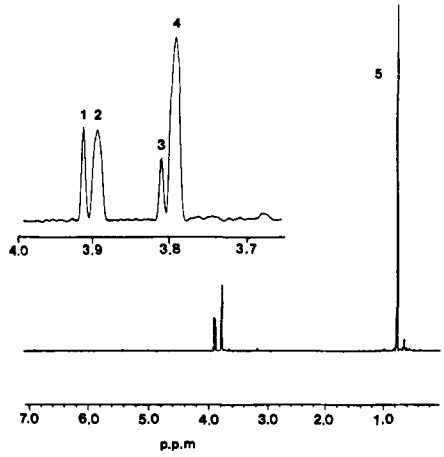

Figure 1. ^3H NMR spectrum (320 MHz, ^1H decoupled) of the (2*R*)-2-acetoxy-2-phenylethanoate derivative of ethanol recovered from the incubation of (*R*)-[1-$^2H_1$,1-$^3H_1$]ethane with MMO: (1) (*R*)-[1-$^3H_1$]-ethanol; (2) (*R*)-[1-$^2H_1$,1-$^3H_1$]ethanol; (3) (*S*)-[1-$^3H_1$]ethanol; (4) (*S*)-[1-$^2H_1$,1-$^3H_1$]ethanol; and (5) [2-$^2H_1$,2-$^3H_1$]ethanol. NMR signal assignments were made according to the method of Parker.[20]

The ethane samples were synthesized by reaction of carrier-free $LiEt_3B^3H$ (5.7 Ci per synthesis)[16] with the known (*R*)- or (*S*)-[1-$^2H_1$]ethyl tosylate (>98 atom % ^2H, 88 and 96% ee, respectively) and incubated with the purified and reconstituted MMO system (hydroxylase specific activity = 870 nmol/min/mg under standard assay conditions[4]). ^3H NMR analysis of the resulting ethanol samples gave an intramolecular primary kinetic isotope effect for hydrogen abstraction from the labeled methyl group of $k_H/k_D = 4.2 \pm 0.2$.[17] The (2*R*)-2-acetoxy-2-phenylethanoate derivatives[20] of the ethanol samples showed well-resolved resonances corresponding to all four possible species carrying ^3H in the methylene group (Figure 1, Table I). (*R*)-[1-$^2H_1$,1-$^3H_1$]Ethane gave predominantly (*S*)-[1-$^2H_1$,1-$^3H_1$]- and (*R*)-[1-$^3H_1$]ethanol, and conversely, (*S*)-[1-$^2H_1$,1-$^3H_1$]ethane afforded predominantly (*R*)-[1-$^2H_1$,1-$^3H_1$]- and (*S*)-[1-$^3H_1$]ethanol. The results show that the hydroxylation of ethane proceeds with predominant retention of configuration, consistent with the mechanistic similarity[4,6] to P450-catalyzed reactions.[18,21] Almost identical results were obtained for the reaction catalyzed by the MMO hydroxylase component alone in the presence of H_2O_2 (data not shown).

The overall retention of configuration of the MMO-catalyzed reaction is accompanied by approximately 35% inversion (Table I). On the basis of the amount of H^3HO observed in the ^3H NMR spectra of the products recovered from the individual incubations (about 10% of the total ^3H), this does not represent racemization due to an exchange process. The relatively high degree of inversion observed thus must be due to "flipping" of a free substrate intermediate that has a sufficiently long lifetime to undergo configurational inversion with appreciable frequency. This intermediate is likely to be an ethyl radical, because an ethyl cation has an exceptionally high energetic barrier to direct formation[22] and is markedly unstable. These results thus support a radical-based mechanism as proposed by Fox et al.[4,11] and argue against mechanisms not involving a free substrate intermediate in the enzyme active site.[14] They do not, however, give any information on the proposed[13] *additional* involvement of a carbocation intermediate.

Table I. Percentage Distribution of ^3H Label in the Methylene Group of the (2*R*)-2-Acetoxy-2-phenylethanoate Derivatives of the Samples Generated by MMO[a]

SUBSTRATE \ PRODUCT	^3H % in methylene group: 4#	1#	2#	3#
(R)	53	12	26	9
	retention = 68 %		inversion* = 32 %	
(S)	27	7	52	14
	inversion* = 36 %		retention = 64 %	

[a] Inversion/retention data have been corrected for the enantiomeric purity of the substrates. * indicates configurational inversion is due to flipping of the intermediate radical. # indicates that the numbering scheme here corresponds with that in Figure 1.

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Asymmetric Titanocene-Catalyzed Hydrogenation of Imines

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Significant progress has been made in the asymmetric reduction of ketones to alcohols.[1,2] The solutions for the analogous production of enantiopure amines from ketimines,[3] while noteworthy, have been less successful. Herein we report our initial results on the use of a chiral titanium catalyst for the hydrogenation[4] of ketimines to enantioenriched amines.

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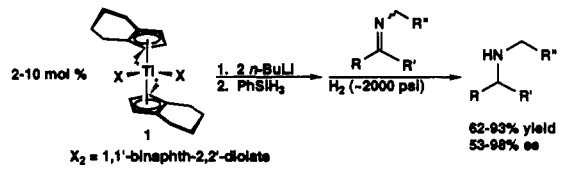
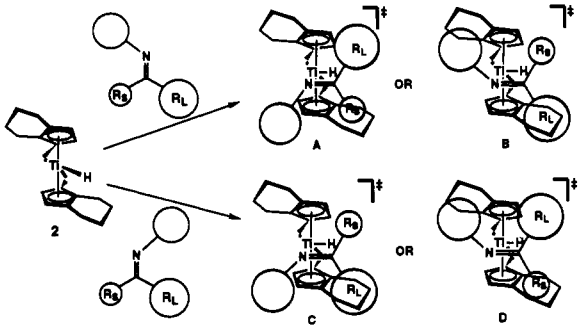
Scheme I



Scheme II

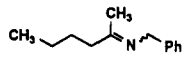
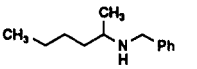
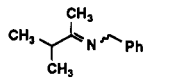
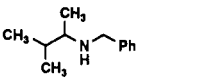
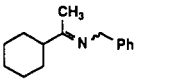
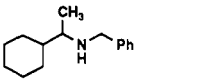
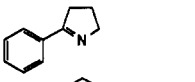
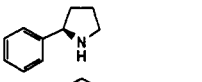
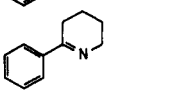
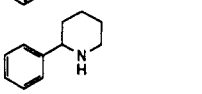
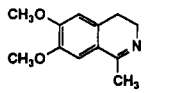
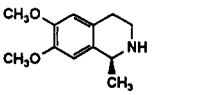
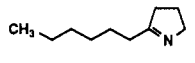
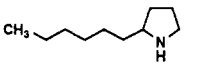
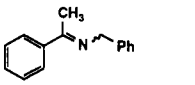
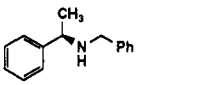
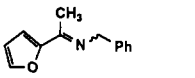
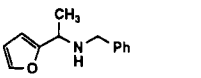
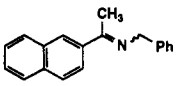
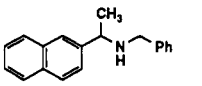


We recently reported an efficient titanocene-based hydrosilylation catalyst system for the conversion of esters to primary alcohols.[5] The success of this work led us to investigate the asymmetric reduction of ketones and imines using related enantiopure catalysts. Of the many chiral titanocene systems available,[4,6] our experience[7a,b] with the *ansa*-metallocene system developed by Brintzinger[8] made it the obvious starting point. Initial studies focused on the development of an asymmetric catalyst for imine hydrosilylation, but we soon found that hydrogen was more effective as the stoichiometric reductant.

The 1,1'-binaphth-2,2'-diolate derivative,[8,9] **1**, serves as a useful precatalyst (Scheme I). Sequential treatment of **1** (2–10 mol %) in THF with 2 equiv of *n*-BuLi and 2.5 equiv of phenylsilane[10] (both relative to **1**) provides the active catalyst. The hydrogenation reactions are then run at 65 °C with a hydrogen pressure of 2000 psig for 8–48 h.[12]

Our initial results for the asymmetric reduction of imines are shown in Table I. As can be seen, a wide range of structural types can be accommodated. While the reduction of acyclic *N*-benzyl imines (entries 1–3) proceeds with moderate to good enantioselectivity, cyclic imines (entries 4–7) are transformed to the corresponding amines with excellent enantioselectivity.[11a] The observed ee of ~98% at 65 °C for these latter cases corresponds to $\Delta\Delta G^{\ddagger}$ = 3.1 kcal/mol between the diastereomeric transition states. *N*-Benzyl imines derived from aryl ketones (entries 8–10)[11b] are also reduced with moderate to very good enantioselectivity, but these reactions are more variable in their selectivity. For example, the *N*-benzyl imine of acetophenone (as a mixture of geometric isomers, approximately identical in each run) has been reduced to the corresponding amine with ee's ranging from 65 to 87% under standard reaction conditions. The reason for this variability is as yet unclear.

Table I. Asymmetric Hydrogenation of Imines

Entry	Imine	Amine[a]	Yield (%)	ee (%)[b]
1			68	58[c]
2			66	76[c]
3			93	76
4			77	98[c,d,f]
5			70	97
6			82	98[e]
7			81	98[f]
8			81 93	77[d,g] 85[h]
9			70	53
10			82	70

[a] Reactions were run using 5 mol % **1** as the (*R,R,R*) diastereomer unless otherwise noted. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. Amines in entries 9 and 10 gave satisfactory elemental analyses, all others are known. [b] Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD HPLC column. [c] With 10 mol % **1**. [d] Determined by optical rotation to be the (*R*) enantiomer. [e] Determined by optical rotation to be the (*S*) enantiomer. [f] Determined by GLC analysis of the (*S*)-Mosher amides using a cyclodex B GC column. [g] ee of product ranged from 65 to 87% for several experiments. [h] With 2 mol % **1**.

Our view of how the reaction proceeds is shown in Scheme II. Activation with *n*-BuLi can occur to form the titanium(III) hydride **2**, as surmised in our ester reduction system.[5] The four diastereomeric transition states for the reaction of **2** with the anti and syn isomers of a ketimine are shown. For the anti ketimine, the single interaction of R_S with the ligand in **A** should make it lower in energy than **B**, in which severe interactions between the ligand and both the nitrogen substituent and R_L are apparent. The absolute configurations of the products in entries 4 and 8 are consistent with this model. When the substrate is a syn imine, as in entry 6, we believe that transition state **C** should be lower in energy than **D**. The absolute configuration of the product is consistent with this formulation. For acyclic imines, which consist mainly of the anti diastereomers, small amounts of the syn isomers may serve to lower the observed ee's by proceeding through **C** (producing amine products of opposite configurations) instead of **A**.

In summary, we have developed the first early transition metal catalyst for the asymmetric reduction of ketimines to enan-

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(10) Silane appears to be required to stabilize the active catalyst.

(11) (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (b) For a biocatalytic route to enantiomerically pure amines, see: Stirling, D. I.; Zeitlir, A.; Matcham, G. W. U.S. Patent 4,950,606, 1990.

(12) Preliminary studies show that lower pressures, in general, give lower ee's.

tioenriched amines. Our results are comparable or superior to those reported using other metal catalysts.[3]

Acknowledgments. We thank the National Institutes of Health for the funding of this research. S.L.B. acknowledges additional support as an Alfred P. Sloan Fellow (1988-1992) and a Camille and Henry Dreyfus Teacher-Scholar. C.A.W. thanks Bristol Myers-Squibb for a graduate fellowship. We acknowledge informative discussions with Drs. Kristina A. Kreutzer, Alberto Gutiérrez, Richard D. Broene, and Robert B. Grossman and Mr. Scott C. Berk. We thank Professor A. I. Meyers for a preprint of ref 11a.

Supplementary Material Available: Detailed experimental procedures for the asymmetric imine hydrogenations, as well as for the preparation and spectroscopic characterization of complex **1**, and the starting materials and products listed in Table I (14 pages). Ordering information is given on any current masthead page.

Direct Hydroxylation at the Meso Position of Gold(III) Tetraphenylporphyrin by Nucleophilic Addition: Novel Hydroxyphlorin Derivatives

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We report the first example of the direct nucleophilic addition of OH^- ion on a nonoxidized porphyrin ring, which affords a meso-saturated adduct having the same electronic structure as phlorin.

Porphyrin derivatives containing saturated meso carbon(s) are important intermediates not only in the biosynthesis[1] and the metabolism[2] of natural porphyrins but also in the redox chemistry and the synthesis[3] of various artificial porphyrins. "Phlorin"[4] and "isoporphyrin",[5] which have one saturated meso carbon, are two typical types of such derivatives and are clearly classified into group I and II as shown in Figure 1.[6] In redox reactions of the porphyrins, the phlorin and the isoporphyrin are formed through a π-dianion (Figure 1a) and a π-dication (Figure 1b), respectively. On the other hand, similar derivatives can be obtained by alternative synthetic procedures without the redox process. For instance, meso-saturated porphyrin derivatives classified into group II have been directly synthesized by electrophilic addition to the porphyrin ring (Figure 1d).[7] In this case, the electrophilic adducts obtained have the same electronic structure as the isoporphyrin. However, direct nucleophilic addition to the nonoxidized porphyrin ring has not been reported except for reduction with BH_4^-.[8] The lack of nucleophilic addition is ascribed to the poor electrophilicity of the conventional metalloporphyrins used so far. With this in mind, direct nucleophilic addition is accomplished by use of gold(III) porphyrins, which are strong electrophiles. The obtained

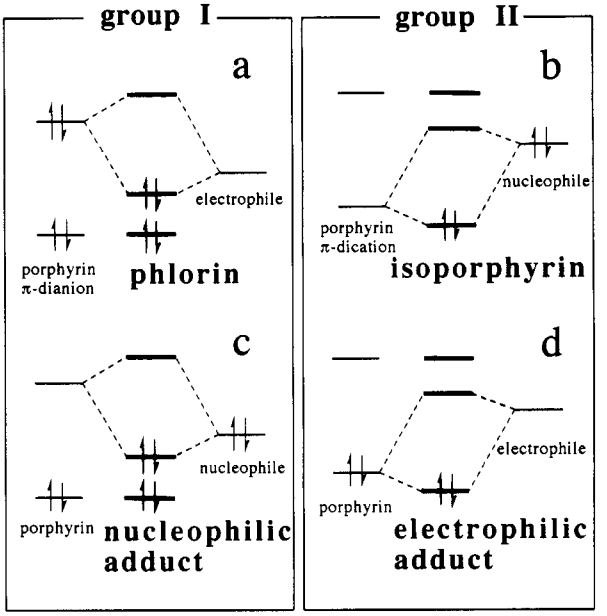


Figure 1. Schematic representation of orbital interactions of porphyrins with nucleophile or electrophile.

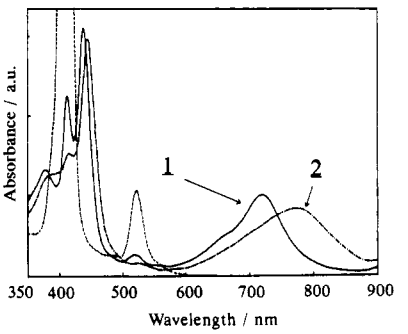
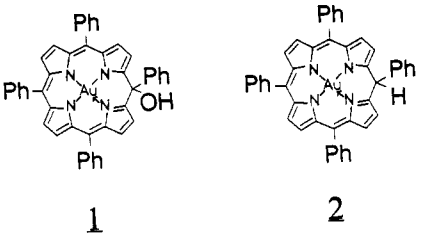


Figure 2. Absorption spectra of $[Au^{III}(TPP)]^+Cl^-$ (---), nucleophilic adduct $[Au^{III}(TPP\text{-}OH)]$ (**1**) (—), and phlorin $[Au^{III}(TPP\text{-}H)]$ (**2**) (-·--·-) in DMSO.

Chart I



products are novel nucleophilic adducts, namely, "hydroxyphlorin", classified into group I.

Tetra-*n*-butylammonium hydroxide (TBAOH) 10% methanol solution or NaOH aqueous solution was used as a source of OH^- ion. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were used as solvents. Gold(III) porphyrins ($[Au^{III}(TPP)]^+Cl^-$, $[Au^{III}(TSPP)]^+Cl^-$, $[Au^{III}(TCPP)]^+Cl^-$, and $[Au^{III}(TPyP)]^+Cl^-$) and the other metalloporphyrins ($Pd^{II}(TPP)$, $Cu^{II}(TPP)$, Cd^{II}-(TPP), and $[Mn^{III}(TPP)]^+Cl^-$) were synthesized and purified by the reported procedures.[9,10]

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(6) The phlorin formed through an electrophilic attack at a meso carbon of a porphyrin dianion (Figure 1a) has two more electrons in the porphyrin moiety than the isoporphyrin formed through a nucleophilic attack at a meso carbon of a porphyrin dication (Figure 1b).
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(10) TPP, *meso*-tetraphenylporphyrin; TSPP, *meso*-tetrakis(4-sulfonatophenyl)porphyrin; TCPP, *meso*-tetrakis(4-carboxyphenyl)porphyrin; TPyP, *meso*-tetrakis(4-pyridyl)porphyrin.

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