Enantioselective Isomerization of Allylic Alcohols Catalyzed by a Rhodium/Phosphaferrocene Complex

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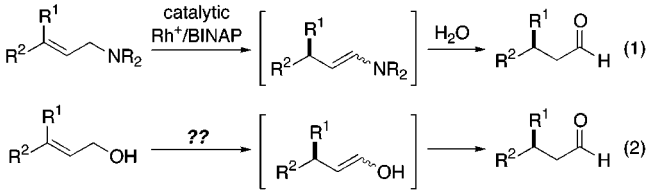
The highly enantioselective isomerization of allylic amines to enamines, catalyzed by a Rh^+/BINAP complex (eq 1), represents one of the most noteworthy accomplishments in the field of asymmetric catalysis, due to its early discovery and to its industrial utility.[2−5] Unfortunately, comparable success has not been achieved for the corresponding isomerization of readily available allylic alcohols (eq 2), despite the obvious usefulness of this



process; to the best of our knowledge, 53% ee is the highest enantioselectivity reported to date (with a Rh^+/BINAP catalyst).[6] During the past few years, we have been pursuing the design and the development of new families of chiral ligands, based on planar-chiral heterocycles.[7] In this Communication, we establish that a Rh^+/planar-chiral phosphaferrocene complex can catalyze the enantioselective isomerization of allylic alcohols with good levels of enantioselectivity (eq 3).

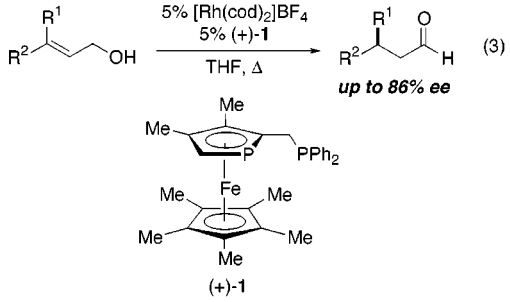
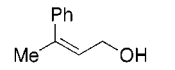
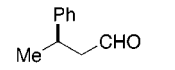
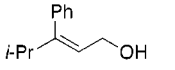
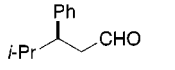
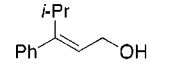
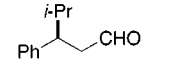
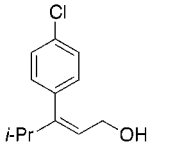
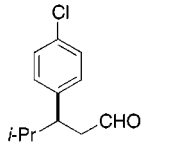
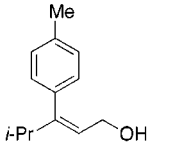
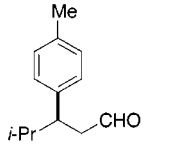
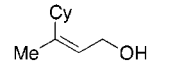
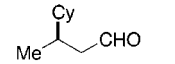


Table 1. Catalytic Enantioselective Isomerization of Allylic Alcohols (5% $[Rh(cod)_2]BF_4$, 5% (+)-**1**, THF, 70 °C)

Entry	Allylic Alcohol	Aldehyde	Yield[a]	ee
1			55	64
2			91	83
3			81	78
4			74	86
5[b]			64	80
6			75	72

[a] Isolated yield, average of two runs. [b] Reaction temperature: 100 °C.

In a previous report, we described the synthesis of C_1-symmetric phosphaferrocene ligand **1** and its application to the rhodium-catalyzed hydrogenation of dehydroamino acids, a test reaction for our ligand design.[7c] Having thus established the potential of our design, we turned our attention to an unsolved problem, the catalytic enantioselective isomerization of allylic alcohols. We were pleased to discover that Rh^+/phosphaferrocene complexes serve as effective catalysts for this process. Optimization experiments revealed that the level of enantioselection is dependent on the counterion and on the solvent (BF_4^- and THF are the best, respectively, among those that we have examined), but not on the temperature.

As illustrated in Table 1, a variety of allylic alcohols undergo isomerization with good selectivity in the presence of 5% $[Rh(cod)_2]BF_4$/(+)-**1**. Rearrangement of the methyl-substituted cinnamyl alcohol derivative occurs with relatively modest ee (entry 1), whereas reaction of the corresponding isopropyl-substituted derivative proceeds with significantly enhanced stereoselection (83% ee, entry 2).[8] We have determined that Z allylic alcohols typically isomerize with higher enantiomeric excess than do E allylic alcohols (e.g., entry 2 vs entry 3). Electronic effects on the level of asymmetric induction appear to be small, as indicated by entries 2, 4, and 5. Importantly, the process is not limited to olefins that bear an aromatic substituent, e.g., Rh^+/**1** isomerizes a cyclohexyl/methyl substituted allylic alcohol with good selectivity (entry 6).

We have applied the Rh^+/**1**-catalyzed enantioselective isomerization process to the first asymmetric synthesis of carboxylic acid **4**, which has served as a key intermediate in racemic syntheses of 7-hydroxycalamenene (**5**) and 7-hydroxycalamenenal

(1) Correspondence concerning the X-ray crystal structure should be directed to M. M.-C. Lo.

(2) (a) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600−601. (b) For an overview, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 3.

(3) Takasago International Corporation annually manufactures ~3700 tons of (−)-menthol and related terpenes through the Rh^+/BINAP-catalyzed enantioselective isomerization of allylic amines: Akutagawa, S. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York, 1992.

(4) For the catalytic enantioselective isomerization of cyclic allylic ethers, see: (a) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287−2289. (b) Hiroya, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2205−2206. (c) Frauenrath, H.; Reim, S.; Wiesner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1103−1106. (d) Brunner, H.; Prommesberger, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3231−3239. (e) Faitg, T.; Soulie, J.; Lallemand, J.-Y.; Mercier, F.; Mathey, F. *Tetrahedron* **2000**, *56*, 101−104.

(5) For the catalytic enantioselective isomerization of an unfunctionalized alkene, see: Chen, Z.; Halterman, R. L. *J. Am. Chem. Soc.* **1992**, *114*, 2276−2277.

(6) Tani, K. *Pure Appl. Chem.* **1985**, *57*, 1845−1854. The isomerization proceeds in modest yield (47%).

(7) (a) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (b) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270−10271. (c) Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168−4169. (d) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377−378.

(8) Replacement of the isopropyl group with a bulkier *tert*-butyl group leads to sluggish isomerization (12% yield, 80% ee after 48 h at 100 °C).

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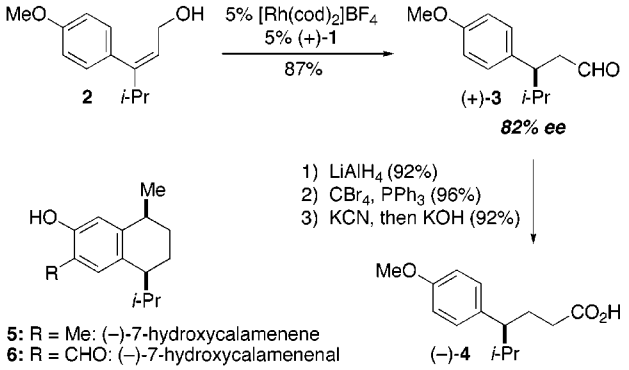

Figure 1. Asymmetric synthesis of (−)-7-hydroxycalamenene and (−)-7-hydroxycalamenenal.

(**6**),[9,10] two naturally occurring sesquiterpenes in the cadinene family.[11] Thus, catalytic asymmetric isomerization of **2** by Rh^+/(+)-**1** furnishes aldehyde (+)-**3** in 82% ee (87% yield; Figure 1).[12] The aldehyde is then homologated through an efficient three-step sequence that affords acid (−)-**4** and thereby completes formal total syntheses of (−)-7-hydroxycalamenene and (−)-7-hydroxycalamenenal.

In an effort to gain insight into the origin of stereoselection of the asymmetric isomerization process, we have obtained an X-ray crystal structure of the PF_6 salt of $[Rh(cod)(\mathbf{1})]^+$ (Figure 2).[13] The RhL_4 complex adopts a distorted square-planar geometry about the rhodium, with Rh−P(1) and Rh−P(2) bond lengths of 2.25 and 2.30 Å, respectively. On the basis of the crystal structure, it is tempting to speculate that the orientation of the phenyl groups that are attached to P(2) may play a significant role in defining the asymmetric environment of the catalyst. Relative to complexes that bear only traditional trivalent, sp^3-hybridized phosphorus sites, we believe that ligand **1** binds to rhodium with a more well-defined conformational preference, due to the strong π-acceptor character of the sp^2-hybridized phosphorus of the phosphaferrocene.[14,15]

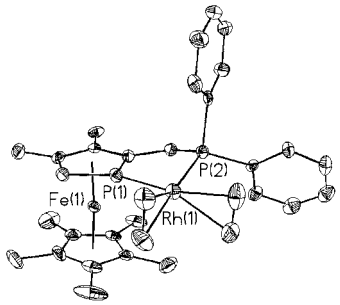

Figure 2. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of $[Rh(cod)(\mathbf{1})]PF_6$. The methylene groups of the cod ligand, as well as the PF_6 counterion, have been omitted for clarity.

In conclusion, although there remains room for improvement, we have developed the most general and enantioselective catalyst reported to date for the asymmetric isomerization of allylic alcohols. Future work will include investigations of ligands that bear elements of central chirality that can amplify the asymmetric environment afforded by the planar chirality of the phosphaferrocene.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002471R

(9) (a) Alexander, J.; Rao, G. S. K. *Tetrahedron* **1971**, *27*, 645−651. (b) Tanaka, J.; Miyake, T.; Iwasaki, N.; Adachi, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2851−2853. (c) Uemura, M.; Isobe, K.; Take, K.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 3855−3858. Uemura, M.; Isobe, K.; Hayashi, Y. *Chem. Lett.* **1985**, 91−94.

(10) The only reported nonracemic syntheses are based on chiral-pool starting materials and are not stereoselective: (a) Takaki, K.; Ohsugi, M.; Okada, M.; Yasumura, M.; Negoro, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 741−745. (b) Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200−1205.

(11) (a) Rowe, J. W.; Toda, J. K. *Chem. Ind. (London)* **1969**, 922−923. (b) Lindgren, B. O.; Svahn, C. M. *Phytochemistry* **1968**, *7*, 1407−1408.

(12) Experimental: **In situ generation of the catalyst** (removal of cod): Under N_2, a solution of (+)-**1** (17.6 mg, 0.0352 mmol) in THF (6.0 mL) was added dropwise to a stirred suspension of $[Rh(cod)_2]BF_4$ (14.3 mg, 0.0352 mmol) in THF (4.0 mL), resulting in a bright-red solution. After completion of the addition, the reaction mixture was stirred for 5 min and then filtered. The resulting filtrate was placed in a 100-mL Schlenk tube and cooled with liquid N_2. After three vacuum/H_2−refill cycles, the valve to the Schlenk tube was closed, and the solution was stirred for 1.0 h at room temperature. The reaction mixture was then filtered, and the filtrate was concentrated to dryness. **Catalytic enantioselective isomerization:** A solution of **2** (145 mg, 0.704 mmol) in THF (7.5 mL) was added to the Schlenk tube containing the catalyst, and the resulting mixture was stirred at 70 °C for 48 h. The THF was then removed, and the reaction mixture was purified by silica gel chromatography (hexanes:Et_2O = 10:1), which afforded **3** (126 mg, 87%) as a colorless oil.

(13) We were unable to obtain X-ray-quality crystals of the BF_4 salt.

(14) For leading references, see: Deschamps, B.; Ricard, L.; Mathey, F. *J. Organomet. Chem.* **1997**, *548*, 17−22.

(15) A referee has noted that the push−pull (sp^3 phosphine−sp^2 phosphine) electronic structure is a distinguishing feature of this ligand design, and that this aspect may play an important role in the utility of the ligand. We thank the referee for this suggestion.