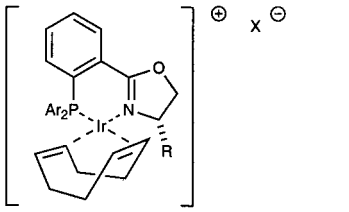
[16] M. Hoffmann, *Synthesis* **1988**, 62 – 64.
[17] a) Y. Kajihara, K. Koseki, T. Ebata, H. Kodama, H. Matsusita, H. Hashimoto, *Carbohydr. Res.* **1994**, *264*, C1 – C5; b) Y. Kajihara, K. Koseki, T. Ebata, H. Kodama, H. Matsusita, H. Hashimoto, *J. Org. Chem.* **1995**, *60*, 5732 – 5735.
[18] For details of the measurement of the $K_i$ values, see ref. [7a].
[19] Commercially available from Aldrich.
[20] Investigation of inhibition with a recombinant rat liver $\alpha$(2-3)-sialyltransferase led to similar results: C. Schaub, Dissertation, in preparation.

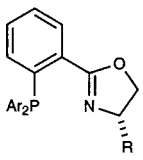
## Enantioselective Hydrogenation of Olefins with Iridium – Phosphanodihydrooxazole Catalysts

Andrew Lightfoot, Patrick Schnider, and Andreas Pfaltz*

Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis, with the most versatile catalysts being rhodium– and ruthenium – diphosphane complexes.[1] However, with a few exceptions, the range of substrates is still limited to certain classes of olefins bearing polar groups that can coordinate to the catalyst. Moreover, even in standard substrate categories derivatives can be found that give unsatisfactory enantioselectivities. There are only a few examples of highly enantioselective hydrogenations of unfunctionalized olefins.[2, 3] The most impressive results in this field have been obtained by Buchwald, who used Brintzinger's chiral titanocene complexes.[3] Although high *ee* values were obtained, the low catalyst activity required that a relatively high catalyst loading ($\geq$5 mol %) was used. Therefore, the search for new catalysts to fill these methodological gaps continues.

We recently reported enantioselective hydrogenation of imines catalyzed by iridium – phosphanodihydrooxazole complexes of the type **1** with $PF_6^-$ as anion.[4] The coordination environment of the iridium center resembles that in Crabtree's catalyst, a cationic iridium complex with a monophosphane and pyridine as ligands.[5] Owing to the remarkable properties of Crabtree's catalyst—that is, the ability to hydrogenate tri- and tetrasubstituted olefins that do not react with rhodium– or ruthenium – phosphane catalysts—we decided to study complexes **1** as catalysts for the hydrogenation of unfunctionalized tri- and tetrasubstituted olefins.




| | | | |
|---|---|---|---|
| **1a** | Ar = Ph | R = *i*Pr | X = $PF_6$ |
| **1b** | Ar = Ph | R = *t*Bu | X = $PF_6$ |
| **1c** | Ar = *o*-Tol | R = *i*Pr | X = $PF_6$ |
| **1d** | Ar = *o*-Tol | R = *t*Bu | X = $PF_6$ |
| **1e** | Ar = Ph | R = *i*Pr | X = BARF |
| **1f** | Ar = *o*-Tol | R = *t*Bu | X = BARF |
| **1g** | Ar = Ph | R = $CH_2t$Bu | X = BARF |

| | | |
|---|---|---|
| **2a** | Ar = Ph | R = *i*Pr |
| **2b** | Ar = Ph | R = *t*Bu |
| **2c** | Ar = *o*-Tol | R = *i*Pr |
| **2d** | Ar = *o*-Tol | R = *t*Bu |
| **2e** | Ar = Ph | R = $CH_2t$Bu |

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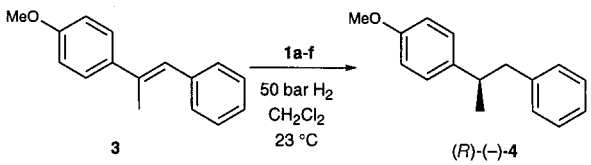
Initial experiments with complex **1a** led to encouraging results. Indeed, the hydrogenation of olefin **3** in $CH_2Cl_2$ with 4 mol % of **1a** [Eq. (1)] gave a good *ee* value of 75 %, albeit with moderate conversion (78 %, Table 1). Lower catalyst loadings led to decreased conversion. Preliminary kinetic data




(1)

with (*E*)-1,2-diphenyl-1-propene as substrate shows a large initial turnover frequency (TOF) of 41 $min^{-1}$ (olefin: 0.31 M, catalyst: 0.003 M), but as the reaction proceeds the TOF decreases to essentially zero within one hour.[6] Deactivation has also been observed with Crabtree's catalyst, which is explained by the formation of inactive hydride-bridged trimers.[5] In our case the origin of deactivation is not known, but traces of water appear to enhance this undesired side reaction. Thus, the addition of molecular sieves to the above system gave an increased conversion. Alternatively, running the reaction under strictly anhydrous conditions, using freshly dried $CH_2Cl_2$ (distilled over $CaH_2$) and standard Schlenk techniques, allows full conversion to be obtained with 4 mol % of **1a** with the same *ee* value as before. Analytically pure product **4** was isolated in essentially quantitative yield by removal of the solvent and distillation.

Table 1. Enantioselective hydrogenation of **3** with use of catalysts **1a**–**f** [Eq. (1)].

| Entry | Cat. (mol %) | Conversion [%] | *ee* [%] |
|---|---|---|---|
| 1 | **1a** (4) | 78 | 75 |
| 2 | **1b** (4) | 98 | 90 |
| 3 | **1c** (4) | > 99 | 91 |
| 4 | **1d** (4) | 57 | 97 |
| 5 | **1e** (0.3) | > 99 | 70 |
| 6 | **1f** (0.3) | > 99 | 98 |

A systematic study of ligands **2a**–**d** led to a highly enantioselective catalyst for the hydrogenation of **3** (Table 1). Thus, replacement of the isopropyl group of ligand **2a** with a *tert*-butyl group (**2b**) increased the *ee* value to 90 %. Alternatively, replacement of the diphenylphosphanyl group of **2a** with a bis(*o*-tolyl)phosphanyl group (**2c**) increased the *ee* value to 91 %. The combined use of a *tert*-butyl group and a bis(*o*-tolyl)phosphanyl group (**2d**) led to the highest enantioselectivity (97 % *ee*, 57 % conversion with 4 mol % of **1d**). Attempts to further increase the conversion by varying the reaction conditions and introducing additives, such as iodide, were met with little success.[7] However, replacement of the $PF_6^-$ anion with BARF (tetrakis[3,5-bis(trifluoromethyl)phe-

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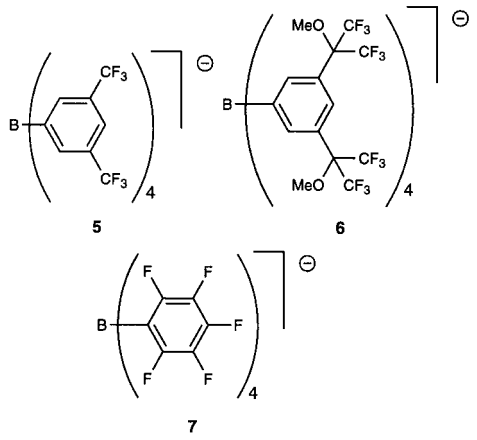
nyl]borate, **5**)[8] had a dramatic effect on the conversion and allowed a reduction in the catalyst loading to typically less than 1 mol%. For example, in a concentrated solution (4 M)



**5** **6** **7**

(*E*)-1,2-diphenyl-1-propene was hydrogenated with 70% *ee* (>99% conversion) with 0.05 mol% of **1e**. Similar weakly coordinating anions such as **6**[9] (0.1 mol% of catatyst, 65% *ee*, >99% conversion) and **7**[10] (0.1 mol% of catalyst, 60% *ee*, 84% conversion) also gave active catalysts, whereas all other anions tested ($SbF_6^-$, $BF_4^-$, $BPh_4^-$, $TfO^-$, halides) resulted in much lower activity. Curiously, the catalysts with BARF as counterion appear to be tolerant of traces of moisture, and the reaction solutions can be prepared in the air without specially dried solvents. The initial TOF of the catalysts with BARF as counterion is even higher than that of the hexafluorophosphate complexes (70–135 $min^{-1}$, olefin **8**: 0.31 M, **1e**: 0.003 M).

The most efficient catalyst in this series proved to be **1f**, which gave high conversions and yields as well as good to excellent *ee* values for a number of trisubstituted olefins (Figure 1). Until now, unfunctionalized olefins of this type could not be hydrogenated with high enantioselectivity using other catalysts at such low loading (0.1–0.5 mol%). (*Z*)-1,2-Diarylolefins are unreactive towards this catalyst, whereas both (*E*)- and (*Z*)-2-(4-methoxyphenyl)-2-butene (**11** and **12**, respectively) gave high conversions but only moderate *ee* values. The major enantiomer derived from the *Z* isomer was found to be opposite to that obtained for the *E* isomer. The allylic acetate **13** was also hydrogenated with high *ee* value. Even the tetrasubstituted olefin **14** could be hydrogenated in high yield, and with remarkable enantioselectivity for this type of substrate, using complex **1g**, which was the best catalyst in this case. Allyl alcohols and $\alpha,\beta$-unsaturated esters, on the other hand, gave only low conversion with the BARF complexes **1e** and **1f**. For these classes of substrates, the hexafluorophosphate complex **1d** proved to be a superior catalyst. Thus, **16** was hydrogenated efficiently with 1 mol% of **1d** (96% *ee*, 95% conversion), demonstrating that these complexes provide an alternative to the ruthenium/BINAP system.[11] The same catalyst was successfully employed in the enantioselective synthesis of the artificial fragrance lilial (Scheme 1).[12] The allyl alcohol **17**[13] was hydrogenated in the presence of 2 mol% of **1d** to give 95% of the corresponding alcohol with 94% *ee*. Oxidation with pyridinium chlorochromate (PCC) led to lilial in 56% yield.

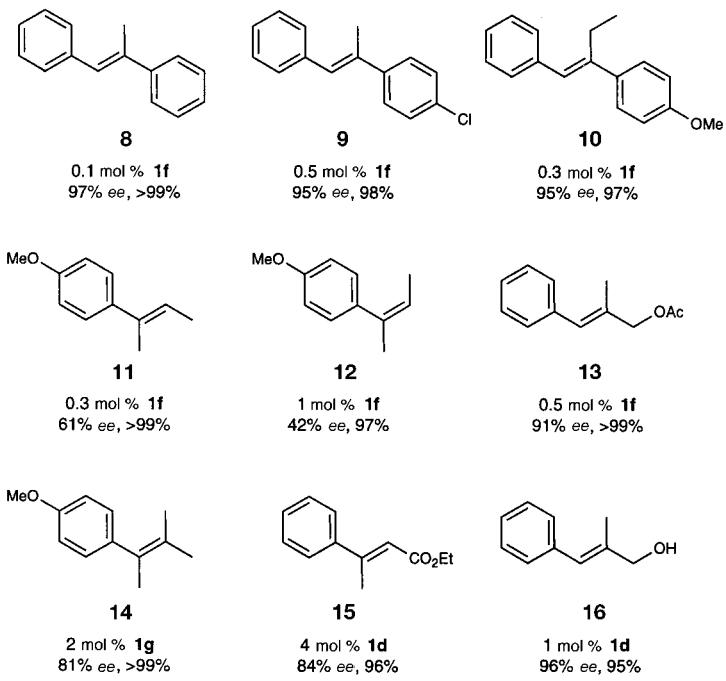
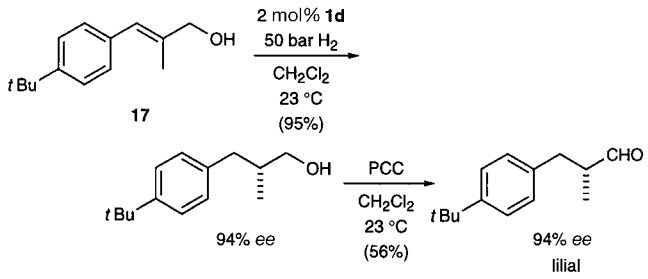



Figure 1. Substrates for hydrogenation with catalysts **1a**–**g** along with catalyst amounts, *ee* values, and conversions.




Scheme 1. Synthesis of lilial. PCC = pyridinium chlorochromate.

We have demonstrated that cationic iridium complexes with chiral phosphanodihydrooxazoles are efficient catalysts for the enantioselective hydrogenation of olefins. The complexes are air-stable and easy to handle. Depending on the counterion, BARF or hexafluorophosphate, certain unfunctionalized aryl-substituted olefins or allyl alcohols can be hydrogenated in high yields and with excellent enantioselectivities.

## *Experimental Section*

**1f**: To a two-necked flask fitted with a condenser was added **2d**[14] (400 mg, 0.96 mmol), [{Ir(cod)Cl}$_2$] (324 mg, 0.48 mmol), and $CH_2Cl_2$ (10 mL). The deep red mixture was heated under Ar to reflux for 1 h, until thin layer chromatography (TLC; silica gel, $CH_2Cl_2$) indicated that **2d** had been consumed. After the mixture was cooled to room temperature, Na[BARF] (1.31 g, 1.5 mmol) was added followed by $H_2O$ (10 mL), and the resulting two-phase mixture was stirred vigorously for 10 min. Counterion exchange from the chloride ($R_f = 0$) to BARF ($R_f = 0.95$) was indicated by TLC (silica gel, $CH_2Cl_2$). The layers were separated, and the aqueous layer was extracted with further portions of $CH_2Cl_2$ ($2 \times 10$ mL). The combined organic extracts were washed with $H_2O$ (10 mL) and evaporated. The residue was taken up in EtOH (10 mL) and crystallized by the slow addition of $H_2O$ (1 mL) to give **1f** (935 mg, 62%) as a dark orange solid. Elemental analysis calcd for $C_{67}H_{54}BF_{24}IrNOP$: C 50.96, H 3.45, N 0.89;

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found: C 51.11, H 3.46, N 0.92; m.p. 200–203 °C (decomp); $[\alpha]_{589} = -160$ ($CDCl_3$, $c = 0.2$, 23 °C); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 0.46$ (br s, 9H; *t*Bu), 1.43 (m, 2H; $CH_2$ (COD)), 1.92 (m, 2H; $CH_2$ (COD)), 2.15–2.33 (m, 8H; 2Me, $CH_2$ (COD)), 2.99 (br s, 3H; CH, $CH_2$ (COD)), 3.37 (br s, 1H; CH (COD)), 3.85 (m, 1H; $CH_2O$), 4.21 (t, $J = 9.45$ Hz, 1H, CHN), 4.45 (m, 1H; $CH_2O$), 4.64 (m, 1H; CH (COD)), 4.75 (br s, 1H; CH (COD)), 6.37 (m, 1H; arom. H), 6.78 (m, 1H; arom. H), 6.96 (m, 1H; arom. H), 7.11–7.17 (m, 4H; arom. H), 7.24–7.37 (m, 4H; arom. H), 7.43 (s, 4H; BARF), 7.52 (m, 2H; arom. H), 7.63 (s, 8H; BARF), 8.13–8.08 (m, 1H; arom. CH); $^{31}$P NMR (100 MHz, $CDCl_3$): $\delta = 11.0$.

Hydrogenation of **3**. To a 35-mL autoclave with magnetic stirrer was added **1f** (1.6 mg, 0.001 mmol, 0.3 mol %), **3** (74 mg, 0.33 mmol), and $CH_2Cl_2$ (0.3 mL). The autoclave was sealed and pressurized to 50 bar with $H_2$, and the mixture was stirred for 2 h. The $CH_2Cl_2$ solvent was removed and replaced with heptane (3 mL), and the solution passed through a short plug of silica (0.5 cm) to remove the metal salts. Analysis by gas chromatography (GC) indicated 99.8 % conversion into **4**. Kugelrohr distillation (130–140 °C/0.04 mbar) afforded **4** as a clear oil (75 mg, 99 %). The reaction of 4 mmol of **3** and 0.3 mol % of **1f** gave the same results. HPLC (Chiralcel OJ, *i*PrOH/heptane 5/95, 0.5 mL min$^{-1}$, 20 °C, 254 nm): $t_R$ (*R*) = 15.6 min, $t_R$ (*S*) = 20.3 min, 98 % *ee*; $[\alpha]_{589} = -94.4$ ($CH_2Cl_2$, $c = 2.93$, 23 °C); $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 1.21$ (d, 3H; $J = 8.3$ Hz, Me), 2.67–3.01 (m, 3H; CH, $CH_2$), 3.77 (s, 3H; OMe), 6.81 (d, 2H; $J = 8.8$ Hz, arom. H), 7.07–7.26 (m, 7H; arom. H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 21.0$ (Me), 40.7 (CH), 45.1 ($CH_2$), 55.5 (OMe), 113.9, 126.1, 128.2, 128.4, 129.5 (arom. CH), 139.5, 141.3, 158.3 (arom. C).

HPLC analysis of the hydrogenation products from **8**–**13** and **15**–**17** (0.5 mL min$^{-1}$, 20 °C, 254 nm): **8** (Chiralcel OJ, *i*PrOH/heptane 1/99): $t_R$ = 12.6 min (major enantiomer), 20.6 min (minor enantiomer); **9** (Chiralcel OJ, *i*PrOH/heptane 1/99): 12.9/15.7 min; **10** (Chiralcel OJ, *i*PrOH/heptane 5/95): 12.1/17.3 min; **11** (Chiralcel OD-H, *i*PrOH/heptane 0.01/99.99): 15.3/13.9 min; **12** (Chiralcel OD-H, *i*PrOH/heptane 0.01/99.99): 14.1/16.0 min; **13** was hydrolyzed (MeOH/$K_2CO_3$), and the resulting alcohol was analyzed (Chiralcel OD-H, *i*PrOH/heptane 5/95, 40 °C): 17.4/15.1 min; **15** (Chiralcel OB-H, *i*PrOH/heptane 0.5/99.5): 18.4/21.4 min; **16** (Chiralcel OD-H, *i*PrOH/heptane 5/95, 50 °C), 16.4/14.6 min; **17** (Chiralcel OD-H, *i*PrOH/heptane 5/95, 40 °C): 18.0/15.6 min. Analysis by GC of the hydrogenation product from **14** (20 % *t*Bu $\beta$-CD, 80 % OV1701, 25 m, 0.5 bar $H_2$, 50–180 °C, 1° min$^{-1}$): $t_R$ = 52.4 min (major enantiomer), 51.2 min (minor enantiomer).

Received: May 27, 1998 [Z11908IE]
German version: *Angew. Chem.* **1998**, *110*, 3047–3050

**Keywords:** asymmetric catalysis · dihydrooxazoles · hydrogenations · iridium · N ligands · P ligands

[1] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**, pp. 16–94; H. Tayaka, T. Ohta, R. Noyori in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, pp. 1–39; A. Pfaltz, *Methods Org. Chem.* (*Houben-Weyl*), 4th ed., Vol. E21, **1995**, chap. 2.5.1.2.1/2, pp. 4334–4359.

[2] R. L. Halterman, K. P. C. Vollhardt, M. E. Welker, D. Bläser, R. Boese, *J. Am. Chem. Soc.* **1987**, *109*, 8105–8107; V. P. Conticello, L. Brard, M. A. Giardello, Y. Tsuji, M. Sabat, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992** *114*, 2761–2762; M. A. Giardello, V. P. Conticello, L. Brard, M. R. Gagné, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10241–10254.

[3] R. D. Broene, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 12569–12570.

[4] P. Schnider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887–891.

[5] R. H. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–338.

[6] D. Blackmond, T. Rosner, Max-Planck-Institut für Kohlenforschung, unpublished results.

[7] For the effect of additives upon iridium-catalyzed hydrogenation of imines, see Y. N. C. Chan, D. Meyer, J. A. Osborn, *J. Chem. Soc. Chem. Commun*. **1990**, 869–871; T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 2661–1664; K. Tani, J.-I. Onouchi, T. Yamagata, Y. Kataoka, *Chem. Lett.* **1995**, 955–956; F. Spindler, B. Pugin, H.-P. Jalett, H.-P. Buser, U. Pittelkow, H.-U. Blaser, *Chem. Ind.* (*Dekker*) **1996**, *68*, 153–168.

[8] H. Nishida, N. Takada, M. Yoshimura, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn*. **1984**, *57*, 2600–2604.

[9] G. H. Zhang, T. Imato, Y. Asano, T. Sonoda, H. Kobayashi, N. Ishibashi, *Anal. Chem*. **1990**, *62*, 1644–1648.

[10] A. G. Massey, A. J. Park, *J. Organomet. Chem*. **1962**, *2*, 245–250.

[11] H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596–1597, 4129.

[12] "Flavours and Fragrances": K. Bauer, D. Garbe, H. Surberg in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. A11*, VCH, Weinheim, **1988**, pp. 141–250; D. Enders, H. Dyker, *Liebigs Ann. Chem*. **1990**, 1107–1110.

[13] Prepared by stereoselective Horner–Wadsworth–Emmons olefination (I. Paterson, K.-S. Yeung, J. B. Smaill, *Synlett* **1993**, 774–776), followed by reduction of the $\alpha,\beta$-unsaturated ester (E. J. Corey, H. A. Kirst, J. A. Katzenellenbogen, *J. Am. Chem. Soc*. **1970**, *92*, 6314–6319).

[14] Prepared by the directed ortho lithiation method: G. Koch, G. C. Lloyd-Jones, O. Loiseleur, A. Pfaltz, R. Prétôt, S. Schaffner, P. Schnider, P. von Matt, *Recl. Trav. Chim. Pays-Bas.* **1995**, *114*, 206–210.

  1433-7851/98/3720-2899 $ 17.50+.50/0 