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The application of Ir-complexes of *trans*-2,5-dialkylpyrrolidinylbenzyldiphenylphosphines to the enantioselective reduction of imines

John P. Cahill,[a] Andrew P. Lightfoot,[b] Richard Goddard,[b] Jörg Rust[b] and Patrick J. Guiry[a,*]
[a]*Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland*
[b]*Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany*

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Abstract

The preparation of iridium (COD) complexes of phosphinamine ligands possessing an enantiopure *trans*-2,5-dialkylpyrrolidinyl unit is described. These complexes were successfully applied to the enantioselective reduction of test substrate imines in excellent conversions with enantioselectivities of up to 52% ee. In attempts to optimize reaction conditions the catalyst loading, time, and hydrogen pressure were varied. X-Ray crystal structures of the iridium (COD) tetrafluoroborate complexes **5** and **6** are discussed. © 1998 Elsevier Science Ltd. All rights reserved.

The important synthetic transformation of the asymmetric reduction of imines[1] is not as well studied as the asymmetric reduction of olefins and ketones. Imine reduction can be carried out using stoichiometric quantities of Al- and B-modified chiral reagents[2] whilst initial catalytic approaches focused on the use of rhodium diphosphine complexes and successful examples have been developed.[3] Titanium(III) hydrides have also given excellent enantioselectivities, particularly for cyclic imines, although this chemistry suffers from the serious limitation of requiring a relatively high catalyst loading of 5 mol%.[4] Iridium(I) complexes have recently been investigated, primarily because of the known catalytic efficiency of Crabtree's catalyst, an Ir^{I}(pyridine)(phosphine) complex, and also because of the activity shown by a range of chiral diphosphine[5] (e.g. Xyliphos **1**) and phosphinamine ligands. The diphenylphosphinooxazolines **2**, reported by the groups of Pfaltz, Williams and Helmchen,[6] have been one of the most successful examples of phosphinamine ligands, affording excellent enantioselectivities for a number of reactions.[7] Pfaltz has investigated the application of their cationic iridium(I) complexes to imine reductions and observed high activities and enantioselectivities.[8] We have recently reported the preparation of a topographically similar class of phosphinamine ligands, **3** and **4**, bearing an enantiopure *trans*-2,5-disubstituted pyrrolidine unit.[9] Preliminary applications of these ligands have been in palladium-catalysed allylic substitution[10] and in

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* Corresponding author. E-mail: patrick.guiry@ucd.ie

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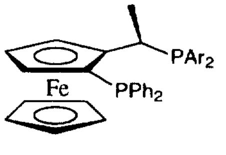
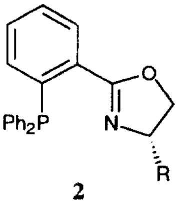
the asymmetric Heck reaction.[11] We now report the preparation of cationic iridium(I) complexes of these ligands and their application to the enantioselective reduction of imines.



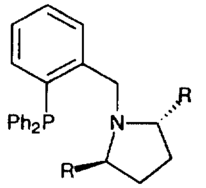
1

Ar = $3,5(Me)_2C_6H_3$



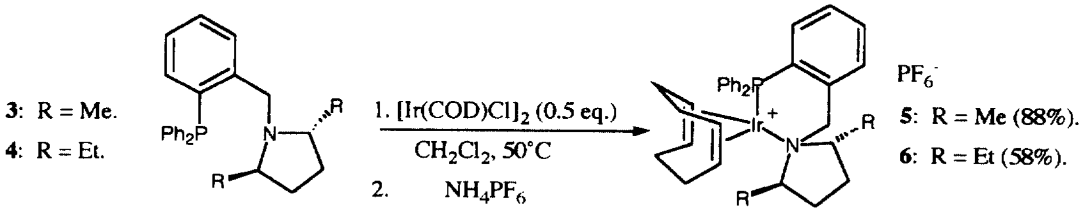
2

R = Bn, *i*-Pr, *t*-Bu, etc.



3: R = Me.; **4**: R = Et.

Using standard chemistry, two equivalents of ligands **3** and **4** were reacted with one equivalent of iridium (1,5-cyclo-octadiene) chloride dimer in methylene chloride at 50°C for 1 h. The resulting iridium chloride complexes were subjected to anion exchange with ammonium hexafluorophosphate to afford the required iridium (1,5-cyclo-octadiene)diphenylphosphinopyrrolidine complexes **5**[12] and **6**[13] in 88 and 58% yields, Scheme 1.



Scheme 1.

Bright red crystals of **5** and orange crystals of **6** suitable for X-ray structure determination were grown from methylene chloride/diethyl ether. The subsequent structure analyses are summarized in Fig. 1, which shows the structure of the cation of **6**.

The geometries of the cations in **5** and **6** are almost identical in spite of different crystal environments, the largest difference being in the torsion angles of the phenyl rings attached to P (<3°). This suggests that the metalladiphenylphosphinopyrrolidine unit is relatively rigid, and indeed, except for the torsion angles involving the phenyl groups attached to P, where the deviations are larger, the diphenylphosphinopyrrolidine ligand in the neutral diphenylphosphinodimethyl-pyrrolidine $PdCl_2$ complex also has the same geometry.[9] The coordination sphere of the Ir atoms in both cations can be thought of as square planar, since the midpoints of the double bonds of the COD ligands, the metal, P and N atoms all lie in a plane (<0.1 Å). Although the Ir–N and Ir–P distances are not directly comparable, the midpoint of the C=C double bond *trans* to P is significantly further away from the metal atom [**6**: 2.092(3) Å; **5**: 2.120(3) Å] than the midpoint of the C=C *trans* to N [**6**: 2.026(3) Å; **5**: 2.019(3) Å] indicating a clear *trans*-effect. A corresponding difference, albeit less significant, is also observed in the C=C distances, with the longer double bond [**6**: C32–C33 1.413(4) Å; **5**: 1.415(5) Å] closer to the metal, so backbonding from the metal appears to be greater *trans* to N.

The results of our preliminary investigations, Scheme 2, using these new iridium(I) complexes in the reduction of the test substrates, the acetophenone-derived imines **7** and **8**, are given in Table 1.

The initial experiments were carried out at room temperature over 12 h using 4 mol% of the iridium complex **5** in a 0.2 M solution of the imine in dichloromethane under a 100 bar pressure of H_2. Under these conditions the imine **7** was reduced in quantitative yield with an ee value of 41% (entry 1). Shorter reaction times were then attempted and quantitative reduction was observed after 3 h and even as short a time as that taken to pressurize the autoclave and immediately release the pressure (estimated as <10 s) led to improved ee values of 49 and 47%, respectively (entries 2–3). In all cases the *S*-enantiomer was

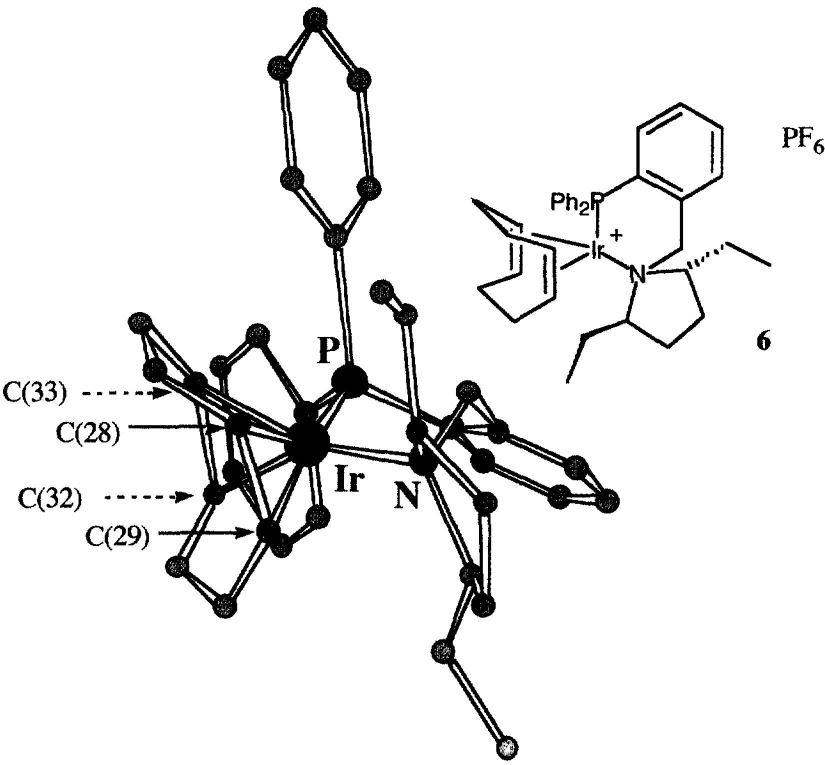
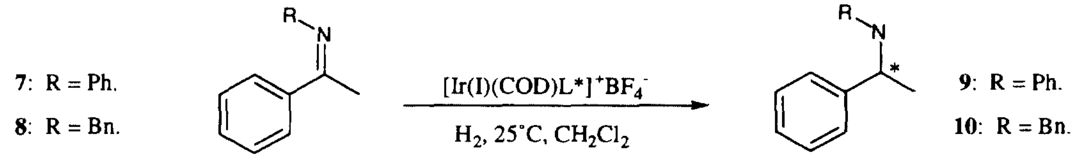


Figure 1. Crystal structure of the cationic Ir–COD complex **6** (H atoms, $[PF_6]^-$ anion and CH_2Cl_2 solvent molecule omitted for clarity). Selected distances (Å) and angles (°): Ir–P 2.310(1), Ir–N 2.250(3), Ir–C28 2.209(3), Ir–C29 2.204(3), Ir–C32 2.138(3), Ir–C33 2.152(3), C28–C29 1.399(5), C32–C33 1.413(4), N–Ir–P 90.69(8)



Scheme 2.

formed in excess as found by comparing the optical rotation of the product to literature values.[8] We then examined the effect of reducing the pressure of H_2 whilst keeping the catalyst loading at 4 mol% and the reaction time at 12 h.

Lowering the pressure to 50 bar gave a 49% ee (entry 4) whilst reactions at 25 and 1 bar (entries 5–6) gave quantitative conversion and enantioselectivities of 51 and 52%, respectively. Keeping the pressure of H_2 at 100 bar, we next looked at the effect of using lower catalyst concentrations. The reductions were carried out over 12 h, 1 h and <10 s and all afforded the amine in quantitative yield with enantioselectivities of 40, 46 and 46%, respectively (entries 7, 8 and 9). Combining low catalyst loading (1 mol%) and a H_2 pressure of 1 bar over 12 h gave the amine in reduced yield (90%) but in 52% ee (entry 10). The second iridium complex **6** was then used in the hope that the larger ethyl substituents on the pyrrolidine unit would give rise to increased enantiofacial discrimination. The results under the optimized conditions determined for **5** show that lower enantioselectivities were obtained compared to the methyl analogue. A disappointing 30% ee was observed using 4 mol% catalyst and at 1 mol%,

Table 1
Application of iridium complexes **5** and **6** to the asymmetric reduction of imines **7** and **8**

Entry	Imine	Catalyst (mol%)	$p(H_2)$ [bar]	Time	% Conversion[a]	% ee (config.)[b]
1	**7**	**5** (4)	100	12 h	100	41 (*S*)
2	**7**	**5** (4)	100	3 h	100	49 (*S*)
3	**7**	**5** (4)	100	< 10 s	100	47 (*S*)
4	**7**	**5** (4)	50	12 h	100	49 (*S*)
5	**7**	**5** (4)	25	12 h	100	51 (*S*)
6	**7**	**5** (4)	1	12 h	100	52 (*S*)
7	**7**	**5** (1)	100	12 h	100	40 (*S*)
8	**7**	**5** (1)	100	1 h	100	46 (*S*)
9	**7**	**5** (1)	100	< 10 s	100	46 (*S*)
10	**7**	**5** (1)	1	12 h	90	52 (*S*)
11	**7**	**6** (4)	100	12 h	100	30 (*S*)
12	**7**	**6** (1)	100	12 h	100	28 (*S*)
13	**8**	**5** (4)	100	12 h	93[c]	21 (*S*)
14	**8**	**6** (4)	100	12 h	100	24 (*S*)

[a] Conversions by GC (Restek Rtx® 1701 column, 30 m, 0.6 bar H_2), 100 °C for 5 min, 3 °C min^{-1}, 250 °C: t_R = 31.7 min for imine **7** and t_R = 31.4 min for amine **9**; 100 °C for 2 min., 7 °C min^{-1}, 250 °C: t_R=19.3 min for imine **8** and t_R = 16.5 min for amine **10**. [b] Enantiomeric excesses were determined by HPLC on a Daicel Chiracel OD column: *n*-heptane/2-propanol 90:10; (t_R=9.8 (*S*) and 12.0 (*R*) min) for amine **9**; *n*-hexane; (t_R = 31(*R*) and 40(*S*) min for amine **10**. [c] Hydrolysis products also formed.

an ee of 28% and a significantly decreased yield of 60% was obtained, indicating that catalyst **5** is more reactive than its ethyl analogue **6** (compare entries 11, 12 to 1 and 7). A second test substrate imine, *N*-(1-phenylethylidene)benzylamine **8** was investigated with both iridium complexes but low enantioselectivities of 21 and 24% ee, respectively, were observed (entries 13–14). This suggests that the bulkier *N*-aryl imine substrate has stronger steric interactions with the ligand scaffold compared to the *N*-alkyl imine **8**.

In conclusion, we have prepared new cationic iridium(I) complexes of diphenylphosphinopyrrolidine ligands bearing *trans*-2,5-dimethyl- and diethyl-pyrrolidine units and applied them with moderate enantioselectivities to the reduction of test imines. Work is currently in progress preparing similar ligands with bulkier groups at the stereogenic centres and testing their complexes in this and other metal-catalysed transformations.

1. Experimental

X-Ray analysis of 5: $[C_{33}H_{40}IrNP]^+[PF_6]^- \cdot CH_2Cl_2$, M_r=903.73 g mol^{-1}, red, crystal size 0.07×0.19×0.34 mm, a=9.5832(2), b=18.9792(4), c=9.8070(2) Å, β=106.771(1)°, U=1707.84(6) $Å^3$, T=100 K, monoclinic, $P2_1$ [No. 4], Z=2, d_{cal}=1.76 g cm^{-3}, μ=4.22 mm^{-1}, Siemens SMART diffractometer, λ=0.71073 Å, CCD ω-scan, 19 897 reflections, 11 358 independent, 10 927 observed, $[I>2\sigma(I)]$ $[(\sin\theta)/\lambda]_{max}$=0.79 $Å^{-1}$, analytical absorption correction (T_{max} 0.53091, T_{min} 0.37682), direct methods,[14] least-squares refinement[15] (on F_o^2), H riding, 415 refined parameters, R=0.025 (obs. data), R_w=0.056 (Chebyshev weights, all data), absolute configuration determined,[16] [Flack parameter: −0.010(4)] final shift/error 0.002, residual electron density +0.78 $eÅ^{-3}$.

X-Ray analysis of 6: $[C_{35}H_{44}IrNP]^{+}[PF_6]^{-}\cdot CH_2Cl_2$, M_r=931.78 g mol^{-1}, orange, crystal size 0.28×0.42×0.77 mm, *a*=13.4045(3), *b*=13.8298(3), *c*=19.8286(4) Å, *U*=3675.9(1) Å^3, *T*=100 K, orthorhombic, $P2_12_12_1$ [No. 19], *Z*=4, d_{cal}=1.68 g cm^{-3}, μ=3.92 mm^{-1}, Siemens SMART diffractometer, λ=0.71073 Å, CCD ω-scan, 42 731 reflections, 13 300 independent, 12 879 observed $[I>2\sigma(I)]$ $[(\sin\theta)/\lambda]_{max}$=0.79 Å^{-1}, analytical absorption correction ($T_{\max}$ 0.44350, $T_{\min}$ 0.16596), direct methods,[14] least-squares refinement[15] (on $F_o{}^2$), H riding, 433 refined parameters, *R*=0.032 (obs. data), R_w=0.083 (Chebyshev weights, all data), absolute configuration determined,[16] [Flack parameter: −0.006(4)] final shift/error 0.01, residual electron density +1.76 eÅ^{-3}.

Full structural details of **5** and **6** have been deposited with the Cambridge Crystallographic Data Centre.

Acknowledgements

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12. Selected analytical data for complex **5**; mp 231–232°C (dec.); found C, 48.43; H, 4.94; N, 1.65; $C_{33}H_{40}F_6NP_2Ir$ requires C, 48.40; H, 4.88; N, 1.71%; $[\alpha]_D^{23}$ −18.5 (*c* 0.5, chloroform); ν_{max} (KBr) 3058 (C=CH), 2956 (C–H aliph.), 1436 (Ar–H),

840 and 558 (PF_6) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.49 (d, 3H, *J* 6.6, Me), 1.65 (d, 3H, *J* 7.0, Me), 1.72–1.80 (m, 1H, H_2C), 1.81–2.84 (m, 7H, H-3$'_a$, H-3$'_b$, H-4$'_a$, H-4$'_b$, HC_2 of COD, HC of COD), 2.26–2.58 (m, 4H, H_2C of COD), 2.70–2.84 (m, 1H, H-2′ or H-5′), 2.84–3.00 (m, 1H, HC of COD), 3.52–3.69 (m, 2H, H-5′ or H-2′, HC of COD), 3.94 (dd, 1H, *J* 13.3, $J_{P\text{–}H}$ 4.4, benzylic–H), 4.21 (d, 1H, *J* 13.3, benzylic–H), 4.71 (m, 1H, HC of COD), 5.24 (m, 1H, HC of COD), 7.21–7.38 (m, 4H, Ar–H), 7.44–7.58 (m, 8H, Ar–H), 7.85–8.01 (m, 2H, Ar–H); δ_C (50.3 MHz, $CDCl_3$) 16.7 (Me), 21.26 (Me), 28.7 (H_2C), 28.8 (H_2C), 29.3 (H_2C), 29.4 (H_2C), 32.1 (CH_2), 32.6 (CH_2), 57.3 (C-5′ or C-2′), 58.3 (d, $J_{P\text{–}C}$ 12.1, benzylic–C), 62.2 (C-2′ or C-5′), 64.5 (HC of COD), 66.9, (HC of COD), 91.9 (d, $J_{P\text{–}C}$ 13.0, HC of COD), 96.6 (d, $J_{P\text{–}C}$ 10.9, HC of COD), 127.65, 128.63, 129.24, 130.07, 131.46, 131.64, 131.82, 131.96, 133.19, 133.75 (arom. C–H), 131.89, 135.08, 135.38, 138.34 (arom. C); δ_P (81.01 MHz, $CDCl_3$) 11.60 (P–Ph_2), 39.14 (septet, $J_{P\text{–}F}$ 8.8, P–F); *m*/*z* (ESI^+) 672 (M–PF_6, 9%), 560 (100).

13. Selected analytical data for complex **6**; mp 233–234°C (dec.); found C, 49.72; H, 5.22; N, 1.63; $C_{35}H_{44}F_6NP_2Ir$ requires C, 49.65; H, 5.20; N, 1.65%; $[\alpha]_D^{23}$ −6.4 (*c* 0.5, chloroform); ν_{max} (KBr) 3060 (C=CH), 2967 (C–H aliph.), 1437 (Ar–H), 875 and 558 (PF_6) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.58 (t, 3H, *J* 7.3 Me), 1.07 (t, 3H, *J* 7.3, Me), 1.21–1.38 (m, 1H, H_2C), 1.49–2.63 (m, 15H, H-3$'_a$, H-3$'_b$, H-4$'_a$, H-4$'_b$, 3×HC_2 of COD, HC of COD, H-6′, H-8′), 2.66–2.81 (m, 1H, H-2′ or H-5′), 2.91–3.06 (m, 1H, HC of COD), 3.09–3.33 (m, 2H, H-5′ or H-2′, HC of COD), 4.01 (dd, 1H, *J* 13.4, $J_{P\text{–}H}$ 4.5, benzylic–H), 4.29 (d, 1H, *J* 13.3, benzylic–H), 4.68–4.84 (m, 1H, HC of COD), 4.90–5.06 (m, 1H, HC of COD), 7.19–7.46 (m, 4H, Ar–H), 7.48–7.63 (m, 8H, Ar–H), 7.74–7.90 (m, 2H, Ar–H); δ_C (50.3 MHz, $CDCl_3$) 11.52 (Me), 11.70 (Me), 24.53 (C-6′ or C-8′), 26.64 (C-6′ or C-8′), 28.15 (CH_2), 28.73 (H_2C), 28.93 (CH_2), 29.45 (H_2C), 30.47 (H_2C), 33.46 (H_2C), 58.10 (C-5′ or C-2′), 58.89 (d, $J_{P\text{–}C}$ 10.6, benzylic–C), 60.77 (C-2′ or C-5′), 71.19 (HC of COD), 73.59, (HC of COD), 92.14 (HC of COD), 95.03 (d, $J_{P\text{–}C}$ 11.4, HC of COD), 127.46, 128.72, 129.17, 129.98, 131.52, 131.71, 131.90, 132.21, 133.24, 133.95 (arom. C–H), 131.99, 134.82, 135.67, 138.56 (arom. C); δ_P (81.01 MHz, $CDCl_3$) 11.72 (P–Ph_2), 39.17 (septet, $J_{P\text{–}F}$ 8.8, P–F); *m*/*z* (ESI^+) 700 (M–PF_6, 10%), 590 (100).
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