Observation of a $[RuCl_2((S)$-(−)-tol-binap)$]_2 \cdot N(C_2H_5)_3$-Catalyzed Isomerization−Hydrogenation Network

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Received August 30, 1995

Hydrogenation of prochiral substrates by late transition metal complexes with chiral diphosphine ligands represents a significant advance in the field of asymmetric catalysis.[1-3] In many cases, however, commonly observed effects of reaction variables such as temperature and pressure on enantioselectivity have yet to be rationalized, and detailed kinetic studies on these systems[3] are rare. Product selectivity is often reported only as a single measurement of the ultimate enantioselectivity at 100% conversion of the substrate. In the experiments we report herein, monitoring of reaction progress over the full course of the reaction enabled us to observe a striking inversion in enantioselectivity in the hydrogenation of geraniol (**I**) with $[RuCl_2((S)$-(−)-tol-binap)$]_2 \cdot N(C_2H_5)_3$ (**II**) [tol-binap = (di-*p*-tolylphosphino)-1,1′-binaphthyl] to (*R*)- and (*S*)-citronellol (**III** and **IV**, respectively).[4]

Figure 1 shows a marked shift from ca. 85% ee[5] to (*S*)-citronellol at the beginning of the reaction to over 40% ee to (*R*)-citronellol at high conversion. This intriguing result was rationalized by our finding that the internal olefin geraniol isomerized to the terminal isomer γ-geraniol (**V**) during the period of catalyst dissolution in the solvent−substrate mixture prior to addition of hydrogen. These two prochiral isomeric olefins underwent hydrogenation with respectively high enantioselectivities to β-citronellol products of opposite absolute stereochemistry (Scheme 1).

Temperature-dependent studies of the isomerization reaction in the absence of hydrogen indicated an equilibrium concentration of about 22% **V** at 318 K and 18% **V** at 293 K, with an isomerization rate appreciable enough[6] to suggest that the presence of some **V** in the reaction mixture is unavoidable using the reaction preparation procedures[7] employed here. Indeed, preliminary results from reaction studies carried out using deuterium suggest that the isomerization reaction effectively

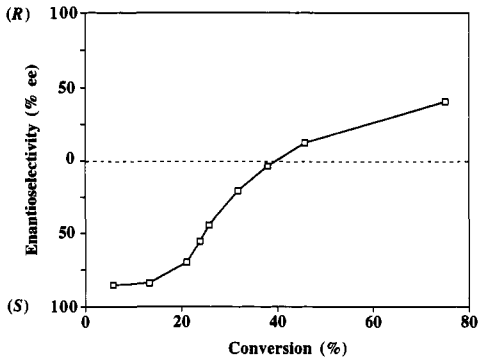
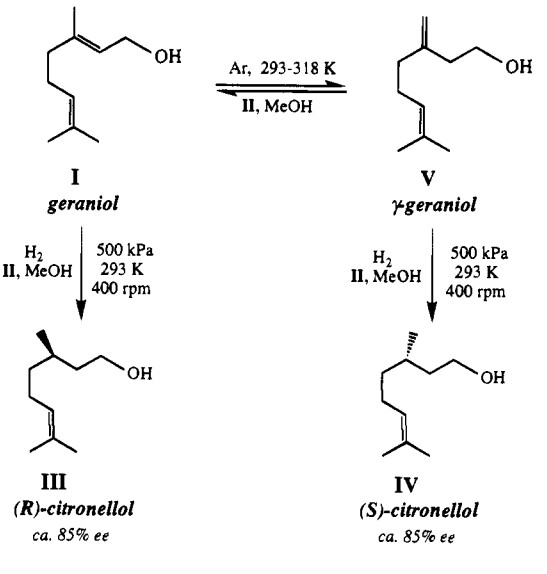


Figure 1. Enantiomeric excess as a function of geraniol conversion in the hydrogenation of geraniol with $[RuCl_2((S)$-(−)-tol-binap)$]_2 \cdot N(C_2H_5)_3$ at 293 K and 500 kPa.

Scheme 1



competes even under hydrogenation conditions.[8] Interestingly, the isomerization was extremely stereoselective,[9] with no observation of the formation of nerol, the (*Z*)-isomer of **I**.[10] Use of nerol itself as a substrate with the same catalyst and conditions did not give isomerization to **I** or **V**. When the isomerization of **I** was performed under identical conditions using $Ru(PPh_3)_3Cl_2$, reaction occurred readily to form a mixture of geraniol, γ-geraniol, nerol, a small amount of β-citronellols, and an unidentified isomer of geraniol.

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(1) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley-Interscience: New York, 1994, Chapter 2.

(2) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

(3) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

(4) Reaction conditions: 293 K, 500 kPa; 350 mL; 1.0 M geraniol in CH_3OH; substrate/Ru molar ratio = 1400; agitation speed 400 rpm. GC analysis by a Chiraldex B-TA column.

(5) Enantioselectivity defined as % ee = $|(R - S)/(R + S)| \times 100$.

(6) Starting with a 1 M solution of **I**, the initial isomerization rates, in units of moles of substrate/moles of Ru/min, were 2.4×10^{-6} and 2.5×10^{-7} at 318 and 293 K, respectively, or approximately 6 and 60 min, respectively, to reach 5% conversion to **V**.

(7) Takaya, H.; Ohta, T.; Inoue, S.-I.; Tokunaga, M.; Kitamura, M.; Noyori, R. *Org. Synth.* **1993**, *72*, 74. Isomerization of **I** occurring prior to commencement of the hydrogenation reaction may be minimized, although not completely suppressed, by dissolving the catalyst in the solvent under H_2 prior to addition of the substrate, thereby decreasing substrate−catalyst contact time.

(8) Competitive isomerization has been noted in the asymmetric hydrogenation of unsaturated carboxylic acids with Ru(binap) catalysts. In that case, the terminal and internal olefinic isomers gave hydrogenation products of the same absolute stereochemistry (Saburi, M.; Takeuchi, H.; Ogasawara, M.; Tsukahara, T.; Ishii, Y.; Ikariya, T.; Takahashi, T.; Uchida, Y. *J. Organomet. Chem.* **1992**, *428*, 155). Observations of isomerization occurring during the directed hydrogenation of chiral allylic alcohols with achiral phosphine-based catalysts have also been reported: Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. The latter study noted that in some cases isomerization may be suppressed under elevated hydrogen pressure. We found that, in our case, the isomerization of one prochiral olefinic isomer to another proceeded under hydrogen as well as under inert gas, as indicated by deuteration experiments, which will be reported separately.

(9) The stereoselective isomerization of **I** to **V** was also achieved using $[Ru(OCOCH_3)_2((R)$-binap)], prepared as described in ref 1.

(10) A recent comprehensive study of isomerization of allylic alcohols with achiral Ru phosphine complexes noted that geraniol failed to isomerize to the aldehyde citronellal, but no mention was made of isomerization to γ-geraniol: Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027.

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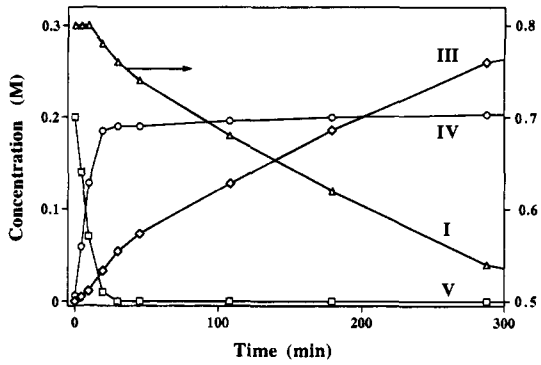

Figure 2. Concentration of reactant and product species as a function of reaction time in the hydrogenation of geraniol (**I**) and its isomer γ-geraniol (**V**) to form (*R*)- and (*S*)-citronellol (**III** and **IV**, respectively) with $[RuCl_2((S)\text{-}(-)\text{-tol-binap})]_2{\cdot}N(C_2H_5)_3$ (**II**) at 293 K and 500 kPa.

The identity of **V** was confirmed by comparative ^1H and ^{13}C NMR studies of **V**[11] prepared both from independent synthesis[12] and from isomerization of **I** as described above. Readily apparent in the reaction mixture after the 2-h isomerization procedure under Ar were the resonances of the methylene group of **V**.[13] Other ^1H NMR and ^{13}C NMR resonances were also attributable to **V**.[14] Integration of the ^1H NMR resonances indicated 23% isomerization, which is consistent with the chromatographic analysis.

Thus the results shown in Figure 1 for an apparent reaction of the original 1 M solution of **I** were in fact those for the hydrogenation of a mixture of 0.8 M **I** and 0.2 M **V**. Since the rate of hydrogenation of the terminal olefin **V** was significantly faster than that of the internal olefin **I**, **V** reacted to completion before appreciable hydrogenation of **I** began, as is shown in Figure 2. After the initial depletion of **V**, the concentration of the (*R*)-citronellol increased and eventually surpassed that of (*S*)-citronellol, as the hydrogenation of **I** became the dominant process. The early production of (*S*)-citronellol in 85% ee diluted the cumulative enantioselectivity of the reaction batch to 40% ee to (*R*)-citronellol, although at high conversion, where the γ-geraniol concentration was very low, the incremental enantioselectivity was in fact over 85% ee to (*R*)-citronellol.

This case is similar to the reduction of imines with chiral titanocene complexes reported by Willoughby and Buchwald[15] in which *anti* and *syn* substrates were found to give products of opposite stereochemistry. The presence of and possible interconversion of the two substrates in the reaction mixture was used to rationalize the higher enantioselectivities achieved at higher pressures where faster hydrogenation rates helped to minimize competition from the isomerization reaction.

Our findings may have implications for the observed effects of pressure on enantioselectivity in Ru(binap)-catalyzed hydrogenation of prochiral olefins. Noyori[7] and co-workers have reported that an increase in hydrogen pressure from 4 to 100 atm results in an increase in enantioselectivity from 70 to 98% ee in the hydrogenation of geraniol, and similar trends have been observed for other allylic alcohols. The fact that the two isomers are directed to hydrogenation products of opposite absolute stereochemistry suggests that competition between the isomerization and hydrogenation rates plays a role in dictating enantioselectivity in asymmetric hydrogenation of this prochiral allylic alcohol.[16] In addition, these results emphasize the importance of monitoring reaction progress whenever the potential for competitive reactions exists. A single measurement of the enantioselectivity at high conversion would in this case have presented a misleading picture of the efficacy of the Ru(binap) catalyst for enantioselective hydrogenation of geraniol under these conditions. Detailed kinetic studies of this isomerization–hydrogenation network will be published separately.

Acknowledgment. Helpful discussions with I. Shinkai, R. A. Reamer, P. J. Reider, T. R. Verhoeven, S. A. King, R. P. Volante, and K. Rossen of the Merck Research Laboratories (MRL) are gratefully acknowledged. J.R.S. (Seton Hall) would like to thank MRL for a grant supporting this research.

JA952987O

(11) The ^1H spectrum of γ-geraniol has been reported in ref 12 and in the following: (a) Mandai, T.; Mizobuchi, K.; Kawada, M.; Otera, J. *J. Org. Chem.* **1984**, *49*, 3403. (b) Bedoukian, R. H.; Wolinsky, J. *J. Org. Chem.* **1975**, *40*, 2154. The ^{13}C NMR spectrum of γ-geraniol has not been reported previously: ^{13}C NMR (75 MHz, ^1H decoupled, $CDCl_3$) δ 147, 132, 124, 112, 60, 39, 36, 25, 24, 17.

(12) Brown, H. C.; Singh, K. P.; Gamer, B. J. *J. Organomet. Chem.* **1963**, *1*, 2.

(13) δ 4.89 (br, s), 4.84 (br, s) in the ^1H NMR (300 MHz, proton decoupled, $CDCl_3$) and δ 112 in the ^{13}C NMR (75 MHz, ^1H decoupled, $CDCl_3$).

(14) ^1H NMR resonances (δ 3.70 t, 2.31 t) and ^{13}C NMR resonances (δ 147, 62, 39, 36). Overlap with excess **I** in the reaction mixture prevented a complete comparison of **V** prepared from the equilibrium isomerization reaction with that prepared from independent synthesis.

(15) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8592. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703.

(16) The observed isomerization reaction represents but one possible factor contributing to the ultimate enantioselectivity achieved in the hydrogenation of allylic alcohols over phosphine-based metal catalysts. We recently observed that kinetics and enantioselectivity in a number of different asymmetric hydrogenation reactions, including the Ru(binap)-catalyzed hydrogenation of both geraniol and nerol, may be strongly influenced by the rate of gas–liquid mass transfer, which is dictated by both pressure and agitation speed (Sun, Y.; Landau, R. N.; Wang, J.; LeBlond, C.; Blackmond, D. G. *J. Am. Chem. Soc.*, in press.