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ASYMMETRIC HYDROGENATION OF α,β-UNSATURATED CARBOXYLIC ACIDS IN SUPERCRITICAL CARBON DIOXIDE

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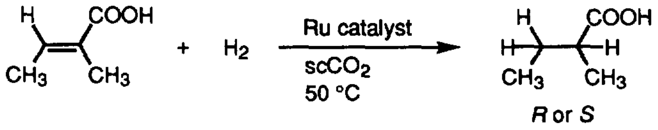
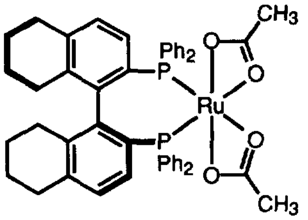
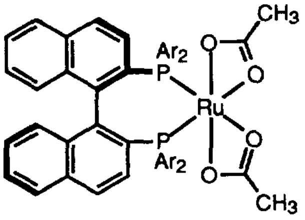
Abstract: Hydrogenation of tiglic acid in supercritical CO_2 catalyzed by a chiral H_8-BINAP–Ru(II) complex proceeds cleanly with cis stereochemistry to afford 2-methylbutanoic acid in up to 89% ee and over 99% yield. Copyright © 1996 Elsevier Science Ltd

Asymmetric catalysis is becoming viable as an efficient method for the synthesis of optically active compounds not only in laboratories but also at the industrial level.[1] Supercritical CO_2 ($scCO_2$) (critical point, $T_c = 31.0$ °C, $P_c = 72.9$ atm) is a practical medium for chemical reactions because of its non-toxicity, non-flammability, ease of removal from the product, and low cost. Furthermore, novel behavior or improved performance of reactions in $scCO_2$ have excited a great deal of interest.[2–5] Principal causes of drastic changes in rate or selectivity include the high miscibility of reactant gases in $scCO_2$, efficient mass transfer, local clustering, and possible weakening of the solvation of reacting species. This report describes the asymmetric catalytic hydrogenation of an olefinic substrate in $scCO_2$.[6]





(*S*)-**1**, $[Ru(OCOCH_3)_2((S)\text{-}H_8\text{-binap})]$



(*R*)-**2**, $[Ru(OCOCH_3)_2((R)\text{-binap})]$
(Ar = Ph)

(*R*)-**3**, $[Ru(OCOCH_3)_2((R)\text{-tolbinap})]$
(Ar = *p*-$CH_3C_6H_4$)

The hydrogenation of tiglic acid catalyzed by [Ru(OCOCH$_3$)$_2$((*S*)-H$_8$-binap)] [(*S*)-**1**] (H$_8$-BINAP = 2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl)[7] with a substrate/catalyst mole ratio (S/C) of 150–160 proceeds smoothly in scCO$_2$ under 25–35 atm H$_2$ and 175 atm CO$_2$ in a 50-mL reactor at 50 °C overnight to give (*S*)-2-methylbutanoic acid in over 99% yield and up to 81% ee.[8] The observed enantioselectivity is comparable with that observed in methanol (82% ee) and hexane (73% ee) at 30 atm H$_2$ and 50 °C. The reaction in scCO$_2$ occurs slowly under H$_2$ pressure below 10 atm. Table 1 summarizes the results obtained in scCO$_2$ and in protic and aprotic liquid solvents, together with the results obtained using the analogous catalyst precursors [Ru(OCOCH$_3$)$_2$((*R*)-binap)] [(*R*)-**2**] (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and [Ru(OCOCH$_3$)$_2$((*R*)-tolbinap)] [(*R*)-**3**] (TolBINAP = 2,2'-bis[di(*p*-tolyl)phosphino]-1,1'-binaphthyl).[11] Complex **1** showed a higher activity and enantioselectivity than **2** and **3** in the hydrogenation in scCO$_2$. For comparison, a reaction in liquid CO$_2$ (liqCO$_2$) at 20 °C using **1** was attempted, affording no hydrogenated product (Table 1). The hydrogenation of the olefin in scCO$_2$ occurs cleanly; no formic acid from CO$_2$ hydrogenation is detected, although Ru(II) complexes are known to be active in scCO$_2$ for this reaction in the presence of bases.[12–15]

Table 1. Asymmetric Hydrogenation of Tiglic Acid by Ru(II) Catalysts in scCO$_2$ and Other Media[a]

			product		
catalyst	reaction medium	H$_2$, atm	% yield	% ee	confign
(*S*)-**1**[b]	liqCO$_2$	30	0	–	–
(*S*)-**1**	scCO$_2$	33	99	81	*S*
(*S*)-**1**	scCO$_2$	7	23	71	*S*
(*S*)-**1**	scCO$_2$/R$_F$OH[c]	5	99	89	*S*
(*S*)-**1**	scCO$_2$/CD$_3$OD[d]	6	81	78	*S*
(*S*)-**1**[e]	methanol	30	100	82	*S*
(*S*)-**1**	hexane	30	100	73	*S*
(*R*)-**2**	scCO$_2$	33	50	37	*R*
(*R*)-**3**	scCO$_2$	29	100	36	*R*

[a] Reactions were conducted overnight (12–15 h) at 50 °C with S/C = 150–160 (catalyst = 4.4–4.7 μmol) in a 50-mL reactor unless otherwise indicated. For reactions in scCO$_2$, the pressure of CO$_2$ was 170–180 atm. [b] 180 atm CO$_2$, at 20 °C. [c] R$_F$OH = CF$_3$(CF$_2$)$_6$CH$_2$OH, 1.5 mmol.
[d] 7.4 mmol. [e] Reaction time 6 h.

Experiments in a window-equipped reactor showed that no liquid phase exists under the conditions used; therefore the reaction takes place in the homogeneous supercritical phase. Both tiglic acid and the saturated product are highly soluble in scCO$_2$. Qualitative tests demonstrated that the solubilities of the chiral diphosphine ligands in scCO$_2$ follow the order, H$_8$-BINAP > TolBINAP ≈ BINAP. The solubilities of the Ru(II) complexes were too low to measure, but it is likely that the H$_8$-BINAP complexes, either catalyst precursor or reaction intermediates, are more soluble than the BINAP and TolBINAP complexes. This must contribute to the higher activity of **1** compared to **2** or **3**.[12]

The addition of alcohols is known to increase the solubility of aromatic compounds in $scCO_2$.[16] In the present study, adding fluorinated alcohols caused an increase in both the conversion and enantioselectivity of the hydrogenation, up to 89% ee in the case of $CF_3(CF_2)_6CH_2OH$ (Table 1).[17]

The extent of asymmetric induction has often been found to depend on the hydrogen pressure in liquid solvents.[1,9] This is also true for the hydrogenation of tiglic acid in methanol catalyzed by **1**. Thus, when the H_2 pressure was lowered from 30 to 5 atm the enantiomeric purity of the product increased from 82% ee to 95% ee. In $scCO_2$, however, such an effect was not observed. Instead, upon decrease of the H_2 pressure from 33 to 7 atm, the optical yield of the product remained similar or slightly decreased (75–81% to 71–72%).

The origin of the hydrogens incorporated into the saturated products has been determined by deuterium labeling experiments. During the reaction of tiglic acid with D_2 (4 atm) catalyzed by the BINAP catalyst **2** in methanol, deuterium from D_2 is primarily introduced to the C(2) position while protons from the solvent are incorporated into the C(3) position.[18] These observations are in accord with a monohydride mechanism.[10,18] In $scCO_2$, unlike in methanol, isotope exchange between molecular hydrogen and protic compounds proceeds rapidly. As a consequence, the labeling experiments gave the isotope scrambled products, regardless of the operating mechanism.[19] Thus the reaction of tiglic acid in $scCO_2$ with D_2 in the presence of (*S*)-**1** (D_2:substrate:catalyst = 12,000:155:1, 28 atm D_2, 175 atm CO_2, 50 °C, 14 h) gave (2*S*,3*S*)-2,3-dideuterio-2-methylbutanoic acid, a cis-dideuterated product. The deuterium incorporation at the C(2), C(3), and acid positions was 97, 97, and 76%, respectively, as judged by ^1H NMR spectroscopy. When CD_3OD was added to the reaction of tiglic acid with H_2 in $scCO_2$ (H_2:CD_3OD:substrate:catalyst = 2,600:1,600:160:1, 6 atm H_2, 170 atm CO_2, 50 °C, 14 h), the deuterium was incorporated about equally at the C(2) and C(3) positions of the product. The NMR analysis of the product indicated the incorporation of 0.31 D and 0.37 D at the C(2) and C(3) positions, respectively. The cis hydrogenation of tiglic acid in $scCO_2$ may proceed via Ru monohydride or polyhydride (either classical or nonclassical) species.[1,18,20–22]

In summary, our results clearly show that $scCO_2$ can be used as a medium for homogeneous catalytic hydrogenation of certain classes of olefinic substrates.[6]

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REFERENCES AND NOTES

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1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**.
2. Subramaniam, B.; McHugh, M. A. *Ind. Eng. Chem. Process Des. Dev.* **1986**, *25*, 1.
3. Brennecke, J. F. In *Supercritical Fluid Engineering Science: Fundamentals and Applications*; Kiran, E., Brennecke, J. F., Eds.; ACS Symposium Series 514; American Chemical Society: Washington, DC, 1993; p 201.
4. Kaupp, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1452.
5. Jessop, P. G.; Ikariya, T.; Noyori, R. *Science* **1995**, *269*, 1065.

6. During the preparation of the manuscript, a study was published describing asymmetric hydrogenation with different classes of catalyst and substrate in scCO_2: Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277.
7. Zhang, X.; Uemura, T.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Takaya, H. *Synlett* **1994**, 501.
8. In a typical hydrogenation in scCO_2, a 50-mL stainless steel reaction vessel, charged under argon with tiglic acid and a catalyst precursor, was pressurized with approximately 20 atm of CO_2 and preheated to the reaction temperature for 2 h. The CO_2 pressure was then topped up to the required level followed by the introduction of hydrogen gas. The reaction was carried out overnight and stopped by cooling the reactor to about –50 °C and then releasing the pressure. Upon warming of the reactor to room temperature, the remaining CO_2 evaporated. Conversion of the substrate was determined by ^{1}H NMR spectroscopy. The enantiomeric purity of 2-methylbutanoic acid was determined by chiral HPLC analysis (Hibar LiChroCART 250-4 column; 30 °C; eluent, a 19:1 mixture of hexane and 2-propanol) after condensation with (*R*)-α-naphthylethylamine using diethyl phosphorocyanidate as a condensation agent.[9] The value was consistent with ^{1}H NMR analysis of the carboxylic acid using (*R*)-α-naphthylethylamine as a chiral shift reagent according to a method modified from reference 10.
9. Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
10. Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589.
11. Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566.
12. Jessop, P. G.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231.
13. Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1994**, *116*, 8851.
14. Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1995**, 707.
15. Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1995**, *95*, 259.
16. Ting, S. S. T.; Macnaughton, S. J.; Tomasko, D. L.; Foster, N. R. *Ind. Eng. Chem. Res.* **1993**, *32*, 1471; Dobbs, J. M.; Wong, J. M.; Lahiere, R. J.; Johnston, K. P. *Ind. Eng. Chem. Res.* **1987**, *26*, 56.
17. Phase tests using a sapphire window-equipped reactor showed that the reactions with or without additives took place in a single homogeneous phase under the conditions used.
18. Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 7189.
19. Reaction of tiglic acid (0.71 mmol) using D_2 catalyzed by (*S*)-**1** (4.6 μmol) in scCO_2 gave (2*S*,3*S*)-2,3-dideuterio-2-methylbutanoic-d_2 acid-*d* in 99% yield and in 77% ee as determined by HPLC analysis:[9] ^{1}H NMR in $CDCl_3$ (400 MHz, 25 °C, TMS): δ 11.30 (br, 0.24 H, CO_2H), 2.32 (m, 0.03 H, ^3J(H,H) = 6.8 Hz, C(2)H), 1.63 (m, 0.03 H, ^3J(H,H) = 6.8 Hz, C(3)H), 1.41 (q, 1H, ^3J(H,H) = 7.6 Hz, C(3)H), 1.10 (s, 3H, C(2)CH_3), 0.87 (d, 3H, C(4)H_3). The deuterium content, as determined by NMR analysis, was C(2) position 0.97, C(3) position 0.97, and carboxylic acid proton position 0.76. This result confirmed D_2/carboxylic acid isotope exchange. The lower value at the carboxylic acid proton position could be caused by adventitious water during workup.
20. Linn, D. E., Jr.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 2969.
21. Kirss, R. U.; Eisenschmid, T. C.; Eisenberg, R. *J. Am. Chem. Soc.* **1988**, *110*, 8564.
22. Jessop, P. G.; Morris, R. H. *Coord. Chem. Rev.* **1992**, *121*, 155.

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