Recycling of Homogeneous Hydrogenation Catalysts by Dialysis Coupled Catalysis

Koen De Smet, Annick Pleysier, Ivo F. J. Vankelecom,* and Pierre A. Jacobs[a]

Abstract: Although transition-metal complexes are very attractive as homogeneous catalysts in fine chemistry, their high prices often limit their applications. A means to recycle those catalysts would solve this problem and would simultaneously facilitate the downstream purification of the product. This is now realized in a new concept in which homogeneous catalysis is coupled to dialysis. The advantages of homogeneous catalysis (off-the-shelf catalysts, high activities and selectivities) are thus combined with those of heterogeneous catalysis (easy catalyst separation from product solution, reuse of catalyst, and possibility for continuous operation). Since the heart of the process is the membrane, self-prepared membranes were preferred as they allow a better control and understanding of the separation characteristics. Rhodamine B was used as a probe molecule to define the working conditions of the membrane. The concept is proven to work for two relevant chiral reactions: a hydrogenation with Ru–BINAP and a hydrogen transfer reaction with Ru–TsDPEN [BINAP = (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine); TsDPEN = tosyl-*N*,*N*′-diphenyl-1,2-ethanediamine].

Keywords: catalyst recycling · dialysis · hydrogenation · membranes · ruthenium

Introduction

Transition-metal complexes (TMCs) are widely used in homogeneous catalysis and are by far the most important class of asymmetric catalysts. However, reusing these expensive TMCs is mostly impossible, and the presence of toxic metals in the prepared products requires extra purification. To avoid these problems, several heterogenization methods have been developed already with varying degree of success.[1]

One of the possible routes is to combine catalysis with membranes.[2] Recently, we reported such a hybrid process in which a solvent-resistant nanofiltration membrane retained the TMC from a homogeneous reaction mixture and let the products permeate.[3] No catalyst modification was needed whenever the right membrane was used under the appropriate conditions. This concept, which was later also illustrated for other catalytic systems,[4] combines the advantages of homogeneous (off-the-shelf catalysts, high activities and selectivities) and heterogeneous catalysis (easy catalyst separation from product solution, reuse of catalyst, and possibility for continuous operation).

We now report on a new membrane/catalysis hybrid process, in which a concentration gradient instead of a pressure difference forms the transmembrane driving force. Similarly to enzymes in biological cells, a selective hydrophobic membrane separates the catalyst here from the bulk solution (Figure 1a). Under influence of the concentration difference, substrate molecules permeate from the bulk phase through the membrane to reach the catalyst phase in which reaction takes place. After reaction, the formed product builds up its own concentration gradient and migrates back to the bulk solution. Compared to the earlier reported nano-

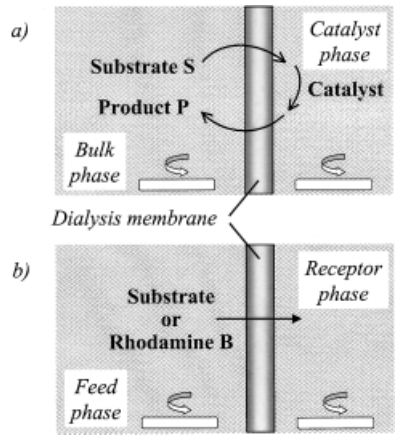

Figure 1. Schematic view of the set-up a) for dialysis-coupled catalytic transfer hydrogenation and b) for determining permeabilities.

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filtration/catalysis hybrid process, no mechanical pressure is needed here. Hence, the mechanical and safety requirements of the set-up are clearly facilitated.

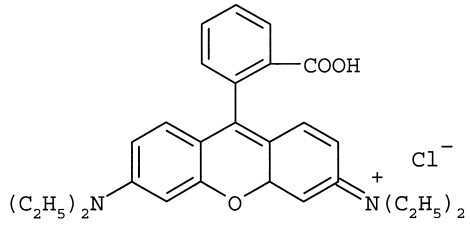
The catalysts applied here to prove the new concept are the chiral Ru–BINAP[5] and Ru–TsDPEN[6] complexes [BINAP = (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine); TsDPEN = tosyl-*N*,*N*′-diphenyl-1,2-ethanediamine], with hydrogen and *iso*-propanol (IPA), respectively, as the reductants (Scheme 1). The industrially relevant Ru–BINAP catalyst is an important tool in asymmetric reductions, as proven by the recent research to find reusable forms.[7] Over the past few years, chemists also show a growing interest in catalytic transfer hydrogenations, since the absence of explosive hydrogen and high-pressure equipment eases safety regulations. Additionally, rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor.[8] Ru–TsDPEN, one of the most efficient transfer hydrogenation catalysts, has already been linked covalently to a polymer.[9]

Earlier reported systems in which either enzymes[10] or enlarged TMCs[2, 11] were separated from the reaction mixture with an ultrafiltration membrane cannot be applied to unmodified TMCs. A careful selection of membrane type and filtration conditions lays the foundation of the new hybrid system that is presented now. In spite of the wide availability of commercial membranes, self-prepared membranes were preferred as they allow a better control and understanding of the separation characteristics.

Results and Discussion

PDMS, a dense elastomer with good thermal, mechanical, and chemical stability, was selected as the membrane material to retain the catalyst, while allowing migration of the substrates and products. Such a dense membrane separates compounds according to the solution–diffusion mechanism: the affinity of an organic compound for the polymer determines the sorption, while diffusion mainly depends on the size of the compound and the swelling of the polymer network.[12] To define conditions of good permeability and retention during the reactions, a PDMS membrane was mounted in a contactor (Figure 1b), that separates an alcoholic feed phase with dissolved solute from a receptor phase containing the pure alcohol. By analyzing the solute concentration in both phases, permeabilities through PDMS were calculated for the two test substrates, dimethylitaconate (DMI) and acetophenone (AP). Both in methanol and IPA, they were found to be sufficiently high, in the order of magnitude of 10^{-10} m^{2}s^{-1}, proving that PDMS is a good choice for the permeation of these substrates.

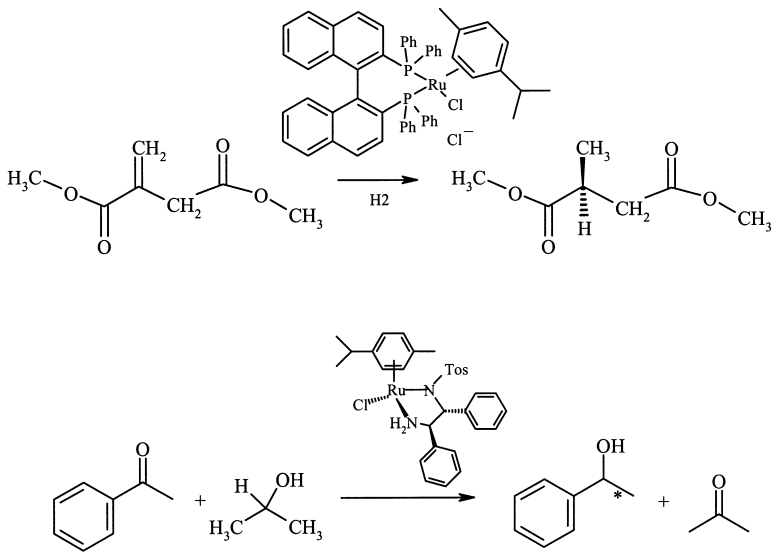
However, the hydrophobic PDMS is expected to swell strongly in a rather apolar solvent like IPA; this would be detrimental for the rejection of compounds with the size of the catalysts (Scheme 1). Hence, Rhodamine B (M_W = 479 Da) was used in the contactor as a probe molecule for



Rhodamine B

the catalyst to estimate the catalyst rejection under different solvent conditions. With methanol (0.3 wt% swelling in PDMS) or ethanol (5 wt% swelling), no Rhodamine B was detected in the receptor phase after 100 h. On the other hand, traces of Rhodamine B were found when IPA (16 wt% swelling) was used. Aiming at a more restricted swelling of the membrane through physical cross-linking, 10 wt% silica filler was added to the PDMS membrane. However, swelling in IPA decreased insufficiently. In an alternative approach, the solvent phase was changed. The idea followed from swelling experiments in mixtures of both solvents (Figure 2), in which an exponential increase in the swelling was observed with increasing IPA content. A 30:70 MeOH/IPA mixture resulted in the complete absence of Rhodamine B in the receptor phase after 100 h with an unfilled PDMS membrane.

With the substrate permeating (and given the chemical resemblance presumably also the product) and the complex rejected, the requirements to realize a TMC recovery system were thus fulfilled. The concept was proven first by hydrogenating DMI with Ru–BINAP and hydrogen gas. The catalyst solution is present in a submerged membrane system, simply pre-



Scheme 1. The reduction of DMI with Ru–BINAP (above) and of AP with Ru–TsDPEN (below).

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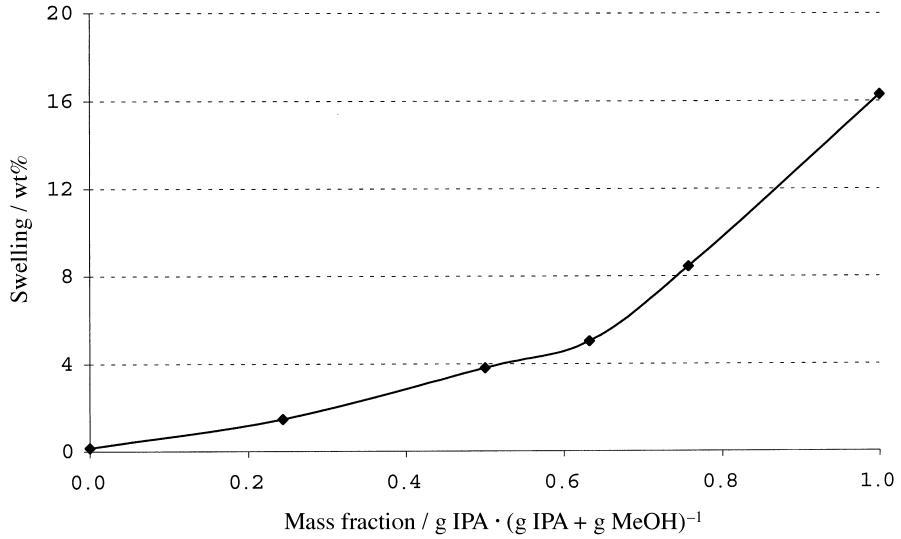

Figure 2. Swelling of PDMS in MeOH/IPA mixtures at room temperature.

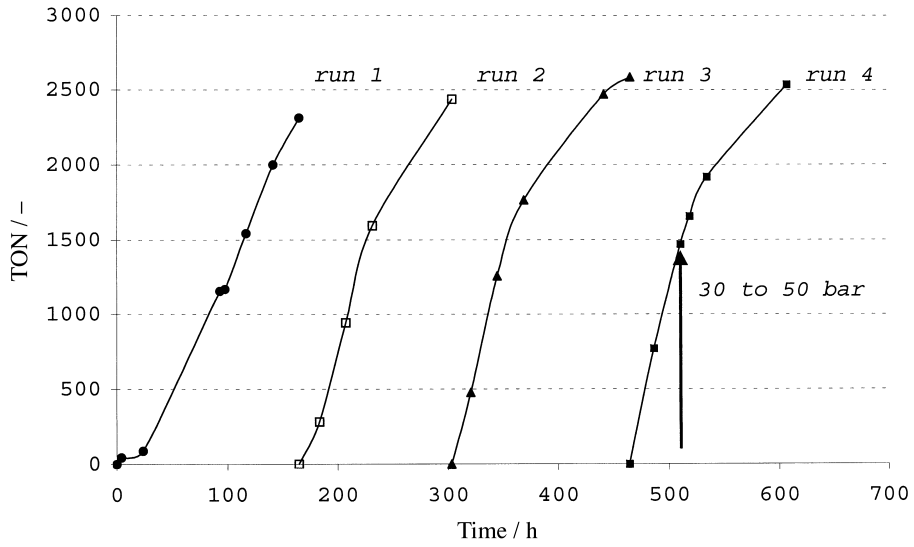

Figure 3. TON for the reduction of DMI with Ru–BINAP as a function of time: room temperature, catalyst = 8 μmol, $[S]_{bulk} = 0.41$ M, $V_{cat} = 4$ mL, $V_{bulk} = 53$ mL, 30 bar H_2.

pared as a sealed "PDMS capsule". The substrate is dissolved in the bulk phase and allowed to come into contact with the PDMS-capsule. Figure 3 shows the turnover number (TON) as a function of time for the membrane-coupled reaction, run at 30 bar. The first run shows an initial transient period during which the substrate first had to permeate through the relatively thick submerged membrane before it reached the stagnant catalyst phase inside the capsule and then diffused back to the bulk phase for sampling. After reaching about 90% conversion, the bulk phase was replaced and similar turnover frequencies (TOF) of 25.01, 27.26 and 27.71 h^{-1} were obtained in the following runs 2, 3 and 4. In runs 2 and 3, the PDMS capsule was removed after 90% conversion and no further activity could be detected in the reaction mixture. Furthermore, the Ru content in the bulk phase was always below the AAS detection level, proving that a truly recyclable Ru–BINAP system was realized. During run 4, the hydrogen pressure was increased from 30 to 50 bar, without any effect on reaction rate. Since a hydrogen pressure increase from 10 to 50 bar in a homogeneous reaction results in a reaction five times faster, this experiment gives in fact another proof for the absence of catalyst leaching. It suggests that substrate availability is probably limiting the reaction, due to its slow permeation through the thick PDMS membrane and the absence of stirring in the capsule. Throughout the four runs, the system maintained its enantiomeric excess (*ee*) of 93% and reached a cumulative TON of around 10000. A way to decrease the time period of the experiment would be to use a properly supported thin composite membrane with an agitated catalyst phase.

Given the destructive effect of oxygen (entries 1, 2 and 3 in Table 1), the catalytic transfer hydrogenation of AP with IPA was studied under nitrogen atmosphere. As reported by Noyori et al. the equilibrium of the reaction is most shifted to the right at AP concentrations below 0.1 M.[6] Indeed, the conversion decreased from 93% to 79%, while the TOF was influenced positively by higher substrate concentrations (entries 3, 4). On the other hand, the reaction rate decreased in the presence of acetone (entry 5) and of reaction product (entry 6).

A contactor-like setup was now applied for the semi-continuous catalytic transfer hydrogenation of AP (Figure 1a). Each run was stopped before reaching the equilibrium (Figure 4) by replacing the solution of the bulk phase.

Table 1. Reduction of AP with Ru–TsDPEN. Standard conditions: room temperature, 10 mL solvent, 0.1 M AP, and 0.5 mM catalyst. Conversions and *ee* were analyzed on a Chirasil-DEX CD (Chrompack) column.

	Conditions	TOF (after 4 h)	*ee* [%]
1	atmosphere	4	95
2	O_2 flush	2	90
3	0.1 M	17	95
4	0.5 M[a]	37	95
5	[AP]/[acetone] = 1	10	95
6	[AP]/[product] = 1.33	11	95
7	IPA/MeOH = 1	16	95
8	IPA/MeOH = 0.1	5	95
9	IPA/MeOH = 0.01	3	95

[a] S/C = 1000.

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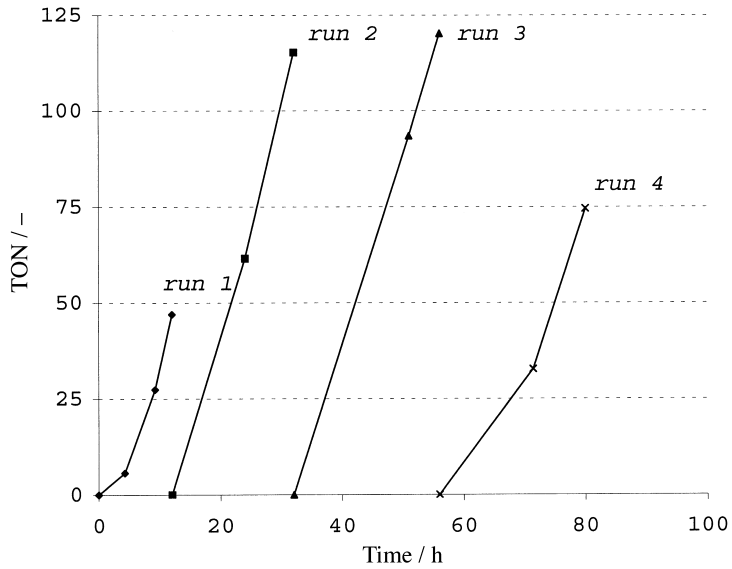

Figure 4. TON for the reduction of AP with Ru–TsDPEN in IPA: room temperature, catalyst = 17 μmol, $[S]_{bulk} = 0.1$M, $V_{cat} = 32$ mL, $V_{bulk} = 40$ mL.

The thus shortened overall reaction time to reach the accumulated TON minimized the risk of catalyst deactivation. A lag phase was again noticed in the first run. In the subsequent runs, the TOF decreased from 5.72 over 5.21 to 3.11. No further activity was observed in any of the removed bulk phases, thus suggesting that no catalyst had permeated. However, AAS showed a Ru leaching of about 5%. The observed light brown-green color of the final bulk phases could thus be attributed to a permeating inactive form of the Ru species. A cumulative TON of 370 was reached at a constant *ee* of 95%

Just like in the above experiments, a complete reduction of catalyst leaching was aimed at by using a MeOH/IPA mixture. As shown in entries 7–9 (Table 1), the replacement of IPA by MeOH largely affected the reaction rate, but a 1:1 mixture still showed a reaction rate and *ee* comparable to those obtained in pure IPA (entry 3). The lag-phase was eliminated now by using a 0.1M AP catalyst phase. The semicontinuous reaction could be repeated four times with a constant *ee* of 95%, but with some loss in activity with TOF's of 4.07, 3.41, 2.57, and 2.47, respectively (Figure 5). Compared to the batch reaction, the *ee* was unchanged, but the activity was lower due to mass-transfer limitations. An unreactive, but this time clear bulk phase was obtained after 24 hours of reaction. Because no ruthenium could be detected now, the decreasing activity was clearly due to a deactivation of the homogeneous complex in the catalyst phase. Indeed, Bayston et al.[9] also observed deactivation upon recycling, even though a completely different immobilisation method was applied. Van Leeuwen and coworkers proposed clustering of the Ru complexes as a possible reason for the deactivation of their aminoalcohol complexes,[13] while traces of water were suggested by Laue et al. to deactivate their related Ru–diamine/diphosphine catalyst.[14] Even though these homogeneous catalysts perform very well in the first screening experiments done during their development,[6] deactivations like that observed here only become apparent in nonleaching, reusable systems. It proves the clear need for more investigations towards homogeneous catalysts with improved long-term stability.

Conclusion

A new and simple method has been reported for the recycling of homogeneous TMCs. The combination of high catalyst rejection with reasonable product/substrate fluxes is the essential membrane property. This requires thin, stable membranes and their use under appropriate conditions. Whenever stable catalysts are available, a continuous or semicontinuous reaction mode under conditions of homogeneous catalysis can thus be developed.

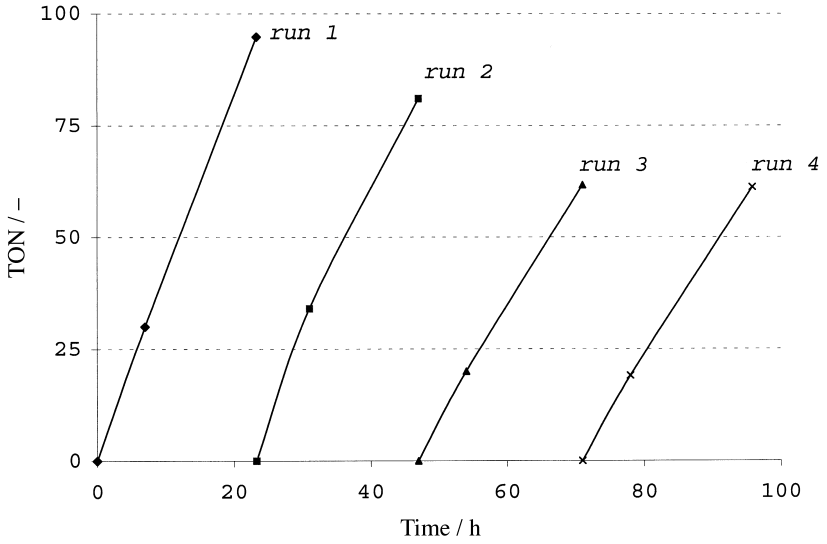

Figure 5. TON for the reduction of AP with Ru–TsDPEN in a 1:1 mixture of MeOH/IPA: room temperature, catalyst = 25 μmol, $[S]_{bulk} = 0.1$M, $V_{cat} = 32$ mL, $V_{bulk} = 40$ mL.

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Experimental Section

Membrane preparation: A 40 wt% PDMS (General Electric, RTV 615 A and B) solution in hexane was pre-polymerized at 60 °C for 0.5 h. It was poured into a petri dish, which was placed in a vacuum oven at 100 °C to complete cross-linking. The membrane thickness was measured with a micrometer. For the filled membranes, silica (Hi-sil 233, PPG) was dried at 300 °C and added after the prepolymerisation.

Preparation of the PDMS capsule: The PDMS capsule was prepared by annealing the borders of two separate 400 μm thick PDMS membranes with RTV 615 B as "glue" to form some kind of "tea bag", which holds the catalyst solution. This resulted in a total effective membrane area of 50 cm^2.

Swelling measurements: PDMS was dried under vacuum and immersed in the solvent mixtures till constant weight. The membrane swelling was expressed as Equation (1):

$$\mathrm{wt}(\%) = \frac{(g_{\mathrm{sorbed}} - g_{\mathrm{initial}})}{g_{\mathrm{initial}}} \times 100 \quad (1)$$

Permeability measurements: The membrane was clamped between two glass cylinders (32 mL) from which samples were taken at certain times (Figure 1b). The active membrane area was 35.2 cm^2. Permeabilities P of organic compounds were calculated from Equation (2):

$$J_{(\mathrm{mol\,m^{-2}s^{-1}})} = P_{(\mathrm{m^2s})} \frac{\mathrm{d}C_{(\mathrm{mol\,m^{-3}})}}{\mathrm{d}X_{(\mathrm{m})}} \quad (2)$$

The concentrations of DMI and AP in MeOH and IPA, respectively, were determined by GC analysis, while Rhodamine B concentrations were determined by UV/Vis spectroscopy (Perkin–Elmer) at 543 nm. The starting solutions had a concentration of 0.4 M for DMI, 0.1 M for AP, and 40 μM for Rhodamine B.

Reduction of DMI: The PDMS capsule was used for the DMI reduction in order to facilitate the pressurization of the reaction vessel. Ru–BINAP (7.5 mg), dissolved in MeOH (4 mL), was placed in the PDMS capsule ("catalyst phase"). The capsule was then submerged in a stirred DMI/MeOH solution (53 mL, 0.4 M) at 30 bar ("bulk phase"). The GC analysis was done on a Chiraldex G-TA column (Chrompack). Ru concentrations were determined by atomic absorption spectroscopy (Varian Techtron AA6).

Synthesis of the TsDPEN ligand: The TsDPEN ligand was synthesized according to ter Halle,[15] followed by an extra column purification over silica with a dichloromethane/diethyl ether (10:1) mixture. The melting point of the prepared ligand was 123 °C compared to the reported 104 °C. The purple metal complex was prepared, according to the procedure reported by Noyori et al.[6]

Reduction of AP: The standard conditions for the batchwise reduction of AP were: solvent (10 mL), AP (0.1 M), and catalyst (0.5 mM). Conversions and enantiomeric excesses were analyzed on a Chirasil-DEX CD (Chrompack).

For the dialysis coupled reactions, Ru–TsDPEN (17 μmol) was dissolved in IPA (32 mL) and was used as catalyst phase, while AP solution (40 mL, 0.1 M) formed the bulk phase. Samples were taken at certain times and the feed solution was replaced after 12, 24, 24, and 90 h. Supernatants were reacted another 24 h and analyzed on their Ru content by atomic adsorption spectroscopy.

In the experiment with reduced leaching and without time lag, Ru–TsDPEN (25 μmol) was dissolved in an IPA/MeOH solvent mixture (32 mL, 1:1 *v*/*v*) that also contained AP (3.2 mmol).

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