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Enantioselective Synthesis of α-Hydroxy and α-Amino Phosphonates via Catalytic Asymmetric Hydrogenation

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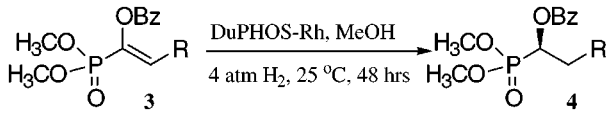
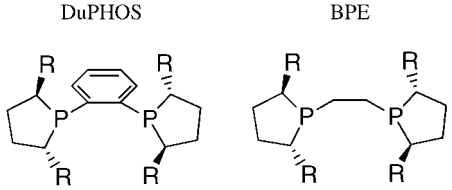
ABSTRACT



68-95% ee

Cationic rhodium catalysts of the C_2 symmetric DuPHOS (1) and BPE (2) ligands have demonstrated the ability to asymmetrically hydrogenate a novel series of enol phosphonates (3) in good to excellent enantiomeric excess under mild conditions. Initial studies toward the catalytic asymmetric hydrogenation of enamido phosphonates (6 and 7) using the DuPHOS–Rh^+ catalysts are also reported.

α-Amino phosphonates and α-hydroxy phosphonates are useful compounds for the inhibition of enzymes due to their ability to mimic hydrolysis transition states.[1,2] These functionalities have been employed in compounds designed to inhibit enzymes such as renin, EPSP synthase, and HIV protease.[3] The stereochemistry of the α-amino phosphonates or α-hydroxy phosphonates can effect the enzyme inhibition,[3b] thus providing the impetus for examining the asymmetric synthesis of these compounds. Cationic rhodium catalysts with DuPHOS (**1**) and BPE (**2**) ligands (Figure 1) have been used to perform asymmetric hydrogenations on a wide variety enamido[4] and enol esters.[4a,5] Herein we describe the first catalytic asymmetric hydrogenation of a series enolbenzoate phosphonates as well as some initial studies directed toward the asymmetric hydrogenation of enamido phosphonates using the DuPHOS-Rh and BPE-Rh catalysts. To date there



1a: R=Me
b: R=Et
c: R=*n*-Pr
d: R=*i*-Pr

2a: R=Me
b: R=*i*-Pr

Figure 1. The DuPHOS and BPE Ligands.

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(1) Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119.

(2) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.

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(5) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345.

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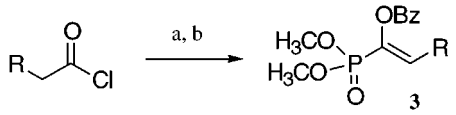
have been two published examples of the catalytic asymmetric synthesis of α-hydroxy phosphonates.[6] The catalytic asymmetric synthesis of α-amino phosphonates has received recent attention, including asymmetric hydrogenation[7] and hydrophosphonylation[8] strategies.

I. α-Hydroxy Phosphonates. Enolbenzoate phosphonate substrates **3** were readily synthesized as shown in Scheme 1. Acyl chlorides were treated with trimethyl phosphite to form α-keto phosphonate intermediates[9] which were then reacted with benzoic anhydride and DBU to form enolbenzoates **3** in yields that ranged from 43 to 86% after purification. Only the *E* isomer of the olefin was observed for **3b**−**h**.[10] To the best of our knowledge the enolbenzoate phosphonates **3** are novel.

Scheme 1

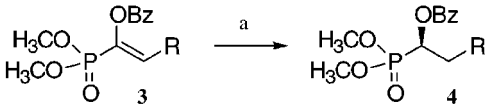


(a) $P(OCH_3)_3$, 0 to 70 °C, 1.5 h. (b) Bz_2O, DBU, 0 to 25 °C, 0.5 h, (THF).

To obtain optimum enantioselectivities for the asymmetric hydrogenation of enolbenzoate phosphonates, the various DuPHOS-Rh and BPE-Rh catalysts were screened against model substrates **3a**−**b**. Reactions were carried out in methanol with an initial hydrogen pressure of 4 atm and the results are shown in Table 1. In the case of **3a**, Et-DuPHOS-Rh (**1b**-Rh) provided the highest enantioselectivity. However, when the hydrogenation of **3b** was attempted with Et-DuPHOS-Rh, the conversion dropped to only 9% after 2 days. Hydrogenation of **3b** with Me-DuPHOS-Rh (**1a**-Rh) and Me-BPE-Rh (**2a**-Rh) were then examined and Me-DuPHOS-Rh effected complete conversion to **4b** after 48 h with 86% ee.

It should be noted that the stereochemical sense of the reduction is consistent with results obtained for the hydrogenation of enamido esters[4b] and enol esters[5] using these catalysts. In the present case however, the *R*/*S* assignment is reversed by replacing a carboxylate ester with a phosphonate ester.

Table 1. Ligand Optimization for the DuPHOS/BPE-Rh-Catalyzed Asymmetric Hydrogenation of Enolbenzoate Phosphonates **3**



(a) [(ligand) Rh (COD)]OTf, S/C 125, MeOH, 4 atm H_2, 25 °C, 24-48 h.

subst	R	ligand	conv[a]	% ee[b]	config[c]
3a	H	(*R*,*R*)-**2a**	27	64	*S*-(−)
3a	H	(*S*,*S*)-**1a**	100	84	*R*-(+)
3a	H	(*R*,*R*)-**1b**	100	96	*S*-(−)
3a	H	(*R*,*R*)-**1c**	100	92	*S*-(−)
3a	H	(*R*,*R*)-**1d**	40	85	*R*-(+)
3b	CH_3	(*R*,*R*)-**2a**	45	60	*S*-(+)
3b	CH_3	(*S*,*S*)-**1a**	100	86	*R*-(−)
3b	CH_3	(*R*,*R*)-**1b**	9	ND	ND

[a] Conversion determined by ^1H or ^{31}P NMR. [b] Enantiomeric excess determined by chiral HPLC on a Daicel Chiralcel OJ column for **6a** and a Chiralpak OT column for **4b**.[11] [c] Configuration assigned on the basis of correlation between HPLC elution order, optical rotation, and catalyst configuration relative to the known compound **5**.

Pressure and solvent effects for catalytic asymmetric hydrogenations can be quite dramatic in terms of reaction rates and enantioselectivity.[12] In the case of enolbenzoate phosphonates, methanol was found to be the superior solvent based on enantioselectivity and reaction rate (complete in <12 h under the conditions given in Table 2). For the hydrogenation of **3a**, ethanol, CH_2Cl_2, hexane, diethyl ether, and DME yielded enantioselectivities above 90% using the Et-DuPHOS-Rh catalyst but required more than 12 h to go to completion. Performance of the hydrogenation reaction with **3a** was particularly poor in benzene and toluene. Recent studies have shown that these aromatic solvents can form stable complexes with the cationic DuPHOS-Rh catalysts in solution and that some classes of substrates are slow to displace the arene ligands thereby resulting in poor conversions and compromised enantioselectivities.[5,13] The influence of initial hydrogen pressure upon the asymmetric hydrogenation of **3a** was tested in a range of 1−6 atms. All reactions were complete in less than 24 h with no observable effect on the enantioselectivity. The effect of higher H_2 pressure

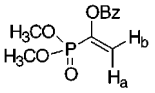
(6) (a) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926. (b) Wynberg, H.; Smaardijk, A. A. *Tetrahedron Lett.* **1983**, *24*, 5899.

(7) Examples of the catalytic asymmetric hydrogenation of enamido phosphonates include: (a) Schmidt, U.; Oehme, G.; Krause, H. *Synth. Commun.* **1996**, *26*, 777. (b) Talley, J. J. US 5,321,153 14.6.94; Appl. 898,253 15.6.92. (c) Schollkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555. Analogous enamido phosphinic acid esters: Dwars, T.; Schmidt, U.; Fischer, C.; Grassert, I.; Kempe, R.; Frohlich, R.; Drauz, K, Oehme, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2851.

(8) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656.

(9) α-Keto phosphonate intermediates of **3a**−**h** proved to be unstable, decomposing over several days at room temperature.

(10) *E*/*Z* assignment was based on J_{PH} coupling constants: $J_{PHa} = \sim 11$ Hz, $J_{PHb} = \sim 35$ Hz(Bentrude, W. D.; Setzer, W. N. In *^{31}P NMR in stereochemical Ananlysis*; Verkade, J. G., Quin, L. D., Eds.; VCH Publishers Inc.: Deerfield Beach, FL, 1987; p 379).



(11) Enantiomeric excess determined by comparison to racemate. Racemates for **4a**, **8**, and **9** were prepared by hydrogenation of the precusor olefins with the [(DiPFc)Rh(COD)]OTf catalyts (DiPFc = 1,1′-bis-(diisopropylphosphino)ferrocenyl). Racemic mixtures for **4b**−**h** were prepared through the hydrogenation of the precursor olefins with 10% Pd/C.

(12) Halpern, J. In *Asymmetric Catalysis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 41. (b) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602. (c) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728.

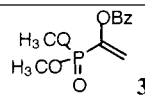
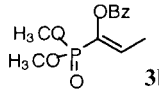
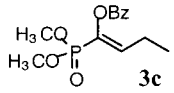
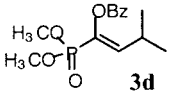
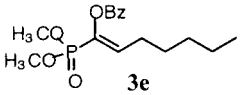
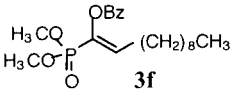
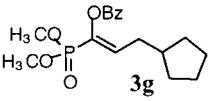
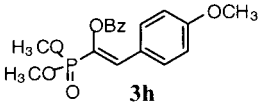
(13) Burk, M. J.; Bienewald, S.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, *64*, 3290.

was not examined. However, in previous studies involving the DuPHOS-Rh and BPE-Rh catalysts, only minor effects on enantioselectivity were observed for the asymmetric hydrogenation of other substrates at elevated H_2 pressures (up to 100 atm).[4] The effect of temperature was not examined for the reaction involving **3**.

Results of the catalytic asymmetric hydrogenation involving a series enolbenzoate phosphonates **3** are shown in Table 2. For the aliphatic substituents, enantioselectivities were good, ranging from 86 to 96%. The highest stereoselectivity for the unsubstituted **3a** was obtained with Et-DuPHOS-Rh catalyst. Alkyl-substituted enolbenzoate substrates **3b**−**g** were reduced with optimum ee's using the less bulky Me-DuPHOS-Rh, consistent with the ligand optimization studies shown in Table 1. In the case of the more sterically demanding *p*-methoxyphenyl substituent on **3h**, the reaction did not proceed with Me-DuPHOS-Rh but did go to partial conversion using the less rigid Me-BPE-Rh catalyst after 2 days, although only modest enantioselectivity was observed.

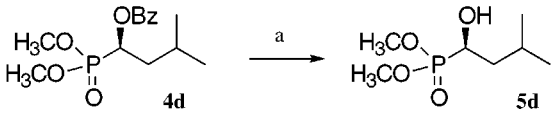
The α-benzoyloxy phosphonates **4** can be simply deprotected using K_2CO_3 in methanol at room temperature for 2 h to afford the corresponding α-hydroxy phosphonates **5**. An example is shown in Scheme 2, where **4d** is converted to the previously reported compound **5d**[6a] with no apparent loss of optical purity.

Table 2. Enolbenzoate Phosphonates **3** Hydrogenated with the DuPHOS/BPE-Rh Catalysts[a]

Substrate	Ligand	% ee[b]	Confi g.
 **3a**	(*R*,*R*)-**1b**	96	*S*-(-)
 **3b**	(*S*,*S*)-**1a**	86	*R*-(-)
 **3c**	(*S*,*S*)-**1a**	92	*R*-(-)
 **3d**	(*S*,*S*)-**1a**	92	*R*-(-)
 **3e**	(*S*,*S*)-**1a**	90	*R*-(-)
 **3f**	(*S*,*S*)-**1a**	88	*R*-(-)
 **3g**	(*S*,*S*)-**1a**	90	*R*-(-)
 **3h**	(*R*,*R*)-**2a**	68[c]	*S*-(+)

[a] Conditions: [(ligand)Rh(COD)]OTf, S/C 125, MeOH, 4 atm H_2, 25 °C, 12−48 h. [b] Enantiomeric excess determined by chiral HPLC on a Daicel Chiralcel OJ column for **6a**, Chiralpak OT column for **6b**−**f** and a Chiracel OB for **6h**.[11] [c] 57% conversion.

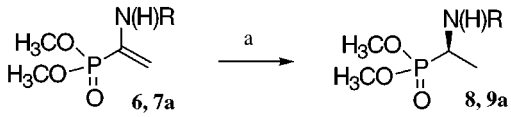
Scheme 2



(a) K_2CO_3, MeOH, 25 °C, 2 h.

II. α-Amino Phosphonates. *N*-acetyl and *N*-Cbz enamido phosphonates **6** and **7a** were synthesized as described in the literature.[14] A practical route to a variety of substituted enamido phosphonates has yet to be demonstrated despite several strategies published in the literature.[7,14] Ligand optimization studies were performed on the *N*-acetyl and *N*-Cbz enamido phosphonates **6** and **7a**. The Et-DuPHOS-Rh catalyst provided optimum enantioselectivities for both the *N*-acetyl **6** and *N*-Cbz **7a** enamido phosphonate substrates as illustrated in Table 3.

Table 3. Ligand Optimization for the DuPHOS/BPE-Rh-Catalyzed Asymmetric Hydrogenation of *N*-acetyl **6** and *N*-Cbz **7** Enamido Phosphonates



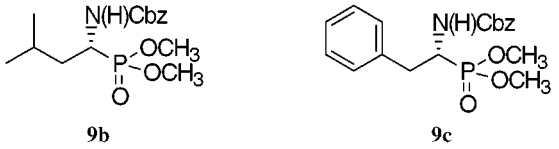
(a) [(ligand) Rh (COD)]$^+$OTf, S/C 100, MeOH, 4 atm H_2, 25 °C, 12-24 h.

subst	R	ligand	conv[a]	% ee[b]	config[c]
6	Ac	(*S*,*S*)-**1a**	100	93	*R*-(−)
6	Ac	(*S*,*S*)-**1b**	100	95	*R*-(−)
6	Ac	(*S*,*S*)-**1c**	90	68	*R*-(−)
6	Ac	(*R*,*R*)-**1d**	6	ND	ND
7a	Cbz	(*S*,*S*)-**2a**	88	88	*R*-(−)
7a	Cbz	(*S*,*S*)-**1a**	72	90	*R*-(−)
7a	Cbz	(*S*,*S*)-**1b**	100	94	*R*-(−)
7a	Cbz	(*S*,*S*)-**1c**	100	81	*R*-(−)
7a	Cbz	(*R*,*R*)-**2b**	93	57	*S*-(+)

[a] Conversion determined by ^{1}H or ^{31}P NMR. [b] Enantiomeric excess determined by chiral GC on a Chirasil-*L*-Val column.[11] [c] Absolute configuration assigned based on data supplied by Talley.[7b]

Ligand optimization reactions were performed in MeOH, however, further studies of the solvent effects showed that in the hydrogenation of **7a** using Et-DuPHOS-Rh, *i*-PrOH gave a marginally higher ee (95%). Hydrogenation reactions involving **7a** did not proceed well in benzene and toluene, presumably analogous to what was observed for the hydrogenation of **3a** in these solvents.

Initial studies involving the catalytic asymmetric hydrogenation of substituted enamido phosphonates include the Et-DuPHOS-Rh reduction of (*E*)-3-methyl-1-benzyloxycarbonylamino-1-dimethylphosphonylbut-1-ene **7b** (not shown) to produce **9b** (Figure 2), a compound previously reported



9b (*S*,*S*)-Et-DuPHOS, 95% ee

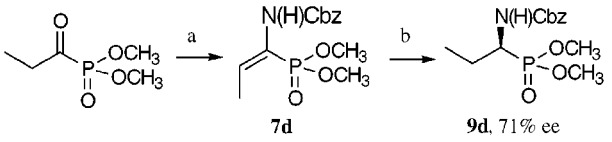
9c (*S*,*S*)-Me-DuPHOS, 76% ee

Figure 2. *N*-Cbz α-amino phosphonates.

by Talley.[7b] The reaction was complete after 12 h at room temperature in MeOH with an initial H_2 pressure of 4 atm, resulting in an enantiomeric excess of 95%. Consistent with results from the enol phosphonate series, aryl-substituted enamido phosphonates appear to give lower enantioselectivities compared to their alkyl counterparts. Reduction of (*E*)-phenyl-substituted *N*-Cbz enamido phosphonate[7b] **7c** (not shown) with Me-DuPHOS-Rh provided **9c** in 76% ee.

The (*Z*)-methyl enamido phosphonate **7d** was prepared in poor yield (11%) in a condensation reaction between dimethylpropionylphosphonate and benzylcarbamate as shown in Scheme 3, conditions similar to those used in the preparation of the unsubstituted parent substrate **7a**.[14] After a failed attempt to hydrogenate **7d** with Et-DuPHOS-Rh, the reduction was attempted with Me-DuPHOS-Rh which allowed complete conversion to afford **9d** in 71% ee. The lower ee achieved in the reduction of (*Z*)-enamide **7d** represents a significant compromise in selectivity compared to the result for **9b** which was obtained from the (*E*)-enamide. This dependence on substrate geometry is somewhat unexpected in light of previous observations for the catalytic asymmetric hydrogenation of various classes of substrates employing the DuPHOS-Rh and BPE-Rh catalysts where *E*- and *Z*-substituted olefins allowed for comparable selectivities.[4b−c,5,15]

Scheme 3



7d **9d**, 71% ee

(a) $BnOCONH_2$, PhH, reflux, 3 h. (b) [(S,S)-Me-DuPHOS Rh (COD)]OTf S/C 125, MeOH, 4 atm H_2, 25 °C, 12 h.

The catalytic asymmetric hydrogenation of enolbenzoate phosphonates using the DuPHOS-Rh and BPE-Rh catalysts provides an efficient route to enantiomerically enriched alkyl-substituted α-hydroxy phosphonates. Given the ease with which substrates **3** are prepared this method is likely to find broad application for the preparation of α-hydroxy phosphonate derivatives. Preliminary studies also have shown that the Et-DuPHOS-Rh catalysts can hydrogenate enamido phosphonates effectively and with moderate to high enantioselectivity, potentially providing a convenient route to α-amino phosphonates in high enantiomeric purity.

Acknowledgment. Thanks to Steve Truckenbrod and George Dubay for acquiring HRMS data. This research was funded by a grant from Pew Charitable Trusts. T.A.S. was supported by a fellowship established by Burroughs-Wellcome. We thank Dr. John Talley of Monsanto for providing substrate **7b**.

Supporting Information Available: Preparations and characterization for **3**, **4**, **8**, and **9a** including ^1H, ^{13}C, and ^{31}P spectra, optical rotations, HRMS, and chiral HPLC and GC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Zon, J. *Synthesis* **1981**, 324.

(15) (a) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1931. (b) Burk, M. J.; Casy, G.; Johnson, N. *J. Org. Chem.* **1998**, *63*, 6084.