# Convenient Synthesis of New Anionic Water-Soluble Phosphanes and Applications in Inter- and Intramolecular Heck Reactions

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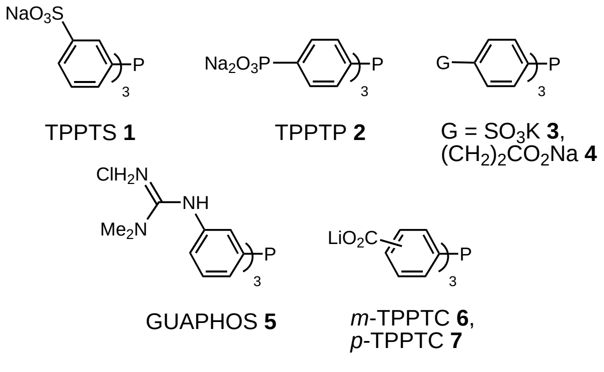
**Abstract:** The versatile preparation of new anionic water-soluble ligands derived from triphenylphosphane is described based on halogen-lithium exchange followed by $CO_2$ quenching. Efficient inter- and intramolecular Heck reactions have been disclosed. Comparison with other anionic and cationic ligands showed that *meta* substitution on the aromatic ring enhanced the reactivity.

**Keywords:** carboxylated phosphane; Heck reactions; homogeneous catalysis; palladium; water-soluble ligand

## Introduction

Homogeneous catalysis continues to be a major research field and is used in both organic syntheses and several industrial chemical processes.[1] Recently, the search for alternative media such as water is targeted at the development of highly productive, environmentally safe, recyclable techniques which can be promoted to large-scale applications. The benefits gained by using homogeneous catalysts in non-usual media include high activity and selectivity, easier product separation, and possible catalyst recycling.[2,3] Water solubility is usually reached through incorporation of strongly hydrophilic ligands bearing charges. In aqueous conditions, one of the most widely studied ligands is the trisodium salt of 3,3′,3″-phosphanotriylbenzenesulfonic acid (TPPTS; **1**)[4] obtained by sulfonation of triphenylphosphane.[5]

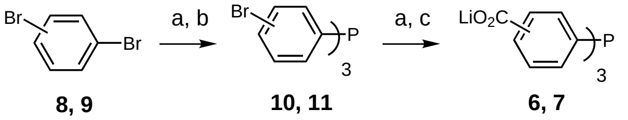
A general method to prepare substituted triphenylphosphane uses organometallic derivatives and phosphorus trichloride. Two examples of phosphanes derived from triphenylphosphane have been recently described, one anionic {$P[C_6H_4\text{-}p\text{-}(CH_2)_2CO_2Na]_3$; **4**} that requires drastic conditions for the reduction of phosphane oxides,[6] and one cationic (GUAPHOS; **5**) which is limited to the meta position on the aromatic rings (Scheme 1).[7] Another efficient route to water-soluble phosphanes [$P(C_6H_4\text{-}p\text{-}SO_3K)_3$; **3**] used phosphane, $PH_3$, and a substituted fluorobenzene in superbasic medium.[8] A phosphonate-functionalized phosphane (TPPTP; **2**) has been described recently using red phosphorus and lithium metal.[9] A new synthetic procedure for the preparation of hydrophilic phosphanes based on the palladium-catalyzed P–C coupling has also been disclosed.[10] Reports on phosphanes bearing carboxylic acid groups are limited to mono- or disubstituted ones[11,10a] or use harsh acid conditions[12] that are prohibited for asymmetric preparation. Palladium-catalyzed reactions have led to high selectivities and new transformations[13] using almost exclusively TPPTS as ligand.[4,14] Our continuing search for water-soluble catalysts prompted us to synthesize alternative anionic ligands via a simple and versatile route. We report herein the generic preparation of *meta*- and *para*-carboxylated phosphanes and our preliminary results in Pd-catalyzed Heck reactions.[15]



Scheme 1.

## Results and Discussion

We have realized the synthesis of a new anionic ligand, TPPTC, starting from tribromotriphenylphosphane by halogen-metal exchange and $CO_2$ quenching[16] (Scheme 2). The advantages are the mild conditions



a) *n*-BuLi, THF, -78 °C;
b) $PCl_3$, –78 °C to rt, (80% for **10**, 99% for **11**);
c) $CO_2$, –78 °C to rt, (95% for **6** and **7**).

**Scheme 2.**

and the possibility of having *meta*- or *para*-substitutents.[17] Moreover, the anionic group is directly linked to the aromatic ring as in the TPPTS ligand, which may confer a similar reactivity due to electronic effects. Commercially available 1,3-dibromobenzene **8** and 1,4-dibromobenzene **9** were cleanly monolithiated and reacted with phosphorus trichloride leading respectively to tris-*meta*-bromotriphenylphosphane **10** and tris-*para*-bromotriphenylphosphane **11** in 80% and 99% yield.[12,18]

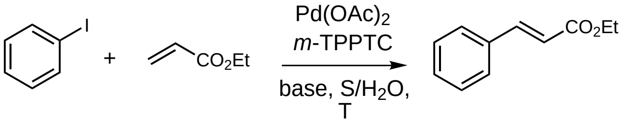
The lithiated trianion was formed at low temperature and quenched by dry ice leading respectively to *m*-TPPTC **6**[19] and *p*-TPPTC **7** in 95% yield.[20] The water-solubility of our new ligands was determined to be 1100 g/L for *m*-TPPTC and 1000 g/L for *p*-TPPTC, which are similar to TPPTS **1** and higher than TPPTP (550 g/L)[9] or $P(C_6H_4\text{-}p\text{-}SO_3K)_3$ (800 g/L)[8b] (Scheme 1).

Preliminary experiments were performed by reacting iodobenzene and ethyl acrylate in the presence of 5 mol % of palladium acetate, 15 mol % of ligand, triethylamine (1.2 equiv.) in a mixture of water/acetonitrile (1/6) at 80 °C. The choice of this solvent system was motivated by: the high polarity of both water, and acetonitrile ($\varepsilon = 78.5$ and 37.5), the homogeneity of the system, and the possibility of recycling by using water-insoluble nitriles as co-solvent. In the absence of phosphane or by using 5 mol % of $Pd(dba)_2$ low conversions were observed after one hour, respectively 35% and 15%. Adding *p*-TPPTC or *m*-TPPTC ligands (15 mol %) increased the conversion up to 100% within the same time. The *trans* isomer was easily isolated by simple filtration on a silica bed with 99% yield and with no traces of the *cis* isomer, or benzene. Comparison rates with other water-soluble ligands such as TPPTS **1** and GUAPHOS **5**[21] showed that the kinetics are slightly higher with *m*-TPPTC even though total conversion is observed after 4 hours with all ligands.

Recyclable biphasic systems are scarce in the literature.[22] Biphasic catalysis has still several drawbacks in this reaction such as leaching of Pd, recycle inability and/or low selectivity to the vinylation products, and palladium deposits at high temperature. As we also observed palladium deposits at high temperature in our system, we decided to reduce the mole fraction of palladium from 5 mol % to 1 mol % and 0.1 mol % (Table 1).

In the presence of 1 mol % of palladium and 3 mol % of *m*-TPPTC **6**, the reaction was complete within 45 minutes (entry 1). In comparison, we have conducted the same reaction, without water, and replacing *m*-TPPTC by triphenylphosphane: 96% conversion was only observed after 3 hours. It has also to be noted that the conditions are milder than the ones described with disulfonated triphenylphosphane in biphasic conditions (iodobenzene, methyl acrylate, 140 °C, 20 h).[5c] Low-

**Table 1.** Heck reaction between iodobenzene and ethyl acrylate



| Entry | $Pd(OAc)_2$ [mol %] | *m*-TPPTC [mol %] | Solvent | Base | T [°C] | t [h] | Conversion [%][e] |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 3 | $CH_3CN$[a] | $Et_3N$ | 80 | 0.75 | 100 |
| 2 | 1 | 5 | $CH_3CN$[a] | $Et_3N$ | 50 | 5 | 100 |
| 3 | 1 | 5 | $CH_3CN$[a] | $Et_3N$ | rt | 120 | 64 |
| 4 | 0.1 | 0.3 | $CH_3CN$[a] | $Et_3N$ | 80 | 20 | 27 |
| 5 | 0.1 | 0.4 | $CH_3CN$[a] | $Et_3N$ | 80 | 20 | 54 |
| 6 | 0.1 | 0.5 | $CH_3CN$[b] | *i*-$Pr_2NEt$ | 80 | 20 | 92 |
| 7 | 0.1 | 0.5 | $CH_3CN$[b] | *i*-$Pr_2NH$[c] | 80 | 20 | 50 |
| 8 | 0.1 | 0.5 | NMP[a, d] | *i*-$Pr_2NH$ | 110 | 20 | 100 |
| 9 | 0.1 | 0.5 | NMP[a, d] | *i*-$Pr_2NH$[c] | 110 | 5 | 100 |
| 10 | 0.1 | 0.5 | NMP[b, d] | *i*-$Pr_2NH$[c] | 110 | 1 | 100 |

[a] $CH_3CN$ or $NMP/H_2O = 6/1$, $[c] = 0.7$ M.
[b] $CH_3CN$ or $NMP/H_2O = 3/1$, $[c] = 2.5$ M.
[c] 3 equivalents.
[d] Screw-topped tube.
[e] Measured by gas chromatography

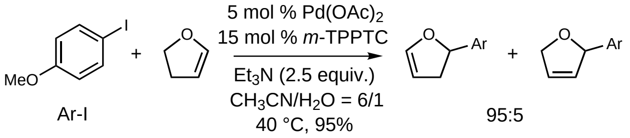
ering the temperature and increasing the ligand mole fraction (5 mol %) to stabilize the hydrosoluble catalyst led to 100% at 50 °C after 5 hours and 64% conversion after 120 hours at room temperature (entries 2 and 3).

The use of 0.1% catalyst required optimization as the reaction was much slower. The quantity of ligand had to be increased to 0.4 mol % to stabilize the hydrosoluble catalyst and reach 54% conversion after 20 hours at 80 °C (entries 4, 5). We tried other organic bases such as diisopropylethylamine (entry 6) and diisopropylamine (entry 7) to increase the Pd(0) regeneration via a complexation of the amine and β-elimination.[23] Higher concentration combined with the use of 0.5 mol % ligand gave also better results (entry 6). Wishing to decrease the reaction time, we decided to use a solvent that has a higher boiling point and a higher polarity such as NMP. The reaction, conducted in screw-topped tube, was complete and still very easy to work-up after 20 hours (entry 8). We were also pleased to see that total conversion could be obtained by using 3 equivalents of diisopropylamine (entry 9). At a higher concentration of the medium (entry 10), total conversion was obtained within 1 hour.

The good results observed for the Heck reaction on activated olefins encouraged us to evaluate the efficiency of *m*-TPPTC **6** in Heck-type reactions with unactivated olefins. The reaction of iodobenzene and styrene was previously described using a water-soluble ligand complexed on glass beads[14c] (1 mol % Pd, toluene, 100 °C, 60 h, 55%). Attempts to submit the iodobenzene to the olefination using our conditions led first to a modest conversion of 64% (Table 2, entry 1). Simple filtration through a silica bed led once again to a very clean product with 60% isolated yield. Switching the base from triethylamine to potassium carbonate or potassium acetate and increasing the mole fraction of ligand did not give better results (entries 2, 3). The use of diisopropylamine slightly improved the conversion of the reaction (entry 4). Shorter reaction time could be achieved by using higher temperature and NMP as solvent. We also preferred to increase the mole fraction of ligand to 5 mol % to stabilize the palladium catalyst. The olefination gave efficiently the desired product within 4 hours and in 80% isolated yield.

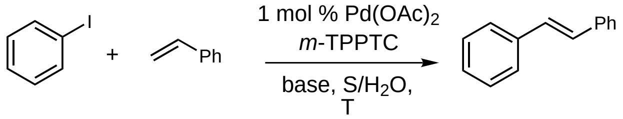
Attractive features exhibited by these systems prompted us to study another classic Heck reaction, which may be interesting for asymmetric synthesis.[24] Pd-catalyzed coupling of 4-methoxyiodobenzene with 2,3-dihydrofuran using 5 mol % of $Pd(OAc)_2$ and 15 mol % of *m*-TPPTC **6** in an acetonitrile/water mixture (6/1) led efficiently under mild conditions to a major regioisomer within 3 hours in 95% yield (Scheme 3). The structure of the major isomer obtained with 95% selectivity was confirmed by $^1H$ NMR spectroscopy.

The same reaction was conducted with other water-soluble ligands and we followed the kinetic rates of the reaction by gas chromatography (Figure 1). The anionic ligands seemed more efficient than the cationic GUAPHOS **5.** Indeed, after 1 hour reaction, the conversion reached 70% with *m*-TPPTC **6** and only 40% with GUAPHOS. The reaction was completed either with the carboxylated ligand *m*-TPPTC and the sulfonated ligand TPPTS. Prolonged heating was necessary to reach 80% yield with GUAPHOS. The use of *p*-TPPTC **7** also gave disappointing results: one explanation could be the presumed smaller Tolman cone angle for the



**Scheme 3.**

**Table 2.** Heck reaction between iodobenzene and styrene.



| Entry | *m*-TPPTC [mol %] | Solvent[a] | Base[b] | T [°C] | t [h] | Conversion (%)[d] |
|---|---|---|---|---|---|---|
| 1 | 3 | $CH_3CN$ | $Et_3N$ | 80 | 18 | 64 |
| 2 | 4 | $CH_3CN$ | $K_2CO_3$ | 80 | 20 | 63 |
| 3 | 4 | $CH_3CN$ | AcOK | 80 | 20 | 30 |
| 4 | 3 | $CH_3CN$ | *i*-$Pr_2NH$ | 80 | 22 | 76 |
| 5 | 5 | NMP[c] | *i*-$Pr_2NH$ | 110 | 4 | 84 |

[a] $CH_3CN$ or NMP/$H_2O$ = 6/1, [c] = 0.7 M.

[b] 3 equivalents.

[c] Screw-topped tube.

[d] Measured by gas chromatography

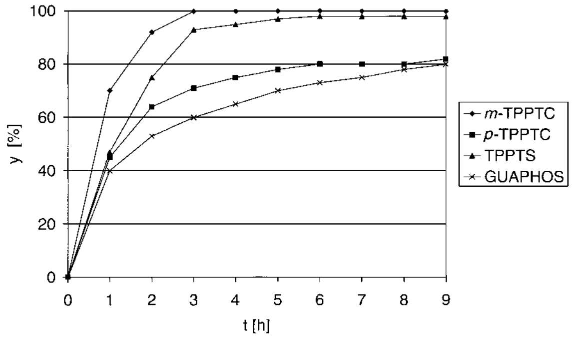
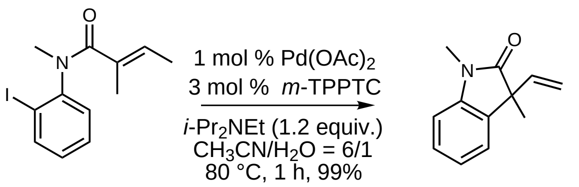


**Figure 1.** Plot of GC yield (y) as a function of reaction time (t) for the catalyzed reaction of 2,3-dihydrofuran with 4-methoxy-iodobenzene.



**Scheme 4.**

*para*-substituted phosphane compared to the *meta*-substituted one[25] that would decrease the reaction rate.

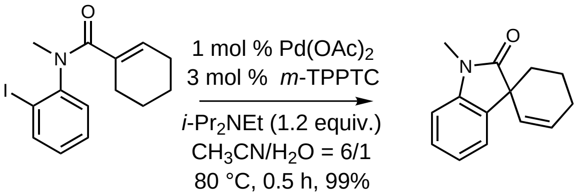
We decided then to broaden the scope of application to intramolecular Heck reactions. We prepared two iodoanilides derived from tiglic acid and cyclohex-2-enecarboxylic acid according to Overman's procedure in three high-yielding steps.[26] The Heck reactions on these substrates were reported with 20 mol % of palladium(0), 5 equivalents of pentamethylpiperidine as the base in dimethylacetamide at 110 °C.

We were pleased to see that the cyclization of the dimethyliodo derivative occurred with our catalyst system (1 mol % of palladium, 3 mol % of *m*-TPPTC **6** or *p*-TPPTC **7**) leading to the desired cyclic amide after 1 h under milder conditions (Scheme 4). In both cases, the formation of the cyclized product was clean, and the catalyst was easily removed leading to the amide with 99% isolated yield.

The cyclohexenyl compound was also subjected to the same conditions. The efficiency of anionic ligands was confirmed leading to 99% of the tricyclic substrate (Scheme 5) in a very short time. The cyclized compounds are isolated by simple filtration over a bed of silica with no traces of side products.

## Conclusion

In conclusion, we have developed a generic methodology that allows for the easy multi-gram scale synthesis of water-soluble ligands bearing anionic substitutents. Catalytic applications showed that these phosphanes are efficient in organo-aqueous palladium-catalyzed Heck reactions. The intramolecular Heck reaction was conducted under mild conditions, with low catalyst loadings and in a shorter time than under anhydrous conditions. The easily prepared ligand *m*-TPPTC gave excellent results, presumably because of the steric and electronic effects of the carboxylic group in *meta*-position. Studies about the electronic properties, and other organometallic applications are currently under active investigations in our laboratory and will be reported in due course.



**Scheme 5.**

## Experimental Section

### General Remarks

$^1$H NMR, $^{13}$C NMR, and $^{31}$P NMR were recorded on a Bruker AC 200 or ARX 400 instrument. All signals were expressed as δ (ppm) down field from $Me_4Si$ for $^1$H and $^{13}$C NMR and $H_3PO_4$ for $^{31}$P NMR used as an internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. GC analyses were performed with a Hewlett-Packard 5890 instrument equipped with a J&W Scientific DB-1701 capillary column (15 m, d 0.254 μm), using a flame ionization detector. All manipulations were carried out under nitrogen and Schlenk techniques for catalytic tests. $Pd(OAc)_2$ was purchased from Acros. TPPTS was generously given by Rhodia (France) as a water solution (30% in weight). Water, acetonitrile, and *N*-methylpyrrolidone were degassed by sparging with nitrogen and/or exposure to vacuum. Column chromatography was performed with E. Merck 0.040 – 0.063 mm Art. 11567 silica gel. Florisil (100 – 200 mesh) was purchased from Acros or Avocado.

### General Experimental Procedures for TPPTC Syntheses

To a solution of dibromobenzene (1 equiv) in anhydrous THF (0.5 mmol $L^{-1}$) at – 78 °C, was added dropwise *n*-butyllithium (1 equiv, 2.5 M in hexane). The solution was stirred for 30 min at – 78 °C, then freshly distilled phosphorus trichloride (1/3 equiv) was slowly added. The mixture was allowed to warm slowly to room temperature within 2 hours. Saturated NaCl was added and the reaction mixture was extracted three times with diethyl ether. The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified on silica gel (1:1 $CH_2Cl_2$/hexane) to give a white solid. To a solution of trisbromophenylphosphane (1 equiv) in anhydrous THF (0.5 mmol $L^{-1}$) at $-78\,^\circ C$, was added dropwise *n*-butyllithium (3 equiv, 2.5 M in hexane). The solution was stirred for 2 hours at $-78\,^\circ C$, then excess crushed dry ice was added. After addition of diethyl ether, the reaction mixture was stirred for 24 h at room temperature. The white precipitate formed was filtered off, rinsed with $CH_2Cl_2$ and dried under vacuum.

Starting from 11.8 g (50 mmol) of 1,3-dibromobenzene **8**, 6.65 g (13.3 mmol) of the tris-*meta*-bromophenylphosphane **10** was isolated. Starting from 3 g (6 mmol) of the tris-*meta*-bromophenylphosphane **10**, 2.35 g (5.7 mmol) of the trilithium salt of 3,3′,3″-phosphanotriylbenzenecarboxylic acid **6** was obtained. Starting from 11.8 g (50 mmol) of 1,4-dibromobenzene **9**, 8.2 g (16.4 mmol) of the tris-*para*-bromophenylphosphane **11** was isolated. Starting from 3 g (6 mmol) of the tris-*para*-bromophenylphosphane **11**, 2.35 g (5.7 mmol) of the trilithium salt of 4,4′,4″-phosphanotriylbenzenecarboxylic acid **7** was obtained.

***m*-TPPTC 6:** $^1H$ NMR ($D_2O$, 200 MHz): $\delta = 7.23$ (m, 6H), 7.67 (m, 6H); $^{31}P$ NMR ($D_2O$, 162 MHz): $\delta = -5.60$; $^{13}C$ NMR ($D_2O$, 100 MHz): $\delta = 128.9$ (d, $J = 6$ Hz), 129.8 (s), 134.0 (d, $J = 23$ Hz), 135.8 (d, $J = 7$ Hz), 136.0 (d, $J = 16$ Hz), 136.8 (d, $J = 7.4$ Hz), 175.0 (s, $CO_2$); mp $>260\,^\circ C$; ES−MS: $m/z = 405.4$ $[M - Li]^-$, 399.3 $[M - 2\,Li + H]^-$, 393.4 $[M - 3\,Li + 2\,H]^-$.

***p*-TPPTC 7:** $^1H$ NMR ($D_2O$, 400 MHz): $\delta = 7.27$ (app. t, 6H, $J = 8.2$ Hz), 7.68 (dd, 6H, $J = 8.2$, 1.5 Hz); $^{31}P$ NMR ($D_2O$, 162 MHz): $\delta = -6.35$.

### General Experimental Procedures for Heck Reactions:

$PdL_2$ was preformed in water (30 mL/mmol Pd) by mixing 1 mol % $Pd(OAc)_2$ and 3 mol % L at 80 °C; during 30 minutes. To the red colored catalyst was added an acetonitrile (2 mL/mmol) solution of the substrate and triethylamine (1.2 equiv.). The homogeneous mixture was heated at 40 °C or 80 °C until completion of the reaction (GC) and then filtered at room temperature on a short pad of florisil gel and evaporated under reduced pressure.

### Arylation of 2,3-Dihydrofuran

To a solution of $Pd(OAc)_2$ (11.2 mg) and *m*-TPPTC (61.8 mg) in water (0.1 mL) preheated at 80° during 30 minutes, was added an acetonitrile (0.6 mL) solution of 2,3-dihydrofuran (230 μL, 3 equiv.), 4-methoxy-iodobenzene (234 mg, 1 equiv.) and triethylamine (348 μL, 2.5 equiv.). The homogeneous mixture was heated at 40 °C for 3 hours and the easy work-up gave the desired compounds; yield: 167 mg (95%).

**1-Methoxy-4-(3*H*)-furanylbenzene**: $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta = 7.27$ (d, 2H, $J = 8.7$ Hz), 6.87 (d, 2H, $J = 8.7$ Hz), 6.39 (app. q, 1H, $J = 2.6$ Hz), 5.43 (dd, 1H, $J = 10.6$, 8.6 Hz), 5.0 (app. q, 1H, $J = 2.6$ Hz), 3.78 (s, 3H), 3.0–2.93 (m, 1H), 2.65–2.5 (m, 1H); GC (70 °C/5 min then at 10 °C $min^{-1}$ to 210 °C): RT (pdt) = 14 min 4 sec (95%), 15 min 1 sec (5%); RT (sm) = 11 min 9 sec.

**Cyclization of 2′-Iodo-*N*-methyl-(*E*)-2-methyl-2-butenanilide:** To a solution of $Pd(OAc)_2$ (0.7 mg) and *m*-TPPTC (4.2 mg) in water (0.1 mL) preheated at 80 °C during 30 minutes, was added an acetonitrile (0.6 mL) solution of the anilide (100 mg) and triethylamine (160 μL, 1.2 equiv.). The homogeneous mixture was heated at 80 °C for 1 h and the easy work-up gave the desired compound; yield: 59 mg (99%).

**1,3-Dimethyl-3-vinyl-1,3-dihydroindol-2-one:** $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta = 7.31$ (td, 1H, $J_o = 7.6$ Hz, $J_m = 1.5$ Hz), 7.22 (dd, 1H, $J_o = 7.4$ Hz, $J_m = 1.3$ Hz), 7.11 (td, 1H, $J_o = 7.4$ Hz, $J_m = 1.3$ Hz), 6.89 (dd, 1H, $J_o = 7.6$ Hz, $J_m = 1.5$ Hz), 5.97 (dd, 1H, $J_{trans} = 17.0$ Hz, $J_{cis} = 10.6$ Hz), 5.18 (dd, 1H, $J_{cis} = 10.6$ Hz, $J_{gem} = 0.8$ Hz), 5.15 (dd, 1H, $J_{trans} = 17.0$ Hz, $J_{gem} = 0.8$ Hz), 3.24 (s, 3H), 1.52 (s, 3H); GC (70 °C/1 min then at 20 °C $min^{-1}$ to 210 °C): RT (pdt) = 7 min 42 sec; RT (sm) = 10 min 46 sec.

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[17] Several conditions for bromination of triphenylphosphane and triphenylphosphane oxide were tested without success.

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[19] *m*-TPPTC stands for the trilithium salt of 3,3′,3″-phosphanotriylbenzenecarboxylic acid.

[20] *m*-TPPTC: $^{31}P$ NMR ($D_2O$, 162 MHz): $\delta = -5.60$ ppm. The *p*-TPPTC was obtained with 70% purity accompanied with mono- and disubstituted isomers. $^{31}P$ NMR ($D_2O$, 162 MHz): $\delta = -6.35$ ppm. The latter could be purified by the formation of the insoluble triacid derivative but was used like this in the catalytic tests.

[21] It is noteworthy that the guanidinium phosphane GUAPHOS was only previously used for Sonogashira cross-coupling and Suzuki reactions in organo-aqueous medium.[7,10b]

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