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Continuous Flow Hydrogenation of a Pharmaceutical Intermediate, [4-(3,4-Dichlorophenyl)-3,4-dihydro-2*H*-naphthalenyidene]-methylamine, in Supercritical Carbon Dioxide

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Abstract: The hydrogenation of complex pharmaceutical intermediate, *rac*-sertraline imine has been optimized as a continuous flow process utilizing a palladium/calcium carbonate ($Pd/CaCO_3$) catalyst and hydrogen in supercritical carbon dioxide ($scCO_2$). Superior levels of selectivity were obtained in the flow system possibly attributable to the heat transfer properties of $scCO_2$ which help to remove excess heat from the catalyst surface.

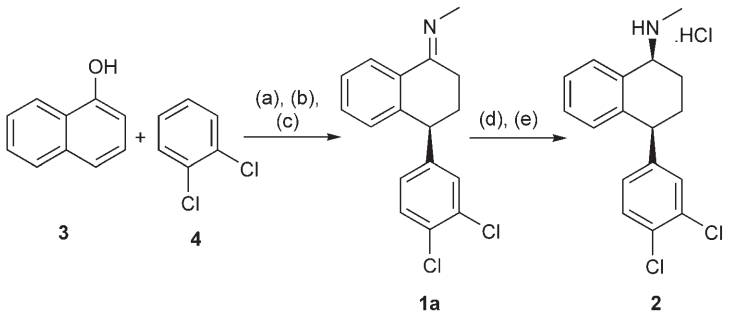
Keywords: carbon dioxide; diastereoselectivity; hydrogenation; sertraline; supercritical fluids

The excessive use of organic solvents in synthesis, purification and cleaning is the largest single contributor to overall chemical waste in the pharmaceutical industry. Therefore, a new technology that minimizes the use of organic solvents will help make pharmaceutical and fine chemical synthesis more sustainable. Supercritical fluids (SCFs) and, in particular, supercritical CO_2 ($scCO_2$), have emerged as alternative green solvents which can help the pharmaceutical industry attain this goal.[1,2] For instance, SCF chromatography[3,4] and SCF extraction[5,6] have proved to be powerful tools for the separation of active pharmaceutical ingredients (APIs) from complex mixtures. $scCO_2$ has also more recently been applied to anti-solvent precipitation of drug particles from solution.[7–10] $scCO_2$ is highly suitable for pharmaceutical processing because it is non-toxic and has relatively mild critical parameters ($T_c = 31\,°C$, $P_c = 74$ bar) so that the advantages of near-critical and $scCO_2$ can be achieved, whilst operating at relatively low temperatures where degradation of sensitive molecules is unlikely.

The application of $scCO_2$ as a solvent for the synthesis of pharmaceuticals has not yet been fully realized. This is because synthetic research in $scCO_2$ has focused largely on model substrates and compounds relevent to the bulk and fine chemicals industry.[11–13] This article explores the use of $scCO_2$ as a solvent for the hydrogenation of a complex pharmaceutical intermediate, [4-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-naphthalenyidene]methylamine, also known as *rac*-sertraline imine **1**.

(4*S*)-Sertraline imine **1a** is an intermediate in the synthesis of *cis*-(1*S*,4*S*)-sertraline hydrochloride **2**, marketed under the name, Zoloft® (Scheme 1), a multi-billion dollar drug developed originally by Pfizer for the treatment of depression and other anxiety related disorders.[14,15] Today Zoloft® is manufactured in relatively few steps by first reacting 1-naphthol, **3**, and 1,2-dichlorobenzene, **4**, with aluminium chloride to provide the racemic intermediate ketone. Simulated moving bed (SMB) chromatography is then used to separate efficiently the (4*S*)- and (4*R*)-enantiomers. Enantiomerically pure (4*S*)-ketone is then reacted with methylamine to afford the imine **1a**. Diastereoselective hydrogenation puts in the second chiral centre to afford (4*S*)-sertraline before conversion to the hydrochloride salt **2** (Scheme 1).

We chose to study the hydrogenation of imine **1a** in $scCO_2$ for a number of reasons. It has both regio- and chemoselectivity challenges, and a large body of information exists relating to this hydrogenation utilizing conventional molecular solvents in batch processes. Separation of dechloro by-products can be problematic and a key goal is to see if continuous hydrogenation in $scCO_2$ can control aryl dechlorination. We used *rac*-imine **1** as the substrate, rather than the optically pure (4*S*)-enantiomer **1a**. Therefore, upon hydrogenation, formation of all four stereoisomers, **5a–d**, is pos-

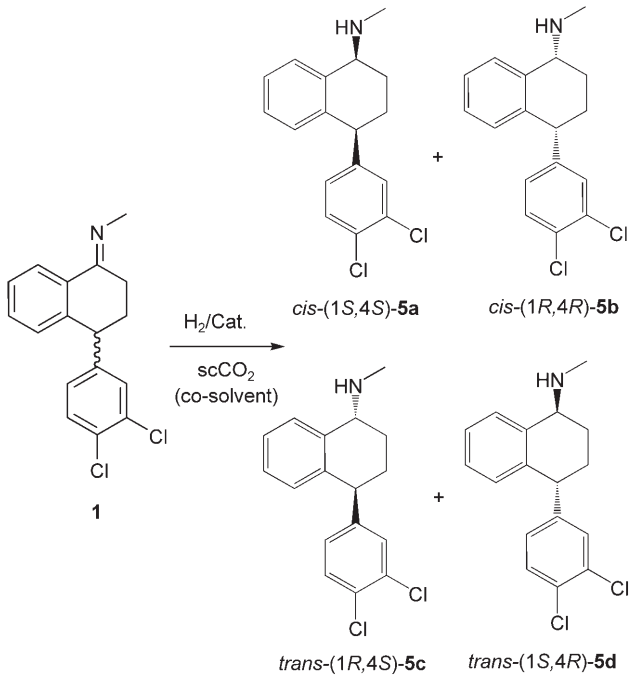


Scheme 1. Current Pfizer synthesis to make Zoloft®. (a) $AlCl_3$; (b) simulated moving bed chromatography (SMB); (c) $MeNH_2$, EtOH; (d) $Pd/CaCO_3$, H_2, EtOH; (e) HCl, EtOH.[14]

sible, the goal being to maximize formation of the required *cis*-isomers, **5a** and **5b** (Scheme 2).

In the original Pfizer process, reduction of *rac*-imine **1**, was performed using $NaBH_4$ to yield the *cis*- and *trans*-diastereoisomers in equal quantities. Pfizer then switched to a process using a Pd/C catalyst and H_2 to enhance diastereoselectivity and provide a *cis*:*trans* ratio of 70:30. Despite improved diastereoselectivity, the presence of dechlorinated by-products led to downstream purification issues. In their current process, Pfizer use a $Pd/CaCO_3$ catalyst which provides excellent diastereoselectivity (*cis*:*trans* ratio of 95:5) and $<1.0\%$ dechlorinated by-products.[15]

The limited solubility of H_2 in conventional liquid phase hydrogenation reactions can be rate limiting. Therefore, large presures of H_2 and long reaction times are often required to achieve high levels of conversion. $scCO_2$ is particularly attractive as a solvent for hydrogenation reactions since H_2 and $scCO_2$ are completely miscible. The absence of interphase mass transport effects means that hydrogenation can be be performed efficently in a continuous flow system.[16] High throughput and increased safety due to a smaller reactor volume make continuous flow technology an attractive alternative to batch processing. A schematic of our flow apparatus is shown in Figure 1.



Scheme 2. Diastereoselective hydrogenation of imine **1** should be performed to maximize formation of *cis*-amines **5a** and **5b**.

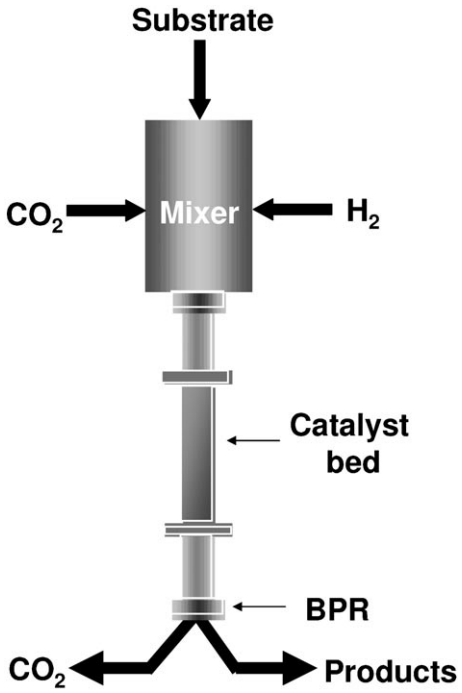


Figure 1. The continuous flow reactor is built from commercially available components. The substrate is mixed with high pressure CO_2 and H_2 before it is pumped over a fixed-bed reactor containing heterogeneous catalyst. System pressure is controlled *via* a back pressure regulator (BPR). Depessurization at the end of system affords separation of the solvent CO_2 (gas) from the product (liquid). A more detailed description can be found elsewhere.[17]

Table 1. Initial catalyst screening for the continuous hydrogenation of imine **1** in $scCO_2$.

Catalyst[a]	*T* [°C]	Conv. [%][b]	*cis*:*trans* ratio[c]	Chemoselectivity [%][b]	
				2a–2d	**6–10**
Pt/C	80	98	56:44	100	0
Pd/C	80	98	87:13	94	6
Pd/$CaCO_3$	80	98	95:5	96	4

[a] *Reaction conditions:* system pressure = 175 bar; mass of 5% metal catalyst = 0.5 g; H_2:substrate ratio = 3:1; concentration of **1** in THF = 0.2 M; flow rates: CO_2 = 1.0 mL min^{-1}, organic = 0.4 mL min^{-1}.
[b] Calculated by GLC using normalized peak areas
[c] Calculated by HPLC using peak areas.

The initial challenge was to find a catalyst that would exhibit high levels of activity in a flow system while delivering high levels of diastereo- and chemoselectivity. Since imine **1** is a solid under ambient conditions, a concentrated THF solution of imine **1** was pumped into the reactor. EtOH can also be used as co-solvent; however, the solubility of imine **1** is significantly lower than in THF.

Three different heterogeneous catalysts were screened. The first, Pt/C, had been shown in model studies to be selective towards imine hydrogenation in the presence of aryl chlorides.[18] However, it was found that while dechlorination did not occur, diastereoselectivity was poor (entry 1, Table 1) and variation in temperature and other perturbations did not lead to any significant improvement.

Changing from Pt/C to a Pd/C catalyst gave a significant improvement in diastereoselectivity but a small amount of dechlorination was observed (entry 2). Even without optimization, the third catalyst Pd/$CaCO_3$ gave a *cis*:*trans* ratio of 95:5, the same as that reported for the current Pfizer process with a similar catalyst. Chemoselectivity was also high with only 4% by-products detected (entry 3).

Amines **6–8** are formed through dechlorination of one or both of the aryl chloro groups, while by-product **9** is formed through further hydrogenolysis of the -NHMe group and increases in concentration at temperatures > 80 °C (Figure 2). Note that we did not observe formation of a stable carbamate of the secondary amine product. On occasions where solids were found in the product stream, these were identified as HCl salts, the HCl being produced *via* dechlorination.

As far as we are aware, the oxidized by-product naphthylamine **10** has not previously been reported as a by-product in any Zoloft® literature. Amine **10** represents *ca.* 50% of all by-products formed in the experiments in Table 1. However, at > 80 °C with H_2:substrate ratios of < 3:1, **10** was detected in larger quantities; for instance, with no H_2 at 120 °C, over the

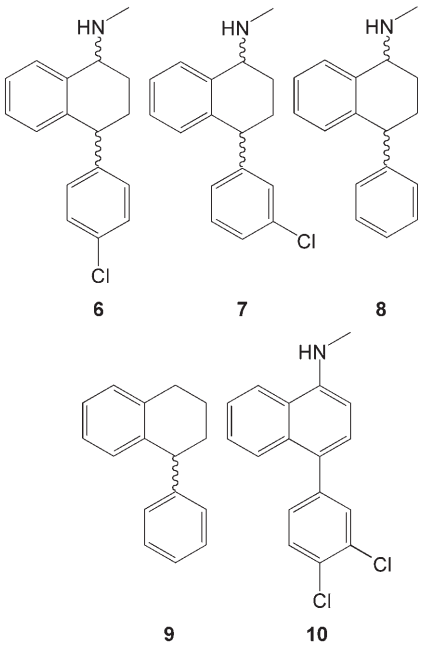
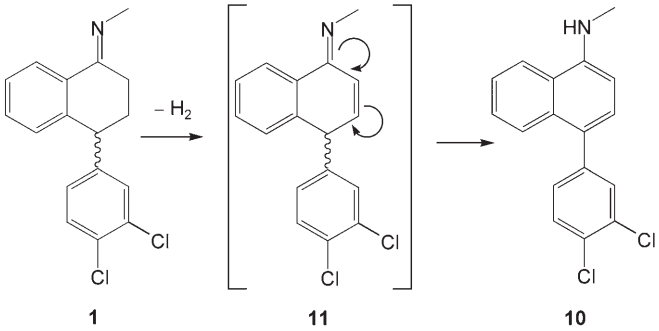


Figure 2. By-products **6–9** formed during the hydrogenation of imine **1** over the Pd/C and Pd/$CaCO_3$ catalysts were identified by GC-MS. By-product **10** was identified using NMR and comparison with an authentic sample.

Pd/$CaCO_3$ catalyst, imine **1** underwent 99% conversion with 80% selectivity to amine **10**. The other products were amines **5a–d**.

Given the high yield of naphthylamine **10** under H_2-starved conditions, it is proposed that **10** is formed *via* a Pd-catalyzed disproportionation of imine **1** to naphthylamine **10** and amines **5a–d** or *via* an oxidative dehydrogenation mechanism (Scheme 3). However, we cannot rule out the conversion of imine **1** to **10** *via* the undetected oxidized intermediate **11.**

As further evidence of the oxidative mechanism leading to **10**, imine **1** was reacted with 3-dichloro-5,6-dicyano-*p*-benzoquinone, DDQ, yielding a product identical by NMR and GLC to **10** isolated in the hydrogenation experiments.[19]



Scheme 3. Amine **10** can be formed from imine **1** over a Pd catalyst on active sites that are devoid of adsorbed H_2.

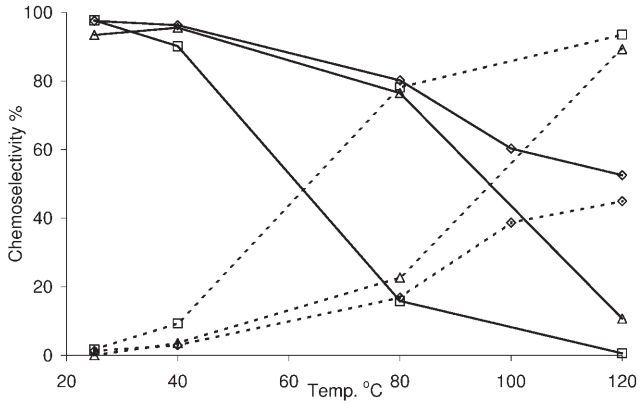


Figure 3. Comparison of overall chemoselectivity towards chlorinated products **5a–d**, ——, and dechlorinated products **6–9**, •••••, in the presence and absence of SCFs. Traces are labelled: □ performed in THF only; △ $scCO_2$+THF *; ◇ scC_3H_8 + THF **. *Reaction conditions:* H_2 $P=1$ bar; 0.05 g of 5% $Pd/CaCO_3$ cat.; 4.5 mL of 0.05 M solution in THF; reaction time = 40 min; * CO_2 $P=175$ bar; ** C_3H_8 $P=175$ bar.

At >100 °C, Pd is known to catalyze the oxidative aromatization of dehydro-1-napthylamines.[20] Formation of **10** may occur, even with excess H_2, as a result of compaction of the Pd catalyst inside the flow reactor. This makes it difficult for H_2 to be evenly distributed and could lead to hydrogen-deficient active sites in the catalyst bed, thereby promoting disproportionation and oxidative dehydrogenation of **1** rather than hydrogenation. This unexpected discovery of **10** highlights possible problems associated with compactable hydrogenation catalysts.

It is important to identify any specific advantages of using $scCO_2$ compared to conventional solvents. Therefore a series of hydrogenation reactions was conducted in THF and also THF + $scCO_2$ mixtures inside a batch autoclave at 25–120 °C. Temperature had little effect on diastereoselectivity; the *cis*:*trans* ratio remaining at between 92:8 and 93:7 in both solvent systems. However, there was a dramatic difference in the temperature dependence of chemoselectivity (Figure 3). Reactions in THF only undergo a change in chemoselectivity at a much lower temperature than those in the presence of $scCO_2$. For instance, at 80 °C, selectivity towards total dechlorinated by-products is reduced from 78% in THF to only 20% when $scCO_2$ is present.

In 2005, Ikariya et al. reported the effects of $scCO_2$ on the chemoselective hydrogenation of chloronitroaromatics over a Pt/C catalyst where lower levels of dechlorinated by-products were found for reactions performed with $scCO_2$ compared with those without.[21] It was suggested that CO, formed *via* the Pt-catalyzed reverse water-gas-shift reaction, poisons selectively the catalytic sites responsible for promoting dechlorination, while still allowing hydrogenation of the nitro group to occur. To establish whether this happens in our system, a series of reactions was performed in THF + C_3H_8 (Figure 3). scC_3H_8 ($T_c=97$ °C, $P_c=43$ bar) was chosen because it has previously been used as a solvent for hydrogenation reactions.[22]

Reactions performed in C_3H_8 exhibit selectivity at least as high as in $scCO_2$, suggesting that CO poisoning is unlikely to be the cause of the enhanced chemoselectivity. However, SCFs are known to exhibit greater diffusivity and lower viscosity than organic solvents which makes them excellent at removing heat.[23] Therefore, the enhanced chemoselectivity might be attributable to the ability of scC_3H_8 or $scCO_2$ to prevent hot-spot formation on the catalyst bed, which would otherwise lead to by-products.[24] It should be noted, however, that C_3H_8 is less suitable than $scCO_2$ for industrial applications since it is highly flammable.

Optimization of hydrogenation of **1** in the flow system using $scCO_2$ showed that by working at 40 °C over $Pd/CaCO_3$, in the presence of a large excess of H_2, it was possible to suppress almost completely all dechlorination and dehydrogenation side reactions, achieving a chemoselectivity of >99%. Diastereoselectivity was also excellent at a *cis*:*trans* ratio of 97:3, which is comparible to the current Pfizer process (Table 2).

In summary, we report the successful hydrogenation of a complex pharmaceutical intermediate in $scCO_2$. The hydrogenation of *rac*-sertraline imine **1** can be performed in continuous flow with higher levels of diastereoselectivity and comparible levels of chemoselectivity to the current process. Under optimized condtions this yields *cis*-sertraline (**5a** and **5b**) in 97% yield (including mass balance from flow apparatus). While diastereoselectivty appears to be affected primarily by the choice of metal and catalyst support, chemoselectivty is affected significantly by the pres-

Table 2. Comparison between the $scCO_2$ flow system and the Pfizer batch system for the hydrogenation of *rac*-sertraline imine **1**.

System	P [bar]	T [°C]	Conv. [%][b]	*cis*:*trans* ratio[c]	Chemoselectivity [%][b]	
					5a–5d	**6–10**
$scCO_2$[a]	175	40	99	97: 3	99	<1
Batch[15]	1	25	99	95: 5	99	<1[d]

[a] *Reaction conditions:* system pressure = 175 bar; mass of 5% $Pd/CaCO_3$ catalyst = 0.5 g; H_2:substrate ratio = 10:1, concentration of **1** in THF = 0.2 M; flow rates: CO_2 = 1.0 mL min^{-1}, organic = 0.4 mL min^{-1}.

[b] Calculated by GLC using normalized peak areas.

[c] Calculated by HPLC using peak areas.

[d] The presence of **10** is not reported in any Zoloft® literature.

ence of $scCO_2$. It is suggested that the excellent heat transfer properties of the $scCO_2$ help to maintain exceptional levels of chemoselectivity, even at elevated temperature. In the future it is hoped that $scCO_2$ flow systems will be successfully applied to other reactions and substrates of interest to the pharmaceutical industry. It will also be interesting in the future to investigate the economic drivers to change from a batch process in conventional solvents to flow reaction in a $scCO_2$ by comparing the investment and operation costs of the two processes.

Experimental Section

All catalysts used in this study were supplied by Johnson Matthey and used as supplied. The starting material, *rac*-imine **1** was prepared using literature procedures with a purity of $>98\%$. Analysis was performed by NMR (Jeol 270 MHz). For all hydrogenation studies, conversion and chemoselectivity were calculated using GLC (Shimadzu 2010) fitted with an FID detector. Relative response factors were used for all accurate calculations. In all cases, an achiral RTX-5 column (0.52 mm ID, 0.25 μm film thickness) was used and He as a carrier gas. A Waters 600 E HPLC machine was used to calculate accurately the *cis*:*trans* ratio. It was fitted with a UV-VIS detector set to 154 nm. A chiral HPLC column (Diacel Chirasil OD-H column, 30 cm) was used with a mobile phase of 2% 2-PrOH in *n*-hexane with 0.2% diethylamine. The flow rate was set to $1.0\,mL\,min^{-1}$ and the temperature isothermal at 25 °C. By-product identification was performed using a Thermo-Finnegan Polaris Q ion trap GC-MS fitted with an RTX-5 MS column attached *via* a heated transfer line to the ion trap mass spectrometer (CI mode) and He carrier gas. The ion-trap was used in the CI mode. All batch reactions were conducted inside a stainless steel autoclave (Mk type 1) sealed to a torque of 220 Nm equipped with a magnetic stirrer bar.

Acknowledgements

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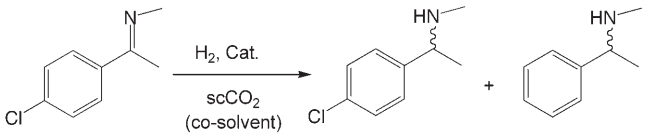
[18] Model studies were performed in the continuous flow apparatus using *N*-[1-(4-chlorophenyl)ethylidene]methanamine (below) to assess the chemoselectivity of imine hydrogenation *vs.* dechlorination. Results are not reported here.



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