

# A Method for the Asymmetric Hydrosilylation of *N*-Aryl Imines

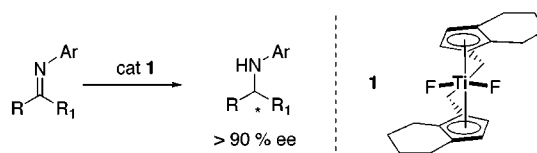
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## ABSTRACT



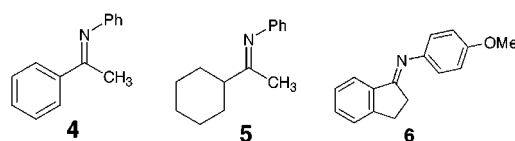
The asymmetric reduction of *N*-aryl imines to yield chiral amines with enantiomeric excesses above 90% was achieved. Ethylenebis( $\eta^5$ -tetrahydroindenyl)titanium difluoride ((EBTHI)TiF<sub>2</sub>, **1**) was employed as the precatalyst with polymethylhydrosiloxane (PMHS) as the stoichiometric reducing agent. A variety of *N*-aryl imines derived from nonaromatic ketones were reduced with high ee.

Despite the importance of chiral secondary amines in the pharmaceutical industry and as components of natural products, their preparation by the asymmetric reduction of ketimines remains a challenge. Although many methods have been developed to carry out this transformation, none have proven to be general.<sup>1–4</sup> Contributing to the difficulty of this problem is the existence of most acyclic imines as inseparable mixtures of *E/Z* isomers and the difference in reactivity among imines containing different nitrogen substituents. Herein we report the first system for the catalytic asymmetric

reduction of a wide variety of *N*-aryl imines derived from nonaromatic ketones.

We recently reported that ethylenebis( $\eta^5$ -tetrahydroindenyl)titanium difluoride ((EBTHI)TiF<sub>2</sub>, **1**) is an efficient precatalyst for the asymmetric reduction of a variety of *N*-alkyl imines regardless of the initial *E/Z* ratio of the starting imine.<sup>2</sup> It was found that slow addition of a primary amine, preferably isobutylamine, to the reaction mixture was important for promoting catalyst turnover and a high enantiomeric excess.

As part of our ongoing effort to explore the scope of this protocol, we have been interested in the extension of our method to the reduction of *N*-aryl imines. Application of our protocol to the imine derived from acetophenone and aniline, **4**, gave a product with only a 13% ee. We were surprised, however, to find that *N*-phenyl cyclohexylmethyl imine, **5**, was reduced to the corresponding amine with 99% ee. Previous attempts to asymmetrically reduce *N*-aryl imines are scarce; to our knowledge, no examples in which enantiomeric excesses greater than 90% have been reported.<sup>3</sup>



(1) For reviews, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. (b) Johansson, A. *Contemp. Org. Synth.* **1995**, 393–408. (c) Hashiguchi, S.; Uematsu, N.; Noyori, R. *J. Synth. Org. Chem., Jpn.* **1997**, *55*, 99–109. (d) Spindler, F.; Blaser, H.-U. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; pp 69–80.

(2) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103–1107.

(3) (a) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558–559. (b) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002–5008. (c) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887–892. (d) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421–6429.

(4) (a) Ringwald, M.; Stürmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, *121*, 1524–1527. (b) Takei, I.; Nishibayashi, Y.; Arikawa, Y.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2271–2274. (c) Zhu, G.; Zhang, X. *Tetrahedron: Asymmetry* **1998**, 2415–2418. (d) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron: Asymmetry* **1999**, 4009–4015.

Further investigation confirmed that *N*-aryl imines derived from nonaromatic ketones could be reduced with excellent enantioselectivities (Table 1). The *N*-aryl substrates were less

**Table 1.** Reduction of *N*-Aryl Imines Derived from Nonaromatic Ketones

(a)  $\text{PhSiH}_3$ , pyrrolidine, methanol

Entry	Imine	Yield(%) <sup>a</sup>	ee(%)
1		63	99
2		79	99
3		79	99
4		NR <sup>b</sup>	
5		NR <sup>b</sup>	
6 <sup>c</sup>		90	98
7 <sup>d</sup>		70	88
8 <sup>e</sup>		68	90

a: Yields refer to isolated products of >95% purity and are an average of two or more runs. All compounds were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and Elemental Analysis. b: No reaction. Starting material was recovered. c: 5 mol % catalyst used. d: E/Z ratio of imine was 2.6/1. e: E/Z ratio of imine was 2.3/1.

reactive than their *N*-benzyl analogues, necessitating the use of a slightly higher catalyst loading (2 mol % vs 0.5–1%) and a slower rate of addition of isobutylamine. Compounds with meta and para substituents on the *N*-aryl group are tolerated while those with ortho substituents failed to react. The absolute configuration of the amine derived from **5** was determined; the assignment of the stereocenter as *S* is in agreement with our previously described model for *N*-alkyl imine reductions.<sup>5</sup>

Ketones containing only straight-chain alkyl substituents are difficult to asymmetrically reduce in high ee.<sup>6</sup> Few reports have appeared concerning the asymmetric reduction of imines

derived from this class of ketone.<sup>2,3a–c,5</sup> In light of this, the reduction of the imines shown in entries 7 and 8 of Table 1 with ee's of 88 and 90%, respectively, is noteworthy.

To rationalize the disparity in ee we observed between the reduction of imines derived from acetophenone and those from nonaromatic ketones, the reduction of several additional imines derived from aromatic ketones was examined (Table 2). In contrast to **4** and related substrates which yielded nearly

**Table 2.** Reduction of *N*-Aryl Imines Derived from Aromatic Ketones

Entry	Imine	Conversion(%) <sup>a</sup>	ee(%)
1		100	13
2		25	6
3		100(90) <sup>b</sup>	97
4		63	75
5 <sup>c</sup>		28	9

a: Conversion was measured by GC analysis. Remainder of material was starting material. b: The number in parenthesis refers to isolated products of >95% purity and is an average of two runs. This compound was characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and Elemental Analysis. c: E/Z ratio of imine was 1.3/1.

racemic amine products, imine **6** was reduced to give a product with an ee of 97% (entry 3, Table 2).<sup>7</sup>

An AM1 calculation suggests that in **4** both of the phenyl groups are perpendicular to the C=N double bond. In the crystal structure of **6**, the C=N double bond and the aromatic group attached to the carbon atom are coplanar. Possibly, the difference between the enantioselectivities with which **4** and **6** are reduced is related to this conformational difference. Although this rationale cannot be used to explain why **5** is reduced in high ee, it is interesting to note that there are several examples in the asymmetric reduction of ketones where aromatic ketones are reduced in high ee and aliphatic ketones are reduced in lower ee,<sup>8</sup> which is opposite to what

(6) See: Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100–1103 and references therein.

(7) We have recently discussed the enantiomeric excess difference between indanone- and tetralone-derived imines. See: Yun, J.; Buchwald S. L. *J. Org. Chem.* **2000**, *65*, 767–774.

(5) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952–8959.

we observe here. Studies to further elucidate these intriguing differences are currently in progress.

In conclusion, we have developed the first system that reduces a variety of *N*-aryl imines in high enantiomeric excess. Imines derived from nonaromatic ketones or those derived from indanone are reduced with good to excellent ee's.

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(8) Nishiyama, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 267–287.

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**Supporting Information Available:** Detailed experimental procedures and spectral data for the substrates and products shown in Tables 1 and 2 and full X-ray characterization of structure **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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