Rh−DuPHOS-Catalyzed Enantioselective Hydrogenation of Enol Esters. Application to the Synthesis of Highly Enantioenriched α-Hydroxy Esters and 1,2-Diols

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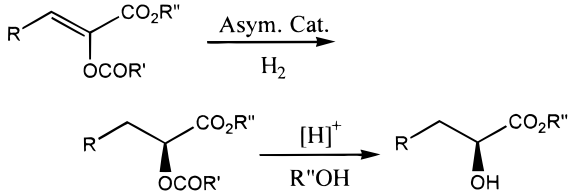
Abstract: The asymmetric hydrogenation of α-(acetyloxy)- and α-(benzoyloxy)acrylates **4** catalyzed by cationic rhodium−DuPHOS complexes has been examined. A wide range of substrates (**4**) were prepared via a convenient Horner−Emmons condensation protocol, and subsequently hydrogenated under mild conditions (60 psi of H_2) at substrate-to-catalyst ratios (S/C) of 500. Overall, enol ester substrates **4** were reduced by the cationic Et−DuPHOS−Rh catalysts with very high levels of enantioselectivity (93−99% ee). Importantly, substrates **4** bearing *β*-substituents could be employed as *E/Z* isomeric mixtures with no detrimental effect on the selectivity. Labeling studies indicated that no significant *E/Z* isomerization of the substrates occurs during the course of these reactions. Details concerning optimization of the reaction, interesting solvent effects, and deprotection procedures for the synthesis of highly enantioenriched α-hydroxy esters and 1,2-diols also are provided.

Introduction

Numerous inherent practical advantages are associated with asymmetric catalytic processes that allow the conversion of prochiral substrates into valuable optically active products.[1] Homogeneous enantioselective hydrogenation constitutes one of the most versatile and efficacious of these methods, and the development of improved catalysts for reduction of a broad range of unsaturated substrates continues to evolve at a rapid pace. Currently, asymmetric hydrogenation catalysts can provide access to a wide variety of chiral compounds with outstanding levels of efficiency and enantioselectivity through reduction of the C=C, C=N, and C=O bonds.[2] Prochiral ketones represent a particularly important and challenging class of substrates. A broadly effective and highly enantioselective method for asymmetric hydrogenation of ketones could allow the production of a plethora of extremely useful chiral alcohols, which are ubiquitous in nature and are in great demand for the design of pharmaceutical and agrochemical agents. Despite various breakthroughs recently reported for the enantioselective reduction of specific types of ketones,[2,3] no general and efficient catalytic system has yet been developed which provides consistently high enantioselectivities for the hydrogenation of α-keto esters to α-hydroxy esters.[4] The latter compounds comprise versatile building blocks in organic synthesis with application, for instance, in the preparation of optically active α-amino acids.[5]

We envisioned that enantioselective hydrogenation of the olefinic bond of enol esters may provide an alternative procedure for the asymmetric catalytic synthesis of α-hydroxy esters (eq 1). Hence, we have set out to establish the feasibility of this approach.



(1)

Structurally, both α-(acyloxy)acrylates of type **A** and α-(acylamino)acrylates of type **B** possess a carbonyl oxygen atom that is situated three atoms from the olefin to be reduced and which is properly aligned to facilitate chelation to a metal center (Figure 1). The topological similitude between **A** and **B**, combined with the great level of success achieved in asymmetric hydrogenation of substrates **B**, intimates the viability of enantioselective reduction of α-(acyloxy)acrylates. Contrary to this expectation,

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(1) (a) Collins, A. N., Sheldrake, G. N., Crosby, J., Eds. *Chirality in Industry*; John Wiley and Sons: New York, 1992. (b) Cornils, B., Herrmann, W., Eds. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996.

(2) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994.

(3) See, for example: (a) 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. (b) Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5876. (c) Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318. (d) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (e) Burk, M. J.; Harper, G. H.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423. (f) Roucoux, A.; Thieffry, L.; Carpentier, J.-F.; Devocelle, M.; Meliet, C.; Agbossou, F.; Mortreux, A. *Organometallics* **1996**, *15*, 2440.

(4) (a) Spindler, F.; Pittelkow, U.; Blaser, H.-U. *Chirality* **1991**, *3*, 370. (b) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

(5) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon Press: Oxford, 1989.

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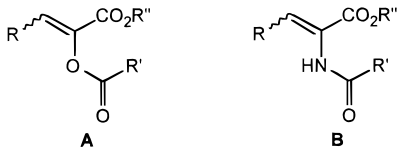


Figure 1.

surprisingly little success has been disclosed regarding the design of a generally effective catalyst for this useful transformation.[6a,7]

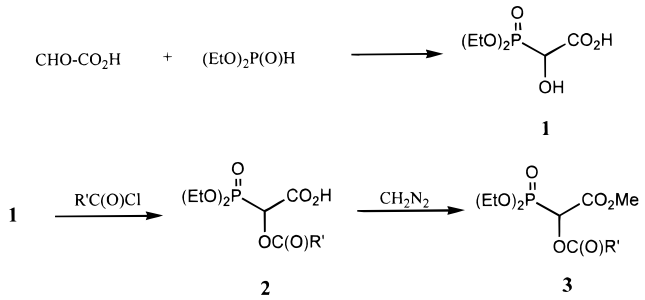
We recently have developed a series of efficient and highly enantioselective Rh- and Ru-based hydrogenation catalysts bearing 1,2-bis(2,5-dialkylphospholano)benzene (DuPHOS) and 1,2-bis(2,5-dialkylphospholano)ethane (BPE) ligands.[3e,6] Several years ago we reported preliminary findings regarding the efficacy of these catalysts for the asymmetric hydrogenation of various enol acetates.[6a] In particular, we demonstrated that the Et−DuPHOS−Rh catalyst smoothly reduced methyl 2-acetoxyacrylate (**A**, R = H) to the corresponding lactate derivative with exceptional levels of absolute stereocontrol (>99% ee). More recently, Schmid and co-workers at Hoffmann La Roche further demonstrated the industrial utility of the Et−DuPHOS−Rh catalyst for asymmetric hydrogenation of a specific enol acetate.[6g] Finally, Schmidt et al.[7a] have reported the hydrogenation of *E*/*Z* isomeric mixtures of several *β*-substituted α-(acyloxy)acrylates with Rh−DIPAMP[8a] or Ru−BINAP[8b] catalysts. However, neither of the latter catalysts displayed broad applicability in these reactions.

Herein we report successful application of our cationic DuPHOS−Rh catalysts in the highly enantioselective hydrogenation of a diverse array of α-acetoxy and α-benzoyloxy enol esters (**4**). On the basis of our auspicious preliminary results, we have endeavored to expand our studies to encompass a wide range of *β*-substituted α-(acyloxy)acrylates. Details concerning optimization of these reactions and the scope of the process are provided herein. These studies culminate in the development of a general and convenient process for the asymmetric catalytic synthesis of α-hydroxy esters and 1,2-diols.

Results and Discussion

1. Preparation of Enol Ester Substrates (4). Synthesis of the parent unsubstituted enol ester substrate, methyl 2-acetoxyacrylate (**4a**−OAc) proceeds readily through reaction between methyl pyruvate and acetic anhydride.[6a] However, attempted extension of this procedure to *β*-substituted α-(acyloxy)acrylate derivatives proved relatively ineffectual. A convenient route to a potentially broad range of enol esters has been reported and involves condensation of aldehydes with a Horner−Emmons reagent such as **3**.[7a] This procedure is analogous to that used for the synthesis of α-enamide esters (i.e., see **B** above). Despite the utility of **3** in the preparation of substrates **4**, the reported synthesis and purification of this reagent was tedious and low yielding in our hands. Thus, during the course of our investigations we have devised an improved preparation of Horner−Emmons reagents **3**, as generally depicted in Scheme 1.

Scheme 1. Synthesis of Horner−Emmons Reagent **3**



In a simple one-pot reaction, glyoxylic acid was condensed with diethyl phosphite to provide in quantitative yield (by NMR) the phosphonate acid **1**. The phosphonate acid **1** is a versatile intermediate that allows introduction of a wide range of different acyl or carbamoyl protecting groups. For instance, reaction with acetyl chloride or benzoyl chloride directly afforded the corresponding acetate or benzoate derivatives, **2**−OAc or **2**−OBz, respectively, in good yield. Importantly, the acids **2** were easily isolated and purified by recrystallization from methylene chloride. Facile esterification with, for example, diazomethane subsequently yielded the desired phosphonate methyl esters **3** in good overall yield for the three steps (60−70%).

With the Horner−Emmons reagent **3** in hand, the ultimate hydrogenation substrates **4** were prepared readily through tetramethylguanidine-mediated condensation with the appropriate aldehyde, as previously described.[7a] The enol acetates and benzoates (**4**) were thus obtained in good yield, and invariably were isolated as *E*/*Z* isomeric mixtures (2:1 to 10:1). The *E* isomer predominated for all substrates examined. Physical separation of the geometric isomers of **4** proved difficult. Isomerization of *E*/*Z* enol acetate mixtures to the pure *Z* isomer previously has been reported in several instances,[7a] although this requires additional synthetic steps and the results are rather capricious. In light of this, development of a catalyst system which could hydrogenate *E*/*Z* isomeric mixtures of substrates **4** with high enantioselectivities would provide a new general method of great synthetic utility. We next explored this possibility.

2. Hydrogenation Reactions: Optimization. We previously have demonstrated that cationic Rh catalysts bearing the DuPHOS ligands are capable of hydrogenating a range of olefinic substrates with exceedingly high enantioselectivities.[6] However, it remains impossible to predict a priori which catalyst will provide high enantioselectivities for a given substrate. Results obtained with one substrate type generally cannot be extended to other substrate types. This circumstance highlights the importance of a modular ligand design which provides facile access to a homologous series of ligands that may be examined systematically in a given transformation. As expounded below, we have explored the efficacy of a series of DuPHOS−Rh catalysts in the asymmetric hydrogenation of enol ester substrates of type **4**. The present study was actuated in an effort to develop a feasible asymmetric catalytic process for the production of highly enantiomerically enriched α-hydroxy esters and 1,2-diols.

2.1. *E*/*Z* Isomeric Enol Benzoates 4−OBz. Our propitious preliminary data involving enantioselective enol ester hydro-

(6) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (c) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 7, 9375. (d) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277. (e) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37. (f) Burk, M. J.; Allen, J. G.; Keisman, W. F. *J. Am. Chem. Soc.* **1998**, *120*, 657. (g) Crameri, Y.; Schmid, R.; Siegfried, T. European Patent No. EP 0691325 A1, 1996.

(7) (a) Schmidt, U.; Langner, J.; Kirchbaum, B.; Braun, C. *Synthesis* **1994**, 1138. (b) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *J. Org. Chem.* **1980**, *45*, 5, 2362. (c) Selke, R.; Pracejus, H *J. Mol. Catal.* **1986**, *37*, 213. (d) Brown, J. M.; Murrer, B. A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 489. (e) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.

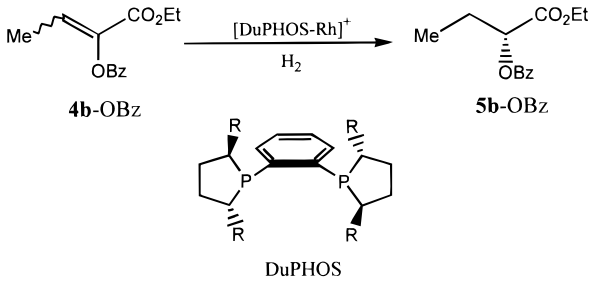
(8) (a) DIPAMP = 1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane; see: Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (b) BINAP = 2,2-bis(diphenylphosphino)-1,1′-binaphthyl; see: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

Table 1. Hydrogenation of **4b**−OBz with DuPHOS−Rh Catalysts[a]

entry	R in the DuPHOS Ligand	conversion[b]	% ee[c]
1	(*S,S*)-Me	100	98.8 (*S*)
2	(*S,S*)-Et	100	97.0 (*S*)
3	(*R,R*)-*n*-Pr	100	98.5 (*R*)
4	(*R,R*)-*i*-Pr	50	52.6 (*S*)
5	(*S,S*)-Cy	30	0

[a] Reactions were carried out at room temperature under an initial H_2 pressure of 60 psig and as 0.2 M solutions of substrate **4b**−OBz in methanol using the catalyst precursor [(COD)Rh(DuPHOS)]OTf (0.4 mol %) for 12 h. [b] Conversions were determined by ^{1}H-NMR. [c] Enantiomeric excesses were determined by chiral HPLC as described in the Experimental Section.

genation was obtained exclusively using the parent unsubstituted substrate **4a**−OAc (R = H).[6a] Examination of the synthesis and hydrogenation of substrates **4** bearing β-substituents was the primary focus of this campaign. As outlined above, the preparation of substrates via Horner−Emmons reagent **3** uniformly afforded inseparable *E*/*Z* isomeric mixtures of enol esters **4**. A critical determinant in our quest was the ability of our Rh−DuPHOS catalysts to hydrogenate both *E* and *Z* enol ester isomers **4** with comparably high enantioselectivity. Hence, we examined the hydrogenation of a standard substrate, ethyl 2-(benzoyloxy)crotonate, **4b**−OBz, to address this issue and to identify the most suitable catalyst.



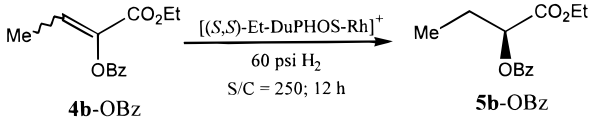
We have investigated the hydrogenation of **4b**−OBz (3:1 *E*/*Z* mixture) using a series of DuPHOS−Rh catalysts derived from the precursor complexes $[(COD)Rh(DuPHOS)]^+OTf^-$ (COD = 1,5-cyclooctadiene, OTf = trifluoromethanesulfonate) under a standard set of reaction conditons (MeOH, 20 °C, 60 psi of H_2, S/C = 250). The results of these studies are listed in Table 1.

The data in Table 1 clearly indicate that very high levels of asymmetric induction are achievable in this reaction and that *E*/*Z* substrate mixtures may be used with little or no adverse influence upon enantioselectivities. Moreover, these results show that catalysts bearing DuPHOS ligands possessing linear alkylphospholane substituents (entries 1−3) all effect complete conversion and provide comparably high enantioselectivities. However, branched phospholane substituents, *i*-Pr and Cy (entries 4 and 5), led to severe reduction in both rate and enantioselection, evidently due to a significant increase in the steric hindrance around the metal.

2.2. Pressure and Solvent Effects. The pressure under which asymmetric catalytic hydrogenations are performed can have a substantial impact on both observed rates and the selectivities achieved in these reactions.[9] These observations may be attributed to either the formation of different catalytically competent species in solution or the operation of kinetically distinct catalytic cycles, at different pressures. Recently,

(9) (a) Halpern, J. In *Asymmetric Synthesis*; 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.

Table 2. Hydrogenation of **4b**−OBz in Different Solvents[a]



entry	solvent	conversion[b]	% ee[c]
1	MeOH	100	97.0
2	*i*-PrOH	100	99.3
3	CF_3CH_2OH	60	98.0
4	EtOAc	60	90.0
5	THF	80	96.5
6	C_6H_6	0	
7	CH_2Cl_2	100	99.8

[a] Reactions were carried out at room temperature under an initial H_2 pressure of 60 psi and as 0.2 M solutions of substrate **4**−OBz using the catalyst precursor [(COD)Rh(*S,S*)-Et−DuPHOS]OTf (0.4 mol %) for 12 h. [b] Conversions were determined by ^{1}H-NMR. [c] Enantiomeric excesses were determined by chiral HPLC as described in the Experimental Section.

Blackmond and co-workers reported compelling data that implicate effective hydrogen concentrations as a key factor controlling enantioselectivities in asymmetric hydrogenations; higher pressures simply furnish higher H_2 concentrations.[10] Consistent with our previous results using the cationic DuPHOS−Rh catalyst systems,[6] we have observed only a nominal influence of pressure upon ee's in the hydrogenation of **4b**−OBz using Et−DuPHOS−Rh over the range 15−90 psi of H_2. We have yet to examine higher pressures in this reaction, although only minor pressure effects have been seen at pressures up to 1500 psi (100 atm) in the hydrogenation of numerous other substrates using these catalysts.[6,11]

Like pressure, the solvent employed in asymmetric catalytic reactions can have a dramatic and unpredictable influence on enantioselectivities and rates.[2] Enantioselectivities manifested by the cationic Rh−DuPHOS hydrogenation catalysts generally exhibit token solvent dependency, although this effect can be governed by substrate type. For example, enantioselectivities in the DuPHOS−Rh-catalyzed hydrogenation of α-(*N*-acylamino)acrylates or α-arylenamides[6,11] show very little solvent effect, while the selectivities achieved in *N*-acylhydrazone hydrogenations are highly solvent dependent.[12]

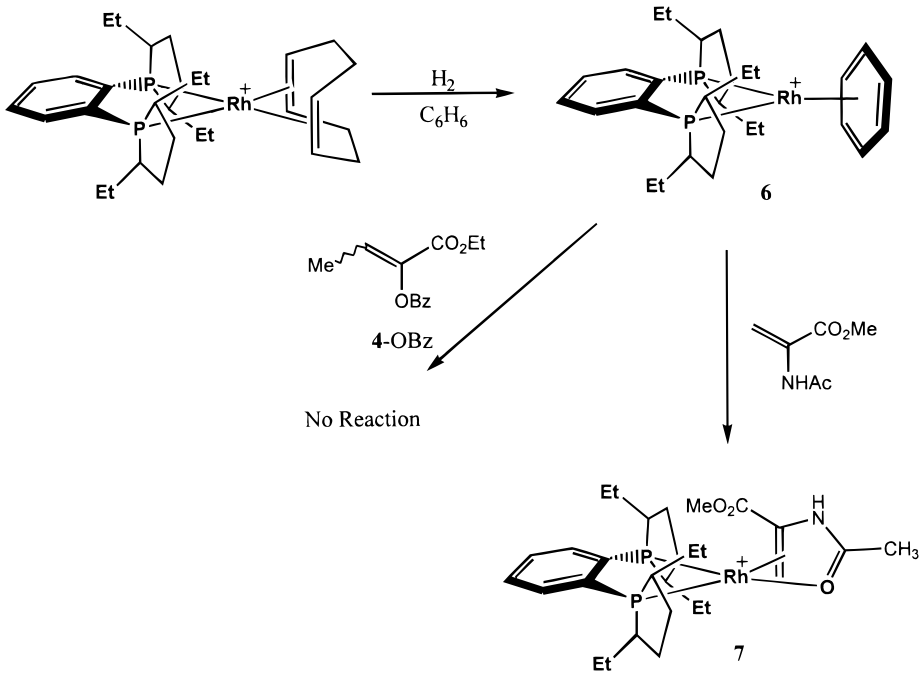
In an effort to further optimize the present reaction conditions, we have examined the influence of solvent on enantioselectivities and relative rates in the Et−DuPHOS−Rh-catalyzed hydrogenation of our standard substrate **4b**−OBz. As the results in Table 2 indicate, commensurately high enantioselectivities may be achieved in most solvents examined, although somewhat diminished ee's were observed in ethyl acetate. In contrast, the relative reaction rates were significantly affected by solvent type. Complete conversion was observed in methanol and 2-propanol over 12 h, while lower conversion (60%) occurred in the more lipophilic and more acidic 1,1,1-trifluoroethanol. Similarly, reduced conversions were seen in polar aprotic solvents such as tetrahydrofuran and ethyl acetate (entries 4 and 5), both of which may be expected to coordinate to the metal and inhibit catalysis. In accord with this trend, the noncoordinating, aprotic solvent methylene chloride was found superior, allowing the attainment of both high ee's and high relative rates.

(10) Sun, Y.; Landau, R. N.; Wang, J.; Lebland, C.; Blackmond, D. *J. Am. Chem. Soc.* **1996**, *118*, 1348.

(11) Burk, M. J.; Lee, J. F.; Wang, Y. M. *J. Am. Chem. Soc.* **1996**, *118*, 5142.

(12) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399.

Scheme 2. Formation and Reactions of Benzene Adduct **6**



This result was particularly useful for the hydrogenation of naphthyl derivative **4k**−OBz, which proved to be practically insoluble in the alcohols mentioned above (vide infra). Overall, inhibition by coordinating solvents such as THF and EtOAc suggests that enol esters **4** are rather poorly coordinating substrates that do not compete well for metal coodination sites. This notion is corroborated further below.

2.3. Benzene Inhibition. A surprising result was obtained when we attempted to perform the reaction in benzene solvent; no hydrogenation of **4b**−OBz was observed (entry 6, Table 2). This result was curious since we previously have found benzene to be a suitable, and sometimes superior, solvent for DuPHOS−Rh-catalyzed hydrogenations.[6c] To categorically rule out the presence of any impurity that may be inhibiting the catalyst, competive hydrogenation of a 2:1 mixture of **4b**−OBz and the readily reduced enamide, methyl α-(*N*-acetylamino)acrylate, was performed in benzene with the Et−DuPHOS−Rh catalyst. After a 24 h reaction period, the enol benzoate **4b**−OBz was recovered unreacted while the enamide was completely reduced to the expected *N*-acetylalanine methyl ester.

In an effort to further explore this effect, a benzene solution of the catalyst precursor [((*S*,*S*)-Et−DuPHOS)Rh(COD)]$^+$OTf$^-$ was hydrogenated in the absence of substrate. After 1 h under 60 psi of hydrogen, ^{1}H NMR studies indicated that cyclooctadiene was cleanly converted to cyclooctane and a new stable Rh complex was formed (Scheme 2). This complex was isolated as a pale yellow solid that displayed characteristic NMR data [i.e., singlet at δ 6.7 ppm in the ^{1}H NMR spectrum for coordinated benzene, and a doublet centered at δ 95.4 ppm ($^1J_{RhP}$ = 204 Hz) in the ^{31}P{^{1}H} spectrum]. These data allowed tentative identification of the complex as the η^6-benzene adduct [(*S*,*S*)-Et−DuPHOS)Rh(η^6-benzene)]$^+$OTf$^-$ (**6**).[13,14] Consistent with this assignment, the addition of strongly coordinating solvents such as acetonitrile to a CD_2Cl_2 solution of **6** led to immediate displacement of the benzene ligand, returning its characteristic proton signal at δ 7.15 ppm.

Formation of the stable adduct **6** indicated that benzene can serve as a suitable ligand for Rh in these systems. Furthermore, these studies suggested that the inhibitory effect of benzene in the present enol benzoate hydrogenations may be due to the inability of substrates **4** to displace the coordinated benzene in **6** and thus form the substrate−Rh intermediate complex required for hydrogenation to proceed. That other substrates such as α-(*N*-acylamino)acrylates, α-arylenamides, and *N*-acylhydrazones are readily hydrogenated by the DuPHOS−Rh catalysts in benzene implies that these types of substrates are more strongly coordinating than **4**, and thus are capable of displacing coordinated benzene from Rh (Scheme 2).

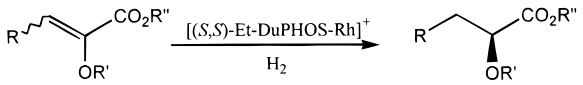
Support for these deductions derived from in situ NMR experiments. The addition of 1 equiv of enol benzoate **4b**−OBz to a CD_2Cl_2 solution of the benzene adduct **6** effected no changes in the NMR spectra relative to free **4b**−OBz and **6**. In contrast, the addition of 1 equiv of methyl α-(*N*-acetylamino)-acrylate to **6** instantaneously liberated benzene (^{1}H NMR δ 7.15 (s)), and produced the known intermediate enamide−Rh−DuPHOS complex **7**.[14b] The ^{31}P{^{1}H} spectrum of **7** revealed two inequivalent phosphorus nuclei appearing as doublets of doublets centered at δ 80.6 ppm and δ 89.8 ppm, respectively ($^1J_{RhP}$ = 159 and 153 Hz, respectively, $^2J_{PP}$ = 34 Hz), as expected. These observations strongly denote that enol benzoates **4** are not hydrogenated in benzene due to the incapability of **4** to effectively compete with benzene as a ligand for Rh. Taking into consideration the binding affinity of RhP_2^+, fragments for arenes,[13,15] competition in the coordination between an aromatic ring and an olefinic bond is plausible, and possibly explains

(13) For other [(η^6-C_6H_6)RhP_2]$^+$ complexes see: (a) Singewald, E. T.; Slone, C. S.; Stern, C. L.; Mirkin, C. A.; Yap, G. P. A.; Liable-Sands, L. M.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 3048. (b) Singewald, E. T.; Shi, X.; Mirkin, C. A.; Schofer, S. J.; Stern, C. L. *Organometallics* **1996**, *15*, 5, 3062. (c) Bleeke, J. R.; Donaldson, A. J. *Organometallics* **1988**, *7*, 1588. (d) Schrock, R. A.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3089.

(14) For other solvate complexes of the fragment RhP_2^+ prepared by hydrogenation, see for example: (a) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245. (b) Armstrong, S. K.; Brown, J. M.; Burk, M. J. *Tetrahedron Lett.* **1993**, *34*, 879.

(15) (a) Chaloner, P. A.; Esteruelas, M. A.; Joo, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1994. (b) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8055.

Table 3. Et−DuPHOS−Rh-Catalyzed Asymmetric Hydrogenation of Enol Esters **4**[a]



4 **5**

substrate	R′	R	R″	*E*/*Z* ratio	% ee[b] (conf)[c]
4a−OAc	Ac	H	Et		>99 (*S*)
4b−OBz	Bz	Me	Et	3	96.0 (*S*)
4c−OBz	Bz	*n*-Pr	Me	3	98 (*S*)
4d−OAc	Ac	*i*-Pr	Et	6	96.1 (*S*)[d]
4d−OBz	Bz	*i*-Pr	Et	6	96.9 (*S*)[d]
4e−OBz	Bz	c-Pr	Me	9	97.5 (*S*)
4f−OBz	Bz	CH_2-i-Pr	Et	2.5	>99 (*S*)
4g−OAc	Ac	*n*-C_5H_{11}	Et	3.5	>99 (*R*)[e]
4g−OBz	Bz	*n*-C_5H_{11}	Et	3.5	>99 (*S*)
4h−OBz	Bz	c-C_6H_{11}	Me	3	95 (*S*)
4i−OAc	Ac	Ph	Et	9	95.6 (*S*)[f]
4i−OBz	Bz	Ph	Me	10	98 (*S*)
4j−OBz	Bz	α-naphthyl	Et	3	93.2 (*S*)[g]
4k−OBz	Bz	2-thienyl	Me	4	97.5 (*S*)

[a] Reactions were carried out at room temperature under an initkal H_2 pressure of 60 psig and as 0.5 M solutions in methanol of substrate using the catalyst precursor [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf (0.2 mol %) for 48 h unless otherwise stated. [b] Enantiomeric excesses were determined by chiral HPLC or chiral capillary GC, as described in the Experimental Section. [c] Absolute configurations were assigned by comparing the sign of optical rotation of derived α-hydroxy esters or 1,2-diols with that of known compounds. [d] Initial pressure 90 psig. [e] Reaction catalyzed by (*R*,*R*)−Et−DuPHOS−Rh. [f] Reaction performed witht the (*S*,*S*)−Me−DuPHOS-Rh catalyst (0.4 mol %). [g] Reaction performed in methylene chloride.

the low reactivity we have observed in attempted hydrogenation of several aryl-containing enol benzoates of type **4** (vide infra).

3. Hydrogenation Reactions: Scope and Limitations. Our overall objective was to develop a practical route to a diverse range of enantiomerically pure α-hydroxy esters and 1,2-diols through development of a broadly effective catalyst for asymmetric hydrogenation of enol acylates of type **4**. On the basis of our promising results outlined above, we next endeavored to explore the scope and limitations of the Et−DuPHOS−Rh catalyst. Our preliminary optimization studies indicated that enol acylates **4** were reduced more slowly than α-enamide or *N*-acylhydrazone substrates under analogous conditions. Nonetheless, under a standard set of mild conditions (MeOH, 20 °C, S/C = 500, 60 psi of H_2, 48 h), the catalyst precursor [(COD)Rh(Et−DuPHOS)]$^+$OTf$^-$ induced the highly enantioselective hydrogenation of a wide array of enol acetates and enol benzoates **4** (Table 3). In all cases, substrates **4** were employed as mixtures of *E* and *Z* isomers.

Substrates lacking β-substituents (**4a**, R = H) or bearing linear or branched β-alkyl substituents (**4b**−**d**, **4f,g**) were hydrogenated with very high enantiomeric excesses ranging from 97% ee to higher than 99% ee. Similarly high enantioselectivities also were seen with β-cycloalkyl substituents; **5e** and **5h** were produced in 95% ee and 97.5% ee, respectively.

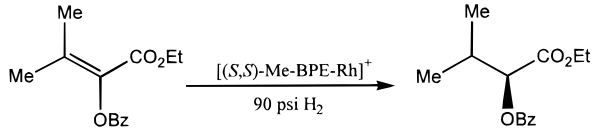
Importantly and unexpectedly, the Et−DuPHOS catalysts also were capable of providing high selectivites with substrates containing various aromatic β-substituents. Thus, the esters **5i**,**j** were obtained with excellent levels of enantioselectivity (98% ee, 95.6% ee, and 93.2% ee, respectively). Even the thiophene-containing substrate **4k** was tolerated by the catalyst and was reduced with high enantioselectivity (97.5% ee).

The attainment of high enantioselectivities in the hydrogenation of *E*/*Z* mixtures of aromatic substrates **4i**−**k** (in which the *E* isomer predominates) is noteworthy. It is well-documented that enantioselectivities dramatically diminish when *E* isomers of aromatic α-enamides (e.g., α-*N*-acetamidocinnamic acid and analogous substrates) are used in asymmetric hydrogenation reactions.[2,8a] Pertinently, the phenyl substrate (*E*)-**4i**−OAc has been reported to be unreactive toward hydrogenation by both the Ru−BINAP and Rh−DIPAMP catalysts previously used to hydrogenate enol acetates.[7a] The latter catalysts ostensibly are substrate specific and are capable of hydrogenating β-aromatic substrates **4** only when prepared in isomerically pure form. In contrast, the Et−DuPHOS−Rh catalyst is a versatile system that may be employed to hydrogenate a broad range of *E*/*Z*-isomeric enol acylates **4**.

Interestingly, several aromatic substrates were found relatively unreactive under the standard reaction conditions originally employed. For example, substrate **4i**−OAc reacted appreciably more slowly than its counterpart benzoate **4i**−OBz, showing only 10% conversion after 2 days of reaction. Curiously, the analogous *o*-, *m*-, and *p*-bromophenyl enol benzoates also reacted sluggishly under similar conditions. In these instances, the less sterically demanding Me−DuPHOS−Rh catalyst often was found to allow hydrogenation with faster rates and with comparably high enantioselectivities. Hence, (*S*,*S*)-Me−DuPHOS-catalyzed hydrogenation of **4i**−OAc afforded the reduced product (*S*)-**5i** in 95.6% ee over 48 h.

We previously have demonstrated that the Me−DuPHOS−Rh and Me−BPE−Rh catalysts are capable of hydrogenating β,β-disubstituted α-acetamidoacrylate substrates with very high enantioselectivities.[6c] The ability of the Rh−DuPHOS catalysts to hydrogenate *E*/*Z*-isomeric mixtures of the enol esters **4** suggested that these catalysts might also tolerate substituents in both *E* and *Z* β-positions of an enol ester substrate. Unfortunately, neither the Et−DuPHOS−Rh nor the less encumbered Me−DuPHOS−Rh catalysts proved to be effective for the hydrogenation of ethyl 2-(benzoyloxy)-3-methylbutenoate **(8)**.

Somewhat greater success was achieved through use of the more electron-rich and sterically least demanding Me−BPE−Rh catalyst. Under the optimum conditions recently employed in our laboratory for the hydrogenation of β,β-disubstituted α-enamides (90 psig of hydrogen, cationic (*S*,*S*)-Me−BPE−Rh catalyst)[6c] the desired product **9** was obtained with reasonable enantioselectivity (82% ee).



8 **9**

82% ee

4. Mechanistic Examination of *E*/*Z* Isomerization. Above we have shown that the DuPHOS−Rh catalysts are capable of hydrogenating *E*/*Z* mixtures of substrates **4** with high levels of enantioselectivity. These results brought to light two questions: (i) Are the *E* and *Z* isomers reduced with comparable enantioselectivities? (ii) If *E* and *Z* isomers are reduced with different selectivites, is isomerization of one isomer to the other occurring (i.e., *E* to *Z*), such that the reduction proceeds through only one isomeric pathway?

To address these issues, we examined separately the Et−DuPHOS−Rh-catalyzed deuteration of individual *E* and *Z* isomers of naphthyl derivative **4j**−OBz, which may be separated by column chromatography.[16] Assuming the expected occurrence of stereoselective metal-catalyzed cis addition of D_2 to

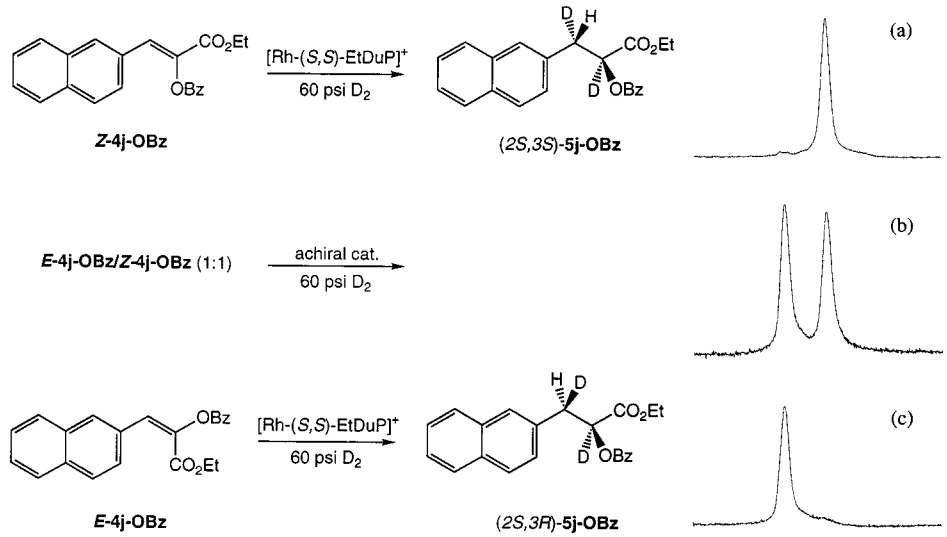


Figure 2. Benzylic region in the ^{1}H NMR (acetone-d_6) spectra of the deuteration products derived from (a) (*z*)-**4j**−OBz, (b) a 1:1 *E/Z* mixture of **4j**, and (c) (*E*)-**4j**−OBz.

the olefinic bond of the substrate **4j**−OBz, deuteration of pure *E* and *Z* isomers should afford diastereomerically distinct products which may be distinguished by ^{1}H NMR spectroscopy (diastereotopic β-protons). Table 3 indicates that the (*S,S*)-Et−DuPHOS−Rh catalyst affords products **5** with *S* absolute stereochemistry at the 2-α-position. Hence, deuteration of the (*Z*)-**4j**−OBz using (*S,S*)-Et−DuPHOS−Rh should furnish (2*S*,3*S*)-**5j**−OBz, while deuteration of *E*-**4j**−OBz should yield the 2*S*,3*R* product (Figure 2). Any degree of isomerization of either *E* or *Z* isomer would create a discernible mixture of diastereomers. In the event of complete isomerization of one isomer to the other, both *E* and *Z* isomers of **4j**−OBz would provide the same diastereomer of product D_2−**5j**−OBz.

Figure 2 shows the benzylic region of the ^{1}H NMR spectra corresponding to the products of such reactions. The center spectrum (b) corresponds to the product derived from deuteration of a 1:1 *E/Z* mixture of isomers with an achiral catalyst.[17] As can be seen, deuteration of (*Z*)-**4j**−OBz and (*E*)-**4j**−OBz produced diastereomers that differ only in the configuration at the β-carbon C3. Comparison of the spectra revealed that negligible isomerization occurred during (*S,S*)-Et−DuPHOS−Rh-catalyzed deuteration of either (*Z*)-**4j**−OBz or (*E*)-**4j**−OBz.

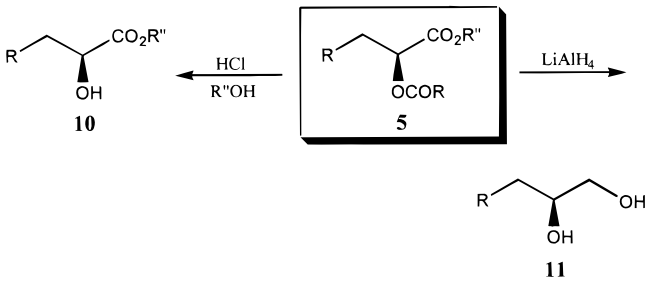
The high enantioselectivites we have acheived in the hydrogenation of isomeric mixtures of enol esters **4** suggests that the Et−DuPHOS−Rh catalysts preferentially induce the same sense of chirality and relative degree of selectivity at the α-carbon (C2) of **4**, with general disregard for the geometric configuration about the β-carbon of the olefinic substrate. In accord with this observation, independent deuteration of isomerically pure (*Z*)-**4j**−OBz and (*E*)-**4j**−OBz with the (*S,S*)-Et−DuPHOS catalyst provided the products (2*S*,3*S*)-**5j** and (2*S*,3*R*)-**5j** in 96% ee and 89% ee, repectively.

These results clearly demonstrate the unique ability of the DuPHOS−Rh catalysts to tolerate substituents, even bulky aromatic substituents, in either the *E* or *Z* β-position of enol ester substrates **4**. Distinctly, few other catalysts presently known display such a combination of substrate structural tolerance and high enantioselectivity in asymmetric hydrogenation reactions.

5. α-Hydroxy Esters and 1,2-Diols. An important application of the hydrogenation reactions described herein conceivably will be the preparation of highly enantiomerically enriched α-hydroxy esters or 1,2-diols directly from hydrogenation products **5**. An obvious requirement is that transformations involving **5** proceed with no loss of enantiomeric purity.

The requisite α-hydroxy esters **10** can be obtained readily in good isolated yield by treatment of the hydrogenation products **5** with a 1:1 mixture of MeOH (or EtOH)-concentrated HCl. Deprotection of acetates **5**−OAc proceeded smoothly at room temperature and were complete within 12 h. In contrast, hydrolysis of benzoates **5**−OBz required somewhat more forcing conditions: 12−24 h under reflux in 1:1 MeOH (or EtOH)-concentrated HCl. In neither case was racemization observed. Conveniently, conversion to α-hydroxy esters **10** may be achieved simply through addition of an equal volume of concentrated HCl to the MeOH solution of **5** formed in the hydrogenation reactions.

By way of example, the benzoyl protecting group of **5i**-OBz (R = Ph) was hydrolytically removed under the above conditions to afford the corresponding α-hydroxy ester **10i** in 85% yield. Enantiomeric excess determination by chiral HPLC confirmed that no racemization had occurred during deprotection of **5i**−OBz. Analogous behavior was observed in the synthesis of other α-hydroxy esters using these procedures.



Rather than hydrolytic conversion to α-hydroxy esters, valuable chiral 1,2-diols **11** may be obtained simply through treatment of hydrogenation products **5** with reducing agents such

(16) Olefin configuration has been assigned on the basis of the value of the coupling constant $^3J_{CH}$ in −*H*C═C(*C*O$_2$Et)(OBz): Fischer, P.; Schweizer, E.; Langner, J.; Schmidt, U. *Magn. Reson. Chem.* **1994**, 567.

(17) Configurations of the deuterated products have been assigned considering cis addition of D_2 to the olefinic bond: (a) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6332. (b) Kirby, G. W.; Michael, J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 115.

as lithium aluminum hydride. Again, no loss of enantiomeric purity was observed in these reactions. This procedure provides an extremely facile entry into a diverse range of important chiral building blocks which are not easily obtained by other asymmetric catalytic methods. For instance, Sharpless's asymmetric dihydroxylation reaction performs exceedingly well with internal olefins, but affords significantly lower enantioselectivites with terminal olefins,[18] which would be required to produce 1,2-diols of type **11**.

6. Conclusions. We have described the development of an extremely effective catalyst for the enantioselective hydrogenation of enol esters of type **4**. In particular, the cationic Et−DuPHOS−Rh catalysts have been found to allow the hydrogenation of *E*/*Z*-isomeric mixtures of **4** with enantioselectivites generally >97% ee. Deuteration studies indicated that no substrate isomerization occurs during these reactions. Benzene was found to inhibit the reaction through formation of a stable adduct between benzene and the cationic Et−DuPHOS−Rh fragment. The hydrogenation products **5** were converted readily to valuable α-hydroxy esters or 1,2-diols with no diminution of enantiomeric purity. The simplicity and versatility of the process described herein suggest many possible applications in the synthesis of a diverse range of important chiral building blocks.

7. Experimental Section

General Procedures. All reactions and manipulations were performed under nitrogen either in a Braun Labmaster 100 glovebox or using standard Schlenk-type techniques. Benzene, diethyl ether (Et_2O), tetrahydrofuran (THF), hexanes, and pentane were distilled from sodium−benzophenone ketyl under nitrogen. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 and methanol (MeOH) from $Mg(OMe)_2$. Chiral DuPHOS ligands and rhodium catalysts were prepared as previously described.[6] Hydrogen gas (99.99%) was purchased from National Welders, Inc. (Raleigh, NC) and used as received. Column chromatography was performed using EM Science Silica Gel 60 (230−400 mesh). All reagents were purchased from commercial suppliers and used as received.

GC analyses were performed by using a Hewlett-Packard Model HP 5890 Series II gas chromatograph. HPLC analyses were performed using a Hewlett-Packard Model HP 1090 Series II liquid chromatograph interfaced to a HP Vectra 486/66U computer workstation. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. HRMS data were obtained using a JEOL JMS−SX 102A mass spectrometer. NMR spectra were obtained on a Varian XL-300 (299.9 MHz, ^{1}H; 121.4 MHz, ^{31}P; 75.4 MHz, ^{13}C) or a GE QE-300 (300.0 MHz, ^{1}H; 75.5 MHz, ^{13}C) spectrometer with chemical shifts reported in ppm (δ) relative to Me_4Si or residual protons in the solvent.

Synthesis of Phosphonate Reagent 3. 2-(Diethylphosphoryl)-2-(*O*-benzoyl) ethanoic Acid (2). Glyoxylic acid monohydrate (2.0 g, 21.7 mmol) and diethyl phosphite (3.0 g, 21.7 mmol) were heated with stirring to 60 °C for 5 h, after which the conversion to **1** was shown to be complete by ^{1}H NMR spectroscopy. Dichloromethane (20 mL), pyridine (1.71 g, 21.7 mmol), and benzoyl chloride (3.05 g, 21.7 mmol) were added and the reaction was allowed to stir for another 6 h. Pyridinium chloride that precipitated was filtered, and the resulting solution was washed with 1 M HCl (2 × 20 mL) and saturated $NaHCO_3$ (20 mL). After the organic layer was dried over $MgSO_4$, the solvent was evaporated using a rotary evaporator. The resulting oil was taken up in a small amount of CH_2Cl_2 and cooled. Colorless crystals of the benzoyl-protected phosphonate acid **2** were thus obtained: yield 5.5 g, 17.3 mmol, 80%; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6H, $-OCH_2CH_3$), 4.28 (m, 4H, $-OCH_2CH_3$), 5.78 (d, $^2J_{PH}$ = 17.7 Hz, 1H, $-P(O)CH-$), 7.40−8.10 (m, 5H, $-OC(O)C_6H_5$), 11.04 (br, 1H, $-COOH$); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ = 5.8 Hz), 64.7 (d, $^2J_{PC}$ = 10.1 Hz), 68.3 (d, $^1J_{PC}$ = 160.2 Hz), 127.5, 128.4, 130.0, 133.7, 164.8, 166.4; HRMS (FAB): *m*/*z* 317.0782 (MH^+ exact mass calculated for $C_{13}H_{18}O_7P$, 317.0790).

Methyl 2-(diethylphosphoryl)-2-(*O*-benzoyl)Ethanoate (3). The acid **2** (2.7 g, 8.6 mmol) was reacted with diazomethane using standard procedures[19] to provide the methyl ester **3** as a colorless oil; yield 2.7 g, 8.2 mmol, 95%; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 6H, $-OCH_2CH_3$), 3.78 (s, 3H, $-COOCH_3$), 4.23 (m, 4H, $-OCH_2CH_3$), 5.65 (d, $^2J_{PH}$ = 16.8 Hz, 1H, $-P(O)CH-$), 7.40−8.05 (m, 5H, $-OC(O)C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, $^3J_{PC}$ = 5.8 Hz), 52.9, 64.0 (d, $^2J_{PC}$ = 7.1 Hz), 68.5 (d, $^1J_{PC}$ = 158.9 Hz), 128.2, 128.4, 129.8, 133.7, 164.9, 165.4; HRMS (FAB) *m*/*z* 331.0952 (MH^+ exact mass calculated for $C_{14}H_{20}O_7P$, 331.0947).

Synthesis of Enol Esters 4. Condensation Reactions: General Procedure. The procedure employed was as described in ref 7a. Phosphonate ester **3** (5 mmol) and LiCl (5.5 mmol) were dissolved in THF (10 mL) and cooled to −78 °C. Tetramethylguanidine (5.5 mmol) was added, and after 15 min of stirring at −78 °C, the appropriate aldehyde (6 mmol) was added. The reaction was then allowed to stir while being warmed to room temperature over a period of 12 h. Ethyl acetate−water, 1:1 (15 mL) was added, the organic fraction washed with 1 N H_2SO_4 (2 × 15 mL) and 1 M $NaHCO_3$ (2 × 15 mL) and dried over $MgSO_4$, and the solvent removed on a rotary evaporator. Column chromatography was then performed to give the desired products **4a**−**m**. Where relevant, all products obtained were identical in all repects to those previously reported.[7a]

Asymmetric Hydrogenations: General Procedure. In a glovebox, a Fisher−Porter tube was charged with substrate, deoxygenated MeOH, and catalyst (0.2 mol % unless otherwise stated). After being removed from the glovebox, the vessel was connected to a hydrogen line and subjected to five vacuum/H_2 cycles, and the tube was pressurized to an initial pressure of 60 psig of H_2. The reaction was allowed to stir for 48 h at room temperature. Once the reaction was finished, the solvent was removed via rotary evaporation. The oily residue was dissolved in ethyl acetate−hexanes (1:1) and passed through a short plug of silica to remove the catalyst. Without further purification the enantiomeric excesses were determined with an aliquot of the crude product thus obtained. Spectroscopic and other analytical data for the hydrogenation products **5** are given below.

(*R*)-2-(Benzoyloxy)butanoic Acid, Ethyl Ester [(*R*)-5b−OAc]: oil; $[\alpha]^{25}_D$ = −1.8° (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, $^3J_{HH}$ = 7.4 Hz, 3H), 1.29 (t, $^3J_{HH}$ 7.1 Hz), 2.04 (m, 2H), 4.24 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 5.18 (t, $^3J_{HH}$ = 6.6 Hz, 1H), 7.47,7,59, 8.09 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.4, 13.9, 24.5, 61.0, 73.6, 128.2, 129.6, 133.0, 133.1, 165.9, 169.9; HRMS (EI, direct insert) *m*/*z* 236.1047 (M^+, exact mass calcd for $C_{13}H_{16}O_4$, 236.1047); ee determination (HPLC, Daicel Chiracel OJ, 0.5 mL/min,15% 2-PrOH−hexanes) *(R)* t_1 = 16.56 min, *(S)* t_2 = 18.50 min.

(*S*)-2-(Benzoyloxy)pentanoic Acid, Methyl Ester [(*S*)-5c−OBz]: oil; $[\alpha]^{25}_D$ = −11.9° (*c* 0.27 MeOH); ^{1}H NMR ($CDCl_3$) δ 0.99 (t, $^3J_{HH}$ = 7.5 Hz 3H), 1.55 (m, 2H), 1.97 (m, 2H), 3.77 (s, 3H), 5.25 (dd, $^3J_{HH}$ = 7.5, 5.1 Hz, 1H), 7.43−8.10 (m, 5H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 13.6, 18.5, 33.2, 52.2, 72.5, 128.3, 129.4, 129.8, 133.2, 166.0, 170.8; HRMS (FAB): *m*/*z* 237.1125 (MH^+ exact mass calculated for $C_{13}H_{17}O_4$, 237.1127); ee determination (HPLC, Daicel Chiracel OJ, 0.5 mL/min, 2.5% 2-PrOH−hexanes) *(R)* t_1 = 20.65 min, *(S)* t_2 = 21.99 min.

(*R*)-2-Acetoxy-4-methylpentanoic Acid, Ethyl Ester [(*R*)-5d−OAc]: oil; $[\alpha]^{25}_D$ = +19.8° (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, $^3J_{HH}$ = 7.9 Hz, 3H), 0.95 (d, $^3J_{HH}$ = 8.1 Hz, 3H), 1.27 (t, $^3J_{HH}$ = 7.1 Hz), 1.62 (m, 1H), 1.74 (m, 1H), 2.13 (s, 3H), 4.20 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 5.00 (m, 1H); ^{13}C{^{1}H}NMR ($CDCl_3$) δ 13.3, 19.8, 20.7, 22.2, 38.9, 60.4, 70.3, 169.7, 169.9; HRMS (EI, direct insert) *m*/*z* 203.1290 (MH^+, exact mass calcd for $C_{10}H_{18}O_4$, 203.1283); ee determination, derivatized to 4-methyl-2-hydroxypentanoic acid, ethyl ester, vide infra.

(*S*)-2-(Benzoyloxy)-4-methylpentanoic Acid, Ethyl Ester [(*S*)-5d−OBz]: oil; $[\alpha]^{25}_D$ = −10.9° (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, $^3J_{HH}$ = 8.4 Hz, 3H), 1.00 (d, $^3J_{HH}$ = 8.4 Hz, 3H), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.79 (m, 1H), 1.90 (m, 1H), 4.22 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 1.79 (m, 1H), 1.90 (m, 1H), 4.22 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 5.25 (dd, $^3J_{HH}$ = 9.7, 3.9 Hz, 1H), 7.45, 7.54, 8.09 (m, 5H); ^{13}C{^{1}H} NMR

(18) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 4, 2483.

(19) Black, T. H. *Aldrichim. Acta* **1983**, *16*, 3.

($CDCl_3$) δ 13.3, 20.9, 22.3, 24.0, 39.1, 60.5, 70.8, 127.9, 129.0, 132.5, 139.8, 165.3, 169.8; HRMS (EI, direct insert) *m/z* 265.1445 (M^+, exact mass calcd for $C_{15}H_{20}O_4$, 265.1440); ee determination, derivatized to 4-methyl-1,2-pentanediol, vide infra.

(*S*)-2-(Benzoyloxy)-3-cyclopropylpropanoic Acid, Methyl Ester [(*S*)-5e−OBz]: oil; $[\alpha]^{25}_D = -12.7°$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.15 (m, 2H), 0.49 (m, 2H), 0.90 (m, 1H), 1.87 (m, 2H), 3.73 (s, 3H), 5.30 (dd, $^3J_{HH} = 7.5, 4.5$ Hz, 1H), 7.40−8.15 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 4.0, 4.7, 7.1, 36.3, 52.2, 73.1, 128.5, 129.4, 129.8, 133.3, 165.9, 170.6; HRMS (FAB) *m/z* 249.1129 (MH^+, exact mass calcd for $C_{14}H_{17}O_4$, 249.1127); ee determination (HPLC, Daicel Chiracel OJ, 0.5 mL/min, 7.5% 2-PrOH−hexanes) *(S)* $t_1 = 21.05$ min, *(R)* $t_2 = 23.39$ min.

(*S*)-2-(Benzoyloxy)-5-methylhexanoic Acid, Ethyl Ester [(*S*)-5f−OBz]: oil; $[\alpha]^{25}_D = -5.8°$ (*c* 0.57, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (d, $^3J_{HH} = 6.6$ Hz, 6H), 1.28 (t, $^3J_{HH} = 7.1$ Hz, 3H), 1.39 (m, 1H), 1.77 (m, 1H), 1.99 (m, 2H), 4.23 (q, $^3J_{HH} = 7.0$ Hz, 2H), 5.19 (t, $^3J_{HH} = 6.3$ Hz, 1H), 7.46, 7.59, 8.08 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.8, 21.9, 22.2, 27.3, 28.8, 33.8, 59.8, 60.8, 128.0, 129.3, 129.4, 133.0, 165.6, 169.8; HRMS (EI, direct insert) *m/z* 279.1593 (M^+, exact mass calcd for $C_{16}H_{22}O_4$, 279.1596); ee determination: derivatized to 5-methyl-1,2-hexanediol, vide infra.

(*S*)-2-Acetoxyoctanoic acid, Ethyl Ester [(*S*)-5g−OAc]: oil; $[\alpha]^{25}_D = -21.1°$ (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, $^3J_{HH} = 6.5$ Hz, 3H), 1.27 (m, 11 H), 2.14 (s, 3H), 4.20 (q, $^3J_{HH} = 7.1$ Hz, 2H), 4.96 (t, $^3J_{HH} = 6.5$ Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.5, 13.6, 20.1, 22.1, 24.6, 28.4, 30.7, 31.2, 60.6, 72.0, 169.8, 169.9; HRMS (EI, direct insert) *m/z* 231.1600 (M^+, exact mass calcd for $C_{12}H_{22}O_4$, 231.1596); ee determination, derivatized to (*S*)-1,2-octanediol, vide infra.

(*R*)-2-(Benzoyloxy)octanoic Acid, Ethyl Ester [(*R*)-5g−OBz]: oil; $[\alpha]^{25}_D = +6.0°$ (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (t, $^3J_{HH} = 6.7$ Hz, 3H), 1.28 (t, $^3J_{HH} = 7.1$ Hz, 3H), 1.36 (m, 6H), 1.49 (m, 2H), 1.49 (m, 2H), 1.96 (m, 2H), 4.23 (q, $^3J_{HH} = 7.1$ Hz, 2H), 5.20 (t, $^3J_{HH} = 6.3$ Hz, 1H), 7.46, 8.08, 8.10 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.6, 13.7, 22.1, 24.8, 28.5, 30.8, 31.2, 60.7, 72, 128.0, 129.2, 129.3, 132.8, 165.5, 169.7; HRMS (EI, direct insert) *m/z* 292.1675 (M^+, exact mass calcd for $C_{17}H_{24}O_4$, 292.1669); ee determination (HPLC, Daicel Chiracel-OJ, 2% 2-PrOH−hexanes, 0.6 mL/min) *(S)* $t_1 = 15.5$ min, *(R)* $t_2 = 16.2$ min.

(*S*)-2-(Benzoyloxy)-3-cyclohexylpropanoic Acid, Methyl Ester [(*S*)-5h−OBz]: oil; $[\alpha]^{20}_D = -13.5°$ (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90−1.95 (m, 11H), 1.26 (t, $^3J_{HH} = 5.4$ Hz, 3H), 4.21 (q, $^3J_{HH} = 5.4$ Hz, 2H), 5.27 (dd, $^3J_{HH} = 7.2, 3.0$ Hz, 1H), 7.40−8.10 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 14.1, 26.0, 26.2, 26.3, 32.3, 33.7, 34.1, 38.5, 61.2, 71.2, 128.4, 129.6, 129.8, 133.2, 166.1, 170.8; HRMS (FAB) *m/z* 291.1588 (MH^+ exact mass calculated for $C_{17}H_{23}O_4$, 291.1596); ee determination (HPLC, Daicel Chiracel-OJ, 2% 2-PrOH−hexanes, 0.6 mL/min) *(S)* $t_1 = 15.5$ min, *(R)* $t_2 = 16.2$ min.

(*S*)-2-Acetoxy-3-phenylpropanoic Acid, Ethyl Ester [(*S*)-5i−OAc]: oil; $[\alpha]^{20}_D = -8.8°$ (*c* 0.41, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (t, 3H, $^3J_{HH} = 5.4$ Hz), 2.08 (s, 3H), 3.13 (m, 2H), 4.17 (q, $^3J_{HH} = 5.4$ Hz, 2H), 5.20 (dd, $J_{HH} = 6.6, 3.6$ Hz, 1H), 7.20−7.60 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.6, 37.3, 61.4, 73.0, 127.0, 128.5, 129.1, 130.0, 162.0, 169.6; HRMS (EI, direct insert) *m/z* 235.0965 ($M - H^+$, exact mass calculated for $C_{13}H_{15}O_4$, 235.0970); ee determination (HPLC, Daicel Chiracel-OD, 3% 2-PrOH−hexanes, 0.5 mL/min) *(R)* $t_1 = 13.1$ min, *(S)* $t_2 = 14.5$ min.

(*S*)-2-(Benzoyloxy)-3-phenylpropanoic Acid, Methyl Ester [(*S*)-5i-OBz]: oil; $[\alpha]^{20}_D = -40.2°$ (*c* 1.85, MeOH); ^1H NMR ($CDCl_3$) δ 3.25 (m, 2H), 3.70 (s, 3H), 5.40 (dd, $^3J_{HH} = 8.1$ Hz, $^3J_{HH} = 5.1$ Hz, 1H), 7.20−8.05 (m, 10H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 37.5, 52.3, 73.4, 127.0, 128.3, 128.5, 129.1, 129.3, 129.7, 133.3, 135.8, 165.8, 170.0; HRMS (FAB) *m/z* 285.1119 (MH^+ exact mass calculated for $C_{17}H_{17}O_4$, 285.1127); ee determination (HPLC, Daicel Chiracel-OJ, 15% 2-PrOH−hexanes, 0.5 mL/min) *(R)* $t_1 = 29.0$ min, *(S)* $t_2 = 39.9$ min.

(*S*)-2-(Benzoyloxy)-3-(β-naphthyl)propionic Acid, Ethyl Ester [(*S*)-5j−OBz]: oil; $[\alpha]^{25}_D = -59.6°$ (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.26 (t, $^3J_{HH} = 6.9$ Hz, 3H), 3.46 (m, 2H), 4.20 (q, $^3J_{HH} = 7.1$ Hz, 2H), 5.52 (dd, $^3J_{HH} = 7.6, 5.3$ Hz, 1H), 7.39, 7.44, 7.58, 7.78, 8.02 (m, aromatics); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 14.3, 38.0, 61.7, 74.2, 126.4−126.9, 128.2−130.2, 133.3−134.6 (aromatics); HRMS (EI, direct insert) *m/z* 348.1368 (M^+, exact mass calcd for $C_{22}H_{20}O_4$, 348.1362); ee determination, derivatized to 3-(β-naphthyl)-1,2-propanediol, vide infra.

(*S*)-2-(Benzoyloxy)-3-(2′-thienyl)propanoic Acid, Methyl Ester [(*S*)-5k−OBz]. $[\alpha]^{20}_D = -27.7°$ (*c* 0.53 MeOH); ^1H NMR ($CDCl_3$) δ 3.54 (m, 2H), 3.76 (s, 3H), 5.50 (m, 1H), 6.96−8.12 (m, 8H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 31.6, 52.3, 72.8, 124.7, 124.9, 126.7, 128.3, 129.0, 129.8, 133.3, 137.2, 165.6, 169.3; HRMS (FAB) *m/z* 291.0684 (MH^+ exact mass calculated for $C_{15}H_{15}O_4S$, 291.0691), ee determination (HPLC, Daicel Chiracel-OJ, 10% 2-PrOH−hexanes, 0.5 mL/min) *(R)* $t_1 = 38.1$ min, *(S)* $t_2 = 41.2$ min.

Synthesis of α-Hydroxy Esters 10 and 1,2-Diols 11 from α-Acyloxy Esters 5. Products **10** and **11** were obtained as described in the text above. All products were authenticated by comparative analysis with the spectroscopic data available in the literature. Comparison of the sign of optical rotation with that reported was used to determine configuration, as well as to corroborate the expected configuration of the hydrogenation products **5** (i.e. the *S,S* configuration in the DuPHOS ligand affords *S* products **5**).

Hydrolysis of Esters 5: General Procedure. The 2-acetoxy esters **5**−OAc were treated at room temperature with a mixture of ethanol (or methanol) and concentrated HCl (1:1 v/v). Complete hydrolysis to **10** was observed after 12 h at room temperature for **5**−OAc derivatives. Following the same procedure, complete hydrolysis required 24 h of heating under reflux for **5**−OBz esters.

(*S*)-2-Hydroxy-4-methylpentanoic Acid, Ethyl Ester:[20] $[\alpha]^{20}_D = -18.1\alpha$ (*c* = 1.2, Et_2O); ^1H NMR ($CDCl_3$) δ 0.94 (d, $^3J_{HH} = 6.7$ Hz, 3H), 0.95 (d, $^3J_{HH} = 6.6$ Hz, 3H), 1.29 (t, $^3J_{HH} = 7.2$ Hz, 3H), 1.54 (m, 2H), 1.89 (h, $^3J_{HH} = 6.7$ Hz, 1H), 2.72 (br s, 1H), 4.19 (m, 1H), 4.23 (q, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$) δ 14.2, 21.5, 23.2, 24.4, 43.5, 61.6, 69.0, 175.9; HRMS (EI, direct insert) *m/z* 160.1105 (M^+, exact mass calcd for $C_8H_{16}O_3$, 160.1099); ee determination (GC, Macherey Nagel FS-Lipodex A, 85 °C, isothermal) *(S)* $t_1 = 9.05$ min, *(R)* $t_2 = 9.42$ min.

(*S*)-2-Hydroxy-3-phenylpropanoic acid, Methyl Ester:[21] $[\alpha]^{25}_D = -21.1°$ (*c* 0.12, C_6H_6); ^1H NMR ($CDCl_3$) δ 1.28 (t, $J_{HH} = 7.2$ Hz, 3H), 2.74 (br, 1H), 3.02 (m, 2H), 4.22 (q, $J_{HH} = 7.2$ Hz, 2H), 4.38 (m, 1H), 7.20−7.35 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ14.0, 40.8, 61.9, 70.6, 126.8, 128.9, 129.0, 136.4, 173.5; ee determination (HPLC Chiralcel OD-H column, 99:1 hexane−*i*-PrOH) *(S)* $t_1 = 29.7$ min, *(R)* $t_2 = 31.5$ min, >98% ee.

Synthesis of 1,2-Diols 11: Typical Procedure. A sample of 2-acyloxy ester **5** (typically ca. 50 mg) was dissolved in 5 mL of diethyl ether cooled to 0 °C, and a 10-fold excess of $LiAlH_4$ was added. The mixture was allowed to warm to room temperature, and then stirred for 12 h. The resulting suspension was cooled to 0 °C and quenched with excess ethyl acetate, after which 5 mL of saturated NH_4Cl was added. The mixture was then evaporated to dryness, the resulting residue extracted into ethyl acetate (ca. 10 mL) and washed with brine and the aqueous washings re-extracted with additional portions of ethyl acetate. The organic fractions were collected, dried over $MgSO_4$, and finally evaporated to afford the corresponding 1,2-diols **11** in good yield.

(*R*)-4-Methyl-1,2-pentanediol:[22] $[\alpha]^{25}_D = +31.8°$ (*c* 0.96, EtOH); ^1H NMR ($CDCl_3$) δ 0.92 (d, $^3J_{HH} = 6.6$ Hz, 3H), 0.97 (d, $^3J_{HH} = 6.6$ Hz, 3H), 1.20 (m, 1H), 1.40 (m, 1H), 1.75 (m, 1H), 2.25 (br s, 2H), 3.42 (m, 1H), 3.64 (m, 1H), 3.80 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 22.0, 23.3, 24.4, 42.0, 67.1, 70.4; ee determination (GC, Chrompack Chirasil-L-Val, 70 °C, isothermal) *(R)* $t_1 = 18.87$ min, *(S)* $t_2 = 19.58$ min.

(*S*)-5-Methyl-1,2-hexanediol: oil; $[\alpha]^{25}_D = -10.6°$ (*c* 0.70, EtOH); ^1H NMR ($CDCl_3$) δ 0.89 (d, $^3J_{HH} = 6.6$ Hz, 3H), 0.90 (d, $^3J_{HH} = 6.5$ Hz, 3H), 1.38 (m, 2H), 1.46 (m, 2H), 1.55 (m, 1H), 1.2−1.6 (m, 5H), 1.6 (vbr s, 2H), 3.45, 3.67 (m, 1H), 3.70 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 22.4, 22.5, 28.1, 31.0, 34.6, 66.8, 72.6; ee determination (GC, Chrompack Chirasil-L-Val, 80 °C, isothermal) *(R)* $t_1 = 23.41$ min, *(S)* $t_2 = 23.99$ min.

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(*S*)-1,2-octanediol:[22] $[\alpha]^{25}_D = -15.4°$ (*c* 0.33, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 3H), 1.30 (br s, 6H), 1.40 (br s, 2H), 2.25 (br s, 2H), 3.45 (m, 1H), 3.70 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 14.0, 22.6, 25.5, 29.3, 31.7, 33.0, 66.7, 72.3; HRMS (EI, direct insert) *m*/*z* 145.1223 ($M - H^+$, exact mass calcd for $C_8H_{17}O_2$, 145.1229); ee determination (GC, Chrompack Chirasil-L-Val, 90 °C, 2 deg/min) *(R)* $t_1 = 20.18$ min, *(S)* $t_2 = 20.96$ min.

(*S*)-3-(*β*-Naphthyl)-1,2-propanediol:[23] $[\alpha]^{25}_D = -32.7°$(*c* 0.55, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.42 (br s, 2H), 2.93 (m, 2H), 3.60 (m, 2H), 4.03 (m, 1H); $^{13}C\{^1H\}$ δ 39.9, 66.0, 72.9, 125.5, 126.1, 127.5, 127.6, 127.8, 128.3, 132.2, 133.5, 135.2; HRMS (EI, direct insert) *m*/*z* 202.0990 (M^+, exact mass calcd for $C_{13}H_{14}O_2$, 202.0994); HPLC Daicel Chiracel-OJ, 25% 2-PrOH/Hexanes, 0.5 mL/min) *(R)* $t_1 = 26.9$ min, *(S)* $t_2 = 29.3$ min.

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Supporting Information Available: Representative chromatograms showing enantiomeric excess determinations for **5**, **10**, and **11** (3 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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