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Heterogenised iridium complexes for the asymmetric hydrogenation of imines

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Abstract

A method for immobilising preformed chiral homogeneous catalysts to a clay support material has been developed. The observed asymmetric induction in the hydrogenation of imines with the supported species was greater than that with the corresponding homogeneous catalysts and, on re-use, the supported species increased their enantioselectivity. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The number of applications of chiral organometallic complexes in asymmetric homogeneous hydrogenations of carbon–nitrogen double bonds has increased in the last few decades.[1] This process is a simple and convenient route to the synthesis of amines, which have long been of great interest due to their physiological activity and their potential as organic intermediates. An interesting example is the recent advances reported on the synthesis of the cough remedy active dextromethorphan, in which the key step is the asymmetric hydrogenation of C=N in a partly saturated isoquinoline with the iridium chelated by a ferrocenylphosphine ligand.[2]

However, although eventually high product enantiomeric excesses have been attained with homogeneous catalysts, the difficulties involved in separating the catalysts from the product still need to be investigated further. Not only can this cause problems for the purity of the product but it can also make it difficult to re-use the catalyst. Heterogeneous catalysts, although easily separable from the reaction mixture and easy to re-use, have only a limited use in asymmetric reactions.[3,4]

Preparing chiral catalytic systems by immobilising active transition-metal complexes on solid supports could link the potential advantages of the traditional homogeneous and heterogeneous catalysts, but since the first attempts were made,[5] there has been a general lack of success in this area. To our knowledge, the separation of the catalytic system from the products in the asymmetric

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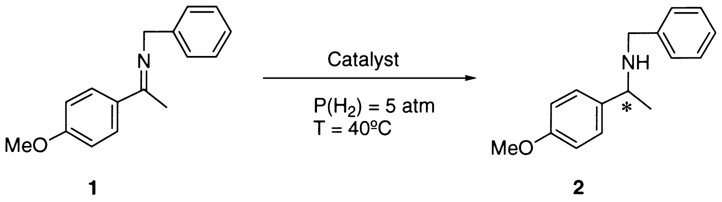
hydrogenation of imines has seldom been studied. The Ir–diphosphine complex immobilised in silicates, metal oxides or polymers,[6] and the Rh–phosphane complexes immobilised in silica gel for the stereoselective hydrogenation of folic acid[7] are the most representative approaches but little attention has been paid to the recovery and reusability of the removable catalytic systems. We have recently resolved this problem by developing efficient and reusable iridium complexes adsorbed on montmorillonite clay for a large number of recycles in the non-enantioselective hydrogenation of *N*-benzylidene aniline with a consistently high rate of activity.[8] Here we report now the behaviour of heterogenised iridium complexes in the asymmetric hydrogenation of imines.

2. Results and discussion

Preliminary homogeneous hydrogenation experiments[9a] revealed that complete conversion of *N*-(α-methyl-*p*-methoxybenzylidene)benzylamine **1** into the corresponding amine **2** could be achieved in the presence of the precursor of catalyst [Ir(COD)((*S*,*S*)-BDPP)]PF_6 **3**, at 5 atm of H_2 and 40°C (Scheme 1). The mild reaction conditions employed contrast with the drastic pressure of hydrogen (70 atm) reported in the literature for the homogeneous hydrogenation of this ketimine.[1] Despite the remarkably high activity of this catalytic species, the enantiomeric excess observed was nil (Table 1, entry 1). Although using BDPP as the chiral ligand has provided enantiomeric excesses in hydrogenation reactions, four possible conformers of a six-membered chelate ring containing metal-((*S*,*S*)-BDPP) are known to be possible,[10] two of which are achiral chair conformations with the phenyl rings in an achiral array. In the previously reported homogeneous hydrogenation of *N*-(α-methylbenzylidene)benzylamine with [Rh(COD)((*S*,*S*)-BDPP)]ClO_4 complex, e.e. of up to 54% for the (*R*)-amine enantiomer was obtained,[10b] assuming that rhodium intermediates involved in the reaction were the chiral δ-skew conformers. The lack of enantioselectivity with the analogous iridium complex [Ir(COD)((*S*,*S*)-BDPP)]PF_6 may therefore be attributed to the prevalence of the achiral chair conformations.



Scheme 1.

To test the supported catalyst on the heterogenised hydrogenation reaction, **3** was immobilised by adsorption onto montmorillonite **K-10**[11] (Scheme 2, path a).

To compare the activity and stability of the supported catalyst **K-10/3** with its homogeneous counterpart **3**, the hydrogenation of **1** was carried out under the same reaction conditions[9b] (5 atm, 40°C). The initial activity of the heterogenised catalyst was similar to that of the homogeneous system (Fig. 1), but surprisingly, asymmetic induction in favour of the (*R*)-amine enantiomer was observed (e.e. = 18% (*R*) Table 1, entry 2).

When the recovered supported catalyst **K-10/3** was used in further consecutive hydrogenation reactions, the catalyst became less active but more enantioselective on re-use (Table 1, entry 2).

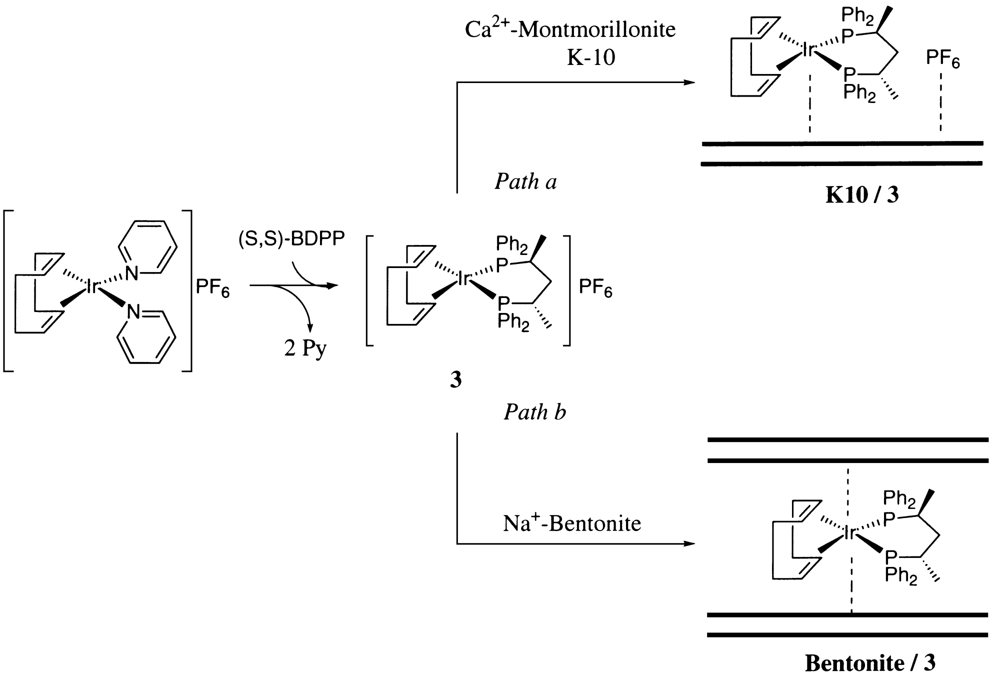
Table 1
Conversion and product e.e.s obtained on hydrogenation of the imine **1** with [Ir(COD)((*S*,*S*)-BDPP)]PF_6 adsorbed to montmorillonite **K-10**[a]

Entry	Catalyst	RUN	t(h)	%C	% e.e.[b]
1	**3**	1	24	99	0
2	K-10/**3**[c]	1	24	99	18(*R*)
		2	24	50	23(*R*)
		3	24	12	48(*R*)
		4	24	6	59(*R*)
3	K-10/**3**[d]	1	24	99	35(*R*)
		2	24	60	53(*R*)
			48	99	54(*R*)
4	**3**-O_2[e]	1	24	84	0
5	K-10/**3**-O_2[e]	1	24	96	40(*R*)
		2	24	60	53(*R*)
			48	93	53(*R*)
6	K-10/**3**[f]	1	24	99	30(*R*)
		2	24	22	50(*R*)

[a]Standard conditions: precursor of catalyst 0.05 mmol [Ir(COD)((*S*,*S*)-BDPP)]PF_6, (0.7 g of K-10/**3**); imine **1**: 2.5 mmol; metal/imine = 1/50; solvent: MeOH (10mL). [b]e.e. of amines measured by ^1H NMR spectroscopy in $CDCl_3$ using (S)-(+)-mandelic acid as chiral shift reagent. [c]Freshly prepared supported precursor of catalyst. [d]Supported precursor of catalyst stored in air for 3-4 days before reaction. [e]Freshly prepared catalyst, treated with O_2 for 10 minutes immediately before use. [f]1st run carried out with supported precursor of catalyst stored in air for 3-4 days before reaction and 2nd run with the recovered immobilised catalyst treated with O_2 for 10 minutes.

Similar asymmetric behaviour has been reported by Augustine et al.[12] for preformed chiral homogeneous catalyst anchored to montmorillonite through a heteropoly acid, in the catalytic hydrogenation of α-enamines, although so far no hypothesis has been made to explain these observations.

On the other hand, when the supported catalyst **K-10/3** was stored in a vial in air for 3–4 days before use, conversion was complete and asymmetric induction was higher than that of a freshly prepared catalyst, even on re-use (Table 1, entry 3). Surprisingly, the interaction of the catalyst with the O_2 enhances enantioselectivity. In order to gain an insight into the influence of the oxygen on the supported catalyst, we next studied the hydrogenation of **1** in the presence of the immobilised catalyst that had previously been treated with O_2 for 10 min, **K-10/3-**$\mathbf{O_2}$. Interestingly, the conversion was quantitative and the enantioselectivity the highest observed in a first run (e.e. = 40%, Table 1, entry 5), which again contrasts with the lack of enantiomeric induction on the homogeneous hydrogenation of **1** in the presence of the soluble catalyst **3** that had previously been treated with O_2 for 10 min (Table 1, entry 4). Finally, we treated the recovered immobilised catalytic system from a standard first run using **K-10/3** with O_2 in order to determine the influence of O_2 on the immobilised active catalytic species rather than on the catalyst precursor, but there



Scheme 2.

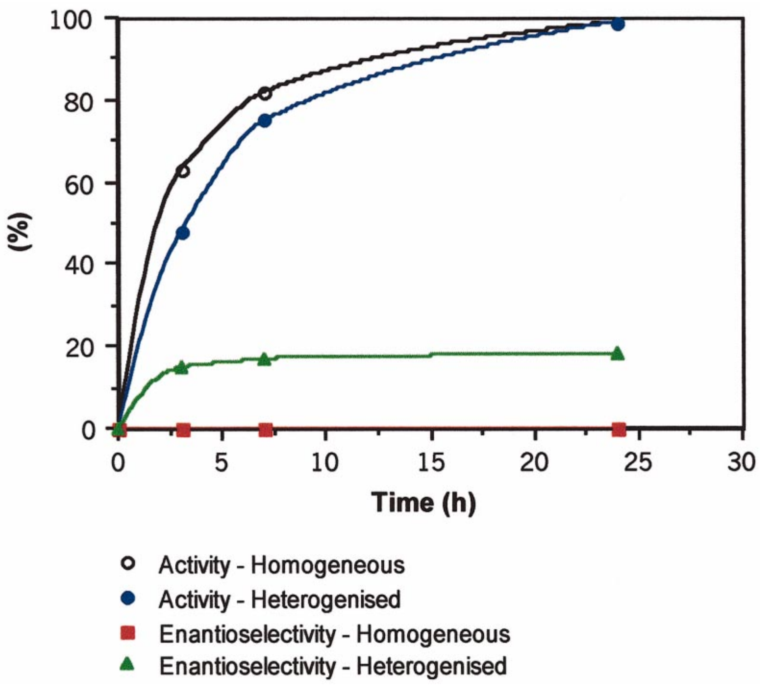


Figure 1. Catalytic activity and enantioselectivity of homogeneous and heterogenised homogeneous hydrogenation of *N*-(α-methyl-*p*-methoxybenzylidene)benzylamine **1**

was no significant increase in product e.e. in the second run (Table 1, entry 6), although the activity dropped significantly.

It seems then that the reported enhanced enantioselectivity of the immobilised catalyst appears to depend not only on the interaction of [Ir(COD)((*S*,*S*)-BDPP)]PF_6 with montmorillonite, but also on a brief exposure of this catalyst to air. The effect of the oxygen on catalyst activity and enantioselectivity has previously been observed in the heterogeneous hydrogenation of pyruvates and has been attributed to a promoted restructuring to the active surface arrangement.[13]

The drop in activity may be due to the leaching of the iridium complex. However, the amount of Ir found on the solid before and after the catalytic consecutive reactions, analysed by X-ray fluorescence (XRF) spectroscopy, does not exceed 25% of the starting adsorbed material. Also, a further hydrogenation reaction with the desorbed iridium metal species does not show any conversion from imine to amine. Therefore, the lower activity and higher enantioselectivity observed could be related to the prevalence of a more enantioselective metal–clay species than a more flexible iridium species.

Looking for the possible effect of the O_2 exposure, we took into account the oxidation of the (*S*,*S*)-BDPP as well as the removal of one of the arms of the chelating ligand. Therefore when an excess of (*S*,*S*)-BDPP (1 equiv.) was added to the **K-10/3** catalytic system to compensate the possible oxidation of a part of the diphosphine, only 10% of conversion and no variation of e.e. values were achieved in the first run (Table 2, entry 1). Also, low conversions were found when 2 equiv. of the monophosphine $PEtPh_2$ were added to the standard reaction (Table 2, entry 2) in order to coordinate the iridium complex in case of an arm-off behaviour of (*S*,*S*)-BDPP. It seems from the above results that the heterogenised hydrogenation of imines by **K-10/3** does not depend on any modification of the ligand.

Table 2
Conversion and product e.e.s obtained on hydrogenation of the imine **1** with **K-10/3** catalytic system and excess of ligand[a]

Entry	Precursor of Catalyst	RUN	%C	% e.e.[b]
1	**K-10/3**[c] + 1 eq. (S,S)-BDPP	1	10	25(R)
		2	- -	- -
2	**K-10/3**[c] + 2 eq.$PEtPh_2$	1	7	24(R)
		2	- -	- -

[a]Standard conditions: precursor of catalyst 0.05 mmol [Ir(COD)((*S*,*S*)-BDPP)]PF_6, (0.7 g de K-10/**3**); imine **1**: 2.5 mmol; metal/imine = 1/50; solvent: MeOH (10mL). [b]e.e. of amines measured by ^1H NMR spectroscopy in $CDCl_3$ using (*S*)-(+)-mandelic acid as chiral shift reagent. [c]Supported precursor of catalyst stored under air for 3-4 days before reaction.

Different supports have been used to immobilise the precursor of catalyst **3**, in order to study how the nature of the solid may affect the catalytic reaction (Table 3). Conversions and product e.e. were similar for the catalytic systems formed by **3** adsorbed on commercial montmorillonite and **3** adsorbed on a montmorillonite previously acidified with HNO_3 (which is characteristic of

Table 3
Conversion and product e.e.s obtained on hydrogenation of the imine **1** with [Ir(COD)((*S*,*S*)-BDPP)]PF_6 adsorbed to different supports[a]

Entry	Support	Treatment of Support	RUN	t(h)	%C	% e.e.[b]
1	MM-K10	--	1	24	99	18(R)
			2	24	50	23(R)
			3	24	12	48(R)
2	MM-K10	Calcined	1	24	100	25(R)
			2	24	24	41(R)
			3	48	13	66(R)
3	MM-K10	HNO_3	1	24	99	18(R)
			2	24	31	38(R)
			3	48	13	40(R)
4	Bentonite	--	1	24	29	25(R)
			2	24	24	36(R)

[a]Standard conditions: precursor of catalyst 0.05 mmol [Ir(COD)((*S*,*S*)-BDPP)]PF_6, (0.7 g of support/**3**); imine **1**: 2.5 mmol; metal/imine = 1/50; solvent: MeOH (10mL). [b]e.e. of amines measured by ^1H NMR spectroscopy in $CDCl_3$ using (*S*)-(+)-mandelic acid as chiral shift reagent.

many Brönsted centres). However, e.e.s were more enhanced when the catalytic system was **3** adsorbed to previously calcined montmorillonite (which is characteristic of many Lewis centres). There was also a marked difference in the hydrogenation activity of **Bentonite/3**, since the catalytic activity was low for a first run, but the recovered catalytic system could be reused in consecutive reactions without a significant loss of activity. This could be because **3** was immobilised to sodium bentonite via intercalation rather than via adsorption, and the Ir–(*S*,*S*)-BDPP complex immobilised into bentonite internal surface might then have a different environment (Scheme 2, path b). Similarly, recent work on the asymmetric hydrogenation of itaconates by a Rh–DIOP complex intercalated into sodium hectorite by cation exchange method[14] exhibits low activities which are associated with the more hindered arrangement for the immobilised complex than that of the complex in solution.

Despite much effort, a detailed mechanism for imine hydrogenation with cationic catalysts is still not clear.[15] That halides[15d,16] and amines[17] influence the enantioselectivity of the process has been well established but it has not been rationalised. More recently Osborn et al. also reported that sulfonate[18] (RSO_3^-) and carboxylate[19] ($OCOR^-$) anions may be responsible for a remarkably enhanced enantioselectivity with Rh–BDPP and Ir–BDPP systems for this catalytic reaction. The same authors[18] also suggested that the high product e.e.s observed in the hydrogenation of imines with monosulfonated Rh–BDPP catalytic systems[20] may be due to the intermolecular coordination of the sulfonate group to the rhodium metal during the enantioselective step.

We therefore suggest that the precursor of catalyst [Ir(COD)((*S*,*S*)-BDPP)]PF_6 immobilised in a clay becomes enantioselective in two possible ways: (a) by the formation of a different catalytic metal intermediate due to interactions with the support and/or (b) by the occupation of a coordination site on the metal by interaction with the aluminosilicate surfaces and limiting the number of diastereomeric species. Both of these possibilities lead to different mechanisms for the heterogenised and homogeneous systems.

3. Conclusions

In summary, the immobilisation of a preformed Ir–BDPP catalyst has established an alternative methodology for performing enantioselective recyclable catalytic hydrogenation of imines. Further work will evaluate the viability of this approach on re-use. Work on the heterogenised hydrogenation of imines in the presence of halides and carboxylic acids is currently in progress.

Acknowledgements

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References

1. (a) James, B. R. *Catal. Today* **1997**, *15*, 209; (b) Spindler, F.; Blaser, H.-U. *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; VCH: Weinheim, 1998; Vol. 2, pp. 69–80; (c) Blaser, H.-U.; Spindler, F. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp. 247–265; Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
2. Werbitzky, O. *Chem. and Eng. News* **1998**, *19*, 64.
3. Osawa, T.; Harada, T.; Tai, A. *Catal. Today* **1997**, *37*, 465.
4. Blaser, H.-U.; Jalett, H.-P.; Muller, M.; Studer, M. *Catal. Today* **1997**, *37*, 441.
5. (a) Dumont, W.; Poulin, J. C.; Dang. T.-P.; Kagan, H. B. *J. Am. Chem. Soc.* **1973**, *95*, 895; (b) Takaishi, N.; Imai, H.; Bertelo, C. A.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5400; (c) Takaishi, N.; Imai, H.; Bertelo, C. A.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 264; (d) Masuda, T.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 268; (e) Bailey, D. C.; Langer, S. H. *Chem. Rev.* **1981**, *81*, 109.
6. (a) Pugin, B. (Ciba-Geigy), WO97102232, 1997; (b) Pugin, B.; Sindler, F.; Müller, M. (Ciba-Geigy), USA 5,252,751, 1992; (c) Jalett, H.-P.; Siebenhaar, B. (Ciba-Geigy), WO97105095, 1997.
7. Brunner, H.; Rublak, P.; Helgel, M. *Chem. Ber.* **1997**, *130*, 55.
8. Margalef-Català, R.; Salagre, P.; Fernandez, E.; Claver, C. *Catal. Lett.* **1999**, *60*, 121.
9. (a) Homogeneous hydrogenation procedure: low-pressure hydrogenation experiments (5 atm) were carried out in a Berghof autoclave, with electric heating and magnetic stirring. In a standard experiment a solution of imine (2.5 mmol) and catalyst (0.05 mmol) in methanol (10 mL) was introduced into the evacuated autoclave and heated with stirring. Once the system had reached thermal equilibrium, hydrogen was introduced to reach the working pressure. At the end of the reaction, the system was allowed to cool and the gas vented. The reaction mixture was then analyzed by GC and ^{1}H NMR spectroscopy. (b) Heterogenised homogeneous hydrogenation procedure: low-pressure hydrogenation experiments (5 atm) were carried out in a Berghof autoclave, with electric heating and magnetic stirring. In a standard experiment a solution of imine (2.5 mmol) in methanol (10 mL) was introduced into the evacuated autoclave, which contains 0.05 mmol of the immobilised catalyst, and heated with stirring. Once the system had reached thermal equilibrium, hydrogen was introduced to reach the working pressure. At the end of the reaction, the system was allowed to cool and the gas vented. The reaction mixture was then filtered off and while the solution was analyzed by GC and ^{1}H NMR spectroscopy, the solid was washed with methanol and introduced into the autoclave for a consecutive hydrogenation.
10. (a) MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273; (b) Bakos, J.; Töth, I.; Heil, B.; Szalontai, G.; Párkányi, L.; Fülöp, V. *J. Organomet. Chem.* **1989**, *370*, 263–276.

11. Adsorption of [Ir(COD)((*S*,*S*)-BDPP)]PF_6 onto the clay. The dichloromethane solution (10 mL) of [Ir(COD)((*S*,*S*)-BDPP)]PF_6 (723 mg, 0.08 mmol) was added into a suspension of montmorillonite **K-10** (0.93 g) in desoxygenated dichloromethane (10 mL), followed by stirring for 24 h under nitrogen at room temperature. After the reaction the suspension was filtered off, washed with dichloromethane and dried in vacuo to analyze the amount of complex adsorbed on the clay.
12. Augustine, R. L.; Tanielyan, S. K.; Anderson, S.; Yang, X. *Conference Chira Tech*. **1998**.
13. Augustine, R. L.; Tanielyan, S. K. *J. Mol. Catal.* **1997**, *118*, 79–87.
14. Sento, T.; Shimazu, S.; Ichikuni, N.; Uematsu, T. *J. Mol. Catal.* **1999**, *137*, 263–267.
15. (a) Longley, C. J.; Goodwin, T. J.; Wilkinson, G. *Polyhedron* **1986**, *5*, 1625; (b) Fryzuk, M. D.; Piers, W. E. *Organometallics* **1990**, *9*, 986–998; (c) Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kutney, J. P.; Kang, G.-J.; Herb, G.; Thorburn, I. S.; Spogliarich, R. *J. Mol. Catal.* **1990**, *62*, 243–253; (d) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002.
16. (a) Sablong, R.; Osborn, J. A.; Faller, J. W. *J. Organomet. Chem.* **1997**, *527*, 65–70; (b) Vastag, S.; Bakos, J.; Tórös, S.; Takach, N. E.; King, B. r.; Heil, B.; Markó, L. *J. Mol. Catal.* **1984**, *22*, 283; (c) Kang, G.-J.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kutney, J. P. *J. Chem. Soc.*, *Chem. Commun.* **1988**, 1466; (d) Spindler, F.; Pugin, B.; Blasser, H. U. *Angew. Chem.*, *Int. Ed. Engl.* **1990**, *29*, 558; (e) Spindler, F.; Pugin, B. (Ciba-Geigy), EP A-0256982; (f) Sablong, R.; Osborn, J. A.; Spindler, F. (Ciba-Geigy), WO 97/05094, 1997.
17. Tani, K.; Onouchi, J.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955–956.
18. Buriak, J. M.; Osborn, J. A. *Organometallics* **1996**, *15*, 3161.
19. Sablong, R.; Osborn, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3059–3062.
20. (a) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc.*, *Chem. Commun.* **1991**, 1684; (b) Bakos, J. *Aqueous Organometallic Chemistry and Catalysis*, NATO ASI Series 3, High Technology, **1994**, *15*, 231; (c) Lensink, C.; de Vries, J. G. *Tetrahedron: Asymmetry* **1992**, *3*, 235.