Catalyst Recycling

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Suzuki Coupling Reactions in Three-Phase Microemulsions**

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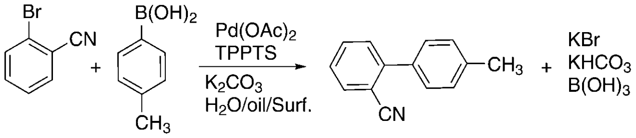
The Suzuki cross-coupling reaction is one of the most widely used reactions for the synthesis of polymers, liquid crystals, agrochemicals, and pharmaceuticals. Because of growing environmental awareness, industry is developing "green" approaches, for example, the prevention of waste rather than its treatment. In this context the use of water instead of organic solvents, which are often toxic and difficult to remove because of their high boiling points, is desirable as well as the use of nontoxic reagents.[1] Based on the development of water-soluble ligands,[2,3] first described in the early 1970s, the easy separation of catalyst dissolved in an aqueous phase and product dissolved in the organic phase has become possible. The Rhône–Poulenc process, the hydroformylation of propene to *n*-butylaldehyde, is so far the only industrial process that employs two-phase catalysis with a water-soluble catalyst.

Today the concept of biphasic catalysis is particulary advanced by the use of fluorous solvents,[4] ionic liquids, and supercritical fluids—all regarded as green solvents. However, these media have not been used for coupling reactions because of unsatisfactory yields and the insolubility of Pd species[5,6] relative to the reactions in conventional solvents. Additionally, the salts generated may retard the reaction and make product isolation and catalyst recovery, for example, from ionic liquids, difficult and expensive.

In our present study, we extended the concept of biphasic catalysis to three-phase systems that allow for easy phase separation and catalyst recycling in one step. The beneficial effect of three-phase systems is well known in phase-transfer catalysis,[7,8] where the third phase is often obtained by accident, because of the solubility of the phase-transfer catalyst in the applied solvents. In our study we used self-assembling surfactant systems[9] with adjustable phase behavior and employ them as the reaction medium for a Suzuki coupling reaction: the synthesis of 4′-methyl-2-biphenylcarbonitrile (Scheme 1), an important intermediate for the production of sartans. We investigated three-phase systems based on nonionic surfactants of the type $C_{12}E_x$ (E = degree of ethoxylation, $x = 5$–8), because the degree of ethoxylation can be used to tune the phase behavior such that the three-phase region occurs at the reaction temperature (see the Supporting Information).[10] Such systems have been described as versatile media for a Heck reaction catalyzed by a supported palladium catalyst.[11]



Scheme 1. Suzuki coupling reaction of 2-bromobenzonitrile and 4-tolueneboronic acid.

Because catalyst recycling is still a challenge in homogeneous catalysis and remains a serious drawback, we set out to find a solution for product separation/isolation, catalyst recycling, and the simultaneous removal of the salts; this has never been reported for Suzuki coupling reactions before. In benchmark experiments we used conventional polar solvents like acetonitrile/water for the coupling reaction. Then the alternative approach was studied by replacement of the polar solvent by an alkane/water/surfactant mixture.

Polar aprotic solvents are often used for coupling reactions because they solubilize high concentrations of both reactants and the required bases. No mass-transfer limitations occur if the catalyst is also dissolved in the same phase as the reactants. It should be noted that the addition of water is necessary and increases the reaction rate, also when a non-water-soluble catalyst is used, because of the activation of boronic acid by the inorganic base.[12] It can be seen from Table 1, entries 1 and 2, that the coupling reaction is very fast in acetonitrile, also when the initial concentrations of reactants are doubled. However, the separation of the product and the catalyst is difficult, and the catalyst cannot

Table 1: Conversion of the Suzuki coupling in different reaction media.[a]

Entry	Media	α[b]	γ[b]	Cat. [mol %]	Conv. [%][c]
1	CH_3CN/H_2O	0.5	–	0.5	98
2		0.5	–	0.25	83
3	heptane/H_2O/ surfactant	0.9	–	0.5	15
4		0.5	–	0.5	77
5		0.5	0.03	0.5	96
6		0.5	0.03	0.25	62

[a] CH_3CN/water = (44.5:38.8) g or heptane/water = (38.8:38.8) g (α = 0.5) as solvent for 5.5 mmol 2-bromobenzonitrile, 6.05 mmol (1.1 equiv) 4-tolueneboronic acid, 6.88 mmol (1.25 equiv) K_2CO_3; or twice the concentration of the reactants at constant catalyst concentration: 6 mg $Pd(OAc)_2$ and 78 mg TPPTS as the water-soluble catalyst at bei 60 °C. [b] α = oil fraction of mixture, γ = surfactant fraction of mixture. [c] Conversion after 1 h.

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be reused without regeneration procedures. Therefore, an alternative solvent is desirable. We found that the reaction in a *n*-heptane/water mixture is slower because of the limited mass transfer of the reactants into the catalyst phase even with a smaller proportion of aqueous phase (Table 1, entry 3). In comparison to entry 3 (increased oil content α) the reaction in entry 4 is faster but stops finally after 80 min with a conversion of 87 %. HPLC analyses indicate an 8 % yield of the homocoupling product, 4,4′-dimethylbiphenyl, which results from the boronic acid preferentially present in the aqueous phase where the catalyst is located as well. The addition of surfactants improves mass transfer and complete conversions are obtained. In addition, no homocoupling product is detected, neither 4,4-dimethylbiphenyl nor 2,2-dicyanobiphenyl (see the Supporting Information).

The use of nonionic surfactants was intended to not only speed up the reaction (Table 1, entries 1 and entry 5) but also improve the phase-separation properies of the reaction mixture crucial to catalyst recovery. Therefore, the phase behavior was investigated; a strong dependence on reactants' addition and reaction progress was observed (Figure 1). The plot of the phase-transition temperatures against the surfactant concentration yields a fish-shaped diagram (see the Supporting Information), in which a one-phase microemulsion is the fish tail and a three-phase system is the body. It can be seen that the addition of each reactant has an effect on the phase boundaries, causing a shift to lower temperatures. The addition of 4-tolueneboronic acid and K_2CO_3 (triangles) has the strongest impact on the phase behavior; the three-phase region within the phase diagram is shifted by 30 K to lower temperature (lipophilic shift) based on the initial heptane/water/Marlipar 24/70 phase diagram. After addition of the catalyst solution, the three-phase region is shifted to higher temperatures, because of the consumption of boronic acid (hydrophilic shift). The change in phase behavior during the reaction time can be utilized to monitor the progress of the reaction. Therefore, the microemulsion system was adjusted such that the three-phase region appears at the reaction temperature only when complete conversion is achieved. Subsequently, the organic phase can easily be separated and the product isolated. The salts can be removed with the aqueous phase, whereas the catalyst is located in the middle phase, the surfactant-rich phase (Figure 2). The catalyst phase remains inside the reactor for further use. A new run is started by addition of a fresh batch of reactants dissolved in heptane and water to the reactor.

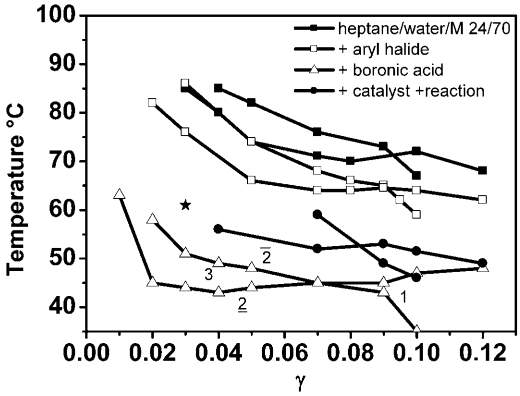


Figure 1. Shift of the phase diagram by addition of substrates: 0.055 mol L^{-1} 2-bromobenzonitrile, 0.06 mol L^{-1} 4-tolueneboronic acid, 2.1 equiv K_2CO_3, and catalyst to the reaction mixture ($\alpha = 0.5$, γ is varied). At $\gamma = 0.03$ and $T = 60$ °C almost complete conversion is obtained with the catalyst located in the middle phase (photo in the Supporting Information). M = Marlipal. 1, 2, 3 = number of phases; * = experimental conditions.

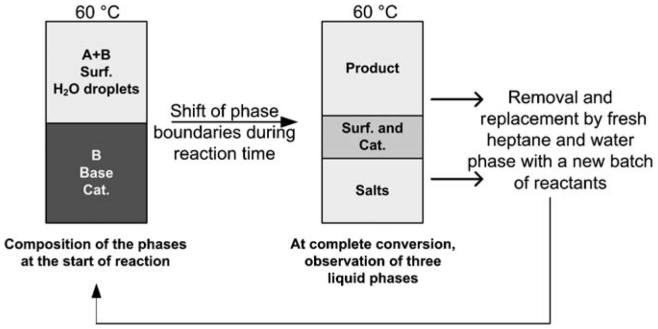


Figure 2. Principle of catalyst recycling, product isolation, and removal of the salts.

For the coupling of 5.5 mmol of 2-bromobenzonitrile with 1.1 equivalents of boronic acid and 2.1 equivalents of base, Marlipal 24/70 was used such that the catalyst could be recycled directly after complete conversion. We investigated the affect of different amounts of base and found that 1.25 equiv K_2CO_3 suffices for the Suzuki coupling reaction, without any decrease of reaction rate. When 1.25 equivalents of base are used, Marlipal 24/50 or Novel 1216CO-8 are the surfactants of choice for the subsequent catalyst recycling. Also the amount of surfactant (3, 6, and 11 wt %) does not affect the reaction rate, although different volume fractions of the phases are established. The type of nonionic surfactant does not affect the reaction rate, as long as micelles are formed that act as phase-transfer agents. However, the surfactant should be selected carefully to provide the required phase behavior for subsequent catalyst recycling. Furthermore, it is necessary to adjust the initial reactant concentration for the particular surfactant to facilitate the described recycling procedure.

The concept of using the three-phase region for the exchange of the aqueous phase arose in the context of the retarding effects caused by the accumulation of the salts after repeated reactions with recycled catalyst. The retarding effect was already described by the groups of Oehme[13] and Genêt.[14] In a comparative study we performed five cycles with two different microemulsion systems, using Marlipal 24/50 and Novel 8. Novel 8 was chosen as the more promising surfactant for the recycling experiment because of its narrow molecular weight distribution of ethoxylated alcohols, which also has a positive effect on the distribution of the surfactant in the middle phase (Figure 3). Therefore, the catalyst

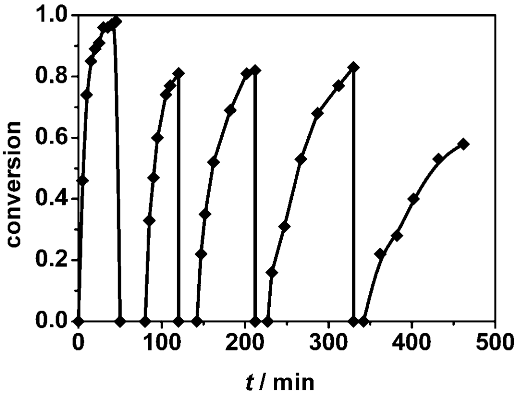
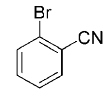
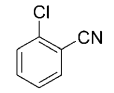
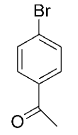
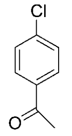
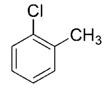
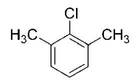


Figure 3. Recycling of the catalyst in a three-phase system at 60 °C using the nonionic surfactant Novel 8 in heptane/water ($\alpha = 0.5$, $\gamma = 0.03$) with the initial concentrations 0.055 mol L^{-1} 2-bromobenzonitrile, 0.06 mol L^{-1} 4-tolueneboronic acid, 1.25 equiv K_2CO_3 for each run.

Table 2: Overview of different coupled aryl halides prepared using the microemulsion three-phase system ($\alpha = 0.5$, $\gamma = 0.03$).[a]

Entry	Aryl halide	Conv. [%]	Entry	Aryl halide	Conv. [%]
1		96	4		94
2		91	5		86
3		0	6		0

[a] 5.5 mmol aryl halide, 6.05 mmol (1.1 equiv) boronic acid, and 6.88 mmol (1.25 equiv) K_2CO_3 along with 6 mg $Pd(OAc)_2$ and 78 mg of TPPTS (entries 1 and 2) or 68 mg S-Phos (entries 3–6) as the water-soluble catalyst at 60 °C with conversions (Conv.) after 1 h.

complex Pd-TPPTS (TPPTS = 3,3′,3″-phosphanetriyltris(benzenesulfonic acid) trisodium salt) is incorporated more efficiently in the surfactant aggregates with Novel 8, than it is with Marlipal 24/50. The individual phases of the Novel 8/water/heptane three-phase system were analyzed regarding product distribution and palladium and phosphorus concentration. When 3 wt % of nonionic surfactant is used, the middle phase, where 30 % of the product is dissolved, has a volume of 23 mL. The water and heptane phases have volumes of 30 and 45 mL, respectively, with 70 % of the product dissolved in the heptane phase. The fraction of the product in the middle phase has no effect on the next run. After each run the aqueous phase was analyzed by ICP-OES (inductively coupled plasma optical emission spectroscopy); Pd concentrations of 10, 4, 1, and < 1 % of the initial concentrations were found along with and a phosphorus content of 20 % of the initial concentration.

This means that the loss of phosphorus is more decisive for a successful recycling process. Therefore more ligand should be added during recycling or a higher initial amount should be used, as is done in the Rhône–Poulenc process, where a ligand to catalyst ratio of 60:1 is used to keep the metal in the aqueous phase.[15] The contamination of the isolated product with leached palladium was determined by ICP to be less than 1 ppm.

Our methodology is applicable for several aryl halide substrates (Table 2); good yields are obtained for the coupling of representative aryl bromides with the Pd-TPPTS catalyst. For the less reactive aryl chlorides another ligand must be applied for the generation of the palladium catalyst. Here the sodium 2′-dicyclohexylphosphino-2,6-dimethoxy-1,1′-biphenyl-3-sulfonate (S-Phos) ligand introduced by Buchwald was chosen. High conversions of activated aryl chlorides (Table 2, entries 4 and 5) provided the desired coupling product, while nonactivated and also sterically challenging substrates did not react (Table 2, entries 3 and 6). The recycling procedure described for Pd-TPPTS is also applicable for this catalyst, because it preferentially accumulates in the middle phase owing to its amphiphilic structure.

In conclusion, we have shown that surfactant-based three-phase systems are suitable reaction media for Suzuki coupling reactions with a broad range of substrates; they offer advantages over conventional solvents in the catalytic reaction and the recycling of the catalyst. The reuse of the catalyst substantially increases the overall turnover number of the catalyst, a desirable factor in cost-effective industrial applications.

Experimental Section

In a representative experiment a mixture of aryl halide (1 g, 5.5 mmol), boronic acid (0.822 mg, 6.05 mmol), and potassium carbonate (0.95 or. 1.6 g, 6.88 or 11.6 mmol) were stirred in a 200 mL reaction vessel containing 98 mL solvent. For the reference experiments a mixture of acetonitrile (44.5 g) and water (38.8 g) was used as solvent. In the case of the microemulsion system of $\alpha = 0.5$ $\gamma = 0.03$, a mixture of 38.8 g water, 38.8 g *n*-heptane, and 2.4 g surfactant was used. The reaction mixture was degassed and purged with nitrogen three times. A thermostat was used to adjust the reaction temperature to 60 °C. When the reaction reaction temperature was reached, the prepared catalyst [254 mg TPPTS solution containing 30.7 wt % (78 mg, 0.14 mmol pure TPPTS, 2.5 mol %) and 6 mg (0.5 mol %) $Pd(OAc)_2$)) was added with a syringe. For the product analysis and the details of the recycling procedure, see the Supporting Information.

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