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Asymmetric Hydrogenation of Isobutyrophenone Using a [(Diphosphine) RuCl₂ (1,4-Diamine)] Catalyst

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ABSTRACT



The use of three chiral 1,4-diamines in the [(diphosphine) $RuCl_2$ (diamine)] catalyst system is demonstrated in the hydrogenation of acetophenone. The use of a 1,4-diamine offers unique properties that allow tuning of the catalyst system. These include the first example of the use of a racemic diamine in combination with a chiral phosphine, which gives 95% ee in the hydrogenation of isobutyrophenone

The preparation of enantiomerically pure secondary alcohols is among one of the most important reactions for the manufacture of pharmaceutical intermediates. The asymmetric reduction of ketones represents the simplest and most powerful method for the production of these chiral alcohols. The use of hydrogen, a clean and inexpensive gas, in the presence of a small amount of a catalyst makes this approach highly viable for industrial application. The most general and efficient catalyst for this reaction was pioneered by Noyori, who showed that ruthenium complexes of the type [(diphosphine)-RuCl₂-(diamine)], used in the presence of a base in 2-propanol, are extremely efficient and selective catalysts for the asymmetric reduction of unfunctionalized 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.³⁻⁷ Much less effort has been dedicated

to the modification of the diamine ligand. Most phosphines have been exclusively used in conjunction with 1,2-diamines, with DPEN and DAIPEN being favored.⁸ We sought 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

(7) Dominguez, B.; Zanotti-Gerosa, A.; Hems, W. Org. Lett. 2004, 6, 1927.

(8) DPEN = 1,2-Diphenylethylenediamine; DIAPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine; see: Wey, S.; O'Conner, K. J.; Burrows, C. J. *Tetrahedron Lett.* **1993**, *34*, 1905.

⁽¹⁾ Noyori, R. Angew. Chem., Int. Ed. **2002**, 41, 2008. (b) Noyori, R.; Ohkuma, T. Angew Chem., Int. Ed. **2001**, 40, 40.

⁽²⁾ Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. J. Am. Chem. Soc. **1998**, 120, 13529. Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. J. Am. Chem. Soc. **2000**, 122, 6510. Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. Org Lett. **2000**, 2, 659.

⁽³⁾ Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung C.-H.; Chan, A. C. S. J. Org. Chem. 2002, 67, 7908. Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. C. S. Chem. Eur. J. 2003, 9, 2963.

^{C.-H.; Chan, A. C. S.} *Chem. Eur. J.* 2003, *9*, 2963.
(4) Scalone, M.; Waldmeier, P. *Org. Process Res. Dev.* 2003, *7*, 418.
(5) Henschke, J. P.; Zanotti-Gerosa, A.; Moran, P.; Harrison, P.; Mullen, B.; Casy G.; Lennon, I. C. *Tetrahedron Lett.* 2003, *44*, 4379.

⁽⁶⁾ Burk, M.; Hems, W.; Herzburg, D.; Malan C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.

working hypothesis for this was that chiral 1,4-diamines would change the orientation of the N–H group by forming a seven-membered chelate with the metal center. Hence, the hydrogen bond interaction with the ketone that is believed to occur in the catalytic cycle will be altered, which may open up the opportunity to tune the catalyst for the reduction of a larger range of ketones.9 Our choice of 1,4-diamines was analogous to the fact that many phosphine ligands exist as a seven-membered chelate with the metal center and that the aryl groups on the phosphorus atoms adopt axial and equatorial positions. Three such phosphorus ligands used in Rh hydrogenation have been DIOP,¹⁰ SK-PHOS,¹¹ and BPPM,¹² and therefore we sought to prepare the structurally analogous diamines. Noyori has very recently reported the use of $[(Xy|Binap) RuCl_2 (1)]$, which gave excellent selectivities in the hydrogenation of cyclic ketones.¹³

Diamines **1** and **3** were synthesized according to literature methodology,¹⁴ and **2** was synthesized from azide displacement of the known dimesylate. The diamines were reacted with chiral Ru phosphine complexes from the Binap and P-Phos families according to literature procedures. Single-crystal X-ray analysis of [(S)-Binap RuCl₂ (R)-**1**] is shown in Figure 2. As expected, the diamine forms a seven-



Figure 1. Diphosphine and diamine structures.

membered chelate with λ configuration. The Binap ligand adopts a δ seven-membered chelate with Ru with the phenyl moieties adopting axial and equatorial arrangements. The catalytic behavior of the catalysts was first examined using acetophenone as a substrate (Table 1).

- (10) Kagan, H. B.; Dang, T.-P. J. Am. Chem. Soc. 1972, 94, 6429.
- (11) Li, W.; Waldkirch, J. P.; Zhang, X. J. Org. Chem. 2003, 67, 7618.
- (12) Achiwa, K. J. Am. Chem. Soc. 1976, 98, 8265.
- (13) Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. Org. Lett. 2004, 6, 2681



Figure 2. (*S*)-Binap-RuCl₂-(*R*,*R*)-1 complex. All hydrogen atoms, except the hydrogens on the diamine, have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Ru–N1 2.239(3), Ru–N2 2.220(3), Ru–P1 2.2996(8), Ru–P2 2.3005(9), Ru–Cl1 2.4216(8), Ru–Cl2 2.4076(8), Cl1–H1A (N1) 2.610, Cl2–H2B (N2) 2.628; N1–Ru–N2 92.00(10), P1–Ru–P2 89.17(3), Cl1–Ru–Cl2 161.97(3).

Preliminary results revealed that extremely rapid hydrogenation of acetophenone was achieved using diamines **1** and **3**. Results with catalysts containing diamine **2** were less promising, with much lower conversions obtained. The hydrogenation started rapidly using this diamine but then appeared to stop, suggesting that although the active Ru hydride species was formed initially, this decomposed during the reaction. Although rapid hydrogenation of acetophenone was observed with diamine **3**, the enantioselectivities were disappointing, the highest being achieved using the sterically bulky phosphine **4b** in accordance with results observed with 1,2-diamines. The results obtained with diamine **1**, however, were much more interesting, as they showed distinct differ-

 Table 1. Hydrogenation of Acetophenone Using
 [(Diphosphine) RuCl₂ (1,4-Diamine)] Catalysts



entry	catalyst	conversion	ee
1	(R)-P-Phos RuCl ₂ (R) -1	>99	75 (R)
2	(S)-P-Phos RuCl ₂ (R) -1	>99	81(S)
3	(R)-Xyl-P-Phos RuCl ₂ (R) -1	>99	55(S)
4	(S) -Xyl-P-Phos $\operatorname{RuCl}_2(R)$ -1	>99	51(R)
5	(R)-TolBinap RuCl ₂ (R) -1	>99	70 (R)
6	(S)-TolBinap RuCl ₂ (R) -1	>99	85(S)
7	(R)-XylBinap RuCl ₂ (R) -1	>99	34(S)
8	(S)-XylBinap RuCl ₂ (R) -1	>99	64(R)
9	(S) -TolBinap RuCl $_2(R)$ -2	47	37(R)
10	(R)-TolBinap RuCl ₂ (R) -2	37	26(S)
11	(S)-Xyl-P-Phos RuCl ₂ (S) -3	>99	42(R)
12	(R)-Xyl-P-Phos RuCl ₂ (S) -3	>99	76(S)

^{*a*} Conversion and ee determined by chiral GC (Chrompack Chirasil DEX-CB column). The absolute configuration was determined by comparison of retention time with literature data.

 ⁽⁹⁾ Sandoval, C. A.; Ohkuma, T.; Muniz, K.; Noyori, R. J. Am. Chem. Soc. 2003, 125, 13490. Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. J. Am. Chem. Soc. 2001, 123, 7473.

^{(14) (}a) For diamine 1: Kim, D.-K.; Kim, G.; Gam, J.; Cho, Y.-B.; Kim, H.-T.; Tai, J.-H.; Kim, K. H.; Hong, W.-S.; Park, J.-G. *J. Med. Chem.* **1994**, *37*, 1471. (b) Diamine **3**: Nagamani, D.; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 103.

ences from the usual catalytic behavior observed with 1,2diamines. First, the use of the less sterically bulky phosphines, P-Phos 4a instead of Xyl-P-Phos 4b, gave the highest enantioselectivity. Second, there appeared to be only a small difference in the enantioselectivities obtained with either the matching or mismatching phosphine/diamine combinations, and third, the configuration of the alcohol produced was reversed to the 1,2-diamine case, with (R)-P-Phos giving the (R)-alcohol, albeit in moderate ee. These subtle differences in the hydrogenation of acetophenone heartened us to screen these catalysts against other ketone substrates. Increasing the steric bulk on the aromatic ring or the alkyl substituent of the ketone appeared to give enhanced results. For example, 93% ee was obtained in the hydrogenation of o-OMe acetophenone using (S)-P-Phos $\operatorname{RuCl}_2(R)$ -1.¹⁵ Therefore, the hydrogenation of isobutyrophenone was studied in more detail. The results are shown in Table 2.

Table 2. Hydrogenation of Isobutyrophenone Using [(Diphosphine) RuCl₂ (1,4-Diamine)] Catalysts



entry	catalyst	$conversion \ (\%)$	ee (%)
1	(R)-XylBinap RuCl ₂ (R) -DAIPEN	>99	99(S)
2	(R)-XylBinap RuCl ₂ (R) -1	>99	68(R)
3	(S)-XylBinap RuCl ₂ (R) -1	>99	58(S)
4	(S)-TolBinap RuCl ₂ (S) -1	>99	94(S)
5	(S)-TolBinap RuCl ₂ (R) -1	>99	97~(S)
6	(R)-TolBinap RuCl ₂ rac -1	>99	95(R)
7	(S)-P-Phos RuCl ₂ (R) -1	>99	97~(S)
8	(S)-P-Phos RuCl ₂ (S) -1	>99	95(S)
9	(S)-P-Phos RuCl ₂ rac-1	>99	96(S)
10	(rac)-P-Phos RuCl ₂ (S)-1	>99	9
11	(R)-Xyl-P-Phos RuCl ₂ (R) -1	>99	46(R)
12	(S)-Xyl-P-Phos RuCl ₂ (R) -1	>99	75(S)

^{*a*} Conversion and ee determined by chiral GC (Chrompack Chirasil DEX-CB column). The absolute configuration was determined by comparison of retention time with literature data.

The direct hydrogenation of isobutyrophenone has been reported using an Ir–Binap catalyst under relatively harsh conditions.¹⁶ Highly enantioselective hydrogenation of isobutyropheone using the Ru Noyori 1,2-diamine catalyst system can be obtained using XylBinap as phosphine in combination with the relatively expensive 1,2-DAIPEN diamine. The use of diamine **1** in combination with XylBinap only gave a modest ee. However, when TolBinap was used, an excellent

ee was obtained. Again the observation of no matching or mismatching phosphine/diamine catalyst combination was highlighted even more starkly with this substrate, as both gave a very high ee. When a catalyst was prepared with (R)-TolBinap and racemic diamine 1, very high enantioselectivity was obtained in the isobutyrophenone hydrogenation. We believe that this is the first example of a racemic diamine used in conjunction with a chiral phosphine in this catalyst system that gives extremely high enantioselectivity in the hydrogenation of an aromatic ketone.¹⁷ The same trend was observed with the P-Phos family of ligands. When (S)-P-Phos was used in combination with racemic 1, a very high ee was obtained. ³¹P NMR experiments confirmed that this (S)-P-Phos RuCl₂ rac-1 complex was a 1:1 mixture of the two diastereoisomers. It was also observed that the reaction rates of (S)-P-Phos RuCl₂ rac-1 and (S)-P-Phos RuCl₂ (S)-1 were identical, which would rule out a process of selective activation of one diasteroisomer of the complex. When a catalyst prepared using racemic P-Phos and chiral diamine 1 was tested, virtually no stereoinduction was observed.

In summary, we have shown that it is possible to tune the catalyst by the use of a structurally different diamine in this catalyst system. We, in parallel with others, have discovered a distinctly useful 1,4-diamine that in combination with Ru and a phosphine exhibits wide scope in the hydrogenation of two classes of aromatic ketones. For example, complementary to Noyori's paper describing the use of diamine 1, we found that the use of (S)-Xyl-P-Phos RuCl₂ (R)-1 gave 96% ee in the hydrogenation of tetralone.¹⁸ Herein, we have modified the catalyst further to show that in combination with Ru P-Phos, high enantioselectivities can be obtained for other aromatic ketones such as acetophenone derivatives. The unique tuning of the complex allows for very high selectivities to be obtained in the hydrogenation of isobutyrophenone even with the use of a racemic diamine in the presence of a chiral phosphine.

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Supporting Information Available: Experimental procedures and NMR characterization data for all new [(diphosphine) RuCl₂ (diamine)] catalysts described in the text, a representative example of the hydrogenation procedure, and also further examples of the hydrogenation of aromatic ketones such as tetralone derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁵⁾ See Supporting Information for a full table of results.

⁽¹⁶⁾ Zhang, Z.; Kumobayashi, H.; Takaka, H. *Tetrahedron: Asymmetry* **1994**, 1179.

⁽¹⁷⁾ For an example of a conformationally flexible phosphine and chiral diamine, see: Mikami, K.; Korrenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. Angew. Chem., Int. Ed. **1999**, 38, 495. Mikami, K., Matsukawa, S. Nature **1997**, 285, 613. Aikawa, K.; Mikami. K. Angew Chem., Int. Ed. **2003**, 42, 5455. Mikami, K.; Korenaga, T.; Yusu, Y.; Yamanaka, M. Adv. Synth. Catal. **2003**, 345, 246.

⁽¹⁸⁾ See Supporting Information for a full table of the hydrogenation of cyclic aromatic ketones such as tetralone.