

CONTINUOUS REACTIONS IN SUPERCRITICAL CO₂

Peter Licence, Daniel N. Carter, Rodrigo Amandi Gomez, Stephen K. Ross^a and
Martyn Poliakoff*

*The School of Chemistry, University of Nottingham,
Nottingham, NG7 2RD, UK*

^a *Thomas Swan & Co Ltd, Crookhall, Consett, Durham, DH8 7ND*

E-mail martyn.poliakoff@nottingham.ac.uk
www.nottingham.ac.uk/supercritical/ www.thoma-swan.co.uk

INTRODUCTION

The global increase in standards of living demanded by an ever larger population and the associated environmental burden are forcing the chemical industry to search continually for new “cleaner” alternatives to current processes.[1] Supercritical CO₂ (scCO₂) has considerable potential as a green solvent; it has several advantages over conventional hydrocarbon solvents, including low-toxicity, non-flammability, and importantly a low cost.[2, 3]

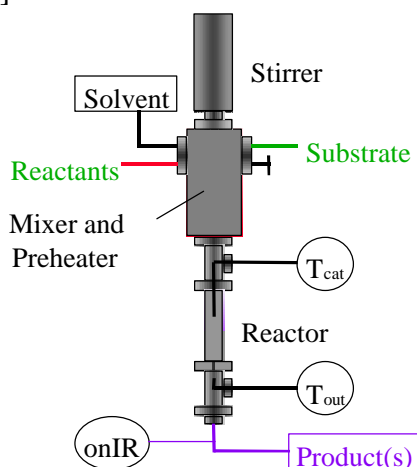


Figure 1: Schematic illustration of the major components of a SCF flow reactor.

The efficient application of scCO₂ in continuous flow systems can give rise to a number of advantages, both chemical and commercial, over more traditional batch type reactors.[4] Such advantages come about as a direct result of efficient process intensification and include lower operation costs and more importantly a safer working environment due to the much smaller volume of material that is under high pressure. It should also be noted at this point that, although the reactor unit itself has only a fraction of the volume of many batch reactors, the total throughput of the system can often be almost equivalent because the flow reactor can run at higher temperatures without decomposition of the product. In fact, a single continuous flow reactor of 5 mL volume has been shown to be capable of producing approx. 7 tons of hydrogenated material *per annum*. [5]

Carbon – carbon bond forming reactions are some of the most fundamental that are regularly carried out by the fine chemicals industry. Unfortunately, they are often the

most costly, both economically and environmentally. Traditional methods of synthesis often employ long established processes including Friedel-Crafts and Barbier-Grignard reactions, which are often perceived to be highly efficient. However, if one examines these technologies from the point of view of atom efficiency[6] and other commonly accepted green metrics,[7] it is quite evident that they are not. In this paper, we highlight some recent findings in our studies of three such reactions; Friedel-Crafts type alkylation, Heck coupling and hydroformylation. Finally we report some preliminary results on an efficient method for carrying out transesterification of simple esters.

FRIEDEL-CRAFTS TYPE ALKYLATION[8]

The industrial application of acid catalysed reactions including etherification and indeed Friedel-Crafts type chemistries, are often seen as attractive routes because they permit the easy conversion of low-cost starting materials into more desirable “value added” products. In general, such processes involve the application of large quantities of traditional (often chlorinated) organic and considerable excesses of strongly oxophilic Lewis-acids including aluminium trichloride, or strong Brønsted acids such as concentrated sulfuric acid or hydrofluoric acid. Large-scale application of these solvent systems and reagent types leads to serious problems both environmental and economic that must be addressed “end of pipe”. Apart from the obvious environmental factors, one of the major problems that chemists face when carrying out Friedel-Crafts alkylations is product selectivity. For commercial viability, the desired product must be easily isolable from the crude reaction mixture without further energy intensive purification steps such as distillation. The inherent tunability of reactions carried out under supercritical conditions offers a distinct advantage for chemistries of this type.

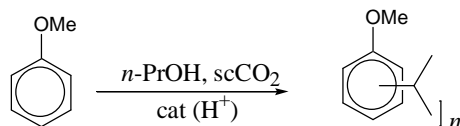


Figure 2: General scheme illustrating the alkylation of anisole in scCO₂.

We are currently carrying out a systematic study of the effect of pressure, reaction temperature and indeed catalyst on the productivity of Friedel-Crafts type alkylations of simple aromatics including anisole (see Figure 2), some preliminary results of this study may be seen in Table 1.

Table 1: Table illustrating the selectivities observed in the alkylation of anisole with *n*-propanol (molar ratio 3:1).

Reaction Pressure ^a / bar	Phase Behaviour ^b	Conversion / %	Mono Selectivity ^c / %
100	Multiphasic	78.4	74.8
200	Near phase boundary	74.4	81.7
300	Monophasic	22.1	92.3
400	Monophasic	41.9	96.4

^a All reactions were carried out over Amberlyst15[®] all experimental conditions were constant, 125 °C, org. conc. 10 % w/w in scCO₂, bulk CO₂ flow 0.65 Lmin⁻¹. ^b The number of phases present was determined in an optical view cell using a standard method, details of which are not presented here. ^c

The selectivity to mono alkylates includes the formation of both *o*- and *p*- isomers, the ratio of these two products has been found to be independent of the temperature and pressure employed.

In summary, we are finding that selective alkylation is possible over a range of commercially available supported catalysts. Furthermore, we have shown that the productivity of the reaction is strongly related to changes in the phase behaviour of the reaction mixture.

HECK COUPLING REACTION

In many circumstances, the Heck reaction is an elegant alternative to Friedel-Crafts type reactions. It is a very reliable, truly catalytic process that leads to the stereospecific generation of substituted olefins. Unfortunately, the homogeneous nature of many Heck catalysts renders them unsuitable for large-scale applications; although there is considerable evidence in the literature to suggest that exciting development of this reaction is taking place in the field of polymer bound catalysis.[9]

It is well known that some of the more reactive substrates undergo Heck coupling reactions when in the presence of minute concentrations of palladium. Indeed, Rayner and co-workers have reported a very efficient cross coupling of aryl halides in batch reactions in *scCO*₂. [10] The aim of our study has been to show that Heck chemistry can indeed be carried out over simple supported catalysts in continuous flow apparatus with *scCO*₂ as the reaction medium.

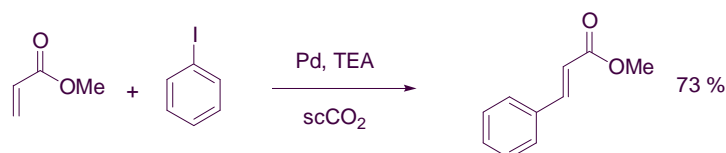


Figure 3: The reaction of methyl acrylate with iodobenzene in the presence of TEA (triethylamine), proceeded with 73 % conversion, conditions employed: Catalyst 5 % Pd on Deloxan™, 80 °C, 120 bar, 0.05 mLmin⁻¹ org. flow, bulk CO₂ flow 0.65 Lmin⁻¹.

The example highlighted in Figure 3 is, as far as we are aware, the only example of a metal catalysed coupling reaction carried out continuously in *scCO*₂. It is a potentially significant development in the pursuit of greener chemistry as it addresses a number of key points highlighted by The Principles of Green Chemistry[11]. The reaction is catalytic and employs an environmentally benign reaction medium. Unfortunately though, the reaction does not score highly in terms of atom efficiency. Just as in traditional Heck type reactions, TEA is used as a base in stoichiometric quantities. TEA reacts with eliminated HI forming the hydro-iodide salt which is then precipitated from the solution. The formation of this salt is easily managed when the flow rate of reactants is small (< 0.1 mLmin⁻¹). However, at higher flow rates our reactor vessel was prone to blockages. This problem, although intrinsic to the reaction, could in principle be overcome by employing a co-solvent that would enable the salt to be dissolved and flushed from the reactor.

HYDROFORMYLATION[12]

Hydroformylation or the “oxo” reaction, may be imagined as the catalytic addition of CO and H₂ (syngas) to olefinic precursors. The reaction products are aldehydes where the original carbon backbone of the olefinic precursor has been extended by the addition of one carbon atom. These materials find further application as precursors and intermediates in both the pharmaceutical and fine chemicals industries.

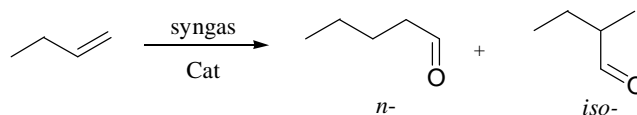


Figure 4: General scheme illustrating the hydroformylation of olefins.

Hydroformylation reactions are traditionally carried out employing homogenous metal catalysts (typically Rh and Co) and are routinely carried out in industry on a multi-ton scale. Typical problems associated with this reaction include post-reaction catalyst isolation, control of the degree of branching within the product and the suppression of competing side-reactions including hydrogenation and olefin isomerisation. Previously we have shown, in collaboration with the group van Leeuwen in Amsterdam that the application of supported homogeneous catalysis in $sc\text{CO}_2$ can offer distinct advantages that may allow these problems to be addressed.[12]

Table 2: Table illustrating the turnover frequencies (TOF), *n-* / *iso-* selectivity and percentage olefin isomerisation observed in the Rh catalysed hydroformylation of 1-octene in $sc\text{CO}_2$.

Catalyst ^a	TOF ^b	<i>n-</i> / <i>iso-</i>	% isom
Deloxan™ HKI (2% Rh)	- ^c	2	- ^c
[HRh(siloxantphos)(CO) ₂]	112	40	3
[HRh(xanthphenoxaphos)(CO) ₂]	127	13	<1

^a Reactions conditions were constant, 80 °C, 120 bar, 0.05 mLmin⁻¹ org. flow, bulk CO₂ flow 0.65 Lmin⁻¹, 5 : 1 syngas : octene ratio. ^b Average TOF was calculated as [aldehyde] [catalyst]⁻¹h⁻¹. ^cNot determined for commercial catalyst.

These results constitute the first examples of continuous hydroformylation of higher olefins using $sc\text{CO}_2$ as the solvent. TOFs were achieved which were up to half those observed using the homogeneous analogues. High *n-* / *iso-* ratios were observed, and olefin isomerisation was suppressed, in some cases to <1 %. Facile catalyst separation was achieved using these immobilised systems in $sc\text{CO}_2$, and no Rh leaching was detectable using ICP-MS analysis. The catalysts were stable for periods as long as two weeks in the flow system.

TRANSESTERIFICATION

Transesterification offers a convenient route that facilitates the efficient inter-conversion of readily available feedstocks including fatty acids and glycerides into value added products that exhibit potential as alternative fuel sources, such as biodiesel.[13] In principle, this process eliminates the use of a variety of alkyl halides and carboxylic acid substrates, which often have problems associated with handling and solubility.

Transesterification can be catalysed by either acid or base, the aim of this study was to investigate the two catalytic routes using $sc\text{CO}_2$ as a replacement solvent. $sc\text{CO}_2$ is an inherently acidic medium and so heterogeneous base catalysts could, in principle, be neutralised *in-situ*.



Figure 5: General reaction scheme illustrating the transesterification of alkyl acetoacetates.

In our studies on simple ester substrates including ethyl acetoacetate, we have shown that it is also possible to produce substituted secondary and tertiary esters by reaction of the substrate and a suitable alcohol over a fixed catalyst bed. In principle this process could also be used to introduce chiral alcohols as auxiliaries that may be used to facilitate induction of stereochemistry for further application in asymmetric synthesis.

Table 3: Selected results illustrating the successful transesterification of ethyl acetoacetate with *iso*-propanol.

Catalyst ^a	Nature	Conversion %
Amberlite [®] IR-120	Basic	73
Amberlite [®] IRC-50S	Basic	46
Amberlyst [®] 15	Acidic	73
Deloxan [™] ASP 1/7	Acidic	0

^areaction conditions: 100 bar, 150 °C, 0.5 mLmin⁻¹ organic substrate - ethyl acetoacetate with *iso*-propanol (molar ratio 1:5), 0.65 Lmin⁻¹ CO₂ bulk flow.

In summary we have shown that scCO₂ can successfully be employed as an efficient medium in which both acid and base catalysed transesterification reactions can be performed. No decarboxylation was observed with either the basic or the mildly acidic catalyst resins. Although, decarboxylation was found to be more common when the reaction was carried out over more strongly acidic resins. This is the first example of a continuous base catalysed reaction in scCO₂. However, it is still unclear how general the use of scCO₂ will be for other base catalysed reactions because of the acidity of CO₂.

CONCLUSIONS

This paper highlights a number of promising new areas of chemistry to which continuous SCF methodologies can be applied. It also highlights the subtle interplay between the phase behaviour of reaction mixtures and the outcome of those reactions. This underlines further the need for constructive collaboration between chemists and engineers to realize the full potential of SCF technology

ACKNOWLEDGEMENTS

We thank EPSRC, the EU FP5 Project CPF-CO2 and the EU Marie Curie Training Programme for financial support. We are grateful to Drs O. Aaltonen, W. K. Gray, J. Hyde, D. Macquarrie, N. J. Meehan, M. Sellin and F. R. Smail for help and advice. We thank Messrs, P. Fields, M. Guyler, K. Stanley and R. Wilson for technical support.

REFERENCES

- [1] POLIAKOFF, M.; FITZPATRICK, J.M.; FARREN, T.R.; ANASTAS, P.T. *Science*, 297, **2002**, p. 807.
- [2] JESSOP, P.G.; IKARIYA, T.; NOYORI, R. *Nature*, 368, **1994**, p. 231.
- [3] McHUGH, M.A.; KRUKONIS, V.J. *Supercritical fluid extraction : principles and practice*, Butterworth-Heinemann: Boston **1994**.
- [4] HYDE, J.R.; LICENCE, P.; CARTER, D.; POLIAKOFF, M. *Applied Catalysis A-General*, 222, **2001**, p. 119.
- [5] HITZLER, M.G.; SMAIL, F.R.; ROSS, S.K.; POLIAKOFF, M. *Organic Process Research & Development*, 2, **1998**, p. 137.
- [6] SHELDON, R.A. *Pure and Applied Chemistry*, 72, **2000**, p. 1233.
- [7] CONSTABLE, D.J.C.; CURZONS, A.D.; CUNNINGHAM, V.L. *Green Chemistry*, 4, **2002**, p. 521.
- [8] HITZLER, M.G.; SMAIL, F.R.; ROSS, S.K.; POLIAKOFF, M. *Chem. Commun.*, **1998**, p. 359.
- [9] ANDRES, C.J.; WHITEHOUSE, D.L.; DESHPANDE, M.S. *Current Opinion in Chemical Biology*, 2, **1998**, p. 353.
- [10] SHEZAD, N.; CLIFFORD, A.A.; RAYNER, C.T. *Green Chemistry*, 4, **2002**, p. 64.
- [11] ANASTAS, P.T.; WARNER, J. *Green Chemistry Theory and Practice*, Oxford University Press, **1998**.
- [12] MEEHAN, N.J.; SANDEE, A.J.; REEK, J.N.H.; KAMER, P.J.C.; VAN LEEUWEN, P.W.M.N.; POLIAKOFF, M. *Chem. Commun.*, **2000**, p. 1497.
- [13] MUNIYAPPA, P.R.; BRAMMER, S.C.; NOUREDDINI, H. *Bioresource Technology*, 56, **1996**, p. 19.