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Nonpolar biphasic catalysis: Sonogashira and Suzuki coupling of aryl bromides and chlorides

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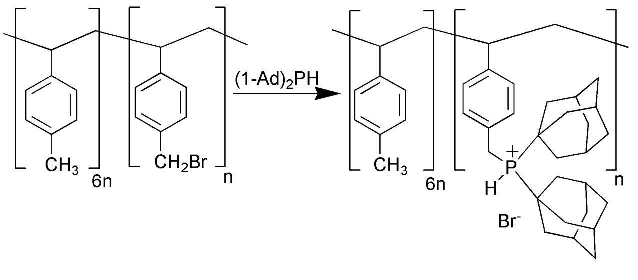
Palladium–phosphine catalysts which are phase-tagged with soluble poly(4-methylstyrene) can be used for efficient carbon–carbon coupling reactions by nonpolar biphasic catalysis with high recyclability as evidenced by high yields, constant tof of the catalyst and the absence of significant leaching of the catalyst into the polar product phase.

Biphasic catalysis utilizing two room-temperature immiscible solvents relies on catalysts which are phase-tagged[1] to be soluble only in one of the two solvents,[2,3] which is termed catalyst phase. The product of the catalytic reaction should be located preferentially in the other solvent, termed product phase. In this manner the separation of catalyst and product boils down to a simple phase separation. While the phase preference of the catalyst can be designed, the products of catalytic reactions have different partition coefficients, depending on their chemical nature. Traditionally biphasic catalysts have been tagged with polar groups [triphenylphosphine-trisulfonate,[4] PEG = poly(ethylene glycol)[5]] to generate the respective polar phase preference for polar biphasic catalysis or with a fluorinated ponytail to be used in fluorous biphasic chemistry.[6] †

While polar biphasic catalysis is best suited for synthesis and separation of nonpolar products, it is obvious that for polar substrates the partition coefficient dictates that the separation of products from the catalyst is facile with catalyst having a nonpolar phase tag.[7,8] We wish to term this nonpolar biphasic catalysis and want to describe here our work aimed towards establishing this type of biphasic catalysis.

We have recently demonstrated that Pd(0) complexes with BnP(1-Ad)$_2$ (Ad = adamantyl), which is a sterically demanding and electron-rich phosphine, are highly active catalysts suitable for the room temperature Sonogashira coupling of aryl bromides.[9] Following minor modifications of the peripheral functional groups this ligand has now been attached to a nonpolar, linear poly(methylstyrene). The anionic polymerisation of 4-methylstyrene was controlled to result in a 5 kDa polymer, which was reacted with substoichiometric amounts of Br$_2$ to convert 15% of the –CH$_3$ groups to –CH$_2$Br. Heating (1-Ad)$_2$PH with the functionalized polymer under toluene reflux gave the phosphinated polymer in quantitative yield (Scheme 1).

We wish to describe here Sonogashira coupling reactions using Pd catalysts supported on soluble poly(methylstyrene)s. Pd(PhCN)$_2$Cl$_2$ was shown to be one of the best metal sources for the Sonogashira coupling[10] and was used together with the phosphinated polystyrene, CuI and the coupling partners to form the catalytically active species after deprotonation of the phosphonium salt by HN^{i}Pr$_2$ and reduction of the Pd(II) to Pd(0). The first task was to find a suitable biphasic solvent system composed of two room temperature immiscible solvents to carry out Sonogashira reactions with high activity. Cyclohexane was the obvious choice as the catalyst phase since the Pd complex with the phosphinated polymer does not dissolve in less polar alkanes. The critical choice is the polar solvent used as a product phase since many solvents are known to inhibit the catalyst activity. Several solvents were tested in combination with cyclohexane: acetonitrile, DMF, DMA, nitromethane and DMSO. The biphasic system composed of DMSO–cyclohexane turned out to be the best choice. In all other solvent mixtures the coupling yields were found to be moderate to low; in addition the yields decrease significantly over the consecutive reaction cycles. Among the various bases tested (Et$_3$N, Na$_2$CO$_3$, K$_3$PO$_4$ and HN^i Pr$_2$) in DMSO–cyclohexane HN^i Pr$_2$ gives the highest yield in the Sonogashira coupling reaction.

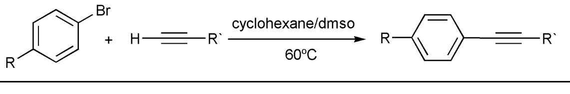


Scheme 1 Poly(methylstyrene) supported phosphine.

The results of the Sonogashira coupling experiments are summarized in Table 1. The overall yields of isolated product for the different reactions after five cycles are between 79 and 96% per cycle. The phase yields listed in the table correspond to the amount of product isolated after separation of the product phase from the catalyst phase. The phase yields only take into account the amount of product in the catalyst phase and thus reflect the partition coefficients of the respective products.[11] The acetylenes with the more polar groups studied here display a favorable distribution between the two solvents.

For the evaluation of catalyst recycling the nearly constant yields of the 4th and 5th reaction cycle point to the high performance of the catalyst. The recyclability of a given catalyst can be demonstrated more convincingly by determining the turnover frequency (tof) for an incomplete reaction over several cycles. We tested this for the coupling of 4-bromoacetophenone and phenylacetylene and found the tof to be virtually constant (cycle (tof): cycle 1 (220 h^{-1}), cycle 2 (220 h^{-1}), cycle 3 (215

Table 1 Nonpolar biphasic Sonogashira coupling



R	R′	Phase yield (%)/cycle 1	2	3	4	5	Extract (%)[a]	Yield (%)[b]
CH$_3$CO	Ph	91	97	105	99	100	2	95
H	Ph	88	95	98	101	95	11	92
OMe	Ph	85	91	98	98	98	3	89
CH$_3$CO	Hexyl	82	87	91	89	89	17	79
COOEt	Ph	95	99	103	102	104	2	96

[a] Extract corresponds to the amount of product extracted from the catalyst phase after five cycles. [b] Yield refers to the amount of product after chromatographic purification. Conditions: 1.0 mol% Pd(PhCN)$_2$Cl$_2$, 2.0 mol% polymer, 2.0 mol% CuI, HN^{i}Pr$_2$, reaction times: 2–12 h depending on the substrates but constant during cycles.

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h^{-1}), cycle 4 (210 h^{-1}), cycle 5 (210 h^{-1})) over five cycles. This indicates excellent stability of the catalyst and suggests that the extent of leaching of the complex catalyst into the product phase is small.

The same ligand which was used for the Sonogashira coupling was utilized for Suzuki type coupling reactions,[12] while $Pd(OAc)_2$ was found to be a better metal source. The main results concerning these coupling reactions are summarized in Table 2.

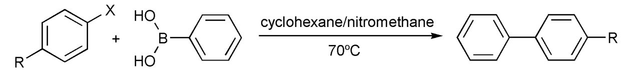
Several biphasic solvent systems were tested; again cyclohexane was combined with various polar solvents: acetonitrile, DMF, DMA, DMSO and nitromethane. Among the various solvent mixtures DMSO–cyclohexane and nitromethane–cyclohexane were found to perform equally well, while the other solvent combinations resulted only in moderate coupling yields and significant decomposition of the catalyst after the first reaction cycle. Due to its much lower boiling point nitromethane was finally preferred over DMSO. In order to further optimize the reactions various bases (NaF, Na_2CO_3, K_3PO_4 and HN^iPr_2) were tested for the coupling reaction; K_3PO_4 gave the highest yield in the Suzuki coupling reaction. It can be seen in Table 2 that both aryl bromides and chlorides can be Suzuki coupled and recycled several times in excellent yields. Again the efficient recyclability of the catalyst is evidenced by the almost constant and high coupling yields over the various reaction cycles. Probing the catalyst performance by the more stringent criterion tof provides evidence of the excellent stability, as the tof remains almost constant over the reaction cycles for the coupling of 4-bromoacetophenone and $PhB(OH)_2$ (cycle (tof h^{-1}): cycle 1 (180 h^{-1}), cycle 2 (182 h^{-1}), cycle 3 (175 h^{-1}), cycle 4 (168 h^{-1}), cycle 5 (165 h^{-1})).

The virtually quantitative retention of the catalyst in the cyclohexane solvent, which is the catalyst phase, is essential for the usefulness of biphasic catalysis. Consequently, the product phase solvent should not strongly solvate Pd(0). For a polar solvent this condition is less obviously met than for a nonpolar solvent used as the product phase in polar biphasic catalysis. However, it should be kept in mind that high catalytic activity requires the presence of low coordinated Pd(0) species. Consequently, high catalytic activity in a given product phase and low leaching into the product phase can go hand in hand.

Thus for the Sonogashira and the Suzuki coupling reactions, using poly(4-methylstyrene) supported Pd catalysts, the absence of significant leaching of the catalyst into DMSO or nitromethane is indicated by the high yields of catalytic transformations and the constant tof over the reaction cycles.

Another critical parameter concerning leaching of the catalyst is the amount of catalyst phase solvent (cyclohexane) soluble in the product phase solvent (here DMSO or nitromethane). By GC we found that there is only a small loss of cyclohexane into DMSO (2%) and nitromethane (3.5%). Furthermore the loss of polymer into the product phase was checked with ^1H NMR spectroscopy. We were not able to detect any polymer in the crude products. We thus estimate the polymer leaching to be significantly smaller than 0.5%. Secondly, the amount of palladium lost into the DMSO or nitromethane product phase was determined by two independent methods: total reflection XRF and UV spectrophotometry using the colorimetric reagent 4,4′-bis(dimethylamino)thiobenzophenone.[13] Results obtained from the two methods were found to be in good agreement and the retention of the catalyst in the cyclohexane layer was found to be $> 99.8\%$.

Table 2 Nonpolar biphasic Suzuki coupling



R	X	Phase yield (%)/cycle 1	2	3	4	5	Extract (%)[a]	Yield (%)[b]
CH_3CO	Br	91	97	105	99	100	6	95
H	Br	88	95	98	101	95	8	92
OMe	Br	85	91	98	98	98	8	90
CH_3CO	Cl	82	87	91	89	89	7	83
CN	Cl	82	90	91	92	90	4	86

[a] Extract corresponds to the amount of product extracted from the catalyst phase after five cycles. [b] Yield refers to the amount of product after chromatographic purification. Conditions: 1.5 mol% $Pd(OAc)_2$, 3.0 mol% polymer, K_3PO_4, reaction times: 6–24 h, depending on the substrates but constant during cycles.

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Notes and references

† *Biphasic Sonogashira reaction*. In a Schlenk tube, $Pd(PhCN)_2Cl_2$ (5.7 mg, 1.5 mol%) and phosphinated polymer (15% loading, 150 mg, 3 mol%) were dissolved in cyclohexane (7 ml). CuI (4.5 mg, 3 mol%), HN^iPr_2 (0.1 ml), PhC≡CH (1.8 mmol), the respective aryl bromide (1.5 mmol) and DMSO (4 ml) were added and the reaction was stirred at 60 °C till completion. After cooling to room temperature, the DMSO layer was evaporated and the remaining crude product purified (see below). Fresh DMSO, HN^iPr_2 and the two substrates were added to the catalyst phase for the next cycle to start the next reaction. After the last cycle, the product in cyclohexane was isolated by evaporating cyclohexane. The crude products from the various cycles were combined and purified by column chromatography (silica, cyclohexane–ethyl acetate) to obtain the respective pure products.

Biphasic Suzuki reaction. In a Schlenk tube, $Pd(OAc)_2$ (3.3 mg, 1.5 mol%) and polymer (150 mg, 3 mol%) were dissolved in cyclohexane (7.0 ml). Aryl halide (1.0 mmol), phenyl boronic acid (183 mg, 1.5 mmol), K_3PO_4 (24 mg, 2 mol%) and nitromethane (4 ml) were added to the solution and stirred at 70 °C until all the starting material was consumed. After cooling, the nitromethane layer was removed and was evaporated to obtain the crude product. Two substrates, K_3PO_4 and nitromethane, were added to the catalyst phase for the next cycle. The same procedure was repeated for the five cycles. After the last cycle, the product in cyclohexane was isolated by evaporating cyclohexane. The crude products from the various cycles were combined and purified by column chromatography (silica, cyclohexane–ethyl acetate) to obtain the respective pure product.

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