Synthesis of a *P*-Stereogenic PNP^{tBu,Ph} Ruthenium Pincer Complex and Its Application in Asymmetric Reduction of Ketones

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A novel *P*-stereogenic PNP^{tBu,Ph} ruthenium complex has been synthesized and characterized enabling the asymmetric hydrogenation of a wide range of aromatic ketones with excellent catalytic activities (up to 98 % conversion) and good levels of enantiodiscrimination (up to 95 % *ee*).

Introduction

Pincer ligands are privileged scaffolds widely employed in a variety of catalytic transformations as a result of their stability, tunability and high activity when coordinated to metals.[1] They are indeed highly modulable and several structural combinations are possible taking into account some structural features such as the nature of coordinating groups, central aromatic ring and spacers. Among the great variety of transition-metal pincer complexes, those with N- or P-donor groups are particularly interesting since outstanding results have been reported in a vast number of organic transformations, including hydrogenation,[2] acceptorless dehydrogenation,[3] C–H or N–H activation reactions,[4] allylation of aldehydes and imines,[5] hydroamination[6] and aldol reactions.[7]

Introduction of chirality in pincer ligands is of growing interest in this field since it might enable ready access to asymmetric catalytic reactions and would extend the application of these ligands in organic synthesis. Different approaches have been reported to this end, the installation of chiral substituents at the benzylic positions (Figure 1, a)[8] or the introduction of donor substituents with predefined chiral entities (Figure 1, b)[9] being the most common strategies. Alternatively, the use of *P*-stereogenic phosphines in chiral pincer metal complexes is still relatively unexplored, probably due to the lack of a natural chiral pool of *P*-stereogenic compounds as well as the relative configurational instability of P atoms.[10,11] Nonetheless, a recent example by Zhang et al.,[12] describing a *P*-stereogenic PCP-Pd complex in the asymmetric addition of diarylphosphines to nitroalkenes demonstrated that *P*-stereogenic pincer ligands are efficient inductors of enantioselectivity (Figure 1, c). Herein, we report the design, synthesis and characterization of a new *P*-stereogenic PNP^{tBu,Ph} ruthenium complex and its catalytic activity in the asymmetric hydrogenation of ketones. The difference between the planar phenyl and the bulky *tert*-butyl group at P atoms is envisioned to create an effective enantiodiscriminating environment for asymmetric catalysis (Figure 1, d).[13]

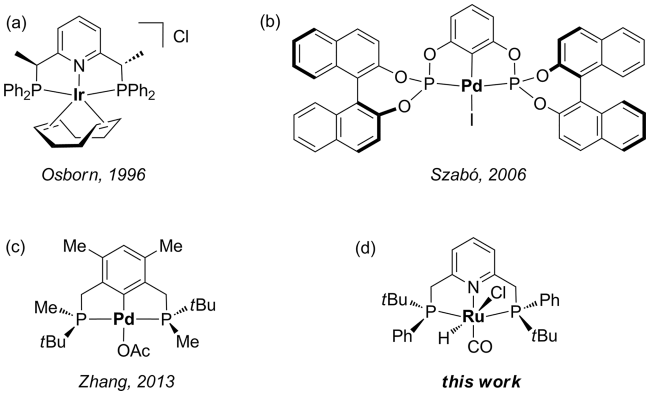

Figure 1. Representative examples of chiral pincer metallic complexes.

Results and Discussion

The straightforward synthesis of **3** was accomplished in two steps, starting from phosphine–borane complex **1** (Scheme 1).[14] Deprotection of these adducts is generally achieved by treatment with a large excess of an amine, namely pyrrolidine, morpholine or DABCO[15] and removal of the corresponding amine–borane byproduct is usually described to proceed by low-temperature sublimation.[14] In our hands, the deprotection of the phosphine–borane moiety resulted more reluctant than expected, and low yields

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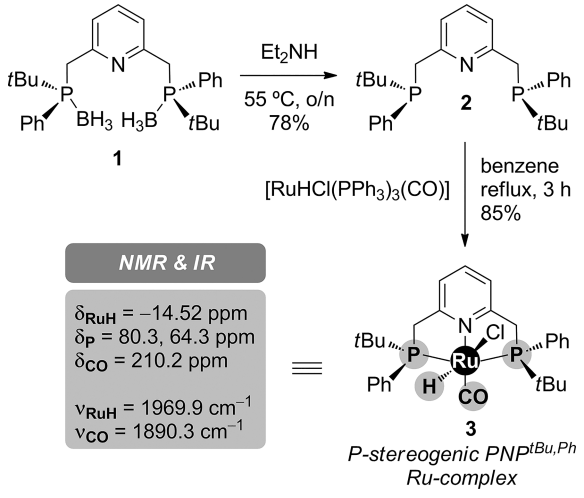
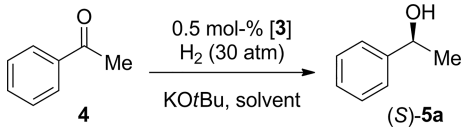
and oxidation of the free ligand were always detected. Other common procedures such as treatment with a strong acid followed by basic aqueous workup,[16] or the use of polymer-supported amines[17] did not provide the unprotected $PNP^{tBu,Ph}$ ligand **2** in reasonable yields and/or purity. Ligand **2** was finally obtained in good yield (78%) by reaction with excess of diethylamine and purification by preparative TLC inside a glove-box. The use of alumina instead of silica plates and careful anhydrous handling were crucial in order to obtain reproducible experiments. The structure of **2** was confirmed by ^{1}H, ^{13}C and ^{31}P-NMR spectroscopy (see Supporting Information).[14] The resulting ligand was treated with $[RuHCl(PPh_3)_3(CO)]$ in refluxing benzene to afford Ru complex **3** in 85% yield as a pale-yellow solid. The CO streatching band in the IR spectrum was observed at 1890.3 cm^{-1} and the ^{31}P-NMR spectrum showed two doublets at δ = 80.3 and 64.3 ppm with J_{PP} = 267.6 Hz, corresponding to the two magnetically different phosphorus atoms. In the ^{1}H-NMR spectrum, the diastereotopic protons at the P-CH_2-pyridine arm resonated at δ = 4.60, 4.14 and 3.96–3.86 ppm. The chemical shift for the hydride (δ = –14.52 ppm, J_{HP} = 23.6 and 15.2 Hz) was consistent with a *trans*-disposition with respect to the chlorine atom, in agreement with other [(PNP)RuHCl(CO)] complexes.[18] These data strongly suggested the coordination of the $PNP^{tBu,Ph}$ ligand in a meridional fashion around the octahedral Ru center.



Scheme 1. Synthesis of *P*-stereogenic $PNP^{tBu,Ph}$ ruthenium complex **3**.

The catalytic performance of *P*-stereogenic $PNP^{tBu,Ph}$ Ru complex **3** was evaluated in the asymmetric hydrogenation of ketones as a model reaction. The optimization of reaction conditions was carried out using acetophenone (**4**)[19] (Table 1). Preliminar experiments established the use of 0.5 mol-% of complex **3** as the more appropriate option due to a better overall reaction time vs. conv. vs. *ee* ratio. Among the various solvents evaluated at room temperature, EtOH was found to be optimal in terms of conversion (up to 98%) and enantioselectivity (up to 64%) towards alcohol **5a** (entries 1–4). When the reaction was carried out in the absence of base, no traces of alcohol were detected (entry 5). In order to increase the enantioselectivity, we next performed the reaction at lower temperatures. Decreasing the reaction temperature improved the enantioselectivity (up to 77%), at the expense of the conversion, which was slightly eroded (entries 6–7). To our delight, at temperatures as low as –40 °C, complete conversions and 87% *ee* were achieved by increasing the equivalents of base with respect to the Ru complex (entry 8).

Table 1. Optimization of reaction conditions for the asymmetric hydrogenation of acetophenone (**4**).[a]

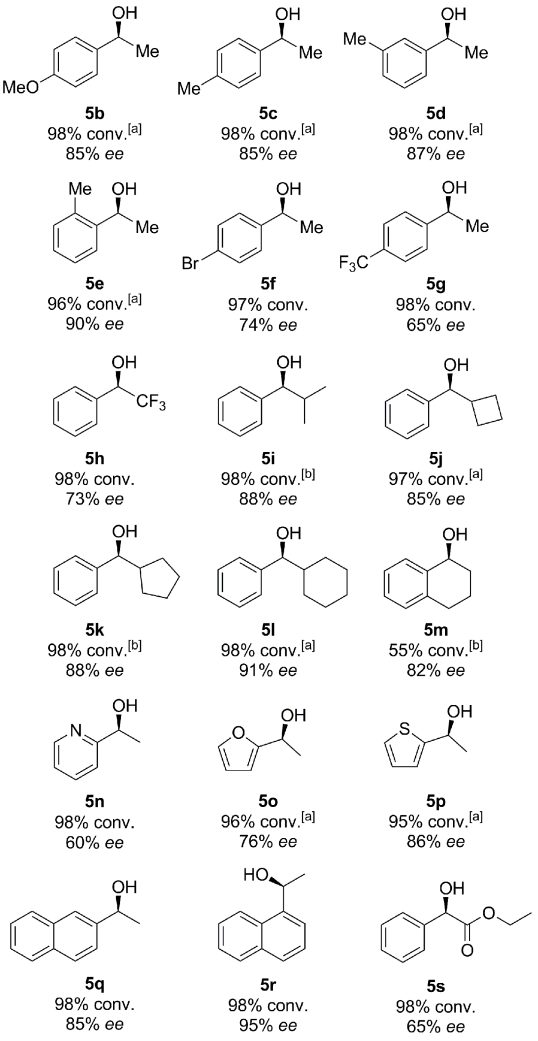


Entry	Solvent	*T* [°C]	Conv. [%][b]	*ee* [%][c]
1	benzene	room temp.	98	*rac*
2	THF	room temp.	98	20
3	MeOH	room temp.	96	32
4	EtOH	room temp.	98	64
5[d]	EtOH	room temp.	–	–
6	EtOH	0	98	71
7	EtOH	–20	91	77
8[e]	EtOH	–40	98	87

[a] General conditions: 0.0025 mmol of Ru complex **3**, 0.0025 mmol of *t*BuOK, 0.5 mmol of acetophenone, EtOH(5 mL), H_2 (30 atm), 16 h. [b] Conversion was calculated by ^{1}H-NMR spectroscopy. [c] Enantiomeric excess was calculated by GC. Absolute configurations were determined to be (*S*) (see the Supporting Information). [d] Control reaction carried out without KO*t*Bu. [e] 0.0025 mmol of Ru complex **3** and 0.025 mmol of KO*t*Bu.

With the optimal reaction conditions in hand, we next evaluated the scope of complex **3** with a wide range of structurally diverse aromatic ketones (Scheme 2). Electron-donating groups in *para*-position delivered the corresponding alcohols (**5b**–**5c**) with good *ee*'s (85%). For the particular case of the aryl methyl ketones, a slight increase of the *ee* (up to 90%) of alcohols (**5d**–**5e**) was observed when the substituent was located in *meta* or *ortho*-positions with respect to that in *para*-position. Ketones bearing electron-withdrawing groups were completely hydrogenated to alcohols (**5f**–**5g**) albeit with lower *ee* values and the same trend was observed with a more electrophilic ketone to give alcohol **5h**. When the methyl group of acetophenone was replaced by either *i*Pr or aliphatic 4-, 5- and six-membered rings, complete conversions and good *ee* values (up to 91%) were observed (**5i**–**5l**). On the other hand, ketones containing benzo-annulated rings were reduced with moderate conversion, probably as a result of an increase in the steric hindrance to give alcohol **5m**. As for heteroaromatic methyl ketones, 2-acetylpyridine was fully hydrogenated with lower *ee* (**5n**). On the contrary, ketones bearing π-excedent heterocycles such as 2-furyl methyl ketone or 2-acetyltiophene were converted to alcohols (**5o**–**5p**) with better enantioselectivity (up to 86%). Replacement of the phenyl ring by naphthalene led to the corresponding alcohols with good

ee values (**5q**–**5r**). Finally, the hydrogenation of ethyl benzoylformate proceeded with total chemoselectivity towards the ketone moiety although with a moderate *ee* (**4s**).



Scheme 2. Substrate scope. General conditions: 0.0025 mmol of Ru complex **3**, 0.025 mmol of *t*BuOK, 0.5 mmol of ketone, EtOH (5 mL), H_2 (30 atm), 16 h, –40 °C. Conversion was calculated by ^{1}H-NMR spectroscopy. Enantiomeric excess was calculated by GC. Absolute configurations were determined to be (*S*) (see Supporting Information). Results average of at least two independent runs.[a] Reaction time: 24 h.[b] Reaction time: 96 h.

Conclusions

We have synthesized and characterized the first *P*-stereogenic PNP$^{t\text{Bu,Ph}}$ Ru complex which has proven to be an efficient catalyst for the asymmetric reduction of a variety of aromatic and heterocyclic ketones. Although the enantioselectivities obtained are not superior to those reported for other commercially available catalysts, we believe that this catalyst, active in very mild operating conditions, could be of significant interest in the chemoselective reduction of ketones in the presence of sensible functional groups.

Experimental Section

Synthesis of Ru Complex 3: A Schlenk flask was charged under argon with [RuHCl(PPh$_3$)$_3$(CO)] (118 mg, 0.12 mmol), 2,6-Bis-*P,P*-[(*tert*-butylphenylphosphanyl)methyl]pyridine (65 mg, 0.14 mmol) and benzene (6.0 mL). The mixture was heated at 80 °C for 3 h and then filtered. The filtrate was concentrated to dryness and then the resulting yellow oil was dissolved in THF (1 mL) and pentane (10 mL). The precipitated solid was filtered, washed with pentane (3× 2 mL) and dried under vacuum to afford Ru complex **3** (63 mg, 85%). ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 7.82–7.78 [m, 4 H, *ortho*-P(*Ph*)$_2$], 7.64 (t, *J* = 7.6 Hz, 1 H, pyridine-*H4*), 7.51–7.48 [m, 6 H, *meta,para*-P(*Ph*)$_2$], 7.37 (dd, *J* = 7.6, 2.8 Hz, 2 H, pyridine-*H3,5*), 4.60 (dd, *J* = 16.0, 10.0 Hz, 1 H, -C*H*H-P), 4.14 (dd, *J* = 16.0, 10.4 Hz, 1 H, -CH*H*-P), 3.96–3.86 (m, 2 H, -C*HH*-P), 1.13 {d, *J* = 14.4 Hz, 9 H, P[C(CH_3)$_3$]$_2$}, 0.91 {d, *J* = 14.0 Hz, 9 H, P[C(CH_3)$_3$]$_2$}, –14.52 (dd, *J* = 23.6, 15.2 Hz, Ru-*H*) ppm. ^{13}C NMR (CD_2Cl_2, 100.6 MHz): δ = 210.2 (s, Ru-CO), 162.5 (dd, *J* = 8.1, 3.3 Hz, Py-*C6*), 162.3 (dd, *J* = 8.2, 3.9 Hz, Py-*C2*), 137.9 (s, Py-*C4*), 136.6 [d, *J* = 39.2 Hz, *ipso*-P(*Ph*)$_2$], 134.0 [dd, *J* = 10.1, 1.6 Hz, *ortho*-P(*Ph*)$_2$], 132.7 [dd, *J* = 10.1, 1.1 Hz, *ortho*-P(*Ph*)$_2$], 131.8 [dd, *J* = 34.7, 2.3 Hz, *ipso*-P(*Ph*)$_2$], 130.2 [d, *J* = 2.2 Hz, *para*-P(*Ph*)$_2$], 130.0 [d, *J* = 2.2 Hz, *para*-P(*Ph*)$_2$], 128.3 [d, *J* = 9.2 Hz, *meta*-P(*Ph*)$_2$], 128.2 [d, *J* = 9.3 Hz, *meta*-P(*Ph*)$_2$], 121.1 (d, *J* = 9.8 Hz, Py-*C5*), 120.3 (d, *J* = 10.2 Hz, Py-*C3*), 40.4 (d, *J* = 22.1 Hz, -*C*H$_2$P-), 38.7 (d, *J* = 20.8 Hz, -*C*H$_2$P-), 34.7 {dd, *J* = 15.1, 5.0 Hz, P[*C*(CH$_3$)$_3$]$_2$}, 31.7 {dd, *J* = 23.8, 2.2 Hz, P[*C*(CH$_3$)$_3$]$_2$}, 26.7 {d, *J* = 4.6 Hz, P[C(*C*H$_3$)$_3$]$_2$}, 25.8 {d, *J* = 5.3 Hz, P[C(*C*H$_3$)$_3$]$_2$} ppm. ^{31}P NMR (CD_2Cl_2, 162 MHz): δ = 80.3 (d, *J* = 267.6 Hz, *Pt*BuPh), 64.3 (d, *J* = 267.4 Hz, *Pt*BuPh) ppm. IR (KBr, neat): $\tilde{\nu}$ = 1969.9 (ν_{RuH}), 1890.3 (ν_{CO}) cm^{-1}. $C_{28}H_{36}ClNOP_2Ru$ (601.07): calcd. C 55.95, H 6.04, N 2.33; found C 55.39, H 5.59, N 2.23.

Typical Procedure for the Asymmetric Hydrogenation of Ketones: An autoclave was charged inside the glove-box with catalyst **3** (0.0025 mmol), *t*BuOK (0.025 mmol), EtOH (5 mL) and ketone (0.5 mmol). The autoclave was then removed from the glove-box and immediately pressurized to the appropriate H_2 pressure and temperature. After the desired reaction time, the autoclave was depressurized. Conversion was calculated by ^{1}H-NMR and enantiomeric excess by GC (Chirasil-Dex CB or β-ciclodex 120).

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