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Note

A chiral [(dipyridylphosphine)$RuCl_2$(1,3-diphenylpropanediamine)] catalyst for the hydrogenation of aromatic ketones

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Abstract

The use of chiral 1,3-diphenylpropanediamine in combination with Ru-Xyl-P-Phos, gave up to 95% ee in the hydrogenation of acetophenone.

Keywords: [(Diphosphine)$RuCl_2$(diamine)]catalyst; Asymmetric hydrogenation

1. Introduction

The asymmetric reduction of simple ketones is an important reaction of great industrial relevance. Pioneering work by Noyori, in the mid 1990s, showed that ruthenium complexes of the type [(diphosphine)-$RuCl_2$-(diamine)] used in 2-propanol in the presence of a base are very efficient and selective catalysts for the asymmetric reduction of unfunctionalised ketones [1]. Since Noyori's work using XylBinap [2] a number of other groups have demonstrated the use of other diphosphines that give rise to high activities and selectivities when used in this catalyst system [3–9]. Until recently much less effort had been dedicated to the modification of the diamine ligand. Most phosphines have exclusively been used in conjunction with 1,2 diamines, with DPEN and DAIPEN [10] being favoured. We undertook a program of research to investigate the effect of other diamines in this catalyst system with the aim of ultimately tuning the selectivity of the catalyst to extend even further the range of potential substrates. Our working hypothesis for this being that changing the ring-size of the chelate between the diamine and metal centre would alter the orientation of the N–H group thus potentially changing the hydrogen bond interaction with the ketone that is believed to occur in the catalytic cycle [11,12]. We and others have reported the use of a 1,4 diamine that alters the properties of the catalyst remarkably allowing, for example, the tuning of the catalyst for the reduction of cyclic ketones such as tetralone in high selectivities [13,14]. Herein, we report our findings on the use of a simple 1,3 diamine in the [(diphosphine)$RuCl_2$(diamine)] system. Our initial step into this area was to investigate the use of 1,3-diphenylpropanediamine (DPPN) in the catalyst system using P-Phos as the ligand [3]. P-Phos was chosen due to both the excellent enantioselectivites achieved with DPEN and also the synthesis of this ligand already undertaken by our group. The synthesis of the enantiomerically pure DPPN is summarized in Scheme 1 and is similar to the synthesis reported by Roos via the corresponding 1,3 propanediol, which in the original synthesis, had been accessed via Sharpless methodology [15].

Our starting point for the synthesis of the chiral diol was the commercially available dibenzoylmethane (**1**). The diketone was reduced under transfer hydrogenation conditions developed by Cossi using [(*N*-tosyl-DPEN)RuCl(*p*-cymene)] as catalyst, with HCOOH:NEt_3 5:2 azeotropic mix as hydrogen source in CH_2Cl_2 [16]. The diol was treated with MsCl to form the dimesylate and then displaced

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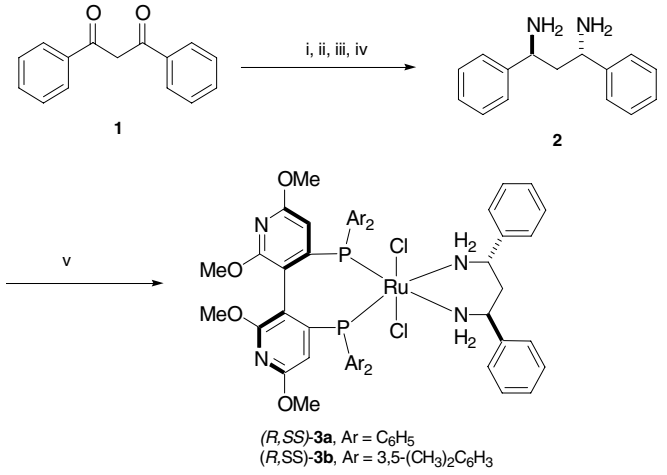


Scheme 1. Reagents and conditions: (i) RuCl(*p*-cymene)(Ts-DPEN), $HCOOH/NEt_3$ 5:2 azeotropic mix, CH_2Cl_2, 50 °C, 24 h, 90%; (ii) MsCl, NEt_3, THF, 0 °C to rt, 3 h; (iii) NaN_3, DMF, rt, 24 h, 80%; (iv) 5% Pd/C, H_2 (5.5 bar), MeOH, rt, 2 h; (v) Xyl-P-Phos-$RuCl_2$-(dmf)*x*, DMF, rt.

with NaN_3 at room temperature in DMF under the conditions developed by Roos [15]. The diazide was reduced using 10% Pd/C in methanol under a hydrogen pressure of 5.5 bar to give the enantiomerically pure diamine **2** in quantitative yield. The catalysts **3a**–**b** were prepared according to the literature methodology [2]. Single crystal X-ray analysis of (*R*, *SS*)-**3b** is shown in Fig. 1.

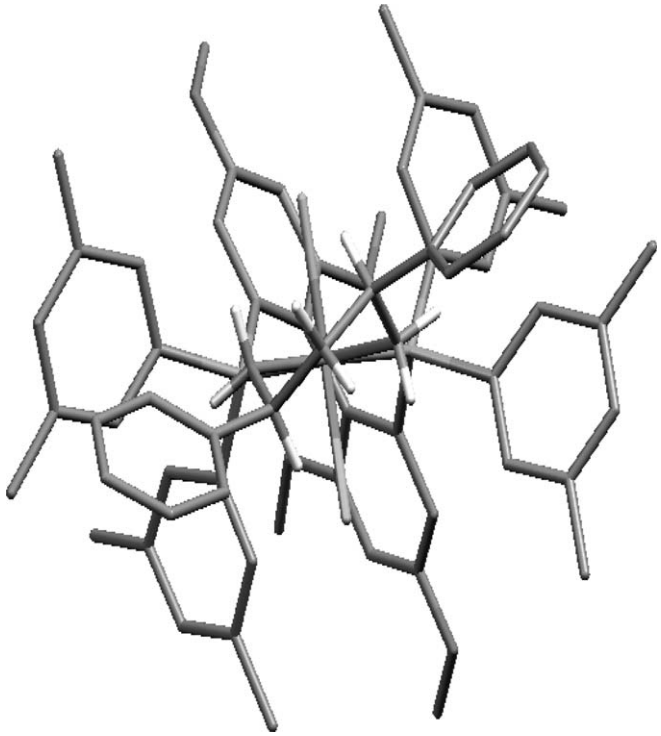
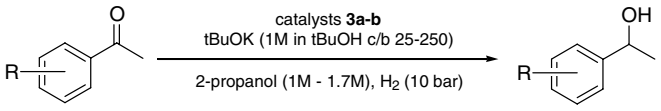


Fig. 1. (*R*)-Xyl-P-Phos-$RuCl_2$-(*S*, *S*)DPPN catalyst. All hydrogen atoms, except the amino and methine hydrogens have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Ru–N1 2.186(5), Ru–N2 2.174(5), Ru–P1 2.2784(15), Ru–P2 2.2822(14), Ru–Cl1 2.4197(14), Ru–Cl2 2.4174(14); N1–Ru–N2 82.51(19), P1–Ru–P2 92.68(5), Cl1–Ru–Cl2 166.37(5).

The ligated DPPN assumes a six membered ring with a λ conformation, with the phenyl substituents oriented in the equatorial direction. The Xyl-P-Phos ligand also adopts a λ seven membered chelate with Ru with the xylyl moieties adopting axial and equatorial arrangements. The catalytic behaviour of the catalysts **3a**–**b** was then examined using acetophenone as the test substrate (Scheme 2 and Table 1).

Preliminary experimental results revealed that rapid and highly enantioselective catalytic hydrogenation of acetophenone was achieved using catalyst **3b**. The hydrogenation of acetophenone using (*R*, *SS*)-**3b** at a molar substrate to catalyst (*s*/*c*) ratio of 1000 under 10 bar H_2 in 2-propanol with *t*BuOK gave >99% conversion in less than 2 h with an ee of 95% of the S alcohol. The importance of the correct combination of ligand components was demonstrated as the (*S*, *SS*)-**3b** catalyst gave only an ee of 69% in the hydrogenation of acetophenone under identical conditions. The importance of the Xyl-P-Phos ligand was also underlined as a significantly lower ee was obtained using the parent P-Phos catalyst **3a**. The practical utility of the catalyst **3b** was demonstrated with the hydrogenation of acetophenone at *s*/*c* 10,000, using catalyst (*S*, *RR*)-**3b**. Acetophenone was smoothly converted to the R alcohol in 95% ee with an average TOF of 1400 h^{-1}. A brief survey of ring substituted aromatic ketones using catalyst **3b** also gave excellent selectivities irrespective of the presence of electron donating or withdrawing substituents on the *para* or *meta* positions. The highly electron deficient 3,5-bis(trifluoromethyl)acetophenone was hydrogenated in high ee. The use



Scheme 2.

Table 1
Hydrogenation of aromatic ketones using catalysts **3a**–**b**[a]

Entry	Ketone	Catalyst	*s*/*c*[b]	ee (%)[c]
1	R = H	(*R*, *SS*)-**3a**	1000	36 (*S*)
2	R = H	(*R*, *SS*)-**3b**	1000	95 (*S*)
3	R = H	(*S*, *SS*)-**3b**	1000	69 (*R*)
4	R = H	(*S*, *RR*)-**3b**	2500	95 (*R*)
5	R = H	(*S*, *RR*)-**3b**	10,000	95 (*R*)
6	R = *p*-F	(*S*, *RR*)-**3b**	2500	95 (*R*)
7	R = *p*-OMe	(*S*, *RR*)-**3b**	2500	97 (*R*)
8	R = *m*-Me	(*S*, *RR*)-**3b**	2500	96 (*R*)
9	R = *o*-Me	(*R*, *SS*)-**3b**	1000	86 (*S*)
10	R = *o*-OMe	(*R*, *SS*)-**3b**	1000	84 (*S*)
11	R = 3,5-CF_3	(*S*, *RR*)-**3b**	1000	95 (*R*)

[a] Reaction conditions: 2–5 mmol substrate; 25 °C. Reaction times 2–24 h to obtain 100% conversion.

[b] Molar ratio of substrate to catalyst.

[c] The ee were determined by chiral GC (Chrompack Chirasil-DEX CB column). The absolute configuration was determined by comparison of the retention time with the literature data.

of catalyst (*S*, *RR*)-**3b** gave the corresponding R alcohol in 95% ee, which is a precursor for the synthesis of potent NK1 receptor antagonists [17]. Substituents in the *ortho* position, however, were not tolerated so well and resulted in a lower ee. In summary, we have shown that the introduction of the chiral 1,3 DPPN diamine in combination with Xyl-P-Phos produces a ruthenium catalyst of broad applicability for the hydrogenation of substituted acetophenones. It emerges from the data collected that the properties largely mirror the analogous 1,2-DPEN catalyst and that the structural modification associated with the presence of the six membered chelate ring instead of the five membered chelate ring do not impart radical new properties on the catalyst. The rates and enantioselectivities obtained using catalyst **3b**, however, are high and therefore make this a practically useful process for the preparation of chiral alcohols.

2. Experimental

*General procedure for preparation of catalyst **3b**:* A solution of Xyl-P-Phos (0.1 mmol) and $RuCl_2$(benzene) dimer (0.5 mmol) in DMF (1 ml) was heated at 100 °C for 2 h. The mixture was cooled to rt and the DPPN ligand (0.1 mmol) added after which the mixture was stirred at rt for 2 h. The solvent was removed in vacuo to give the catalyst as a golden brown solid which was used without further purification for the hydrogenation reactions. Catalyst (*S*, *RR*)-**3b** ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.57 (s); (*R*, *RR*)-**3b** ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.94 (s). Single crystals of (*S*, *RR*)-**3b** were obtained by slow diffusion of hexane into a CH_2Cl_2 solution of (*S*, *RR*)-**3b**. A single crystal was placed in a capillary tube and mounted on a Nonius Kappa CCD X-ray diffractometer. The structure was solved using direct methods (SHELXS-97). Crystal data: $C_{63}H_{70}Cl_2N_2O_4P_2Ru$, C_6H_{14}, $M = 1239.29$, orthorhombic, $a = 21.04380(10)$, $b = 25.2877(2)$ $c = 25.3512(2)$ Å, $U = 13{,}490.62(16)$ Å^3, $T = 180$ K, space group $P2_12_12$, $Z = 8$, μ(Mo Kα) = 0.405 mm^{-1}, $F_{obs} = 5928$, 30,064 reflections measured, 27,700 unique ($R_{int} = 0.0780$) which were used in all calculations. The final $wR(F^2)$ was 0.2107 (all data), R factor = 0.0071, goodness of fit = 1.073, Flack parameter = 0.03(3). The X-ray crystallography data (the cif file) for (*S*, *RR*)-**3b** (CCDC 249622) has been deposited with the Cambridge Crystallographic Data Center as supplementary material.

Hydrogenation of acetophenone at *s*/*c* 10,000: Catalyst (*S*, *RR*)-**3b** (0.5 μmol) was placed in an Argonaut Endeavor reaction pressure vessel. To this was added acetophenone (5 mmol), *t*BuOK (1 M in *t*BuOH, *b*/*c* 250) and 2-propanol (5 ml). The mixture was pressurised with H_2 (10 bar) and stirred at 1000 rpm until hydrogen consumption had ceased (6 h). The pressure was released and a sample analysed by chiral GC (Chrompack Chirasil-DEX CB column).

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