Angewandte Chemie
International Edition

DOI: 10.1002/anie.201302718

Solventless Synthesis

A Single Enantiomer (99 %) Directly from Continuous-Flow Asymmetric Hydrogenation**

*Rubén Duque, Peter J. Pogorzelec, and David J. Cole-Hamilton**

Sir John Cornforth has suggested: "It does, for example, no good to offer an elegant, difficult and expensive process to an industrial manufacturing chemist, whose ideal is something to be carried out in a disused bathtub by a one-armed man who cannot read, the product being collected continuously through the drain hole in 100 % purity and yield".[1]

We now report a reaction that almost conforms to this ideal except that we replace the bath, a continuously stirred tank reactor, which cannot give 100 % conversion in continuous-flow mode, by a shower, which is a plug-flow reactor so can give 100 % conversion (Figure 1). In our system, the solventless asymmetric hydrogenation of dibutyl itaconate gives a single enantiomer of dibutyl 2-methylsuccinate uncontaminated by catalyst or starting material. No further purification is required. This is a particularly difficult challenge, since it must be carried out in neat substrate and must give 100 % conversion, 100 % *ee* with no leaching of the homogeneous catalyst.

As far as we are aware, the closest previous approaches to this ideal system in selective hydrogenation reactions involve supercritical CO_2 as the flowing solvent. Two examples are the work of Poliakoff and co-workers on the regioselective hydrogenation of isophorone to 3,3,5-trimethylcyclohexanone (99.4 %), which was commercialized[2] and that of Leitner and co-workers, who reported the asymmetric hydrogenation of dimethyl itaconate in a supported ionic liquid phase.[3] For the asymmetric hydrogenation, decompression of the CO_2 afforded a single uncontaminated enantiomer (*ee* $>98\,\%$) of dimethyl 2-methylsuccinate over the first 30 h of the reaction. The only problems with this system are the high pressure required and the use of $scCO_2$, the recycling of which requires substantial energy for decompression/recompression.

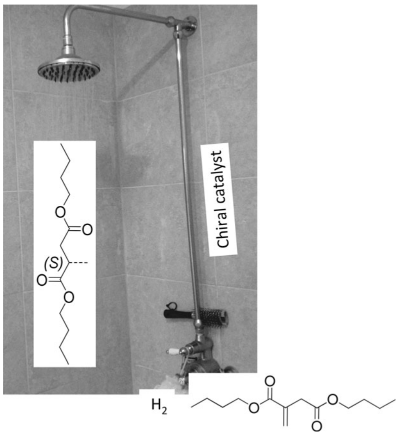

Figure 1. Concept of a continuous-flow asymmetric hydrogenation reaction giving a pure single enantiomer directly.

Our approach required the use of a supported catalyst, which would be compatible with a liquid phase flow and would not exhibit leaching.

Many immobilization methods can be found in the literature,[4] but we were attracted by the method introduced by Augustine et al.,[5] where the catalyst is immobilized onto alumina by using heteropoly acids as anchoring agents. The heteropoly acid coordinates both to the alumina and to the metal atom of the catalyst through its surface oxygen atoms. Since the ligands on the metal complex are not involved in the anchoring of the catalyst, the chirality is not altered and the catalyst can be as active and selective as its homogeneous counterpart. Besides, there is no significant limitation on the type of ligands that may be used.[6] As an example, Poliakoff and co-workers performed the continuous asymmetric hydrogenation of dimethyl itaconate by using different catalysts containing a variety of diphosphine ligands, not including (*R*,*R*)-MeDuPHOS, immobilized by this method. However, moderate conversions (70 % max.) and *ee* (83 % max.) were achieved,[7] and $scCO_2$ was used as solvent, presenting the same problems of pressure and decompression/recompression as discussed above.

For our experiments we used phosphotungstic acid (PTA) as anchor and the (*R*,*R*)-1,2-bis(2,5-dimethylphospholano)-benzene (MeDuPHOS) ligand. This ligand was first introduced by Burk[8] and, when combined with Rh (Figure 2, **1**), results in a very active and selective catalyst for asymmetric hydrogenation reactions of prochiral olefinic substrates.[9] This type of catalyst has been shown to give excellent conversion (99 %, 114 catalyst turnovers per hour)[10] and selectivity (99.8 % *ee*) in the asymmetric hydrogenation of dimethyl itaconate under flow conditions, but only in the presence of added solvents such as ethanol or ethyl acetate so that the product is obtained as a dilute solution requir-

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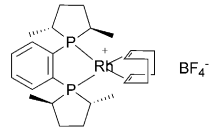

Figure 2. [{(*R*,*R*)-MeDuPHOS}Rh(cod)]BF_4 catalyst. cod = cycloocta-1,5-diene.

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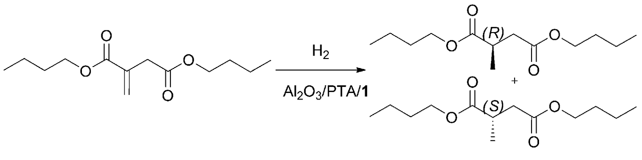
[*] R. Duque, P. J. Pogorzelec, Prof. D. J. Cole-Hamilton
EaStCHEM, School of Chemistry, University of St. Andrews
North Haugh, St. Andrews, Fife, KY16 9ST (UK)
E-mail: djc@st-and.ac.uk
Homepage: http://chemistry.st-andrews.ac.uk/staff/djc/group/

[**] We thank Dr. Reddy's for a sample of the rhodium catalyst and The EU for support from the ITN programme, NANOHOST, No. PITN-GA-2008-215193 (R.D.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302718.

ing further purification. Excellent results (> 99 % conversion, 93–99 % *ee*) have also been obtained by using 1,1′-bi-2-naphthol-based phosphoramidates either as molecular species[11] or incorporated into polymeric supports[12] for the hydrogenation of α-dehydroaminoacids under flow conditions, but again a solvent such as ethyl acetate[11] or toluene[12] is required.

We chose the hydrogenation of the prochiral alkene dibutyl itaconate (DBI) as a model reaction (Scheme 1), since DBI is liquid at room temperature and could be introduced pure into the continuous-flow system without the addition of any solvent. Solventless reactions are potentially the most environmentally acceptable of all reactions. Asymmetric hydrogenation reactions of DBI have only rarely been reported[13] and in general the *ee* values obtained are disappointing, with the best being 88.3 % when using a rhodium complex of (*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine supported in hydrotalcite.[13d]



Scheme 1. Hydrogenation of dibutyl itaconate.

Initial tests in the continuous-flow system showed that both PTA and alumina were required for the immobilization of catalysts. Thus, when the reaction was carried out without PTA, a high degree of catalyst leaching was observed, which led to low conversions and *ee* (Figure 3). When silica was used instead of alumina, similar behavior was observed obtaining conversions under 20 % and *ee* under 10 %. For further experiments the combination Al$_2$O$_3$/PTA/**1** was used.

Optimization of the reaction conditions was carried out under continuous-flow conditions. The effect of H$_2$ pressure on the reaction was analyzed first in a reaction at room temperature with a substrate flow of 0.1 mL min^{-1} and a H$_2$ flow of 0.2 L min^{-1} (all H$_2$ flows are quoted at 0 °C and 1 atm). The pressure was decreased from 20 bar to 5 bar, and as a result a slight increase in the conversion was observed while the *ee* remained stable at around 86 % (Figure 4). In the next reaction the effect of the H$_2$ flow rate was determined at a constant pressure of 5 bar. By decreasing the H$_2$ flow from 0.2 L min^{-1} to 0.05 L min^{-1} a large decrease in the conversion was observed, while the *ee* also decreased from 89 % to 70 % (Figure 5). Finally the effect of the substrate flow was studied at 5 bar of constant pressure and a H$_2$ flow of 0.2 L min^{-1} (Figure 6). At an initial DBI flow of 0.1 mL min^{-1} the conversion increased from 29 % to 75 % while the *ee* increased from 57 % to 82 %. A flow decrease to 0.05 mL min^{-1} led to an increase of conversion up to 95 %, while the *ee* remained stable. A final increase of DBI flow to 0.2 mL min^{-1} led to a substantial decrease of conversion to 31 % and *ee* to 73 %. In summary, the conditions that would lead to longer residence times and good H$_2$–substrate mixing, such as upward flow through the reactor, low H$_2$ pressures with high H$_2$ flows, and low substrate flows, were found to be optimal.

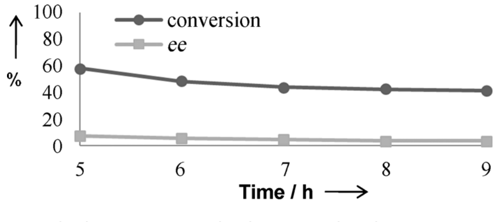


Figure 3. DBI hydrogenation with Al$_2$O$_3$/**1** and without PTA.

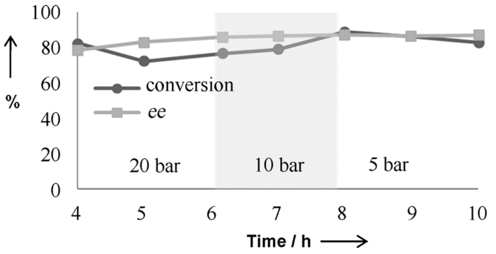


Figure 4. DBI hydrogenation with Al$_2$O$_3$/PTA/**1**. Effect of pressure.

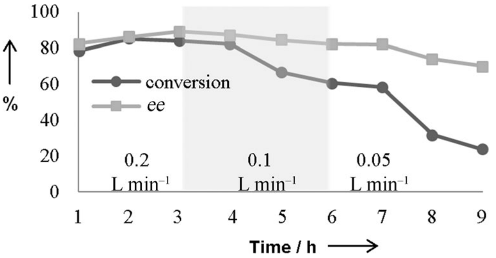


Figure 5. DBI hydrogenation with Al$_2$O$_3$/PTA/**1**. Effect of H$_2$ flow.

A reaction was then carried out for a prolonged period of time using the optimized flow conditions for DBI (0.05 mL min^{-1}, 0.2 mmol min^{-1}) and H$_2$ (5 bar, 0.2 normal L min^{-1}, 9 mmol min^{-1}; molar ratio H$_2$/DBI = 45; Figure 7).

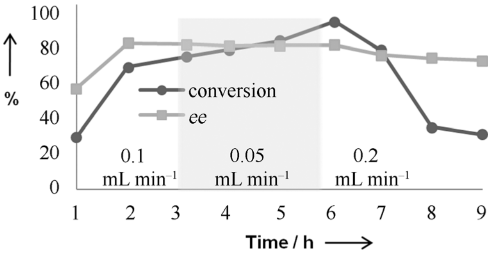


Figure 6. DBI hydrogenation with Al$_2$O$_3$/PTA/**1**. Effect of DBI flow.

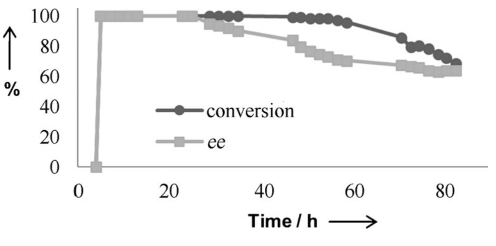


Figure 7. DBI hydrogenation with Al$_2$O$_3$/PTA/**1**. Stability over time at 5 bar pressure and room temperature.

Conversion over 99 % was achieved during the first 47 h and decreased afterwards to 68 % in the 83rd hour showing some catalyst degradation. Remarkably, during the first 23 h the product consisted of 99 % of a single enantiomer ($ee = 98\,\%$), but the enantioselectivity decreased progressively afterwards to 65 %.

After 4 days of continuous reaction a $\mathrm{TON} > 12\,900$ was achieved with Rh leaching between 44 and 625 ppb as determined by inductively coupled plasma mass spectrometry (ICP-MS) analysis. In summary, continuous production of a single enantiomer (without further purification steps) is possible under mild reaction conditions and with low catalyst leaching. For the first 23 h of the reaction, the products collected in simple glass vials directly from the outflow of the reactor consisted of an essentially pure (99 %) single enantiomer of dibutyl 2-methylsuccinate. The rhodium content was approximately 45 ppb.

As indicated above, we have used an upward flow through the reactor, which is similar to bubble column operation, because it prevents compacting of the catalyst, allows for excellent mixing of the hydrogen with the substrate and of the substrate with the catalyst, and it gives longer residence times on the catalyst bed. The disadvantage of this mode of operation is that an excess of hydrogen (H_2/substrate = 45) is required, presumably because it bubbles up through the liquid and any unreacted hydrogen is lost. A referee has suggested that downward flow, mimicking a trickle bed reactor, may allow operation with a lower excess of hydrogen. We have, therefore, carried out preliminary experiments under exactly the same conditions as those used for the reaction shown in Figure 7 but with the flow of substrate and hydrogen being downwards through the reactor. The initial conversion and *ee* were close to 100 %, but the conversion after 4 h stabilized at about 97–98 %. Reducing the H_2 flow rate by half ($0.1\ \mathrm{L\,min^{-1}}$, H_2/substrate = 22.5) led to significantly lower conversion (75–80 %) and a drop in *ee* to 82 %, a rather similar behavior to that observed in the upward flow experiments. Restoring the initial conditions increased the yield to 92 % and stabilized the *ee* at approximately 82 %. Reducing the pressure also reduced the conversion to 60 % with an *ee* of 75 %, but the conversion could be returned to > 80 % by reestablishing the original conditions. It appears that there are advantages from using upward flow (higher conversions) under our reaction conditions. The results for the downward flow reaction are presented in Figure S1 in the Supporting Information.

Having in hand a pure enantiomer, it was possible to measure the optical rotation, $[\alpha]_D^{20} = -3.53 \pm 0.01°$ ($c = 2.9\ \mathrm{g\ (100\ mL)^{-1}}$) and identify it as the (*S*)-(−) enantiomer by comparison (chiral GC) of the dimethyl ester, which was obtained from it by transesterification with methanol, with an authentic sample of dimethyl-(*R*)-(+)-methylsuccinate.

In conclusion, continuous-flow solventless asymmetric hydrogenation of DBI was successfully performed at room temperature under 5 bar H_2 with an Rh–MeDuPHOS catalyst immobilized onto alumina through phosphotungstic acid. More than 99 % conversion and 99 % (*S*)-(−)enantiomer, $ee = 98\,\%$ (< 50 ppb Rh) were achieved for the first 23 h of reaction. During this time, 68 g (278 mmol) of a pure (99 %) (*S*)-(−)-dibutyl 2-methylsuccinate with no need for further purification was produced by using only 41 mg of Rh–MeDuPHOS (0.06 mmol Rh) (2638 turnovers).

Although a significant excess of hydrogen is currently employed, the low operating pressure makes recycling of excess hydrogen comparatively straightforward. It would be possible to collect the product without decompression, thereby making the energy requirements for recycling very low. We are now working to improve the long-term stability of the catalyst and to reduce the pressure to 1 bar.

Received: April 2, 2013
Revised: June 5, 2013

Keywords: asymmetric catalysis · continuous flow · solventless synthesis · synthetic methods

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