A Novel Water-Soluble *m*-TPPTC Ligand: Steric and Electronic Features – Recent Developments in Pd- and Rh-Catalyzed C–C Bond Formations

Emilie Genin, Rémi Amengual, Véronique Michelet,* Monique Savignac,* Anny Jutand, Luc Neuville, Jean-Pierre Genêt*

Ecole Nationale Supérieure de Chimie de Paris, Laboratoire de Synthèse Sélective Organique et Produits Naturels, UMR 7573, 11 rue P. et M. Curie, 75231 Paris Cedex 05, France and Ecole Normale Supérieure, Département de Chimie, UMR 8640, 24 rue Lhomond, 75231 Paris Cedex 05, France
Fax: (+33)-1-44-07-10-62, e-mail: michelet@ext.jussieu.fr, savignac@ext.jussieu.fr, genet@ext.jussieu.fr

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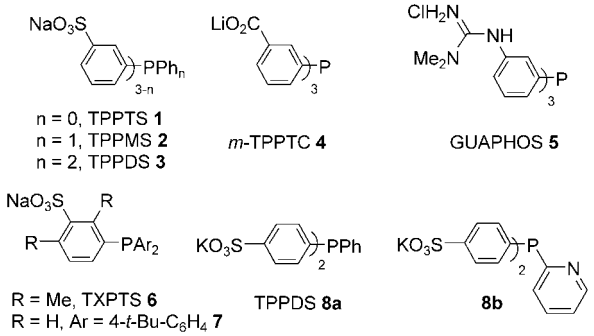
Abstract: The steric and electronic features of the novel water-soluble phosphane *m*-TPPTC have been determined using NMR, IR and UV-VIS spectroscopic methods and compared to the well-known sulfonated analogue TPPTS. The higher basicity of *m*-TPPTC compared to TPPTS had an influence (selectivity and efficiency) either on Pd- or Rh-catalyzed C–C bond formations reactions. The Sonogashira copper-free cross-couplings of aryl iodides and *ortho*-functionalized aryl iodides were efficiently performed using the carboxylated phosphane *m*-TPPTC leading to the alkynes in high yields. The Pd/*m*-TPPTC system was found to be efficiently recycled under mild biphasic conditions in the Sonogashira reaction.

Keywords: palladium; phosphane basicity; recycling; rhodium; Sonogashira cross-couplings; water-soluble ligand

Introduction

Over the past few years, significant research has been directed toward the development of new technologies for environmentally benign processes.[1] Among them, the application of water as solvent in organic syntheses and in homogeneous transition-metal catalyzed reactions has been steadily growing.[1,2] Indeed, water is not toxic and non-inflammable, the most attractive feature being its utility in the development of efficient environmentally safe systems. The industrial hydroformylation of propene in a biphasic system medium (water/organic) using the water-soluble ligand TPPTS **1** by Rhône–Poulenc has stimulated the interest for new organometallic systems either for C–H or C–C bond formations.[3,4] Several groups including ours[5,6] have worked intensively in finding new applications for the sulfonated ligand TPPTS and in preparing new water-soluble analogues of triphenylphosphane bearing anionic or cationic groups (Scheme 1).[7] Various hydrosoluble ligands such as **2**,[8] **3**[9] and **5**[7c–d] have been described and showed interesting and similar properties in Pd-catalyzed C–C bond formations compared to the well-known TPPTS ligand. The Shaughnessy group described the synthesis of a sterically demanding phosphane, TXPTS **6**, which showed a higher activity than the TPPTS ligand for the Heck reaction.[7a] The Monflier group reported the synthesis of amphiphilic phosphane **7** and showed that the palladium-catalyzed cleavage of undecyl allyl carbonate was highly accelerated.[7h] The Lautens group prepared the sulfonated ligands **8a** and **8b** which offered a higher activity compared to the TPPTS ligand.[10] Recently, we have reported a versatile preparation of the water-soluble ligand *m*-TPPTC **4** functionalized by carboxylated moieties, which presents a very high solubility (1100 $g \cdot L^{-1}$).[6]

Preliminary studies on the Pd-catalyzed Heck reaction of aryl iodides pointed out that this ligand displays a high efficiency compared to its sulfonated analogue with some benefits in term of kinetics of the reactions.[6]



Scheme 1.

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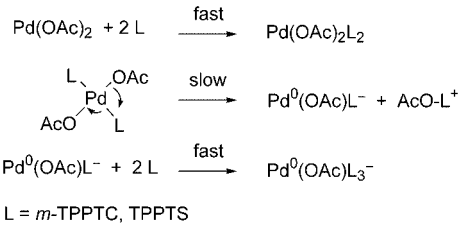
We also found that some Rh-catalyzed couplings, such as the addition of boronic acids to alkene and alkynes, were particularly effective in the presence of the *m*-TPPTC ligand.[11] Indeed, the use of the *m*-TPPTC ligand allowed better results in terms of activity, selectivity compared to its sulfonated analogue TPPTS. In the meantime, these results prompted us to investigate the steric and electronic properties of our new ligand. We report herein the stereoelectronic properties of the carboxylated ligand *m*-TPPTC, and some applications in palladium- and rhodium-catalyzed reactions including the recycling of the [Pd]/*m*-TPPTC catalysts.

Results and Discussion

Steric and Electronic Features of the *m*-TPPTC Ligand

In order to get information about the influence of the carboxy group on the ligand, we decided to evaluate the steric parameters and the electronic properties on phosphorus and the acid-base profile of the substituents. These data may indeed have a crucial influence on the exit of the reaction catalyzed by their transition metal complexes. To evaluate the bulkiness generated by the phosphane, we turned our attention towards a method that proved to be valuable for substituted triarylphosphanes. It has been shown that the ^{31}P NMR chemical shift of *trans*-$(PAr_3)_2PdCl_2$ complexes correlates well with the bulkiness of phosphane ligands such as TPPTS and GUAPHOS,[7g] for example.[12] The palladium complex derived from the carboxylated ligand *m*-TPPTC was commonly prepared by the reaction of bis(benzonitrile)palladium dichloride and 2 equivalents of phosphane in a CH_2Cl_2/H_2O mixture. For a better comparison, the same experiment was conducted with the TPPTS ligand and the result was in good accordance with literature reports. As presented in Table 1 and as expected, the carboxylated and the sulfonated ligands have a similar cone angle and therefore generate the same steric bulk.[13] It is noteworthy that the effective bulk of these ligands is significantly larger than that of triphenylphosphane ($\theta_{Tol} = 145°$), due to the presence of *meta* substituents.

Concerning the electronic properties of our phosphane, general and simple methods have been described in the literature to assess the σ-donor/π-acceptor character of the phosphane.[14] The magnitude of $^1J(^{77}Se\text{-}^{31}P)$ in phosphane selenides derived from the reaction of a tertiary phosphane and selenium was shown to be much dependent upon the nature of the organic groups bound to phosphorus.[13,15] Electron-withdrawing groups on phosphorus will cause the coupling constant to increase whereas electron-donating groups and bulky groups will cause it to decrease. The phosphane selenides were obtained *via* the reaction of the corresponding ligands with an excess of selenium in refluxing ethanol. As the bulkiness was identical for the sulfonated and the carboxylated ligands, the $^1J(^{77}Se\text{-}^{31}P)$ value differences could be attributed to a better donor ability for the *m*-TPPTC ligand. The same trend was observed when measuring the ν(CO) stretching frequency by infra-red spectroscopy of the complexes *cis*-$(CO)_4MoL_2$,[7g,16] derived from norbornadiene(tetracarbonyl)molybdenum and the corresponding ligands *m*-TPPTC or TPPTS. Finally, a method based on a Pd^0 formation kinetic study described by Jutand and Amatore also attracted our attention.[17] In the course of their study of the Heck mechanism, they also showed that the formation of the palladium(0) complex was sensitive to electronic and steric factors of the phosphane used to generate it. Considering the same bulk environment of *para*-substituted triarylphosphanes, they reported that the more the triarylphosphane is substituted by electron-withdrawing groups, the faster the reaction is. Therefore, to ascertain the electronic properties of our new ligand compared to the TPPTS ligand, and as we were studying various Pd-catalyzed cross-coupling reactions, we decided to determine the rate constant of the formation of palladium(0) complexes. Moreover, as the ligands display the same hindrance, the measurement of the rate constant would give us additional information on the electronic properties of both ligands. The proposed mechanism for the formation of the Pd^0 complex implies a fast complexation of the ligand PAr_3 leading to $Pd(OAc)_2(PAr_3)_2$, which slowly evolves to a palladium(0) complex $[Pd(OAc)(PAr_3)]^-$ (Scheme 2). The last step consists of the formation of $[Pd(OAc)(PAr_3)_3]^-$.



Scheme 2.

Table 1. Electronic and steric parameters for the carboxylated ligand *m*-TPPTC compared to TPPTS.

Ligand	*trans*-$PdCl_2L_2$ δ ^{31}P [ppm]	θ_{Tol} [°]	Se=PAr_3 $^1J_{P\text{-}Se}$ [Hz]	*cis*-$Mo(CO)_4L_2$ ν_{CO} [cm^{-1}]
m-TPPTC	34.1	166	733	2020
TPPTS	34.3	166	757	2025

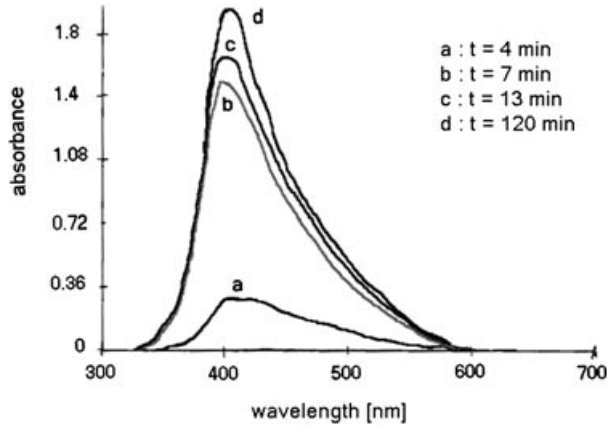


Figure 1. Absorbance data of the Pd^0 complex generated from $Pd(OAc)_2$ (3.3 mM) and 10 equivalents of *m*-TPPTC in a 1/1 NMP/ethylene glycol system at various times.

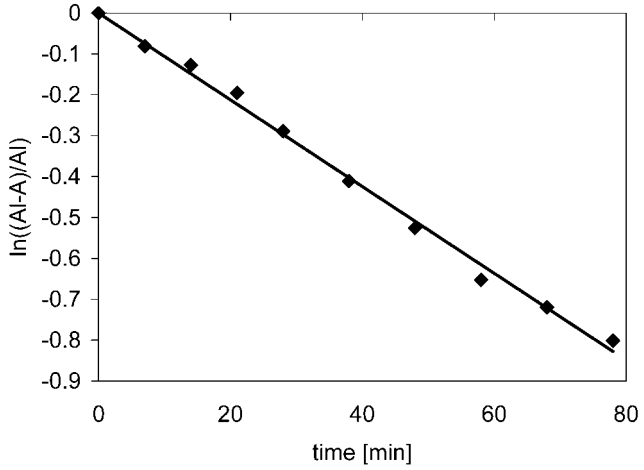


Figure 2. Kinetics of formation of the Pd^0 complex from $Pd(OAc)_2$ (3.3 mM) and 10 equivalents of *m*-TPPTC in a 1/1 NMP/ethylene glycol system: variation of ln((Al−A)/Al) as a function of time.

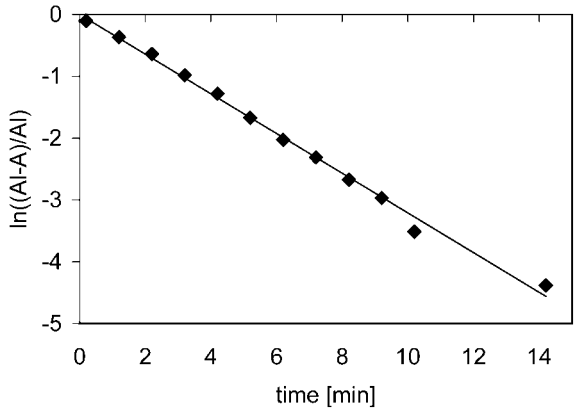


Figure 3. Kinetics of formation of the Pd^0 complex generated from $Pd(OAc)_2$ (3.3 mM) and 10 equivalents of TPPTS in a 1/1 NMP/ethylene glycol system: variation of ln((Al−A)/Al) as a function of time.

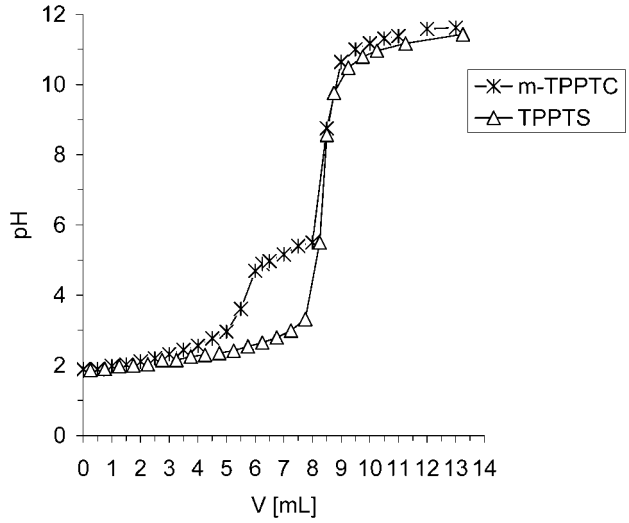


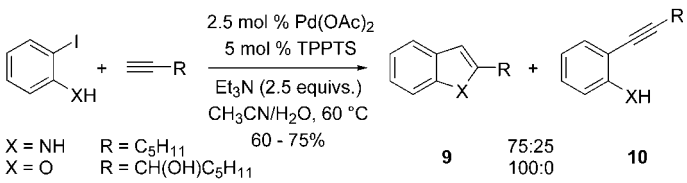
Figure 4. Potentiometric titration curves for the carboxylated *m*-TPPTC phosphane and the sulfonated TPPTS ligand.

We attempted to observe the formation of zero-valent palladium using cyclic voltammetry, but no reproducible cyclic voltammograms were obtained. The formation of the Pd^0 species was therefore observed by UV-VIS spectroscopy at room temperature. The UV absorbance of $[Pd^0(OAc)(PAr_3)_3]^-$ ($\lambda = 430$ nm) increased stepwise upon mixing $Pd(OAc)_2$ and the respective triarylphosphane *m*-TPPTC (Figure 1) or TPPTS. The rate constants were determined by plotting the variation of ln((A1 – A)/A1) as a function of time, where Al is the absorbance at infinite time and A the absorbance at time *t*. These data afforded a straight line (first-order kinetics in palladium species), the slope providing directly the rate constant of Pd^0 formation. From the experimental values, the rate constants were found to be $1.8 \cdot 10^{-4}\ s^{-1}$ for the *m*-TPPTC ligand (Figure 2) and $5.3 \cdot 10^{-3}\ s^{-1}$ for the TPPTS ligand (Figure 3).

These results show that the formation of the palladium(0) complex is favored with the sulfonated ligand compared to the carboxylated one. Consequently, as the rate-determining step can be assimilated to a reduction, the *m*-TPPTC phosphane is more electron-rich than TPPTS.

We also determined the pK_a values of the phosphanes according to the procedure described by Bartik et al.[18] Figure 4 shows the overlaid titration curves for both the TPPTS and the *m*-TPPTC ligand. The potentiometric measurements were recorded in the course of the addition of an aqueous solution of sodium hydroxide to an acidified water-solution of the *m*-TPPTC or TPPTS ligands. As already described by Bartik, the sulfonated ligand shows a unique acidity for the three sulfonated functionalities ($pK_a = 2.1$). The carboxylated phosphane displays a different behavior as buffering plateaus are

observed. The first wave corresponds to the titration of two carboxylic groups ($pK_a = 2.2$), whereas the second wave corresponds to the titration of the third more basic carboxylic group ($pK_a = 5.3$). This higher basicity may therefore influence the global basicity of the phosphane.

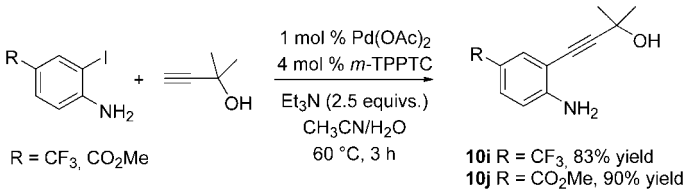


Scheme 3.

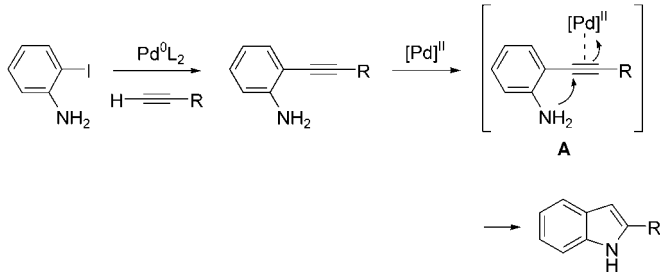
Pd-Catalyzed Sonogashira Reactions – Rh-Catalyzed Arylation of Alkynes

Having in hand a new water-soluble ligand displaying interesting electronic properties, we decided to extend its area of metal-catalyzed applications. We turned our attention to the Sonogashira coupling of aryl halides, which constitutes one of the most powerful and mild methods for the creation of C–C bonds.[19] We[20] and others[21,22] had reported that copper salts were not compulsory for such cross-coupling in the presence of the water-soluble ligand TPPTS. Functionalized 2-amino- or 2-hydroxyaryl iodides appear to be of interest to compare the selectivity between the sulfonated and the carboxylated ligands as it was reported (Scheme 3) that the cross-couplings of such substrates led either to a mixture of **9** and **10** in favor of the cyclized product **9** (X = NH) or to the benzofuran (X = O).[20b] The formation of *ortho*-functionalized alkynes, indoles and benzofurans constitutes an access to important building blocks for the synthesis of natural and biologically active compounds.[23]

We were pleased to find that the couplings were as efficient with *m*-TPPTC as with the TPPTS ligand and were able to decrease the mole fraction of palladium to 1 mol % using either triethylamine (Conditions A) or diisopropylamine (Conditions B) as exemplified in Table 2. The reaction of 2-iodoanilines with various alkynes afforded this time exclusively the linear products **10a–d**, with no traces of the cyclized indoles (entries 1–4). The isolated yields were generally good with unprotected anilines **10a**[24] and **10b** (entries 1 and 2) and quite modest with the acetyl-protected substrates **10c**[25] and **10d** (entries 3 and 4). The Sonogashira cross-coupling/intramolecular cyclization sequence was observed in the case of the oxygenated compounds, as the functionalized benzofurans **9e**[26a] and **9f**[26b] were respectively isolated in 80% and 60% yields (entries 5 and 6). This substrate dependence observation was quite surprising considering the nucleophilicity of oxygen and nitrogen.[24,27] One reasonable explanation may be that the phenol moiety is partially deprotonated under the basic reaction conditions and therefore may attack across the C–C triple bond, activated by the coordination to a Pd^{II} complex. This could be confirmed when subjecting the benzylic substrates to the same conditions (entries 7 and 8). The corresponding linear alcohols **10g**[28a] and **10h**[28b] were this time obtained in good yields (68 and 87%) and no traces of the cyclized adducts were detected.



Scheme 4.

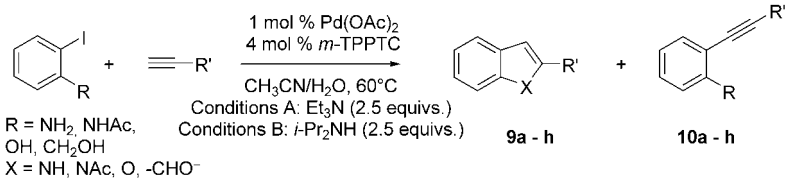


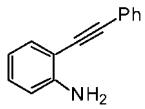
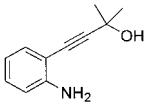
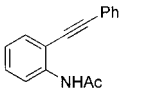
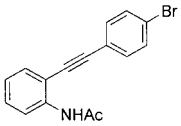
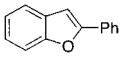
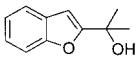
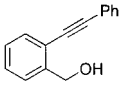
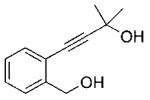
Scheme 5.

The cross-couplings were as expected highly efficient with 2-iodoanilines bearing electron-withdrawing groups. The corresponding functionalized alkynes **10i**, **10j** were isolated in 83% and 90% yields (Scheme 4).

These results on the Sonogashira cross-couplings therefore illustrate the specific selectivity generated by the use of the *m*-TPPTC ligand. Similarly to its sulfonated analogue TPPTS, no copper salts are necessary to enable the reaction. Nevertheless, a different selectivity is observed as the reaction of 2-aminoaryl iodides affords the classic linear adduct in the presence of the *m*-TPPTC phosphane, or the indole derivative in the presence of the TPPTS ligand. One plausible explanation may involve the intrinsic properties and the differences of both ligands. The well-accepted catalytic cycle for the formation of the linear derivative involves a classic oxidative addition leading to the Ar-[PdL_n]-I, then a transmetallation presumably generated *via* an alkynylpalladium intermediate and finally a reductive elimination to create the substituted alkyne.[20b] The cyclization may then occur through a first activation of the functionalized alkyne followed by a nucleophilic attack of the amino group (Scheme 5).[23,27]

Table 2. Sonogashira cross-couplings of *ortho*-substituted aryl iodides.

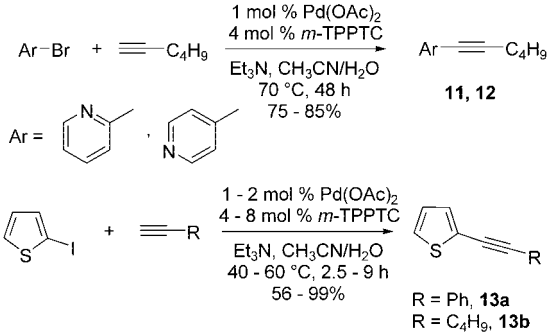


Entry	R	R′	*t* [h]	Product		Conditions	Yield [%][a]
1	NH_2	Ph	20		**10a**	B	85
2	NH_2	CMe_2OH	22		**10b**	A	80
3	NHAc	Ph	20		**10c**	B	20
4	NHAc	4-Br-C_6H_4	20		**10d**	B	22
5	OH	Ph	20		**9e**	B	81
6	OH	CMe_2OH	20		**9f**	B	60
7	CH_2OH	Ph	16		**10g**	A	87
8	CH_2OH	CMe_2OH	16		**10h**	A	68

[a] Isolated yields.

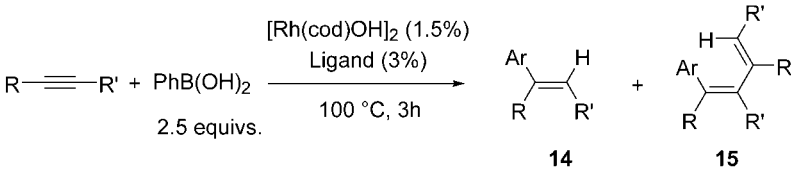
The ability of the catalytic system to perform or not the cyclization step on 2-iodoaniline may come from the reactivity of the intermediate **A**. Having shown that the *m*-TPPTC ligand is more basic than the TPPTS phosphane, the electron density transfer is higher in the case of the carboxylated ligand, which therefore disfavors the formation of indoles.

We took advantage of the high efficiency of the water-soluble ligand *m*-TPPTC and prepared other useful alkynes *via* Sonogashira cross-couplings (Scheme 6). Functionalized alkynes are important building blocks to prepare a wide variety liquid crystals, conducting polymers and other engineering materials.[29] For example, precursors of novel fluorophores had been reported recently.[30] The pyridinyl and thiophenyl derivatives were also synthesized in the same way and were evaluated for Rh-catalyzed regio- and stereoselective preparations of trisubstituted alkenes.[11] Using only 1 mol % palladium at 70 °C in acetonitrile/water mixture and without a copper co-catalyst (Scheme 6), the 2-(1-hexynyl)pyridine



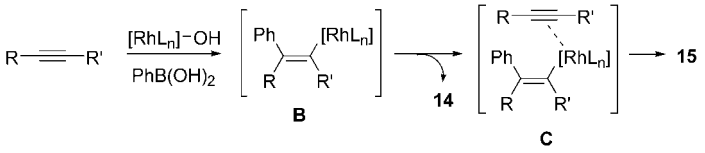
Scheme 6. Preparation of substituted alkynes.

Table 3. Rh-catalyzed arylation of alkynes with phenylboronic acid.



Entry	Ligand	R	R′	Solvent	Ratio of **14**/**15**	Yield [%][a]
1	*m*-TPPTC	C_3H_7	C_3H_7	H_2O	80/20	95
2	*m*-TPPTC	C_3H_7	C_3H_7	H_2O/toluene	98/2	90
3	TPPTS	C_3H_7	C_3H_7	H_2O	60/40	63
4	TPPTS	C_3H_7	C_3H_7	H_2O/toluene	85/15	89
5	*m*-TPPTC	Ph	Me	H_2O/toluene	96/4	95
6	TPPTS	Ph	Me	H_2O/toluene	70/30	60

[a] Isolated yields.



Scheme 7.

11[10a] and 4-(1-hexynyl)pyridine **12**[10a] were isolated in good yields (75–85%). The 2-(1-phenyl)thiophene **13a**[31] and 2-(1-hexynyl)thiophene **13b**[32] were also obtained in good to excellent yields and in shorter reaction time and temperature.

Anticipating that the differences between the *m*-TPPTC and TPPTS may be observed with other organometallic species, we compared their reactivity through the Rh-catalyzed arylation of alkynes. We recently described the Rh-catalyzed addition of boronic acids to substituted alkynes in water and in biphasic media using the *m*-TPPTC ligand,[11] which provides a convenient preparation of trisubstituted alkenes in excellent yields and purity. The addition of phenylboronic acid to oct-4-yne led to an 80/20 alkene **14** to diene **15** ratio in a very good 95% yield (entry 1, Table 3). In biphasic conditions, the reaction was found to be highly selective in favor of the alkene **14** (entry 2).

The use of the TPPTS ligand gave quite different outcomes in term of efficiency (entry 3) and selectivity (entries 3 and 4) whatever the solvent involved. The same trend was observed with 1-phenylpropyne (entries 5 and 6). The use of the carboxylated ligand afforded higher yield and selectivity toward the desired trisubstituted alkene **14**.

In the same manner as previously, one may explain the observed selectivity in view of the conceivable intermediates **B** and **C** (Scheme 7). The key intermediate **C** may be either hydrolyzed to give the alkene **14** or may complex another alkyne molecule leading after protonation to **15**. As the *m*-TPPTC ligand is more basic than the sulfonated phosphane TPPTS, the second complexation of the alkyne leading to **C** is disfavored, which brings about a better alkene/diene ratio.

Having shown a remarkable activity and selectivity of the *m*-TPPTC ligand, we further pursue our study by testing the recyclability of the [Pd]/*m*-TPPTC system.

A Recyclable Pd/*m*-TPPTC System

A major challenge in homogeneous catalysis is to permit the simple isolation of products from economical and industrial viewpoints. Recyclable catalysts constitute a good alternative to the product/catalyst separation and to the use of low mole fractions of expensive transition metals. A key advantage of a water-soluble phosphane lies in the recycling possibility of the catalyst.[1–5] Despite the widespread studies towards recyclable catalysts for the metal-catalyzed formation of C–C bonds, there are only scarce examples described in the literature for the Sonogashira reaction.[21,33] In most cases, an efficient recycling could be performed using 5 mol % catalyst, high temperature or/and long reaction time. We explored the recyclability of our $Pd(OAc)_2$/*m*-TPPTC system in the reaction of 2-iodothiophene with phenylacetylene under mild conditions at 40 °C. The acetonitrile/water medium could be easily transposed to a biphasic butyronitrile/water system. As shown in Figure 5, four cycles were performed using only 1 mol % of the catalyst system. It is noteworthy that the reaction times were short for the three cycles (2.5–5 h) and needed to be increased to three days for the fourth cycle. After completion of the reaction, the organic phase was separated, the aqueous phase was then extracted two times with butyronitrile and reloaded with substrates. The alkyne was isolated with 98–99% yield and with excellent purity (>95%).

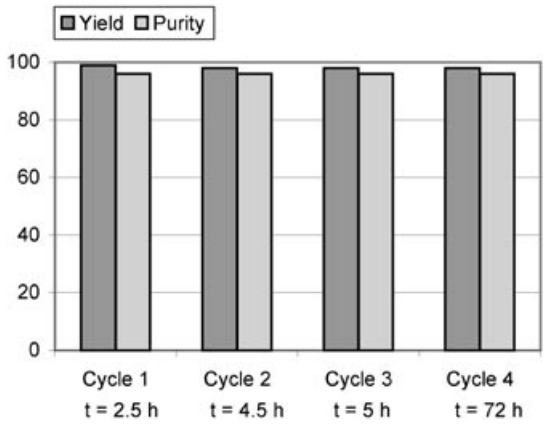


Figure 5. Recycling of the $Pd(OAc)_2$/*m*-TPPTC system in an H_2O/C_3H_7CN system.

Conclusion

The steric and electronic features of the novel water-soluble phosphane *m*-TPPTC have been determined and compared to the well-known sulfonated analogue TPPTS. We have shown through several methods including NMR, IR and UV-VIS spectroscopy, that the *m*-TPPTC phosphane is more basic than the sulfonated TPPTS ligand. Various copper-free Pd-catalyzed Sonogashira cross-couplings on aryl iodides and *ortho*-functionalized aryl iodides were efficiently performed using the carboxylated phosphane *m*-TPPTC. This phosphane induced a different selectivity compared to its sulfonated analogue, which may be explained by the difference of basicity between both ligands. Moreover, further studies in the rhodium-catalyzed arylation reactions provided similar differences in terms of selectivity and efficiency between the water-soluble ligands. We also performed highly efficient recycling of the Pd/*m*-TPPTC system under mild conditions in the Sonogashira reaction. Further applications of other metal/*m*-TPPTC systems are currently under investigation in our laboratory and will be reported in due course.

Experimental Section

General Remarks

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200, AV 250 or ARX 400 instrument. All signals are expressed as (δ) ppm downfield from Me_4Si used as an internal standard for ^1H and ^{13}C NMR. 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. Elemental analyses were performed at the University of Pierre et Marie Curie (UPMC Paris VI). Mass spectrometric analyses were performed at the Ecole Nationale Supérieure de Chimie de Paris with a Hewlett-Packard HP 5989 A. Direct introduction experiments were done by electronic impact. 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). Water, acetonitrile and butyronitrile 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. The spectral data of alkynes **10a**,[24] **10c**,[25] **9e**,[26a] **9f**,[26b] **10g**,[28a] **10h**,[28b] **11**,[10a] **12**,[10a] **13a**,[31] **13b**,[32] **14**,[11a] and **15**[11a] are identical to those published in the literature.

General Experimental Procedure for Sonogashira Reactions

PdL_2 was preformed in water (30 mL/mmol Pd) by mixing 1 mol % of palladium acetate and 4 mol % of *m*-TPPTC at 80 °C during 30 minutes. To the red-colored catalyst was added an acetonitrile (2 mL/mmol) solution of the substrate and the base (2.5 equivs.). The homogeneous mixture was stirred at 60 °C until completion of the reaction (GC), cooled to room temperature, then filtered on a short pad of florisil gel and evaporated under reduced pressure. The residue was purified by silica gel chromatography if needed.

4-(2-Aminophenyl)-2-methylbut-3-yn-2-ol (10b): ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.16 (dd, 1H, *J* = 1.8, 7.8 Hz), 7.02 (td, 1H, *J* = 1.8, 7.8 Hz), 6.60 (dd, 1H, *J* = 1.3, 7.8 Hz), 6.56 (td, 1H, *J* = 1.3, 7.8 Hz), 4.10 (brs, 2H), 2.90 (brs, 1H), 1.54 (s, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 148.1 (C_q ar.), 132.5 (CH ar.), 130.0 (CH ar.), 118.4 (CH ar.), 114.9 (CH ar.), 108.0 (C_q ar.), 100.0 (C_q), 79.0 (C_q), 66.1 (C_q), 32.1 (2 CH_3); GC (70 °C/1 min then 20 °C min^{-1} to 210 °C): RT = 9.0; mp 55 °C.

***N*-[2-(4-Bromophenylethynyl)-phenyl]acetamide (10d):** ^1H NMR (DMSO, 200 MHz): δ = 9.53 (brs, 1H), 7.77 (d, 1H, *J* = 7.8 Hz), 7.67 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 1H, *J* = 7.8 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 7.40 (t, 1H, *J* = 7.8 Hz), 7.18 (t, 1H, *J* = 7.8 Hz), 2.13 (s, 3H); ^{13}C NMR (DMSO, 100 MHz): δ = 168.8 (C_q), 139.4 (C_q ar.), 133.6 (2 CH ar.), 132.3 (CH ar.), 132.0 (2 CH ar.), 129.6 (CH ar.), 124.7 (CH ar.), 124.0 (CH ar.), 122.4 (C_q ar.), 121.9 (C_q ar.), 115.4 (C_q ar.), 93.7 (C_q), 87.4 (C_q), 23.8 (CH_3); mp 195 °C.

4-(2-Amino-5-trifluoromethylphenyl)-2-methylbut-3-yn-2-ol (10i): ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.51 (s, 1H), 7.33 (d, 1H, *J* = 8.5 Hz), 6.71 (d, 1H, *J* = 8.5 Hz), 4.51 (brs, 2H), 2.31 (brs, 1H), 1.65 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 150.1 (C_q ar.), 129.4 (CH ar.), 126.4 (CH ar.), 120.6 (C_q ar.), 118.7 (CF_3), 113.6 (CH ar.), 106.8 (C_q, C_q ar.), 100.3 (C_q), 65.7 (C_q), 31.5 (2 CH_3); GC (70 °C/1 min then 20 °C min^{-1} to 210 °C): RT = 5.2; mp 118 °C; GC/MS (EI): *m/z* = 243 $(M)^+$; anal. calcd. for $C_{12}H_{12}F_3NO$: C 59.26, H 4.97, N 5.76; found: C 60.08, H 5.06, N 5.60.

Methyl [4-Amino-3-(3-hydroxy-3-methylbut-1-ynyl)]benzoate (10j): ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.65 (s, 6H), 2.27 (brs, 1H), 3.88 (s, 3H), 4.61 (brs, 2H), 6.66 (d, 1H, *J* = 8.5 Hz), 7.79 (dd, 1H, *J* = 2, 8.5 Hz), 7.97 (d, 1H, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 166.5 (C_q), 151.4 (C_q ar.), 134.1 (CH ar.), 131.1 (CH ar.), 118.6 (C_q ar.), 113.0 (CH ar.), 106.3 (C_q ar.), 99.7 (C_q), 77.3 (C_q), 65.4 (C_q), 51.5 (CH_3), 31.3 (2 CH_3); GC (70 °C/1 min then 20 °C min^{-1} to 210 °C): RT =

8.7; mp 128 °C; GC/MS (EI): $m/z = 233$ $(M)^+$; anal. calcd. for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N, 6.00; found: C 66.36, H 6.74, N, 6.07.

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