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LETTERS

Semi-continuous nanofiltration-coupled Heck reactions as a new approach to improve productivity of homogeneous catalysts

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Abstract—Substantial increase in homogeneous catalyst productivity for a well known Heck coupling was achieved by nanofiltration-coupled catalysis. The use of nanofiltration membranes enabled catalyst separation and allowed subsequent catalyst recycle and reuse. This new technique demonstrated potential for general applicability to homogeneously catalysed organic syntheses. © 2001 Elsevier Science Ltd. All rights reserved.

Many organic syntheses require expensive homogeneous transition metal catalysts (TMCs) to effect the reactions.[1–4] Separation of these catalysts from the reaction products and solvents is difficult, requiring the use of energy intensive and waste-generating downstream processing.[5] Moreover, few if any of the industrially employed separations are aimed at recovering the catalyst in an active form: rather, they focus on obtaining a pure (metal-free) product/solvent phase by removing any residual catalyst and catalyst decomposition fragments.

Hybrid processes combining catalysis with membrane separations seem promising. It has been demonstrated that TMC-catalysed reactions can be carried out homogeneously with dendritic catalysts in continuous membrane reactors.[6] Nanofiltration (NF) membranes were shown to retain 10,000 Da dendrimers in dichloromethane. The same membranes also retained enlarged oxazaborolidines,[7] but suffered poor performance due to swelling in the applied solvents. Under more carefully selected conditions,[8] membrane selectivity improved such that catalyst enlargement was no longer required. Hydrogenation was effected in methanol using a continuous stirred tank reactor, with activities and selectivities consistent with a homogenous reaction. The reaction mixture was contacted with an NF membrane which rejected the catalyst but allowed product permeation, and several reactor volumes were processed using one catalyst charge. However, while the reported continuous operation mode for nanofiltration-coupled catalysis may be useful for process control, there is little flexibility in its operating conditions: the conditions for both reaction and filtration must be identical and will usually be limited by the membrane stability. While membrane manufacturers set temperature tolerance limits at 50°C, optimal membrane separation will only occur at lower temperatures (15–20°C). This immediately rules out reactions occurring at higher temperature, unless the user is willing to compromise separation capability. Furthermore, for economic and product purity reasons, high conversions are required in continuous operation, mostly implying low reaction rates and thus higher reactor occupancy. 100% conversion is not feasible as some reactant loss across the membrane will always occur. All the above studies[6–8] have utilised the same composite solvent resistant MPF-50 or MPF-60 membranes produced by Koch USA.

In our new generic approach, the catalysis and NF stages are still coupled but operate independently, allowing more flexible operating conditions and lower reactor occupancy.

Keywords: Heck reaction; homogeneous catalysis; nanofiltration; catalyst recycle.

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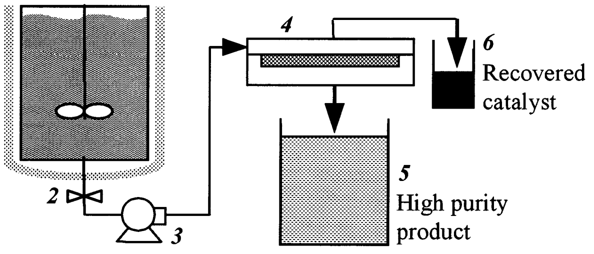
A Heck coupling reaction was selected to illustrate the new concept. The Heck reaction has been the subject of much interest as it is known to be the only single step method for the arylation of olefins.[2,9,10] In addition to the problem of difficult post-reaction separation, as is true of many homogeneously catalysed reactions, a further drawback of Heck catalysis is catalyst deactivation due to the inherent instability of the catalyst at certain stages of the catalytic cycle.[11] Consequently, the lifetime of the active catalyst is finite and low. The conventional approach to increase the productivity of a given catalyst system in Heck chemistry has thus far mostly been through adapting the catalyst ligands,[11–17] or the use of additives.[18–22] The means by which the additives impart these advantageous effects remains, in most cases, unclear. Beneficial effects due to temperature and pressure have also been reported.[23–25]

Alternatively, Heck catalyst productivities have been increased by reusing the catalyst after separating it from the products. Liquid–liquid and solid–liquid systems are the most commonly reported.[11,26–28] Success was limited due to the trade-off between catalyst efficiency (limited interaction with the substrate) and separation capability (catalyst transfer to reagent phase). Some individual successes have been reported in pseudo-homogeneous systems utilising 'in situ phase separation' of catalysts and products, but it is not yet clear whether they will have generic applicability. In near-critical fluids, vaporisation of volatile organic reactants reduces conversion, and side reactions at high temperature reduce selectivity and cause product decomposition.[29] This can only be avoided by minimising product exposure to these effects and by accepting lower conversions (20–50%). A major problem for Heck reactions in ionic liquids is the accumulation of inorganic by-products in the reaction medium, limiting its recyclable lifetime.[30–32]

Materials and methods

Reactions were performed in a 27 ml glass reactor (Scheme 1). The amounts of $Pd(OAc)_2(PPh_3)_2$, P(*o*-tol)$_3$, iodobenzene, styrene, triethylamine and water were added to the reactor and the volume was made up to 27 ml with the desired solvent. The reactor was placed in a heating jacket (**1** in Scheme 1) controlled at 60±10°C. Sampling was carried out until a 95–100% conversion of iodobenzene had been reached. The reactor was cooled to 20°C and with valve **2** opened and pump **3** switched on, the post-reaction mixture was transferred from the reactor to the nanofiltration cell **4**. 85% of the feed volume was permeated across the polyimide solvent resistant nanofiltration (SRNF) membrane (W.R. Grace & Co., MD, USA)[33] into a collection receptacle **5**. Both retentate and permeate were sampled for GC analysis. With the valve **3** now closed, the retentate was recycled back to the reactor from which the precipitated salt was removed. The reactor was topped up again with fresh reactants, base and solvent **6**. The reaction was then re-initiated. The volumes and weights used in the three different solvent systems studied are outlined below.



Scheme 1. Scheme of the NF-coupled catalysis configuration.

Reactant concentrations: iodobenzene (2.7 ml, 1.2 equiv.); styrene (2.3 ml, 1 equiv.); triethylamine (2.8 ml, 1 equiv.); $Pd(OAc)_2(PPh_3)_2$ (0.05 g, 0.004 equiv.); P(*o*-tol)$_3$ (0.08 g, 0.012 equiv.).

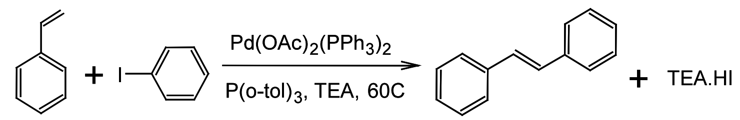
Solvent systems: 'EA', 50:50 mixture of ethyl acetate and acetone (17.7 ml), H_2O (1.49 ml); 'MTBE', 40:60 mixture of methyl-*tert*-butyl ether and acetone (18.6 ml), H_2O (0.54 ml); 'THF', tetrahydrofuran (18.1 ml) and H_2O (1.08 ml).

The cumulative turnover number (TON) is calculated as the total moles of product synthesised over repeated reaction cycles per mole of catalyst initially added in the first run.

The membrane performance was assessed in terms of flux and rejection. Flux was expressed as the volume permeated per unit area over a time period (l m^{-2} h^{-1}) at a transmembrane pressure of 30 bar. Rejection of a species was defined as $R=100*(1-(C_p/C_r))$, with C_p and C_r representing final permeate and retentate concentrations of that species. An R value of 100% corresponds to perfect retention of the species and 0% to no separation.

Results and discussion

The tested Heck-catalyst was $Pd(OAc)_2(PPh_3)_2$ with P(*o*-tolyl)$_3$ as a stabilising agent. A standard reaction to form *trans*-stilbene from styrene and iodobenzene (see Scheme 2) was studied in three different solvents in order to match membrane and catalyst performances as well as possible. Polyimide membranes with stable NF properties in solvents have been demonstrated on an



Scheme 2. Heck-coupling of styrene and iodobenzene to *trans*-stilbene.

industrial scale.[33] A recently developed Grace SRNF membrane was preferred to the MPF-type membranes reported in earlier work, since the former showed better separation characteristics and higher fluxes in screening experiments with similar solvents and TMCs. Figs. 1–3 show the iodobenzene conversion and cumulative TON as a function of time for solvent systems EA, MTBE and THF, respectively. The abrupt discontinuity in conversion is attributable to the filtration, addition of new reagents and re-initiation of the reaction at zero conversion of iodobenzene in the following cycle. The number of times the reaction–filtration sequence was performed on each system was arbitrarily set at five, allowing four catalyst recycles for each system. A selectivity of 100% to *trans*-stilbene was observed in every reaction. Even though cumulative TONs gradually tapered off with each subsequent recycle, every reaction went to near completion and a total TON of 1200 was thus realised.

The membrane results summarized in Table 1 are mean values obtained over the four membrane separations carried out, one before each recycle. In the THF system, the membrane had to be replaced after each run since lower retentions were noticed in subsequent filtration. The total time given in the table is the cumulative time needed for the five successive reactions to reach completion.

Fig. 1 shows that the EA system achieved near-complete conversion of the first batch in about 3 h. In the subsequent filtration, a Pd rejection of 90% was realised while permeating 23 ml of the total reactor volume (85% of the reaction mixture). Although the exact mechanism of SRNF is still unknown, we assume that the loss of catalyst was due to the formation of smaller Pd entities, including Pd(0), during the reaction cycle. As mentioned by Beletskaya and Cheprakov,[11] the physical chemistry of the phenomena involved in catalyst deactivation and the formation of Pd nanoparticles is extremely complex and relevant data is still lacking. Nevertheless, a complete conversion in a rather short time was realised in the four subsequent runs. The solvent dependency of catalyst activity and deactivation is generally accepted. In this membrane-coupled catalysis however, changing the solvent also changes the separation properties of the SRNF-membranes: it alters the swelling of the membrane as well as the interaction of the permeating components with the membrane phase. Two other solvent systems were thus tested for their catalytic and separation properties. In both the MTBE and the THF system, rejections of 96% for Pd and more than 97% for the phosphine additive were obtained. Unfortunately, the catalytic activity was markedly lower in these systems.

For all three reactions, neither the product nor remaining reactants were retained during the filtration (data not shown). The ammonium salt formed as a by-product during the reaction precipitated out and could be easily removed from the reactor before refilling it for a subsequent run. Consequently, a cleaner form of the product in the corresponding solvent is obtained at the

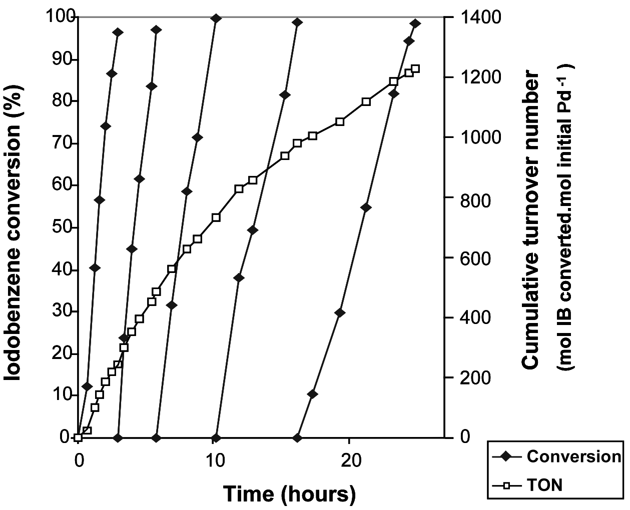


Figure 1. Iodobenzene conversion and cumulative turnover number versus time for the EA system.

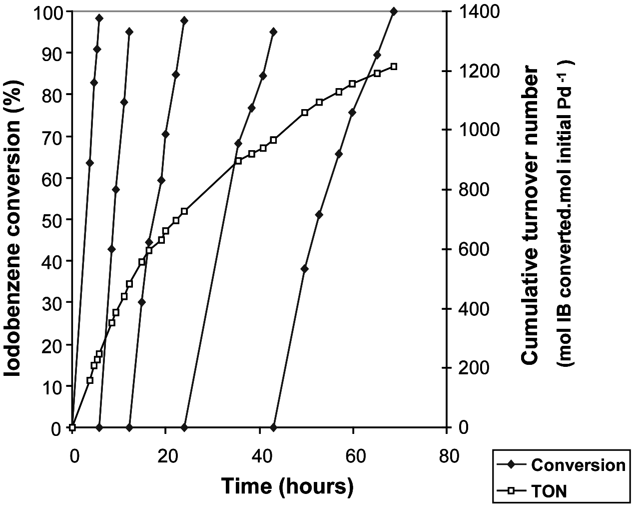


Figure 2. Iodobenzene conversion and cumulative turnover number versus time for the MTBE system.

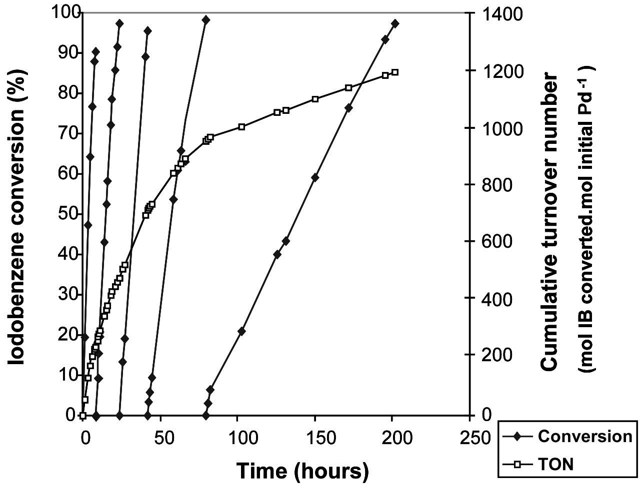


Figure 3. Iodobenzene conversion and cumulative turnover number versus time for the THF system.

Table 1. Summary of the membrane performance and reaction characteristics in the different solvent systems

Solvent system	Flux ($l\ m^{-2}\ h^{-1}$)	R_{Pd} (%)	$R_{P(tol)_3}$ (%)	Cumulative time (h)
EA	32.3	90	88	25
MTBE	11.3	96	97	69
THF	45.8	96	98	206

permeate side. Mean solvent fluxes across the membranes of between 11 and 46 $l\ m^{-2}\ h^{-1}$ were observed, depending on the solvent system used.

In conclusion, it was proven that the semi-continuous NF coupled catalysis is a convenient technique to run catalytic reactions with catalyst recycling, thus saving catalyst, preventing metal contamination of the products and increasing reactor productivity. The semi-continuous approach allows reactions to take place under conditions that are incompatible with membrane separation. For the reported Heck-coupling, these preliminary experiments show a trade-off between better membrane performance and higher catalyst activity in a given solvent. More generally, dealing with the low stability of a given TMC under reaction conditions—as reflected in the breakdown to smaller fragments or the loss of charges—remains an important challenge for chemists to allow implementation of the reported concept to a wide range of organic synthesis reactions.

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