

# Use of scandium tris(trifluoromethanesulfonate) as a Lewis acid catalyst in supercritical carbon dioxide: efficient Diels–Alder reactions and pressure dependent enhancement of *endo*:*exo* stereoselectivity

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Received (in Liverpool, UK) 20th May 1999, Accepted 15th June 1999

The Diels–Alder reaction between various acrylates and cyclopentadiene in supercritical CO<sub>2</sub> are catalysed by scandium tris(trifluoromethanesulfonate); optimisation of CO<sub>2</sub> density leads to increased *endo*:*exo* selectivities compared to those obtained in conventional solvents.

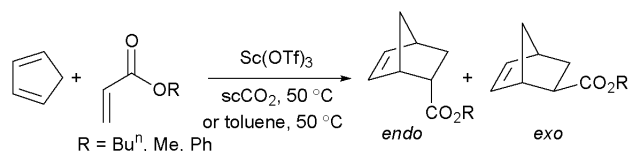
The use of supercritical carbon dioxide (scCO<sub>2</sub>) as an environmentally friendly non-toxic alternative to common organic solvents is an area of significant current interest.<sup>1</sup> Alongside the environmental aspects, scCO<sub>2</sub> also has additional benefits as a reaction medium, such as its ready availability, ease of removal and disposal and/or recycling. Other advantages which are particularly relevant for carrying out reactions in scCO<sub>2</sub> are: fine control of solvent properties by changes in temperature and pressure (*vide infra*); the ability to homogenise reaction substrates, electrically neutral metal complexes and gases like oxygen and hydrogen; enhanced diffusion rates; and potential for product processing.<sup>2</sup>

More recently, it has become apparent that there are more significant benefits to carrying out reactions in scCO<sub>2</sub>. In our own laboratories we have recently reported that dramatic enhancements of diastereoselectivity are possible compared to those obtained in conventional solvents, simply by switching to scCO<sub>2</sub> and optimising the pressure and hence density of the reaction medium.<sup>3</sup> We have also recently shown that it is possible to fine tune the *endo*:*exo* selectivity of the Diels–Alder reaction between cyclopentadiene and methyl acrylate by controlling the density of the reaction medium by varying the temperature and pressure of the scCO<sub>2</sub>.<sup>4</sup> It proved possible to change the *endo*:*exo* ratio from approximately 3:1 to 4:1. Whilst such a variation could be effected by changing solvent in a liquid phase reaction, it was of interest that similar variations could also be achieved in the same solvent, simply by altering its density. Such levels of selectivity and the slow rate of reaction were however of limited preparative value, and hence further investigations were warranted.

It is well known that Lewis acids catalyse Diels–Alder reactions and can improve their rate and stereoselectivity.<sup>5</sup> However, examples of conventional Lewis acid catalysis in scCO<sub>2</sub> are very limited.<sup>6</sup> It is known that fluorinated organometallic complexes have enhanced solubility in scCO<sub>2</sub>, a factor we have recently exploited in the development of new C–C bond forming processes in scCO<sub>2</sub> using palladium sources such as Pd(OCOFCF<sub>3</sub>)<sub>2</sub>.<sup>7</sup> We reasoned that related Lewis acidic complexes should also be capable of enhancing the rate and stereoselectivity of a Diels–Alder reaction such as that described above. Initial results of these studies are described below.

To follow on from our previous work, we decided to investigate catalysis of the Diels–Alder reaction between a variety of acrylates and cyclopentadiene (Scheme 1). Our initial studies concentrated on using *n*-butyl acrylate as dienophile as this was particularly convenient for product isolation and purification.

Scandium tris(trifluoromethanesulfonate) is widely used as a Lewis acid in a variety of reaction media.<sup>8</sup> Owing to its fluorinated nature, we believed it would also be suitable for use



Scheme 1

in scCO<sub>2</sub>. Initial results were encouraging. The reaction went to completion within 15 h at 50 °C, whereas the uncatalysed reaction was only 10% complete after 24 h under otherwise very similar conditions. In addition, a significant increase in *endo*:*exo* selectivity was observed as is common for Lewis acid catalysed Diels–Alder reactions.<sup>5</sup> We found that 6.5 mol% Sc(OTf)<sub>3</sub> catalyst gave good results, with no significant improvement at greater catalyst loading. In a conventional solvent such as toluene, an equivalent reaction gave a ratio of 10:1 *endo*:*exo* stereoselectivity. Changing to a significantly more polar solvent such as chloroform only had minimal effect on the selectivity (11:1 *endo*:*exo*). In scCO<sub>2</sub> at the same temperature (50 °C), variation of pressure (Fig. 1) allowed us to optimise the selectivity of this process,<sup>9</sup> with a maximum of 24:1 *endo*:*exo* being achieved, which is a considerable improvement, and further confirms our previous findings that significant enhancements of diastereoselectivity can be obtained by carrying reactions out in scCO<sub>2</sub> and optimising by varying the pressure and hence density of the reaction medium. Similar observations were observed with both phenyl and methyl acrylates, with *endo*:*exo* selectivities improving from 2:1 (toluene) to >8:1 (scCO<sub>2</sub>, 1.09 g ml<sup>-1</sup> density), and 4:1 (toluene) to >10:1 (scCO<sub>2</sub>, 1.12 g ml<sup>-1</sup> density) respectively.

It is of interest to note that, as was observed in our previous work, as pressure increases, the stereoselectivity rises to a maximum, and then begins to decrease. Note that this maximum

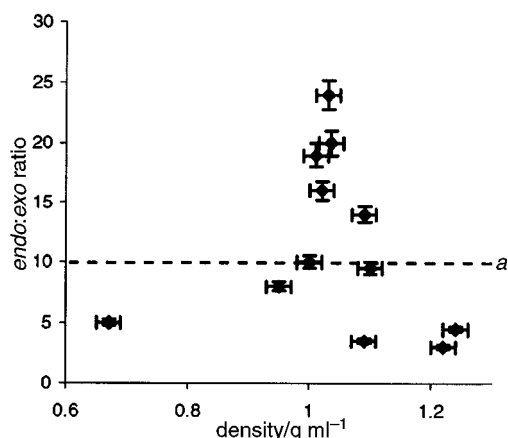


Fig. 1 Pressure dependent enhancement of *endo*:*exo* selectivity for Diels–Alder reaction between *n*-butyl acrylate and cyclopentadiene in scCO<sub>2</sub> catalysed by Sc(OTf)<sub>3</sub> at 50 °C. <sup>a</sup> 10:1 *endo*:*exo* selectivity observed in toluene at atmospheric pressure added for comparison.

occurs above the critical density of the medium and so is unlikely to be associated with clustering of molecules as is often proposed for effects observed around the critical point in near-supercritical fluids.<sup>10</sup> These new observations are consistent with the 'potential tuning' effect proposed in our previous paper<sup>4</sup> where the optimisation of the position and number of nearest neighbour solvent molecules with respect to a particular transition state was used to explain such a phenomenon. In such a case, an effect is observed which can be likened to a state of resonance between the solvent and reagents leading to an optimal selectivity for the reaction.

This work has now demonstrated the potential of Lewis acid catalysed reactions in scCO<sub>2</sub>, and shown that enhanced rates and selectivities are possible. We are now further studying the origin and potential of this effect with respect to Diels–Alder reactions and other Lewis acid mediated reactions. The results of these studies will be reported in due course.

We are very grateful to the following members of the Leeds Cleaner Synthesis Group and their respective companies for funding and useful discussions: Dr Andrew Bridge, Rhône-Poulenc Rorer; Dr Mike Loft, Glaxo Research and Development; Julie MacRae, Pfizer Central Research; Dr William Sanderson, Solvay Interco; and Dr Ken Veal, SmithKline Beecham Pharmaceuticals.

## Notes and references

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- 9 Apparatus used is as previously described in ref. 3. *Typical procedure*: scandium tris(trifluoromethanesulfonate) (95 mg, 0.18 mmol, 6.5 mol%) was placed in a pressure vessel which was then sealed and charged to 50 bar pressure with CO<sub>2</sub>. Agitation and heating was commenced, and a period of 20 min allowed for equilibration of conditions. *n*-Butyl acrylate (270 µl, 3.0 mmol) was injected into the system and the pressure increased to 80 bar. Cyclopentadiene (500 µl, 6.0 mmol, freshly cracked monomer) was injected and the pressure increased to the desired level. After 15 h, agitation and heating was stopped and the pressure released through a trap of diethyl ether (25 ml). The system was cleaned by further diethyl ether washes (2 × 1 ml). Filtration through Celite followed by solvent removal yielded the crude product mixture from which diastereomeric ratios were measured by <sup>1</sup>H NMR. Conversions were typically >90%, and isolated yields >80%. Density calibration was achieved by metering known amounts of carbon dioxide into the reaction vessel under standard reaction conditions (including reagents) using an ISCO 100D programmable syringe pump. Knowing the amount of carbon dioxide, the reactor volume and by observing the pressure, a calibration curve can be plotted for density versus pressure at constant temperature.
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Communication 9/04136B