Pressure-dependent enantioselectivity in the organozinc addition to aldehydes in supercritical fluids

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Abstract

Amino alcohol-catalyzed asymmetric alkylation of benzaldehydes by dialkylzincs can be achieved in supercritical fluoroform (scCHF$_3$) and supercritical ethane (scC$_2$H$_6$) with high conversion and enantioselectivity. The higher enantioselectivity in ethane compared to CHF$_3$ suggests that solvent polarity affects the reaction. The enantioselectivity in scCHF$_3$ is strongly pressure dependent. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Because liquid solvents have very low compressibility, pressure has very little effect on the enantioselectivity of asymmetric catalysis in liquid solvents, except at extremely high pressures [1–6] or when the high pressure is induced by one of the reagents, as in hydrogenation [7]. However, the high compressibilities of supercritical fluids (SCFs), especially near their critical points, make pressure effects on reactions in SCFs far more likely to occur at low pressures. Observations of altered selectivities [8–15] or rates [10,16–26] of reactions in SCFs as functions of pressure have been reported by a number of research groups. Several reviews have been published in this field over the last 15 years [27–30]. To date, however, there has been only one clear example of pressure-dependent asymmetric homogeneous catalysis in a SCF, reported recently by Wynne et al. [14,15]. In that work, the enantiomeric purity (reported as enantiomeric excess (e.e.) defined in Eq. (1), below) of a cyclopropanation product was found to vary monotonically with the pressure, and hence the dielectric constant, of CHF$_3$.
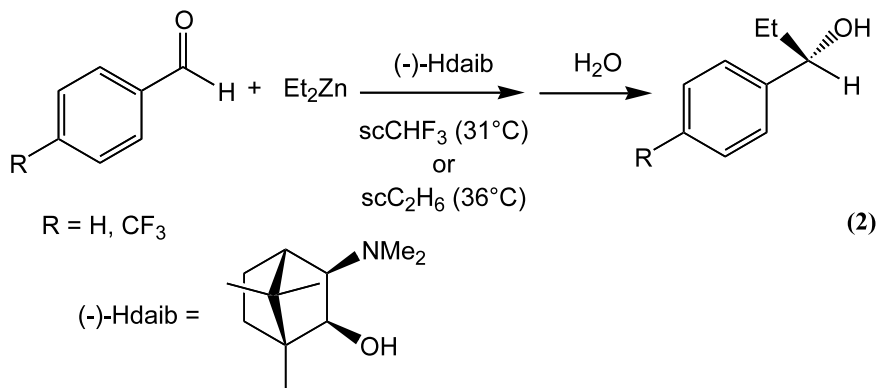
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$$e.e. = \left(\frac{\%A - \%B}{\%A + \%B}\right) \times 100\%, \qquad (1)$$

where A is the major enantiomer and B is the minor enantiomer.

In the present communication, we describe another example of pressure-dependent enantioselective catalysis in SCFs; namely, the alkylation of benzaldehydes with dialkylzincs (Eq. (2)).

$$(2)$$

The dinuclear zinc complex, $Zn_2(R)_2(daib)_2$ (daib = $(2S)$-($-$)- or $(2R)$-($+$)-3-*exo*-(dimethyl-amino)isoborneolate, $R = CH_3$ or C_2H_5), shown to be a catalyst precursor for the alkylation of aldehydes in liquid solvents [31–35], has now been found to be effective for this reaction in supercritical media such as scCHF$_3$ ($T_c = 26$ °C, $P_c = 48$ bar) or scC$_2$H$_6$ ($T_c = 32$ °C, $P_c = 49$ bar). There were indications in the liquid phase studies [35] that varying enantioselectivities in different solvents might be inversely related to solvent polarity, measured as the dielectric constant. However, it is also a possibility that solvent coordinating ability plays a role in determining selectivity. Since the dielectric constants of SCFs are known to change monotonically with pressure, SCFs are an ideal medium to study certain solvent effects. In particular, the dielectric constant of scCHF$_3$ at 30 °C rises from 1.0 at 0 bar to approximately 7.0 (comparable to THF) at high pressures, while the coordinating ability of CHF$_3$ is assumed to be negligible at all pressures within this range (see Appendix A). Thus, tests of this reaction in scCHF$_3$ at different pressures allow one to evaluate the effect of dielectric constant on enantioselectivity, independent of solvent coordination effects.

2. Experimental

Since our work was performed in the near-critical regime, extremely dilute conditions were used in order to guarantee solubility of the reagents in the SCF. Our experimental method was as follows. First, a 50 ml steel vessel was dried, in an otherwise empty oven, at 100 °C overnight, cooled under vacuum, and filled with argon. To this vessel were added 0.30 ml of a 1.0 M $Zn(C_2H_5)_2$ hexane solution and either 5 μmol of $Zn_2(CH_3)_2(daib)_2$ or 10 μmol of Hdaib. (Although the reaction is famous for exhibiting the phenomenon of amplification of chirality when optically impure Hdaib is used [31], only pure ($-$)-Hdaib was used in the present study.)

The vessel was then heated to the reaction temperature for 2 h under a few bars pressure of the SCF (CHF$_3$, C$_2$H$_6$, or CO$_2$). After this, the SCF pressure was increased. While the SCF was being pumped into the reaction vessel, 200 μmol of benzaldehyde was injected into a sample loop connected to a switching valve. When the pressure in the vessel reached 80–90% of the desired level, the valve was rotated so that the remaining SCF flowed through the sample loop, carrying the sample of benzaldehyde contained therein into the reaction vessel. This was the start of the reaction. After 2 h, the vessel was cooled in a bath of dry ice/CH$_2$Cl$_2$ until the pressure was constant. The remaining pressure was released and the vessel allowed to warm to room temperature. A large excess (~ 15 ml) of a concentrated NH$_4$Cl

aqueous solution was injected into the vessel to quench the reaction. The organic materials were extracted from the resulting solution with ethyl acetate, dried with anhydrous sodium sulfate, and filtered. After removal of the ethyl acetate, the conversion was determined by ^{1}H NMR spectroscopy of the product mixture in $CDCl_3$. The conversion was typically between 99 and 100%. An experiment with a reaction time of only 30 s at 60 bar and 32 °C had a conversion of 6.7%. In the absence of any Hdaib or $Zn_2(CH_3)_2(daib)_2$, no product was observed after 2.5 h at 51 or 60 bar. The potential byproducts benzoic acid, benzyl alcohol, acetophenone and propiophenone were never detected in the NMR spectra. However, when the alkylation was performed in $scCO_2$, benzyl alcohol was detected by gas chromatography. The e.e. of 1-phenylpropanol was determined by GC of the product mixture. The absolute configuration was determined by comparison to the GC of a known sample of (S)-1-phenylpropanol. GC analysis was performed with a Chrompack CP-cyclodextrin-β-236-M-19 fused silica 50 m × 0.25 mm capillary column at 125 °C, injector at 200 °C, detector at 230 °C, carrier gas He 150 kPa, 69 ml/min, 50:1 split. The scatter on the e.e. of a single sample was less than 0.2%, determined by multiple injections of a typical sample.

The alkylation of 4-(trifluoromethyl)benzaldehyde was performed similarly. The identification of 1-(4-(trifluoromethyl)phenyl)-1-propanol was confirmed by GC/MS (30 m × 0.25 mm TC-17 column, 100–130 °C at 1 °C/min, injector and detector at 200 °C, carrier gas He at 70 kPa, 1.1 ml/min, split injection 91:1). The highest detected peak was the molecular peak and the strongest peak was $(M - C_2H_5)$.

Unlike the dimethyl catalyst precursor, $Zn_2(C_2H_5)_2(daib)_2$ cannot be isolated and must be prepared in situ from $Zn(C_2H_5)_2$ and either Hdaib or $Zn_2(CH_3)_2(daib)_2$. Tests at 60 bar in $scCHF_3$ showed that the same e.e. and conversion were observed with Hdaib or with $Zn_2(CH_3)_2(daib)_2$.

In the alkylation of benzaldehyde in mixed benzaldehyde/hexanes, the benzaldehyde was purified by first washing with 1 M sodium hydroxide, followed by saturated sodium sulfite and

water. The organic layer was then dried over magnesium sulfate and filtered. The dried benzaldehyde was then distilled trap-to-trap under high vacuum. Finally, the benzaldehyde was dried over neutral activated alumina and filtered. The alkylation was carried out in a nitrogen-filled inert atmosphere glove box under positive pressure. To a 25-ml cone-shaped flask was added 7.9 mg of (−)-Hdaib, followed by 3.0 ml of benzaldehyde and 2.35 ml of 1 M diethylzinc in hexanes solution. A stir vane was added and the reaction was allowed to proceed for 5 h, at which time the reaction was quenched with approximately 5 ml of saturated ammonium chloride. The organic layer was analyzed directly by capillary gas chromatography as above.

It is known that, as any batch of the catalyst precursor ages, the first noticeable effect is that the enantioselectivity begins to drop. Therefore, the series of reactions was carefully scheduled to make sure that such aging was not the cause of the observed pressure effects. So, after a reaction giving a low e.e., another reaction was run at high pressure to make sure that the low e.e. was not caused by catalyst precursor decomposition.

Visual observations of reactions and phase behavior were made by use of a vessel fitted with sapphire windows. This vessel enabled us to perform qualitative solubility tests on the system. By using this vessel, it was found that diethylzinc/hexane (0.31 ml of 1 M solution) was insoluble in 50 ml of $scCHF_3$ at 36 bar, but soluble at 47 bar. Benzaldehyde (50 μl, 0.5 mmol) was insoluble in 50 ml of $scCHF_3$ at 46 bar, but soluble at 50 bar. At the latter pressure, "waviness" was observed, but this effect disappeared at 57 bar. Visible observations of actual reaction conditions showed no sign of precipitation of reagents when pressurized beyond 50 bar (the system was not visually observed below this pressure).

3. Results

The results show that both $scCHF_3$ and scC_2H_6 as media for this reaction allow high enantioselectivity even at temperatures as high as 36 °C (Table

1). Also, the conversions in these reactions were uniformly high, at 98–99.7%. Use of scC_2H_6 at 36 °C gives a high e.e., equal to that obtained in liquid toluene at 0 °C, while $scCHF_3$ at 31 °C gives enantioselectivities comparable to that obtained in THF/toluene at lower temperatures.

Variation of the pressure of $scCHF_3$ has a very unusual effect on the enantioselectivity (Fig. 1a). Well above the critical pressure, the enantiomeric excess is constant at 86–89% (six results at pressures from 59 to 209 bar). Below the critical pressure, the e.e. is higher (92–95%); at these low pressures the reaction probably takes place in the liquid hexane which remains undissolved in the insufficiently-dense CHF_3 phase. Near the critical pressure, the e.e. drops to only 77–79% (five results at 49–52 bar in addition to an outlier of 70% at 52 bar). Ethylation of 4-(trifluoromethyl)benzaldehyde gave the same unusual pressure effect. Plotting the e.e. versus ε_r in $scCHF_3$ and scC_2H_6 results in the non-monotonic curve seen in Fig. 1b.

Table 1
Comparison of liquid and supercritical media for the ethylation of benzaldehyde, in order of increasing dielectric constant

Solvent	ε_r[a]	T (°C)	e.e. (%)
scC_2H_6 (240 bar)	1.3[b]	36	98[c]
$scCO_2$ (150 bar)	1.5[d]	36	25[c]
2:1 Hexane/toluene	2.3	0	98[e]
Toluene	2.3[f]	50	89[e]
Toluene	2.4[f]	0	98[e]
2:1 Ether/toluene	3.8	0	99[e]
$scCHF_3$ (60 bar)	5.2[g]	31	89[c]
2:1 THF/toluene	5.8	0	91[e]
1:1 Benzaldehyde/hexanes	8.5[h]	25	96[c]

[a] Estimated dielectric constants, except where noted, were obtained by a mixture of extrapolation and interpolation of data compiled by Akhadov [59].
[b] Reported by Younglove and Ely [60].
[c] This work.
[d] Reported by Moriyoshi et al. [61].
[e] Reported by Noyori et al. [35].
[f] Reported by Bergholm [62].
[g] Reported by Makita et al. [63], as summarized in Downing [64].
[h] Dielectric constant is for a 1:1 mixture of octane and benzaldehyde at 25 °C.

A number of experiments were undertaken to determine the effect of changing certain conditions. When dimethylzinc was used as the alkylating agent, the alkylation was unsuccessful in $scCHF_3$. (In liquid solvents the methylation reaction is known to be approximately 20 times slower than the corresponding ethylation [36].) Also, the ethylation does not proceed in liquid solvents at the high dilutions used in the supercritical experiments. This could be due to sensitivity of this reaction to trace impurities in the liquid solvents. Indeed, we have seen in the present study that impurities in the gas supply cause low yield and selectivity. Use of 1:1 benzaldehyde/hexanes as the solvent yielded a higher enantioselectivity than 2:1 THF/toluene, even though benzaldehyde has a much higher dielectric constant than THF. Finally, this reaction was also attempted in $scCO_2$, but a somewhat lower conversion (less than 90%, based on loss of benzaldehyde) was obtained, along with drastically lower chemo- and enantioselectivities.

4. Discussion

In literature examples of pressure-dependent rates or selectivities near the critical point, a number of inter-related causes have been suggested; dielectric constant changes [14,15,17], viscosity/diffusivity changes [21,25,37,38], solubility changes, clustering effects [10,21,22,25,26,39,40], cage effects [41,42], solvent parameter changes, and electrostriction/partial molar volume/activation volume effects [18–20,23,24,43]. In many of the literature studies it has not been possible to conclusively identify the factors which are responsible for the pressure dependence. This is also the case in the present study. However, several factors can be considered as potentially contributing to the effect. The true reason may be a combination of these factors.

4.1. Solvent polarity

As described in the introduction, the liquid phase results in the literature are not definitive in showing whether the alkylation selectivity is con-
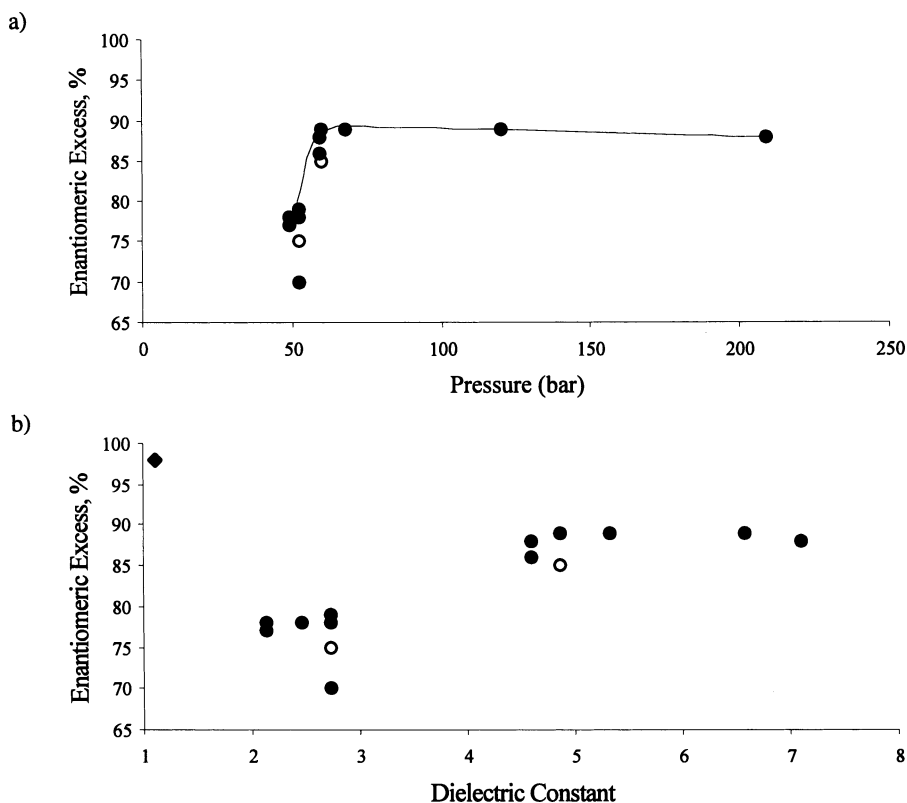
Fig. 1. Enantioselectivity (as % e.e.) of alkylation as a function of (a) SCF pressure and (b) dielectric constant: ●, C_6H_5CHO in CHF_3 at 31 °C; ○, $4-F_3C-C_6H_4CHO$ in CHF_3 at 31 °C; ◆, C_6H_5CHO in C_2H_6 at 36 °C. Note that the dielectric constants are for the pure SCFs and not the reaction mixtures. The difference may be significant for the near-critical pressures.

trolled by the solvent's polarity or its coordinating ability. It would be chemically reasonable to suppose that both factors are involved, at least in liquid solvents. The new results in high pressure SCFs (that is, well above P_c) lend strength to the argument that the e.e. is dependent on dielectric constant—the e.e. in scC_2H_6 was much greater than that in $scCHF_3$. Neither of these SCFs has any significant coordinating ability.

There are some discrepancies, however. First, in the original work [35], it was seen that an ether/toluene solution gave the highest e.e., even though the dielectric constant of that mixed solvent was intermediate between THF/toluene and pure toluene. Second, a reaction performed in benzaldehyde/hexanes (considerably more polar than THF/toluene) gave a much higher e.e. than in THF/toluene. Finally, there is the issue of the odd

behavior of the relationship between e.e. and pressure of CHF_3 seen in Fig. 1a and the non-monotonic dependence of the e.e. on the dielectric constant of the SCF (Fig. 1b).

This behavior contrasts with the case of olefin cyclopropanation [14,15] in $scCHF_3$, which shows a monotonic dependence of enantioselectivity on pressure. (In a case of enzyme-catalyzed transesterification in $scCHF_3$, a graph was presented of subtilisin Carlsberg enantioselectivity versus pressure, in which it appears that non-monotonic behavior is seen [12]. However, this appears to be an artifact of the curve fitting.)

A possible explanation for the dip is the effect of the solvent dielectric constant on all four of the possible transition states. As shown in Fig. 2a, there are two Si-transition states (leading to the S product), and two Re-transition states (leading to

the *R* product). Calculations by Yamakawa and Noyori [44] for the methylation of benzaldehyde show that the *syn* transition states, with their 1,3-*syn* oriented Zn^+–R^- bonds, are higher in energy than the *anti* transition states. Calculated dipole moments [45] show that the *syn*–*Re* and especially the *syn*–*Si* transition states are also significantly more polar. The *syn* transition states would therefore be preferentially stabilized in a

polar medium. Although the *anti*–*Si* pathway predominates in a nonpolar solvent, the *syn* pathways would compete more effectively in a polar solvent. If the preferential solvation of the *syn* transition states overwhelms the difference between the gas-phase energies of the *anti*–*Si* and *syn*–*Si* transition states, then *syn*–*Si* would become the major pathway (Fig. 2b). At the point where the two *Si* transition energies cross, the
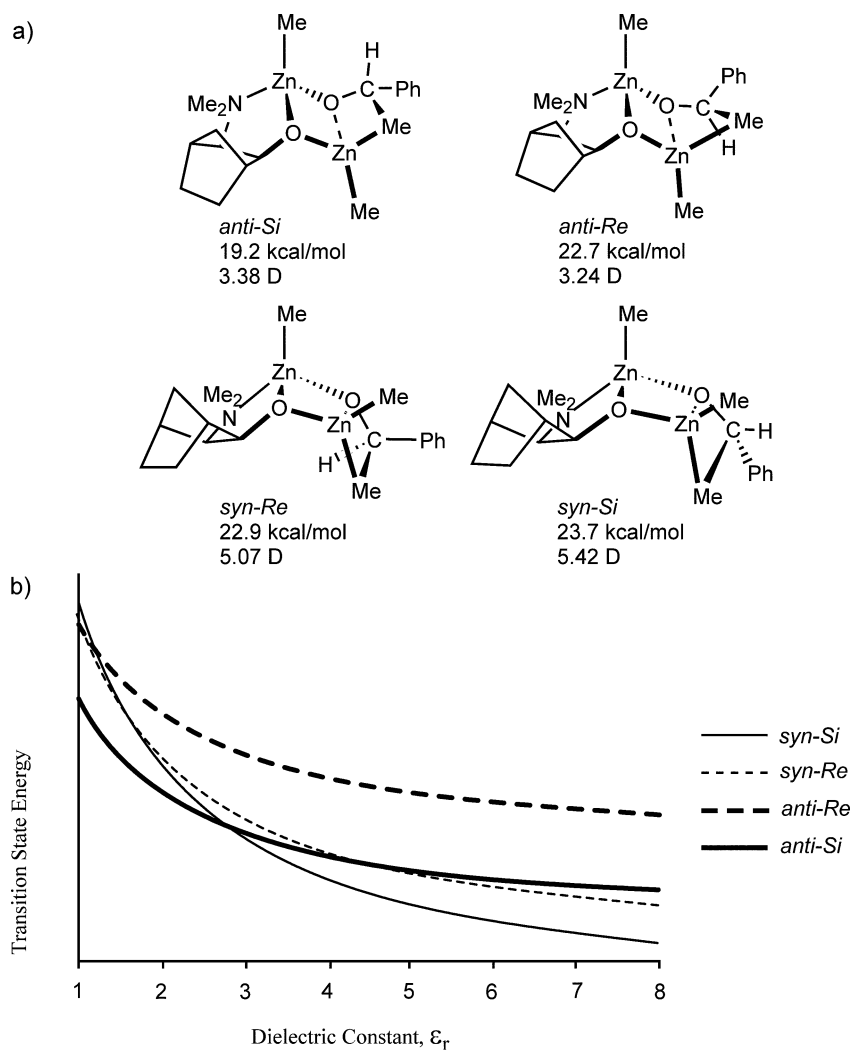

Fig. 2. (a) The structures, gas-phase energies, and dipole moments for the four transition states predicted in an ab-initio molecular orbital study by Yamakawa for the Hdaib catalyzed methylation of benzaldehyde by $ZnMe_2$ [45]. The methyl groups on Hdaib are omitted for clarity. (b) Possible dependence of the transition state energies on solvent dielectric constant, ε_r, showing that the two *syn* transition states, being more polar, drop in energy more rapidly than the *anti* states. If the curves were to cross, as shown here, then a dip in the curve at that dielectric constant would be expected.

syn–Re pathway is best able to compete, causing a drop in selectivity. The selectivity would rise again at higher dielectric constant as the energy gap between the *syn–Si* and *syn–Re* transition states continues to increase. However, there is no evidence at this point that the solvation energy is strong enough for this scenario to occur.

4.2. Solubility

The cause of the non-monotonic behavior is not likely to be insolubility of the reagents; the $ZnEt_2$/hexane solution (0.31 ml) and benzaldehyde are both soluble in $scCHF_3$ at 31 °C and 50 bar and at the concentrations used in the reactions. At lower pressures, however, both of these reagents are insoluble in CHF_3, and the reaction proceeds in liquid hexanes. If, despite the visual observations, there were an indetectably small volume of liquid phase remaining in the vessel at 50–51 bar, then the enantioselectivity could be affected. If the liquid phase were predominantly hexane or benzaldehyde, then a much higher e.e. would be expected based upon experiments in liquid hexane and in liquid benzaldehyde. This would not explain the observed selectivity. An equally unlikely explanation would be a liquid phase of predominantly fluoroform, because the dielectric constant of that phase would not be much higher than that of high-pressure $scCHF_3$. The only likely mechanism by which an undetected liquid phase could cause the lower e.e. values is the existence of partitioning effects between the liquid and fluid phases, causing an unequal distribution of reagents, which would have an unpredictable effect on the e.e. Although visual observations do not support the existence of a liquid phase at those pressures, it cannot be entirely ruled out until a more thorough phase behavior study of the reaction mixture is performed.

4.3. Clustering

Solute/solute clustering is also unlikely to be the cause. We suspected that clustering of the benzaldehyde about the catalyst molecule could have occurred at near-critical pressures, and therefore the local environment around the catalyst would have had a higher dielectric constant and a higher benzaldehyde concentration than the bulk. To simulate this phenomenon, a trial reaction was performed with mixed 1:1 benzaldehyde/hexanes as the solvent. This gave a high e.e. of 96% when performed at room temperature. Therefore, it is unlikely that this is the cause of the low e.e. at near-critical pressures.

4.4. Electrostriction

A fourth possibility is electrostriction, in which dipolar attractive forces result in local compression of the solvent around the solute. If the four diastereomeric transition states in the stereoselective step have different dipole moments, and therefore cause electrostriction of the solvent to different extents, the activation volumes and energies of the competing reactions would be altered. With electrostriction, polar species are stabilized preferentially over nonpolar species in a polar medium. The more polar the species is, the more it would be stabilized in a polar medium. The same might be true for transition states. Thus, if the difference in polarities of the four transition states is greater than the differences in polarities of reactants and of products, a dip in enantioselectivity might be seen. This concept is discussed in more detail in Appendix B and in the accompanying paper by Parsons et al. [46], who predict that, although electrostriction will most likely play a role, it is unlikely to be the cause of the non-monotonic behavior.

4.5. Other factors

Differences in activation volume due to bond breaking or forming can be large [47]. This, and any of the other factors mentioned above, could influence one or more of the many preequilibria in this system.

5. Conclusion

In conclusion, we have demonstrated the alteration of the enantioselectivity of homogeneous

alkylation by adjusting the pressure of the reaction medium close to its critical point. However, a dip in the enantioselectivity at the critical point was not predicted, and could not be explained as an effect of solubility, clustering or electrostriction. The cause of the dip is unclear, but may lie in the effect of changing solvent polarity on the relative energies of the four transition states, in an unobserved phase transition in the reaction mixture, or in the effect of a combination of factors on the many preequilibria in this complicated catalytic system [31,35,36].

Appendix A. The coordinating ability of fluoroform

It is believed to be unlikely that fluoroform is sufficiently coordinating to influence a transition-metal complex catalyzed reaction, but there is little direct evidence for or against this supposition. Circumstantial evidence suggests that hydrofluorocarbons such as fluoroform are weaker ligands than chloroform or methylene chloride and stronger than hexane.

The ability of a solvent to coordinate is often quantified in terms of its donicity (electron-pair donating ability) on any of several scales. Although the donicity of saturated hydrofluorocarbons such as CHF_3 is not available, the donor number of CF_3CH_2OH is zero (equal to hexane) [48], and the donor number of fluorobenzene ($DN = 3$) shows that it is less donating than $CHCl_3$ (4) and more than hexane [49]. Perfluoroalkanes are less donating than alkanes and $CHCl_3$ according to both the Kamlet–Taft β parameter and the SB parameter [49].

Hydrofluorocarbons may be more coordinating than fluorocarbons, but there is no data confirming this. Another way to evaluate this would be to look at whether chloroform has greater donicity than CCl_4. The donor number of $CHCl_3$ ($DN = 4$) is greater than CCl_4 (zero) but much less than ether (19) [49]. The SB parameter of $CHCl_3$ ($SB = 0.071$) is not much greater than CCl_4 (0.044) and much less than ether (0.562). In terms of the Kamlet–Taft β parameter, $CHCl_3$ ($\beta = 0.10$) is no more donating than CCl_4 (0.10) and much less than ether (0.47) [49]. By analogy, CHF_3 is not expected to be much more coordinating than a perfluorocarbon.

We also note that there are no examples, in the Cambridge Crystallographic Database, of a fluorocarbon or a hydrofluorocarbon as an unsupported ligand on a metal (other than alkali metals) while there are known examples of complexes containing CH_2Cl_2 as a ligand [50,51]. Reviews have listed examples of weak *intra*molecular interactions between a metal and a carbon-bound fluorine [52,53], including one example of a weak intramolecular interaction between Zn^{2+} and a CF_3 group (Zn–F distance 2.8 Å, sum of van der Waals radii 2.86 Å) [54]. The lack of intermolecular examples suggests that this type of interaction is particularly weak.

Fast time-resolved IR measurements [55] have examined the reactivity of fluoroform to unsaturated $Cr(CO)_5$ moiety in scCHF_3. Preliminary results indicate that fluoroform is not significantly more coordinating than conventional alkanes such as heptane. Further work is in progress to quantify the differences in reactivity of these weakly coordinating token ligands.

In conclusion, fluoroform is likely to be more weakly coordinating than solvents such as $CHCl_3$ or CH_2Cl_2, which are normally considered to be "noncoordinating". Any interaction between fluoroform and a metal center is likely to have a very

short lifetime. We cannot, however, rule out the possibility that fluoroform could interact with other species in solution, for example by hydrogen bonding.

Appendix B. A model illustrating the potential effect of electrostriction on enantioselectivity

One of the factors that might have caused the dip in the graph of e.e. versus pressure of CHF_3 is *electrostriction*, which is the increase in density of the solvation sphere due to favorable intermolecular electrostatic forces between solute and solvent [56]. Electrostriction only occurs to a significant extent if the solute is polar and the solvent is compressible [57]. Within the "compressible region" of a supercritical solvent (typically within approximately 10 degrees and 10 bar of the critical point) the compressibility is high enough for electrostriction to be facile and significant. If electrostriction occurs around the reagents or transition states of a reaction, then the local dielectric constant is enhanced, relative to that of the bulk solvent; polar solutes or transition states are thus stabilized [58].

How could electrostriction around the transition states affect enantioselectivity? The following is a model illustrating that it is possible. Consider a system in which the observed product e.e. is greater if the reaction is performed in a nonpolar liquid solvent. The two enantiomeric products are formed via two diastereomeric transition states, which will be called $[R]^{\ddagger}$ and $[S]^{\ddagger}$ respectively. Let us assume that the selectivity is due to the energy difference between the transition states. If S is the major product, then $[R]^{\ddagger}$ is higher in energy than $[S]^{\ddagger}$ (Fig. 3a). The lower e.e. in polar media indicates that $[S]^{\ddagger}$ is less polar than $[R]^{\ddagger}$, although both transition states must have some polarity. The relative energies of the two transition states vary with the dielectric constant of the medium as illustrated by the solid lines in Fig. 3a. The ΔE ($= E_{[R]^{\ddagger}} - E_{[S]^{\ddagger}}$), which is related to the selectivity, varies as shown in Fig. 3b (solid line). As the dielectric constant is decreased from high values (or as the pressure of the SCF is lowered from high values), the selectivity increases. Electrostric-
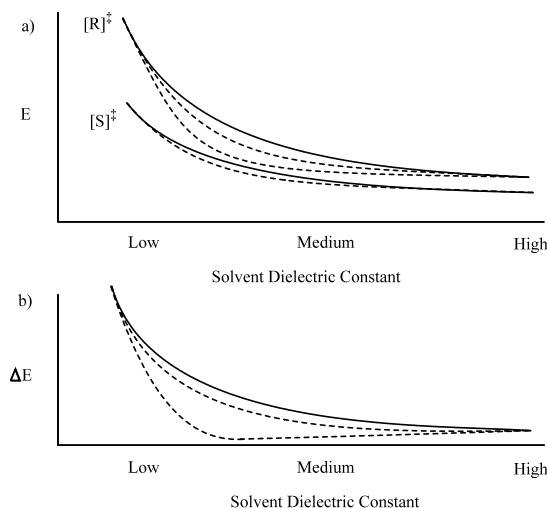

Fig. 3. (a) Energy levels for the transition states $[S]^{\ddagger}$ and $[R]^{\ddagger}$, which lead to the S and R products, respectively. The solid lines assume that dielectric constant is the only factor which affects the transition state energy, while the dashed lines include the effect of electrostriction at intermediate dielectric constants (i.e. intermediate SCF densities). Two dashed lines for the more polar transition state $[R]^{\ddagger}$ are shown; the lower of these represents a stronger case of electrostriction. All curves are monotonic. (b) The dependence of ΔE ($= E_{[R]^{\ddagger}} - E_{[S]^{\ddagger}}$) on dielectric constant, based upon the above curves. If the electrostriction around $[R]^{\ddagger}$ is significantly stronger than that around $[S]^{\ddagger}$, then a non-monotonic curve of ΔE vs. ε_r would result (lowest dashed curve, based upon the stronger case depicted in Fig. 3a).

tion only becomes a factor near the critical point of the SCF, where the SCF becomes compressible and its dielectric constant is in the middle of its range. In this compressible regime, electrostriction can occur, increasing the local dielectric constant around the more polar transition state $[R]^{\ddagger}$ to a greater extent than around the less polar transition state $[S]^{\ddagger}$ and thus stabilizing $[R]^{\ddagger}$ more than $[S]^{\ddagger}$ as shown by the dashed lines in Fig. 3a [58]. Thus, the selectivity at the critical point is decreased by electrostriction relative to what you would expect from dielectric constant control, as shown by the dashed lines in Fig. 3b. As one lowers the dielectric constant of the solvent (or the pressure of the SCF) from high values to medium values, the enantioselectivity rise expected due to the dielectric constant change is diminished by the effect of electrostriction. One

can then predict that *electrostriction, when it occurs, will counteract the effect that a decrease in dielectric constant has on the enantioselectivity*.

In an extreme case, it is possible that electrostriction could more than compensate for the dropping dielectric constant, driving the e.e. in the other direction and giving a non-monotonic dependence of selectivity on ε_r (Fig. 3b, lowest curve). However, this extreme case is not supported by the calculations of Tucker et al. [46].

We have assumed, in this analysis, that increasing solvent polarity would not result in changes in the structures of the transition states. If, however, the structures were to change, then the situation would become considerably more complicated and the potential energies would deviate unpredictably from the generic curves presented in Fig. 3.

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