Asymmetric Hydrogenation of Enamines with a Chiral Titanocene Catalyst

Nancy E. Lee and Stephen L. Buchwald*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received March 23, 1994

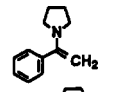
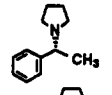
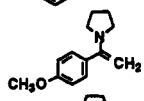
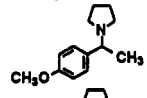
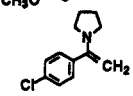
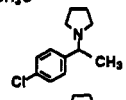
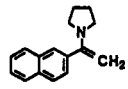
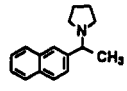
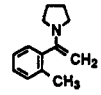
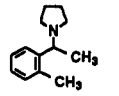
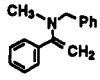
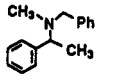
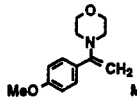
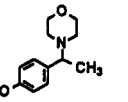
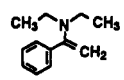
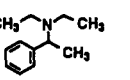
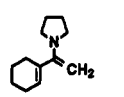
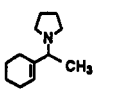
The synthesis of optically active amines is of considerable interest due to the presence of such compounds in natural products and in other molecules which manifest interesting biological activities. Recently, we demonstrated the highly enantioselective hydrogenation of imines[1] and unfunctionalized trisubstituted olefins[2] using **1**.[3] While the enantioselective hydrogenation of enamides[4] has been successfully effected using ruthenium[5] and rhodium catalysts[6] the corresponding reduction of enamines, to our knowledge, has not been reported. In this communication, we describe the first enantioselective, catalytic hydrogenation of 1,1-disubstituted enamines.

The active catalyst employed in our study is generated by the addition of 2 equiv of *n*-BuLi followed by 2.5 equiv of phenylsilane to a solution of **1** in THF under a hydrogen atmosphere. The hydrogenation reactions were conducted either at room temperature and 1 atm H_2 (Table 1, entries 1–4) or at 65 °C and 80 psig (Table 1, entries 5–9) for ~24 h (Scheme 1). The fact that these substrates are hydrogenated under considerably milder conditions than those utilized for trisubstituted olefins is presumably due to the faster rate of insertion of a 1,1-disubstituted olefin into the Ti–H bond.[7]

As is shown in Table 1, 1,1-disubstituted enamines are reduced to the corresponding tertiary amines with high enantiomeric excesses. Changing the substituents on the nitrogen or on the aromatic ring had little effect on the enantioselectivity. Of note is that the enantioselectivity of the reaction is independent of hydrogen pressure. For example, 1-(1-pyrrolidinyl)-1-(4-methoxyphenyl)ethene (entry 2) was reduced under the following conditions: 2000 psig, 65 °C; 80 psig, 65 °C; 80 psig, room temperature; and 15 psi, room temperature. In all cases, the product obtained had an enantiomeric excess of ~94%. This result is in stark constrast to that seen for the hydrogenation of acyclic imines.[1a]

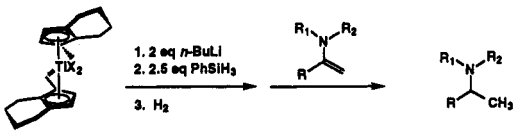
Not surprisingly, the hydrogenation reaction is sensitive to the sterics of the substrate; as the bulk of the double-bond substituents was increased (entries 5–9), higher pressures (80 psig) and temperatures (65 °C) were required to obtain reasonable reaction rates. When a more sterically demanding substrate, the pyrrolidine enamine of pinacolone, was employed, only unreacted starting material was recovered.[8]

Table 1. Asymmetric Hydrogenation of Enamines[a]

entry	enamine	amine	pressure[b]	yield, %[c]	ee, %[d]
1			15	75	92[e]
2			15	72	92
3			15	89	89
4			15	77	96
5			80	87	98
6			80	83	96
7			80	88	91
8			80	78	94
9			80	72	95

[a] Reactions were run using 5 mole % (*S,S,S*)-(EBTHI)TiO_2Binap (**1**) as the catalyst. [b] Units of pressure: 15 psi and 80 psig. [c] Yields of isolated materials (>95% pure); all products were characterized by ^1H NMR, ^{13}C NMR, HRMS, and IR spectroscopy. [d] The enantiomeric excess for the amines were determined by ^1H NMR analysis of diastereomeric salt resulting from the addition of (*R*)- or (*S*)-*O*-acetylmandelic acid to the amine in $CDCl_3$.[14,15] [e] Determined by optical rotation to be the (*R*) enantiomer.

Scheme 1



5 mol % **1** (X_2= 1,1'-binaphth-2,2'-diolate)

An additional limitation of the reaction is that the catalyst system, in its present form, does not tolerate aromatic bromides. For example, when 1-pyrrolidinyl-1-(4-bromophenyl)ethene was subjected to the usual reaction conditions, mostly unreacted starting material was recovered along with a small amount of debrominated enamine. This presumably occurs via reduction of aryl bromides by titanium(III) hydride, as has been previously suggested.[9]

As previously postulated, titanium(III) hydride **2** is believed to be the active catalyst. According to the analysis of the molecular orbitals of Cp_2MH by Hoffmann and Lauher,[10] the olefin is believed to approach the Ti–H complex from the side (see Scheme 2) to obtain maximum overlap between the LUMO of the olefin

(1) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562. (b) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627. For leading references on the use of late transition metals in the asymmetric hydrogenation of imines, see: Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

(2) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569. For leading references on the asymmetric hydrogenation of 1,1-disubstituted olefins using titanocene derivatives, see: Halterman, R. L.; Vollhardt, K. P. C. *Organometallics* **1988**, *7*, 883. Halterman, R. L.; Vollhardt, K. P. C.; Welker, M. E.; Blaser, D.; Boese, R. *J. Am. Chem. Soc.* **1987**, *109*, 8105.

(3) Wild, F. R. W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233.

(4) For reviews of asymmetric hydrogenation, see: (a) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 1–39. (b) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901.

(5) (a) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297. (b) Noyori, R. *Science* **1990**, *248*, 1194 and references therein.

(6) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125 and references therein.

(7) Preliminary results indicate that the insertion step is rate limiting.

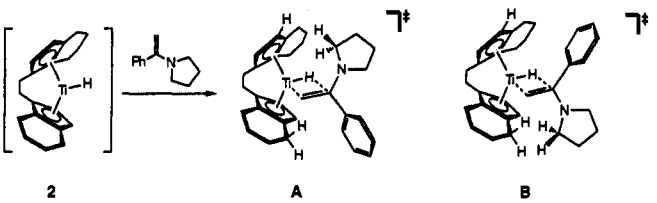
(8) Conditions used: 80 psig, 65 °C, 7 days.

(9) Corriu, R.; Colomer, E. *J. Organomet. Chem.* **1974**, *82*, 367.

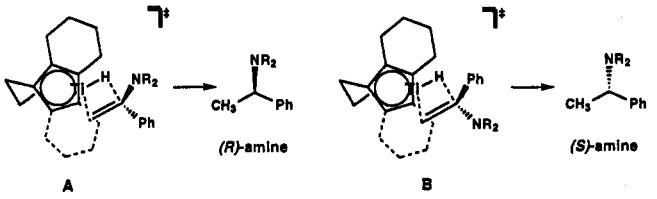
(10) (a) Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729. (b) Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911. (c) Willoughby, C. A.; Buchwald, S. L., manuscript in preparation (a more thorough discussion of the proposed mechanism will be presented in this paper).

0002-7863/94/1516-5985$04.50/0

Scheme 2



Scheme 3



and the HOMO of the metal hydride. In this approach, the phenyl group of the substrate is twisted out of conjugation with the olefin, whereas the nitrogen's lone pair remains conjugated with the olefin.[11] The difference between the two approaches of the substrate can be seen more clearly from a top view, as shown in Scheme 3. The larger group, the *N*,*N*-dialkyl substituent, prefers to approach the complex as in **A**, which minimizes the interaction between the cyclohexyl portion of the tetrahydroindenyl ligand and the alkyl groups on the nitrogen. In **B**, the alkyl groups on the nitrogen are forced to interact with the tetrahydroindenyl moiety as the substrate approaches the catalyst. Reaction via **A** is consistent with our experimental result, in which (*R*)-amine is produced when (*S*,*S*,*S*)-**1** catalyst is used.[12]

In summary, we have described the first catalytic asymmetric reduction of enamines. The reaction represents a new method to produce highly enantiomerically enriched tertiary amines from ketones in good yields. We are currently examining the extension of this methodology for the hydrogenation of a variety of different classes of enamines and related substrates.

Acknowledgment. We thank the National Institutes of Health (GM46059) for support of this research. S.L.B. acknowledges the Camille & Henry Dreyfus Foundation for a Teacher-Scholar Award. N.E.L. acknowledges the National Institutes of Health for a postdoctoral fellowship (1F32-CA61633). We are grateful to C. A. Willoughby for helpful discussions.

Supplementary Material Available: Experimental procedures for the preparation and spectroscopic characterization for enamines and amines (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Burger, B. J.; Santarsiero, B. D.; Trimmer, M. S.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 3134.

(12) As expected, when 1-pyrrolidinyl-1-phenylethene was reduced with (*R*,*R*,*R*)-(EBTHI)TiO_2Binap (5 mole %) using general procedure A (see supplementary material), we obtained (*S*)-1-pyrrolidinyl-1-phenylethane in 90% yield and 94% ee. $[\alpha]^{20} = -63.1°$ (c = 2.41, $CHCl_3$); lit.[13] value $[\alpha]^{20} = -66.9°$ (c = 10.19, $CHCl_3$).

(13) Baba, N.; Nishiyama, K.; Oda, J.; Inouye, Y. *Agric. Biol. Chem.* **1976**, *40*(7), 1441.

(14) Addition of a chiral acid, (*R*)- or (*S*)-*O*-acetylmandelic acid, to a solution of the amine in $CDCl_3$ generated two separate doublets in the ^1H NMR spectrum corresponding to the methyl group of the amine. Typically, the difference between the chemical shifts induced by the two enantiomers is in the range of 0.05–0.08 ppm. (*Note*: Various chiral HPLC columns, chiral capillary GC columns, and chiral shift reagents were tried but were unsuccessful in allowing the determination of the enantiomeric purity of the products).

(15) (a) Based on a detailed study by Parker and Taylor on determining enantiomeric excesses by adding *O*-acetylmandelic acid to amines, we estimate the error of our enantiomeric excess values to be ±2%. For details, see: Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5451. (b) For a study of other chiral acids used to determine optical purity of amines, see: Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335. (c) For a review of determining enantiomeric purity using NMR, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441.