The Journal of
Organic
Chemistry

VOLUME 58, NUMBER 27 DECEMBER 31, 1993

Communications

Synthesis of Highly Enantiomerically Enriched Cyclic Amines by the Catalytic Asymmetric Hydrogenation of Cyclic Imines

Christopher A. Willoughby and Stephen L. Buchwald*

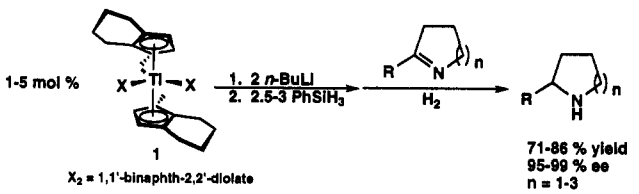
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received October 15, 1993•

Summary: The asymmetric hydrogenation of cyclic ketimines with a chiral titanocene catalyst affords amines with excellent enantioselectivity under a variety of conditions. The reaction is general for cyclic imines of ring size 5–7 and exhibits a high degree of functional group compatibility.

The catalytic, asymmetric hydrogenation of prochiral imines serves as an attractive route to enantiomerically enriched amines.[1,2] However, the catalytic[2] and stoichiometric[3] asymmetric reductions of cyclic imines have been only moderately successful. We recently reported our initial results on the first early transition metal catalyst for asymmetric imine hydrogenation.[4] A striking feature of the reaction was the excellent enantioselectivity observed for the hydrogenation of cyclic imines. These results, in addition to the prevalence of chiral cyclic amines in many classes of natural products,[5,6] prompted us to search for reaction conditions which would expand the scope and utility of this reaction.

Scheme I



A limitation of our system was the requirement of elevated hydrogen pressures to achieve high levels of enantioselectivity. After some experimentation we discovered that cyclic imines are reduced (Scheme I) at much lower pressures without effecting the observed enantiomeric excesses (Table I). One significant advantage of using lower hydrogen pressure is that, in most cases, a standard Fisher–Porter bottle can be used in place of a high-pressure autoclave. The reactions can be carried out either at lower pressure (80 psig) and higher temperatures (65 °C) or at medium pressure (500 psig; high pressure autoclave required) and lower temperature (21–45 °C) with little or no change in ee (entries 1, 3, and 5). Five-, six-, and seven-membered cyclic imines are reduced with excellent enantioselectivity. As little as 1 mol % of 1 can be used (entry 1, footnote b); however, 5 mol % was generally used to achieve convenient reaction rates.

Although we normally use 2.5–3 equiv of phenylsilane (based on 1), we have found that the silane is not required when the catalyst is generated under a hydrogen atmo-

• Abstract published in *Advance ACS Abstracts,* November 15, 1993.

(1) (a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 7266 and references cited therein. (b) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684. (c) Spindler, F.; Pugin, B.; Blaser, H. U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558.

(2) (a) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kand, G.-J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002. (b) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (c) Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem.* **1985**, 97.

(3) (a) Kawate, T.; Nakagawa, M.; Kakikawa, T.; Hino, T. *Tetrahedron: Asymmetry* **1992**, *3*, 227 and references cited therein. (b) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265.

(4) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562 and references cited therein.

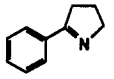
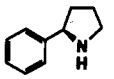
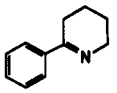
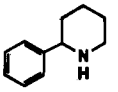
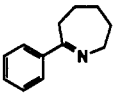
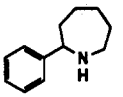
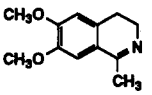
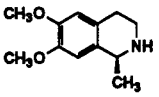
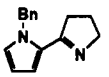
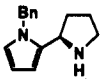
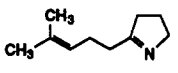
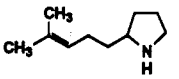
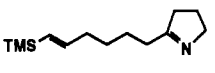
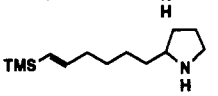
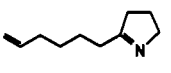
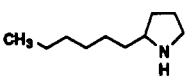
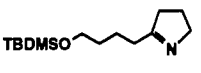
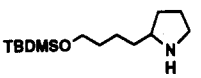
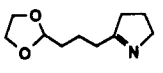
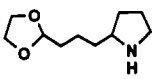
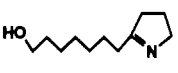
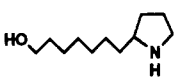
(5) For recent reviews: (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17. (b) Michael, J. P. *Nat. Prod. Rep.* **1991**, *8*, 553.

(6) For a synthesis of enantiomerically enriched 2-alkyl pyrrolidines cf.: Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656.

(7) (a) Bercaw, J. E.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1969**, *91*, 7301 and references cited therein. (b) Bercaw, J. E.; Marvich, R. H.; Bell, L. G.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1972**, *94*, 1219. (c) For an example of a structurally characterized Ti(III) hydride cf.: Pattiasina, J. W.; Bolhuis, F.; Teuben, J. H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 330.

0022-3263/93/1958-7627$04.00/0

Table I. Asymmetric Hydrogenation of Cyclic Imines[a]

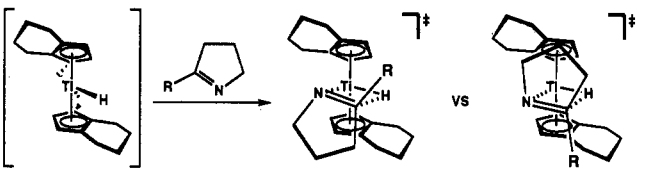
entry	imine	amine	time (h)	pressure (psig)	T (°C)	yield (%)	ee (%)
1			24	500	21	86	99
			7	80	65	84	99
			42	80	65	83	99[b]
			8	80	65	80	99[c]
2			24	500	65	78	98
3			24	500	45	71	98
			30	80	65	74	97
4			50	80	65	79	95
5			24	500	23	83	99
			6	80	65	72	99
6			23	80	50	79	99
7			27	80	50	73[d]	99
8			23	80	45	72	99
9			10	80	65	82	99
10			16	80	65	82	99
11			8	80[e]	65	84	99

[a] All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD HPLC column. The absolute configurations in entries 1, 4, and 5 were determined by optical rotation. Yields refer to isolated yields of products of >95% purity unless otherwise noted. [b] With 1 mol % catalyst. [c] No silane used. [d] This yield includes 5–8% of the saturated compound and <1% of the Z isomer; the ee was determined on the product mixture. [e] With 1.1 equiv of phenylsilane/imine.

sphere (entry 1, footnote c). This is consistent with our hypothesis that phenylsilane is only required to stabilize the active catalyst during its manipulation.[4]

In our working model of the reduction reaction, the key catalytic species is titanocene hydride, **2**.[7] As titanium hydrides are highly reactive toward a variety of functional groups,[7,8] we felt that an examination of the functional group compatibility of the catalyst system was in order. The reaction is compatible with several common functional groups, such as acetals,[9] silyl ethers, and trisubstituted olefins, affording the amines in good yields with excellent levels of enantioselectivity. Reduction of terminal olefins was observed[10] under standard reaction conditions; however, the ee of the resulting amine was ≥99%. For disubstituted olefins, differing degrees of reduction and isomerization were observed depending on the nature and substitution of the olefin. For example, an imine containing an (*E*)-vinyltrimethylsilyl group (entry 7) was converted to the amino olefin with 5–8% olefin reduction and <1% isomerization to the *Z* isomer. The ee of the amino olefin formed was ≥99%. For a substrate containing a simple *Z* olefin, (*Z*)-2-(1-non-6-enyl)-1-pyrroline, a mixture of products was obtained. The mixture consisted of the *E* amino olefin as the major product along with lesser amounts of the *Z* amino olefin and the saturated amine. This mixture of products was converted to the saturated amine and the ee was determined to be 99% (see supplementary material). Particularly interesting was

Scheme II



(8) (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Luinstra, G. A.; Teuben, J. H. *J. Am. Chem. Soc.* **1992**, *114*, 3361. (c) Sato, F.; Takamasa, J.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2171. (d) Sato, F.; Takamasa, J.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2175. (e) Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, *82*, 367. (f) Lehmkuhl, H.; Tsien, Y.-L. *Chem. Ber.* **1983**, *116*, 2437.

(9) In a competition experiment between 2-phenylpyrroline (entry 1) and acetophenone, no reduction of the imine was observed. In the presence of excess phenylsilane, under otherwise standard conditions (80 psig H_2, 65 °C, the ketone was completely hydrosilylated before any amine was produced.

(10) (a) Monitoring of the reaction by GC/MS showed that the olefin was reduced much faster than the imine. (b) We have been investigating the use of this catalyst for the asymmetric hydrogenation of trisubstituted olefins: Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.*, in press.

(11) (a) Bedard, T. C.; Corey, J. Y. *J. Organomet. Chem.* **1992**, *428*, 315. (b) Warner, B. P.; Buchwald S. L. Unpublished results.

the highly enantioselective conversion of an imino alcohol (entry 11), in the presence of excess phenylsilane, to an amino alcohol. Presumably, the alcohol was silylated[11] prior to reduction of the imine and the silyl group was subsequently cleaved during workup.[8a] A substrate containing a benzyl protected pyrrole reacted smoothly (entry 5); however, the corresponding free pyrrole deactivated the catalyst, while the *N*-(trimethylsilyl) and *N*-lithio derivatives failed to react under standard conditions.

Our rationale for the high enantioselectivity is given in Scheme II, where **A** and **B** represent two possible transition states[12] for the reduction of a cyclic imine by the titanium hydride, **2**. Although initial coordination of the imine likely occurs via the lone pair of electrons on nitrogen, the geometry shown in **A** and **B** is required in order to allow proper overlap of the imine π^* orbital with the Ti–H σ orbital.[13] In this four-center transition state the nitrogen atom becomes bound to the titanium, placing the nitrogen substituent in close proximity to the tetrahydroindenyl ligand. Therefore, we believe that the alkyl substituent on nitrogen plays the dominant role in controlling the stereochemical outcome of the reaction. In **B**, a steric interaction between this substituent and the tetrahydroindenyl ligand is apparent, while in **A** no significant interaction occurs. The absolute configurations of the products in entries 1, 4, and 5 are consistent with this model.

The higher enantioselectivities observed for the reduction of cyclic imines compared to acyclic imines[4] is probably due to the fact that cyclic imines can only exist as a single isomer while acyclic imines are usually available as mixtures of *E* and *Z* isomers. The model that we favor for the reduction of acyclic imines suggests that *E* and *Z* imines react to give opposite enantiomers of the amine product. Thus, cyclic imines are expected to react with much higher enantioselectivity.

Cyclic imines are also hydrogenated much faster, in general, than acyclic imines. This can be explained on steric grounds. Preliminary kinetic data indicate that hydrogenolysis of the Ti–N bond in the intermediate titanium amide is rate limiting.[14] In the titanium amide intermediate[15] formed from the reaction of **2** with a cyclic imine, both nitrogen substituents are "tied back". This titanium amide is, therefore, expected to react with hydrogen more rapidly, via a comparably less crowded transition state, than the titanium amide formed from **2** and an acyclic imine.

In summary, we have shown that the asymmetric, titanocene-catalyzed hydrogenation of cyclic imines proceeds under mild conditions. The reaction affords amines in excellent enantiomeric excesses for ring sizes of 5–7 and exhibits a high degree of functional group compatibility. A detailed investigation of the mechanism of this reaction as well as studies directed toward the improvement of its scope and efficiency are currently in progress.

Acknowledgment. This research was supported by the National Institutes of Health (GM 46059), to whom we are grateful. S.L.B. acknowledges additional support as a Fellow of the Alfred P. Sloan Foundation and as a Camille & Henry Dreyfus Teacher–Scholar. We thank Professor Satoru Masamune and Dr. Yaping Hong for providing us with 2-[2-(*N*-benzylpyrrolyl)]-1-pyrroline (entry 5) and for determining the absolute configuration of the reduction product.

Supplementary Material Available: Detailed experimental procedures for the asymmetric imine hydrogenations, as well as for the preparation and spectroscopic characterization of the starting materials and products listed in Table I (28 pages). This material is contained in 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.

(12) This model is related to that proposed for the enantioselective hydrogenation of 1,1 disubstituted olefins using related zirconium catalysts; cf.: Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911.

(13) For a discussion of the electronic structure of bis(cyclopentadienyl)-metal complexes cf.: Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729.

(14) Willoughby, C. A.; Buchwald, S. L. Unpublished results.

(15) For examples of isolated Ti(III) amide complexes cf.: (a) Feldman, J.; Calabrese, J. C. *J. Chem. Soc., Chem. Commun.* **1991**, 1042. (b) Pattisina, J. W.; Heeres, H. J.; Bolhuis, F.; Meetsna, A.; Teuben, J. H.; Spek, A. L. *Organometallics* **1987**, *6*, 1004.