35 mg (64%).

Typical procedure for the catalytic transfer hydrogenation: The ruthenium complex (3.0 μmol) was dissolved in 2-propanol (3 mL). The ketone (2 mmol) was dissolved in 2-propanol (18.6 mL), and the solution was heated to 60 °C under argon. Addition of NaOiPr (0.1 M, 400 μL) and the solution containing the ruthenium complex (1.0 mL) led to the reduction of the ketone. The yield was determined by GC with a MEGADEX-ETTDMS-β chiral column (ketone/[Ru]/NaOiPr = 2000:1:40; 0.1 M ketone).

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- [10] [Ru]/Josiphos/Pyme = 1:1.5:1; acetophenone/Ru/NaOiPr = 2000:1:40; TOF at 50% conversion.
- [11] NMR spectroscopic data for **1–5** and the X-ray crystal analysis of **1** and **2** are provided as Supporting Information.
- [12] ³¹P{¹H} NMR spectrum in toluene with CD₂Cl₂ (10% in volume) as internal lock: δ = 61.6 (d, ²J_(P,P) = 40.9 Hz) and 41.1 ppm (d, ²J_(P,P) = 40.9 Hz), compound **1**, major product; δ = 59.2 (d, ²J_(P,P) = 38.6 Hz) and 39.2 ppm (d, ²J_(P,P) = 38.6 Hz); δ = 58.8 (d, ²J_(P,P) = 39.3 Hz) and 47.4 ppm (d, ²J_(P,P) = 39.3 Hz), minor product.
- [13] ³¹P NMR spectrum in CD₂Cl₂: δ = 49.2 (d, ²J_(P,P) = 38.5 Hz) and 46.8 ppm (d, ²J_(P,P) = 38.5 Hz).
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