

Asymmetric Catalytic Hydrogenation Reactions in Supercritical Carbon Dioxide

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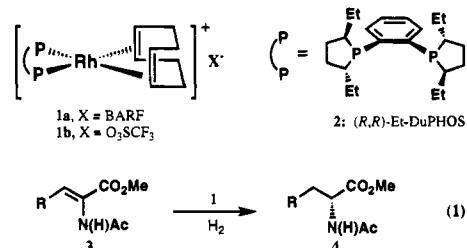
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The design of stereoselective reactions remains an important challenge in modern organic chemistry and plays a critical role in both the pharmaceutical and agrochemical industries.¹ Asymmetric catalysis potentially represents one of the most powerful and cost-effective methods for producing enantiomerically-enriched compounds.² Despite obvious advantages, practical application of asymmetric catalysis remains limited, due in part to the fact that high enantioselectivities often can be achieved in only a restricted range of solvents, many of which are environmentally hazardous.³ That solvent type can so dramatically influence enantioselectivities² is not surprising considering the small energy differences between diastereomeric transition states of stereoselective reactions ($\Delta\Delta G^\ddagger = 1.5\text{--}3.4$ kcal/mol for 85–99% enantiomeric excess, ee).⁴

The use of supercritical fluids (SCFs) as reaction media offers the opportunity to replace conventional organic solvents and also to optimize and potentially control the effect that solvent properties can have on selectivities.^{5,6} A unique and potentially advantageous characteristic of supercritical fluid solvents is that their density, polarity, viscosity, diffusivity, and overall solvent strength can be dramatically varied by relatively small changes in the pressure and/or temperature.⁶ The relatively mild critical point of carbon dioxide (CO₂: $T_c = 31$ °C, $P_c = 72.9$ atm) and its benign nature are particularly attractive for asymmetric catalytic applications. Several recent reports have shown that supercritical CO₂ (SC CO₂) can replace organic solvents in various transformations such as free radical reactions, polymerizations, and homogeneous catalytic reactions.^{7,8} Herein, we demonstrate that asymmetric catalytic hydrogenation reactions can be conducted in supercritical CO₂ and that, in some cases, higher enantioselectivities can be achieved in this solvent relative to conventional solvents.

Our initial studies in supercritical CO₂ have focused on enantioselective hydrogenation of prochiral α -enamides **3** using

cationic rhodium catalysts (**1**) which incorporate the chiral bidentate (*R,R*)-1,2-bis(*trans*-2,5-diethylphospholano)benzene ((*R,R*)-Et-DuPHOS) ligand **2**.⁹ These cationic DuPHOS–Rh complexes have been found to catalyze the efficient hydrogenation of α -enamide esters **3** to valuable α -amino acid derivatives **4** with very high enantioselectivities ($\geq 98\%$ ee) in organic solvents (eq 1).⁹ The highly lipophilic counteranion tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate¹⁰ (BARF) was employed in order to enhance the solubility of our cationic rhodium complexes. Catalyst precursor **1a** was found to be soluble in both hexane and supercritical CO₂, on the basis of UV–vis solubility studies.¹¹ Complex **1b**, containing the trifluoromethanesulfonate counterion (CF₃SO₃), also was found to be sufficiently soluble to allow catalysis to proceed in supercritical CO₂.



Hydrogenation reactions were performed in supercritical CO₂ by charging a cylindrical stainless steel reactor (35 mL capacity) with catalyst and enamide **3** (substrate/catalyst = 500), followed by pressurization with hydrogen gas (200 psig) and CO₂ (3000 psig). A homogeneous supercritical phase (observed through a sapphire window) was produced (5000 psig total pressure) upon warming to 40 °C, and the reactions were allowed to proceed for 24 h.^{12,13} Product analysis by ¹H and ¹³C NMR, as well as mass spectrometry, was used to confirm complete hydrogenation. We also have conducted each hydrogenation reaction in methanol and hexane at the same temperature and reaction time to compare our results in supercritical CO₂. Hexane was selected to serve as a condensed-phase model for the nonpolar environment of supercritical CO₂.

Table 1 lists enantioselectivities achieved in the hydrogenation of four α -enamide substrates **3a–d** using the BARF (**1a**) and triflate (**1b**) Rh catalysts in hexane, methanol, and supercritical CO₂. The reduction of enamides **3** proceeded cleanly and quantitatively to provide the α -amino acid derivatives (*R*)-**4** with high enantioselectivity (90.9–99.7% ee) in each solvent.

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(11) UV–vis absorption data were recorded on a Hewlett-Packard 8452A diode array spectrophotometer. The absorption coefficient for **1a** at 455 nm in dichloromethane was determined to be 2.29×10^3 . The solubility of **1a** in supercritical CO₂ was found to be at least 0.030 mM at 40 °C and 5000 psi.

(12) For a discussion of H₂/CO₂ phase behavior, see: Tsang, C. Y.; Streett, W. B. *Chem. Eng. Sci.* **1981**, 36, 993.

(13) Full experimental details are provided as supporting information. Kinetic studies are in progress to determine actual hydrogenation rates in supercritical CO₂.

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(4) This energy difference can be calculated from the Eyring equation. Enantiomeric excess (% ee) is defined as the percentage difference of the two enantiomeric products, i.e., ee = % major enantiomer – % minor enantiomer.

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Table 1. Asymmetric Hydrogenation of α -Enamides **3** with (*R,R*)-Et-DuPHOS–Rh Catalysts (**1**)^a

substrate	R	catalyst	% ee ^b		
			MeOH	hexane	Sc CO ₂
3a	H	1a	98.7	96.2	99.5
		1b	99.4	99.1	99.1
3b	Ph	1a	97.5	98.3	99.1
		1b	99.0	98.7	90.9
3c	3,5-(CF ₃) ₂ C ₆ H ₃	1a	93.2	96.6	91.9
		1b	99.1	98.6	94.6
3d	Et	1a	98.7	96.8	98.8
		1b	99.7	99.6	98.8

^a Reaction conditions in methanol or hexanes: substrate/catalyst = 500, 60 psig of H₂, 40 °C, 24 h. Reaction conditions in supercritical CO₂: substrate/catalyst = 500, 200 psig of H₂, 5000 psig (overall), 40 °C, 24 h. ^b Enantioselectivities were determined by chiral capillary gas chromatography methods using a 25 m Chirasil-L-Val column purchased from Chrompack Inc.

Table 2. Hydrogenation of β,β -Disubstituted α -Enamides with Catalysts **1**^a

substrate	catalyst	% ee		
		MeOH	hexane	SC CO ₂
5	1a	62.6	69.5	84.7
	1b	67.4	70.4	88.4
7	1a	81.1	76.2	96.8
	1b	95.0	91.2	92.5

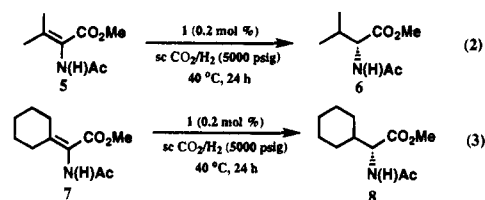
^a See Table 1 for reaction conditions and methods of ee determination.

Significantly, the results in Table 1 clearly indicate that enantioselectivities achieved with this catalyst system in supercritical CO₂ are very high and are comparable to those achieved in conventional solvents.⁹

We also have studied the hydrogenation of β,β -disubstituted α -enamide esters, which have been a difficult class of substrates to reduce with high enantioselectivity. For example, the highest enantioselectivity reported for the hydrogenation of dehydrovaline derivative **5** in conventional solvents was 55% ee using a cationic DIPAMP–Rh catalyst.¹⁴ We have found that the Et-DuPHOS–Rh catalysts **1** outperform all other reported catalysts in the hydrogenation of two representative β,β -disubstituted α -enamide esters, **5** and **7** (eqs 2 and 3). Hydrogenation of enamide **5** in MeOH (60 psig of H₂, 40 °C) led to the valine derivative (*R*)-**6**, in 62.6% ee (catalyst **1a**) and 67.4% ee (catalyst **1b**), respectively (Table 2). Hydrogenation of **5** in supercritical CO₂ (eq 2) led to an exciting result. The enantioselectivity was significantly higher than in methanol or hexane, with (*R*)-**6** being obtained in 84.7% ee (**1a**) and 88.4% ee (**1b**), respectively (Table 2). Enantioselective hydrogenation of enamide **7** with **1a** in supercritical CO₂ afforded the α -cyclohexylglycine derivative **8** in 96.8% ee!

The enantioselectivities observed in the hydrogenation of β,β -disubstituted enamide **5** in supercritical CO₂ are by far the highest achieved with this substrate to date.¹⁴ In order to assess

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the role that high reaction pressure may be playing in our attainment of high selectivities, we carried out two hydrogenation reactions of **5** in hexane at 40 °C with **1a**: one under 200 psig of H₂ pressure and the other under 200 psig of H₂ and a total pressure of 5000 psig with nitrogen gas. Enantioselectivities observed under these conditions were 69.5% ee and 74.5% ee, respectively. These results indicate that simple pressure effects are not responsible for high ee's in the hydrogenation of **5** with catalysts **1**, and they suggest that selectivity enhancement is specifically associated with the use of supercritical CO₂ as a reaction solvent.

To our knowledge, this study is the first report of asymmetric catalysis in supercritical media.^{15,16} These preliminary studies effectively demonstrate the feasibility of conducting highly enantioselective hydrogenation reactions in supercritical CO₂. Importantly, we have shown that higher enantioselectivities may be achieved in supercritical CO₂ relative to conventional solvents. Mechanistic and in-situ kinetic studies as well as further studies on pressure effects have been initiated in an attempt to understand the nature of selectivity enhancement observed in supercritical CO₂. Moreover, we are further optimizing these and other reactions in SCFs in an effort to define the potential of these novel media for asymmetric catalysis.

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Supporting Information Available: Description of high-pressure view cell as well as procedures for catalytic hydrogenations, product analyses, UV–vis studies on catalyst solubility, and synthesis of catalyst **1a** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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