Novel Organic Synthesis in Supercritical Carbon Dioxide

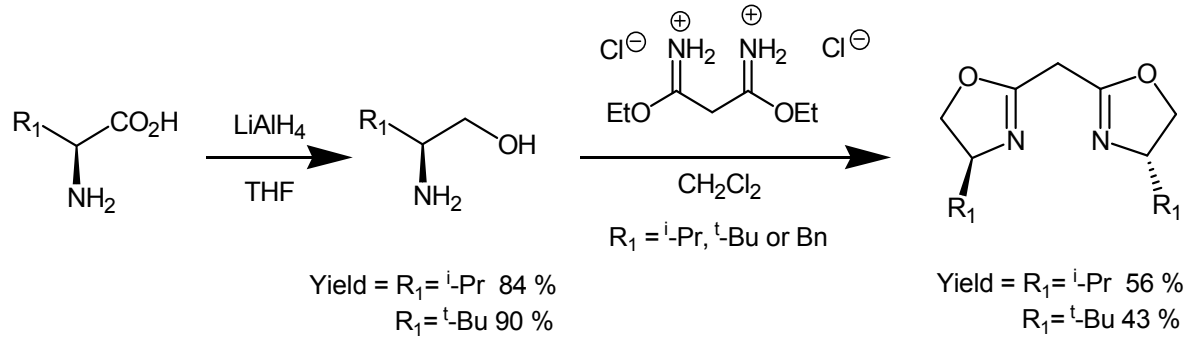
Sarah A. Brough, Christopher M. Rayner* and Anthony A. Clifford, Department of Chemistry, University of Leeds, Leeds, LS2 9JT, UK, C.M.Rayner@leeds.ac.uk, Fax +44 113 343 6565

INTRODUCTION

We have pursued a programme of investigating the substitution of environmentally benign supercritical carbon dioxide ($scCO_2$) for organic solvents in synthetic chemistry [1]. The focus of the present study is to synthesise novel bis-oxazoline (BOX) ligands for use as catalysts in asymmetric cyclopropanation reactions utilising $scCO_2$ as a solvent [2-3]. BOX ligands have become one of the most successful, versatile and commonly used class of ligands for asymmetric catalysis [4], and can be applied in a wide range of metal catalysed organic transformations [5].

FORMATION OF BOX LIGANDS

The majority of BOX ligands are derived from readily available amino acids.

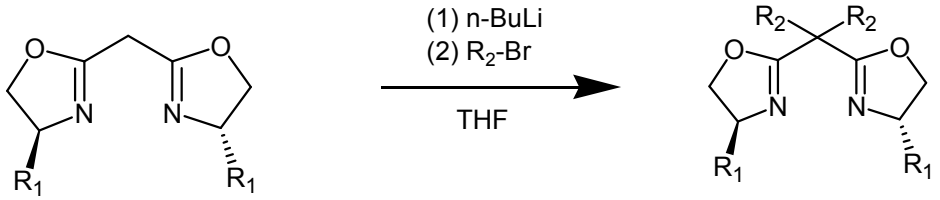


Yield = R_1= ^{i}-Pr 84 %
R_1= ^{t}-Bu 90 %

Yield = R_1= ^{i}-Pr 56 %
R_1= ^{t}-Bu 43 %

Scheme 1

Alkyl, ester or amide groups were incorporated in the R_2 position to enhance the solubility of the ligand in $scCO_2$.

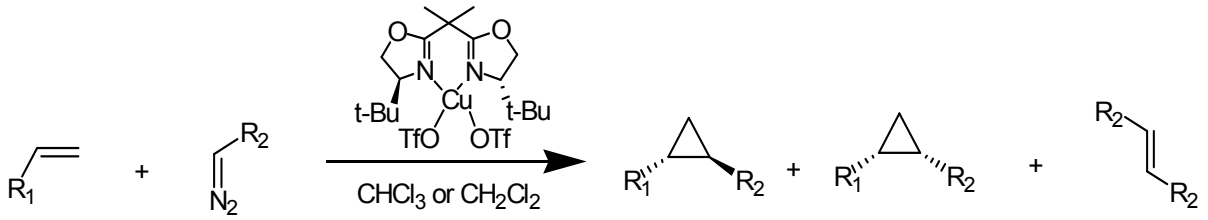


R_1 = ^{i}-Pr, ^{t}-Bu or Bn
R_2 = ^{n}-Bu, Me, CH_2CO_2Et or CH_2CONEt_2

Scheme 2

BOX CATALYSED ASYMMETRIC CYCLOPROPANATION REACTIONS

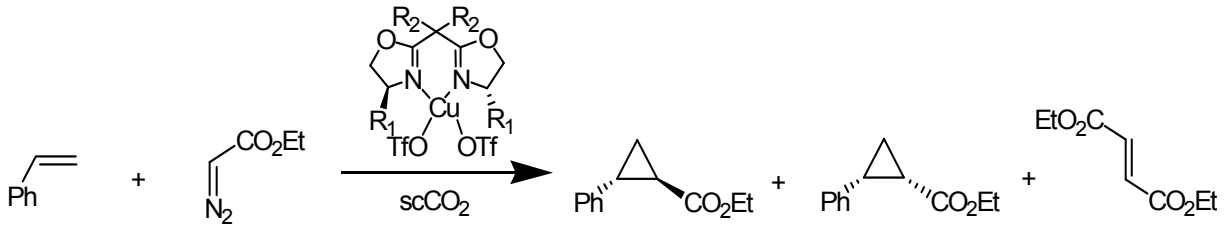
The cyclopropyl group is found as a basic structural element in a wide range of naturally occurring plants and micro-organisms [2,6]. Asymmetric cyclopropanation reactions have been extensively studied, and are usually carried out in conventional solvents such as $CHCl_3$ and CH_2Cl_2. Studies have also been carried out in $scCHF_3$ demonstrating interesting solvent effects [7]. In conventional solvents, the gem-dimethyl derivative typically gave the best enantioselectivity, hence is the most widely used chiral BOX ligand [8].

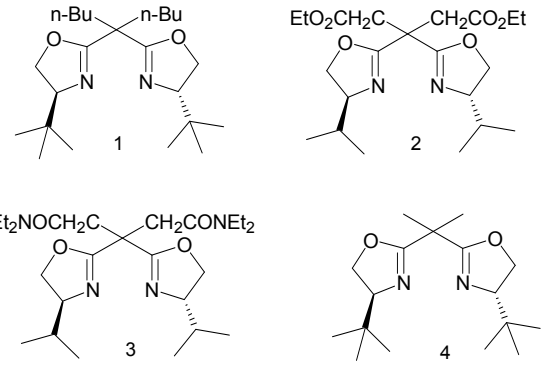


Scheme 3

BOX CATALYSED CYCLOPROPANATION REACTIONS IN $scCO_2$ COMPARED WITH CONVENTIONAL SOLVENTS

Cyclopropanation reactions of styrene and ethyl diazoacetate were performed in $scCO_2$ using 1 mol% BOX catalyst at different pressures to identify conditions for optimum selectivity. The same reactions were also carried out in chloroform and toluene as conventional solvents comparison. Results are presented for the four ligands shown in Scheme 4.

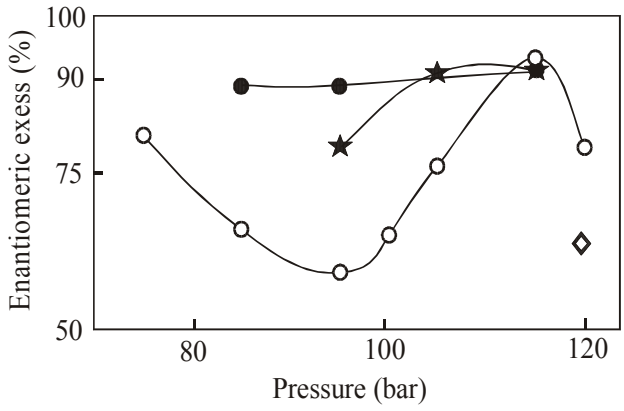




Scheme 4

Table 1: Enantiometric excess (%) for the reaction in conventional solvents for the four ligands

Ligand	Chloroform	Toluene
1	>95	80
2	45	23
3	59	58
4	87	88



Ligand 1: ○ Ligand 2:★ Ligand 3:◇ Ligand 4: ●

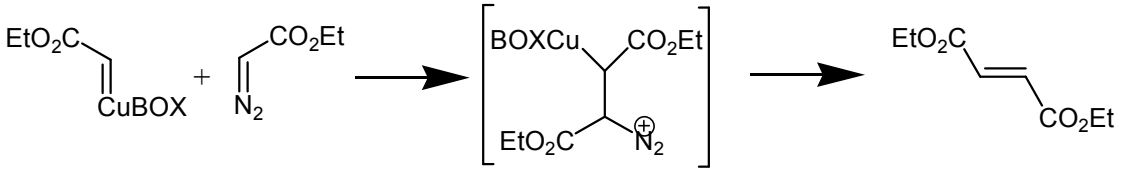
Figure 1: ee values for the cyclopropanation reaction studies in $scCO_2$.

Enantiomeric excess values were determined using HPLC (chiracel OJ column and elution with hexane/2-propanol (98:2) and a flow rate of 0.5 ml/ minute, after reduction to the primary alcohol). Table 1 shows results for the enantiomeric excess (ee) obtained in conventional solvents. Ligands 1 and 4 perform relatively well, with >95% ee obtained for Ligand 1 in chloroform, but the others perform badly.

Results for experiments carried out in $scCO_2$ are summarised in Figure 1. As can be seen, the pressure can be altered to optimise enantioselectivity, with the optimum pressure around 115 bar. Ligand 2 gave most interesting results as low ee was observed in chloroform (45%) and toluene (23%), but was much higher in $scCO_2$ at 115 bar (91%). Such high selectivities are rare with valine-derived BOX ligands. Thus, cheaper L-valine (€4.00 per g) derived BOX can be used in place of L-*tert*-leucine (€33.50 per g) derived BOX ligands for cyclopropanation reactions in $scCO_2$ at 115 bar.

YIELD OPTIMISATION

Literature procedures for the reaction of styrene and ethyl diazoacetate in conventional solvents gave optimum yields (~50-95 %) if the diazoacetate was added over 24 hours *via* a syringe pump [9]. This reduced unwanted dimerisation of ethyl diazoacetate.



Scheme 5

As this cannot be achieved using $scCO_2$ on current small scales, we have constructed a system, shown in Figure 2, which allows the ethyl diazoacetate to be added slowly to a 250 ml reactor over a fixed period of time. Initial results show that slow addition of diazoacetate can decrease the extent of dimerisation, and this is currently being optimised.

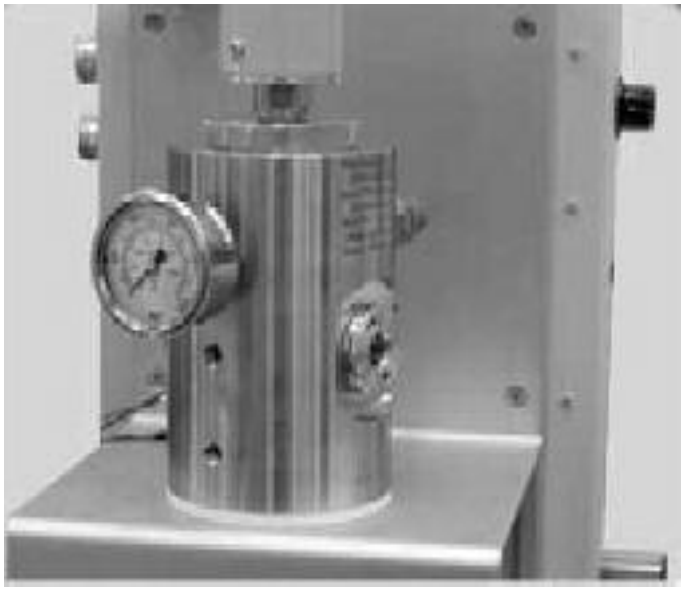


Figure 2: 250 mL reactor

CONCLUSIONS

1. It is possible to optimise the enantioselectivity of the asymmetric cyclopropanation reaction using BOX ligands in $scCO_2$ using pressure.
2. In some cases higher selectivities are obtained, than those available in conventional solvents with comparable ligands.
3. In particular, cheaper L-valine derived BOX ligands can be used in place of L-*tert*-leucine derived BOX ligands in asymmetric cyclopropanation reactions, with an optimum enantiomeric excess of 91%.

REFERENCES:

[1] OAKES, R.S.; CLIFFORD, A.A.; RAYNER, C.M. J. Chem. Soc., Perkin Trans. 1, **2001**, p. 918

[2] GHOSH, A.K.; MATHIVANAN, P.; CAPPIELLO, J. Tetrahedron asymmetry, Vol. 9, **1998**, p. 1

[3] DOYLE, M.P.; PROTOPOPOVA, M.N. Tetrahedron, **1998**, p. 7919

[4] MCMANUS, H.A.; GUIRY, P.T. Chem. Rev., **2004**, p. 4151

[5] CHRISTENSEN, C.; JULH, K.; JORGENSEN, K.A. Chem. Comm., **2001**, p. 2222

[6] LEBEL, H.; MARCOUX, J-F.; MOLINARO, C.; CHARETTE, A.B. Chem. Rev., **2003**, p. 997

[7] WYNNE, D.C., JESSOP, P.G. Angew. Chem. Int. Ed., Vol. 38, **1999**, p. 1143

[8] SALAUN, J. Chem. Rev., **1989**, p. 147

[9] LOWENTHAL, R.E.; ABIKO, A.; MASUME, S. Tetrahedron Lett., Vol. 31, **1990**, p. 6005