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LETTERS

Enantioselective Hydrogenation of β-Keto Esters Catalyzed by P-Chiral Bis(dialkylphosphino)ethanes–Ru(II)

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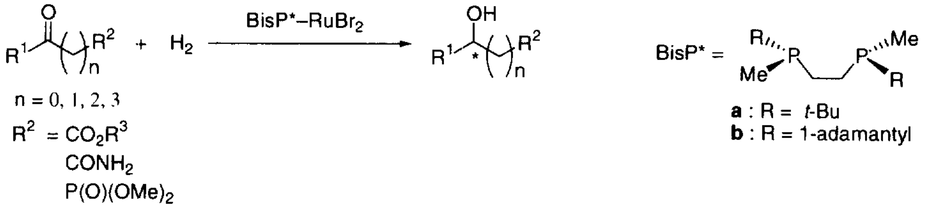
Abstract: Asymmetric hydrogenation of keto esters using a BisP*–RuBr$_2$ catalyst is reported. High enantioselectivities up to 98% were achieved in the hydrogenation of β-keto esters.

Chiral phosphine ligands having the stereogenic center at the phosphorus atom, P-chiral phosphine ligands, have received considerable attention in various transition-metal-catalyzed asymmetric reactions.[1-3] The proximity of the stereogenic center to the reaction center is anticipated to provide high enantioselectivity. Among P-chiral phosphine ligands, despite their relative scarcity, 1,2-bis(alkylmethylphosphino)ethanes (abbreviated to BisP*) have proved to be highly effective ligands in the asymmetric hydrogenation of α-(acylamino)acrylic derivatives.[3] Herein, we wish to report our preliminary results on the asymmetric hydrogenation of keto esters[4] (Scheme 1) to indicate their broad applicability to a wide variety of catalytic asymmetric reactions.



Scheme 1

Preparation of the BisP*–RuBr$_2$ complex was carried out by reacting BisP* with (COD)Ru(2-methylallyl)$_2$, followed by treatment with methanolic HBr in acetone according to the method utilized by Burk in the preparation of the BPE–RuBr$_2$ complex.[5,6] The asymmetric hydrogenations were carried out at 50 - 70 °C, and an initial H_2 pressure of 6 kg/cm^2 in the presence of the BisP*–RuBr$_2$ complex (catalyst/substrate = 0.13 - 1.4 mol %).[7]

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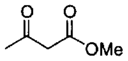
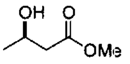
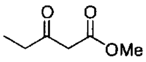
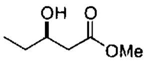
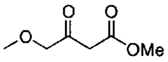
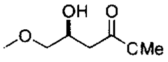
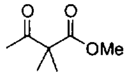
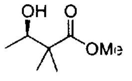
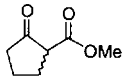
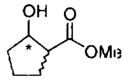
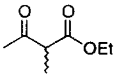
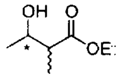
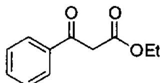
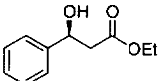
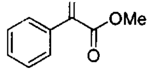
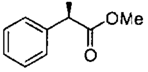
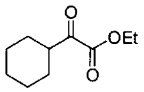
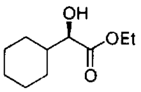
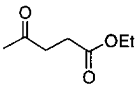
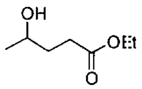
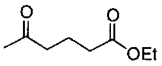
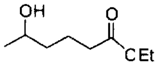
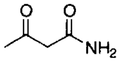
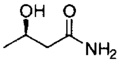
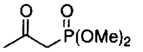
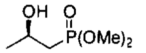
Table 1. Asymmetric hydrogenation of keto esters with BisP*– Ru(II) catalysts[a]

Entry	Substrate	BisP*	Product	Yield (%)	% ee [b]
1		**a**		86	97
2[c]		**a**		96	98
3		**b**		18	87
4		**a**		100	81
5		**a**		81	98
6[d]		**a**		(*syn*) 13 (*anti*) 70	91 96
7		**a**		(*syn*) 39 (*anti*) 45	96 97
8		**a**		100	89
9		**a**		90	70
10		**a**		77	50
11		**a**		No reaction	
12		**a**		No reaction	
13[e]		**a**		100	89
14[f]		**a**		51	85

a) Reaction conditions: substrate 2 mmol, catalyst/substrate = 0.5 mol %, 70 °C, 6 kg/cm^2. b) See ref. 8. c) See ref. 7; substrate 82 mmol, catalyst/substrate = 0.13 mol %. d) At 50 °C. e) Substrate 0.7 mmol, catalyst/substrate = 1.4 mol %, 50 °C. f) At 60 °C.

As can be seen from Table 1, most β-keto esters were smoothly hydrogenated under relatively mild conditions in high chemical yields and high enantioselectivities up to 98% (entries 1–8). Asymmetric hydrogenation of α-keto esters, however, showed moderate enantioselectivities (entries 9 and 10). On the other hand, γ and δ-keto esters were hardly hydrogenated even under severe reaction conditions (entries 11 and 12). As an alkyl group on BisP*, the *t*-butyl group (**a**) seems to be superior to the 1-adamantyl group (**b**) in the asymmetric hydrogenation of methyl 3-oxopentanoate (entries 2 and 3). Methyl 2,2-dimethylacetoacetate, which lacks an α-proton to form an enol tautomer, was also hydrogenated smoothly in excellent enantioselectivity (entry 5). Simple α-monoalkylated β-keto esters, 2-methoxycarbonylcyclopentanone and ethyl 2-methyl-3-oxobutanoate, were hydrogenated in low diastereoselectivities (entries 6 and 7). From these findings, it may be deduced that the hydrogenation by the BisP*–Ru catalyst proceeds via a keto form rather than enol form.9) Both β-keto amide and β-keto phosphonate were also hydrogenated in high enantioselectivities (entries 13 and 14). It is noted that all the hydrogenation products possess the same stereochemical integrity at the secondary alcohol moiety. It should be also mentioned that ethyl (*S*)-3-hydroxy-3-phenylproionate (entry 8) is a key chiral intermediate for (*R*)-(–)-Tomoxetine, which is an anti-depressant and an agent for urinary disorder.10)

In conclusion, this study has demonstrated that *t*-Bu-BisP*–RuBr$_2$ promotes the asymmetric hydrogenation of β-keto esters. The high enantioselectivities and the easy preparation of the ligand *t*-Bu-BisP* render this method synthetically useful.

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7 A typical procedure for asymmetric hydrogenation: In a glass autoclave were added BisP*–$RuBr_2$ 52 mg, methyl 3-oxopentanoate 10.7 g(82.2 mmol), and degassed methanol/water (10/1) 200 ml under argon atmosphere. Then argon gas was replaced with hydrogen. The hydrogenation was performed at 70 °C under 6 kg/cm^2 of hydrogen for 10 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to afford (*R*)-(–)-methyl 3-hydroxypentanoate (10.4 g, 96%, 98% ee) as a colorless oil [b.p. 75 - 76 °C (12 mmHg)].

8

Entry	Enantiomer excess (% ee)	Absolute configurataion (*R*/*S*)
1	HPLC using CHIRALCEL OD, *n*-hexane/2-propanol (95/5).	$[\alpha]_D^{23} = -39.4°$ ($c = 0.32$, $CHCl_3$). *lit.* $[\alpha]_D^{20} = +41.3°$ ($c = 0.32$, $CHCl_3$) for (*S*) (*J. Am. Chem. Soc.* **1995**, *117*, 4423).
2, 3	HPLC using CHIRALCEL OD, *n*-hexane/2-propanol (95/5).	$[\alpha]_D^{21} = -34.8°$ ($c = 0.32$, $CHCl_3$). *lit.* $[\alpha]_D^{20} = +34°$ ($c = 0.27$, $CHCl_3$) for (*S*) (*J. Am. Chem. Soc.* **1995**, *117*, 4423).
4	HPLC using CHIRALCEL OD-H, *n*-hexane/2-propanol (95/5)	$[\alpha]_D^{20} = -12.4°$ ($c = 0.37$, $CHCl_3$). *lit.* $[\alpha]_D^{20} = +16.2°$ ($c = 0.32$, $CHCl_3$) for (*R*) (*J. Am. Chem. Soc.* **1995**, *117*, 4423).
5	MTPA ester was analyzed by HPLC using CHIRALCEL OD 2 pieces, *n*-hexane/2-propanol (995/5).	$[\alpha]_D^{25} = -10.4°$ ($c = 1.0$, $CHCl_3$). *lit.* $[\alpha]_D^{20} = +13.6°$ ($c = 0.23$, $CHCl_3$) for (*S*) (*J. Am. Chem. Soc.* **1995**, *117*, 4423).
6	HPLC using CHIRALCEL OD *n*-hexane/2-propanol (95/5).	not determined.
7	GLC using CHIRALDEX B-DM. GLC using ULBON HR-20M for *syn*/*anti* ratio.	not determined.
8	HPLC using CHIRALCEL OD, *n*-hexane/2-propanol (95/5).	$[\alpha]_D^{23} = -30.4°$ ($c = 1.0$, $CHCl_3$). *lit.* $[\alpha]_D^{22} = -40.8°$ ($c = 1.03$, $CHCl_3$) for (*S*) (*J. Chem. Soc., Chem. Comm.* **1985**, 138).
9	HPLC using CHIRALCEL OD, *n*-hexane/2-propanol (95/5).	$[\alpha]_D^{23} = -144.0°$ ($c = 1.0$, $CHCl_3$). *lit.* $[\alpha]_D^{25} = -174.2°$ ($c = 0.58$, $CHCl_3$) for (*R*) (*J. Am. Chem. Soc.* **1984**, *106*, 1530).
10	GLC using CHIRALDEX B-DM.	$[\alpha]_D^{23} = -8.8°$ ($c = 0.5$, $CHCl_3$). *lit.* $[\alpha]_D^{20}=-31.3°$ ($c=2.36$, $CHCl_3$) for (*R*) (*Tetrahedron Lett.* **1992**, *33*, 3431).
13	Triphenylsilyl ether was analyzed by HPLC using CHIRALCEL OD, *n*-hexane/2-propanol (95/5).	HPLC retention time 42 min (minor 39 min) in comparison with the reported time (*Tetrahedron Asymmetry* **1997**, *8*, 3035).
14	GLC using CHIRALDEX B-DM.	The modified Mosher's method (*J. Am. Chem. Soc.* **1995**, *117*, 2931).

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