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Communications to the Editor

Asymmetric Hydrogenation of Unfunctionalized Trisubstituted Olefins with a Chiral Titanocene Catalyst

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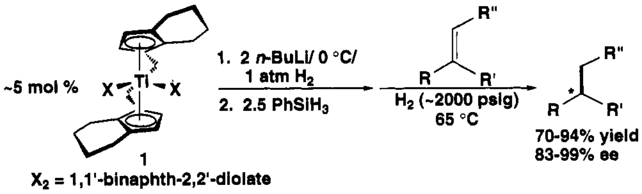
Trisubstituted olefins with suitably disposed chelating substituents can be hydrogenated or isomerized with high levels of enantioselectivity using a chiral cobalt, rhodium, or ruthenium catalyst.[1-3] To our knowledge, the application of these catalysts to the asymmetric reduction of unfunctionalized trisubstituted olefins has not been accomplished with good enantioselectivity.[2,4] Chiral titanocene-catalyzed hydrogenation of geminally-disubstituted unfunctionalized olefins was first reported by Kagan. He showed that 2-phenyl-1-butene was hydrogenated with low to moderate enantioselectivity using a menthyl-substituted titanocene catalyst.[5] The reaction was subsequently optimized and applied to other 1,1-disubstituted olefins by Vollhardt and Halterman, who utilized titanocene derivatives containing novel annulated cyclopentadienyl ligands.[6,7] The extension of this reaction to the more challenging asymmetric reduction of trisubstituted olefins has not, to date, been reported. In light of our recent success in the hydrogenation of ketimines using a C_2-symmetric titanocene catalyst,[8] we decided to examine the corresponding reduction of trisubstituted olefins. In this communication, we report the first highly enantioselective, catalytic hydrogenations of unfunctionalized trisubstituted olefins.

The geometric similarity between ketimines and trisubstituted olefins suggested that the catalyst system which was employed for the enantioselective asymmetric reduction of ketimines would be an appropriate starting point for the reduction of olefins.[9-11] This catalyst is generated from the C_2-symmetric ethylene bis(tetrahydroindenyl)titanocene-1,1′-binaphthyl-2,2′-diolate, **1**, first reported by Brintzinger.[12] Addition of 1.95 equiv of *n*-BuLi to a THF solution of (*S,S,S*)-**1** under H_2 at 0 °C (Scheme I) generates the active catalyst, which is stabilized by the addition of 2.5 equiv (relative to **1**) of phenylsilane. The catalyst mixture is then combined with substrate (ca. 20 equiv) under an inert atmosphere in a Parr high-pressure reaction vessel, charged to 2000 psig of H_2, and heated for 9–184 h at 65 °C. The results of the hydrogenation reactions are presented in Table I.

Scheme I[a]



[a] X_2 + 1,1′-binaphth-2,2′-diolate

As is shown in Table I, the reaction works well for both cyclic and acyclic olefins; products are isolated in good chemical and excellent optical yields. We have found that the time and pressure necessary to effect complete reaction are highly substrate dependent. In general, *Z* olefins are reduced much more slowly than their *E* isomers. For instance, (*E*)-1,2-diphenylpropene is completely reduced at 80 psig of H_2 and 65 °C in 9 h, while only 3% reduction of the *Z* isomer is observed after 48 h at 70 °C and 2000 psig of H_2. Additionally, entries 4 and 5 show that similar *Z* olefins may be reduced at very different rates; application of our transition-state model (Scheme II) to these substrates shows that the transition-state structure leading to product in entry 4 is much less hindered than that for entry 5. Reduction of a 64:36 mixture of (*E*)- and (*Z*)-2-(4-methoxy)-2-butene (entry 3) gave product which was 31% ee. This is the result expected if the individual geometric isomers are reduced with an approximately equivalent level but opposite sense of enantioselectivity. The effective asymmetric hydrogenation of functionalized olefins of the types exemplified by entries 8 and 9 by the chiral rhodium or ruthenium catalyst systems discussed earlier has not been reported. Using our conditions, however, they react to give products with high ee's and in good chemical yield.[13]

The phenylsilane added prior to the substrate under the standard reaction conditions seems only to stabilize the catalyst during its manipulation in the drybox: it does not appear to be a hydrogen source under the reaction conditions employed. To support this hypothesis, (*E*)-1,2-diphenylpropene was reduced under 80 psig of D_2 (20 equiv of substrate, 2.5 equiv of $PhSiH_3$, based on catalyst) to provide 1,2-diphenylpropane which was 98% D_2 by GC MS. The deuterium was incorporated exclusively at the methylene and methine positions, as evidenced by ^2H and ^{13}C NMR, revealing that no olefin isomerization occurred competitively with hydrogenation under these conditions.

A difficulty which we initially faced in this work was how to determine the enantiomeric excesses of the products. For most of the examples studied, we found that the ee's of the products could be determined by HPLC using a chiral stationary phase. The methoxy group on the phenyl substituents in entries 2, 4, 5, and 9 was incorporated to facilitate the separation of the enantiomers by HPLC; it was not required for the reaction to be

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[1] Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339–345.

[2] (a) Noyori, R. *Science* **1990**, *248*, 1194–1199. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 1–39 and references therein.

[3] Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901–6939 and references therein.

[4] Tanaka, M.; Ogata, I. *J. Chem. Soc., Chem. Commun.* **1975**, 735. These workers hydrogenated 2-phenyl-2-butene to 2-phenylbutane with an ee of 14%.

[5] Cesarotti, E.; Ugo, R.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 779–780.

[6] Halterman, R. L.; Vollhardt, K. P. C. *Organometallics* **1988**, *7*, 883–892.

[7] Halterman, R. L.; Vollhardt, K. P. C.; Welker, M. E.; Bläser, D.; Boese, R. *J. Am. Chem. Soc.* **1987**, *109*, 8105–8107.

[8] Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562–7564.

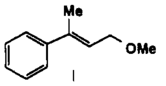
[9] Similar zirconium-based catalysts incorporating this ligand have been used in the reduction of 1,1-disubstituted olefins. Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911–4914 and ref 10.

[10] Grossman, R. B.; Doyle, R. A.; Buchwald, S. L. *Organometallics* **1991**, *10*, 1501–1505.

[11] Asymmetric reductions of 1,1-disubstituted olefins using related lanthanide catalysts have been reported: Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761–2762.

[12] Wild, F. R. W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233–247.

[13] Using *rac*-**1**, X = Cl, as the precatalyst and **I** as the substrate, none of the desired product was observed. We speculate that the titanium alkyl resulting from hydride insertion into the olefin undergoes a *β*-alkoxide elimination reaction. For related processes, see: Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1988**, *7*, 2324–2328.



I

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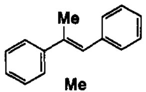
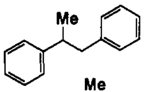
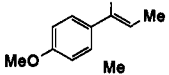
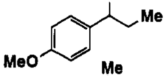
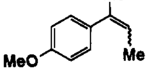
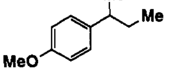
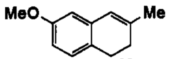
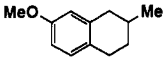
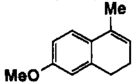
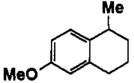
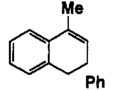
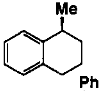
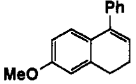
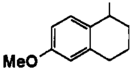
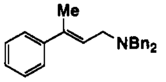
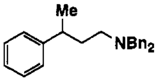
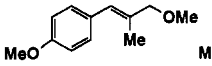
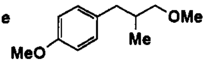
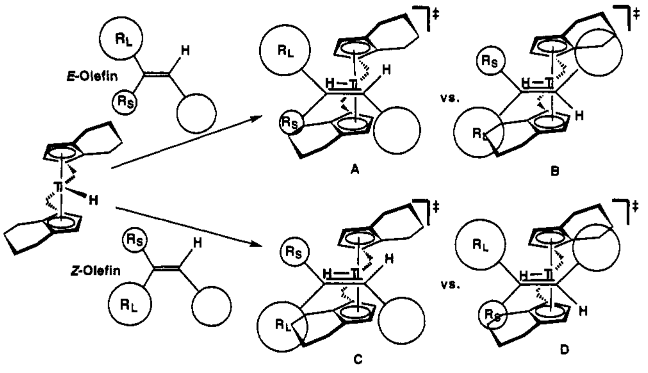
Table I[a]

Entry	Starting Material	Product	ee (%)	Time (h)	Yield (%)
1			>99[c] >99[d] >99	48[e] 9 14[f]	91 94 80
2			95[d]	48	79
3	 64/36 E/Z		31	146	80
4[b]			92	44	77
5			93	132[g]	70
6			83[h]	184	70
7			83	169[i]	87% Conversion
8			95	43	75
9			94 93	48	86 80

[a] Reactions were done at 2000 ± 100 psig H_2 in THF with 5 ± 1 mol % (*S*,*S*,*S*)-**1** except as noted. Numbers given for ee, time, and yield represent averaged values for two or more runs. [b] Starting material contained 6% 7-methoxy-1,4-dihydro-2-methylnaphthalene. [c] (*R*,*R*,*R*)-**1** was used in this experiment; *S* (+) isomer was obtained. [d] *R* (−) isomer was obtained. [e] 6.7 mol % **1**. [f] 80 psig. [g] 1800 psig. [h] *S* (+) isomer. [i] 2400 psig, 9.6 mol % **1**.

Scheme II



successful. When it was not possible to employ the chiral HPLC method for the determination of optical purity, the ee's were determined by polarimetric methods.[14]

We believe that these olefins are reduced through a mechanism similar to that suggested for the reduction of ketimines,[8] involving transition states **A** and **C** (Scheme II). This involves approach of the olefin from the "front" of the complex, as was previously suggested for the hydrogenation of 1,1-disubstituted olefins by a related zirconium catalyst system.[9] In this view, the less-substituted olefin carbon bonds to the titanium center as the hydride is transferred to the tertiary carbon. This arrangement minimizes the steric interaction between the large substituents on the olefin and the cyclohexyl portion of the tetrahydroindenyl ligand. This view is also consistent with the fact that the rate of reduction for *Z* olefins (via **C**) is slower than it is for *E* olefins (via **A**), reflecting the energetically unfavorable interaction between one of the large olefin substituents and the ligand in the transition state for the *Z* olefin. This model suggests that the orientation of the group on the monosubstituted end of the olefin should control the stereochemical outcome of the reduction, as is seen in entry 3, because the steric environment encountered by that carbon is much more demanding than that seen at the other olefinic carbon. This model also predicts the correct absolute configuration of the products in entries 1, 2, and 6, as confirmed by comparison to known rotations.[15] The absolute stereochemistry observed in the reduction of these olefins is also of the same sense as that seen for the reduction of ketimines with this catalyst system.[8]

In conclusion, we have described the first examples of catalytic asymmetric hydrogenation of unfunctionalized trisubstituted olefins with high enantioselectivity. The reaction proceeds in good chemical and excellent optical yields. Further work to expand the scope of this catalyst system is in progress.

Acknowledgment. Support for this work was generously provided by the National Institutes of Health (GM 46059). R.D.B. is a trainee of the National Cancer Institute (CA 09112), which we thank. S.L.B. acknowledges additional support as an Alfred P. Sloan Fellow and a Camille & Henry Dreyfus Teacher-Scholar.

Supplementary Material Available: Detailed experimental procedures for the asymmetric alkene hydrogenations, as well as for the preparation and spectroscopic characterization of the starting materials and products listed in Table I (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.

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(14) The enantiomers of racemic entry 1, unfortunately, were not resolved acceptably by either chiral HPLC or GC methods. The rotation found for entry 1, $[\alpha]_D = -78.6°$, $c = 2.02$ in $CHCl_3$, $T = 22$ °C (average rotation for three runs using (*S*,*S*,*S*)-**1**), is greater than the literature value of $[\alpha]_D = -76.3°$, $c = 2.0$ in $CHCl_3$, reported both by Paquette[14a] and in the *Dictionary of Organic Compounds*;[14b] we favor this value because these sources provide rotations for both optical isomers, while the others report a value for only one of the two isomers. We have found two other values for material reported to be optically pure, ranging from $[\alpha]_D = -63.5°$, $c = 2.3$ $CHCl_3$, $T = 25$ °C,[14c] to $[\alpha]_D = +80.7$, $c = 2.341$ in $CHCl_3$, $T = 20$ °C.[14d] (a) Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6858–6860. (b) *Dictionary of Organic Compounds*, 5th ed.; MacMillan: New York, 1982; Vol. 2, p 2334. (c) Barnes, R. A.; Juliano, B. R. *J. Am. Chem. Soc.* **1959**, *81*, 6462–6466. (d) Watson, M. B.; Youngson, G. W. *J. Chem. Soc. C* **1968**, 258–262.

(15) See supplementary material for details.