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

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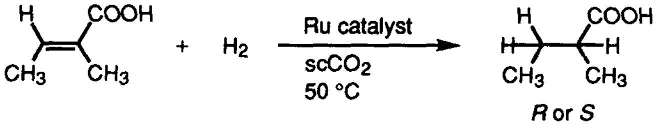
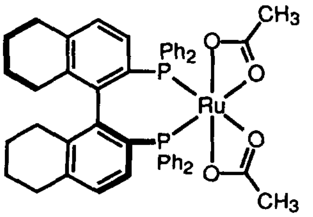
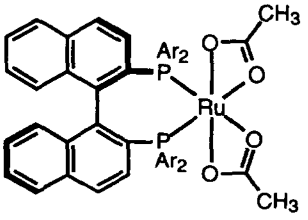
Abstract: Hydrogenation of tiglic acid in supercritical CO_2 catalyzed by a chiral H_8-BINAP–Ru(II) complex proceeds cleanly with cis stereochemistry to afford 2-methylbutanoic acid in up to 89% ee and over 99% yield. Copyright © 1996 Elsevier Science Ltd

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*)-H_8-binap)]



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

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

The hydrogenation of tiglic acid catalyzed by $[Ru(OCOCH_3)_2((S)\text{-}H_8\text{-binap})]$ [(*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 $[Ru(OCOCH_3)_2((R)\text{-binap})]$ [(*R*)-**2**] (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and $[Ru(OCOCH_3)_2((R)\text{-tolbinap})]$ [(*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**	$scCO_2/R_FOH$[c]	5	99	89	*S*
(*S*)-**1**	$scCO_2/CD_3OD$[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] $R_FOH = CF_3(CF_2)_6CH_2OH$, 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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