Homogeneous Catalysts Supported on Soluble Polymers: Biphasic Sonogashira Coupling of Aryl Halides and Acetylenes Using MeOPEG-Bound Phosphine–Palladium Catalysts for Efficient Catalyst Recycling

Axel Köllhofer and Herbert Plenio*[a]

Abstract: The Sonogashira coupling of various aryl bromides and iodides with different acetylenes was studied under biphasic conditions with soluble, polymer-modified catalysts to allow the efficient recycling of the homogeneous catalyst. For this purpose, several sterically demanding and electron-rich phosphines of the type R_PPR_2 were synthesised. They are covalently linked to a monomethyl polyethylene glycol ether with a mass of 2000 Dalton ($R_P = MeOPEG_{2000}$) R_PPR_2: $-PR_2 = -CH_2C_6H_4CH_2P(1\text{-}Ad)_2$, $-C_6H_4\text{-}P(1\text{-}Ad)_2$, $-C_6H_4\text{-}PPh_2$. To couple aryl iodides and acetylenes, the catalyst $[(MeCN)_2PdCl_2]/2\,R_P\text{-}C_6H_4\text{-}PPh_2$ was used in $CH_3CN/Et_3N/n$-heptane (5/2/5). The combined yields of coupling product over five reaction cycles are between 80–95%. There is no apparent leaching of the catalyst into *n*-heptane, as evidenced by ^1H NMR spectroscopy. The new catalyst $[(MeCN)_2PdCl_2]/2\,(1\text{-}Ad)_2PBn$ can be used for room-temperature coupling of various aryl bromides and acetylenes in THF with $HNiPr_2$ as a base. A closely related catalyst $Na_2[PdCl_4]/2\,R_P\text{-}CH_2C_6H_4CH_2P(1\text{-}Ad)_2$ linked to the polymer was used to couple aryl bromides and acetylenes in DMSO or DMSO/*n*-heptane at 60 °C with 0.5 mol% $Na_2[PdCl_4]$, 1 mol% R_PPR_2 and 0.33 mol% CuI. The combined yield of coupling products over five cycles is always greater than 90%, except for sterically hindered aryl bromides. The determination of the turnover frequency (TOF) of the catalyst indicates only a small decrease in activity over five cycles. Leaching of the catalyst into the product containing *n*-heptane solution could not be detected by means of ^1H NMR and TXRF; this is indicative of >99.995% catalyst retention in the DMSO solvent.

Keywords: homogeneous catalysis · biphasic catalysis · C–C coupling · palladium · polymers

Introduction

The problems associated with the recovery of catalysts after product formation pose a serious drawback for large-scale applications of homogeneous catalysis and are the main reason why heterogeneous catalysis has a share of more than 80% in industrial processes.[1]

Consequently, numerous approaches that deal with the problem of catalyst recovery, such as thermal or chemical recovery,[2] immobilisation of catalysts on solid, liquid or aqueous supports,[3] membrane processes[4] or multiphase systems (phase-transfer catalysis, thermoregulated phase-transfer catalysis, liquid–liquid biphasic catalysis),[5] have been studied.[6]

The huge commercial success of the Ruhrchemie/Rhône-Poulenc hydroformylation[7] and the SHOP process [8] demonstrates that homogeneous catalysis with precious metals is economically competitive as soon as efficient options for catalyst recovery are at hand. Hydroformylation relies on a biphasic aqueous/organic solvent system, with the catalyst $[HRh(CO)(TPPTS)_3]$ residing exclusively in the aqueous phase, whereas the product is located within the organic solvent.[9] Hence simple phase separation affects the separation of catalyst and product; losses of precious Rh are negligible.[10] Consequently, several liquid–liquid biphasic concepts are currently studied for applications in catalysis:[11] aqueous/organic,[12] fluorous/organic,[13, 14] ionic liquids,[15, 16] polymer-supported catalysts[17] and amphiphilic catalysts.[18]

Palladium-catalysed C–C coupling reactions are powerful synthetic methods[19] which have been receiving tremendous interest in recent years, especially since significant progress in this field has been made, as represented by publications of the groups of Beller,[20] Buchwald,[21] Fu,[22] Hartwig,[23] Herrmann,[24] Reetz[25] and others.[26] Nevertheless, the high price of Pd renders commercial processes based on Pd less attractive[27] unless extremely active and/or recyclable catalysts are available.[28] This is all the more important as heterogeneous Pd catalysts in coupling reactions rarely match the activity of the homogeneous ones[29, 30] and they also suffer from deactivation after recycling.[31]

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[a] Prof. Dr H. Plenio, Dipl.-Chem. A. Köllhofer
Institut für Anorganische Chemie, TU Darmstadt
Petersenstrasse 18, 64287 Darmstadt (Germany)
Fax: (+49) 6151-166040
E-mail: plenio@tu-darmstadt.de

0947-6539/03/0906-1416 $ 20.00+.50/0

Applications of the liquid–liquid biphasic concept to Pd-catalysed C–C coupling reactions are rare and mainly[32] limited to the work of the Bergbreiter group who has demonstrated that poly(*N*-isopropylacrylamide) linked to SCS–PdCl complexes yields recyclable Heck–Mizoroki and Suzuki–Miyaura catalysts.[33–36] However, the activity of these catalysts with respect to substrates other than aryl iodides is low, while for these substrates good heterogeneous catalysts are also available. Consequently, more active catalysts are needed to access less reactive aryl bromides or chlorides for biphasic C–C coupling reactions.

Apart from Bergbreiter's research, the biphasic concept that employs soluble polymer-supported catalysts has only been applied to other metal-catalysed reactions, such as hydrosilylation,[37] hydrogenation[38] (asymmetric)[39] and hydroformylation.[40, 41] The less well-developed status of this field is somewhat surprising as the concept of the use of soluble polymer-supported catalysts has been suggested as early as 1976 by Beyer and Schurig.[42–44] Compared with the fluorous biphasic concept, the use of soluble polymer-supported catalysts appears to have a number of advantages: 1) Polymers, such as polyethylene glycol (PEG), are extremely cheap, quite in contrast to perfluorinated molecules. 2) Standard organic solvents can be applied to biphasic solvent systems that use PEG-supported catalysts;[45] perfluorinated solvents used for fluorous catalysis are not needed.[46] 3) Polyethylene glycol is environmentally benign,[47] whereas fluorocarbons are persistent and pose certain risks related to ozone damage and the greenhouse effect. 4) Leaching of polymer-supported catalysts into the product phase is negligible, whereas this often poses a problem with fluorous biphasics.

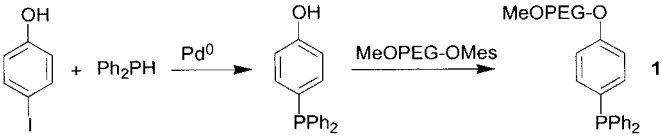
Consequently, we have initiated a program to develop polymer-tagged palladium–phosphine complexes for carbon–carbon bond-forming reactions, such as Heck, Suzuki and Sonogashira coupling. The Sonogashira reaction[48] is now widely applied to the synthesis of natural compounds, pharmaceuticals, liquid crystalline polymers and optical or electronic materials.[49, 50, 51] We decided to use monomethyl polyethylene glycol (MeOPEG) as a cheap and chemically robust support for the attachment of sterically demanding and electron-rich phosphines, to allow the efficient recycling of the catalyst and its multiple use. We report here on our results on the palladium-catalysed Sonogashira coupling of aryl halides and acetylenes under biphasic conditions and the efficient recycling of the catalysts.

Results and Discussion

Synthesis of phosphines covalently bonded to MeOPEG: A soluble polymer used for attachment to a phosphine coordinated to a catalytically active metal should fulfil several basic requirements. Firstly, the polymer must not have functional groups along the chain which might react during catalysis. Secondly, it should not coordinate to the catalytically active metal. Thirdly, for use in biphasic catalysis, the ideal polymer also has to be fairly polar (which unfortunately readily interferes with the first and second conditions) so it is soluble in the polar solvent and completely insoluble in the non-polar solvent to prevent any leaching of the catalyst. Fourthly, it also has to posses one or a few functional groups that can be used to attach the catalytically active complex efficiently. Since it is assumed that the catalytically active species in Pd-catalysed coupling reactions is a $[Pd(PR_3)_1]$ complex,[52] a high spatial density of phosphines groups attached to the polymer is not desirable, as this would favour chelated and thus higher coordinated and less active complexes.

For application of these restrictions, monomethyl polyethylene glycol (MeOPEG) appears to be a good choice. The ether groups are rather unreactive, coordination of the ether oxygen to the catalytically active Pd^0 species is unfavourable while the $-OH$ is suitable for the attachment of the catalytically active group. The linear polyether is highly soluble in a number of polar solvents, but completely insoluble in alkanes.[43] Furthermore, MeOPEG is available commercially in various molecular weights ranging from 350 to 5000 Dalton.[53]

A simple polymer-tagged phosphine was synthesised (Scheme 1) by first reacting 4-iodophenol with Ph_2PH under Pd catalysis.[54] The respective phenol, formed in virtually quantitative yield, is treated with mesylated MeOPEG-OMes ($MeOPEG = CH_3(OCH_2CH_2)_nOH$, here $n_{max} = 44$, 2000 Dalton) to give $MeOPEG-O-C_6H_4PPh_2$ in 81% yield.[55, 56] We decided to use the 2000 Dalton polymer because preliminary ^1H NMR experiments had shown that this molecular weight is sufficient to prevent any leaching of the phosphine into *n*-heptane.

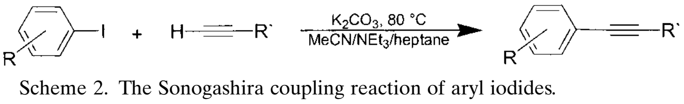


Scheme 1. Synthesis of a simple polymer-tagged phosphine.

It should be noted that this phosphine and all other MeOPEG phosphines synthesised by us display solubility in water, which should also allow their use in aqueous/organic solvent systems.[57]

Biphasic Sonogashira reactions of aryl iodides: To validate the concept of effective catalyst recycling by means of liquid–liquid biphasic catalysis, we applied the standard Sonogashira coupling reaction to a biphasic system. These conditions include the classic catalyst[58] consisting of $[(PPh_3)_3PdCl_2]$, CuI and an amine as the base. Initially, we studied the Sonogashira coupling of 1-hexyne, 1-octyne, PhC≡CH and $Et_3SiC≡CH$ with aryl iodides (Scheme 2).

The coupling reactions of the aryl iodides were performed in a ternary solvent mixture of $CH_3CN/Et_3N/n$-heptane (5:2:5; vol) as a biphasic system. The catalyst was prepared in situ from $[(CH_3CN)_2PdCl_2]$ and two equivalents of the



Scheme 2. The Sonogashira coupling reaction of aryl iodides.

MeOPEG-linked PPh_3 (**1**). Et_3N acts not only as a base, but also as a solubility mediator for this biphasic system, which helps to produce complete miscibility of the solvents (i.e. monophasic conditions) above 80 °C. The biphasic reaction mixture was heated above the critical mixing temperature[59] and the reaction was allowed to proceed for the specified period of time after which it was cooled to room temperature whereupon phase separation occurred. Each reaction was repeated five times in the biphasic solvent mixture with a single batch of catalyst added prior to the first cycle (Figure 1).

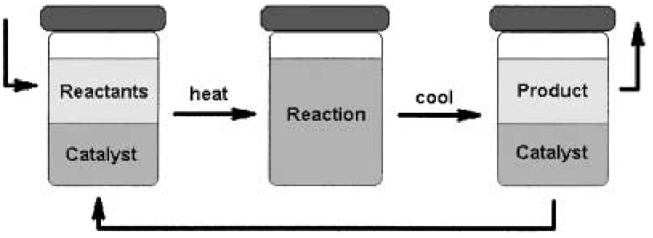


Figure 1. Biphasic catalysis.

Following each reaction the *n*-heptane solution containing most of the product (according to the respective partition coefficient) was separated, the volatiles were removed in vacuum to isolate the crude product. The evaporated solvents, mainly *n*-heptane and some leached Et_3N and CH_3CN,[60] can be 100% recycled by adding the mixture to the CH_3CN solution containing the catalyst prior to the next cycle. For each consecutive cycle one equivalent of the respective aryl iodide and the respective acetylene were added to the catalyst in the acetonitrile solution. The main results of the catalytic reactions are summarised in Table 1.

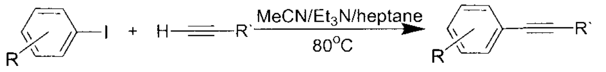
Initially, perfect miscibility in the ternary solvent system is possible. However, monophasic conditions are more and more difficult to achieve after the first cycles as a result of the formation of $HNEt_3^+I^-$, which dissolves in acetonitrile leading to an increase in the polarity of this solvent. This problem, however, can be solved by adding K_2CO_3 as a second base to regenerate Et_3N by deprotonation of the ammonium salt. Excess salt ($KHCO_3$, KI) can be removed by filtration after a number of cycles.

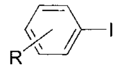
The overall yields for all coupling reactions after a few hours are higher than 80% or even 90% after chromatographic purification. This compares favourably to results of a brief report by Bergbreiter et al.;[61] Bannwarth and Markert recently reported on a fluorous biphasic Sonogashira catalysis of aryl iodides.[62] However, the amount of isolated product from the *n*-heptane layer after each cycle (i.e. phase yield) can be much lower during the first cycles. This is not caused by a reduced activity of the catalyst during the first cycles. Independent tests have shown that the yields of product after the first cycle are consistently higher than 90%.

Instead, depending on the nature of the coupling product, its distribution coefficient between CH_3CN and *n*-heptane is not always favourable. The isolated yields of the products from the *n*-heptane layer (phase yields) increase after each cycle sometimes to values larger than 100% (Table 1), once the polar CH_3CN/NEt_3 phase is saturated with the product. The probable explanation is the partial solubility of $Et_3NH^+I^-$ in CH_3CN/NEt_3 leading to an increasing polarity of the lower phase after each cycle. This will result in a decrease of the product solubility in the polar acetonitrile layer.

Attempted biphasic Sonogashira coupling of aryl bromides and acetylenes: Encouraged by the positive results with aryl iodides, the same procedure was tested for the Sonogashira coupling of aryl bromides, which are commercially more attractive on account of their lower price, while from a reactivity point of view they are more challenging substrates. However, reactions of various aryl bromides with PhCCH in several biphasic systems (acetonitrile/*n*-heptane, DMSO/*n*-heptane, DMF/*n*-heptane, propylene carbonate/*n*-heptane) gave modest-to-poor yields of the desired coupling product. Even with extended reaction times of up to 24 h per cycle, only modest (30–50%) yields with reactive substrates such as 4-bromoacetophenone were isolated. Deactivated substrates,

Table 1. Biphasic Sonogashira coupling of aryl iodides and acetylenes.[a]



Entry		Acetylene	Time [h]	**1** [%]	**2** [%]	**3** [%]	**4** [%]	**5** [%]	Extraction after last cycle [%]	Overall yield [%]
1	4-Me	$n\text{-}C_4H_9C{\equiv}CH$	3	89	93	93	97	89	19	88
2	4-Me	$PhC{\equiv}CH$	3	52	83	89	92	94	64	91
3	4-Me	$Et_3SiC{\equiv}CH$	1.5	80	101	99	102	102	16	96
4	4-MeO	$n\text{-}C_4H_9C{\equiv}CH$	2	82	89	96	99	99	15	85
5	4-MeO	$PhC{\equiv}CH$	2	32	74	74	109	117	96	83
6	4-MeO	$Et_3SiC{\equiv}CH$	2	73	89	98	108	105	5	86
7	4-Cl	$n\text{-}C_4H_9C{\equiv}CH$	3	78	90	98	99	100	13	89
8	4-Cl	$PhC{\equiv}CH$	3.5	46	76	76	96	109	90	91
9	4-Cl	$Et_3SiC{\equiv}CH$	4	81	92	95	104	108	7	95

[a] Conditions: solvents $CH_3CN/Et_3N/n\text{-}heptane$ (5:2:5), 1 mol% $[(CH_3CN)_2PdCl_2]$, 2 mol% $MeOPEGOC_6H_4PPh_2$ **1**, 4 mol% CuI. The yields given for the cycles 1–5 are phase yields of the crude products, which are different from the chemical yields of the respective reaction as they are influenced by the partition coefficient of the product between the two solvents in the biphasic system. Extraction after the last cycle corresponds to the amount of product extracted completely with *n*-heptane from CH_3CN after the fifth cycle. The overall yields correspond to the amount of isolated products after chromatographic purification.

such as 4-bromotoluene or 4-bromoanisole, gave less than 10% of the coupling product.

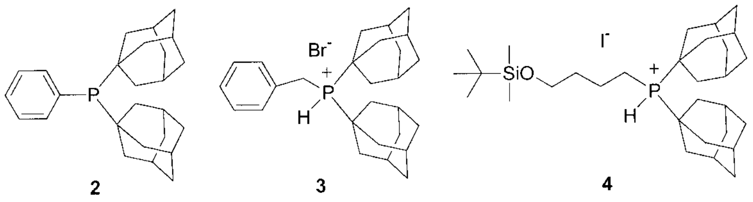
At this point, we decided to investigate in more detail the reason for this failure. There are three probable causes: a) the attachment of the MeOPEG polymer to the catalyst, b) the influence of the polar solvent or c) the standard Sonogashira conditions may not be suitable for such biphasic solvent systems and need to be re-optimised.

The basic lesson learned from the recent work on Pd-catalysed coupling reactions is that low-coordinate PdL_1 complexes are the most active catalysts.[63] Consequently, it is clear both the coordinating solvent CH_3CN as well as the less bulky polymer-linked PPh_3 are detrimental to high catalytic activity.

Our next task, therefore, was to synthesise a sterically demanding and electron-rich phosphine co-catalyst that could be readily attached to a MeOPEG polymer.

Synthesis of sterically demanding phosphines: Bulky and electron-rich phosphines, such as $PtBu_3$, are responsible for excellent activity of the respective Pd complexes in C–C coupling reactions.[20–24] The catalyst $[(PhCN)_2PdCl_2]/PtBu_3$ is the only one known to allow room-temperature Sonogashira coupling.[50, 51] Since the phosphine in this catalyst appears to be unsuitable for the attachment to MeOPEG, we decided to synthesise various di-(1-adamantyl)phosphines ($(1\text{-}Ad)_2$-phosphines) as Beller et al. showed that $(1\text{-}Ad)_2PBu$ is an excellent co-catalyst in Suzuki coupling reactions.[20] $(1\text{-}Ad)_2PH$ is readily accessible in quantities > 100 g on account of its facile preparation starting from adamantane and PCl_3.[64] To obtain high activity catalysts for biphasic Sonogashira coupling, we had to synthesise suitable phosphines that carry additional functional groups to allow the covalent attachment to the MeOPEG backbone.

Prior to the synthesis of MeOPEG-tagged $(1\text{-}Ad)_2$-phosphines, three low molecular weight analogues **2**–**4**, were prepared to study their catalytic performance in the monophasic Sonogashira reaction (Scheme 3).

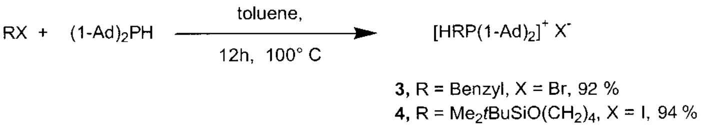


2 **3** **4**

Scheme 3. Low molecular weight analogues **2**–**4** of the MeOPEG-tagged $(1\text{-}Ad)_2$-phosphines.

Phosphine **2** was prepared from PhLi/CuI and $(1\text{-}Ad)_2PCl$, the latter being readily accessible in quantitative yield from $(1\text{-}Ad)_2PH$ and CCl_4. The phosphonium salts **3** and **4** were obtained by reacting the respective alkyl halides with $(1\text{-}Ad)_2PH$ in toluene at 100 °C; precipitation from the reaction mixture gave air-stable, colourless powders in quantitative yields. It is convenient to store the phosphonium salts rather than the respective phosphines, since the protonated form is stable towards oxidation (Scheme 4).

Phosphine **2** and the phosphonium salts **3** and **4** could be used directly for catalysis as the latter two are deprotonated under the basic reaction conditions of Sonogashira coupling. All three phosphines are easily modified to incorporate additional functional groups which allow their attachment to a MeOPEG polymer.



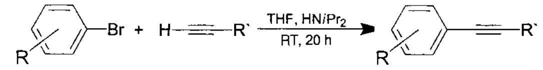
$$RX + (1\text{-}Ad)_2PH \xrightarrow[12h,\ 100°\ C]{toluene,} [HRP(1\text{-}Ad)_2]^+\ X^-$$

3, R = Benzyl, X = Br, 92 %
4, R = $Me_2tBuSiO(CH_2)_4$, X = I, 94 %

Scheme 4. Synthesis of phosphonium salts **3** and **4**.

Room-temperature Sonogashira coupling: Next, the performance of the $(1\text{-}Ad)_2$-phosphine-based co-catalysts **2**–**4** was tested. (Table 2). The only catalyst which gave virtually quantitative yields for all coupling reactions tested is $[(PhCN)_2PdCl_2]/(1\text{-}Ad)_2PBn$. It should be stated at this point that our catalytic system has the same activity as the one relying on $[(PhCN)_2PdCl_2]/PtBu_3$ described recently by Buchwald, Fu et al.[50] The next step was to attach the top performers $(1\text{-}Ad)_2PBn$ (**3**) and $(1\text{-}Ad)_2PPh$ (**2**) to the MeOPEG polymer and study the coupling reaction under biphasic conditions.

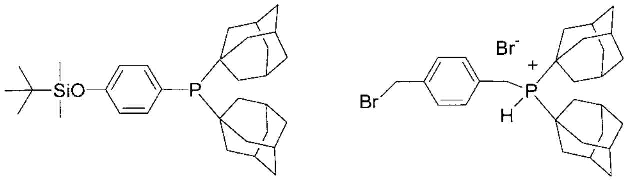
Table 2. Yields of room-temperature Sonogashira reactions of aryl bromides and acetylenes.[a]



R′	PR_3	R		
		4-CH_3CO [%]	H [%]	4-CH_3O [%]
Ph	**4**	92	< 10	< 5
Ph	**2**	> 95	45	60
Ph	**3**	> 95	> 95	> 95
n-C_6H_{13}	**3**	> 95	> 95	> 95

[a] Yields given correspond to isolated compounds after chromatographic purification. Catalyst: 4 mol% PR_3, 2 mol% $[(PhCN)_2PdCl_2]$, 1.5 mol% CuI.

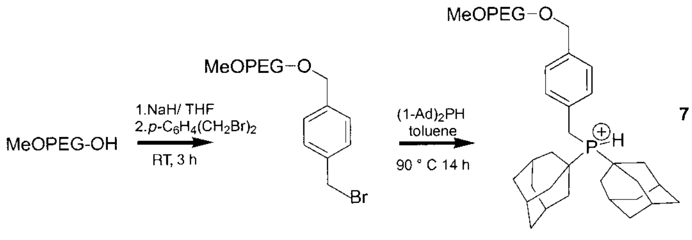
Synthesis of sterically demanding and electron-rich phosphines covalently linked to MeOPEG: To synthesise MeOPEG-tagged analogues of **2** and **3**, phosphines **5** and **6** were prepared as described for the respective unsubstituted relatives **2** and **3** (Scheme 5).



5 **6**

Scheme 5. Sterically demanding and electron-rich phosphines **5** and **6** to be covalently linked to MeOPEG.

To our surprise, a simple Williamson-type etherification of $MeOPEG_{2000}OH$ with **6** was not successful. On the other hand, **7** could be readily synthesised from the reaction of MeOPEG-OH and $1,4-(CH_2Br)_2C_6H_4$ with NaH as a base to produce $MeOPEG-O-CH_2C_6H_4CH_2Br$, which upon reaction with $(1-Ad)_2PH$ generates the respective air-stable phosphonium salt in almost quantitative yield. The loading of the $(1-Ad)_2P$ group on the polymer is in excess of 90%, as determined by ^1H NMR spectroscopy (Scheme 6).



7

Scheme 6. Synthesis of **7**.

Deprotection of phosphine **5** with CsF and reaction of the respective phenol with mesylated MeOPEG-OH gave the corresponding polymer-tagged phosphine **8** with >90% loading of the phosphine.

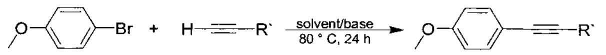
Optimising the coupling reaction in solvents suitable for biphasic catalysis: For liquid–liquid biphasic catalysis, a solvent is needed which is immiscible at room temperature with simple alkanes used as the product phase. Low-polarity solvents (such as dioxane) are not suitable as a catalyst phase, moreover, the selection of polar solvents is limited as a typical polar solvent almost invariably has donor groups which can block the active palladium complex and thus reduce its catalytic activity. Consequently, the right choice of solvent is the key for the success of biphasic catalysis.

For a solvent/base screen of the Sonogashira coupling of phenylacetylene and 1-octyne with co-catalyst **2**, we chose the deactivated substrate *p*-bromoanisole with different solvent/base combinations. This first screen is based on estimated TLC spot intensity of the reaction mixtures. Furthermore, we decided to use $Na_2[PdCl_4]$, which is reasonably soluble in polar solvents, as a simple palladium source since it is cheaper than $[(PhCN)_2PdCl_2]$.

More forcing conditions are required (compared to the use of dioxane or THF as a solvent), for coupling reactions in polar and coordinating solvents (Table 3). The screening clearly shows that DMSO gives the highest yield both with Na_2CO_3, K_2CO_3 and $HNiPr_2$ as bases. A more detailed screen revealed $HNiPr_2$ to be the best base for Sonogashira coupling reactions in DMSO.

Biphasic Sonogashira coupling of aryl bromides and acetylenes by the use of polymeric phosphines: Next, the Pd complexes of the MeOPEG-linked phosphines **7** and **8** were tested under biphasic conditions in DMSO/heptane with $HNiPr_2$ as a base and $Na_2[PdCl_4]$ as the Pd source. It immediately became clear that **7** performed much better than **8**, which then was not studied in more detail.

Table 3. Solvent and base screening for Sonogashira coupling.[a, b]



	MeCN		DMA		DMF		DMSO		PC[c]	
	Ph	C_6H_{13}	Ph	C_6H_{13}	Ph	C_6H_{13}	Ph	C_6H_{13}	Ph	C_6H_{13}
NEt_3	−	−	−	−	−	−	−	−	+−	+−
Na_2CO_3	+−	−+	−	−	−	−	++	++	±	±
K_2CO_3	±	−+	−	−	−	−	++	++	−	−
Cs_2CO_3	±	−	++	±	++	±	+	±	±	±
K_3PO_4	−	−	−	−	−	−	−	−	−	−
NaOAc	−	−	−	−	−	−	−	−	−	−
$HNiPr_2$						−	++	++		−

[a] Catalyst: $(1-Ad)_2PBn$ (4 mol%), $Na_2[PdCl_4]$ (2 mol%), CuI (1.5 mol%). $[Pd(OAc)_2]$ was used for reactions with NaOAc. [b] Conversions: − <40%, ± 40–80%, + >80%, ++ near quantitative. [c] Propylene carbonate.

The reaction of several aryl bromides (bromoacetophenone, bromobenzene, 4-bromochlorobenzene, 4-bromoanisole, 2-bromotoluene) and acetylenes (PhCCH, Me_3SiCCH, 1-octyne) was tested under the conditions described in Table 4. The reaction times depend on the substrate and were optimised for all reactions, by monitoring the progress of the reaction by TLC. The time needed for apparent completion of the reaction (TLC test, absence of starting material) in the first cycle was doubled and used for all consecutive cycles. When following this procedure, the yield of the reaction is a useful criterion for the evaluation of catalyst recyclability. The fact that during each individual cycle from 1–5 the reaction is quantitative for the coupling of PhCCH and Me_3SiCCH with most aryl bromides indicates that there is no significant deactivation of the catalyst. The concentration of the catalyst can be lowered slightly to 0.5 mol% of $Na_2[PdCl_4]$ with only a small reduction in the yield (Table 5).

Further lowering of the catalyst concentration (PR_3 0.4 mol%, $Na_2[PdCl_4]$ 0.2 mol%, CuI 0.17 mol%) in the reaction of 4-bromoanisole and PhCCH led to a significant increase in times needed to achieve quantitative yields, which is considered impractical.

Much to our surprise, the catalyst performance in the coupling reactions involving 1-hexyne and 1-octyne deteriorated rapidly after the first cycle. While initially almost quantitative yields are produced, the coupling yields in the 2nd to the 5th cycle drop drastically. We also noticed that in contrast to the other coupling procedures, the reaction mixture invariably turns black during the first cycle, indicating formation of insoluble Pd black. Information from the vendors revealed that 1-hexyne and 1-octyne are contaminated with up to 3% of alkyl bromides.[65] We reasoned that this could be a cause for catalyst deactivation. Consequently, commercially available alkynes were treated with Et_2NH to remove the alkyl bromides and tested again. Unfortunately, this treatment did not result in an improvement of the coupling reaction in the second cycle.

The chemical yield of the coupling reaction is easy to determine, but it may not be a perfect criterion to evaluate the recyclability of catalysts according to Gladysz.[66] Therefore, we probed the yield of the catalytic reaction during several cycles after fixed periods of time to obtain TOF data. The reactions of PhCCH with 4-bromoacetophenone, bromoben-

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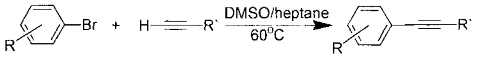
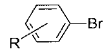
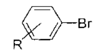
Table 4. Biphasic Sonogashira coupling of aryl bromides with acetylenes.[a]



Entry		R	Time [h]	Run 1 [%]	Run 2 [%]	Run 3 [%]	Run 4 [%]	Run 5 [%]	Extraction after last cycle [%]	Overall yield [%]
1	4-CH_3CO	Ph	0.5	36	79	92	109	123	72	94
2	H	Ph	0.5	73	99	107	109	108	21	94
3	4-Me	Ph	1	90	99	104	103	104	13	96
4	4-Cl	Ph	1	87	97	102	105	105	16	94
5	4-MeO	Ph	2	48	88	93	100	103	77	94
6	2-Me	Ph	3	94	100	103	104	104	10	96
7	H	Me_3Si	3	80	88	103	100	105	25	92
8	4-Cl	Me_3Si	3	93	99	101	103	103	9	93
9	4-Me	Me_3Si	3	94	107	110	100	104	9	94
10	4-CH_3CO	Me_3Si	2	76	93	99	102	103	25	92
11	4-MeO	Me_3Si	4	92	99	103	105	108	5	93
12	2-Me	Me_3Si	5	83	87	88	90	90	6	81
13	4-CH_3CO	n-C_6H_{13}	12	95	80	52	36	25	6	57
14	4-Me	n-C_6H_{13}	12	95	77	47	33	16	6	52
15	4-MeO	n-C_6H_{13}	12	81	61	31	15	6	0	37

[a] Conditions: catalyst: PR_3 (**7**, 2 mol %), [Na_2PdCl_4] (1 mol %), CuI (0.7 mol %), DMSO/*n*-heptane, 60 °C. Reactions involving 1-octyne and 1-hexyne were conducted at 75 °C. The yields given for the cycles 1–5 are phase yields of the crude products (taking account of the partition coefficient of the product). Extraction after last cycle corresponds to the amount of product extracted with *n*-heptane from DMSO after the fifth cycle. The overall yields correspond to the amount of isolated products after chromatographic purification.

Table 5. Biphasic Sonogashira coupling of aryl bromides with acetylenes (0.5 mol % Pd).[a]

Entry		R	Time [h]	Run 1 [%]	Run 2 [%]	Run 3 [%]	Run 4 [%]	Run 5 [%]	Extraction after last cycle [%]	Overall yield [%]
1	4-CH_3CO	PhCCH	1	46	83	96	104	115	45	93
2	H	PhCCH	3	82	91	105	104	109	13	91
3	4-MeO	PhCCH	4	63	87	97	103	110	56	90

[a] Conditions: catalyst: PR_3 (**7**, 1 mol %), $Na_2[PdCl_4]$ (0.5 mol %), CuI (0.35 mol %), DMSO/*n*-heptane, 60 °C. See also the legend to Table 4.

zene and 4-bromoanisole were conducted and GC samples taken, prior to completion of the reaction.[67] The individual yields (run, TOF) of the coupling reactions were as follows: 4-bromoanisol for 30 min 84 % (run 1, 336 h^{-1}), 80 % (run 2, 320 h^{-1}), 73 % (run 3, 292 h^{-1}), 65 % (run 4 260 h^{-1}), 63 % (run 5, 252 h^{-1}); bromobenzene for 20 min: 75 % (run 1, 440 h^{-1}), 72 % (run 2, 432 h^{-1}), 65 % (run 3, 390 h^{-1}), 56 % (run 4, 336 h^{-1}), 52 % (run 5, 312 h^{-1}); 4-bromoacetophenone for 10 min: 96 % (run 1, 1150 h^{-1}), 93 % (run 2, 1120 h^{-1}), 85 % (run 3, 1020 h^{-1}), 76 % (run 4, 912 h^{-1}), 73 % (run 5, 880 h^{-1}), 83 % (run 6, 1000 h^{-1}). In all three test reactions there is a small but significant decrease in the chemical yield over the five cycles probed. It is, however, pleasing to note that the addition of CuI after the 5th cycle reactivates the catalysts. In this manner, the catalytic coupling of 4-bromoacetophenone rises to 83 % yield (TOF 1000 h^{-1}) in a 6th cycle (from 73 %, TOF 880 h^{-1} in the 5th run) after having added the same amount of CuI as used initially. We thus believe the deactivation of the catalyst to be mainly caused by adventitious oxidation of Cu^I to Cu^{II}.

Comparison of the catalysts—polymeric versus low molecular weight: As can be seen from the Tables above, the polymeric catalyst derived from phosphine **7** in DMSO solution is slightly less efficient than the small molecule catalyst with phosphine $(1\text{-Ad})_2PBn$ (**3**) in THF solvent. We wanted to find out the reason for this somewhat lower activity of the polymeric catalyst in DMSO. To do this, we compared the performance of $Na_2[PdCl_4]/(1\text{-Ad})_2PBn$ and $Na_2[PdCl_4]/R_P\text{-}OCH_2C_6H_4CH_2P(1\text{-Ad})_2$ in DMSO and that of $[(PhCN)_2PdCl_2]/(1\text{-Ad})_2PBn$ and $[(PhCN)_2PdCl_2]/R_P\text{-}OCH_2C_6H_4CH_2P(1\text{-Ad})_2$ in THF. There is no significant difference between the two catalysts in DMSO, while the polymeric catalyst is less efficient in THF.

Retention of the catalyst in DMSO: The absence of leaching, that is the virtually quantitative retention of the catalyst in the polar solvent solution, is very important for the evaluation of biphasic catalysis. As evidenced by ^1H NMR spectra of the crude product there seems to be no leaching of MeOPEG-phosphine from CH_3CN or DMSO into the *n*-heptane layer during the reactions of the aryl halides. Because of the large signal associated with the polymer, the detection limit for phosphine leaching is fairly low and the absence of a signal shows that retention of the catalyst must be much larger than 99.5 %. We also studied catalyst leaching by means of total reflection X-ray fluorescence (TXRF), which is a very sensitive technique for metal (here palladium and copper) detection. The amount of palladium lost into the *n*-heptane is extremely small and below the detection limit of the TXRF method, this means that the retention of the catalyst within the DMSO solution must be >99.995%![68] The same applies to copper leaching.

During each cycle there is, however, a small loss of the polar solvent DMSO into the *n*-heptane layer, since a saturated *n*-heptane solution contains 1.1% (vol.) of DMSO.[69]

Conclusions

Sterically demanding and electron-rich phosphines were covalently linked to soluble monomethyl polyethylene glycol polymer R_P (R_P = $MeOPEG_{2000}$). The use of a suitable palladium source yields highly effective palladium–phosphine catalysts for Sonogashira-type coupling reactions with aryl iodides and bromides, which can be conducted under biphasic conditions, to allow the efficient recycling of the polymeric catalyst.

Aryl iodides can be coupled to acetylenes in almost quantitative yields during several cycles by means of a ternary biphasic solvent system consisting of $MeCN/Et_3N/n$-heptane and a simple catalyst derived from $MeOPEG-OC_6H_4PPh_2$ and $[(MeCN)_2PdCl_2]$. To use less reactive substrates, a new catalyst $[(PhCN)_2PdCl_2]/(1-Ad)_2PBn$ was synthesised, which is able to couple aryl bromides with acetylenes in quantitative yields at room temperature. A closely related catalyst was $Na_2[PdCl_4]/R_P-OCH_2C_6H_4CH_2P(1-Ad)_2$ tested under biphasic conditions. By the use of DMSO as a polar catalyst phase and *n*-heptane as the product phase, aryl bromides can be coupled with various acetylenes with 0.5 mol% catalyst at 60°C in almost quantitative yields over five catalytic cycles. The leaching of the catalyst into the *n*-heptane layer appears to be negligible because TXRF measurements show the retention of the catalyst in the DMSO solution to >99.995%. The stability of the catalyst over several cycles was demonstrated by the almost quantitative yields of the coupling reaction and by a nearly constant turnover frequency of the catalyst. The concept of sterically demanding phosphines as highly active co-catalysts can be applied to polymer-tagged phosphines. Comparative experiments have also shown that the MeOPEG polymer chain has no detrimental effect on catalyst performance in aryl bromide coupling. The application of the concept of MeOPEG-supported carbon–carbon bond-forming catalysts appears to be quite general as biphasic Heck–Mizoroki and Suzuki coupling reactions are also possible.[70, 71]

Experimental Section

General: $MeOPEG_{2000}OH$, aryl halides and acetylenes were used as received. Solvents were purified by standard procedures.[72] Carbonate and acetate bases were dried at 80°C under vacuum. Reactions were performed under an atmosphere of argon by means of standard Schlenk techniques.

Column chromatography was performed on silica MN60 (63–200 μm), and thin-layer chromatography (TLC) on Merck plates coated with silica gel60, F254. Yields of the coupling reactions were determined by ^1H NMR spectroscopy. Gas chromatography was carried out with an Perkin Elmer Autosystem. NMR spectra were recorded at 293 K with a Bruker AC300 (^1H NMR 300 MHz, ^{13}C NMR 75 MHz) or a Bruker 200AC (^1H NMR 200 MHz, ^{31}P NMR 81 MHz) spectrometer. ^1H NMR were referenced to residual protonated impurities in the solvent, ^{13}C NMR to the solvent signal ($CDCl_3$: $\delta(^1H) = 7.24$ ppm, $\delta(^{13}C) = 77.0$ ppm) and ^{31}P NMR spectra were referenced to PMe_3 (38% in benzene $\delta = -62$ ppm) as an external standard. Starting materials were commercially available or prepared according to literature procedures: $(1-Ad)_2PH$,[64] $MetBu_2SiO(CH_2)_4I$,[73] $[(PhCN)_2PdCl_2]$ and $[(CH_3CN)_2PdCl_2]$.[74]

Screening experiments: To evaluate the yield in the first solvent, base screening of coupling reactions was carried out by estimating the TLC spot intensities.

$4-BrC_6H_4OSitBuMe_2$: To 4-bromophenol (3.46 g, 20 mmol) in CH_2Cl_2 (50 mL), were added triethylamine (2.53 g, 25 mmol) and $ClSitBuMe_2$ (3.02 g, 20 mmol) at room temperature with vigorous stirring. The solution was stirred for 12 h at room temperature and subsequently added to a separatory funnel containing water (50 mL) and CH_2Cl_2 (50 mL). The phases were separated and the organic phase was washed with water (2 × 50 mL). After drying and evaporation of the solvent, the oily residue was purified by chromatography on silica with cyclohexane. Yield 5.63 g (98%) with spectroscopic data identical to those previously reported.[75]

$4-(HO-C_6H_4)PPh_2$ (1): This compound was prepared according to a procedure reported by Stelzer and co-workers with a modified workup.[54] The crude product, dissolved in cyclohexane/ethyl acetate (4:1), was filtered over a silica plug to yield $4-(HO-C_6H_4)PPh_2$ (**1**) as a pale yellow solid in 92% yield (literature value: 67%).

$(1-Ad)_2PCl$: $(1-Ad)_2PH$ (12.1 g, 40 mmol), dissolved in dry and degassed CCl_4 (100 mL), was stirred at 50°C for 16 h. After removal of the solvent and drying in a vacuum, the pure product was obtained as a colourless powder with spectroscopic data identical to those reported by Schmutzler et al.[64] Yield: 13.5 g (100%).

$(1-Ad)_2PPh$ (2): CuBr (1.44 g, 10 mmol) was added at room temperature to the freshly prepared Grignard reagent, made from bromobenzene (1.46 g 10 mmol) and Mg turnings (270 mg, 11.1 mmol) in THF (50 mL). The mixture was stirred for 20 min to effect a complete transmetallation. After addition of **2** (3.37 g, 10 mmol) the mixture was heated under reflux for 14 h. The solvent was removed, the dark residue was extracted with hot cyclohexane and filtered to yield a yellow solution containing the product as the Cu^I complex. This solution was extracted repeatedly with 10% aqueous ammonia (50 mL) until the aqueous phase remained colourless. After the organic layer ($MgSO_4$) had been dried and the solvent removed, the crude product was obtained as a sticky yellow solid which was recrystallised from ethanol to yield $(1-Ad)_2PPh$ (**3**) as a pale yellow powder. Yield 2.46 g (65%); ^1H NMR ($CDCl_3$): $\delta = 7.65-7.45$ (m, 2H; ArH), 7.30–7.20 (m, 3H; ArH), 2.10–1.55 (m, 30H; AdamantylH); ^{13}C NMR ($CDCl_3$): $\delta = 134.5$, 130.9, 128.8, 127.3, 42.4, 36.6, 34.8, 28.9; ^{31}P NMR ($CDCl_3$): $\delta = 41.9$.

$4-(tBuMe_2SiO)C_6H_4P(1-Ad)_2$ (5): This compound was prepared as described for **2** from $4-(tBuMe_2SiO)$-bromobenzene (2.87 g, 10 mmol) instead of bromobenzene. Yield 3.21 g (63%); ^1H NMR ($CDCl_3$): $\delta = 7.60-7.40$ (m, 2H; ArH), 6.77 (d, 2H; $^3J = 8.1$ Hz, ArH), 2.10–1.50 (m, 30H; AdamantylH), 0.96 (s, 9H; $SiC(CH_3)_3$), 0.20 (s, 6H; $SiCH_3$); ^{13}C NMR ($CDCl_3$): $\delta =$ 15 6.6, 125.8, 119.2, 118.9, 41.7, 37.0, 36.2, 28.9, 25.7, 18.3, −4.3; ^{31}P NMR ($CDCl_3$):$\delta = 39.4$.

General procedure for the synthesis of alkyl-di-(1-adamantyl)phosphonium halides: $(1-Ad)_2PH$ (1.21 g, 4 mmol) and the respective alkyl halide (5 mmol) were dissolved in toluene (20 mL) and stirred at 90°C. In all reactions, precipitation of the product started after a few minutes. After 14 h heating of the reaction mixture ended. The product was filtered through a fritted funnel and washed with toluene (20 mL) and ether (3 × 20 mL). After drying in a vacuum the phosphonium salts were obtained as colourless powders.

$(1-Ad)_2PBn \cdot HBr$ (3): Prepared from benzyl bromide (0.86 g, 5 mmol). Yield: 1.75 g (92%); ^1H NMR ($CDCl_3$): $\delta = 7.95$ (dt, $^1J(P,H) = 478$, $^3J =$ 6.0 Hz, 1H; PH), 7.63 (d, $^3J = 7.2$ Hz, 2H; ArH), 7.40–7.10 (m, 3H; ArH), 3.83 (dd, $^2J(P,H) = 13.3$, $^3J = 6.0$ Hz, 2H; $ArCH_2$), 2.40–1.55 ppm (m, 30H; AdamantylH); ^{13}C NMR ($CDCl_3$): $\delta = 130.7$ (d, $^2J(P,C) = 7.5$ Hz), 130.3 (d, $^3J(P,C) = 5.8$ Hz), 129.6, 128.2, 38.6, 38.2, 35.6, 27.6, 19.6 ppm (d, $^1J(P,C) =$ 37.2 Hz); ^{31}P NMR ($CDCl_3$): $\delta = 23.6$ ppm.

$4-BrC_6H_4CH_2P(1-Ad)_2 \cdot HBr$: Prepared from 4-bromobenzyl bromide (1.25 g, 5 mmol). Yield: 1.96 g (89%); ^1H NMR ($CDCl_3$): $\delta = 8.32$ (dt, $^1J(P,H) = 480$, $^3J = 6.1$ Hz, 1H; PH), 7.60 (d, $^3J = 8.2$ Hz, 2H; ArH), 7.48 (d,

$^3J = 8.2$ Hz, 2H; ArH), 3.75 (dd, $^2J(\mathrm{P,H}) = 13.1$, $^3J = 6.1$ Hz, 2H; ArCH$_2$), 2.40–1.55 ppm (m, 30H; AdamantylH); ^{13}C NMR (CDCl$_3$): $\delta = 132.7$, 132.1 (d, $^3J(\mathrm{P,C}) = 5.7$ Hz), 130.1 (d, $^2J(\mathrm{P,C}) = 7.6$ Hz), 38.7, 38.3, 35.6, 27.6, 19.1 ppm (d, $^1J(\mathrm{P,C}) = 37.8$ Hz); ^{31}P NMR (CDCl$_3$):$\delta = 23.3$ ppm.

4-BrCH$_2$C$_6$H$_4$CH$_2$P(1-Ad)$_2$·HBr (6): Prepared from 1,4-(CH$_2$Br)$_2$C$_6$H$_4$ (1.00 g, 3.79 mmol). Yield: 1.69 g (79%); ^{1}H NMR (CDCl$_3$): $\delta = 8.14$ (dt, $^1J(\mathrm{P,H}) = 478$, $^3J(\mathrm{H,H}) = 5.8$ Hz, 1H; PH), 7.6 (d, $^3J = 7.8$ Hz, 2H; ArH), 7.34 (d, $^3J = 7.8$ Hz, 2H; ArH), 4.40 (s, 2H; CH$_2$Br), 3.78 (dd, $^2J(\mathrm{P,H}) = 13.2$, $^3J(\mathrm{H,H}) = 5.8$ Hz, 2H), 2.4–1.6 ppm (m, 30H; 1-AdH); ^{31}P NMR (CDCl$_3$): $\delta = 23.1$ ppm.

***t*BuMe$_2$SiO(CH$_2$)$_4$P(1-Ad)$_2$·HI (4):** Prepared from *t*BuMe$_2$SiO(CH$_2$)$_4$I (1.57 g, 5 mmol). Yield: 2.32 g (94%); ^{1}H NMR (CDCl$_3$): $\delta = 7.39$ (dt, $^1J(\mathrm{P,H}) = 464$, $^3J = 3.6$ Hz, 1H; PH), 3.59 (t, $^3J = 5.6$ Hz, 2H; OCH$_2$), 2.40–1.50 (m, 36H; AdamantylH and C*H$_2$*C*H$_2$*C*H$_2$*P), 0.77 (s, 9H; SiC(CH$_3$)$_3$), −0.05 ppm (s, 6H; SiCH$_3$); ^{13}C NMR (CDCl$_3$): $\delta = 60.8$, 38.7, 38.0, 36.1, 32.9, 27.5, 25.8, 23.3, 18.3, 12.0, −5.7 ppm; ^{31}P NMR (CDCl$_3$): $\delta = 22.7$ ppm.

MeOPEG$_{2000}$OTs (9) and MeOPEG$_{2000}$OMes (10): A solution of MeOPEG$_{2000}$OH (20 g, 10 mmol), triethylamine (2.02 g 20 mmol) and the respective sulfonyl chloride (TsCl, 2.86 g 15 mmol or MesCl 1.72 g 15 mmol) in dry CH$_2$Cl$_2$ (200 mL) were stirred for 10 h at room temperature. The reaction mixture was added to a separating funnel containing CH$_2$Cl$_2$ (800 mL) and water (100 mL). The organic layer was washed with water (2 × 100 mL), dried over MgSO$_4$ and evaporated to yield a sticky, pale yellow solid. The solid was stirred with diethyl ether (200 mL) for 2 h, filtered and washed again with diethyl ether to remove traces of excess amine and sulfonyl chloride. Drying in a vacuum yielded the desired products as nearly colourless solids.

MeOPEG$_{2000}$OTs: Yield 19.6 g (91%): ^{1}H NMR (CDCl$_3$): $\delta = 4.35$–4.28 (m, 2H; SO$_2$OCH$_2$), 3.80–3.45 (m, ≈170–180H; PEGH), 3.32 (s, 3H; CH$_3$OPEG), 2.35 ppm (s, 3H; CH$_3$Ar).

MeOPEG$_{2000}$OMes: Yield 17.9 g (86%): ^{1}H NMR (CDCl$_3$): $\delta = 4.35$–4.28 (m, 2H; SO$_2$OCH$_2$), 3.80–3.45 (m, ≈170–180H; PEGH), 3.32 (s, 3H; CH$_3$OPEG), 3.03 ppm (s, 3H; CH$_3$SO$_2$); ^{1}H NMR spectroscopy showed almost quantitative coverage of the polymer with OTs or OMes groups.

4-(MeOPEG$_{2000}$OCH$_2$)C$_6$H$_4$CH$_2$Br (12): To a solution of MeOPEG$_{2000}$OH (10 g, 5 mmol) in THF (50 mL) was added NaH (50 wt% suspension in mineral oil, 960 mg, 20 mmol) and the mixture was stirred for 30 min at room temperature. Solid 1,4-dibromomethylbenzene (10 g, 37.8 mmol) was added and the resulting yellow solution was stirred at room temperature for another 3 h. After filtration over Celite, the solution was concentrated to 20 mL in a vacuum. Diethyl ether (100 mL) was added which yielded a pale yellow precipitate that was collected by filtration. To remove impurities (mainly excess 1,4-dibromomethylbenzene), the precipitate was suspended in ether (100 mL), stirred for 1 h and filtered again. This procedure was repeated 3–4 times until virtually all impurities had been removed (TLC). After drying in a vacuum, the desired product was obtained as a pale yellow powder. Yield 9.7 g (89%). ^{1}H NMR spectroscopy showed almost quantitative etherification of the terminal OH group (> 90%).

4-(MeOPEG$_{2000}$O)C$_6$H$_4$PPh$_2$ (13): MeOPEG$_{2000}$OMes (10.4 g 5 mmol) **9**, 4-(HO-C$_6$H$_4$)PPh$_2$ (**1**, 2.09 g 7.5 mmol) and K$_2$CO$_3$ (2.8 g 20.2 mmol) in CH$_3$CN (100 mL) were heated under reflux for 14 h. The mixture was cooled to room temperature and filtered over Celite. The solvent was removed in a vacuum and the brownish residue was dissolved in warm ethanol (25 mL). The product precipitated upon addition of diethyl ether (100 mL) and cooling to 4°C. This precipitate was collected by filtration, suspended in diethyl ether (100 mL), stirred for 2 h at room temperature and filtered again to obtain the pure product as a pale yellow powder, which was dried in a vacuum. Yield: 10.1 g (85%); ^{1}H NMR (CDCl$_3$): $\delta = 7.54$–7.25 (brm, 12H; ArH), 6.93 (d, $^3J = 7.9$ Hz, 2H; ArH), 4.14, (m, 2H; α-CH$_2$), 3.9–3.4 (m, ≈170–180H; PEGH), 3.34 ppm (s, 3H; CH$_3$OPEG); ^{31}P NMR (CDCl$_3$): $\delta = -6.9$ ppm. ^{1}H NMR spectroscopy showed 90–95% coverage with the phosphine moiety.

[4-(MeOPEG$_{2000}$O)C$_6$H$_4$PPh$_2$]$_2$PdCl$_2$ (14): 4-(MeOPEG$_{2000}$O)C$_6$H$_4$PPh$_2$ (**12**, 2.76 g, 1 mmol) and [(CH$_3$CN)$_2$PdCl$_2$] (130 mg 0.5 mmol) were stirred in CH$_2$Cl$_2$ (10 mL) for 15 min to yield a yellow solution. The solvent was removed in a vacuum and the sticky residue was treated with diethyl ether (25 mL) until a fine yellow powder remained. The diethyl ether was removed by careful decantation and the product was dried in a vacuum. Yield: 2.80 g (99%); ^{31}P NMR spectroscopy showed quantitative conversion; ^{1}H NMR (CDCl$_3$): $\delta = 7.69$–7.52 (m, 6H; ArH), 7.40–7.22 (m, 6H; ArH), 6.86 (d, $^3J = 78.4$ Hz, 2H; ArH), 4.14, (m, 2H; α-CH$_2$), 3.9–3.4 (m, ≈170–180H; PEGH), 3.34 ppm (s, 3H; CH$_3$OPEG); ^{31}P NMR (CDCl$_3$): $\delta = 34.4$ ppm.

4-(MeOPEG$_{2000}$OCH$_2$)C$_6$H$_4$CH$_2$P(1-Ad)$_2$·HBr (15): 4-(MeOPeg$_{2000}$CH$_2$)-C$_6$H$_4$CH$_2$Br (**11**, 4.4 g, 2 mmol) and (1-Ad)$_2$PH (1.2 g, 4 mmol) were dissolved in toluene (50 mL) and heated to 90°C for 14 h whereupon a small amount of colourless precipitate was formed. The warm reaction mixture was filtered over Celite, concentrated to ≈15 mL in a vacuum and added to diethyl ether (60 mL) with vigorous stirring. The precipitate was collected by filtration, washed with diethyl ether and dried in a vacuum. Yield 4.6 g (92%); ^{1}H NMR (CDCl$_3$): $\delta = 7.55$ (d, $^3J = 7.6$ Hz, 2H; ArH), 7.32 (d, $^3J = 7.6$ Hz, 2H; ArH), 4.50 (s, 2H; ArCH$_2$O), 3.8–3.4 (brs, 170–180H; PEG), 3.33 (s, 3H; *H$_3$*COPEG), 2.4–1.6 ppm (m, 30H; AdH); ^{31}P NMR (CDCl$_3$): $\delta = 23.7$ ppm; ^{1}H NMR spectroscopy showed 80–85% coverage of the polymer with the phosphine.

General procedure for the biphasic Sonogashira coupling of aryl iodides and acetylenes: To a thoroughly deoxygenated mixture of *n*-heptane (10 mL), acetonitrile (10 mL) and Et$_3$N (4 mL), were added 1.5 mmol of the respective aryl iodide, 1.7 mmol of the respective acetylene, MeOPEG$_{2000}$O(C$_6$H$_4$)PPh$_2$ (70 mg, 1 mol%), (MeOPEG$_{2000}$O-(C$_6$H$_4$)PPh$_2$)$_2$PdCl$_2$ (140 mg, 2 mol%) (alternatively a mixture of two equivalents of the phosphine and [(MeCN)$_2$PdCl$_2$] can be used), CuI (12 mg, 4 mol%) and K$_2$CO$_3$ (210 mg, 1.5 mmol). The mixture was heated under reflux until the starting materials were consumed (TLC). After cooling to room temperature the upper layer was separated by means of a cannula. The solvent was evaporated to yield the crude product. The reaction vessel was recharged with degassed *n*-heptane (10 mL), triethylamine (2 mL), K$_2$CO$_3$ (210 mg, 1.5 mmol) and the two substrates and the next catalytic cycle was started. After the last cycle, the lower phase was extracted with *n*-heptane (3 × 10 mL) to isolate the remaining product. The crude products from the different runs were combined and purified by column chromatography on silica (*n*-heptane) to yield the respective pure compounds.

General procedure for the room-temperature Sonogashira coupling of aryl bromides and acetylenes: HN*i*Pr$_2$ (0.3 mL, 2.1 mmol), [(PhCN)$_2$PdCl$_2$] (11.5 mg, 2 mol%), CuI (3.8 mg, 1.3 mol%) and the respective phosphine (4 mol%) were added to THF (2 mL). The mixture was sonicated until all compounds had dissolved (5–10 min). The respective aryl bromide and acetylene were added and the mixture was stirred at room temperature. Precipitation of HN*i*Pr$_2$·HBr occurred after a few minutes. After 12 h, the reaction mixture was filtered over Celite, evaporated to dryness and purified by chromatography on silica.

General procedure for the biphasic Sonogashira coupling of aryl bromides and acetylenes: To thoroughly deoxygenated DMSO (5 mL) were added 1.5 mmol of the respective halide, 1.8 mmol of the acetylene, 4-(MeOPEG$_{2000}$OCH$_2$)C$_6$H$_4$CH$_2$P(1-Ad)$_2$·HBr (75 mg, 2 mol%), Na$_2$[PdCl$_4$] (4.5 mg, 1 mol%), CuI (2 mg, 0.7 mol%) and HN*i*Pr$_2$ (0.5 mL, 3.5 mmol). The mixture was heated to 60°C until the starting materials were consumed (TLC). After the mixture had been allowed to cool to room temperature, *n*-heptane (15 mL) was added and the mixture was stirred for 5 min. The upper layer was removed by means of a cannula and evaporated to yield the crude product. The reaction vessel was recharged with HN*i*Pr$_2$ (0.5 mL, 3.5 mmol) and the two substrates and another reaction cycle was started. After the last cycle, the DMSO was extracted with *n*-heptane (3 × 10 mL) to isolate the remaining product. The crude products from the different runs were combined and purified by column chromatography on silica (*n*-heptane or cyclohexane/ethyl acetate 4:1) to yield the respective pure compounds.

General procedure for the TOF experiments over five cycles: To a mixture of Na$_2$[PdCl$_4$] (2.2 mg, 0.5 mol%), R$_\mathrm{P}$-OCH$_2$C$_6$H$_4$CH$_2$P(1-Ad)$_2$ (**7**, 45 mg, 1 mol%) and CuI (1.0 mg, 0.4 mol%) in DMSO (3 mL) and HN*i*Pr$_2$ (0.5 mL, 3.6 mmol) held at 60°C, were added the respective aryl bromide (1.5 mmol) and PhCCH (220 μL, 2 mmol). The reaction was stirred for 30 min (in the case of 4-bromoacetophenone for 10 min) and a 50 μL sample was taken. This was added to a 0.043 M solution of diethylene glycol dibutyl ether in acetone (1 mL) and examined by GC. After taking the GC sample, the reaction was reheated and run to completion, then the whole procedure was repeated.

Acknowledgement

Support of this work by the DFG through grant Pl-178/8 and the TU Darmstadt is acknowledged. We thank Dipl.-Ing. J. Saroukh and Prof. Dr. H. Ortner for the TXRF determinations of Pd and Cu leaching.

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Received: October 2, 2002 [F4473]