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A new chiral dipyridylphosphine ligand Xyl-P-Phos and its application in the Ru-catalyzed asymmetric hydrogenation of β-ketoesters

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Abstract—A new chiral dipyridylphosphine ligand Xyl-P-Phos has been synthesized and the structure of (*S*)-Xyl-P-Phos oxide has been characterized by single crystal X-ray diffraction. The ruthenium complex of this ligand, Ru(*R*-Xyl-P-Phos)(C_6H_6)Cl_2, has been found to be a highly active, enantioselective and air-stable catalyst for the asymmetric hydrogenation of β-ketoesters and shows good potential for industrial applications. © 2002 Published by Elsevier Science Ltd.

The transition-metal-catalyzed asymmetric hydrogenation reaction is one of the most efficient methods for preparing a wide range of enantiomerically pure compounds.[1] The quest for highly efficient chiral ligands plays a crucial role in expanding the utility of this strategy. Consequently, the number of novel chiral ligands for catalytic asymmetric hydrogenation is growing rapidly and chiral bisphosphines (e.g. DIPAMP, BINAP, BIMAP, DIOP, DuPhos, BDPP, etc.) have proved to be among the most useful and versatile ligands.[1,2] In contrast to the tremendous success achieved in the use of chiral arylphosphine ligands in Rh- and Ru-catalyzed asymmetric reactions, chiral phosphine ligands containing heterocyclic moieties such as pyridyl groups have been relatively unexplored even though the expansion of the scope of the metal phosphine chemistry with the rich chemistry of heterocyclic functionalities is quite obvious. Some transition-metal complexes with pyridylphosphine ligands have been synthesized and found to be inactive in homogeneous hydrogenations.[3] We have developed a class of dipyridylphosphine ligands (Fig. 1), P-Phos **1**[4a,4b] and

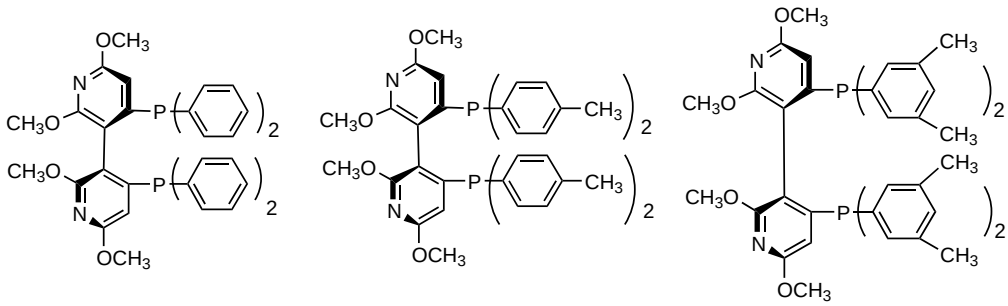

Figure 1.

Keywords: asymmetric hydrogenation; dipyridylphosphine ligands; ruthenium complex; β-ketoester.

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Tol-P-Phos **2**,[4c] and found their Ru(II) complexes to be highly effective in the catalytic asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid and β-ketoesters.

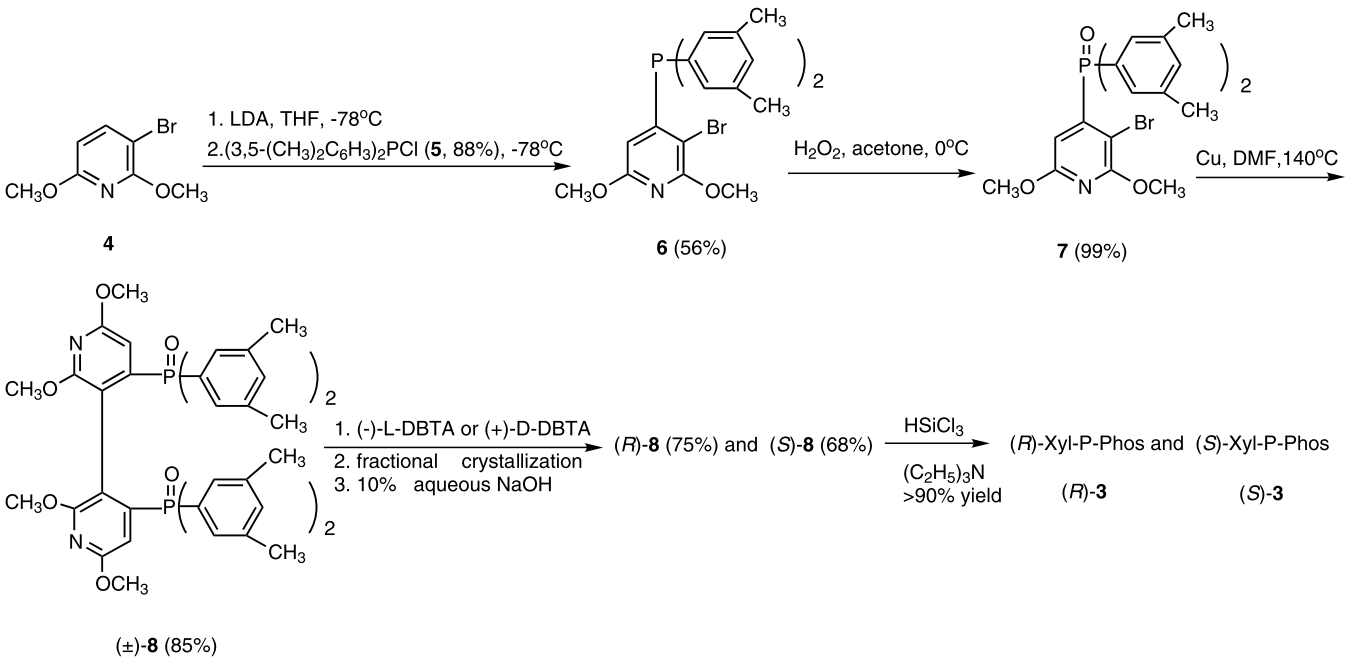
Since steric hindrance effects are important in the development of effective chiral ligands, in this study, we have now synthesized a new P-Phos derivative 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridine (Xyl-P-Phos **3**) by introducing 3,5-dimethyl groups into the four phenyl rings in P-Phos as a means to tune its electronic and steric properties. The results revealed that the new ligand **3** was even more effective than **1** and **2** in the Ru-catalyzed hydrogenation of β-ketoesters. Herein, we report the synthesis of **3** (Scheme 1), the molecular structure of the complex of (*S*)-**3** oxide with (+)-dibenzoyl-D-tartaric acid ((+)-DBT), as well as the application of this new ligand in asymmetric hydrogenations.

Our synthetic approach to the enantiomerically pure ligands (*R*)- and (*S*)-**3** is depicted in Scheme 1. The *ortho*-lithiation[5] of **4** with lithium diisopropylamide (LDA) in THF at −78°C followed by the addition of bis(3,5-dimethylphenyl)chlorophosphine (**5**) produced **6** in 56% yield. Substituted pyridine **4** was prepared according to a literature method[4c,6] whilst the chlorophosphine species **5** was obtained by treating $(Et_2N)PCl_2$ with 2 equiv. of ArMgBr (Ar = 3,5-$(CH_3)_2C_6H_3$) followed by the treatment with dry HCl (88% yield).[7] The oxidation of **6** with H_2O_2 in acetone at 0°C provided **7** (99% yield) which was transformed to the racemic oxide **8** of Xyl-P-Phos (85% yield) via an Ullmann coupling reaction. Reduction of the resolved phosphine oxide **8** by trichlorosilane in the presence of triethylamine afforded optically pure ligand Xyl-P-Phos **3** which was characterized by ^1H, ^{13}C, ^{31}P NMR and mass spectroscopy and elemental analysis.[8]

The optical resolution of the racemate (±)-**8** was carried out via the formation of complexes with resolving agents (2*R*,3*R*)-(−)- and (2*S*,3*S*)-(+)-DBT.[9] The absolute configuration of (−)-**8** was established as *S* by a single crystal X-ray analysis of the diastereoisomerically pure 1:1 complex of (−)-**8**-(+)-DBT (Fig. 2).[10] In the complex, equimolar (−)-**8** and (+)-DBT are connected in a regularly alternating manner through two intermolecular hydrogen bonds between the hydrogen atoms of the COOH groups of (+)-DBT and the oxygen atoms [O(1) and O(2)] of the P=O groups in compound **8** thus building up infinite close-packed chains. The O(1)···O(7) and O(2A)···O(10) distances are 2.505 and 2.488 Å, respectively. The enantiomeric purity of (+)-**8**, resolved by this method, was over 99.9% ee according to HPLC analysis.[11]

To examine the efficiency of the new chiral ligand **3** in transition-metal-catalyzed asymmetric hydrogenation reactions in comparison with those of **1** and **2**, we first prepared Ru(*R*-Xyl-P-Phos)$(C_6H_6)Cl_2$ [(*R*)-**9**] using the method of Mashima et al. (Scheme 2).[12] The coordination of benzene to ruthenium makes the two phosphorus atoms of (*R*)-**3** magnetically non-equivalent, therefore the ^{31}P NMR spectrum of (*R*)-**9** displayed an AB pattern centered at δ 33.49 (J_{PA-PB} = 62.1 Hz) and 39.96 (J_{PA-PB} = 62.5 Hz). The absorption observed at δ 5.65 in the ^1H NMR spectrum is assignable to the η^6-coordinated benzene moiety.

(*R*)-**9** was tested in the asymmetric hydrogenation of a variety of β-ketoesters **10a–d** to give optically active β-hydroxy carboxylic esters, which are an important class of intermediates for the synthesis of various compounds such as carbacephems, tetrahydrolipstatin or (+)-brefeldin A.[13] The experimental results are summarized in Table 1. The hydrogenation of **10a** as a standard substrate was attempted first and it was found



Scheme 1. The synthetic route towards Xyl-P-Phos **3**.

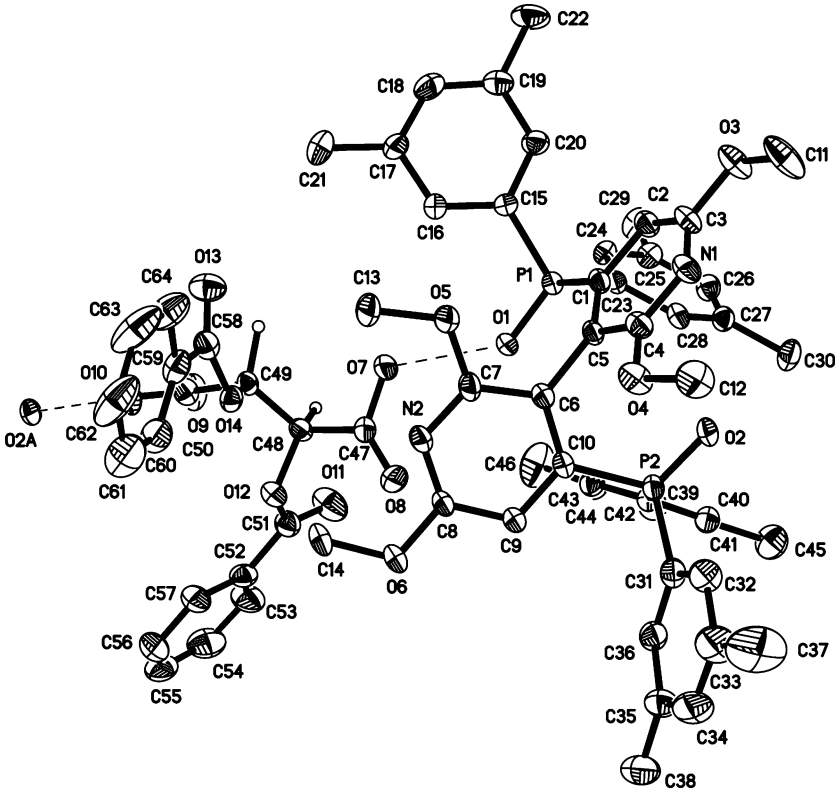


Figure 2. ORTEP drawing of the complex (*S*)-**8**-(+)-DBT with numbering schemes. Selected bond distances (Å): C(5)–C(6) = 1.500(4), P(1)–C(1) = 1.813(3), P(2)–C(10) = 1.818(3), P(1)–O(1) = 1.497(19), P(2)–O(2) = 1.497(2), O(1)···O(7) = 2.505, O(2A)···O(10) = 2.488.

$$[RuCl_2(C_6H_6)]_2 + (R)\text{-Xyl-P-Phos} \xrightarrow[EtOH\text{-}C_6H_6\ (8:1)]{50\text{-}60^oC,\ 1\ h} Ru(R\text{-Xyl-P-Phos})(C_6H_6)Cl_2$$

(*R*)-**3** (*R*)-**9** (88%)

Scheme 2.

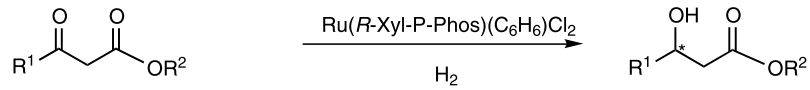
that the reaction at 70°C under 200 psi of H_2 was completed in only 1 h with 97.1% ee (entry 1). Further studies on the hydrogenation of other β-ketoesters confirmed the consistently high activity and enantioselectivity of **9** in these reactions (entries 2–7).

While enantioselectivity is a major concern in asymmetric synthesis, the demonstration of high substrate-to-catalyst ratio with consistently high enantioselectivity is an important measure of the commercial feasibility of a reaction. In this study, it was found that the high ee values were essentially maintained when a high substrate-to-catalyst ratio was used. The hydrogenation of **10d** (30 g) catalyzed by (*R*)-**9** with an S/C ratio of 7500 (M/M) proceeded smoothly and afforded a useful pharmaceutical intermediate (*S*)-3-hydroxy-3-phenyl propionate (**11d**) with 93.2% ee in 98% yield (Table 1, entry 11), whereas, when using Ru(*R*-P-Phos)(C_6H_6)Cl_2 and Ru(*R*-Tol-P-Phos)(C_6H_6)Cl_2 as catalysts under identical reaction conditions, the yields were 84% (90.6% ee, entry 12) and 90% (91.3% ee, entry 13),[4c] respectively.

Most metal phosphine catalysts are air-sensitive in solution and even trace amounts of air in the reaction system may lead to a significant decrease of the catalyst activity and enantioselectivity. The rigorous degassing of reaction systems using nitrogen gas is essential to keep the activities of many catalysts, which makes industrial applications more difficult. In this study, we found the Ru(*R*-Xyl-P-Phos)(C_6H_6)Cl_2 catalyst system to be air-stable even in the solution state. When experimental procedures prior to the introduction of hydrogen were performed in air, the rate and enantioselectivity of the hydrogenation of **10d** showed no variation (100% conversion, 96.1% ee, entry 7) from the air-purged system (100% conversion, 96.2% ee, entry 8). Even when the solution of (*R*)-**9** was exposed to air for 10 h, its activity and enantioselectivity remained essentially unchanged (100% conversion, 95.5% ee, entry 9).

A ^{31}P NMR study also supported the above results and proved the high air-stability of **9**. The catalyst solution, which had been stirred for 10 h under air, had the same ^{31}P NMR spectrum [$CDCl_3$, 500 MHz, δ 33.49 (d, J = 62.9 Hz), 39.96 (d, J = 62.5 Hz)] as that obtained under N_2. The excellent air-stability of **9** makes the experimental operation more convenient and shows a good potential for its industrial application.

Table 1. The asymmetric hydrogenation of β-ketoesters[a]



R^1=CH_3, R^2=C_2H_5, **10a** **11a**

R^1=CH_3, R^2=$CH_2C_6H_5$, **10b** **11b**

R^1=CH_2Cl, R^2=C_2H_5, **10c** **11c**

R^1=C_6H_5, R^2=C_2H_5, **10d** **11d**

Entry	Substrate	S/C (M/M)	PH_2 (psi)	T (°C)	Time (h)	Conv. (%)	ee (%)
1[b,c]	**10a**	400	200	70	1	100	97.1
2[b,c]	**10b**	400	300	80	2	100	96.6
3[b,c]	**10b**	800	300	80	3	100	96.1
4[b,c]	**10b**	2800	300	80	15	100	94.5
5[b,c]	**10c**	400	300	80	2	100	94.8
6[b,c]	**10c**	2800	300	80	13	100	93.7
7[b,d]	**10d**	800	300	90	2	100	96.2
8[d,e]	**10d**	800	300	90	2	100	96.1
9[d,f]	**10d**	800	300	90	2	100	95.5
10[d,g]	**10d**	5000	350	90	10	100	93.3
11[d,g]	**10d**	7500	350	90	15	98	93.2
12[d,g]	**10d**	7500	350	90	15	84	90.6
13[d,g]	**10d**	7500	350	90	15	90	91.3

[a] Ru(*R*-Xyl-P-Phos)(C_6H_6)Cl_2 was used as catalyst in entries 1–11; Ru(*R*-P-Phos)(C_6H_6)Cl_2 was used as catalyst in entry 12; Ru(*R*-Tol-P-Phos)(C_6H_6)Cl_2 was used as catalyst in entry 13; the substrate and catalyst were added to the stainless steel autoclave under N_2 and the solvents were degassed and dried prior to use except when otherwise stated.

[b] Reaction conditions: 100–400 mg substrate; substrate concentration = 1.04–2.92 M in EtOH/CH_2Cl_2.

[c] The conversion yield and the ee were determined by chiral GC with a Chrompack Chirasil-DEX CB column after converting the products to the corresponding acetyl derivatives.

[d] The conversion yield and the ee were determined by 500 MHz ^1H NMR and HPLC analysis (Daicel Chiralcel OD column).

[e] The substrate and catalyst were added to the stainless steel autoclave in air and the solvents were not degassed or dried prior to use.

[f] The catalyst solution in EtOH and CH_2Cl_2 was stirred for 10 h under air before the addition of substrate and H_2.

[g] 30 g substrate; substrate concentration = 4.11 M; the substrate and catalyst were added to the stainless steel autoclave under N_2 and the solvents were degassed and dried prior to use.

In summary, we have developed a new dipyridylphosphine ligand Xyl-P-Phos (**3**) and found its Ru complex **9** to be air-stable and highly effective in the asymmetric hydrogenation of β-ketoesters. The unique air-stability of this class of complexes makes the experiments convenient to operate and shows a good potential for their industrial application.

Acknowledgements

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8. Spectral data for **3**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.20 (s, 12H, PhCH_3), 2.25 (s, 12H, PhCH_3), 3.37 (s, 6H, OCH_3), 3.83 (s, 6H, OCH_3), 6.06 (d, $J=1.5$ Hz, 2H, PyH), 6.79–6.92 (m, 12H, PhH). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 21.54 (d, $J=4.78$ Hz), 53.06, 53.43, 105.47, 115.39 (t, $J=37.07$ Hz), 130.47 (d, $J=33.81$ Hz), 131.46 (t, $J=20.99$ Hz), 132.42 (t, $J=21.74$ Hz), 135.69 (t, $J=10.05$ Hz), 136.88 (t, $J=12.82$ Hz), 137.39 (t, $J=8.04$ Hz), 137.71 (t, $J=7.16$ Hz), 154.64, 154.70, 154.75, 160.76 (t, $J=11.18$ Hz), 162.30. ^{31}P NMR ($CDCl_3$, 500 MHz): δ −11.99. LSMS [M$^+$] calcd $C_{46}H_{50}N_2O_4P_2$: 756.85. Found: 757. Anal. calcd for $C_{46}H_{50}N_2O_4P_2$: C, 73.00; H, 6.66; N, 3.70. Found: C, 72.59; H, 6.89; N, 3.27.
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10. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172510. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
11. The optical purities of the resolved **8** were determined by HPLC analysis (Diacel-AD column, eluted by hexane:2-propanol=4:96, flow rate=1.0 mL/min, $\lambda_{max}=254$ nm, t_R of (*S*)-**8**, 9.33 min; t_R of *R* isomer, 15.25 min). $[\alpha]_D^{20}$ of (*R*)-**8**: +253.2° (*c* 1.01, $CHCl_3$).
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