Design of Diastereomeric Self-Inhibiting Catalysts for Control of Turnover Frequency and Enantioselectivity

Jaume Balsells and Patrick J. Walsh*

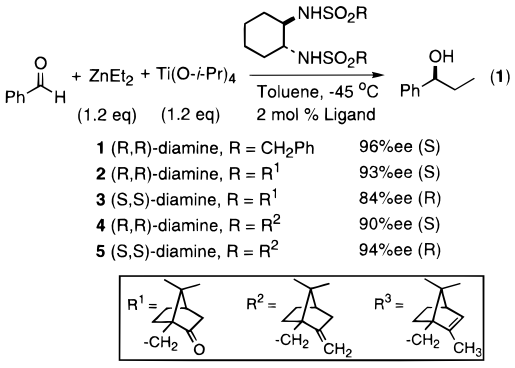
P. Roy and Diane T. Vagelos Laboratories
Department of Chemistry
University of Pennsylvania, 231 South 34th Street
Philadelphia, Pennsylvania 19104-6323

Received November 2, 1999

Asymmetric catalysis is a powerful tool for the synthesis of optically active molecules.[1] Practical and economic considerations have stimulated interest in defining the limits of catalytic asymmetric reactions. As a result, remarkable catalytic processes have been developed in which catalysts of low enantiopurity exhibit high levels of enantioselectivity[2,3] through nonlinear behavior.[4,5] Positive nonlinear effects can eliminate the need to use enantiopure catalysts.[6,7] This is particularly useful when the chiral component of the asymmetric catalyst is not derived from the chiral pool but has been prepared as a nonracemic mixture of enantiomers. A similar, but more complex problem arises in the direct use of nondiastereopure catalysts in which case the product ee is dependent not only on the enantioselectivity of each catalyst but also on their relative turnover frequencies (TOF).[8−12]

One possible way to control the TOF of a catalyst would be to reversibly block its binding site with a nonreactive substrate analogue.[13] The degree of deactivation would depend on the difference in energy between the bound and unbound states, ΔG. Incorporation of a chiral substrate analogue into the two enantiomeric forms of a catalyst would result in diastereomeric catalysts that would exhibit different degrees of inhibition (Figure 1). The difference in the ΔG's for the two diastereomeric catalysts ($\Delta\Delta G$) controls the relative concentrations of the *active* forms of the catalysts, which directly impacts the TOF's. In this paper we demonstrate the viability of this new strategy.

We have examined this concept in the context of the asymmetric addition of alkyl groups to aldehydes employing bis-(sulfonamide)-based catalysts (eq 1). This efficient reaction was



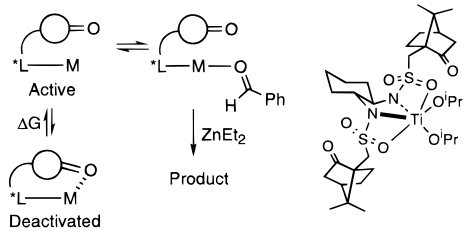


Figure 1.

developed by Ohno and Kobayashi[14,15] and the broad scope defined by Knochel.[16−18] The mechanism of this process was proposed to involve in situ the formation of bis(sulfonamido)-Ti(O-*i*-Pr)$_2$.[15,18,19]

Use of the (*R*,*R*)-dibenzyl ligand **1** (eq 1) provided the product (*S*)-1-phenyl-1-propanol in 96% ee. We wanted to explore substitution of the phenyl group in **1** with a chiral substrate analogue to permit differential inhibition of the two enantiomers of the catalyst. From our understanding of the binding of bis-(sulfonamido) ligands to titanium (Figure 1),[19] substitution of both enantiomers of a substrate analogue at this remote position would be unlikely to greatly affect the enantioselectivity of the catalyst. We chose the camphorsulfonyl group for this study.

The ligands **2** and **3** were prepared by reaction of (1*S*)-(+)-10-camphorsulfonyl chloride with the *R*,*R* and *S*,*S* enantiomers of *trans*-1,2-diaminocyclohexane in 86−90% yield. Examination of diastereomeric ligands **2** and **3** in eq 1 indeed showed that there was a relatively minor difference in enantioselectivity between the two catalyst. Catalysts formed from **2** and **3** furnished 1-phenyl-1-propanol cleanly in 93% (*R*) and 84% (*S*) ee, respectively.[20] Ligands **2** and **3** were isolated from the reaction mixtures in 95% yield and determined to be intact (500 MHz NMR).

Since the sense of enantioselectivity with **2** and **3** is *opposite*, it can be concluded that the chiral *trans*-cyclohexanediamine backbone controls the enantioselectivity. Furthermore, the similarity in enantioselectivities suggests that the chirality of the camphor group was distant from the bond-forming process.

We next examined the TOF's of diastereomeric catalysts derived from **2** and **3** by running the reactions side-by-side and following the conversion by quenching aliquots (Figure 2). Our hypothesis was confirmed by the fact that **2** had a significantly

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
(2) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922−2959.
(3) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron Asym.* **1997**, *8*, 2997−3017.
(4) Blackmond, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 13349−13353.
(5) Blackmond, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 12934−12939.
(6) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.
(7) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.-i.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088.
(8) (a) Bolm, C.; Muniz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491−494. (b) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; A, R. *Synthesis* **2000**, 165−176. (c) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579−12580. (d) Fu, P.-F.; Brard, L.; Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1995**, *117*, 7157−7168. (e) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241−10254.
(9) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 495−497.
(10) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842.
(11) Zhang, S. Y.; Girard, C.; Kagan, H. B. *Tetrahedron Asym.* **1995**, *6*, 2637−2640.
(12) Blackmond, D. G.; Rosner, T.; Neugebauer, T.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2196−2199.
(13) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804−805.
(14) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700.
(15) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095−7098.
(16) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229−8243.
(17) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895−7898.
(18) Ostwald, R.; Chavant, P.-Y.; Stadtmuller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143−4153.
(19) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423−6424.
(20) Initial ee's were used due to variations in the ee's with conversion. The Δee is +1% for **2** and −12% for **3**. See: Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171−2209. Balsells, J.; Walsh, P. J. Work in progress.

10.1021/ja993887b CCC: $19.00 © 2000 American Chemical Society
Published on Web 03/18/2000

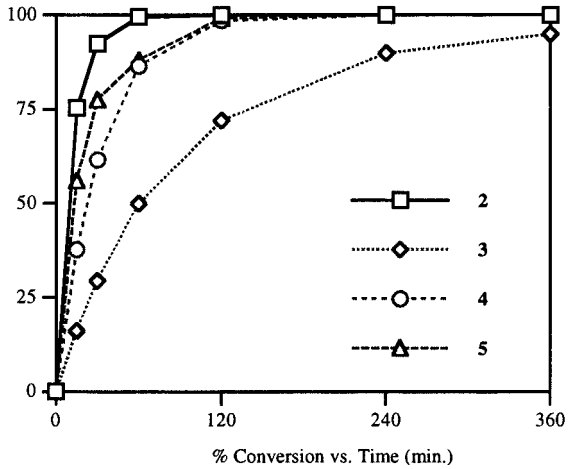


Figure 2. Percent conversion vs time (min).

higher TOF than **3**. For example, after 15 min the reaction employing **2** was 75% complete while reaction with **3** had only 16% conversion (Figure 2).

The large difference in TOF's between diastereomeric catalysts formed from **2** and **3** was attributed to a stronger interaction of the camphor carbonyl group with the titanium in **3**. If this assertion were correct, replacement of the carbonyl group with an isosteric group devoid of Lewis basic sites would be predicted to provide ligands that form highly enantioselective catalysts. Furthermore, these catalysts should not exhibit the marked difference in turnover frequency observed for **2** and **3**. To examine this hypothesis, ligands **2** and **3** were converted to their methylene analogues **4** and **5** (eq 1), respectively, via a two-step sequence involving treatment with methyllithium followed by elimination of the resulting alcohol with thionyl chloride. Under these conditions, the exocyclic methylene complex was the major product but contained 6% of the endocyclic counterpart ($R = R^3$, eq 1). We were unable to separate the endo and exocyclic alkene products. The exocyclic and endocyclic isomers are very sterically similar and should exhibit similar reactivity.

Employing ligands **4** and **5** in the asymmetric addition reaction resulted in generation of 1-phenyl-1-propanol with ee's of 90% (*S*) and 94% (*R*), respectively. Monitoring of the conversion as a function of time indicated that **4** and **5** do not exhibit the large difference in TOF's observed with **2** and **3** (Figure 2). These results suggest that camphor groups in **2** and **3** control the TOF's by competitive inhibition.

The large difference in TOF's of these diastereomeric catalysts suggests that use of catalysts with little or no de may provide product of high enantiopurity. Use of such mixtures can simplify ligand or catalyst preparation and reduce costs. We therefore investigated the possibility of using *racemic trans-diamine* and diamine with low ee with (1*S*)-(+)-10-camphorsulfonyl chloride to synthesize diastereomeric mixtures of **2** and **3**. These mixtures were then examined in the asymmetric addition reaction. When the benzaldehyde was quickly added to the mixture containing diastereomers **2** and **3** (eq 1, 2 mol % each), the ee of the product alcohol was 74% (*S*). A mechanistic scenario could be envisioned where fast addition of the substrate could saturate the catalysts. To avoid this possibility, the reaction was reexamined using a syringe pump to slowly add the aldehyde (0.7 mmol/h). The ee of the 1-phenyl-1-propanol under these conditions was 84% (*S*). Catalysts with 20 and 30% de (major diastereomer **2**) were examined under these conditions and afforded the product alcohol in 88 and 91% ee, respectively. Reaction of (1*S*)-(+)-10-camphorsulfonyl chloride with technical grade 1,2-diaminocyclohexane (90%), which consisted of approximately a 3:2 ratio of racemic *trans*-diamine to *cis*-diamine along with 1,6-diaminohexane impurity, gave a mixture of ligands. Use of this mixture in the asymmetric addition reaction gave (*S*)-1-phenyl-1-propanol with an acceptable 80% ee.

Other systems are known where one diastereomer gives high enantioselectivity and the mixture of diastereomers generates the product of high ee.[8−12] The unique feature of our system is that it has been designed with an internal substrate analogue that controls the TOF's. When the camphor carbonyl oxygens are not coordinated to the metal the difference in energy between the diastereomers is small. When one carbonyl of each ligand is coordinated to titanium the chiral camphor groups are brought into close contact with the titanium/chiral bis(sulfonamide) moiety (Figure 1). In the deactivated state we believe that the two diastereomers have dissimilar energies.

We postulate that the camphor acts as a competitive inhibitor, reversibly binding to the active site of the catalyst. Like an enzyme, our catalyst has a chiral pocket that can discriminate between the two enantiomers of the inhibitor. It should be possible to design other highly enantioselective diastereomeric catalyst mixtures that use internal competitive inhibition to control TOF's and thus influence enantioselectivities when employing diastereomeric mixtures of catalysts.

Acknowledgment. This work was supported by the National Science Foundation in the form of a Career Award to P.J.W. (CHE-9733274) and the National Institute of Health (GM58101).

Supporting Information Available: The synthesis and characterization of ligands **2**−**5** and the details of the asymmetric additions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA993887B