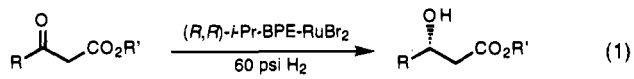
Highly Enantioselective Hydrogenation of β-Keto Esters under Mild Conditions

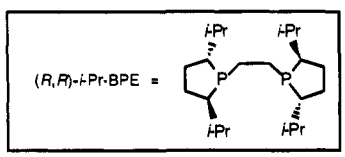
Mark J. Burk,* T. Gregory P. Harper, and Christopher S. Kalberg

Department of Chemistry, Duke University
P. M. Gross Chemical Laboratory
Durham, North Carolina 27706

Received December 22, 1994

The design of catalysts for enantioselective hydrogenation of ketones remains a challenging endeavor. To date, few catalysts have been found to deliver chiral alcohol products with both high levels of absolute stereocontrol and high catalytic efficiencies.[1] High enantioselectivities (>98% ee) have been observed in the hydrogenation of a variety of β-keto esters using 2,2′-bis(phosphino)-1,1′-biaryl-derived catalysts such as Ru-BINAP,[2] but high temperatures (80–100 °C) and/or high hydrogen pressures (100 atm) generally are required for reasonable catalytic rates in the absence of added acid cocatalysts.[3] Recent results suggest that electron-rich diphosphine ligands may play an important role in the attainment of high catalytic efficiencies in ketone and aldehyde hydrogenations.[4] Given the demonstrated stereoinductive properties and electron-rich nature of our recently introduced bis(phospholane) ligands,[5] we anticipated that catalysts derived from 1,2-bis(*trans*-2,5-dialkylphospholano)benzene (DuPHOS) ligands and 1,2-bis(*trans*-2,5-dialkylphospholano)ethane (BPE) ligands may prove effective in asymmetric ketone reductions. We herein describe the development of new *i*-Pr-BPE-Ru catalysts (*i*-Pr-BPE = 1,2-bis(*trans*-2,5-diisopropylphospholano)ethane) that allow the highly enantioselective hydrogenation of β-keto esters (**1**) under mild conditions (eq 1). Since the resulting β-hydroxy esters (**2**) may be used to generate our phospholane ligands, we effectively have developed a reaction that can breed its own chirality.[6]

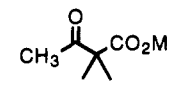
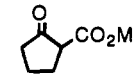
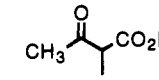




Initial studies were aimed at uncovering the optimum bis(phospholane)-based catalyst for the hydrogenation of β-keto esters to β-hydroxy esters. A series of DuPHOS-RuBr$_2$ and BPE-RuBr$_2$ catalyst precursors were prepared by reacting the DuPHOS and BPE ligands (R at 2,5-position of phospholanes = Me, Et, Pr, *i*-Pr) with [(COD)Ru(2-methylallyl)$_2$], followed by treatment with methanolic HBr in acetone.[7] Scouting reactions were performed using the model substrate, methyl acetoacetate (**1**; R, R′ = Me), and a standard set of reaction conditions (60 psig of H_2, 0.4 mol % catalyst, 35 °C, 18 h). In order to suppress undesired formation of the β-dimethylketal of methyl acetoacetate, a 10% water/methanol (v/v) solvent mixture was employed in these reactions. The results achieved with this series of catalysts indicated that the *i*-Pr-BPE-Ru catalyst was superior in terms of both rates and enantioselectivities (100% conversion, 99.3% ee).

Further studies involving the (*R*,*R*)-*i*-Pr-BPE-Ru catalyst revealed that complete conversion could be achieved in just 4 h under our standard conditions above, or over 10 h at, 22 °C, to yield (*S*)-(+)-methyl 3-hydroxybutyrate in 99.3% and 99.6% ee, respectively. For comparison, the analogous Ru-BINAP catalyst was prepared in the same fashion and afforded less than 10% product under the latter conditions. Low conversions (<10%) were observed with the (*R*,*R*)-*i*-Pr-BPE-Ru catalyst in *i*-PrOH and in aprotic solvents such as CH_2Cl_2 and THF. Interestingly, the choice of low-pressure conditions for our initial studies was fortuitous, as lower enantioselectivities were observed at higher hydrogen pressures (78% ee at 50 atm of H_2; 71% ee at 100 atm of H_2).

Table 1. (*R*,*R*)-*i*-Pr-BPE-Ru-Catalyzed Asymmetric Hydrogenation of β-Keto Esters **1**[a]

entry	R	R′	%ee[b]	config[c]
1	CH_3	CH_3	99.3	(*S*)-(+)
2	CH_3	t-Bu	99.4	(*S*)-(+)
3	C_2H_5	CH_3	98.6	(*S*)-(+)
4	C_3H_7	C_2H_5	98.8	(*S*)-(+)
5	$(CH_3)_2CH$	C_2H_5	99.0	(*R*)-(+)
6	$C_{11}H_{23}$	CH_3	98.7	(*S*)-(+)
7	CH_3OCH_2	CH_3	95.5	(*R*)-(+)
8	$ClCH_2$	CH_3	76	(*R*)-(+)
9	c-C_6H_{11}	CH_3	99.1	(*R*)-(+)
10			95.0[d]	(*S*)-(+)
11			98.3 (anti)[e] 96.4 (syn)	(1*S*,2*S*)-(+) (1*R*,2*S*)-(+)
12			96.2 (anti)[f]	(2*R*,3*S*)-(-)

[a] Reactions were carried out at 35 °C with an initial H_2 pressure of 60 psig and 0.25–0.10 M solutions of substrate in MeOH/H_2O (9/1), using the catalyst precursor (*R*,*R*)-*i*-Pr-BPE-RuBr$_2$ (0.2 mol %), unless otherwise stated. Reaction time allowed for complete (100%) conversion was 20 h. [b] Enantiomeric excesses were determined by chiral HPLC or chiral capillary GC, as described in the supplementary material. [c] Absolute configurations were assigned by comparing the sign of optical rotation of product or derivative with that of known alcohols (see supplementary material). [d] Reaction time 96 h. [e] *Anti/syn* ratio 24/1. [f] *Syn/anti* ratio 1.4/1; ee for *syn* diastereomer not determined.

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993; Chapter 1. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994; Chapter 2. (c) Koenig, K. E. Applicability of Asymmetric Homogeneous Catalytic Hydrogenation. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 3.

(2) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (c) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (d) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1. (e) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897. (f) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51.

(3) (a) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (b) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

(4) (a) Burk, M. J.; Harper, T. G. P.; Lee, J. R.; Kalberg, C. *Tetrahedron Lett.* **1994**, *35*, 4963. (b) Tani, K.; Suwa, K.; Tanigawa, E.; Yoshida, T.; Okano, T.; Otsuka, S. *Chem. Lett.* **1982**, 261.

(5) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (c) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (d) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* (Symposium-in-Print) **1994**, *50*, 4399.

(6) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.

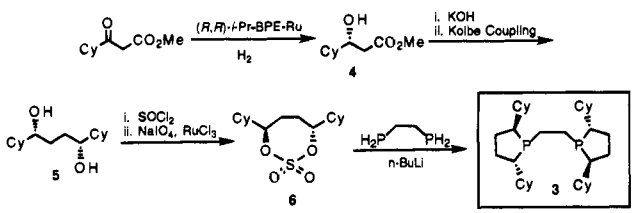
(7) (a) Genêt, J. P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555. (b) Genêt, J. P.; Pinel, C.; Ratovelomanana- Vidal, V.; Mallart, S.; Pfister, X.; Caño De Andrade, M. C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665. (c) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Caño De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675.

0002-7863/95/1517-4423$09.00/0

As shown in Table 1, a variety of β-keto esters were smoothly hydrogenated to β-hydroxy esters with very high enantioselectivities using the (*R*,*R*)-*i*-Pr-BPE-Ru catalyst (60 psi, 35 °C, 0.2 mol % catalyst, 20 h). The nature of the ester group appeared to have little influence on the enantioselectivities. Virtually all substrates containing alkyl-substituted β-keto groups were hydrogenated with enantioselectivities in the range 98 → 99% ee. The substrate possessing a methoxymethyl group also was hydrogenated with high selectivity (95.5% ee, entry 7), although entry 8 shows that a chloromethyl substituent led to lower ee's. Methyl 2,2-dimethylacetoacetate (entry 10) was hydrogenated with high selectivity, although a longer reaction time (96 h) was necessary for complete conversion. This result, together with deuteration studies,[8] suggests that, like the Ru-BINAP catalysts,[9] the present *i*-Pr-BPE-Ru catalyst hydrogenates the keto form rather than the enol tautomer of β-keto esters. High levels of both diastereoselectivity (24/1; *anti*/*syn*) and enantioselectivity (98.3% *anti*; 96.4% ee *syn*) were attained through dynamic kinetic resolution[9] in the hydrogenation of methyl 2-oxocyclopentanecarboxylate (entry 11).

Enantiomerically pure β-hydroxy esters are valuable intermediates in synthetic and natural product chemistry.[10] For example, entry 6 demonstrates the preparation of an important β-hydroxy acid component of lipid A and analogues of the phospholipid subunit of endotoxin.[11] Furthermore, enantiomerically pure β-hydroxy esters have served as key intermediates in our synthesis of a new class of chiral phospholane ligands.[5,12] Thus, highly enantioselective hydrogenation of β-keto esters under mild conditions using the *i*-Pr-BPE-Ru catalyst provides a direct route to the chiral precursors used to prepare the DuPHOS and BPE ligands. Interestingly, hydrogenation of ethyl isobutyrylacetate (entry 5) using the Ru catalyst derived from (*R*,*R*)-*i*-Pr-BPE afforded (*R*)-ethyl 3-hydroxy-4-methylpentanoate (99.0% ee), a chiral intermediate employed in the synthesis of the *i*-Pr-BPE ligand. By converting this intermediate, as well as antipodal (*S*)-ethyl 3-hydroxy-4-methylpentanoate, to the corresponding ligands as previously described,[5,12] we thus have developed a self-generative process for production of the *i*-Pr-BPE ligands.

Scheme 1. Asymmetric Catalytic Route to (*S*,*S*)-Cy-BPE Ligand **3**



We also have used this process to synthesize new ligands such as (*S*,*S*)-Cy-BPE **3** via the route depicted in Scheme 1. Hydrogenation of methyl cyclohexanoylacetate[13] (entry 9) using the (*R*,*R*)-*i*-Pr-BPE-Ru catalyst provided (*R*)-methyl 3-cyclohexyl-3-hydroxypropionate (**4**) (99.1% ee). Following our previously outlined procedures,[5,12] saponification and electrochemical Kolbe coupling afforded the (*R*,*R*)-1,4-dicyclohexyl-1,4-butanediol (**5**) (>99.5% ee) in 42% yield for the three steps. Conversion of **5** to the diol cyclic sulfate **6**, and reaction with 1,2-diphosphinoethane in the presence of *n*-BuLi yielded (*S*,*S*)-Cy-BPE (**3**) in enantiomerically pure form. The analogous Ru complex [(*S*,*S*)-Cy-BPE-RuBr$_2$] also was found to serve as an excellent catalyst for β-keto ester hydrogenations, producing (*R*)-(−)-methyl 3-hydroxybutyrate in 98.6% ee and (*S*)-methyl 3-cyclohexyl-3-hydroxypropionate (**4**) in 98.2% ee. The latter product is an intermediate in the synthesis of the Cy-BPE ligand **3** and thus provides another example of ligand self-generation.

We have developed a non-biarylphosphine-based catalyst system that is broadly effective for the highly enantioselective hydrogenation of a range of β-keto esters. The *i*-Pr-BPE-Ru catalyst performs efficiently under low hydrogen pressures and provides practical access to valuable β-hydroxy esters, which among other applications may be used for the synthesis of new chiral phospholane ligands. Rare examples of "asymmetric ligand breeder" processes have been developed for the self-generative synthesis of the *i*-Pr-BPE and Cy-BPE ligands. Further applications of bis(phospholane)−Ru catalysts in enantioselective ketone hydrogenations currently are being examined.

Acknowledgment. We thank Dr. G. Dubay for obtaining HRMS data. M.J.B. thanks Duke University, Union Carbide (Innovative Recognition Award), and Pew Charitable Trusts (Pew Scholar Award) for financial support.

Supplementary Material Available: Experimental details, including catalyst preparations, hydrogenation procedure, spectral and analytical data, and ee determinations for all β-hydroxy ester products, and spectral and analytical data for new compounds **3**−**6** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, and can be downloaded from the Internet see any current masthead page for ordering information and Internet access instructions.

JA944118P

(8) Mechanistic and kinetic studies involving this system are in progress and will be reported in due course.

(9) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

(10) (a) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. (b) Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J.A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 19. (c) Ohashi, T.; Hasegawa, J. In *Chirality in Industry;* Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York; Chapters 12 and 13.

(11) Christ, W. J.; McGuinness, P. D.; Asano, O.; Wang, Y.; Mullarkey, M. A.; Perez, M.; Hawkins, L. D.; Blythe, T. A.; Dubue, G. R.; Robidoux, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 3637.

(12) (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Burk, M. J.; Harlow, R. L. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1462. (c) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569.

(13) (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. (b) Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994**, *59*, 4749.