

Continuous biphasic catalysis: palladium catalyzed cross coupling reactions

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The immobilisation of polymer tagged catalysts in a stationary solvent in a reactor and the flow of reactants dissolved in another immiscible solvent through it, allows the conversion of a continuous feed of reactants into a product stream, as exemplified by the Sonogashira coupling of aryl halides and acetylenes.

The fixed bed reactor is used to perform heterogeneously catalyzed processes. It consists of a flow through reactor with a heterogeneous catalyst immobilized on a porous support, while a feed of reactants moving over the catalyst bed is converted into a product stream.¹ We are interested in liquid/liquid biphasic catalysis² and have recently synthesized a number of efficient phase-tagged catalysts used for polar and nonpolar biphasic catalysis of the Heck, Suzuki and the Sonogashira type.^{3–6} We now want to demonstrate that biphasic catalysis in standard organic solvents can be applied in a homogeneous catalyst relative of a fixed bed reactor. Related concepts utilizing ionic liquids and supercritical CO₂ have become popular recently from work of Leitner, Wasserscheid *et al.*,⁷ Cole-Hamilton *et al.*,⁸ Jessop *et al.*⁹ and Baker, Tumas *et al.*¹⁰ In order to demonstrate the feasibility of our approach relying on cheap organic solvents and without the need for pressurized equipment, we have chosen the Sonogashira coupling reaction, primarily because the biphasic chemistry of this catalytic reaction is well understood.

Instead of immobilizing a heterogeneous catalyst on a solid support, we decided to use a phase-tagged catalyst dissolved in an organic solvent, which is stationary within the reactors we have designed (Scheme 1). A solution of the reactants in another organic solvent is continuously pumped into the reactor filled with the catalyst solution, thereby the substrates undergo the catalytic transformation to generate the product. At the other end of the reactor the product containing solution is continuously removed from the catalyst phase. It is essential in this

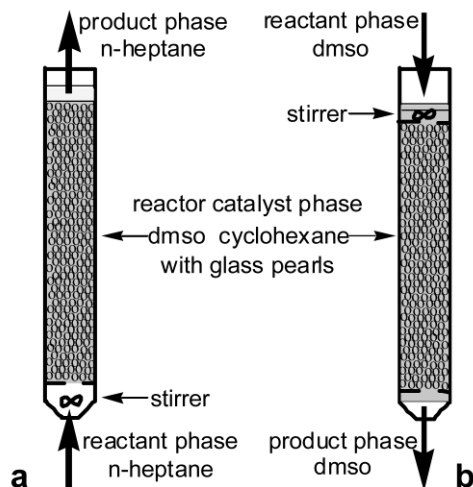
respect that the two solvents composing the stationary phase (catalyst solvent) and the mobile phase (reactant/product solvent) are immiscible under the conditions of catalysis. Based on our previous experiments we have chosen dmsO and an alkane (*n*-heptane or cyclohexane) as the solvents for the reactions described here.^{3–5}

There are two different setups for the reactor based on whether the catalyst resides in the solvent of higher (Scheme 1a) or of lower density (Scheme 1b). The polar and high density solvent dmsO hosts the catalyst when a polar phase tag is attached to it; alternatively, a catalyst with a nonpolar phase tag is localized in the nonpolar and low density solvent (alkane).

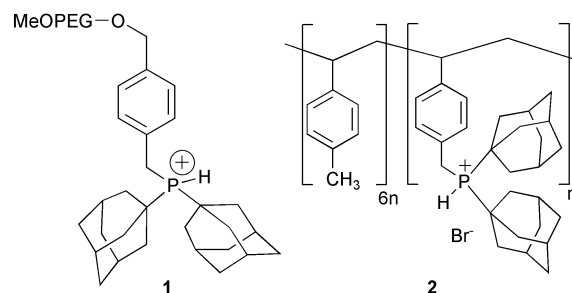
In the case of continuous polar biphasic catalysis, the reactant containing solvent *n*-heptane is fed into the bottom of the reactor, vigorous stirring generates small droplets, which slowly rise to the top of the reactor. During this time the reactants migrate into the catalyst phase and are converted into the products, which migrate back to the reactant/product solvent.¹¹ Finally, the product containing *n*-heptane is pumped off from the top of the reactor. In the case of continuous nonpolar biphasic catalysis the reactant containing dmsO feed is introduced on top of the reactor, the reactant/product solvent dmsO slowly sinks towards the bottom of the reactor, catalysis takes place and finally the dmsO solution of the product is pumped off.

Both approaches can be useful, since reactants and products will be distributed between the two solutions according to their partition coefficients. In order for the catalyst to work efficiently a significant amount of the reactant(s) needs to migrate into the catalyst phase, while for an efficient removal of the product(s) a significant amount of the product(s) needs to be present in the product phase.

In order to evaluate the efficiency of this reactor setup we decided to use the Sonogashira coupling reaction. The reactor consists of a glass tube (20 × 1.6 cm) filled with a dmsO solution (10 mL) of the catalyst precursors (0.03 mmol Na₂PdCl₄, 0.06 mmol phosphine **1**³ (Scheme 2) and 0.02 mmol CuI). The reactants (1 equiv. aryl bromide, 1.2 equiv. phenyl acetylene) were dissolved in 50 mL of *n*-heptane and pumped through the solution. The reactor was heated to 60 °C by immersing it into a thermoregulated aluminium casing. Into the bottom of the reactor was pumped a *n*-heptane solution of reactants with HNⁱPr₂ base and bubbles of *n*-heptane rose to the top of the reactor.¹² However, when using an open glass tube it turned out quickly that the retention time of the reactants in the



Scheme 1 Reactors for continuous biphasic catalysis. Bold arrows denote the up (a) or down (b) movement of the reactant/product solvent.



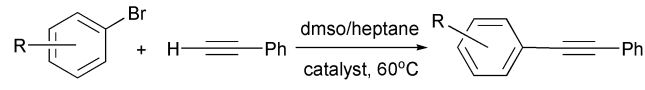
Scheme 2 Polymeric phosphines.

reactor is much too short to effect their catalytic transformation. Consequently, we decided to slow down the transport of reactants by adding a filling to the reactor. We tested several different glass pearls with diameters of 1.5–2 mm, 3 mm and 4 mm, saddle rings and glass rings with respect to the permeation of the reactant/product carrying solvent. The 3 mm glass pearls turned out to be the best choice. The medium transport times of the model compound 4-*tert*-butyltolane were determined by gas chromatography and for the 3 mm glass pearls found to be 35 min with a feed of 3 ml of solvent per hour and 70 min with a feed of 1.2 ml h⁻¹. The latter time is ideal to effect the catalytic transformation of the reactants in the Sonogashira coupling.

The composition of the product containing stream was monitored by GC. It can be seen that for a 4.5 mmol loading (corresponding to 0.6 mol% of catalyst) of the reactor with reactants the amount of catalyst present as well as the reaction time are sufficient to ensure excellent conversions of the various reactants (Table 1). On increasing the loading of the reactor by a factor of three to 13.5 mmol (corresponding to 0.2 mol% of catalyst) several coupling reactions are not complete; obviously the capacity of the present reactor with the extremely small catalyst loading is exceeded for some reactions. In order to boost the capacity of such a reactor one can simply increase the amount of catalyst and the dimensions of the reactor.

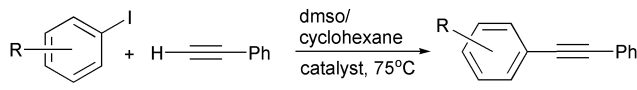
It is very important in this respect to note that there is no leaching of the catalyst into the product phase, which was already known from our work on related biphasic catalysis.^{3–5} Furthermore we need to take a closer look at the partition coefficients α of the reactants as well as of the products between the reactant phase (heptane) and the catalyst phase (dmsO). Low coefficients lead to a higher concentration of the reactants in the catalyst phase and increase the rate of the catalytic transformation, while on the other hand the efficient elution of product from the catalyst phase with heptane solvent requires high values of α . According to our experience partition coefficients for reactants and products in the range of 0.2 and 20 are useful and allow the efficient operation of the reactor.¹³ We have determined several such partition coefficients α for the distribution of aryl bromide reactants and of the respective phenyl acetylene coupled products between *n*-heptane and dmsO: C₆H₅Br, product (0.85, 0.21), 4-CH₃C₆H₄Br (1.6, 0.51), 4-*t*BuC₆H₄Br (15.1, 0.93), 4-ClC₆H₄Br (0.41, 0.30), 4-CH₃COC₆H₄Br (0.01, 0.04). Obviously for the more polar substrates the problem of very small distribution coefficients is imminent. The obvious solution to this problem is the simple inversion of the nature of the catalyst phase tag and that of catalyst and reactant/product phase to result in a nonpolar biphasic catalysis. In this manner the catalyst has a nonpolar phase tag (poly-4-methylstyrene, Scheme 1)⁵ and resides exclusively in the nonpolar solvent (cyclohexane), while the polar reactant/product solvent dmsO is responsible for the transport (Scheme 1b).

Table 1 Continuous polar biphasic Sonogashira catalysis of aryl bromides and phenyl acetylene

		
R =	Substrate 4.5 mmol conversion (%) ^a	Substrate 13.5 mmol conversion (%) ^a
H	> 98	83
4-CH ₃	> 98	70
4- <i>t</i> Bu	> 98	53
4-Cl	88	81
3-CF ₃	> 98	85

^a Conversion is the averaged content of product in the product stream relative to the solutes.

Table 2 Continuous nonpolar biphasic Sonogashira catalysis of aryl iodides and phenyl acetylene

		
R =	Substrate 4.5 mmol conversion (%) ^a	
H	80	
4-CH ₃	60	
4-Cl	77	
4-OMe	65	
3-CF ₃	84	

^a Conversion is the averaged amount of product in the product stream. Catalyst: 0.02 mmol (PhCN)₂PdCl₂, 0.04 mmol phosphine **2**, 0.04 CuI corresponds to 0.44 mol% catalyst.

Consequently, we have studied the Sonogashira reaction of several substrates under the conditions of nonpolar biphasic catalysis, utilizing a cyclohexane catalyst phase and a dmsO reactant/product phase.

The data in Table 2 show that good conversions are obtained, though not quantitative as the activity of the present catalyst in cyclohexane is significantly reduced with respect to that in dmsO. An advantage when using dmsO as the product phase is the solubility of the ammonium salts formed in the course of reaction, which are removed efficiently together with the products from the reactor.

In conclusion, the immobilisation of polymer tagged catalysts in a stationary solvent and the flow through of reactants dissolved in another immiscible solvent, allows the conversion of a continuous feed of reactants into a product stream, as exemplified by the Sonogashira coupling of aryl halides and acetylenes. The present approach certainly is not limited to the Sonogashira reaction and we are currently working towards expanding the scope of continuous biphasic catalysis to other reactions such as Heck and Suzuki coupling as well as olefin metathesis.

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- This is not a directed movement, but a consequence of diffusion and the respective partition coefficients.
- In order to avoid loss of the catalyst containing solution at the bottom of the reactor and to maintain a simple reactor setup (no seals required), the reactant containing solvent is pumped into the bottom (polar catalysis) of the reactor *via* a steel capillary inserted from the top of the reactor. As the separation of the organic phases at the top of the reactor occurs rapidly, droplet formation or even emulsions pose no problem and the two solvents are separated efficiently. In principle, the same applies for the nonpolar setup of the reactor.
- α is defined as the amount of reactant or product in the heptane solution divided by the amount of reactant or product in the dmsO solution.