

Asymmetric Hydrogenation of Unfunctionalized Tetrasubstituted Olefins with a Cationic Zirconocene Catalyst

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The asymmetric hydrogenation of olefins is a powerful method of generating optically pure compounds.¹ Among double bond-containing substrates that are suitable as targets for asymmetric reduction, tetrasubstituted olefins are of particular interest because the products may contain two new stereogenic centers. At the same time, tetrasubstituted olefins are generally the least reactive class of olefins in hydrogenation reactions; steric hindrance compromises their ability to bind to most transition metal complexes. Asymmetric hydrogenations of tetrasubstituted *N*-acylaminoacrylic esters and aryl acrylic acids have been achieved by using cationic Rh catalysts with bidentate phosphine ligands.² Coordination of nearby heteroatoms to the Rh is necessary for these reductions to proceed with high efficiency and enantioselectivity. Crabtree's catalyst, $[\text{Ir}(\text{COD})(\text{PCy}_3)(\text{py})]^+[\text{PF}_6]^-$, is highly effective for the hydrogenation of tetrasubstituted olefins,³ but attempts to develop asymmetric versions have, until recently, not been very successful.⁴ Pfaltz has recently described a highly active and enantioselective Ir catalyst for the hydrogenation of unfunctionalized trisubstituted olefins.⁵ In this paper, he also reported the reduction of the tetrasubstituted olefin 2-(*p*-methoxyphenyl)-3-methyl-2-butene to the corresponding aryl-substituted alkane with an ee of 81%.

We have previously described a highly selective asymmetric reduction of unfunctionalized trisubstituted olefins,⁶ using (*S,S*)-(EBTHI)TiH (EBTHI = ethylenebistetrahydroindenyl) as catalyst. At 65 °C, under 80–2000 psig H₂, the olefins were hydrogenated to products with ee's of 83–99%. Even at high pressures the reductions of some substrates required several days to reach completion, presumably due to steric hindrance about the trisubstituted double bonds. In the case of tetrasubstituted olefins, this problem would likely be exacerbated.

We have begun investigating cationic titanocene and zirconocene complexes as hydrogenation catalysts for tri- and tetrasubstituted olefins, based on the idea that they should be particularly effective at binding highly substituted olefins due to their high electrophilicity. Cationic metallocenes of the type $[\text{Cp}_2\text{MMe}]^+$ (M = Ti, Zr)⁷ have been extensively investigated in Ziegler–Natta-type polymerizations.⁸ Under a hydrogen atmo-

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(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 16–94. (b) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; pp 367–388.

(2) (a) Hayashi, T.; Kawamura, N.; Ito, Y. *J. Am. Chem. Soc.* **1987**, *109*, 7876. (b) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (c) Sawamura, M.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9602. (d) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.

(3) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331.

(4) Cabeza, J. A.; Cativiela, C.; Diaz de Villegas, M. D.; Oro, L. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1881.

(5) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897.

(6) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569.

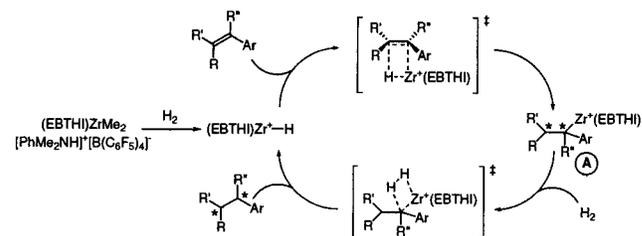
(7) (a) Hlatky, G. G.; Turner, H. W.; Eckman, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 2728. (b) Chien, J. C. W.; Tsai, W.-M.; Rausch, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 8570.

Table 1. Asymmetric Hydrogenations of Tetrasubstituted Olefins with (*R,R*)- or (*S,S*)-(EBTHI)ZrMe₂[PhMe₂NH]⁺[(BC₆F₅)₄]⁻ ^a

Entry	Olefin	Product ^b	H ₂ Pressure (psig)	Catalyst Loading (mol %)	Yield ^c (%)	ee (%)	cis:trans
1			80 1700	8 8	79 77	84 96	
2			80 1700	5 8	76 87	86 93	95:5 >99:1
3			80	8	96	92	99:1
4			80 1000	5 5	34 ^d 89 ^e	97 99	98:2
5			1000 1500	5 8	65 ^d 94 ^f	97 98	>99:1
6			80 1000 1700	5 5 8	57 ^d 80 ^d 95	5 40 52	9:1 95:5 95:5
7			80 2000	5 8	44 ^{d,g} 94	29 ^h 78	>99:1 >99:1
8			2000	5	91 ⁱ	92	>99:1

^a Reactions were run at 0.25 M [olefin], at room temperature, for 13–21 h. ^b The relative stereochemistry was determined for products in entries 2, 7, and 8. The absolute stereochemistry was assigned for the product in entry 2. ^c Yields are the average of two isolated yields of >95% purity as determined by GC, ¹H NMR and, for new compounds, elemental analysis. ^d Percent conversion is reported. ^e Reaction time was 39 h. ^f Reaction time was 65 h. ^g Reaction time was 30 h. ^h When the hydrogenation was performed at 2000 psig, the major enantiomer was the opposite of that obtained at 80 psig. ⁱ Yield includes 9% 5,6-dimethyl-1,2,3,4-tetrahydronaphthalene that was present with the product.

Scheme 1



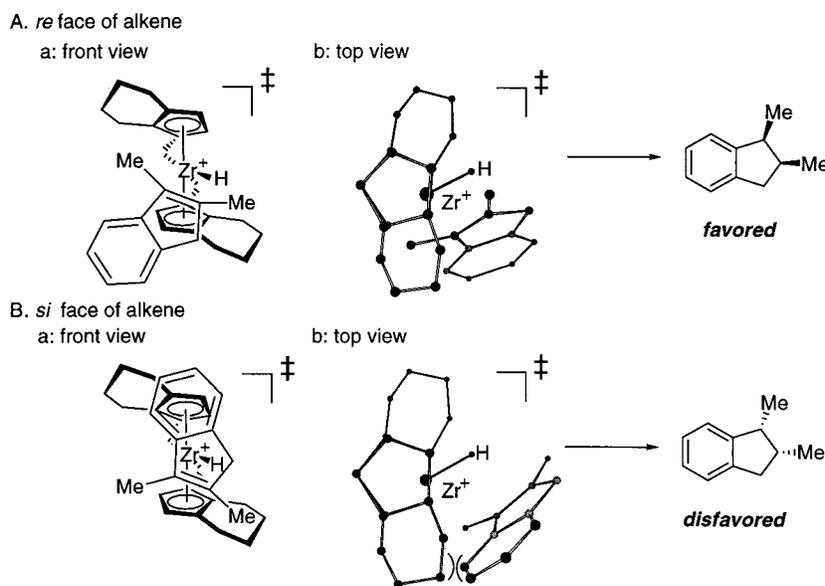
sphere these complexes can be converted into cationic metallocene hydrides.⁹ The chiral zirconocene (EBTHI)ZrMe₂ (**1**), in the presence of methylaluminoxane or $[\text{PhMe}_2\text{NH}]^+[\text{Co}(\text{C}_2\text{B}_9\text{H}_{11})_2]^-$, has been applied to the asymmetric reduction of 1,1-disubstituted olefins; the ee's of the products did not exceed 36%.¹⁰ We now

(8) (a) Jordan, R. F. *Adv. Organomet. Chem.* **1991**, *32*, 325. (b) Marks, T. J. *Acc. Chem. Res.* **1992**, *25*, 57. (c) Kesti, M. R.; Coates, G. W.; Waymouth, R. M. *J. Am. Chem. Soc.* **1992**, *114*, 9679. (d) Bochmann, M. *J. Chem. Soc., Dalton Trans.* **1996**, 255. (e) Kaminsky, W.; Arndt, M. *Adv. Polym. Sci.* **1997**, *127*, 143.

(9) Jordan, R. F.; Bajgur, C. S.; Dasher, W. E.; Rheingold, A. L. *Organometallics* **1987**, *6*, 1041.

(10) (a) Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911. (b) Grossman, R. B.; Doyle, R. A.; Buchwald, S. L. *Organometallics* **1991**, *10*, 1501.

Scheme 2



report a catalyst generated from **1** and $[\text{PhMe}_2\text{NH}]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ (**2**) that can reduce tetrasubstituted olefins with very high enantioselectivities.

The hydrogenations were carried out at room temperature in aromatic hydrocarbon solvents using (*R,R*)- or (*S,S*)-**1** and **2** at either 80 or 1000–2000 psig H_2 . In some cases, the rate and enantioselectivity of the reaction depended markedly on H_2 pressure. As shown in Table 1, under the appropriate reaction conditions, products with ee's over 90% could be obtained in most instances.

The relative stereochemistry of two of the products, 1,2-dimethylindane from 2,3-dimethylindene (Table 1, entry 2) and 1,2-dimethyl-1,2,3,4-tetrahydronaphthalene from 3,4-dimethyl-1,2-dihydronaphthalene (entry 8), were determined to be *cis* by comparison to spectral data;¹¹ the stereochemistry of 2-methyl-1-phenylindane from 2-methyl-3-phenylindene (entry 7) was determined to be *cis* by nOe studies.¹² The other indane products are assumed to also be *cis* by analogy. The *absolute* configurations of most of the products are not known since these hydrocarbons have not been previously synthesized with a high degree of enantiopurity. However, we were able to assign the absolute configuration of the 1,2-dimethylindane product, obtained from the reduction of 2,3-dimethylindene using (*R,R*)-**1**, as (*S,S*) based on the crystal structure of the $\text{Cr}(\text{CO})_3$ complex of the indane product.¹²

The mechanism for the hydrogenation is thought to be analogous to that previously proposed for the hydrogenation of trisubstituted olefins.⁶ In this scenario, the carbon–carbon double bond inserts into the zirconium hydride to form intermediate **A** (Scheme 1).¹³ Intermediate **A** then undergoes hydrogenolysis,⁹ giving the product and regenerating the zirconium hydride. This mechanism predicts a *cis* configuration for products from the reduction of cyclic substrates.

If the mechanism proceeds as described in Scheme 1, the product configuration from the reduction of 2,3-dimethylindene indicates that this olefin reacts at the *re* face. In the transition state that leads to (*S,S*) product, the double bond of the indene

inserts into the Zr–H bond as shown in Scheme 2. In the transition state that would lead to (*R,R*) product, unfavorable steric interactions between the aromatic ring of the indene and the tetrahydroindenyl portion of the ligand would disfavor this reaction pathway. The reduction of 3-ethyl-2-methylindene (entry 6) proceeded with decreased enantioselectivity compared to the reduction of 2,3-dimethylindene. This result is in accord with Scheme 2; the larger ethyl substituent in the benzylic position should increase unfavorable steric interactions in the preferred transition state of the reduction. Intriguingly, the sense of enantioselectivity in the reduction of 2-methyl-3-phenylindene (entry 7) depended on hydrogen pressure,¹⁴ indicating that the mechanism of hydrogenation may be quite complex and substrate dependent.

In conclusion, the combination of **1** and **2** is a highly enantioselective catalyst for hydrogenation of unfunctionalized tetrasubstituted olefins. Previous attempts to use $(\text{EBTHI})\text{ZrH}^+$ for the asymmetric hydrogenation of disubstituted olefins have resulted in low levels of enantioselectivity.¹⁰ The increased steric hindrance of tetrasubstituted olefins most likely allows the catalyst to discriminate more effectively between the enantiotopic faces of the double bond. The cationic nature of these catalysts renders them sufficiently electrophilic to overcome the reluctance of most metal complexes to bind to such hindered olefins. Further work to examine the scope and mechanism of this catalyst system is in progress.

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Supporting Information Available: Preparation and characterization of **1** and all substrates and products (PDF) and crystallographic data for chromium tricarbonyl complex of (*S,S*)-1,2-dimethylindane (CIF format). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA990535W

(11) (a) *cis*-1,2-dimethylindane: Beckwith, A. L. J.; Gerba, S. *Aust. J. Chem.* **1992**, *45*, 289. (b) *cis*-1,2-dimethyl-1,2,3,4-tetrahydronaphthalene: Morin, F. G.; Horton, W. J.; Grant, D. M.; Dalling, D. K.; Pugmire, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 3992.

(12) See Supporting Information for details.

(13) Prior to insertion, coordination of the aromatic portion of the substrate to the Zr cation could direct the regioselectivity of the insertion. Coordination of a phenyl group of BPh_4^- to a cationic zirconocene complex has been observed: Horton, A. D.; Frijns, J. H. G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1152.

(14) For other examples of reversals in reaction enantioselectivity with changes in reaction conditions, see: (a) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (b) Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 1348. (c) Sun, Y.; Wang, J.; LeBlond, C.; Reamer, R. A.; Laquidara, J.; Sowa, J. R., Jr.; Blackmond, D. G. *J. Organomet. Chem.* **1997**, *548*, 65. (d) Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201.