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The Continuous Catalytic Debenzylation of 1,4-Dibenzyloxybenzene with H_2 in THF Expanded with High Pressure CO_2

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Abstract:

The continuous debenzylation of 1,4-dibenzyloxybenzene (1a) with H_2 and supported Pd catalysts has been studied in high-pressure CO_2 + tetrahydrofuran. A range of parameters and catalysts have been tested, with one of the most successful results giving 86% conversion and 86% selectivity to the monodebenzylated product, 1,4-(benzyloxy)phenol (2a). In the absence of CO_2, the reaction was unselective with no formation of 2a. When complete debenzylation was required, the best catalyst was 5% Pd supported on Deloxan APII, giving quantitative yields of hydroquinone (3), the completely debenzylated product, at temperatures as low as 50 °C. This Deloxan-supported catalyst was also substantially active at only 30 °C.

Introduction

Continually increasing consumer and regulatory pressures on the pharmaceutical industry are strong drivers for reduced use of organic solvents throughout the manufacturing chain.[1] One potential strategy is to replace some of the organic solvents with supercritical fluids (SCFs),[2] typically supercritical CO_2 ($scCO_2$). CO_2 is attractive because of its low cost, low reactivity, and relatively accessible critical conditions (31.1 °C and 73.8 bar). Unfortunately, $scCO_2$ has a low polarity so is unsuitable for dissolving the majority of pharmaceutical molecules of interest. Indeed, in some cases these molecules are barely soluble in the majority of common organic solvents. Adding small quantities of 'modifiers', organic solvent (typically <10 mol %), to the $scCO_2$ improves the solvent power of the fluid significantly, thereby rendering the $scCO_2$ more useful for a wider range of organic intermediates, while still retaining some of the benefits of reduced organic solvent use.[3] However, it is important to acknowledge that there is a significant energy cost in compressing the CO_2. In a recent life-cycle analysis of preparative supercritical fluid chromatography (SFC) versus preparative HPLC,[4] the overall energy cost for SFC was larger than for HPLC, precisely because of the high energy costs of cooling and heating CO_2 to recycle it. When larger quantities of organic modifiers are used, the fluid may then be termed a gas-expanded liquid[5,6] (GXL), which has improved solvent power compared to modified $scCO_2$, but still reduces the volume of organic solvent required.[3]

One barrier to the application of GXLs in complex organic reactions is the paucity of research on pharmaceutically relevant molecules.[6] The most obvious examples in this area include the complexation of indomethacin with copper acetate,[7] the hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid to form (*S*)-naproxen,[8,9] the selective hydrogenation of *rac*-sertraline imine,[10] and the asymmetric hydrogenation of methyl-(*Z*)-α-acetamidocinnamate.[11] In an attempt to rectify this situation, this paper describes work on the *O*-debenzylation of a model compound, 1,4-dibenzyloxybenzene (**1a**). Benzyl groups are frequently used as protecting groups for hydroxyl and amine moieties.[12−20] Like many compounds of interest as pharmaceutical intermediates, **1a** has a relatively low solubility in common organic solvents, and it is also symmetric, making selective removal of only one of the benzyl groups a challenge. Simplistically, the overall reaction probably takes place in two

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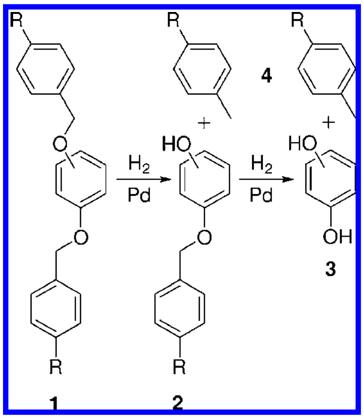
(1) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. Green Chem. **2007**, *9*, 411–420.
(2) *Handbook of Green Chemistry, Volume 4: Supercritical Solvents*; Leitner, W., Jessop, P. G., Eds.; Wiley-VCH: Weinheim, 2010.
(3) Wei, M.; Musie, G. T.; Busch, D. H.; Subramaniam, B. J. Am. Chem. Soc. **2002**, *124*, 2513–2517.
(4) Van der Vorst, G.; Van Langenhove, H.; De Paep, F.; Aelterman, W.; Dingenen, J.; Dewulf, J. Green Chem. **2009**, *11*, 1007–1012.
(5) Jessop, P. G.; Subramaniam, B. Chem. Rev. **2007**, *107*, 2666–2694.
(6) Akien, G. R.; Poliakoff, M. Green Chem. **2009**, *11*, 1083–1100.
(7) Warwick, B.; Dehghani, F.; Foster, N. R.; Biffin, J. R.; Regtop, H. L. Ind. Eng. Chem. Res. **2000**, *39*, 4571–4579.
(8) Combes, G. B.; Dehghani, F.; Lucien, F. P.; Dillow, A. K.; Foster, N. R. Asymmetric Catalytic Hydrogenation in CO_2 Expanded Methanol: An Application of Gas Anti-Solvent Reactions (GASR). In *Reaction Engineering for Pollution Prevention*; Abraham, M. A., Hesketh, R. P., Eds.; Elsevier: Amsterdam, 2000; pp 173−181.
(9) Combes, G.; Coen, E.; Dehghani, F.; Foster, N. J. Supercrit. Fluids **2005**, *36*, 127–136.
(10) Clark, P.; Poliakoff, M.; Wells, A. Adv. Synth. Catal. **2007**, *349*, 2655–2659.
(11) Shariati, A.; Sheldon, R. A.; Witkamp, G. J.; Peters, C. J. Green Chem. **2008**, *10*, 350–354.
(12) Baltzly, R.; Buck, J. S. J. Am. Chem. Soc. **1943**, *65*, 1984–1992.
(13) Baltzly, R.; Russell, P. B. J. Am. Chem. Soc. **1950**, *72*, 3410–3413.
(14) Baltzly, R.; Russell, P. B. J. Am. Chem. Soc. **1953**, *75*, 5598–5602.
(15) Baltzly, R.; Russell, P. B. J. Am. Chem. Soc. **1954**, *76*, 5776–5777.
(16) Sajiki, H.; Kuno, H.; Hirota, K. Tetrahedron Lett. **1997**, *38*, 399–402.
(17) Blaser, H. U.; Indolese, A.; Schnyder, A.; Steiner, H.; Studer, M. J. Mol. Catal. A: Chem. **2001**, *173*, 3–18.
(18) Clayden, J.; Greeves, N.; Warren, S.; Wothers, S., *Organic Chemistry*, 7th ed.; Oxford University Press: Oxford, 2001.
(19) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. Org. Process Res. Dev. **2005**, *9*, 253–258.
(20) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Org. Biomol. Chem. **2006**, *4*, 2337–2347.

10.1021/op100136g

Scheme 1. **Reaction scheme for the debenzylation of a dibenzyloxybenzene (1) with H_2 using a Pd catalyst, to form the corresponding (benzyloxy)phenol (2) and the side-product toluene (4); 2 can then be subsequently debenzylated to form the hydroquinone (3a) or its isomers, catechol and resorcinol**[a]



[a] The suffix describes various different analogues: a) *para*-, R = H; b) *meta*-; R = H, c) *para*-, R = OMe; d) *para*-, R = OCF_3. The other by-products observed in this work are those where the aromatic core has been fully or partially hydrogenated.

steps, as shown in Scheme 1, with the sequential removal of the benzyl groups.

The hydrogenation of **1a** to yield selectively the intermediate 1,4-(benzyloxy)phenol (**2a**) was investigated by Sajiki et al. some years ago.[16] Using 5% Pd/C and H_2 at atmospheric pressure, the terminal product, hydroquinone (**3a**), was obtained in quantitative yields.[16] When 0.5 equiv of pyridine were added, the partially poisoned catalyst then only produced a 17:83 ratio of **2a**:**3a** (the yield was not specified). Others have used different hydrogen sources: a 90% yield of **2a** was possible with tetralin and 10% Pd/C in ethanol,[21] but only 46.5% using cyclohexene and 5% Pd/C.[22] The presence of both reacted and unreacted transfer hydrogenation sources may complicate later separation of the products from the reaction mixture, so we thought it worthwhile to investigate the potentially greener direct hydrogenation of **1a** instead.

Thus, this paper presents a study on the catalytic reaction of **1** with H_2 in a GXL, with the aim of establishing how much the selectivity of the reaction can controlled while achieving as high as possible a yield of **2** using commercially available heterogeneous catalysts.

Experimental Section

Materials. The following materials were used without further purification: acetone (laboratory reagent grade, Fisher Scientific), air (99.9%, BOC Gases), cesium carbonate (99.5%, Fisher Scientific), chloroform (laboratory reagent grade, Fisher Scientific), chloroform-*d* (99.8% D, Sigma-Aldrich), CO_2 (SFC grade, 99.999%, BOC Gases), 1,4-cyclohexanediol (99%, Lancaster), 1,4-cyclohexanedione (>99%, Fluka), dichloromethane (laboratory reagent grade, Fisher Scientific), *N*,*N*-dimethylformamide (anhydrous, 99.8%, Sigma-Aldrich), H_2 (99.995%, BOC Gases), HCl ($\sim$12.0 mol·dm^{-3}, Fisher Scientific), helium (He) (99.999%, BOC Gases), hydroquinone (**2a**, USP grade, Sigma), *m*-(benzyloxy)phenol (**2b**, Wako), *m*-dibenzyloxybenzene (**1b**, 98%, Alfa Aesar), methylcyclohexane (>99.5%, Fluka), 1,4-benzoquinone (98+%. Alfa Aesar), 1,4-(benzyloxy)phenol (**2a**, 99+%, Aldrich), 1,4-dibenzyloxybenzene (**1a**, 98%, Alfa Aesar), ethyl acetate (laboratory reagent grade, Fisher Scientific), magnesium sulfate (anhydrous, Fisher Scientific), 4-methoxybenzyl chloride (98%, Sigma-Aldrich), nitrogen (≥99.99%, BOC Gases), 2% Pd/C (charcoal, pellets, Johnson Matthey, batch number: M02161), 2% Pd/Al_2O_3 (type 335 powder, Johnson Matthey, batch number: M05226), 2% Pd/SiO_2 (egg-shell type 0.8 mm spheres, Johnson Matthey, batch number: 99046), 2% Pd/SiO_2−Al_2O_3 (type 31, Johnson Matthey, batch number: 113031054), 5% Pd/Al_2O_3 (type 5R335, Johnson Matthey, batch number: M05227), 5% Pd/$CaCO_3$ (type 21 powder, Johnson Matthey, batch number: DLR0320), petroleum ether (40−60 °C, laboratory reagent grade, Fisher Scientific), potassium carbonate (laboratory reagent grade, Fisher Scientific), resorcinol (**3b**, ACS 99+%, Alfa Aesar), THF (laboratory reagent grade 99.5%, Fisher Scientific), toluene (**3**, laboratory reagent grade, Fisher Scientific), 4-(trifluoromethoxy)benzyl bromide (>99%, Fisher Scientific). Deionised water was supplied from an Elga PureLab S water purification system.

The pellets of 2% Pd/C and 2% Pd/SiO_2 catalysts were too large for the reactor; thus, they were crushed, and only the 63−125 μm sieved particles were used. The rest of the catalysts (with the exception of 5% Pd/$CaCO_3$. which was much finer) were mainly supplied in the 125−250 μm size range.

The details of the synthesis of **1c** and **1d** are included in Supporting Information.

Reaction Analysis. Analysis of the reaction mixtures was carried out with a Shimadzu GC-2010 equipped with an AOC-20s autosampler, and fitted with a Restek RTX-5 column (10 m × 0.10 mm internal diameter, 0.1 μm film thickness) using He as the carrier gas, with detection using a flame ionisation detector (FID). The method used for the separation of the reaction mixture from the debenzylation of **1** was as follows: 0.2 μL injection volume, 250 °C inlet temperature, 50:1 split ratio, temperature program 45 °C for 5 min, increasing to 320 °C at a rate of 50 °C·min^{-1}, held for a further 2 min, 350 °C FID temperature, samples dissolved in THF. Products were identified by comparison with authentic samples and by GC−MS (Thermo Finnegan TraceGC 2000 fitted with a PolarisQ MS detector). Mass balance experiments showed quantitative recovery of the substrates, so quantitative analysis was performed with the aid of external standards.

Reactions. *Safety Note. Flow reactors have a comparatively small volume under pressure. Nevertheless, equipment with the appropriate pressure and temperature rating should always be used for high-pressure experiments.* The continuous flow equipment was essentially identical to that used previously for the hydrogenation of sertraline imine,[10] apart from the mixer being replaced by another tube identical to the reactor, but filled with 1−1.5 mm glass beads and heated to the same temperature as the reactor. Fresh catalyst was used for each experiment.

1a is largely insoluble in most solvents, apart from THF, dichloromethane, and chloroform. Earlier work has shown THF

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(21) Li, G.; Wang, P.; Zhao, W.; Chen, J. *Zhejiang Yike Daxue Xuebao* **1987**, *16*, 154–156.

(22) Li, L.; Pang, Q. Huaxi Yauxue Zazhi **1996**, *11*, 234–236.

to be a good solvent for *N*-debenzylations;[23] thus, it was selected for this investigation, using a **1** concentration of 0.05 mol·dm^{-3} (1.93 wt %). THF is also capable of dissolving large quantities of CO_2,[27] giving an excellent opportunity to tune the reaction. The standard conditions for each experiment were, unless otherwise stated, flow 0.5 mL·min^{-1} THF solution, 0.5 mL·min^{-1} CO_2, 100 °C, 100 bar, 5.5 equiv of H_2, with ~300 mg of 2% $Pd/SiO_2-Al_2O_3$ catalyst, prereduced under N_2/H_2 at 100 °C and 100 bar for 2 h. For experiments where parameters were varied, each value was held for at least 30 min, and samples were collected every 5 min. The first sample at each new value was discarded, and the mean and standard deviation (shown with error bars) were calculated from the remaining samples. For the experiments where the conditions were fixed, samples were collected every 10 min, and no averaging was applied to the data. Experiments varying the residence time (not shown) indicated that the reaction was kinetically controlled.

Results and Discussion

Overall Strategy. As explained above, our aim has been to achieve a yield of **2** as high as possible using H_2 as the hydrogen source with commercially available heterogeneous catalysts. Originally, we intended to study a wide range of compounds. However, there was little difference between the debenzylation of the para (**1a**) and meta (**1b**) isomers of **1**, although **1b** produced more byproducts in the first 45 min and the terminal product, resorcinol (**3b**), was not detected at all. By comparison ~5 mol % of **3a** was detected from the debenzylation of the para isomer. Overall however, the differences were still small, and consistent with previous observations[24] that, for debenzylations, electronic effects are more important than steric ones.

By changing the substituents on the benzyl group, the electronic properties can be changed, possibly changing the selectivities. To this end, the 1,4-methoxybenzyl (**1c**) and 1,4-trifluoromethoxybenzyl (**1d**) analogues of **1a** were synthesised (see Supporting Information). Unfortunately, **1c** was found to be too insoluble to be reacted in the equipment used here. On the other hand, **1d** was noticeably more soluble than **1a**, but did not react until 200 °C, producing only small quantities of unidentified products with GC retention times approximately a minute later than the starting material.

Therefore, our study has focused on the reactions of the para isomer (**1a**). The first stage of the investigation focused on using a single catalyst, 2% $Pd/SiO_2-Al_2O_3$, and on identifying the effects of individual parameters, including temperature, pressure, and CO_2 flow rate, while the other parameters were held constant. The study was then extended to a wider range of other Pd catalysts to establish the extent to which the nature of the catalyst affects the control of the reaction.

Effect of Temperature at Constant Pressure. Past experience[10,25,26] suggests that temperature is one of the most important parameters for controlling conversion and selectivity in a continuous reaction in $scCO_2$. Therefore, the effects of temperature were investigated first.

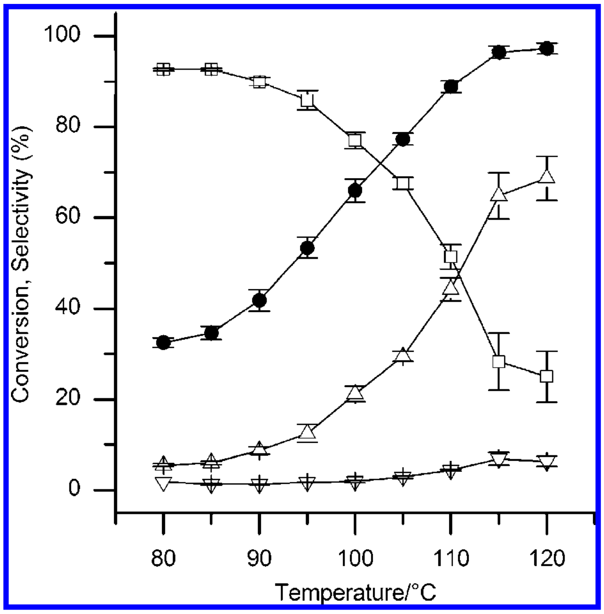

Figure 1. **Debenzylation of 1a over 2% $Pd/SiO_2-Al_2O_3$; the effects of increasing the temperature from 80 to 120 °C in 5 °C increments at 100 bar pressure. For other conditions, see the Experimental Section. For simplicity, the plots in all figures in this paper are labeled in the same way, namely, conversion of 1 (●), selectivity for 2 (□), selectivity for 3 (Δ), selectivity for byproducts (▽).**

Figure 1 shows that increasing the temperature increases the conversion, but it also reduces the selectivity for **2a** by promoting further debenzylation of **2a** to form the doubly debenzylated product hydroquinone, **3a**. Under these conditions, a phase transition from a single liquid phase to a liquid–vapor biphase is expected[27] at approximately 100 °C. A phase transition is likely to have an effect on the residence time in the reactor with a concomitant change in the conversion and selectivity. Thus, one might expect a discontinuity in the plots at 100 °C. However, Figure 1 shows that, surprisingly, this transition does not have any significant effect; there is no sudden change in conversion and selectivity at this temperature.

Effect of Changing the Ratio H_2:1a. In an attempt to improve the selectivity for **2a**, the amount of H_2 available for the reaction was varied by changing the ratio of H_2:**1a** by a factor of 10, while maintaining the temperature and pressure constant.

Figure 2 shows that, at 110 °C, increasing the ratio of H_2:**1a** from 1.45 to 14.5 increases the conversion of **1a** as might be expected, but also decreases the selectivity for **2a**. As with temperature, there is a clear trade-off between high conversion and high selectivity. At higher H_2:substrate ratios, there is a notable leveling off; further increases in the amount of H_2 have little effect, suggesting that mass-transport limitations were overcome under these conditions.

Effect of Pressure at Constant Temperature. Figure 1 indicated that there was little apparent effect on the reaction of a phase transition from two phases to one, promoted by increasing temperature. However, the phase state of a binary mixture, CO_2 + organic solvent, can also be manipulated

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(23) Clark, P. D. Synthesis of Drug Intermediates in Carbon Dioxide. Ph.D. Thesis. University of Nottingham: Nottingham, U.K., 2006.

(24) Gaunt, M. J.; Yu, J. Q.; Spencer, J. B. *J. Org. Chem*. **1998**, *63*, 4172–4173.

(25) Bourne, R. A.; Stevens, J. G.; Ke, J.; Poliakoff, M. *Chem. Commun*. **2007**, 4632–4634.

(26) Chapman, A. O.; Akien, G. R.; Arrowsmith, N. J.; Poliakoff, M. *Green Chem*. **2010**, *12*, 310–315.

(27) Yuan, H. M.; Olesik, S. V. *J. Chromatogr., A* **1997**, *785*, 35–48.

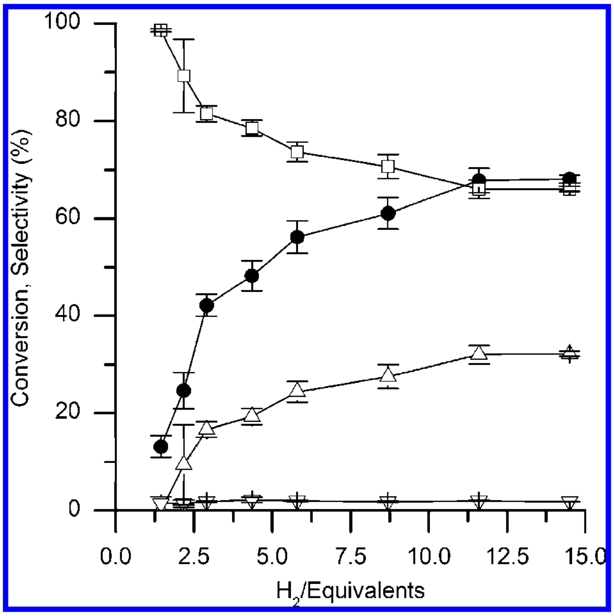

Figure 2. **Debenzylation of 1a, varying the H_2:1a ratio at 110 °C; for labelling of plots, see Figure 1.**

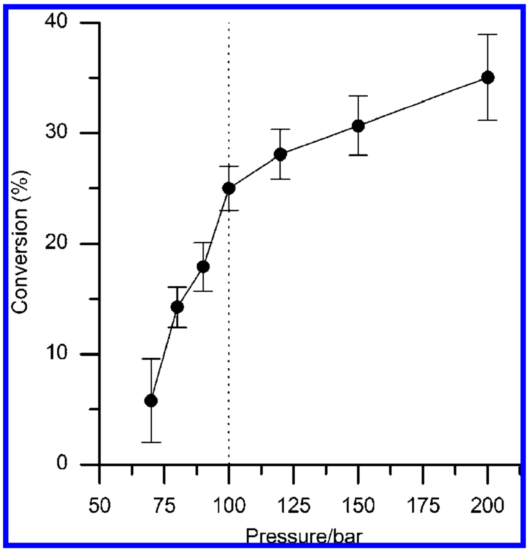

Figure 3. **Debenzylation of 1a, increasing the pressure at 100 °C without changing the ratio of CO_2 to organic solvent. 2a was the sole product (i.e the selectivity was ∼100%). So, in this Figure, we merely show the conversion of 1a. The dashed vertical line indicates the pressure at which the system switches from two phases to one.**

between single and multiphase by changing the applied pressure.[28] Of course, in a continuous reactor, increasing the pressure will also change the residence time. However, previous work on the desymmetrisation of a diol in $scCO_2$,[29] showed that it was possible to change the outcome of the reaction completely by inducing a phase change by changing the pressure. Figure 3 shows the effect of pressure on the debenzylation of **1a** at 100 °C.

Generally speaking, increasing the pressure increases the conversion, but in Figure 3, the increase in conversion shows two distinct parts. The increase in conversion is rapid up to the dashed line at 100 bar and slower thereafter, probably reflecting a phase transition from two phases to a single phase at approximately 100 bar (for the CO_2 + THF system).[27] Other experiments using the pressure drop method[30] showed that the influence of the other components (H_2 and **1a**) is small enough to be ignored. The effect of pressure on the fluid is different for different numbers of phases. When there are two phases, the system is in effect a trickle-bed reactor; increasing the pressure will increase the quantity of CO_2 and H_2 dissolved in the liquid phase, improving both the mass transport and the liquid-phase H_2 concentration. On the other hand, when there is a single phase (>100 bar), increasing the pressure increases the density of the reaction mixture, therefore increasing the residence time. The change in overall density for a biphasic system is more difficult to quantify, and the increase in dissolved CO_2 will also affect the solubility of the substrate in the liquid phase.

It should be noted that the phase behavior in an operating reactor will be slightly different from that of the binary mixtures which are usually studied because the actual composition of the mixture changes along the length of the reactor as H_2 is consumed and **1a** is converted to **2**.

A comparison of Figures 1 and 3 hints at an apparent contradiction. In Figure 1, the phase transition at 100 °C has no apparent effect on the reaction, while in Figure 3 the phase change at 100 bar does have an effect. The likely reason for this is that the phase transitions are not the same. In Figure 1, the transition is from two phases to a *less dense* single phase, whereas as the pressure increases in Figure 3, the system is going from two phases to a *relatively denser* single phase.

Increase in CO_2 Flow Rate. Figure 4 shows the effect of increasing the CO_2 flow rate is increased conversion of **1a** with, initially at least, only a modest drop in selectivity towards **2a**; this is surprising in view of the probable decrease in residence time caused by the dilution of the starting material. However, increasing the proportion of CO_2 causes a considerable drop in the solvent power of the THF solvent.[5,6] Therefore, one should be cautious in drawing conclusions about the effect of high flow rates of CO_2 on the hydrogenation because the points in Figure 4 do not necessarily represent results at a steady state. For example, at the highest CO_2 flow rate it was only possible to collect a single sample, before precipitation of **1a** by the antisolvent power of CO_2 blocked the equipment and ended the experiment prematurely.

There is likely to be a change from one phase to two phases when the CO_2 composition (flow rate) is increased beyond 70 mol % CO_2. When there are two phases, an increased CO_2 flow rate means an increased superficial gas velocity, which leads to increased catalyst wetting and a reduced liquid film thickness,[31] and hence to better usage of the catalyst and higher conversions. Such an effect has been reported before by Baiker

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(28) McHugh, M. A.; Krukonis, V. J. *Supercritical Fluid Extraction: Principles and Practice*, 2nd ed.; Butterworth-Heinemann: Boston, 1994.

(29) Licence, P.; Gray, W. K.; Sokolova, M.; Gray, W. K.; Poliakoff, M. *J. Am. Chem. Soc.* **2005**, *127*, 293–298.

(30) Akien, G. R.; Skilton, R. A.; Poliakoff, M. *Ind. Eng. Chem. Res.* **2010**, *49*, 4974–4980.

(31) Al-Dahhan, M. H.; Larachi, F.; Dudukovic, M. P.; Laurent, A. *Ind. Eng. Chem. Res.* **1997**, *36*, 3292–3314.

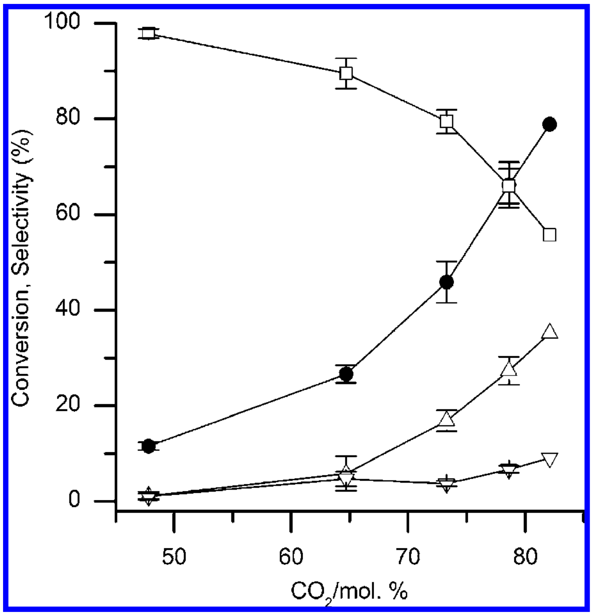

Figure 4. **Debenzylation of 1a; the effect of changing the CO_2 flow rate, hence the mol % of CO_2 in the reaction mixture at 100 °C and 100 bar, and therefore the overall composition of the fluid. The data correspond to a change in flow rate from 0.125 to 1.25 mL·min^{-1}. For labeling of the plots, see Figure 1.**

Table 1. **Variation of mobile phase for the debenzylation of 1a**[a]

		selectivity (%)		
gas	conversion of **1a** (%)	**2a**	**3a**	by-products
CO_2	44.0	88.7	11.2	0.1
N_2	100	0.4	59.4	40.3
H_2 only	100	0	65.3	34.7

[a] Standard conditions were used: 0.5 mL·min^{-1} CO_2, 0.5 mL·min^{-1} THF solution (0.05 mol·dm^{-3} **1a**), 100 °C, 100 bar, 5.5 equiv of H_2, with ~300 mg of 2% Pd/SiO_2−Al_2O_3 catalyst, prereduced under N_2/H_2 at 100 °C and 100 bar for 2 h. Where CO_2 was replaced with N_2, it was at the same *mass* flow rate.

and co-workers in the Pd-catalysed dehydrogenation of 1-phenylethanol in high pressure CO_2.[32]

Effect of CO_2 versus Other Gases. Figure 4 indicated that increasing the quantity of CO_2 in the solvent mixture increases the conversion of **1**, so the presence of CO_2 appears to be important for the selectivity of the reaction. To gain further insight into the possible role of CO_2, three separate experiments were conducted under conditions which would allow direct comparisons between different gases: the first experiment was with CO_2, the second with N_2 replacing CO_2 as the “mobile phase”, and the third with no additional gas at all, i.e. only with H_2, but still at high pressure. The results are summarized in Table 1.

Table 1 shows that the results of the three experiments were strikingly different. The effects of changing the gas are large, namely (i) The conversion of **1a** is much higher with N_2 than with CO_2; presumably, this is because CO_2 has a higher solubility in the liquid phase, thereby diluting the liquid phase more and, hence, reducing the rate of reaction and the conversion. (ii) When only H_2 is present, the conversion is again much higher than with CO_2; this may be a secondary effect due to the much longer residence time in the reactor, because smaller volumes of gas correspond to a necessarily higher overall density. (iii) Unexpectedly, significant amounts (5−10 mol %) of monodebenzylated cyclohexyl products, **5** and **6** (Figure 5), were observed when N_2 and/or H_2 was used; we can find no precedent for this in the literature. (iv) Most importantly, the reaction is almost completely unselective when CO_2 is absent; therefore, we have the key result that the presence of CO_2 is introducing selectivity towards **2a**.

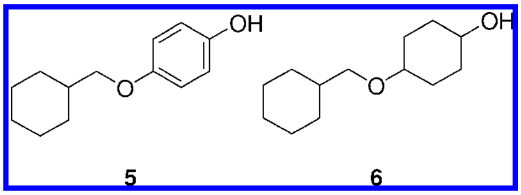

Figure 5. **Structures of the unexpected byproducts 5 (4-(cyclohexylmethoxy)phenol) and 6 (4-(cyclohexylmethoxy)cyclohexanol).**

Variation of Pretreatment of the Catalyst. We encountered some reproducibility issues in the course of this work, at least some of which appeared to have been the result of inadvertent variations in the pretreatments of the catalyst *in situ*, before the reaction mixture was flowed through the reactor. The manufacturers of the 2% Pd/SiO_2−Al_2O_3 catalyst suggest that it may be preferable not to pretreat heterogeneous Pd catalysts, since the activity of untreated catalysts is higher for debenzylations.[33] Since the conversion is strongly linked to the selectivity, it was hoped that pretreating the catalyst would not only affect the activity but might also influence the selectivity. To this best of our knowledge, there is no information in the primary literature on the effects of different pretreatments for selective debenzylation with heterogeneous catalysts.

Our results are summarized in Figure 6, and they confirm that the most active catalyst was the one which had undergone no prereduction at all. There was a considerable difference between the activity of the catalyst after the different pretreatments. There was also variability between the experiments, with some differences between repeats under nominally identical conditions. This is indicated in Figure 6 by the gradually increasing conversion in the long experiment (~8 h), where a true steady state never seemed to be reached. It seems doubtful that metal sintering is the cause of this instability, since this usually occurs only higher temperatures (>500 °C).[34−36] The selectivity towards **2a** is not shown explicitly in Figure 6 because it was broadly the same for all pretreatments, although selectivity was generally slightly lower for the untreated catalyst than in other experiments. Thus, despite the variability in the results, it seems reasonable to conclude that pretreatment is unlikely to be a useful tool for tuning the selectivity of the catalyst in this reaction.

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(32) Burgener, M.; Mallat, T.; Baiker, A. J. Mol. Catal. A: Chem. **2005**, *225*, 21–25.

(33) *A New Series of Catalysts for Deprotection Reactions*; Johnson Matthey: London; www.jmcatalysts.com/pharma/pdfs-uploaded/O%20Debenz%20Flyer_1.pdf (accessed Jan 5, 2009).

(34) Chen, J. J.; Ruckenstein, E. J. Catal. **1981**, *69*, 254–273.

(35) Maxted, E. B.; Ali, S. I. J. Chem. Soc. **1964**, 1127–1132.

(36) Liu, R. J.; Crozier, P. A.; Smith, C. M.; Hucul, D. A.; Blackson, J.; Salaita, G. Appl. Catal., A **2005**, *282*, 111–121.

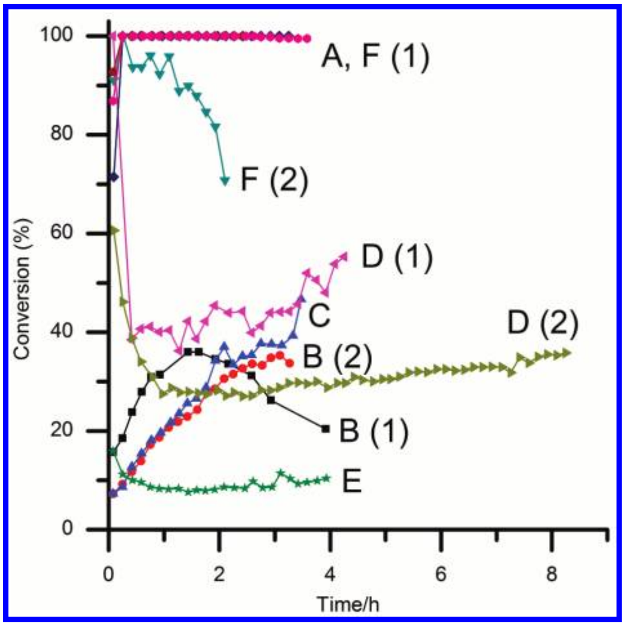

Figure 6. **Observed conversion during debenzylation of 1a over 2% Pd/Al_2O_3 under constant conditions (100 bar, 100 °C, 5.5 equiv of H_2, 0.5 mL·min^{-1} both for CO_2 and THF solution), varying pretreatment methods for the catalyst. The selectivities were largely the same for a given conversion level and so are not shown. Pretreatment conditions: (A) no pretreatment, (B) brief prereduction under CO_2 at 100 °C for 30 min with 0.71 mol % H_2; (C) extensive prereduction under CO_2 at 150 °C for 2 h with 7.56 mol % H_2; (D) extensive prereduction under N_2 at 150 °C with 500 mL$_N$·min^{-1} N_2 (equivalent to the same mass flow rate as 0.636 mL·min^{-1} liquid CO_2) for 2 h with 3.94 mol % H_2, (E) high temperature prereduction under N_2 at 250 °C for 2 h with 7.56 mol % H_2; and (F) heating under pure N_2 at 150 °C with 500 mL$_N$·min^{-1} for 2 h.**

Debenzylation Using Other Catalysts. *5% Pd/Deloxan APII: Variation of Temperature.* The investigation was now widened to other catalysts in a search for greater selectivity for the debenzylation of **1a** in CO_2-expanded THF. The results with the Degussa catalyst 5% Pd/Deloxan APII were particularly striking. Figure 7 shows that the catalyst was active at surprisingly low temperatures. This catalyst gave levels of conversion and selectivity at only 30 °C, similar to those observed with 2% Pd/SiO_2−Al_2O_3 at much higher temperatures.

Under these conditions, the residence time in the reactor is only ~30 s; so this is a remarkable reaction. The catalyst was also capable of cleanly producing hydroquinone in almost quantitative yields at only 50 °C. Given this excellent performance, it is disappointing that the Deloxan catalysts are no longer available commercially.

Conversion vs Selectivity. The results described above suggest a consistent trade-off between conversion of **1a** and selectivity towards **2a**, as would be expected from a reaction where the rates of the two steps, **1a** → **2a** and **2a** → **3a**, are comparable. Thus, as the final stage of our study, we investigated the correlation of the conversion of **1a** versus selectivity for **2a** for a whole series of catalysts and reaction conditions. The results are summarized in Figure 8.

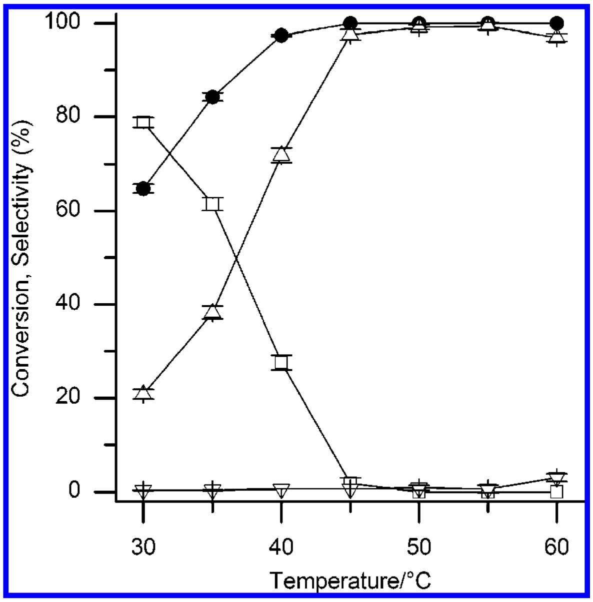

Figure 7. **Debenzylation of 1a over 5% Pd/Deloxan APII, variation of temperature; for labelling, see Figure 1.**

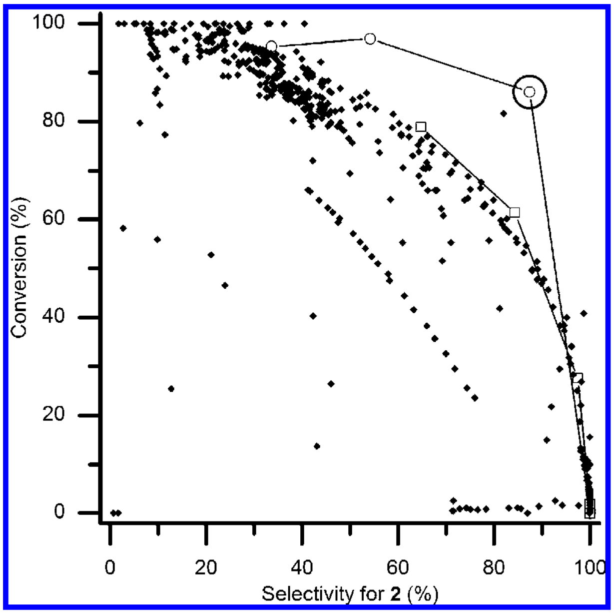

Figure 8. **Conversion versus selectivity for 2a for all 36 experimental runs of the debenzylation of 1. Two temperature ramps are highlighted with lines joining the points: 60−100 °C with 5% Pd/$CaCO_3$ (○), and 30−60 °C with 5% Pd/Deloxan APII (□). The best combination of conversion and selectivity (both ~85%) was obtained with 5% Pd/$CaCO_3$.**

Figure 8 shows that the majority of data points lies approximately on the arc of a circle. This implies that the relationship between conversion and selectivity is similar for most of the catalysts and conditions with a few performing rather worse. However, there is one catalyst that really stands out. 5% Pd/$CaCO_3$ gave 86% conversion and 86% selectivity for **2a** at only 65 °C (the circled point in Figure 8).

Catalysts in continuous reactors can easily give rise to local hotspots during exothermic reactions such as these.[37] This makes $CaCO_3$ particularly interesting as a support for reactions in $scCO_2$ because the CO_2 is likely to suppress degradation to CaO if the catalyst were to overheat locally.

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(37) Hyde, J. R.; Walsh, B.; Poliakoff, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7588–7591.

Conclusions

In this paper we have described the first systematic study of a continuous *O*-debenzylation in CO_2-expanded solvents. Although experimentally challenging, the continuous debenzylation of **1a** with H_2 and supported Pd catalysts in high-pressure CO + THF has been quite successful. We have established the effects on the reaction of varying temperature, H_2:substrate ratio, CO_2 flow rate, pressure, prereduction, and catalyst. The overall conclusion is that those reaction parameters which increase the conversion all have energy or materials costs associated with them. Therefore, a more detailed economic analysis is still needed to identify strategies for increasing the yield at the lowest possible cost.

Nevertheless, our study has produced three key results: (i) the reaction can give good selectivity towards the monodebenzylated product **2a**—that is towards the desymmetrisation of the symmetrical substrate, **1a**; (ii) this selectivity was only observed in the presence of CO_2, a rare example of a major effect directly attributable to CO_2; and (iii) the most effective catalyst was 5% Pd/$CaCO_3$, which gave 86% conversion with 86% selectivity. These results strongly suggest that it will be rewarding to study further the reactions in CO_2-expanded solvents of large molecules of potential pharmaceutical interest.

Supporting Information Available

Details of the synthesis of **1c** and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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