Cyclopropanation Enantioselectivity Is Pressure Dependent in Supercritical Fluoroform**

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In liquid solvents the enantioselectivity of asymmetric catalysis is dependent on the solvent pressure, but only over extremely large pressure ranges of several kbar.[1–3] Supercritical fluids (SCFs), with their tunable dielectric constants and high compressibilities, offer the possibility of pressure-dependent selectivity at much lower pressures. This possibility has been realized for uncatalyzed diastereoselective reactions,[4, 5] enzymatic catalysis,[6, 7] and conformational equilibria,[8] but not yet for homogeneous catalysis. Herein we describe the first example of enantioselective homogeneous catalysis that is dependent on solvent pressures below 100 bar.

A number of factors can affect the rates or selectivities of reactions in SCFs,[9–12] but the dielectric constant (ε) is the factor we have chosen to exploit in our preliminary studies. At 30 °C the dielectric constant of fluoroform (scCHF$_3$, T_c = 25.9 °C, P_c = 48.2 bar) varies greatly with pressure (Figure 1, right axis).[13] At low pressures the dielectric constant of scCHF$_3$ is 1–3, meaning that it is a very nonpolar solvent analogous to liquid pentane. At high pressures, however, the dielectric constant is 6–8, and the solvent is as polar as ethyl acetate or THF. Thus it is possible, by changing the pressure, to test the effect of changing the solvent's dielectric constant on the enantioselectivity of a reaction *without changing solvents.*

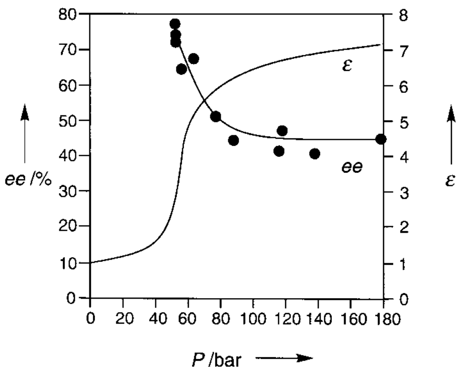
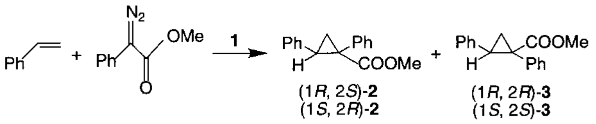


Figure 1. The dependence of the *ee* of product **2** and the dielectric constant[13] of scCHF$_3$ on the pressure. Conditions: 1 h reaction, 30 °C, 0.69 µmol catalyst, 56 µmol diazo reagent, 440 µmol styrene, 160 mL vessel.

We chose to test a cyclopropanation reaction between styrene and methyl phenyldiazoacetate catalyzed by the *tert*-butylbenzenesulfonyl-L-prolinate dirhodium catalyst **1**[14, 15] in scCHF$_3$ [Eq. (1)]. Liquid-phase studies of this reaction[16] and a related reaction[15, 17] have found a strong solvent dependence. The enantiomeric excess (*ee*) of the major product **2** was 61% for the reaction in methylene chloride (ε = 9.08) and 85% in pentane (ε = 1.84), the major enantiomer being (1*R*,2*S*).[16] The explanations offered by Davies et al.[17] and Doyle et al.[16] invoke only the polarity of the solvent rather than its coordinating ability or any other solvent property. Hence we anticipated that the enantioselectivity of this reaction should be strongly pressure dependent in scCHF$_3$.



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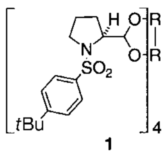

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Our results (see Figure 1) show that this is indeed the case, especially near the critical point of the solvent. The reaction was performed repeatedly in scCHF$_3$ at 30 °C, each reaction at identical molar concentrations of reagents and catalyst but with different pressures of the SCF. Although the critical pressure of CHF$_3$ is 48.2 bar, no experiments were attempted at pressures below 52 bar because of insufficient solubility of the reagents under such conditions (see the supporting information). Very low concentrations of reagents were used so that the critical point of the mixture would be very close to that of pure CHF$_3$. The enantiomeric excess of product **2** varied from 40% *ee* for reactions performed at pressures above 100 bar ($P_r = P/P_c = 2.07$) to as high as 77% *ee* for those at 52 bar ($P_r = 1.08$).

In contrast, the enantioselectivity is pressure independent in scCO$_2$, within experimental error. At 34 °C the selectivity was 83% *ee* at 79 bar ($P_r = 1.07$), 84% *ee* at 96 bar ($P_r = 1.30$), and 80% *ee* at 110 bar ($P_r = 1.49$). The lack of variation in enantioselectivity is presumably due to the fact that the dielectric constant of scCO$_2$ increases only slightly with pressure, ranging between 1.3 and 1.5 under these conditions.[18] Thus, varying the pressure and density has little effect on enantiomeric excess in the absence of a dielectric constant change. We can also conclude that cyclopropanation enantioselectivities in scCO$_2$ are as good as the best results in liquid solvents.

If the selectivity trends observed in scCHF$_3$ are due to the variation in dielectric constant, then the enantioselectivity should change in scCHF$_3$ as the dielectric constant changes near the critical point. It is evident from Figure 1 that this is the case. An alternative presentation of the data, a plot of enantiomeric ratio versus the dielectric constant of the reaction medium (Figure 2), shows that the scCHF$_3$ data

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[**] We gratefully acknowledge Dr. Huw Davies and Dr. Susan Tucker for helpful discussions, UC-Davis and the EPA/NSF Partnership for Environmental Research for funding, Mrs. Heidi Sickafoose for assistance in equipment design, and especially Dr. Michael Doyle for advice and a preliminary supply of catalyst.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

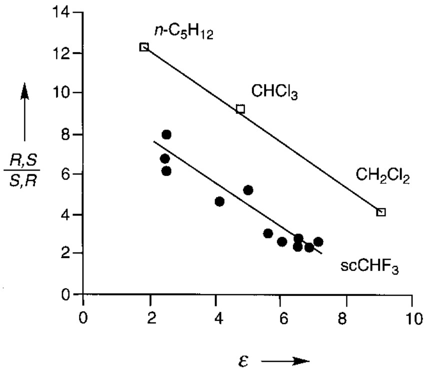

Figure 2. The dependence of the ratio of enantiomers of **2** on the dielectric constant of scCHF_3 at the conditions of Figure 1. The result in liquid chloroform is new data, while the results in CH_2Cl_2 and pentane are those reported by Doyle et al.[16]

exactly parallels the trend observed in liquids. There are two other explanations of the results, but they are both considered less plausible than a dielectric constant effect: a) the catalyst could be less soluble in scCHF_3 at the lower pressures, but that would most likely cause a decrease in the *ee*, not an increase (see the supporting information for more evidence against this explanation), and b) the delivery of the diazoacetate into the vessel could be slower or less complete at lower pressures of scCHF_3 than at higher pressures, but tests showed that halving the amount of diazoacetate at 150 bar has no effect on the enantiomeric excess within experimental error. We are currently investigating the cause of the lower selectivity in scCHF_3 relative to liquids. Whatever the cause, it does not seem to decrease the enantioselectivity in scCO_2. The development of a method for the gradual addition of the diazoacetate may increase the enantioselectivity.

The solvent dependence of the enantioselectivity has been proposed to be due to the stabilizing effect of polar solvents on charge-separated transition states,[17] although the stability of different rotamers of the catalyst may also be affected by solvent polarity.[16, 17] Our data is entirely consistent with a polarity effect, and there is no need to invoke either the coordinating ability of the solvent or "clustering" near the critical point to explain the observations.

SCFs are unique tools for probing solvent effects because the properties of a single medium can be varied continuously. This example demonstrates that pressure-controlled variation of the dielectric constant allows the researcher to tune the selectivity of a reaction by adjusting the pressure. Thus, SCFs are the tunable analogues of liquid solvents, just as homogeneous catalysts are the tunable analogues of heterogeneous catalysts.

Experimental Section

Reactions were performed by placing **1** (0.69 μmol), styrene (440 μmol), and a stir bar in a 160-mL high-pressure vessel, which was then sealed and warmed to 303 K in a water bath. The vessel was purged and pressurized with CHF_3 to at least P_c but below the desired reaction pressure. After a 10 min delay to allow for dissolution of the styrene, methyl phenyldiazoacetate (56 μmol) was injected with an HPLC-style injector. This diazoacetate was then flushed into the vessel by the remaining CHF_3 required to bring the pressure up to the desired level. After 1 h the reaction was stopped by submerging the vessel in a dry ice/acetone bath until the pressure fell to approximately 1 bar. The vessel was then vented and allowed to warm to room temperature. The product was dissolved in acetone and the *ee* determined by GC (Chirasil-DEX CB column, 170 °C). Tests to ensure repeatability and solubility are described in the supporting information.

Received: September 10, 1998 [Z12398IE]
German version: *Angew. Chem.* **1999**, *111*, 1213–1215

Keywords: enantioselective reactions · homogeneous catalysis · pressure effects · solvent effects · supercritical fluids

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