Homogeneous Catalysts Supported on Soluble Polymers: Biphasic Suzuki–Miyaura Coupling of Aryl Chlorides Using Phase-Tagged Palladium–Phosphine Catalysts

Markus an der Heiden and Herbert Plenio*[a]

Abstract: The Suzuki–Miyaura coupling of aryl chlorides and $PhB(OH)_2$ under biphasic conditions (DMSO/heptane) can be performed in almost quantitative yields over several cycles by means of polymeric Pd catalysts with soluble polyethylene glycol phase tags. Three sterically demanding and electron-rich phosphines 1-CH_2Br,4-$CH_2P(1\text{-}Ad)_2$-C_6H_4, and 2-PCy_2,2′-OH-biphenyl, and 2-P$t$$Bu_2$,2′-OH-biphenyl were covalently bonded to 2000 Dalton MeOPEG-OH. The catalysts, which were formed in situ from $Na_2[PdCl_4]$, the respective polymeric phosphine, KF/K_3PO_4, and $PhB(OH)_2$, efficiently couple aryl chlorides at 80 °C at 0.5 mol% loading, resulting in a >90% yield of the respective biphenyl derivatives. The use of polar phase tags allows the efficient recovery of palladium–phosphine catalysts by simple phase separation of the catalyst-containing DMSO solution and the product-containing *n*-heptane phase. The high activity (TOF) of the catalyst remains almost constant over more than five reaction cycles, which involve the catalytic reaction, separation of the product phase from the catalyst phase, and addition of new reactants to initiate the next cycle. The Buchwald type biphenyl phosphines form the most active Pd catalysts, which are 1.3–2.8 times more active than catalysts derived from diadamantyl–benzylphosphine, but appear to be less robust in the recycling experiments. There is no apparent leaching of the catalyst into the heptane solution (<0.05%), as evidenced by spectrophotometric measurements, and contamination of the product with Pd is avoided.

Keywords: aryl chlorides · biphasic catalysis · palladium · polymers · Suzuki coupling

Introduction

Liquid/liquid biphasic catalysis[1,2,3] is a success story as evidenced by the large-scale application of the Ruhrchemie/Rhône-Poulenc hydroformylation,[4] the Shell Higher Olefins Process (SHOP),[5] and the Kuraray telomerization.[6,7] The most important advantage of such processes is the facile recovery of catalysts from the reaction mixture,[8] which is done by a simple phase separation of two immiscible solutions, of which one contains the product of the catalytic transformation and the other one the phase-tagged catalyst. Furthermore this approach also limits contamination of the organic products by catalyst metal.[9] Although it took several years for biphasic catalysis to attract researchers from academia,[10] several different concepts are now being vigorously studied by various research groups: organic/organic liquid biphasic catalysis[11,12] often with polymer-supported catalysts,[13,14,15,16] fluorous/organic systems,[17,18] ionic liquids,[19,20] supercritical solvents,[21] and aqueous/organic solvent systems.[2] SAPC (supported aqueous phase catalysis),[22] micellar catalysts,[23] and interphase catalysis[24] are related approaches.

Palladium-catalyzed carbon–carbon bond-forming reactions are powerful synthetic methods.[25] Among these the Suzuki–Miyaura coupling of organoboron reagents and organic halides,[26,27,28] is the most efficient strategy for the synthesis of unsymmetrical biaryls.[29,30] Nonetheless, the high price of Pd[31] renders processes based on this metal less attractive unless extremely active or recyclable catalysts are available.[32] The biphasic concept appears to be a good alternative for less reactive substrates, since current "heterogeneous"[33] Pd catalysts rarely match the activity of the homogeneous ones in coupling reactions.[34]

Applications of the liquid/liquid biphasic concept to Pd-catalyzed C–C coupling reactions have been reported by Bannwarth et al.,[35] Quici et al.,[36] and Gladysz et al.,[37] who demonstrated the viability of this approach for fluorous biphasic chemistry. Pioneering work was done by the Bergbreiter group,[38] who showed that poly(*N*-isopropylacrylamide) or polyethylene glycol supported SCS-PdCl complexes yield recyclable Heck–Mizoroki and Suzuki–Miyaura catalysts.[39,40,41,42] However, the activity of these catalysts

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with respect to substrates other than aryl iodides is low and several more efficient heterogeneous catalysts are known.[34] There are other reports on biphasic Suzuki coupling of aryl bromides and iodides, utilizing soluble and recyclable Pd catalysts under biphasic conditions.[43,44] However, the usefulness of such catalytic systems has to be re-evaluated because recently Leadbeater and Marco reported on microwave-promoted Suzuki reactions using aryl bromide substrates, which do not require a metal catalyst.[45]

Examples of recyclable catalysts for the Suzuki coupling of the more challenging aryl chloride substrates are rare.[46] Buchwald and Parish reported on a highly active Pd–biphenyl phosphine linked to insoluble, cross-linked polystyrene, which initially gave excellent yields and reaction rates for aryl chloride coupling; however the catalyst slows down considerably after only three reaction cycles.[47] Nájera and Botella presented a highly active oxime–carbapalladacyclic catalyst that gave quantitative yields for various aryl chlorides in boiling water with excellent turnover frequencies. However, this catalyst also deactivates after two or three cycles.[48] Corma, García, et al. recently reported on a silica-immobilized version of this catalyst, preliminary data indicate good activities and recyclability.[49]

Consequently, we have initiated a program aimed at developing monomethyl polyethyleneglycol (MeOPEG) tagged palladium phosphine complexes for Suzuki carbon–carbon bond-forming reactions. We decided to use MeOPEG as a cheap and chemically robust support for the attachment of sterically demanding and electron-rich phosphines and wish to report here on our results with palladium-catalyzed Suzuki reactions of aryl chlorides and $PhB(OH)_2$ under biphasic conditions, including a careful optimization of the catalyst activity, efficient recycling, and multiple use of the catalysts.

Results and Discussion

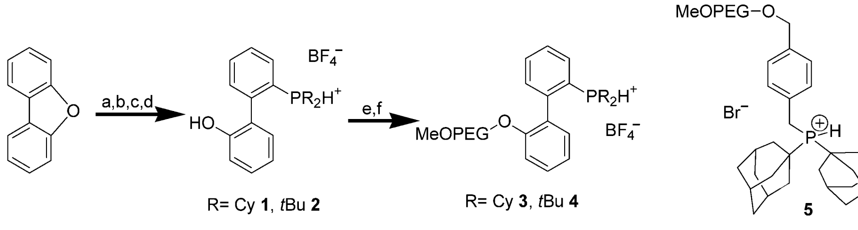
Synthesis of polymer-supported phosphine ligands: A sterically demanding and electron-rich phosphine $BnP(1\text{-}Ad)_2$ ligand was supported on polyethylene glycol as described previously, resulting in $MeOPEG\text{-}CH_2C_6H_4CH_2\text{-}P(1\text{-}Ad)_2$ (**5**), which was previously used for Sonogashira reactions.[50] In addition, two new PEG-supported phosphines of the Buchwald type were prepared from dibenzofuran, the respective dialkyl chlorophosphines, and MeOPEG-OTs. For the synthesis of 2,2′-substituted biphenyl phosphines a procedure by Heinicke et al.[51] was adapted for our purpose (Scheme 1).

Dibenzofuran was reductively ring-opened with lithium (ultrasound), resulting in the respective 2,2′-dianion, which on addition of $ClPR_2$ (R = Cy, *t*Bu) reacted first at the carbanion and then with $ClSiMe_3$ on the oxygen nucleophile. To obtain pure products the key step is the protonation of the biphenyl phosphine with $HBF_4{\cdot}Et_2O$, which results in the clean precipitation of the respective ether-insoluble phosphonium salts **1** and **2** in 55% and 69% yield (Scheme 1). It should be noted here that the respective non-protonated phosphines have been previously prepared by Buchwald in two steps using 2-methoxy-phenyl-MgBr and 1-bromo,2-chlorobenzene.[47] The present one-pot procedure is useful and yields about 5–10 g of the phosphonium salt in a single batch. The MeOPEG-polymer (2000 Dalton) is attached by reacting **1** or **2** with MeOPEG-OTs, resulting in the formation of polymer-supported phosphines, which are most conveniently isolated as the respective phosphonium salts **3** and **4** after protonation with HBF_4.[52] The phosphine loading of the respective polymers is about 90%, as determined by ^1H NMR spectroscopy.

Finding the best solvents for biphasic catalysis: Since the catalyst used here is tagged with a polar polymer, the solvent required for the catalyst phase will be a polar one, while the product-receiving phase has to be a nonpolar solvent. Simple alkanes (cyclohexane, heptane, etc.) were shown to be useful as the nonpolar component, while the choice of the polar solvent is critical, since it can have a decisive influence on the activity of the catalyst. Consequently, two conditions need to be met by such pairs of solvents: a) The two solvents must form two separate phases at room temperature and their mutual solubility should be small. This specifically applies to the solubility of the polar solvent in the alkane. b) Neither of the two solvents should interfere with the catalytic activity, which requires a careful selection of the polar solvents as these typically contain Lewis basic atoms such as oxygen or nitrogen, which tend to coordinate to the metal center.

Consequently, the choice of the polar solvent is critical to the success of biphasic catalysis. Based on these conditions we have tested a number of different solvents (Figure 1).

It is clear from the data in Figure 1 that DMSO is by far the best solvent in terms of catalyst activity. The same solvent was also found to be ideal for biphasic Sonogashira coupling reactions.[50] Other polar aprotic solvents such as DMF, DMA, NMP, and ACN are less efficient. The use of nitromethane (NM) does not result in any Suzuki product at all, which is most likely due to the high CH acidity of this solvent and its propensity to undergo C−C coupling.[53]



Scheme 1. a) ultrasound, Li; b) $ClPR_2$; c) Me_3SiCl; d) HBF_4; e) Na_2CO_3, MeOPEG-OTs; f) HBF_4.

Phosphine/palladium ratio: To further improve catalyst performance in DMSO we also studied the influence of the phosphine/palladium ratio (Figure 2). The coupling of 4-chloroacetophenone was monitored after two different reaction times (90 min and 17 h),

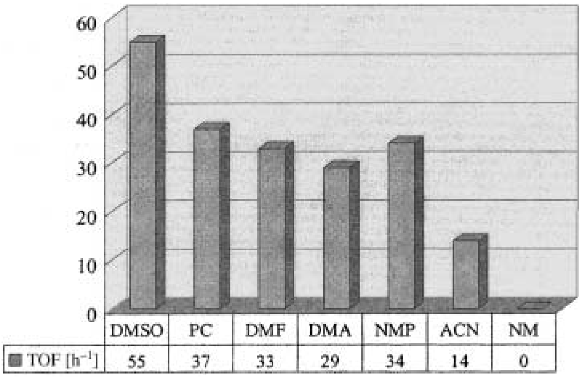


Figure 1. Solvent-dependent Suzuki coupling of 4-chloroacetophenone and $PhB(OH)_2$. Conditions: 4-chloroacetophenone (1 mmol), $Na_2[PdCl_4]$ (0.5 mol%), phosphine **5** (1.75 mol%), $PhB(OH)_2$ (1.5 mmol), K_3PO_4 (0.14 mmol), KF (3 mmol), $T = 75$ °C. Samples were taken after 90 min. DMSO = dimethyl sulfoxide, PC = propylene carbonate, DMF = dimethylformamide, DMA = dimethylacetamide, NMP = *N*-methylpyrrolidone, ACN = acetonitrile, NM = nitromethane.

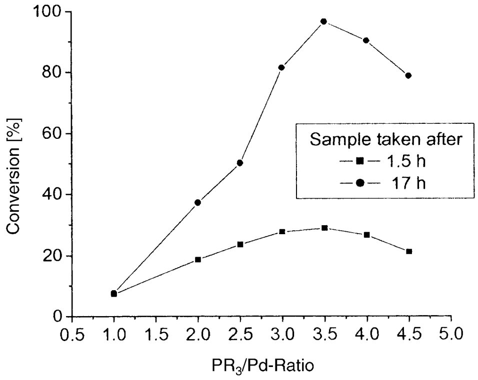


Figure 2. Determination of the ideal ratio PR_3/Pd for Suzuki reactions in DMSO. Conditions: 4-chloroacetophenone (1 mmol, 1 equiv), $Na_2[PdCl_4]$ (0.1 mol%), phosphine **5**, (varied from 0.1 mol% to 0.45 mol%), K_3PO_4 (0.14 mmol), KF (3 mmol), $PhB(OH)_2$ (1.5 mmol), $T = 75$ °C.

but in both cases the most active catalyst had a phosphine/palladium ratio of close to 3.5:1. This observation is somewhat surprising as the P/Pd ratios in closely related Suzuki catalysts is typically 2:1 or 1:1.[28m,n] Normally this rationalized by assuming a low-coordinate palladium species, possibly of the $[Pd(PR_3)_1]$ type, to be the most catalytically active species.[54] Nonetheless, for various catalysts and depending on the nature of the phosphine ligand, the situation appears less clear cut. In a recent and very detailed study by Bedford et al. on ortho-metalated catalysts with an additional phosphine ligand, the activity of Pd catalyst for Suzuki coupling peaked at a P/Pd ratio of 1:1 or 2:1 for some phosphines (PCy_3, P*t*Bu_3), whereas with other phosphines (Cy_2P(*o*-biphenyl)) the most active catalysts were obtained only with much higher P/Pd ratios (ca. 3:1 or 4:1).[55] This is in line with observations made by Beller et al. on Heck reactions.[56]

Screening of the bases: A detailed screening of various bases for the polymeric catalysts was performed, because we anticipated that the polyether chain attached to the catalyst could influence the properties of certain metal-ion-containing bases, as was observed with Sonogashira reactions.[16b] Amines like Et_3N (TOF 0.5 h^{-1}) and *i*Pr_2NH (TOF 1 h^{-1}) gave poor results, as did acetates KOAc (TOF < 0.5 h^{-1}) and alcoholates KO*t*Bu (TOF < 0.5 h^{-1}); carbonates Na_2CO_3 (TOF 7 h^{-1}), K_2CO_3 (TOF 8 h^{-1}), and $CsCO_3$ (TOF 9 h^{-1}) and hydroxides NaOH (TOF 5 h^{-1}) and KOH (TOF 7 h^{-1}) are only slightly better. Finally, the established bases KF (TOF 56 h^{-1}) and K_3PO_4 (TOF 48 h^{-1}) result in the most active catalysts. Since KF alone, however, may not be sufficiently basic to deprotonate the phosphonium salt, we decided to use it in combination with K_3PO_4. We soon found out that the ratio of KF/K_3PO_4 also has a small influence on the catalytic activity (Figure 3).

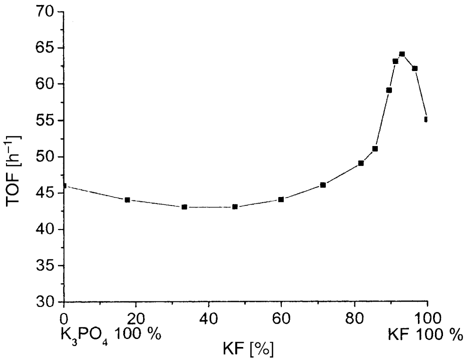


Figure 3. Activity of the catalyst for Suzuki coupling of 4-chloroacetophenone and $PhB(OH)_2$ in DMSO depending on the ratio of KF/K_3PO_4. TOF samples were taken after 60 min. Conditions: 4-chloroacetophenone (0.5 mmol), $Na_2[PdCl_4]$ (0.5 mol%), phosphine **5** (1.75 mol%), $PhB(OH)_2$ (0.75 mmol), $T = 80$ °C, DMSO. Each data point is the average of three independent determinations.

Influence of water on the catalyst activity: Water is known to influence the activity of Suzuki catalysts.[55] This is, however, difficult to quantify, since the problems involved in drying $PhB(OH)_2$ to a defined water content are well known.[57] Nonetheless, we find that adding small amounts of water (close to one equivalent with respect to the substrates) to the reaction mixtures leads to a significant increase in the activity of the catalyst.

Palladium source: Following the optimization of numerous coupling parameters using $Pd(OAc)_2$ as the only metal source, we again checked for the suitability of different palladium complexes (Table 1). However, it turned out that the nature of palladium containing species is not critical to the success of the reaction.[58] To us $Na_2[PdCl_4]$ appeared to be

Table 1. Palladium sources.[a]

Pd source	$Na_2[PdCl_4]$	$Pd(dba)_2$	$Pd(OAc)_2$	$[PdCl_2(PhCN)_2]$	$PdCl_2$
TOF [h^{-1}]	66	61	60	64	58

[a] Conditions: 4-chloroacetophenone (1 mmol), Pd compound (0.5 mol%), phosphine **5** (1.75 mol%), K_3PO_4 (58 mg, 0.27 mmol), KF (174 mg, 3 mmol), $PhB(OH)_2$ (1.5 mmol), $T = 80$ °C, DMSO solvent.

most convenient, since it is cheaper (per mol) than most other Pd compounds.

Catalyst activity, the PEG chain and solvent effects: To evaluate the influence of the polyethylene glycol polymer chain on the activity of the Suzuki catalysts we tested the activity of Pd complexes with the polymer-supported phosphines **3**, **4**, and **5** and with BnP(1-Ad)$_2$ under identical conditions in DMSO and THF. It can be seen in Table 2 that the TOF for the polymeric catalysts are almost the same in both solvents. Consequently in the highly polar DMSO solvent used in the biphasic catalysis the polymer appears to have no influence on the catalyst activity. On the other hand, on comparing the four phosphines in THF solution, the activity of the low-molecular-weight catalyst using BnP(1-Ad)$_2$ is doubled (with respect to its performance in DMSO), while that of the polymeric catalyst is roughly the same.

Table 2. Comparison of TOF values of low and high molecular weight catalysts in DMSO and THF solvent.[a]

Ligand	TOF [h^{-1}] DMSO	THF
3	122	126
4	110	113
5	61	50
BnP(1-Ad)$_2$	70	137

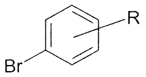
[a] Conditions: 4-chloroacetophenone (0.5 mmol), Na$_2$[PdCl$_4$] (0.5 mol%), ligand (1.75 mol%), K$_3$PO$_4$ (0.14 mmol), KF (1.5 mmol), H$_2$O (1.5 mmol), PhB(OH)$_2$ (0.75 mmol), T = 65 °C. The TOF data were determined on incomplete conversion of reactants.

Preparation of the catalyst: A precatalyst is prepared by dissolving Na$_2$[PdCl$_4$] (0.5 mol%), the phosphonium salt (1.75 mol%), and K$_3$PO$_4$ (2 mol%) in DMSO at 60 °C. This yellow stock solution is added to the mixture of the reactants and KF in DMSO/heptane, whereupon the reaction immediately commences.

Suzuki coupling—recycling experiments, aryl bromides: In the present study we invested comparatively little work on the coupling reactions of aryl bromides, since these substrates are not challenging, especially following the work of Leadbeater and Marco on microwave-promoted Suzuki reactions of aryl bromides in the absence of palladium.[45]

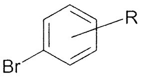
The Pd catalyst of phosphine **5** shows excellent reactivity and recyclability for the coupling of three aryl bromide substrates with PhB(OH)$_2$. The main results of the coupling reactions are summarized in Tables 3 and 4. We tested 4-bromotoluene, 4-bromoanisole, and 4-bromoacetophenone with PhB(OH)$_2$ at 0.1 mol% catalyst concentration and 75 °C. The same catalyst batch was recycled and used for six consecutive reactions, which resulted—after exhaustive extraction and chromatographic purification of the product—in yields of 87, 94, and 90%, respectively. The activity of the catalyst as evidenced by TOF data is quite good (Table 4) and experiences only a small drop to 89–92% of its initial activity after six reaction cycles.

Table 3. Suzuki coupling of aryl bromides and PhB(OH)$_2$ over six cycles.

Entry		Time [h]	Cycle 1 [%]	Cycle 2 [%]	Cycle 3 [%]	Cycle 4 [%]	Cycle 5 [%]	Cycle 6 [%]	Yield[a] [%]
1	4-Me	5	91	90	90	89	88	87	535/600
2	4-MeO	5	98	96	96	96	95	88	569/600
3	4-COCH$_3$	5	99	98	98	97	97	84	573/600

[a] The numbers given for the individual cycles correspond to conversions as determined by GC. Yields correspond to the amount of isolated material after chromatographic purification. Conditions: aryl bromide (1 mmol), Na$_2$[PdCl$_4$] (0.1 mol%), ligand **5** (0.2 mol%), KF (3 mmol), PhB(OH)$_2$ (1.5 mmol), T = 75 °C, DMSO, TOF data were determined after 30 min reaction time.

Table 4. Suzuki coupling of aryl bromides and PhB(OH)$_2$ over six cycles, TOF data.

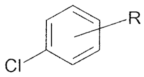
Entry		Time [h]	Cycle 1 [h^{-1}]	Cycle 2 [h^{-1}]	Cycle 3 [h^{-1}]	Cycle 4 [h^{-1}]	Cycle 5 [h^{-1}]	Cycle 6 [h^{-1}]	Residual activity[a] [%]
1	4-Me	0.5	516	508	490	486	472	458	89
2	4-MeO	0.5	920	914	870	860	856	850	92
3	4-COCH$_3$	0.5	1298	1248	1230	1208	1202	1192	92

[a] Conditions as described above. Residual activity is the relative activity of the catalyst after six cycles compared with that of the first cycle normalized to 100% activity. The TOF data were determined on incomplete conversion of reactants.

Suzuki coupling—recycling experiments, aryl chlorides: Owing to the stability of the carbon–chlorine bond, aryl chlorides are challenging substrates for various coupling reactions.[59] As outlined in the introduction, examples of catalysts capable of repetitive aryl coupling are rare and even those suffer from rapid deactivation after a few reaction cycles. The examples presented by us demonstrate that soluble-polymer-supported catalysts in biphasic catalysis can be recycled efficiently over several cycles. The yields of the coupling reactions for the various aryl chlorides are in the 83–98% range, with most reactions being higher than 90% (Table 5, Table 6, Table 7).

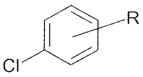
The TOF data for the various Suzuki coupling reactions (Table 6) are more indicative of the high recycling efficiency than are chemical yields. Typically there is some loss of activity after the first cycle, but after that the catalysts remain almost constant in activity. We have observed the catalyst to be most sensitive when it is in the resting state, without sub-

Table 5. Suzuki coupling of aryl chlorides and $PhB(OH)_2$ over three or six cycles.

Entry		Time [h]	Cycle 1[a] [%]	Cycle 2[a] [%]	Cycle 3[a] [%]	Cycle 4[a] [%]	Cycle 5[a] [%]	Extraction after last cycle [%][b]	Yield[c] [%]
1	4-MeO	18	69	83	119	93	92	34	490/500
2	4-Me	18	61	84	110	100	100	32	490/500
3	Ph	18	59	82	109	103	98	18	470/500
4	4-$COCH_3$	18	14	87	100	101	100	23	425/500
5	4-CN	18	35	40	67	103	120	97	460/500
6	4-CF_3	18	75	37	156	101	99	21	490/500
7	4-NO_2	18	45	67	100	108	93	28	450/500
8	4-COPh	18	68	71	100	86	87	80	490/500
9	4-CO_2Et	18	22	104	99	62	69	121	475/500
10	3-MeO	18	53	90	114	–	–	16	273/300
11	3-CN	18	56	41	105	–	–	54	255/300
12	3-$COCH_3$	18	2.5	65	100	–	–	81	249/300
13	3-CO_2Et	18	53	84	119	–	–	22	279/300
14	3-CF_3	18	49	86	117	–	–	23	276/300

[a] The yields listed for the individual cycles are phase yields and correspond to the amount of product isolated from the heptane extract; conversions were always close to quantitative. [b] Extraction after last cycle denotes the amount of product isolated after exhaustive extraction of the DMSO solution after the last reaction cycle. [c] Yields correspond to the amount of isolated material after chromatographic purification. Conditions: aryl chloride (0.5 mmol), $Na_2[PdCl_4]$ (0.5 mol%), ligand **5** (1.75 mol%), K_3PO_4 (0.14 mmol), KF (1.5 mmol), H_2O (1.5 mmol), $PhB(OH)_2$ (1.5 mmol), $T = 80\,°C$, DMSO.

Table 6. Suzuki coupling of aryl chlorides and $PhB(OH)_2$ over three or six cycles, TOF data.

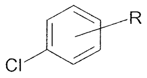
Entry		Time [h]	Cycle 1 [h^{-1}]	Cycle 2 [h^{-1}]	Cycle 3 [h^{-1}]	Cycle 4 [h^{-1}]	Cycle 5 [h^{-1}]	Residual activity[a] [%]
1	4-MeO	1	40	37	37	36	36	90
2	4-Me	1	31	29	29	29	28	90
3	H	1	46	42	43	42	40	87
4	4-$COCH_3$	1	61	58	57	57	57	93
5	4-CN	1	77	73	72	70	68	88
6	4-CF_3	1	60	57	56	58	57	95
7	4-NO_2	1	94	95	92	87	83	88
8	4-COPh	1	35	34	34	32	32	91
9	4-CO_2Et	1	42	39	40	39	38	90
10	3-MeO	1	25	22	22	–	–	88
11	3-CN	1	48	43	42	–	–	88
12	3-$COCH_3$	1	51	48	47	–	–	92
13	3-CO_2Et	1.5	65	61	61	–	–	94
14	3-CF_3	1.5	54	50	49	–	–	91
15	3-NO_2	1.5	100	96	93	–	–	93
16	3-CH_3	1.5	12	11	11	–	–	92
17	2-CN	1	109	102	102	–	–	94
18	2-CF_3	1	111	103	103	–	–	93
19	2-MeO	1	27	25	24	–	–	89

[a] Residual activity is the relative activity of the catalyst after six (three) cycles compared with that of the first cycle defined as 100% activity. Conditions: aryl chloride (0.5 mmol), $Na_2[PdCl_4]$ (0.5 mol%), ligand **5** (1.75 mol%), K_3PO_4 (0.14 mmol), KF (1.5 mmol), H_2O (1.5 mmol), $PhB(OH)_2$ (1.5 mmol), $T = 80\,°C$, DMSO. The TOF data were determined on incomplete conversion of reactants.

strate. Consequently, to increase the catalyst longevity it is important to shorten the time between the various cycles of the coupling reaction.

As both phosphines of the Buchwald type display similar activities (Table 2) for the Suzuki coupling, we tested the Pd catalyst of phosphine **4** for the coupling of aryl chlorides (Table 7). It is evident from these data that this catalyst is typically between 1.3 and 2.8 times more reactive than the Pd complexes of phosphine **5**. An exceptionally high activity is observed for entry 4 in Table 7 with *para*-CF_3. The increase in activity is most pronounced for the electron-deficient substrates (entries 3 and 4, Table 7) and less so for the electron-rich substrates (entries 1 and 2, Table 7). On the other hand, we also noticed that the catalyst derived from $Na_2[PdCl_4]$ and **4** is significantly more sensitive than the one derived from phosphine **5**.[60] Consequently, much more care has to be exercised to allow its successful recycling.

Table 7. Suzuki coupling of aryl chlorides and PhB(OH)$_2$ with Pd/**4** over three cycles, TOF data.

Entry		Time [h]	Cycle 1 [h^{-1}]	Cycle 2 [h^{-1}]	Cycle 3 [h^{-1}]	Residual activity[a] [%]
1	4-MeO	1	54	52	50	93
2	4-Me	1	55	51	49	89
3	4-COCH$_3$	1	108	104	96	89
4	4-CF$_3$	1	171	162	158	92

[a]Residual activity is the relative activity of the catalyst after six (three) cycles compared with that of the first cycle defined as 100% activity. Conditions: aryl chloride (0.5 mmol), Na$_2$[PdCl$_4$] (0.5 mol%), ligand **4** (1.75 mol%), K$_3$PO$_4$ (0.14 mmol), KF (1.5 mmol), H$_2$O (1.5 mmol), PhB(OH)$_2$ (1.5 mmol), $T = 80°C$, DMSO. The TOF data were determined on incomplete conversion of reactants. Yields of all coupling reaction are >95% over all cycles.

Determination of catalyst leaching: The virtually quantitative retention of the catalyst in the DMSO catalyst phase is very important for maintaining a high catalyst activity and avoiding contamination of the product with traces of palladium. A first test involved probing the crude product obtained from evaporation of the product-receiving phase by ^{1}H NMR spectroscopy, which confirmed the absence of polymeric phosphine. Owing to the limited sensitivity of this spectroscopic technique, this proves catalyst retention in DMSO to be in excess of 99.5%. To be more accurate, we applied a spectrophotometric determination using the colorimetric reagent 4,4′-bis(dimethylamino)thiobenzophenone, which is characterized by an extremely large extinction coefficient of the respective Pd complex (212000 L mol^{-1} cm^{-1}) and a correspondingly high sensitivity.[61,62] Again the amount of palladium was found to be below the detection level of the analytical technique in the crude product, which corresponds to a Pd retention higher than 99.95%.

Conclusion

We have developed highly active, phase-tagged catalysts for the Suzuki coupling of aryl chlorides in organic/organic biphasic solvent mixtures. The polymeric catalysts are Pd complexes of sterically demanding and electron-rich phosphines (MeOPEG-OCH$_2$C$_6$H$_4$CH$_2$-P(1-Ad)$_2$ or 2-MeOPEG-O-2′-dialkylphosphinobiphenyl) with soluble polyethylene glycol tags. DMSO constitutes the catalyst phase, since the Pd complex catalyst modified with a polar phase tag exclusively dissolves in the polar solvent, while *n*-heptane forms the product-receiving phase. Following the catalytic reactions the coupling products can be efficiently separated from the catalyst by a simple phase separation of the two room temperature immiscible solvents. Alternatively, the reactions can be performed in DMSO solvent alone, followed by extraction of the product with heptane after the coupling reaction. It is very important to note that the leaching of the catalyst into the product-containing solution appears to be negligible (<0.05%), consequently, the coupling products are virtually free from palladium. The recyclability of the catalyst over up to six cycles is evidenced by the excellent yields of the coupling reactions, which typically exceed 90%. Furthermore, the activity (TOF) of the two catalysts studied remains virtually constant after the second coupling cycle. Depending on the substrates the catalysts derived from Buchwald type phosphines are more active, however, the BnP(1-Ad)$_2$ derived catalysts appear to be more robust.

Following our work on recyclable catalysts for the Sonogashira coupling,[50] we have now demonstrated that high-activity catalysts for the repetitive Suzuki reaction of aryl chlorides are available. It should therefore be possible to extend the principle of highly active biphasic catalysis to various other types of Pd-catalyzed coupling reactions.

Experimental Section

General: MeOPEG$_{2000}$OH, aryl halides, and PhB(OH)$_2$ were used as received. Solvents were purified by using standard procedures.[63] Bases were dried at 80 C under vacuum. Reactions were performed under an atmosphere of argon using standard Schlenk techniques. Column chromatography was carried out on silica MN60 (63–200 μm), TLC on Merck plates coated with silica gel 60, F254. Yields of the coupling reactions were determined by ^{1}H NMR spectroscopy. Gas chromatography was performed on a Perkin Elmer Autosystem with a CP-SIL8CB-column, nitrogen carrier gas, and FID. NMR spectra were recorded at 293 K with a Bruker Avance (^{1}H 500 MHz, ^{13}C 125 MHz, ^{31}P 203 MHz), Bruker AC 300 (^{1}H 300 MHz, ^{13}C 75 MHz), or a Bruker 200 AC (^{1}H 200 MHz, ^{31}P 81 MHz) spectrometer. ^{1}H NMR chemical shifts were referenced to residual protonated impurities in the solvent, ^{13}C NMR chemical shifts to the solvent signal (CDCl$_3$: $\delta_H = 7.24$ ppm, $\delta_C = 77.0$ ppm), and ^{31}P NMR spectra were referenced to PMe$_3$ (38% in benzene $\delta = -62$ ppm on the Bruker AC 200) as an external standard or aqueous 85% H$_3$PO$_4$ (on all other NMR machines). Experimental details of the colorimetric palladium determination of catalytic reactions have been reported previously.[62] A stock solution of the precatalyst was freshly prepared prior to each set of reactions. All Suzuki reactions were done in a self-made parallel synthesizer, which allows eight reactions to be performed simultaneously under Schlenk conditions.[64] Starting materials were commercially available (MeOPEG-OH was used as received) or prepared according to literature procedures: (1-Ad)$_2$PH[65], BnP(1-Ad)$_2$,[50] MeOPEG-OCH$_2$C$_6$H$_4$CH$_2$P(1-Ad)$_2$,[50] *t*Bu$_2$PCl,[66] Cy$_2$PCl[67], MeOPEG-OTs.[50]

General procedure for the synthesis of 2′-hydroxy-2-dialkylphosphoniumbiphenyl tetrafluoroborates: (modified from Heinicke et al.):[51] A suspension of lithium (972 mg, 42 mmol, 30% (w/w) in mineral oil), dibenzofurane (3.36 g, 20 mmol), and 4,4′-di-*tert*-butyl-biphenyl (274 mg, 1 mmol, 5 mol%) in diethyl ether (60 mL) was heated to reflux for 24 h in a sonification bath (160 W, ultrasound bath) resulting in a brown suspension. After the reaction mixture was cooled to below 5°C, the corresponding R$_2$PCl (19 mmol) dissolved in diethyl ether (20 mL) was added dropwise. The reaction mixture was stirred for 15 h at room temperature, followed by addition of ClSiMe$_3$ (2.46 mL, 19 mmol) and stirring for another 15 h. The mixture was filtered under argon with celite and after cooling to 0°C, HBF$_4$·Et$_2$O (5.2 mL, 38 mmol, 54% in Et$_2$O) was added, whereupon the crude product precipitated. The solid was collected by filtration and washed with diethyl ether (5×20 mL) and dried in vacuum. The 2′-hydroxy-2-dialkylphosphonium biphenyl tetrafluoroborates are obtained as colorless powders.

2′-Hydroxy-2-di-cyclohexylphosphonium-biphenyl tetrafluoroborate (1): After addition of $ClPCy_2$ (4.23 mL, 19 mmol) the color of the suspension changed to dark grey and after stirring for 15 h the suspension had a dark brown color. The crude phosphonium salt precipitated and was obtained as a pink product. Recrystallization from acetone/Et_2O gave **1** as a colorless powder (5.0 g; 55%). ^{1}H NMR (200 MHz, [D$_6$]acetone/[D$_6$]DMSO v/v = 2:1): δ = 10.15 (s, 1H; OH), 8.07 (dd, 1H, J = 11.3, 8.05 Hz; ArH), 7.88 (t, 1H, J = 7.5 Hz; ArH), 7.71 (t, 1H, J = 7.15 Hz; ArH), 7.47 (dd, 1H, J = 7.15, 4.47 Hz; ArH), 7.37 (t, 1H, J = 7.67 Hz; ArH), 7.13 (d, 1H, J = 7.4 Hz; ArH), 7.03 (d, 1H, J = 8.1 Hz; ArH), 6.99 (t, 1H, J = 7.5 Hz; ArH), 6.43 (d, 1H, $^1J_{P,H}$ = 482 Hz; P−H), 3.12 (brs, 2H; P−CH), 2.14–1.05 ppm (brm, 22H; CyH); ^{13}C NMR (125 MHz, [D$_6$]acetone/[D$_7$]DMSO v/v = 2:1): δ = 154.3, 146.4, 134.0, 133.5, 132.7, 129.3, 126.4, 121.1, 117.1, 116.1 (d, *tert*, $^1J_{P,C}$ = 72 Hz; CP), 28.1, 26.7–25.8 ppm (not resolved); ^{31}P NMR (81 MHz, [D$_6$]acetone/[D$_6$]DMSO v/v = 2:1): δ = 37.4 ppm (d, $^1J_{P,H}$ = 488 Hz).

2′-Hydroxy-2-di-*tert*-butylphosphonium-biphenyl tetrafluoroborate (2): ClP*t*Bu$_2$ (3.6 mL, 3.42 g, 19 mmol). Recrystallization from acetone/Et_2O gave **2** in the form of a colorless powder to (5.27 g; 69%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 10.23 (s, 1H; OH), 8.02 (t, 1H, J = 8.8 Hz; ArH), 7.88 (t, 1H, J = 7.6 Hz; ArH), 7.71 (t, 1H, J = 7.8 Hz; ArH), 7.74 (dd, 1H, J = 7.8, 4.36 Hz; ArH), 7.37 (dd, 1H, J = 7.4, 8.21 Hz; ArH), 7.13 (d, 1H, J = 7.6 Hz; ArH), 7.03 (d, 1H, J = 8.2 Hz; ArH), 6.99 (t, 1H, J = 7.4 Hz; ArH), 6.4 (d, 1H, $^1J_{P,H}$ = 488 Hz; P−H), 1.54 (d, 9H, J = 17.5 Hz; *t*Bu−H), 1.26 ppm (d, 9H, J = 17.5 Hz; *t*Bu−H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 152.9, 145.2, 134.4, 132.9, 131.7, 128.0, 125.0, 119.8, 116.0, 115.1 (d, *tert*, $^1J_{P,C}$ = 72 Hz; CP), 33.8 (dd, $^1J_{P,C}$ = 61.6, 35.2 Hz; CP), 28.0, 26.4 ppm; ^{31}P NMR (202 MHz, [D$_6$]acetone): δ=30.8 ppm (dm, $^1J_{P,H}$ = 487 Hz); ^{31}P NMR (81 MHz, $CDCl_3$): δ = 37.4 ppm (d, $^1J_{P,H}$ = 488 Hz).

General procedure for the synthesis of 2′-MeOPEG$_{2000}$O-2-dialkylphosphonium-biphenyl tetrafluoroborates: NaH (164 mg, 3.9 mmol, 60% in mineral oil) was added to a cooled solution (0–5 °C) of the respective 2′-hydroxy-2-dialkylphosphonium-biphenyl tetrafluoroborate (1.24 mmol), dissolved in THF (30 mL). The cooling bath removed and the mixture was stirred for 1.5 h at room temperature. This solution was added dropwise by cannula to a stirred solution of MeOPEG$_{2000}$OTs (2.5 g, 1.16 mmol) in THF (50 mL). After the reaction mixture had been stirred at room temperature for 8 h it was filtered through celite, cooled to 0 °C, and $HBF_4{\cdot}Et_2O$ (469 µL, 1.86 mmol, 54% in Et_2O) was added. The solution was concentrated to 20 mL and diethyl ether (80 mL) was added to precipitate the product at 4 °C. The precipitate was collected by filtration, thoroughly washed with diethyl ether (5×20 mL), and dried in vacuum. The 2′-MeOPEG$_{2000}$O-2-dialkylphosphonium biphenyl tetrafluoroborates were obtained as colorless powders.

2′-MeOPEG$_{2000}$O-2-di-cyclohexylphosphonium biphenyl tetrafluoroborate (3): The deprotonation of 2′-hydroxy-2-di-cyclohexylphosphonium biphenyl tetrafluoroborate (0.85 g, 1.87 mmol) led to a pale yellow suspension from which **3** was obtained as a colorless powder (2.9 g, 1.2 mmol; 63%). ^{1}H NMR spectroscopy showed 92% etherification of the terminal OH group. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.13 (dd, 1H J = 11.6, 7.6 Hz; ArH), 7.96 (t, 1H, J = 7.5 Hz; ArH), 7.80 (t, 1H, J = 7.2 Hz; ArH), 7.62 (dd, 1H, J = 7.2, 4.25 Hz; ArH), 7.53 (t, 1H, J = 7.5 Hz; ArH), 7,29 (d, 1H, J = 7.27 Hz; ArH), 7.27 (d, 1H, J = 7.95 Hz; ArH), 7.17 (t, 1H, J = 7.5 Hz; ArH), 6.34 (d, 1H, $^1J_{P,H}$ = 484 Hz; P−H), 3.74–3.45 (m; PEG-H), 3.30 (s, 3H; PEGO-CH_3), 3.07 (br, 2H; P−CH), 1.97–1.12 ppm (brm, 22H; Cy-H); ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 156.7, 146.8, 135.9, 134.5, 134.1, 132.9, 132.5, 130.1, 128.8, 122.7, 115.2, 114.0 (d, tert, $^1J_{P,C}$ = 71 Hz; CP), 73.1, 71.0, 70.3, 59.24, 28.8–26.2 ppm (not resolved); ^{31}P NMR (81 MHz, [D$_6$]acetone): δ = 16.0 ppm (d, $^1J_{P,H}$ = 484 Hz).

2′-MeOPEG$_{2000}$O-2-di-*t*butylphosphonium-biphenyl tetrafluoroborate (4): The deprotonation of 2′-hydroxy-2-di*t*butylphosphonium biphenyl tetrafluoroborate (0.5 g, 1.24 mmol) led to a pale yellow suspension from which **4** was obtained as a colorless powder (2.68 g, 1.04 mmol; 90%). ^{1}H NMR spectroscopy showed 90% etherification of the terminal OH group. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.86 (t, 1H, J = 8.8 Hz; ArH), 7.73 (t, 1H, J = 7.6 Hz; ArH), 7.56 (t, 1H, J = 7.7 Hz; ArH), 7.49 (m, 1H; ArH), 7.17 (s, 1H; ArH), 7.06 (d, 1H, ArH; J = 7.6 Hz), 6.98- 6.92 (m, 2H; ArH), 6.5 (d, 1H, $^1J_{P,H}$ = 488 Hz; P−H), 3.96–3.21 (m; PEG-H), 1.50 (d, 9H, J = 17.5 Hz; *t*Bu−H), 1.32 ppm (d, 9H, J = 17.5 Hz; *t*Bu−H); ^{31}P (202 MHz, [D$_6$]acetone): δ = 34.2 ppm (dm, $^1J_{P,H}$ = 488 Hz; Ad_2PAr); ^{31}P (81 MHz, $CDCl_3$): δ = 37.4 ppm (d, $^1J_{P,H}$ = 488 Hz).

General procedure for the extractive/biphasic Suzuki coupling of aryl chlorides and phenyl boronic acid (recycling experiments): The corresponding aryl chloride (1 mmol), 1.5 mmol phenyl boronic acid (182 mg), distilled water (27 µL, 1.5 mmol), and KF (174 mg, 3 mmol) were added to thoroughly deoxygenated DMSO (3 mL) under stirring, followed by the appropriate amount of the catalyst stock solution with 1.75 mol% of the appropriate ligand [(2′-MeOPEG$_{2000}$O-2-dicyclohexylphosphonium biphenyl tetrafluoroborate (**3**, 48 mg), 2′-MeOPEG$_{2000}$O-2-di*t*butylphosphonium biphenyl tetrafluoroborate (**4**, 46.5 mg), or (4-(MeOPEG$_{2000}$OCH$_2$)C$_6$H$_4$CH$_2$P(1-Ad$_2$)·HBr (**5**, 44 mg)], $Na_2[PdCl_4]$ (1.45 mg, 0.5 mol%), and K_3PO_4 (58 mg, 0.27 mmol) in DMSO. The mixture was heated to 80 °C until the aryl chloride reactant was consumed (GC). The mixture was allowed to cool to room temperature and was extracted with *n*-heptane (2×10 mL). The upper layer was removed by cannula and filtered over a short column with silica gel. Evaporation of the solvent yielded the Suzuki coupling product. The reaction vessel was recharged with KF (174 mg, 3 mmol), phenyl boronic acid (145 mg, 1.2 mmol), and the corresponding aryl chloride (1 mmol), and another reaction cycle was started. After the last cycle, distilled water (1 mL) was added to the reaction mixture, which was then extracted with *n*-heptane (3×10 mL) to isolate all of the remaining product after evaporation of the solvent.

General procedure for the biphasic Suzuki coupling of aryl bromides and phenyl boronic acid (recycling experiments): This procedure was identical to the coupling of aryl chlorides, see legend of Table 3 for differing conditions.

General procedure for the determination of the TOF in multicycle experiments: From the respective reaction mixture (see relevant procedure) a 20 µL sample was taken after the appropriate time (1–1.5 h, depending on the reactivity of the aryl chloride) and the reaction was run to completion. To precisely determine the TOF for the second and consecutive cycles, an additional 20 µL sample had to be taken as a calibration reference before each coupling reaction after the first cycle. This is necessary to compensate for the incomplete extraction of products after the first (and consecutive cycles) from the catalyst phase. All samples taken for GC studies were treated in the following manner: Water (10 µL) was added to the DMSO sample solutions and the product and reactants extracted with *n*-heptane (50 µL). The upper layers (heptane solutions) were examined by GC.

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