Asymmetric Catalysis

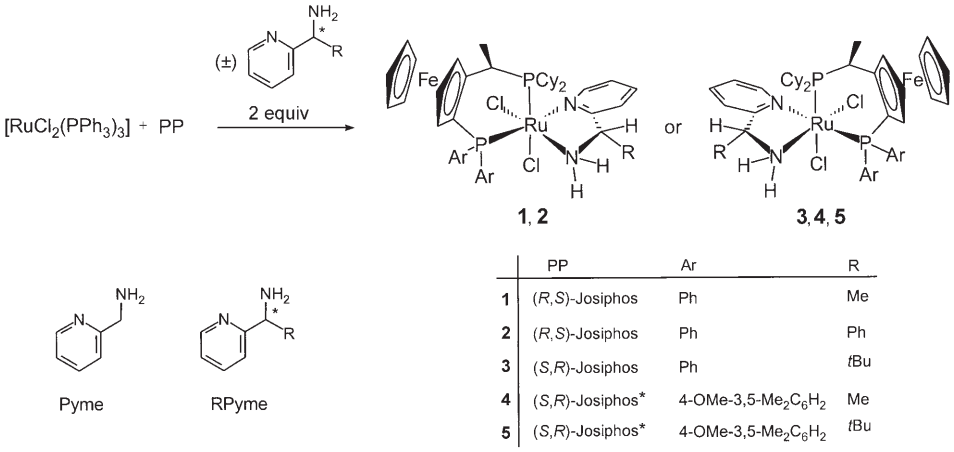
DOI: 10.1002/ange.200702278

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*-[$RuCl_2$(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 [$RuCl_2$(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 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 NH_2 function.



	PP	Ar	R
1	(*R*,*S*)-Josiphos	Ph	Me
2	(*R*,*S*)-Josiphos	Ph	Ph
3	(*S*,*R*)-Josiphos	Ph	*t*Bu
4	(*S*,*R*)-Josiphos*	4-OMe-3,5-$Me_2C_6H_2$	Me
5	(*S*,*R*)-Josiphos*	4-OMe-3,5-$Me_2C_6H_2$	*t*Bu

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

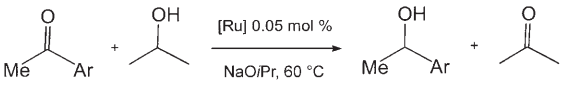
We report herein the single-diastereomer complexes *cis*-[$RuCl_2$(Josiphos)RPyme], obtained by a one-pot reaction of [$RuCl_2(PPh_3)_3$] with a Josiphos diphosphane (1-[diarylphosphano]-2-[1-(dicyclohexylphosphano)ethyl]ferrocene) and a *racemic* mixture of RPyme (R = alkyl, Ph). These complexes catalyze the transfer hydrogenation of ketones with very high turnover frequency (TOF up to 70000 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.

[*] Prof. W. Baratta, Dr. S. Magnolia, Dr. K. Siega, Prof. P. Rigo
Dipartimento di Scienze e Tecnologie Chimiche
Università di Udine
Via Cotonificio 108, 33100 Udine (Italy)
Fax: (+39) 0432-558-803
E-mail: inorg@dstc.uniud.it
Dr. G. Chelucci
Dipartimento di Chimica
Università di Sassari
Via Vienna 2, 07100 Sassari (Italy)
Dr. E. Herdtweck
Lehrstuhl für Anorganische Chemie
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)

[**] This work was supported by the Ministero dell'Università e della Ricerca (MUR). We thank Johnson-Matthey/Alfa Aesar for a generous loan of ruthenium, and Stephan D. Hoffmann (TU München) for his help during the course of the X-ray measurements.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

In situ generated *cis*-[$RuCl_2$((*R*,*S*)-Josiphos)Pyme], prepared by heating at reflux a 2-propanol solution of [$RuCl_2$-(PPh_3)$_3$] and the C_1-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)].



(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 ^{31}P NMR spectroscopic control experiment reveals that the $RuCl_2$–(*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*-[$RuCl_2$((*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)°],

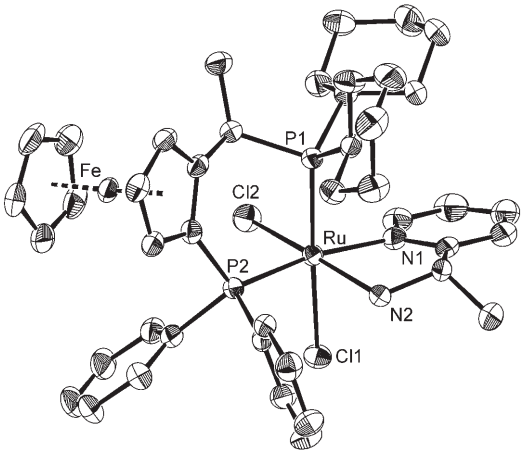


Figure 1. ORTEP drawing of **1**. Thermal ellipsoids are set at 50% probability; hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Ru-Cl1 2.4868(10), Ru-Cl2 2.4453(11), Ru-P1 2.3140(10), Ru-P2 2.2854(10), Ru-N1 2.127(3), Ru-N2 2.100(3); Cl1-Ru-Cl2 89.54(3), N1-Ru-N2 76.50(12).

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

When the $RuCl_2$–(*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 [$RuCl_2$((*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 $RuCl_2$–(*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*-[$RuCl_2$(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 [$RuCl_2$(PPh_3)$_3$] 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 NaO*i*Pr (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 [%][b]	t [min]	TOF [h^{-1}][c]	*ee* [%][b]
1	Ph	97	5	63 000	96 (*R*)
1	2′-MeC_6H_4	95	10	44 000	98 (*R*)
1	3′-$MeOC_6H_4$	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_6H_4	98	40	26 000	97 (*S*)
3	2′-ClC_6H_4	99	30	27 000	98 (*S*)
3	2′-$MeOC_6H_4$	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_6H_4	99	30	24 000	97 (*S*)
5	2′-$MeOC_6H_4$	98	30	25 000	98 (*S*)
5	3′-$MeOC_6H_4$	97	10	26 000	>99 (*S*)

[a] Conditions: MeCOAr (0.1 M), complexes **1**–**5** (0.05 mol%), and NaO*i*Pr (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*-[$RuCl_2$((*S*,*R*)-Josiphos*)(*R*)-RPyme] (R = Me (**4**), *t*Bu (**5**)),[11] bearing 4-MeO-3,5-$Me_2C_6H_2$ in place of phenyl groups have been successfully isolated by treating [$RuCl_2(PPh_3)_3$] 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 atropos 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*-[$RuCl_2$(PP)Pyme].[5a]

In conclusion, we have described herein a practical procedure for the simple preparation of the single-diastereomer catalysts *cis*-[$RuCl_2$(Josiphos)RPyme]—also in situ—from [$RuCl_2(PPh_3)_3$], 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 [$RuCl_2(PPh_3)_3$] (175 mg, 0.182 mmol) and (*R*,*S*)-Josiphos·C_2H_5OH (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·C_2H_5OH (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: [$RuCl_2(PPh_3)_3$] (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 NaO*i*Pr (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-ETTBDMS-β chiral column (ketone/[Ru]/NaO*i*Pr = 2000:1:40; 0.1 M ketone).

Received: May 23, 2007
Published online: August 27, 2007

Keywords: asymmetric catalysis · chiral resolution · hydrogen transfer · phosphane ligands · ruthenium

[1] a) *The Handbook of Homogeneous Hydrogenation*, *Vol. 1–3* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**; b) *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U, Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; c) *Comprehensive Asymmetric Catalysis*, Supplements 1–2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**;

d) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.

[2] a) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703; b) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40.

[3] a) J. W. Faller, A. R. Lavoie, J. Parr, *Chem. Rev.* **2003**, *103*, 3345; b) P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297; c) K. Muñiz, C. Bolm, *Chem. Eur. J.* **2000**, *6*, 2309; d) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, S. Matsukawa, *Acc. Chem. Res.* **2000**, *33*, 391; e) T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086; f) J. W. Faller, D. W. I. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 1217; g) K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789.

[4] K. Mikami, M. Yamanka, *Chem. Rev.* **2003**, *103*, 3369.

[5] a) W. Baratta, E. Herdtweck, K. Siega, M. Toniutti, P. Rigo, *Organometallics* **2005**, *24*, 1660; b) T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288.

[6] a) W. Baratta, P. Da Ros, A. Del Zotto, A. Sechi, E. Zangrando, P. Rigo, *Angew. Chem.* **2004**, *116*, 3668; *Angew. Chem. Int. Ed.* **2004**, *43*, 3584; b) W. Baratta, A. Del Zotto, G. Esposito, A. Sechi, M. Toniutti, E. Zangrando, P. Rigo, *Organometallics* **2004**, *23*, 6264; c) W. Baratta, J. Schütz, E. Herdtweck, W. A. Herrmann, P. Rigo, *J. Organomet. Chem.* **2005**, *690*, 5570.

[7] a) J. S. M. Samec, J. E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226; c) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201.

[8] a) P. Braunstein, M. D. Fryzuk, F. Naud, S. J. Rettig, *J. Chem. Soc. Dalton Trans.* **1999**, 589; b) H. Yang, M. Alvarez-Gressier, N. Lugan, R. Mathieu, *Organometallics* **1997**, *16*, 1401; c) P. Dani, T. Karlen, R. A. Gossage, S. Gladiali, G. van Koten, *Angew. Chem.* **2000**, *112*, 759; *Angew. Chem. Int. Ed.* **2000**, *39*, 743.

[9] For a review on the stereoselective synthesis of optically active 1-substituted-1-(pyridin-2-yl)methanamines, see: a) G. Chelucci, *Tetrahedron: Asymmetry* **2005**, *16*, 2353. For resolution processes, see: b) L. E. Iglesias, V. M. Sánchez, F. Rebolledo, V. Gotor, *Tetrahedron: Asymmetry* **1997**, *8*, 2675; c) H. E. Smith, L. J. Schaad, R. B. Banks, C. J. Wiant, C. F. Jordan, *J. Am. Chem. Soc.* **1973**, *95*, 811.

[10] [Ru]/Josiphos/Pyme = 1:1.5:1; acetophenone/Ru/NaO*i*Pr = 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] $^{31}P\{^{1}H\}$ NMR spectrum in toluene with CD_2Cl_2 (10% in volume) as internal lock: $\delta = 61.6$ (d, $^{2}J_{(P,P)} = 40.9$ Hz) and 41.1 ppm (d, $^{2}J_{(P,P)} = 40.9$ Hz), compound **1**, major product; $\delta = 59.2$ (d, $^{2}J_{(P,P)} = 38.6$ Hz) and 39.2 ppm (d, $^{2}J_{(P,P)} = 38.6$ Hz); $\delta = 58.8$ (d, $^{2}J_{(P,P)} = 39.3$ Hz) and 47.4 ppm (d, $^{2}J_{(P,P)} = 39.3$ Hz), minor product.

[13] ^{31}P NMR spectrum in CD_2Cl_2: $\delta = 49.2$ (d, $^{2}J_{(P,P)} = 38.5$ Hz) and 46.8 ppm (d, $^{2}J_{(P,P)} = 38.5$ Hz).

[14] a) O. Pàmies, J. E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052; b) A. Aranyos, G. Csjernyik, K. J. Szabó, J. E. Bäckvall, *Chem. Commun.* **1999**, 351; c) W. Baratta, G. Chelucci, S. Gladiali, K. Siega, M. Toniutti, M. Zanette, E. Zangrando, P. Rigo, *Angew. Chem.* **2005**, *117*, 6370; *Angew. Chem. Int. Ed.* **2005**, *44*, 6214.

