4098 *Organometallics* **2003,** *22,* 4098−4103

Recyclable Catalyst with Cationic Phase Tags for the Sonogashira Coupling of Aryl Bromides and Aryl Chlorides

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Received June 10, 2003

The new phase-tagged phosphines 1-($CH_2NEt_3^+$), 4-($CH_2P(1\text{-}Ad)_2$)C_6H_4·Br^- and 1-($CH_2PPh_3^+$), 4-($CH_2PH^+(1\text{-}Ad)_2$)C_6H_4·$2Br^-$ were prepared in the reaction of 1-(CH_2Br), 4-($CH_2PH^+(1\text{-}Ad)_2$)C_6H_4·Br^- with Et_3N or PPh_3, respectively. The Pd(0)-phosphine catalysts formed on reaction of Na_2PdCl_4, CuI, phosphine, and acetylene are able to Sonogashira couple aryl bromides and aryl chlorides in high yields in DMSO or in DMSO/heptane mixtures. The products of the coupling reactions can be isolated from the DMSO solution by extraction with heptane or by separation of the product containing heptane solvent. The phase-tagged catalysts remain in the DMSO solution and can be reused for at least five consecutive coupling reactions. The catalysts retain their high activity throughout all cycles, as evidenced by the high reaction yields and, more importantly, by the almost constant turn-over frequency. Leaching of the catalyst into the product containing heptane solvent is negligible (>99.95% retention in the DMSO catalyst phase) as evidenced by TXRF and by photometric palladium determination.

Introduction

Developing efficient strategies for the separation of homogeneous catalysts from the products of catalytic reactions is now recognized to be an important subject in catalysis research.[1] One key motivation is to increase the competitiveness of homogeneous catalysts with respect to that of heterogeneous catalysts.[2] In this vain, the manipulation of catalysts by attaching groups that determine the solubility of the respective molecules in a precise manner (phase tags) is one of several strategies.[3] Consequently, a number of phase tags are applied for synthesis in solid phases,[4] for aqueous phases,[5] for polar or nonpolar organic solvents,[6,7] for fluorous solvents,[8] for ionic liquids,[9] or for supercritical phases.[10]

When using soluble, phase-tagged catalysts, there are two approaches for carrying out catalytic reactions followed by the recovery of the catalyst via phase separation techniques. Either the reaction can be performed in a single solvent and product or catalyst is extracted (or precipitated) from this solution after the reaction using a second solvent,[11] or, alternatively, the catalytic reaction can be done in a biphasic manner—simple separation of two liquid phases of the reaction mixture will effect the separation of catalyst from the product of the catalytic reaction. In biphasic solvent systems, we need to distinguish between permanently biphasic or switched biphasic systems, of which the most important one is thermomorphic (thermoregulated)[12] catalysis.[13−15] These terms describe a solvent system for catalysis that forms a single phase above a critical mixing temperature and is biphasic below this temperature.[16] The most notable advantage of thermomorphic

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10.1021/om030450a CCC: $25.00
Publication on Web 08/23/2003

catalysis is the complete miscibility of both solvents above a certain temperature, which turns out to be a real benefit in the case of very fast reactions. Slower reactions, such as carbon−carbon coupling reactions, in which the transport of the reactants across the phase boundary is faster than the catalytic reaction, can be carried out equally well in permanently biphasic solvent systems or in single solvents.[17,18] Consequently, the transport of reactants across the phase boundary should not determine the overall rate, and it appears that reactions in a permanently biphasic solvent system or in a single solvent followed by extraction can be an alternative.

We are interested in developing phase-tagged catalysts for carbon−carbon coupling reactions[19−23] and have recently published polymer-tagged catalysts for Sonogashira,[24] Suzuki,[25] and Heck coupling reactions[26] suitable for polar and nonpolar biphasic catalysis.[27] Obviously the activity of such catalysts needs to be maximized in order to be competitive with the best heterogeneous catalysts available.[28]

We recently presented the first general and high-yielding catalyst for the Sonogashira coupling of activated and deactivated aryl chlorides.[29] We have now adapted this catalyst for easy recovery from the reaction mixture by attaching ammonium and phosphonium phase tags and demonstrate its applicability in the Sonogashira coupling of aryl bromides and chlorides.

Results and Discussion

Synthesis of Phase-Tagged Phosphines. To obtain highly active catalysts for Sonogashira reactions, sterically demanding and electron-rich phosphines are best suited as ligands in Pd(0) complexes, which are generated from suitable palladium sources.[30] We have recently shown that ligands such as BnP(1-Ad)$_2$ and P(*tert*-Bu)$_3$ in combination with Na$_2$PdCl$_4$ are excellent catalysts, suitable for the efficient Sonogashira coupling of aryl chlorides.[29] The phosphine BnP(1-Ad)$_2$ can be easily modified for polymer attachment, whereas this is less obvious for P(*tert*-Bu)$_3$. Recently, we have used a MeOPEG-tagged version of BnP(1-Ad)$_2$ for biphasic Sonogashira coupling of aryl bromides.[24] Catalysts based on this phosphine are highly active for the Sonogashira coupling of aryl bromides but inactive for aryl chloride coupling. This suggests that the lower activity could be due to the polyether chain used in the former phosphine. Consequently, we became interested in different polar phase tags for such catalysts. Instead of using polymers for this purpose, charged groups should have the same effect, and indeed numerous phosphines with anionic or cationic groups have been described in the literature,[31,32] most of them with a view toward aqueous phase applications.[33] It was our aim to synthesize a sterically demanding and basic phosphine derived from BnP(1-Ad)$_2$ with ionic phase tags.

The reaction of 1,4-(CH$_2$Br)$_2$C$_6$H$_4$ with HP(1-Ad)$_2$ in toluene results in the selective formation of the monosubstituted product 1-(CH$_2$Br), 4-(CH$_2$P$^+$H(1-Ad)$_2$)C$_6$H$_4$·Br$^-$, which precipitates from solution in a yield of 79%. The phosphonium salt can be reacted with Et$_3$N to produce the corresponding ammonium salt 1-(CH$_2$NEt$_3^+$), 4-(CH$_2$P(1-Ad)$_2$)C$_6$H$_4$·Br$^-$ in 75% yield or with Ph$_3$P to result in the diphosphonium salt 1-(CH$_2$PPh$_3^+$), 4-(CH$_2$PH$^+$(1-Ad)$_2$)C$_6$H$_4$·2Br$^-$ in 91% yield as colorless solids (Scheme 1).

Sonogashira Coupling Reactions. The phase-tagged phosphines were used to form the catalyst for the Sonogashira coupling by combining 2 equiv of the respective phosphine, Na$_2$PdCl$_4$, and the reactants (acetylene and aryl halide) using CuI as a cocatalyst and HN^{i}Pr$_2$ or Na$_2$CO$_3$ as a base. CuI is required as an additive because otherwise the coupling reactions are slowed down drastically. This catalyst recipe is closely related to the one for the Sonogashira coupling of aryl chlorides.[29] First, we tested a number of coupling reactions of aryl bromides and acetylenes (PhCCH and Me$_3$SiCCH) and attempted to further optimize the catalyst composition for a given ionic phosphine by varying the base (HN^{i}Pr$_2$, Et$_3$N, K$_2$CO$_3$, or Cs$_2$CO$_3$) or the palladium source [Pd$_2$(dba)$_3$ or (PhCN)$_2$PdCl$_2$], which, however, did not lead to further improvements. In the biphasic solvent mixture the nonpolar component (product phase) is always heptane; however, depending on the boiling point of the solvent and the reaction

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(17) Under the assumption that the catalytic reaction primarily takes place in the catalyst phase and less so on the phase boundary.

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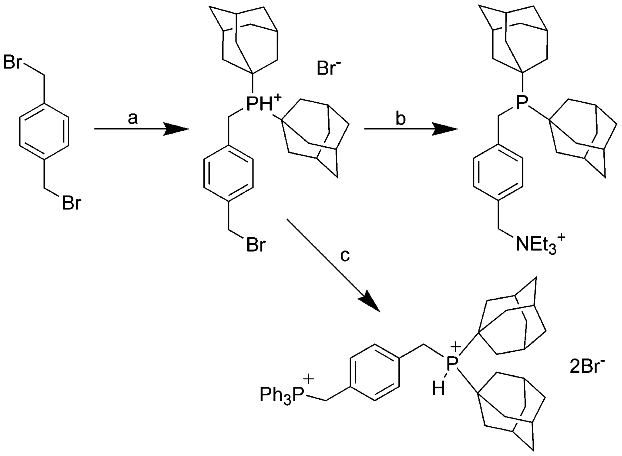
Scheme 1. Synthesis of BnP(1-Ad)$_2$ Type Phosphines with Ionic Phase Tags[a]



[a] (a) HP(1-Ad)$_2$, toluene, 90 °C; (b) NEt$_3$, CH$_2$Cl$_2$, rt; c) PPh$_3$, CHCl$_3$, 50 °C.

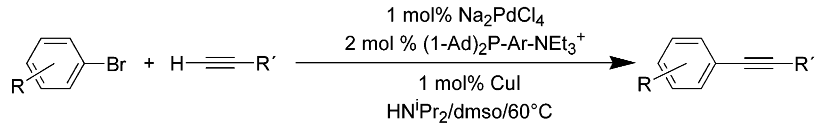
temperature, any other alkane or a mixture of alkanes is possible. Among the polar solvents (DMSO, CH_3NO_2, CH_3CN, DMF, DMA, and propylene carbonate) tested as the catalyst phase, DMSO consistently gave by far the best yields.

As outlined before we have chosen two different approaches for conducting the coupling reactions. Normally, a single solvent (DMSO) was used for the Sonogashira reactions mediated by the phase-tagged catalyst, which was then followed by extraction of the products using heptane. Alternatively, a biphasic mixture of DMSO and heptane was applied, and the nonpolar product phase separated after each cycle. It is worth noting that the heptane applied as a second phase or as the extractant was always reused for the next reaction cycle following its evaporation from the product. Both approaches are equivalent in the coupling of PhCCH with various aryl halides, whereas coupling reactions using $^iPr_3SiCCH$ and Me_3SiCCH are rather slow in the biphasic solvent system and are best conducted in DMSO followed by extraction of the product with heptane. The reason for this is the unfavorable distribution coefficients of $^iPr_3SiCCH$ and Me_3SiCCH, which almost exclusively reside in the heptane phase, consequently resulting in a low reactant concentration in the polar catalyst phase.

The main results of the aryl bromide couplings are listed in Table 1. Each of the reactions was repeated five times using a single batch of catalyst, which can be recovered efficiently by reusing the catalyst containing DMSO solution (catalyst phase) after separation from the product containing heptane solution (product phase). First of all, it should be noted that the overall yields of the coupling reactions are between 72 and 96% of purified product. The numbers for the first and second cycles (phase yields) can be low but often rise above 100% for the fourth or fifth cycle. This apparently strange behavior reflects the changing distribution coefficient of the product between DMSO and heptane caused by the increasing polarity of the catalyst phase due to salt formation. The initially unfavorable partition coefficient improves during the reaction. Consequently, more and more of the product dissolved in the DMSO solution is found in the heptane extract. The low initial phase yields also arise as the extraction of product was done exhaustively only after the last cycle. There is no need to do this after the initial cycles as in the long run no product is lost. It is possible, however, to obtain quantitative yields of products after the first reaction cycle, either by exhaustively extracting the products from the DMSO solution or by adding 10 vol % of water to the DMSO phase, which drastically changes the partition coefficient to allow isolation of all products after a single extraction step but damages the catalyst. In conclusion, the high yields of the coupling reactions indicate that the catalyst can be recycled efficiently, without significant loss in activity.

Aryl Chloride Coupling. Until recently[29] aryl chlorides had proved to be very difficult substrates for Sonogashira coupling reactions.[34,35] We were interested in whether phase-tagged catalysts could be used to couple aryl chlorides and if they could be recycled in an efficient manner. It should be noted here that this was not possible previously using the MeOPEG-supported

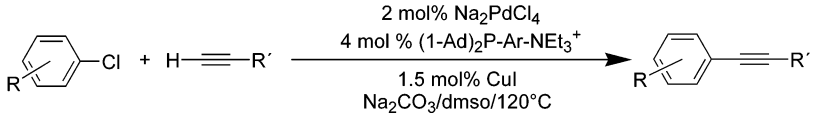
Table 1. Sonogashira Coupling of Aryl Bromides Using the − NEt_3^+-Tagged Catalyst



R	R′	time (h)	cycle 1[a] (%)	cycle 2[a] (%)	cycle 3[a] (%)	cycle 4[a] (%)	cycle 5[a] (%)	extract[b] (%)	yield[c] (%)
4-Cl	Ph	2	70	70	82	102	110	16	89
4-Cl	TMS	5	59	69	69	79	99	3	74
4-CH_3CO	Ph	2	37	77	96	108	130	72	96
4-CH_3CO	TMS	5	65	72	85	94	99	55	92
2-CH_3	Ph	2	71	71	104	74	92	3	80
2-CH_3	TMS	5	78	85	89	92	105	29	85
H	Ph	2	82	71	124	108	106	10	91
H	TMS	5	72	81	84	87	94	4	80
4-Me	Ph	2	58	71	50	82	105	30	72
4-Me	TMS	5	73	79	85	88	100	4	80
4-MeO	Ph	2	55	76	101	102	143	16	82
4-MeO	TMS	5	80	84	97	103	107	35	94

[a] The phase yields per cycle listed here correspond to the amount of crude product isolated from the heptane solution only. [b] Extract corresponds to the amount of product extracted from the catalyst phase after five cycles relative to the yield of a single cycle. [c] Yield refers to the amount of isolated product after chromatographic purification. Conditions: 1.0 mol % Na_2PdCl_4, 2.0 mol % phosphine, 2.0 mol % CuI, HN^iPr_2.

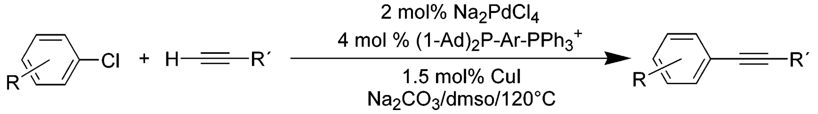
Table 2. Sonogashira Coupling of Aryl Chlorides Using an − NEt_3^+-Tagged Catalyst



R	R′	time (h)	cycle 1[a] (%)	cycle 2[a] (%)	cycle 3[a] (%)	cycle 4[a] (%)	cycle 5[a] (%)	extract[b] (%)	yield[c] (%)
4-NO_2	Ph	18	34	56	74	82	94	64	78
4-CH_3CO	Ph	18	39	68	83	91	103	101	82
H	Ph	18	47	77	66	39	29	5	46
4-MeO	Ph	18	64	83	62	51	61	5	49

[a] The phase yields per cycle listed here correspond to the amount of crude product isolated from the heptane solution only. [b] Extract corresponds to the amount of product extracted from the catalyst phase after five cycles relative to the yield of a single cycle. [c] Yield refers to the amount of isolated product after chromatographic purification.

Table 3. Sonogashira Coupling of Aryl Chlorides Using a −PPh_3^+-Tagged Catalyst



R	R′	time (h)	cycle 1[a] (%)	cycle 2[a] (%)	cycle 3[a] (%)	cycle 4[a] (%)	cycle 5[a] (%)	extract[b] (%)	yield[c] (%)
4-NO_2	Ph	6	35	66	78	85	88	102	84
4-NO_2	TIPS	14	40	64	75	78	79	24	72
4-CH_3CO	Ph	8	46	71	98	102	95	61	90
4-CH_3CO	TIPS	14	63	76	80	81	79	11	74
4-CF_3	Ph	6	73	89	88	92	95	22	87
4-CF_3	TIPS	14	67	78	85	90	90	10	77
H	Ph	24	35	51	49	55	60	8	45
4-Me	Ph	24	45	50	57	55	59	7	49
4-MeO	Ph	24	39	49	47	53	55	12	47

[a] The phase yields per cycle listed here correspond to the amount of crude product isolated from the heptane solution only. [b] Extract corresponds to the amount of product extracted from the catalyst phase after five cycles relative to the yield of a single cycle. [c] Yield refers to the amount of isolated product after chromatographic purification.

catalyst based on the phosphine 1-($MeOPEGCH_2$), 4-($CH_2P(1\text{-}Ad)_2)C_6H_4$ described recently.[24]

For these challenging coupling reactions we tested both the $-CH_2NEt_3^+$- and the $-CH_2PPh_3^+$-tagged phosphine. The catalyst is formed in situ from Na_2PdCl_4 (2 mol %), CuI (1.5 mol %), the phase-tagged phosphine (4 mol %), and the reactants, with Na_2CO_3 being by far the best base. The main results of the coupling reaction are summarized in Tables 2 and 3.

Excellent yields of between 72 and 90% are observed for the coupling of the electron-deficient aryl chlorides with PhCCH and $^iPr_3SiCCH$,[36] which are maintained throughout the various reaction cycles, whereas the more electron-rich and thus deactivated aryl chlorides form the respective coupling products only in modest yields of close to 50%. There is no significant difference in performance of the two ionic phosphines, but we prefer to use the phosphonium-tagged catalyst because the respective phosphine is easier to synthesize and handle.

By now we can also understand why the MeOPEG-tagged $BnP(1\text{-}Ad)_2$ is not active for aryl chloride coupling, generating decomposition products instead. As reported before,[24] the activity of MeOPEG-supported catalysts does not suffer from the presence of the polyether chains when amine bases are used in the coupling reactions, because the activity of Pd catalysts with $BnP(1\text{-}Ad)_2$ ligands is virtually the same. However, using metal carbonates as bases (which are required for aryl chloride coupling) in combination with MeOPEG-supported catalysts does make a big difference. Due to the effect of the polyether chain, Na_2CO_3 (K_2CO_3 or $CsCO_3$) becomes soluble in DMSO, and this obviously drastically changes the effective (kinetic) basicity of the carbonate unit in an unfavorable way, resulting in the formation of undefined decomposition products from the coupling reactions.

Table 4. Turn-over Frequencies of Sonogashira Coupling Reactions over Five Reaction Cycles

cycle	tof[a] (h^{-1})	tof[b] (h^{-1})
1	103	60
2	102	58
3	100	56
4	97	54
5	96	48

[a] Coupling of 4-bromoacetophenone and PhCCH. [b] Coupling of 4-chloroacetophenone and PhCCH; conditions are the same as in Table 3.

Catalyst Recycling. Reliable information concerning the recyclability of the catalysts can be obtained by monitoring the turn-over frequency (tof) of the respective catalyst during several reaction cycles. The corresponding data concerning the coupling of phenyl acetylene with 4-bromoacetophenone or with 4-chloroacetophenone are listed Table 4. For each reaction the conversion was determined by GC after approximately half of the reactants had been consumed. It can be seen

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(36) $^iPr_3SiCCH$ has to be used in the aryl chloride coupling, because with Me_3SiCCH the tms protective group is cleaved during the reaction.

from these data that the tof for the coupling of 4-bromoacetophenone is almost constant (100% initial activity to 93% activity after five cycles), whereas that of 4-chloroacetophenone drops slightly to 80% relative to 100% at the beginning.

Another critical parameter concerning the recyclability of the catalyst is its retention in the catalyst phase, that is, the insolubility on the product phase. The absence of ligand signals in the ^{1}H NMR spectra of the crude products already indicates the absence of significant catalyst leaching. In addition, two sensitive techniques were applied to obtain more detailed information. The amount of palladium lost into the heptane solvent was determined by using total reflection XRF and UV spectrophotometry by means of the colorimetric reagent 4,4′-bis(dimethylamino)thiobenzophenone.[37] Both methods were found to be in good agreement, and the retention of the catalyst in the DMSO solvent was found to be >99.9% by spectrophotometry and >99.95% by TXRF.

Monophasic, Permanently Biphasic, or Thermomorphic Biphasic? The homogeneous reaction conditions of thermomorphic catalysis above the critical mixing temperature and the spontaneous phase separation below this temperature can be regarded as the most significant benefits of this approach, which, on the other hand, also has some limitations: (a) in thermomorphic systems the mutual solubility of the two solvents used can be significant, inevitably leading to some loss of catalyst phase solvent or—more importantly—of catalyst; (b) many catalysts show their optimum performance only in a few selected solvents, and consequently both solvents need to be compatible with the catalytic transformation and the substrates; (c) the number of suitable thermomorphic solvent mixtures is limited; (d) the solvent mixture resulting above the critical mixing temperature has rather different solvent properties, eventually leading to the precipitation of the phase-tagged catalyst or the reactants.

Consequently, for slower reactions permanently biphasic solvent mixtures can be excellent alternatives as some of the above-mentioned restrictions do not apply. However, our work also illustrates drawbacks of this approach. In a permanently biphasic solvent system the partition coefficients of the reactants (which can be very different from those of the products!) also have to be taken into account. In the case of polar biphasic catalysis and highly lipophilic reactants, its effective concentration in a polar catalyst phase can be low, leading to a significant retardation of the coupling reaction. For such substrates this is difficult to avoid because the nature of the phase tag at the catalyst (polar or nonpolar biphasic catalysis) must be adapted to the partition coefficients of the product to allow an efficient separation of catalyst and products. To avoid problems with unfavorable partition coefficients of the reactants, a monophasic (= single solvent) approach appears to be useful with phase-tagged catalysts, even though it requires an additional extraction step after the reaction in order to separate the phase-tagged catalyst from the products of the catalytic reaction.

Obviously, each of the three approaches discussed here has pros and cons. The decision of which is the best can be made only for a clearly defined reaction.

Summary and Conclusions

We have synthesized two sterically demanding and electron-rich phosphines with cationic phase tags ($-CH_2-NEt_3^+$, $-CH_2-PPh_3^+$), which, upon reaction with Na_2PdCl_4 in the presence of CuI, acetylenes, aryl bromides or chlorides, and a suitable base (HN^iPr_2 or Na_2CO_3), can be used to efficiently form the respective carbon−carbon coupled phenyl acetylenes in excellent yields. Both phase-tagged catalysts can be recovered virtually quantitatively (>99.95% recovery) from the reaction mixture, either by separating the catalyst phase solvent from the product phase solvent (biphasic catalysis) or by extracting the product from the reaction mixture (monophasic catalysis) with heptane. In both cases the catalyst containing solutions can be reused for the next coupling reaction without significant loss in activity, which is demonstrated by high yields of the coupling reactions, the almost constant tof, and the absence of detectable catalyst leaching.

Which solvent strategy (single solvent, permanently biphasic, or thermomorphic) is best for a certain reaction with phase-tagged catalysts will depend on a number of parameters, of which the partition coefficient requires special consideration. In a thermomorphic solvent system and in a single solvent (monophasic, followed by extraction of the product with a second solvent), only the partition coefficients of the products need to be taken into account for the efficient separation of catalyst and product. Whereas the distribution of reactants and products has to be considered in permanently biphasic solvent mixtures, an unfavorable distribution of one reactant can lead to a significant decrease in the speed of the reaction. In conclusion, each of the solvent strategies presented here is best suited only for certain catalytic transformations.

Experimental Section

General. Aryl halides, acetylenes, CuI, and Na_2PdCl_4 were used as received. Solvents were purified using standard procedures: DMSO was dried over molecular sieves, toluene was dried with sodium, and CH_2Cl_2 was dried over CaH_2.[38] Carbonate bases were dried at 80 °C under vacuum, and amines were distilled from CaH_2. Reactions were performed under an atmosphere of argon using standard Schlenk techniques. Column chromatography was performed with silica MN60 (63−200 μm), TLC on Merck plates coated with silica gel 60, F254. Gas chromatography was performed on a Perkin-Elmer Autosystem. NMR spectra were recorded at 293 K with a Bruker AC 300 (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) or a Bruker AC 200 (^{1}H NMR 200 MHz, ^{31}P NMR 81 MHz) spectrometer. ^{1}H NMR spectra were referenced to residual protonated impurities in the solvent and ^{13}C NMR to the solvent signal ($CDCl_3$): δ_H 7.24, δ_C 77.0), and ^{31}P NMR spectra were referenced to PMe_3 (38% in benzene δ −62) as an external standard. Starting materials were commercially available or prepared according to literature procedures: $(1\text{-Ad})_2PH$,[39] 1-($BrCH_2$), 4-($CH_2PH^+(1\text{-Ad})_2$)C_6H_4·Br.[24] The NMR data of the coupling products synthesized here are identical to those reported in the literature.[20h]

Synthesis of 1-($CH_2NEt_3^+$), 4-($CH_2P(1\text{-Ad})_2$)C_6H_4·Br^-. To a solution of the phosphonium salt 1-(CH_2Br), 4-(CH_2PH^+(1-

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Ad)$_2$)C_6H_4·Br^- (608 mg, 1.0 mmol) in CH_2Cl_2 was added Et_3N (0.5 mL, 3.6 mmol) and the reaction mixture stirred for 24 h at room temperature. The volatiles were evaporated in vacuo, and the residue was extracted with degassed water (2 × 5 mL) and ether (10 mL). The residue was dried in vacuo to result in 0.47 g (75%, 0.8 mmol): ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 4 H, ArH), 4.62 (s, 2 H, ArH), 3.41 (d, $J = 4.7$ Hz, 6 H, Et-CH_2), 2.76 (d, $J = 3.3$ Hz, 2H, ArCH_2), 2.04−1.33 (m, 30 H, Ad-H), 1.63 (s, 9 H, Et-CH_3); ^{31}P NMR ($CDCl_3$) δ 34.9.

Synthesis of 1-($CH_2PPh_3^+$), 4-(CH_2PH^+(1-Ad)$_2$)C_6H_4·2Br^-. A solution of 1-(CH_2Br), 4-(CH_2PH^+(1-Ad)$_2$)C_6H_4·Br^- (1.8 g, 3.00 mmol) and PPh_3 (850 mg, 3.2 mmol) in $CHCl_3$ (15 mL) was heated to 50 °C. After a few minutes, a colorless precipitate was formed, and stirring was continued for an overall time of 3 h. The precipitate was filtered off and washed with $CHCl_3$ (2 × 5 mL) and diethyl ether (2 × 10 mL). After drying in vacuo, the product was obtained as a colorless powder: yield 2.35 g (2.7 mmol, 91%); ^{1}H NMR (DMSO-d_6) δ 8.34 (s, 1H, P$\underline{H}$), 7.95−7.55 (m, 15H, PPh_3−Ar$\underline{H}$) 7.35 and 7.00 (AA′BB′ 4H, ^3J = 7.6 Hz, Ar$\underline{H}$), 5.25 (d, 2H, ^2J = 15.8 Hz, ArC$\underline{H}_2PPh_3$), 3.96 (s, br, 2H, ArC$\underline{H}_2$PAd), 2.20−1.55 (m, 30 H, 1-Ad$\underline{H}$); ^{13}C NMR (DMSO-d_6) δ 135.0, 134.0, 131.4, 130.0, 118.0, 37.6, 36.8, 36.0, 34.9, 26.8. (some signals are hidden below the solvent peak); ^{31}P NMR (DMSO-d_6) δ 37.56 (s), 29.20 (s); ^{1}H NMR (H_2O/acetone-d_6 1:1) δ 8.34 (s, 1H, P$\underline{H}$), 7.95−7.55 (m, 15H, PPh_3−Ar$\underline{H}$), 7.35 and 7.00 (AA′BB′ 4H, ^3J = 7.6 Hz, Ar$\underline{H}$), 5.25 (d, 2H, ^2J = 15.8 Hz, ArC$\underline{H}_2PPh_3$), 3.96 (s, br, 2H, ArC$\underline{H}_2$PAd), 2.20−1.55 (m, 30 H, 1-Ad$\underline{H}$); ^{31}P NMR (H_2O/acetone-d_6 1:1) δ 25.63 (s), 19.81 (s).

General Procedure for the Biphasic Sonogashira Catalysis of Aryl Bromides. The catalyst precursors Na_2PdCl_4 (4.4 mg, 15 μmol, 1 mol %), CuI (1.9 mg, 10 μmol, 0.67 mol %), and 1-($CH_2NEt_3^+$), 4-(CH_2P(1-Ad)$_2$)C_6H_4·Br^- (17.5 mg, 30 μmol, 2 mol %) were added to DMSO (3 mL) and heptane (10 mL) followed by the acetylene (2.0 mmol), the aryl bromide (1.5 mmol), and HN^iPr_2 (3 mmol). The stirred reaction mixture was heated to 60 °C during the respective time (1−2 h). After the reaction, the heptane layer was removed. This solution was evaporated to dryness and the remaining crude product purified by chromatography over silica. For the multicycle experiments the DMSO solution (catalyst phase) was used again for the next catalytic reaction after the addition of fresh reactants (1.5 mmol of aryl bromide, 2.0 mmol of acetylene), HN^iPr_2 (3 mmol), and heptane (10 mL). After the last cycle, water (1 mL) was added to the DMSO, which then was extracted two times with *n*-heptane (10 mL) to isolate all of the remaining product. The crude products from the different runs were combined and purified by column chromatography on silica (cyclohexane/ethyl acetate) to yield the respective pure compounds.

General Procedure for Monophasic Sonogashira Catalysis of Aryl Bromides with Extraction of Product. The catalyst precursors Na_2PdCl_4 (4.4 mg, 15 μmol, 1 mol %) CuI (2.9 mg, 10 μmol, 0.66 mol %), and 1-($Et_3N^+CH_2$), 4-(CH_2P(1-Ad)$_2$)C_6H_4·Br^- (17.5 mg, 30 μmol, 2 mol %) were added to DMSO (3 mL) followed by the acetylene (2.0 mmol), the aryl bromide (1.5 mmol), and HN^iPr_2 (3 mmol). The stirred reaction mixture was heated to 60 °C during the respective time (1−2 h). After the reaction, the product containing DMSO solution was extracted with heptane (2 × 10 mL). The combined heptane solutions were evaporated to dryness. For the multicycle experiments the DMSO solution (catalyst phase) was used again for the next catalytic reaction after the addition of fresh reactants (1.5 mmol of aryl bromide, 2.0 mmol of acetylene) and HN^iPr_2 (3 mmol). After the last cycle, water (1 mL) was added to the DMSO, which then was extracted two times with *n*-heptane (10 mL) to isolate all of the remaining product. The crude products from the different runs were combined and purified by column chromatography on silica (cyclohexane/ethyl acetate) to yield the respective pure compounds.

General Procedure for Monophasic Sonogashira Catalysis of Aryl Chlorides with Extraction of Product. The catalyst precursors Na_2PdCl_4 (8.8 mg, 30 μmol, 2 mol %), CuI (3.8 mg, 20 μmol, 1.5 mol %), and 1-($CH_2NEt_3^+$), 4-(CH_2P(1-Ad)$_2$)C_6H_4·Br^- (35 mg, 60 μmol, 4 mol %) or 1-($CH_2PPh_3^+$), 4-(CH_2PH^+(1-Ad)$_2$)C_6H_4·2Br^- (50 mg, 4 mol %) were added to DMSO (3 mL) followed by the acetylene (2.0 mmol), the aryl chloride (1.5 mmol), and Na_2CO_3 (3 mmol). The stirred mixture was heated to 120 °C during 6−18 h. After the mixture had cooled to room temperature, *n*-heptane (2 × 10 mL) was added and stirred for 5 min, and the upper layer was separated via cannula and evaporated to yield the crude product. The combined heptane solutions were evaporated to dryness. For the multicycle experiments the DMSO solution (catalyst phase) was used again for the next catalytic reaction after the addition of fresh reactants (1.5 mmol of aryl chloride, 2.0 mmol of acetylene) and Na_2CO_3 (2 mmol). After the last cycle, water (1 mL) was added to the DMSO, which then was extracted two times with *n*-heptane (10 mL) to isolate all of the remaining product. The crude products from the different runs were combined and purified by column chromatography on silica (cyclohexane/ethyl acetate) to yield the respective pure compounds.

Spectrophotometric Determination of Palladium. Determination of palladium using 4,4′-bis(dimethylamino)-thiobenzophenone[20] was linear in the range of 0−0.8 μg mL^{-1} with the coefficient of regression (R^2) of 0.9989 at pH 3.0−4.5. Test Sonogashira reactions were carried out, and the product phase solvent heptane from the reaction was treated with 4,4′-bis(dimethylamino)thiobenzophenone solution (2 mL, 1 mM in ethanol) maintained at pH 3.5. The final volume of the solution was made to 20 mL using ethanol, and the amount of Pd leached out in the product phase was determined photometrically at 523 nm. The limit of detection of Pd photometrically is 0.1%; that is, the retention can be checked up to 99.9%.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (DFG), the TU Darmstadt (TUD), the Fonds der Chemischen Industrie (FCI), and the Freunde der TUD. We thank Prof. H. Ortner and Dipl.-Ing. J. Saroukh for TXRF measurements and Dr. A. Datta for assistance with spectrophotometric determinations.

OM030450A