New Synthetic Applications of Water-Soluble Acetate Pd/TPPTS Catalyst Generated *in Situ*. Evidence for a True Pd(0) Species Intermediate

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Studies on the sp–sp intermolecular coupling reactions with the palladium water-soluble catalyst prepared *in situ* from palladium(II) acetate and sulfonated triphenylphosphine $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (TPPTS) in a homogeneous acetonitrile–water system, without Cu(I) promotor, afford diynes with moderate yields (45–65%). Under the same conditions, the sp^2–sp coupling of 2-iodophenols or 2-iodoanilines and terminal alkynes followed by intramolecular cyclization gives indolic and furanic products in good yields (60–99%). Under these aqueous conditions, an efficient and short synthesis of eutypine illustrated the synthetic potentiality of the coupling. Furthermore, through a series of kinetic and ^{31}P NMR experiments, we have demonstrated that a mixture of $Pd(OAc)_2$ and TPPTS affords spontaneously a palladium(0) complex, through formation of bivalent complex $Pd(OAc)_2(TPPTS)_2$. A detailed mechanism of the reaction has been investigated thoroughly and the pertinent rate constants measured. The resulting palladium(0) complex reacts with phenyl iodide via an oxidative addition. This complex is considerably less reactive than the corresponding complex generated from PPh_3, probably due to steric effects.

Introduction

Rapid developments in the field of catalysis are leading to an increased demand for new catalysts. However, one of the greatest drawbacks of homogeneous metal catalysts is the separation of the organic product from the active catalyst, which is sometimes toxic and costly. A solution to this problem consists of anchoring the catalyst on an organic or inorganic polymer[1] insoluble in the media. Another solution consists in using water-soluble catalysts which are poorly soluble in organic media. These water-soluble complex catalysts combine the advantadges of homogenous and heterogeneous catalysis: simple and complete separation of the product from the catalyst, high reactivity, and high selectivity. Following the introduction to industry of the valuable Ruhrchemie/Rhône-Poulenc process[2] in 1984, sulfonated phosphines at present constitute the most widely used class of ligands in water-soluble metal complexes, especially in catalysis, *e.g.* TPPMS[3] and TPPTS.[4]

The industrial applications in the field of hydrogenation[5] and hydroformylation[6] have already indicated the wide scope of this type of catalysts. So the annual production of 300 000 tons of butyraldehyde by using Rh(COD)Cl/TPPTS catalyst has demonstrated the industrial importance of the concept.

The reduction of saturated and unsaturated aldehydes catalyzed by metal–sulfonated phosphine complexes (Rh or Ru)[7] was another valuable application. Coupling reactions have been achieved in such biphasic systems with rhodium catalysts including telomerization of dienes[8] and isoprenylation of CH-acidic compounds.[9] An efficient synthesis of isofeprazone has also been described.

Until recently, palladium-catalyzed alkylations in aqueous solvents with water-soluble catalysts were largely unexplored. Recently it has been shown that the $Pd(OAc)_2$ catalyzed coupling of aryl iodides with acrylic acid in aqueous media[10] and the $Pd(PPh_2\text{-}m\text{-}C_6H_4SO_3M)$ complex catalyzed the cross-coupling reactions of aryl vinyl boronic acids or terminal acetylenes with aryl halides.[11] In the same way, the allylic nucleophilic substitution was catalyzed by palladium complexes associated with sulfonated phosphines in a two-phase system.[12] In our continuing interest in the area of palladium chemistry,[13,14] we have shown that the palladium water-soluble catalyst prepared *in situ* from palladium(II) acetate and TPPTS in homogeneous acetonitrile–water is a practical system for the cross-coupling reaction,[15] nucleophilic substitution,[16] and removal of an (allyloxy)carbonyl group

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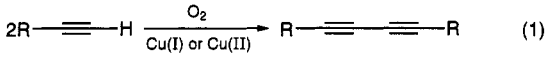
from oxygen and nitrogen.[17] In this paper, we present some new synthetic applications of this water-soluble catalyst, especially in the sp−sp coupling reactions without Cu(I) promoter and in the sp^2−sp-type coupling followed by intramolecular cyclization. Moreover we report some evidence for a true Pd zero-valent valent species intermediate formed from $Pd(OAc)_2$/TPPTS in acetonitrile/water as the active catalyst.

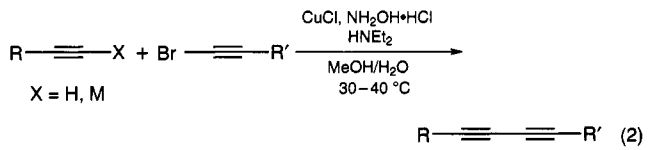
Results and Discussions

sp−sp Coupling Reactions Using Water-Soluble Palladium Catalyst. The preparation of symmetrical butadiyne molecules by an sp−sp-type coupling reaction has been known for some time[18] (eq 1).



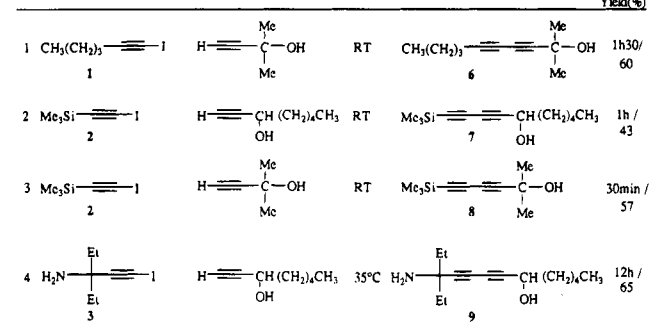
This methodology for carbon−carbon bond creation was largely studied by Glaser[19] and Eglington,[20] who demonstrated that it necessitated the use of stoichiometric or catalytic quantities of copper(I or II) species. More recently, in 1985, Rossi and Carpita[21] reported a new method for this type of homocoupling reactions using zero-valent palladium catalyst in association with copper iodide, in the presence of chloroacetone and triethylamine. Under this procedure symmetrical diynes were prepared in quasiquantitative yields, and the mild conditions constitute an important improvement as compared with the precedent-setting research of Glaser. Nevertheless, a serious limitation appears to be the fact that only symmetrical compounds can be prepared under these conditions.

In the 1950's, Cadiot and Chodkiewicz[22] proposed the synthesis of unsymmetrical butadiynes by an sp−sp coupling reaction between acetylenic bromides and terminal alkynes or alkynyl cuprates (eq 2); the reaction was performed in organoaqueous medium, in the presence of diethylamine and catalytic amounts of copper chloride and hydroxylamine chlorohydrate, to produce the coupling products with good yields ranging from 50 to 90%.



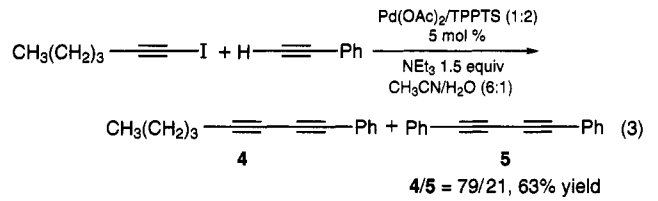
To our knowledge, very few methods for the synthesis of unsymmetrical diynes using organopalladium catalysts have been described.[23] We report herein the sp−sp heterocoupling reaction of terminal alkynes with alkynyl iodides in aqueous medium, using the water-soluble catalyst formed *in situ* from $Pd(OAc)_2$ and the water-soluble ligand TPPTS, without any copper(I) promotor.

Table 1. sp-sp Heterocoupling Reactions Using Water-Soluble $Pd(OAc)_2$/TPPTS Catalyst[a]



[a] Conditions: NEt_3 2.5 equiv CH_3CN/H_2O (6/1).

When 1-iodohex-1-yne[24a] was allowed to react with phenylacetylene (1.5 equiv) in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of TPPTS, and triethylamine (2.5 equiv), in an acetonitrile/water (6:1) medium (eq 3), 1-phenylocta-1,3-diyne (**4**) was formed as the major product in 49% yield; the competitive homocoupling reaction of phenylacetylene resulted in the formation of 1,4-diphenylbuta-1,4-diyne in 14% yield.



This first example shows the possibility of preparing unsymmetrical butadiyne compounds using the water-soluble $Pd(OAc)_2$/TPPTS catalyst under very mild conditions. This reaction was further investigated with other terminal alkynes and various alkynyl iodides which are easily prepared[25] from the corresponding alkynes upon reaction with *N*-iodosuccinimide, in the presence of catalytic $AgNO_3$ (see general procedure for the synthesis of alkynyl iodides). Our results are summarized in Table 1.

First, phenylacetylene was replaced by 3-methylbut-1-yn-3-ol (entry 1); at room temperature, only the sp−sp heterocoupling reaction on 1-iodobut-1-yne took place and 1-(trimethylsilyl)-5-methylhexa-1,3-diyn-5-ol (**6**) was iso-

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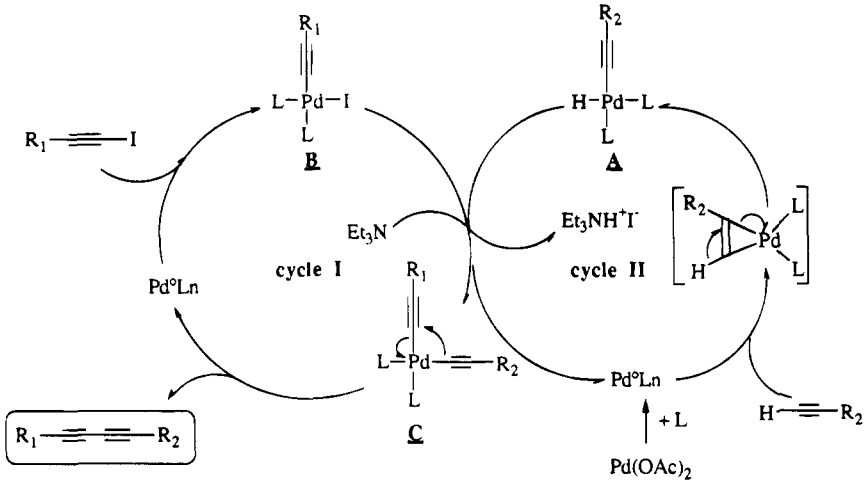
Scheme 1. Proposed Mechanism for sp–sp Coupling Reaction in the Presence of $Pd(OAc)_2$/TPPTS Catalyst



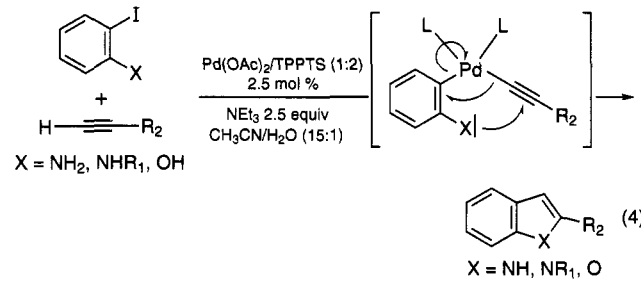
lated in 60% yield. The same procedure was also performed with 1-iodo-2-(trimethylsilyl)acetylene,[24b] which was coupled with but-1-yn-3-ol (entry 2) and 3-methylbut-1-yn-3-ol (entry 3) in the presence of 5% Pd(0) catalyst to give the corresponding butadiyne compounds **7** and **8** with 43 and 57% yield, respectively. It is noteworthy that, in these cases, no homocoupling reaction was observed, suggesting that this side reaction is limitated to phenylacetylene. It was also possible to synthesize another difunctionalized butadiyne molecule (**9**) starting from 1,1-diethyl-3-iodoprop-2-ynylamine (entry 4) under the above conditions. The moderate yields of these sp–sp coupling reactions are basically due to the instability of the resulting diyne substrates which easily decompose during purification by chromatography.

The proposed mechanism for this heterocoupling reaction involves two linked catalytic cycles (Scheme 1). On the one hand (cycle II), oxidative addition of Pd(0) on the terminal alkyne affords the hydridoalkynylpalladate complex A by insertion of palladium in the carbon–hydrogen bond.[26] On the other hand (cycle I), the Pd(0) intermediate attacks the alkynyl iodide through oxidative addition, leading to the iodoalkynylpalladate complex B which can react with A under the effect of triethylamine. The resulting dialkynyl palladate species C decomposes through reductive elimination to give the butadiyne derivative with regeneration of the zero-valent palladium catalyst.

In this way the water-soluble catalyst formed *in situ* from $Pd(OAc)_2$ and TPPTS allowed sp–sp heterocoupling reactions between various alkynyl derivatives without any copper(I) promotor; the conditions are very mild and the resulting unsymmetrical diynes can bear different functions on the carbon skeleton (primary amine, secondary and tertiary alcohols). Furthermore, compounds **7** and **8** may be desilylated to give powerful nucleophilic reagents that can be used in organic synthesis. These diyne molecules can also be very useful for the preparation of new materials possessing interesting physical properties (photoconductivity, optical nonlinear susceptibility).[27]

sp^2–sp Coupling/Intramolecular Cyclization Reactions Using Water-Soluble Palladium Catalyst. The efficient water-soluble catalyst $Pd(OAc)_2$/TPPTS was also largely developed in sp^2–sp coupling reactions in aqueous medium.[15] We report herein, in particular, the synthesis of indolic and furanic derivatives by sp^2–sp-type coupling followed by intramolecular cyclization of the organopalladate intermediate. The synthesis of indoles and furans via this two-step sp^2–sp coupling/intramolecular cyclization sequence has been studied for a long time, and at the beginning, strong conditions were used in the presence of copper(I) species.[28] Recent developments in this type of reaction are directed toward the use of palladium catalysts under anhydrous conditions; generally, high temperatures and a phase transfer agent are required to give the cyclized products in moderate to good yields.[29]

In this paper, we report this sequential two-step reaction in aqueous medium, starting from 2-iodoaniline or 2-iodophenol in the presence of 2.5 mol % $Pd(OAc)_2$, 5 mol % TPPTS, triethylamine (2.5 equiv), and again without any copper(I) promotor (eq 4).



Our results are summarized in Table 2. When 2-iodoaniline was allowed to react with hex-1-yne (1.5 equiv)

(26) Such hydridoalkynylpalladate intermediates have already been postulated in the formation of vinylidene metal complexes and in the metal-mediated synthesis of enynes. See: Sebald, A.; Stader, C.; Wrackmeyer, B.; Bensch, W. *J. Organomet. Chem.* **1986**, *311*, 233. Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahaschi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1977**, 291. Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486–3487.

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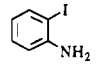
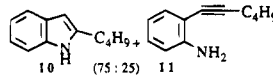
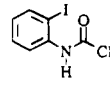
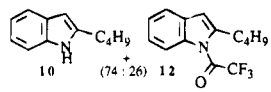
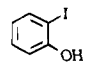
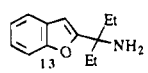
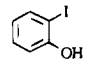
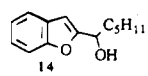
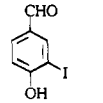
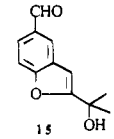
Table 2. sp^2–sp Cross-Coupling/Intramolecular Cyclization Sequence Using $Pd(OAc)_2$/TPPTS Catalyst[a]

Entry	Substrates	Temp. (°C)	Products	Yields (%)
1		65	 10 (75:25) 11	75
2		RT	 10 (74:26) 12	70
3		RT	 13	57
4		RT	 14	60
5		RT	 15	99

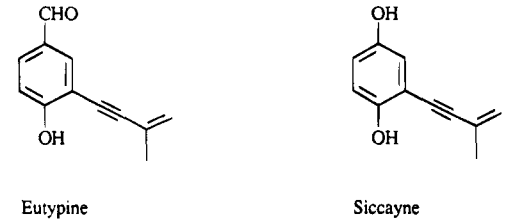
[a] Conditions: $Pd(OAc)_2$/TPPTS (1/2) 2.5 mol %; CH_3CN/H_2O (15/1); NEt_3 2.5 equiv; 72 h.

under the previously described conditions at 60 °C, 2-butylindole (**10**)[30] was obtained in 56% yield (entry 1). 1-(2-Aminophenyl)hex-1-yne (**11**)[31] resulting from the simple sp^2–sp coupling reaction was also isolated in 19% yield, suggesting that the organopalladate intermediate was not reactive enough to undergo complete cyclization. To activate this intermediate, we thought to introduce a trifluoroacetyl group on the amino function. Thus, *N*-(trifluoroacetyl)-2-iodoaniline was treated under the above conditions and proved to be more reactive since, at 25 °C, the reaction led to a mixture of 2-butylindole and its N-trifluoroacetylated analog **12** in a 74:26 ratio, with 70% overall yield (entry 2). In this case the product of simple sp^2–sp coupling was not observed and the complete sequence sp^2–sp coupling/intramolecular cyclization, accompanied by partial spontaneous cleavage of the trifluoroacetyl moiety under these conditions, was achieved within 72 h.

The same strategy was applied to the preparation of furanic compounds. 1,1-Diethylpropargylamine (entry 3) or oct-1-yn-3-ol (entry 4) first reacted with 2-iodophenol in the presence of 2.5% $Pd(OAc)_2$/TPPTS catalyst and triethylamine to form the sp^2–sp carbon–carbon bond; the resulting molecules readily underwent *in situ* cyclization by capture of the organopalladate complex by the phenol moiety to produce 2-(1-amino-1-ethylpropyl)-benzofuran (**13**) and 1-(2-benzofuryl)hexan-1-ol (**14**)[32] in 57 and 60% yields, respectively. Finally, this methodology was used with 3-iodo-4-hydroxybenzaldehyde which, upon reaction with 3-methylbut-1-yn-3-ol under the above conditions, led to the formation of the difunctionalized benzofurane derivative **15**[33] in quantitative yield (entry 5).

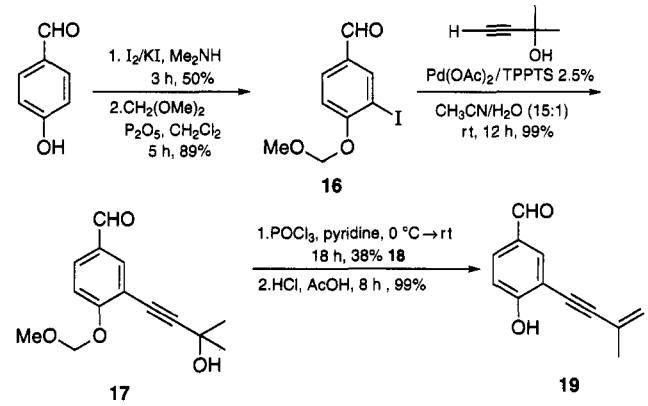
In summary, it was possible to prepare indolic and furanic substrates through one-pot sp^2–sp coupling/intramolecular cyclization, under very mild conditions (rt to 65 °C), using water-soluble $Pd(OAc)_2$/TPPTS catalyst

Scheme 2



Eutypine Siccayne

Scheme 3. Synthesis of Eutypine



without any copper(I) promotor. The resulting bicyclic molecules are obtained in moderate to excellent yields ranging from 56 to 99%, and the method is very easy to handle since the catalyst and the base are eliminated by simple water treatment affording, after extraction, very clean crude products.

Synthetic Application of sp^2–sp Coupling Reaction: a Short Synthesis of Eutypine. We reasoned that it would be possible to utilize the Pd cross-coupling reaction developed as the key step in the synthesis of eutypine (**19**, 4-hydroxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde),[34] which is an antibacterial substance isolated from the culture medium of *Eutypa lata*[35] (Scheme 2). The fungus *E. lata* attacks several woody species, and it is responsible, in particular, for a vineyard disease known as eutypiosis which damaged many wine-growings in France during the past decade.

A precursor of the 3-methylbut-3-en-1-ynyl substituent present on the aromatic cycle of eutypine could be introduced by palladium-catalyzed sp^2–sp coupling on 3-iodo-4-hydroxybenzaldehyde. As shown previously, the proximity of the iodo and hydroxy groups leads to cyclization of the coupling intermediate (Table 2, entry 5), and no product resulting from direct coupling can be obtained. This problem was encountered in our previous synthesis of siccayne,[36] a metabolite having a structure similar to that of eutypine with the 3-methylbut-3-en-1-ynyl group next to the phenolic function (Scheme 2). To prevent cyclization, the strategy involved protection of the alcohol prior to sp^2–sp coupling.

An analogous synthetic pathway was thus adopted for the preparation of eutypine (Scheme 3); the methoxymethyl group was introduced on the phenol to give the protected intermediate **16** in 89% yield, which was then allowed to react with 3-methylbut-1-yn-3-ol under the

(30) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.
(31) (a) Kondo, Y.; Sakamoto, T.; Yamanaka, H. *Heterocycles* **1989**, *29*, 1013. (b) Clemence, F.; Fortin, M.; Haesslein, L. Roussel-Uclaf EP 498723 A1 920812, 1992.
(32) Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, 749.
(33) Donnelly, D. M.; Fukuda, N.; Kuono, I.; Martin, M.; O'Reilly, J. *Phytochemistry* **1988**, *27*, 2709.
(34) Defranq, E.; Zesiger, T.; Tabacchi, R. *Helv. Chim. Acta* **1993**, *76*, 425.
(35) Renaud, J. M.; Tsoupras, G.; Stoeckli-Evans, H.; Tabacchi, R. *Helv. Chim. Acta* **1989**, *72*, 1262–1267.
(36) Pinault, M.; Frangin, Y.; Genêt, J. P.; Zamarlik, H. *Synthesis* **1990**, 935–936.

catalytic conditions described above. The reaction resulted in the expected coupling product 3-(3-hydroxy-3-methylbutynyl)-4-(methoxymethoxy)benzaldehyde (**17**) in quantitative yield, within 12 h. This key step was followed by dehydratation using $POCl_3$ to produce 4-(methoxymethoxy)-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (**18**) in nonoptimized 38% yield; this poor result ensued from the difficulty to isolate the product from the reaction mixture. The final step of the synthesis involved subsequent deprotection of the aromatic alcohol under acidic conditions to give eutypine **19** in 99% yield.

In conclusion, a short and efficient five-step synthesis of eutypine was performed using sp^2-sp coupling methodology in aqueous medium as the key step of the sequence. Here, the water-soluble catalyst $Pd(OAc)_2$/TPPTS (1:2) allows the reaction to occur under milder conditions, with excellent yields.

However, in all the reactions described above, a bivalent palladium complex cannot be the true catalyst since only zero-valent palladium complexes are able to activate aryl and alkynyl halides. We[14] have reported that mixtures of $Pd(OAc)_2$ and triphenylphosphine in either DMF or THF spontaneously afford palladium(0) complexes able to activate aryl halides whereas the phosphine is oxidized to triphenylphosphine oxide. The reduction of the bivalent palladium was shown to proceed via an inner sphere mechanism within the complex $Pd(OAc)_2(PPh_3)_2$ (instantaneously formed upon mixing), and this reaction was the rate determining step of the overall process.[14b] Owing to the change of medium, *viz.* the presence of water, when water-soluble phosphines such as TPPTS are used, we decided to investigate the origin of the palladium(0) formed from the mixtures of $Pd(OAc)_2$ and TPPTS.[37]

Evidence of the Formation of Zero-Valent Palladium from $Pd(OAc)_2$ and TPPTS. 1. Investigation of the Mixture $Pd(OAc)_2$ + 4TPPTS. A mixture of $Pd(OAc)_2$ (2 mM) and 4 equiv of TPPTS (0.6 M in water) in a mixed solvent (11 mL of acetonitrile and 1 mL of water) containing n-Bu_4NBF_4 (0.3 M) led to a yellow cloudy biphasic solution from which it was not possible to get reproducible voltammograms. To obtain a clear solution, it was necessary to add an ammonium salt such as n-Hex_4NBF_4 (20 mM) as a surfactant. Reproducible cyclic voltammograms were obtained under these conditions, but we always observed formation of a cloudy solution within a few minutes after mixing. The resulting mixture contained a bivalent palladium complex that was detected and characterized by its irreversible reduction peak at $E^p_{red} = -0.835$ V *vs* SCE.

Under the same experimental conditions, the ligand TPPTS (8 mM) alone in the same solvent was oxidized at $E^p_{ox} = +0.895$ V. Introduction of $Pd(OAc)_2$ (2 mM) resulted in a decrease by a factor of 2 of the oxidation peak of the ligand, evidencing that a fast reaction occurred between $Pd(OAc)_2$ and two ligands to form a bivalent palladium complex, presumably $Pd(OAc)_2(TPPTS)_2$, detected by its reduction peak:

$$Pd(OAc)_2 + 2TPPTS \xrightarrow{fast} Pd(OAc)_2(TPPTS)_2 \quad (5)$$

Figure 1a shows that the bivalent complex $Pd(OAc)_2(TPPTS)_2$ resulting from the mixture of $Pd(OAc)_2$ and 4TPPTS was not stable since its reduction peak current decreased as a function of time. At the same time, when the cyclic voltammogram was first performed toward positive potentials, an irreversible oxidation peak was detected at $E^p_{ox} = +0.355$ V with a current increasing as a function of time (Figure 1b).

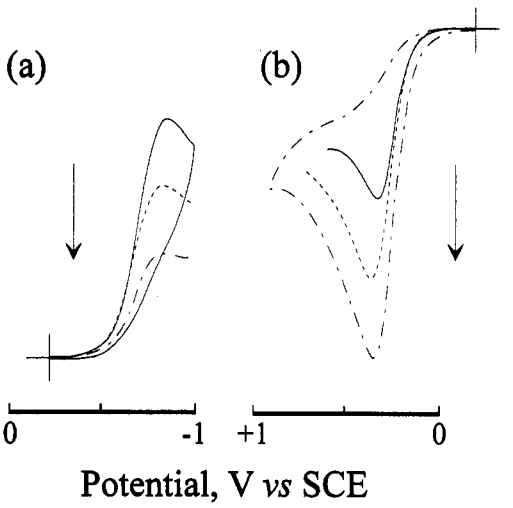


Figure 1. (a) Cyclic voltammetry of $Pd(OAc)_2(TPPTS)_2$ generated from $Pd(OAc)_2$ (2 mM) and TPPTS (8 mM) in a mixed solvent (11 mL of acetonitrile and 1 mL of water) containing n-Bu_4NBF_4 (0.3 M) and n-Hex_4NBF_4 (20 mM) at a stationary gold disk electrode (i.d. = 0.5 mm) with a scan rate of 0.2 V s^{-1}. The cathodic scan, from −0.2 to −1.0 V, has been performed as a function of time: (—) 4, (- - -), 8, (- • -) 20 min. (b) Cyclic voltammetry of the palladium(0) complex generated in situ from $Pd(OAc)_2$ (2 mM) and TPPTS (8 mM) at the same electrode with the same scan rate. The anodic scan, from −0.2 to +1 V, has been performed as a function of time: (—) 3, (- - -) 7.5, (- • -) 21 min. Only forward scans are shown for 3 and 7.5 min for simplification.

In the presence of phenyl iodide (10 equiv) the oxidation peak was no longer detected, proving that the complex detected by its oxidation peak was a zero-valent palladium complex able to react with phenyl iodide. Although an authentic sample of $Pd(OAc)_2(TPPTS)_2$ has not been availaible until recently, we may conclude by analogy with our previous investigations with triphenylphosphine[14a] that the mixture of $Pd(OAc)_2$ and 4TPPTS first affords rapidly the bivalent complex $Pd(OAc)_2(TPPTS)_2$ which spontaneously and slowly evolves to form a zero-valent palladium complex.

$$Pd(OAc)_2(TPPTS)_2 \xrightarrow{slow} \text{“Pd(0)(TPPTS)}_n\text{”} + \text{products} \quad (6)$$

To confirm these results, ^{31}P NMR spectroscopy was performed on a solution of $Pd(OAc)_2$ (0.013 mM) with 4 equiv of TPPTS in a mixture of 3 mL of acetonitrile and 1 mL of deuterated water. Ten minutes after mixing, the ^{31}P NMR spectrum exhibited four signals. A sharp signal at $\delta_1 = -4.84$ ppm was that of the free ligand TPPTS as shown by comparison with an authentic sample. A second sharp signal was observed at $\delta_2 = +31.64$ ppm and assigned to that of the TPPTS oxide (noted O=TPPTS).[38] A major broad signal ($\Delta H = 140$ Hz) was observed at $\delta_3 = +29.71$ ppm together with an even broader signal ($\Delta H = 320$ Hz) at $\delta_4 = +2.25$ ppm.

(37) (a) The formation of a palladium(0) complex from a mixture of $Pd(OAc)_2$ and 12.5 equiv of TPPTS in water has been observed very recently by ^{31}P NMR spectroscopy. See (b) Monteil, F.; Kalck, P. *J. Organomet. Chem.* **1994**, *482*, 45.

(38) Since an authentic sample of O=TPPTS was not available, its ^{31}P NMR signal was detected in an NMR tube containing an authentic sample of pure TPPTS submitted to a vigorous oxygen bubbling.

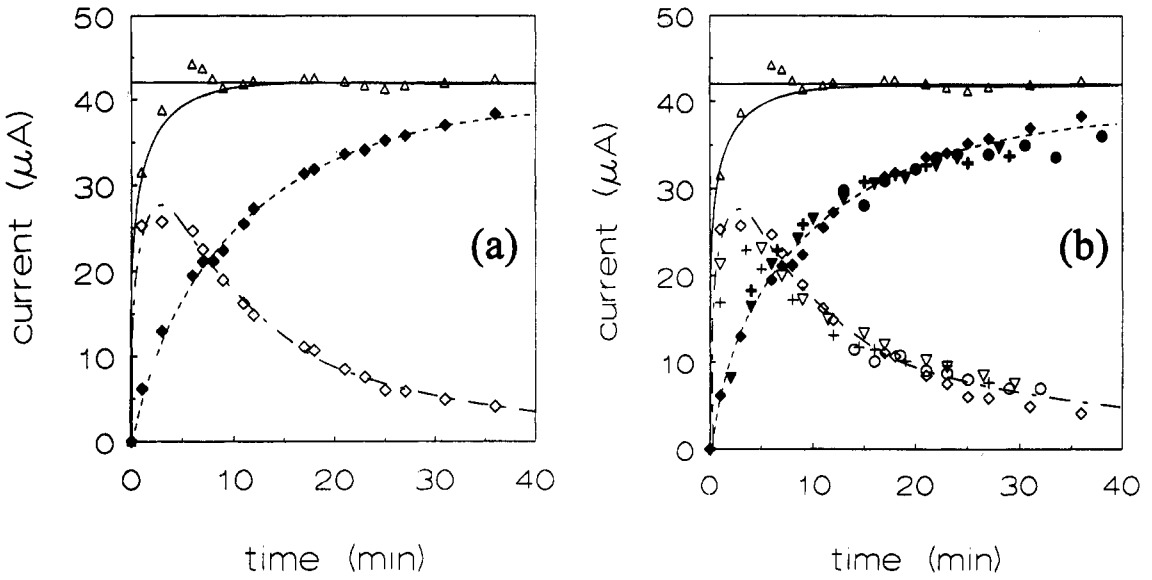


Figure 2. Variation of the peak currents at a stationary gold disk electrode (i.d. = 0.5 mm; $\nu = 0.2$ V s^{-1}) of the system Pd(OAc)2 and TPPTS as a function of time in a mixed solvent (11 mL of acetonitrile and 1 mL of water) containing *n*-Bu_4NBF_4 (0.3 M) and *n*-Hex_4NBF_4 (20 mM) at 20 °C. (a) Variation of the reduction current at a potential of −0.83 V of the divalent palladium complex formed in situ from the mixture $Pd(OAc)_2$ (2 mM) and TPPTS (20 mM) (◇). Variation of the oxidation current at a potential of +0.35 V of the zero-valent palladium generated from the mixture $Pd(OAc)_2$ (2 mM) and TPPTS (20 mM) (♦). Sum of the experimental reduction and oxidation currents (△). (b) Variation of the reduction current at a potential of −0.83 V of the divalent palladium complex formed in situ from the mixture $Pd(OAc)_2$ (2 mM) and TPPTS (20 mM) (◇); TPPTS (14 mM) (▽); TPPTS (14 mM) (+); TPPTS (8 mM) (○). Variation of the oxidation current at a potential of +0.35 V of the zero-valent palladium generated from the mixture $Pd(OAc)_2$ (2 mM) and TPPTS (20 mM) (♦); TPPTS (14 mM) (▽); TPPTS (14 mM) (+); TPPTS (8 mM) (●).

When ^{31}P NMR spectroscopy was performed as a function of time, we observed that the characteristic peak of the free ligand continuously decreased whereas that of the oxide O=TPPTS increased. By that time, the signal at δ_3 slowly decreased until complete disappearance whereas the broad signal at δ_4 increased, became sharper, and shifted to lower field (ΔH =220 Hz and δ_4 = +13.53 ppm after complete reaction). The latter signal disappeared in the presence of phenyl iodide and is thus characteristic of a zero-valent palladium complex. The signal at δ_3 which disappeared concomitantly with the formation of the palladium(0) complex can be reasonably assigned to that of the bivalent complex $Pd(OAc)_2(TPPTS)_2$. When the palladium(0) complex was generated *in situ* from $Pd(OAc)_2$ and PPh_3, we also observed that the signal of the palladium(0) shifted to lower field and sharpened as a function of time.[14a] We demonstrated that this behavior was typical of that of a palladium(0) complex in fast equilibrium with a less ligated one and the ligand, the concentration of which becomes lower during the continuous formation of the palladium(0) complex.[39a]

$$Pd(0)L_3 \rightleftharpoons Pd(0)L_2 + L \qquad (7)$$

So in the case of the ligand TPPTS, ^{31}P NMR spectroscopy showed a behavior similar to that already reported for PPh_3:[14a] mixtures of $Pd(OAc)_2$ and TPPTS result first in the rapid formation of the complex $Pd(OAc)_2(TPPTS)_2$ which slowly affords a palladium(0) complex whereas the ligand TPPTS is oxidized to TPPTS oxide.[39b]

Whereas in the case of PPh_3 the free ligand could never be detected because of its involvement in the fast equilibrium (7),[14a] in the case of TPPTS, some free ligand was always observed in the ^{31}P NMR spectra (signal at δ_1). Since the investigated solutions remained biphasic, we certainly observed two kinds of ligand TPPTS. One is located in the phase containing the palladium(0) complex and involved in the fast equilibrium (7) and therefore detected together with the palladium(0) at δ_4 while the other one is alone in the second phase and so is observable as the free ligand at δ_1.

2. Kinetic Data on the Formation of Zero-Valent Palladium from $Pd(OAc)_2$ + *n*TPPTS (*n* > 2). Since the oxidation peak current of the palladium(0) complex increased as a function of time at the expense of the reduction peak current of $Pd(OAc)_2(TPPTS)_2$, kinetic investigation of this system could be achieved using cyclic voltammetry performed at a stationary disk electrode as a function of time. This can be performed by monitoring the two complexes either in reduction (Pd(II)) or in oxidation (Pd(0)). Due to the expected instability of palladium(0) complexes generated from the mixture $Pd(OAc)_2$ and 2TPPTS, kinetic investigations were achieved in the presence of excess TPPTS ($n \geq 4$) to get a stable complex ligated by at least three ligands.[40]

Plotting the variation of the oxidation current at E^p_{ox} = +0.355 V and that of the reduction current at E^p_{red} = −0.835 V as a function of time affords the kinetics of formation of the palladium(0) together with that of disappearance of the palladium(II) complex (Figure 2a).

Whereas the formation of the palladium(0) complex is represented by a smoothly increasing curve evidencing that the palladium(0) complex is continuously formed with time, the curve representing the variation of the palladium(II) complex concentration exhibits a maximum at short times (at $t < t_{1/2}$ = 8 min). At short times, the

(39) (a) It has been observed that in water the broad ^{31}P NMR signal of an authentic sample of $Pd(TPPTS)_3$ was shifted toward high field in the presence of added TPPTS.[37b] (b) In the ^{31}P NMR investigation of the mixture $Pd(OAc)_2$ and 12.5 equiv of TPPTS in water, the authors observed only two signals, one for $Pd(TPPTS)_3$ and the other one for O=TPPTS.[37b]

(40) The complex $Pd(TPPTS)_3$ has been synthesized by exchange of phosphine from $Pd(PPh_3)_4$. See: Hermann, W. A.; Kellner, J.; Riepel, H. *J. Organomet. Chem.* **1990**, *389*, 103.

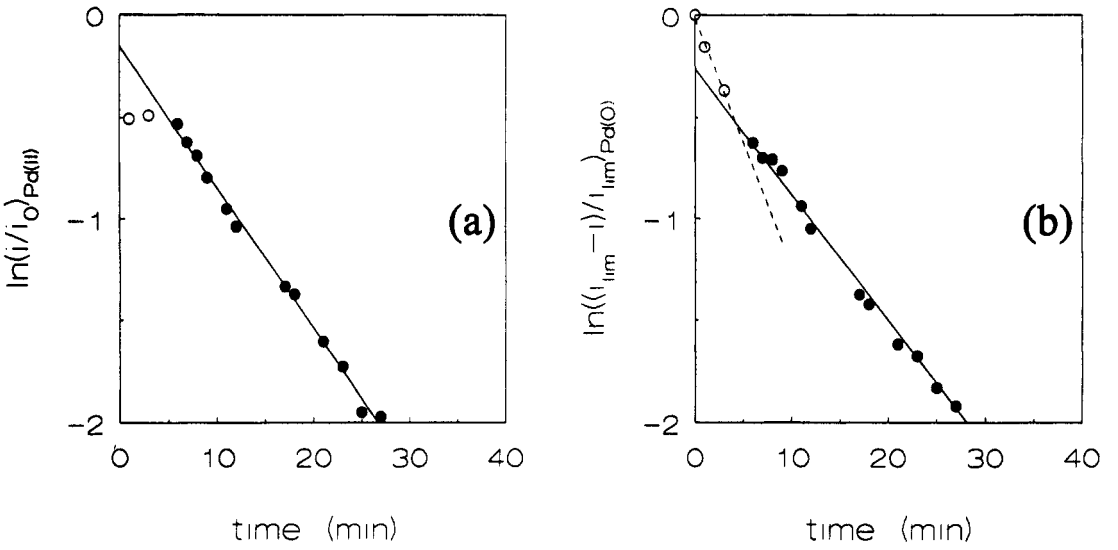


Figure 3. Kinetics of the disappearance of the palladium(II) complex and of the formation of the palladium(0) complex from the mixture $Pd(OAc)_2$ (2 mM) and TPPTS (20 mM) in a mixed solvent (11 mL of acetonitrile and 1 mL of water) containing *n*-Bu_4NBF_4 (0.3 M) and *n*-Hex_4NBF_4 (20 mM) at 20 °C. (a) Variation of the reduction current of the palladium(II) complex, $\ln(i/i_0)$ as a function of time. (b) Variation of the oxidation current of the palladium(0) complex, $\ln((i_{lim} - i)/i_{lim})$ as a function of time.

sum of the oxidation and reduction currents is not constant and is less than that obtained at long times. This phenomenon proves that a fraction of palladium is not electroactive at initial times.

The rate of disappearance of the complex $Pd(OAc)_2(TPPTS)_2$, represented by the plot of the variation of $\ln(i/i_0)_{Pd(II)}$ (i, reduction current at −0.835 V at t; i_0 at t = 0) as a function of time, follows a kinetic law first order in palladium(II) at long times (t > 6 min) yet with a non-zero intercept. The corresponding rate constant was determined: $k_{Pd(II)} = 1.1 \times 10^{-3}$ s^{-1} at 20 °C (Figure 3a).

The rate of formation of the palladium(0) complex represented by the plot of the variation of $\ln((i_{lim} - i)/i_{lim})_{Pd(0)}$ (i, oxidation current at +0.355 V at t; i_{lim}, limit of i at infinite time) as a function of time follows a kinetic law first order in palladium(0) at long times (t > 6 min) also with a non-zero intercept. The rate constant was determined: $k_{Pd(0)} = 1.0 \times 10^{-3}$ s^{-1} at 20 °C (Figure 3b). The fact that the values of $k_{Pd(II)}$ and $k_{Pd(0)}$ are identical within the accuracy of their determination evidences that at long time the rate of disappearance of the palladium-(II) complex and that of formation of the palladium(0) are the same. This stresses that no intermediate complex accumulates during the reaction. It is noteworthy that at short times (t < 6 min) the rate of formation of the palladium(0) complex is higher than that at long times (Figure 3b).

From the curves presented in Figure 2b, one observes that the rate of formation of the palladium(0) is not affected by the TPPTS concentration, demonstrating that this reaction is zero order in TPPTS. All these results indicate that the palladium(0) complex is spontaneously produced from the bivalent complex $Pd(OAc)_2(TPPTS)_2$ by an intramolecular reaction which is the rate determining step of the overall process, as was observed in the case of triphenylphosphine.[14b] In the case of PPh_3, this rate constant was found to be 1.9×10^{-4} s^{-1} in DMF at 20 °C.[14b] Thus the rate of formation of the palladium-(0) complex from the mixture $Pd(OAc)_2$ + *n*TPPTS (k = 1.0×10^{-3} s^{-1}) is about five times higher than that from the mixture $Pd(OAc)_2$ + *n*PPh_3.

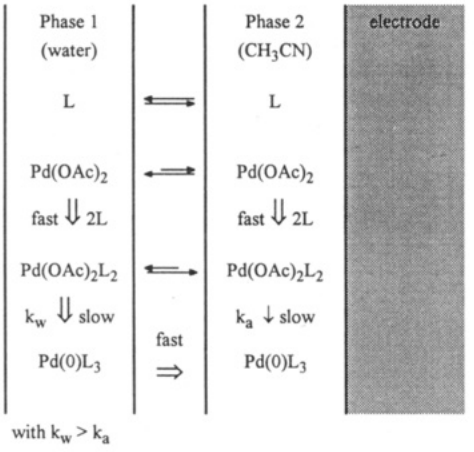
As in the case of PPh_3,[14b] the rate of formation of the palladium(0) complex increases with temperature (*e.g.* $t_{1/2}$ = 22 min at 10 °C and $t_{1/2}$ = 8 min at 20 °C). The maximum for the concentration of $Pd(OAc)_2(TPPTS)_2$ was always observed at short times whatever the temperature.

The rate of disappearance of the palladium(II) complex is not affected by the TPPTS concentration at long times (Figure 2b). At short times (t < $t_{1/2}$), we always observed a maximum value for the concentration of the complex $Pd(OAc)_2(TPPTS)_2$, but due to the poor reproducibility of the data in this time range (see for example two sets of experiments with 7 equiv of TPPTS in Figure 2b), the position and the magnitude of the maximum could not be related to the TPPTS concentration. It seems that some palladium(II) complex cannot be detected by the cathode at the very beginning of the reaction. One might think that this was due to the formation of a nonelectroreducible intermediate complex, maybe a less ligated complex such as $Pd(OAc)_2(TPPTS)$. But this hypothesis can be ruled out by the fact that, as described above, we observed that two TPPTS were rapidly consumed by $Pd(OAc)_2$ upon mixing $Pd(OAc)_2$ and TPPTS (reaction 5). This reaction occurred within less than 1 min (time needed for mixing and performing a first voltammogram), which is a shorter time than that observed for the maximum (6 min). Another hypothesis considers that the complex $Pd(OAc)_2(TPPTS)_2$ is quantitatively formed at the very beginning of the reaction but cannot be quantitatively detected by the cathode because present in two phases.

$$Pd(OAc)_2 + 2TPPTS \rightarrow [Pd(OAc)_2(TPPTS)_2]_{phase\ 1} + [Pd(OAc)_2(TPPTS)_2]_{phase\ 2} \quad (5')$$

Indeed, were the complex $Pd(OAc)_2(TPPTS)_2$ present in both phases, the one present in the organic phase only would be detected by the electrode.[41] Nevertheless, the palladium(0) complex would be produced from $Pd(OAc)_2(TPPTS)_2$ in both phases. The palladium(0) produced in the aqueous phase would rapidly shift to the organic phase where it is more soluble and so would be quanti-

Scheme 4



tatively detected by the electrode. Scheme 4 could rationalize our results.

So the complex $Pd(OAc)_2(TPPTS)_2$ would first be rapidly formed in the aqueous phase and would afford the palladium(0) complex with the rate constant k_w. Some part of this complex would enter the organic phase where it would be detected at the electrode.[44] In this organic phase, it would afford the same palladium(0) complex but with a slower rate constant k_a (the rate constant that we observed at long times). Thus the hypothesis that the palladium(II) complex might afford the palladium(0) complex at two different rates in the different phases could interpret the fact that the palladium(0) was produced with a higher rate at short times (Figure 3b).

As above reported, we observed by ^{31}P NMR spectroscopy two different signals for the ligand TPPTS, the latter being present in the two phases. Therefore we should also observe two different signals at short times for $Pd(OAc)_2(TPPTS)_2$: one for the complex in the organic phase and another one for the complex in the aqueous phase. In fact it was not possible to perform the ^{31}P NMR spectroscopy at short times. The first spectrum was recorded after 10 min (this time was already higher than the half time of the reaction, see parts a and b of Figure 2). At that time, the $Pd(OAc)_2(TPPTS)_2$ complex has already completely moved to the organic phase; this is why we only observed one signal for it at δ_3. Whereas the ^{31}P NMR signal of $Pd(OAc)_2(PPh_3)_2$ in DMF or THF was sharp,[14a] the signal of $Pd(OAc)_2(TPPTS)_2$ was rather broad (see above). This suggests that this complex is involved in a fast equilibrium, maybe under the usual square planar configuration and an unusual tetrahedral configuration due to the bulkiness of the TPPTS ligand.

In previous works[14] we demonstrated that the spontaneous formation of palladium(0) complexes from mixtures of $Pd(OAc)_2$ and tertiary phosphines in organic solvents was a general reaction. In the present paper we demonstrate that this reaction also works in the case of the water-soluble phosphine TPPTS and that it obeys the general mechanism already reported: fast formation of a bivalent palladium complex $Pd(OAc)_2(TPPTS)_2$ followed by a slow inner sphere reduction that affords a palladium(0) complex whereas the phosphine is oxidized to the corresponding phosphine oxide. In this work, we notice that the rate of formation of the palladium(0) complex from $Pd(OAc)_2$ and TPPTS is about five times higher than that generated from PPh_3. We reported previously that the rate of formation of the palladium(0) complex was sensitive to electronic and steric factors.[14b] In the case of triarylphosphines, we found that the reaction was faster when the aryl group was substituted by an electron withdrawing group but two opposing effects were observed when considering the cone angle of the phosphine. In the case of the TPPTS, electronic factors are expected to be weak since the substituent SO_3^- is a poor electron withdrawing group when substituted in the meta position ($s_{meta} = +0.05$). The cone angle of the ligand TPPTS is 170°,[45] which is considerably larger than that of PPh_3 (145°)[46] and larger than 129°, which was calculated as the optimum value for the influence of steric parameters.[14b] It seems that in the case of TPPTS we have therefore to consider other factors, maybe related to the fact that the reaction proceeds in the presence of water. Indeed, although in the case of PPh_3 we did not observe any effect of the water concentration on the kinetics of formation of the palladium(0) complex,[14] it was reported that the rate of formation of the palladium(0) complex was higher in the presence of water, in the case of the ligand BINAP.[47] This result would also confirm our above explanation about the fact that the rate of formation of the palladium(0) complex was higher at the beginning of the reaction, when most of the bivalent palladium resides in the water phase, *i.e.* the rate constant of formation of the palladium(0) complex would be higher in water than in acetonitrile ($k_w > k_a$ in Scheme 4).

3. Kinetic Data on the Oxidative Addition of Phenyl Iodide with the Palladium(0) Complex Generated from $Pd(OAc)_2$ and TPPTS. The oxidation peak at $E^p = +0.215$ V of the palladium(0) complex generated from the mixture of $Pd(OAc)_2$ (2 mM) associated with 4 equiv of TPPTS disappeared in the presence of phenyl iodide, demonstrating that the oxidative addition in eq 9 took place. This reaction was also observed in ^{31}P NMR spectroscopy. Addition of phenyl iodide resulted in the disappearance of the palladium(0) complex and formation of two new signals at $\delta_5 = 14.5$ and $\delta_6 = 24.18$ ppm respectively assigned to $PhPd(OAc)(TPPTS)_2$ and $PhPdI(TPPTS)_2$[48] by analogy with our previous observation with PPh_3.[14a,49]

$$Pd(0)(TPPTS)_3 \underset{k_{-1}}{\overset{k_1}{\rightarrow}} Pd(0)(TPPTS)_2 + TPPTS \quad (8)$$

(41) The solution was biphasic but the volume of the aqueous phase was less than the original volume of water introduced at the beginning of the reaction (1 mL). This means that the acetonitrile phase contained water pools due to the presence of the surfactant (as in reversed micelles).[42] For electrochemical investigations in micellar media, see ref 43 and references cited therein.

(42) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic Press, Inc.: London, 1975; p 314.

(43) Meyer, G.; Nadjo, L.; Savéant, J. M. *J. Electroanal. Chem.* **1981**, *119*, 417.

(44) A more detailed electrochemical investigation of this system at short times was not possible for several reasons. Many species are involved in this reaction, and we have a dynamic system which evolves as a function of time: Pd(II) → Pd(0). Moreover, the time scale where the palladium(II) complex is not quantitatively detected is about 6 min, which is too short for a fine study using electrochemical techniques.

(45) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524.

(46) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(47) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

(48) The ^{31}P NMR signal of an authentic sample of $PhPdBr(TPPTS)_2$ was observed at 25.8 ppm in water.[37b]

$$Pd(0)(TPPTS)_2 + PhI \xrightarrow{k_2} ArPdX(TPPTS)_2^{49} \quad (9)$$

The reactivity of the zero-valent palladium complex in the oxidative addition could be monitored by cyclic voltammetry. After complete conversion of the palladium(II) complex to the palladium(0) one, cyclic voltammetry was performed at a stationary disk electrode after addition of phenyl iodide and the oxidation peak current i for Pd(0) was measured as a function of time.

A plot of the variation of $\ln(i/i_0)$ (i, oxidation current at +0.355 V at t; i_0 at $t = 0$) as a function of t[PhI]/[TPPTS] affords a straight line (Figure 4, $\ln(i/i_0) = -(k_1k_2/k_{-1})t$[PhI]/[TPPTS]), demonstrating that the oxidative addition is first order in palladium(0) and in phenyl iodide and negative first order in the ligand. The value of the apparent rate constant of the oxidative addition was then deduced from the slope of the straight line represented in Figure 4. One obtains $k_1k_2/k_{-1} = 2.3 \times 10^{-4}$ s^{-1} at 20 °C. In the case of PPh_3, this global rate constant was 200 times higher: $k_1k_2/k_{-1} = 5 \times 10^{-2}$ s^{-1} at 20 °C in DMF.[14b]

So the palladium(0) complex generated from the mixture $Pd(OAc)_2$ and nTPPTS is considerably less reactive (about 200 times less) than the corresponding complex generated from PPh_3. It is reported that the rate of the oxidative addition of palladium(0) complexes with phenyl iodide is not sensitive to the solvent, and it was concluded that this reaction proceeds via a concerted mechanism rather than via a mechanism involving electron transfer.[51] In our previous paper we found that the rate of the oxidative addition was sensitive to electronic factors, it was slower when the aryl group of the phosphine was substituted by an electron withdrawing group.[14b] As mentioned above, in the case of TPPTS, variations of electronic factors are not expected to be important *vs* PPh_3 and cannot explain the difference of reactivity. However the cone angle of the ligand TPPTS is considerably larger than that of PPh_3 and the oxidative addition could be very sensitive to steric factors.

Conclusion

We have shown that the water-soluble catalyst prepared *in situ* from $Pd(OAc)_2$ and TPPTS is an efficient catalyst for sp–sp and sp^2–sp coupling without Cu(I) promoter in aqueous acetonitrile medium. Furtermore we have found that the mixture of $Pd(OAc)_2$ and nTPPTS generates *in situ* a zero-valent palladium. The TPPTS can reduce divalent palladium acetate and is oxidized to the TPPTS oxide. The use of water-soluble catalysts for industrial production can simplify product separation and is also attractive because of the economy and safety of using water as a solvent.

(49) We have some evidence that the palladium(0) complex generated from the mixture of $Pd(OAc)_2$ and PPh_3 is ligated by an acetate anion[50] and that its oxidative addition with phenyl iodide produces some $ArPd(OAc)(PPh_3)_2$ complex presumably via the intermediacy of a pentacoordinated complex, $ArPdI(OAc)(PPh_3)_2^-$.[14b] By analogy, in the mechanism proposed in Scheme 1 the zero-valent palladium catalyst Pd^0Ln is certainly ligated by an acetate anion and the intermediate B resulting from its oxidative addition with the acetylenic iodide should also be ligated by an acetate anion. However, since Scheme 1 is used here only as a tentative proposition and not as a fully kinetically established reaction mechanism, the notation Pd^0Ln was adopted for simplification.

(50) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. In press.

(51) Amatore, C. Pflüger, F. *Organometallics* **1990**, *9*, 2276.

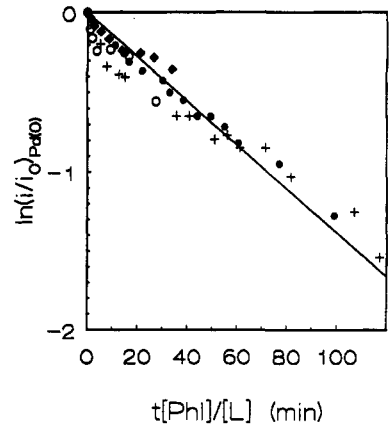


Figure 4. Oxidative addition of phenyl iodide with the palladium(0) complex qualitatively generated in situ from $Pd(OAc)_2$ (2 mM) and TPPTS in a mixed solvent (11 mL of acetonitrile and 1 mL of water) containing n-Bu_4NBF_4 (0.3 M) and n-Hex_4NBF_4 (20 mM) at 20 °C. Variation of $\ln(i/i_0)$ as a function of time (i, oxidation peak current of the palladium(0) complex at +0.35 V, at a stationary gold disk electrode (i.d. = 0.5 mm; $\nu = 0.2$ V s^{-1})): TPPTS (20 mM) and PhI (71.4 mM) (+); TPPTS (20 mM) and PhI (14.9 mM) (♦); TPPTS (14 mM) and PhI (44 mM) (●); TPPTS (30 mM) and PhI (45 mM) (○).

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin-Elmer 983G spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 200 instrument at 200 MHz; chemical shifts (δ) are reported in ppm units, by reference to Me_4Si, and coupling constants (J) are reported in hertz and refer to apparent peak multiplicities. Abbrevations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument at 50 MHz, and ^{31}P NMR spectra were recorded at 162 MHz using H_3PO_4 as an external reference. Mass spectra were performed on a Ribermag Instrument. Elemental analyses were made at the Regional Service of Microanalysis (University P. et M. Curie, Paris). Thin-layer chromatography was carried out on silica gel plates (Merck F_{254}), and spots were detected by UV and Kagi-Mösher or $KMnO_4$ revelators. Tetrahydrofuran and diethyl ether were distilled on sodium/benzophenone, and dichloromethane was distilled on CaH_2. The other commercial solvents were used without any further purification. Unless stated otherwise, all reactions were run under an atmosphere of argon in a flame-dried vessel. For the reactions involving the $Pd(OAc)_2$/TPPTS catalytic system, acetonitrile, water, and triethylamine were degazed for 15 min prior to the experiment.

Electrochemical Setup and Electrochemical Procedure for Cyclic Voltammetry. Cyclic voltammetry was performed with a homemade potentiostat and wave-form generator, PAR Model 175. The cyclic voltammograms were recorded with a Nicolet 3091 digital oscilloscope. Experiments were carried out in a three-electrode cell connected to a Schlenk line. The cell was equipped with a double envelope in order to perform the reactions at constant temperature, using a thermostat Lauda M3. A 12 mL volume of solvent (11 mL of acetonitrile and 1 mL of water) containing n-Bu_4NBF_4 (20 mM) was poured into the cell. The counter electrode was a platinum wire of ca. 1 cm^2 apparent surface area; the reference was a saturated calomel electrode (Tacussel) separated from the solution by a bridge containing 2 mL of the same solution as described above. A 5.4 mg amount (2×10^{-3} M) of $Pd(OAc)_2$ was then added followed by a suitable amount of TPPTS (from a 0.6 M solution in water). The cyclic voltammetry was performed at a stationnary disk electrode (a gold disk made from a cross-section of wire, i.d. = 0.5 mm, sealed into glass) at a scan rate of 0.2 V s^{-1}.

General Procedure A for the Preparation of Alkynyl Iodides. To a stirred solution of the terminal alkyne (15

mmol) in 15 mL of THF was added $AgNO_3$ (1.5 mmol) followed by *N*-iodosuccinimide (15 mmol). After 15 to 30 min a white precipitate was observed in the reaction mixture, and stirring was continued for 2 h. Hydrolysis of the reaction was then carried out with glacial water, and the mixture was extracted with diethyl ether. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting crude product was purified by flash chromatography.

General Procedure B for Pd(0)-Catalyzed sp–sp Cross-Coupling Reactions. In a Schlenck tube equipped with a magnetic bar, the alkynyl iodide was dissolved in an acetonitrile/water (6/1) solution (3 mL for 0.8 to 1 mmol). Triethylamine (2.5 equiv) and the terminal alkyne (1.5 equiv) were added; $Pd(OAc)_2$ (5 mol %) and TPPTS (10 mol %) were quickly poured into the Schlenck and the mixture was vigorously stirred. After total consumption of the alkynyl iodide (the reaction was monitored by TLC), the reaction mixture was filtered through Celite. The filtrate was treated with water and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting crude product was purified by flash chromatography on silica gel or Florisil.

General Procedure C for Pd(0)-Catalyzed sp–sp² Coupling/Intramolecular Cyclization Reactions. In a Schlenck tube equipped with a magnetic bar, the aromatic iodide was dissolved in an acetonitrile/water (15/1) solution. Triethylamine (2.5 equiv) and the terminal alkyne (1.5 equiv) were added, followed by $Pd(OAc)_2$ (2.5 mol %) and TPPTS (5 mol %). After completion, the reaction mixture was treated as described in General Procedure.

1-Iodohex-1-yne (1)[24a] was prepared according General Procedure A starting from hex-1-yne to produce a yellow oil (80% yield): ^{1}H NMR ($CDCl_3$) δ 2.39 (t, J = 6.9 Hz, 2H), 1.50 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 94.7, 30.4, 21.8, 20.4, 13.4, −7.8; TLC, R_f = 0.81 (AcOEt/cyclohexane 1/1); IR (film) 2836 (ν(C≡C)) cm^{-1}; GC/MS m/z 208 (M)$^{+\bullet}$, 166 (M − C_3H_7 + 1)$^+$, 79 (M − I + 2)$^+$.

1-Iodo-2-(trimethylsilyl)acetylene (2)[24b] was prepared according General Procedure A starting from (trimethylsilyl)-acetylene to give a pale orange oil (89% yield): ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 104.1, 20.1, −0.2; TLC, R_f = 0.76 (AcOEt/cyclohexane 1/1); IR (film) 2957, 2896 (ν(CH_3)), 2099 (ν(C≡C)), 1407, 1249 ($\delta$$CH_3$), 842 ($\nu$(Si−$CH_3$)) cm^{-1}; GC/MS m/z 224 (M)$^{+\bullet}$, 209 (M − CH_3)$^+$, 179 (M − $3CH_3$)$^+$, 97 (M − I)$^+$.

1,1-Diethyl-3-iodoprop-2-ynylamine (3) was prepared according General Procedure (A) from 1,1-diethylpropargylamine to give a white solid (83% yield): ^{1}H NMR ($CDCl_3$) δ 1.75 (br s, 2H NH_2), 1.56 (m, 4H), 1.06 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 99.9, 54.8, 34.5, 8.6, −3.4; TLC, R_f = 0.44 (AcOEt/cyclohexane 1/1); GC/MS m/z 220 (M − NH_2 − 1)$^+$, 208 (M − C_2H_5)$^+$, 178 (M − $2C_2H_5$ − 1)$^+$. Anal. Calcd for $C_7H_{12}NI$: C, 35.44; H, 5.06; N, 5.91. Found: C, 35.36; H, 4.99; N, 5.95.

1-Phenyloct-1,3-diyne (4) was prepared according General Procedure B from 1-iodohex-1-yne (**1**) and phenylacetylene to give an orange oil (50% yield): ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 2H arom), 7.38 (m, 3H arom.), 2.41 (t, J = 6.8 Hz, 2H), 1.78 to 1.38 (m, 4H), 0.97 (t, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 132.4, 128.7, 128.2, 121.7, 84.7, 81.3, 67.6, 64.6, 30.2, 21.9, 19.2, 13.4; TLC, R_f = 0.63 (AcOEt/cyclohexane 1/40); IR (film) 3055 (ν(C−H) arom), 2202 (ν(C≡C)), 1594, 1486 (ν(C=C) arom) cm^{-1}; GC/MS m/z 182 (M)$^{+\bullet}$, 165 (M − CH_3 − 2)$^+$, 152 (M − C_2H_5)$^+$, 139 (M − C_3H_7)$^+$. Anal. Calcd for $C_{14}H_{14}$: C, 92.31; H, 7.69. Found: C, 92.28; H, 7.30.

2-Methyldeca-3,5-diyn-2-ol (6) was prepared according General Procedure B from 1-iodohex-1-yne (**1**) and 2-methylbut-1-yn-2-ol to give a light brown oil (60% yield): ^{1}H NMR ($CDCl_3$) δ 2.28 (t, J = 6.8 Hz, 2H), 2.11 (br s, 1H, OH), 1.52 (s, 6H), 1.59 to 1.32 (m, 4H), 0.91 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 81.8, 79.7, 67.3, 65.4, 64.2, 31.1, 21.8, 18.2, 13.3; TLC, R_f = 0.76 (AcOEt/cyclohexane 1/1); IR (film) 3375 (ν(O−H)), 2250 (ν(C≡C)), 1153 (ν(C−O)); GC/MS m/z 164 (M)$^{+\bullet}$, 149 (M − CH_3)$^+$, 135 (M − C_2H_5)$^+$, 107 (M − C_4H_9)$^+$. Anal. Calcd for $C_{11}H_{16}O$: C, 80.49; H, 9.76. Found: C, 80.61; H, 9.37.

1-(Trimethylsilyl)deca-1,3-diyn-5-ol (7) was prepared according General Procedure B from 1-iodo-2-(trimethylsilyl)-acetylene (**2**) and oct-1-yn-3-ol to produce an orange oil (43% yield): ^{1}H NMR ($CDCl_3$) δ 4.42 (m, 1H), 1.91 (d, J = 5.7 Hz, 1H, OH), 1.73 (m, 2H), 1.44 (m, 2H), 1.32 (m, 4H), 0.9 (t, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 87.5, 87.1, 78.6, 69.6, 62.7, 37.3, 31.3, 24.6, 22.4, 13.9, −0.6; TLC, R_f = 0.49 (Et_2O/pentane 1/2); IR (film) 3311 (ν(O−H)), 2220, 2106 (ν(C≡C)), 1249 (δ-(Si−CH_3)), 1024 (ν(C−O)), 843 (ν(Si−CH_3)); MS (DCI/NH_3) m/z 223 (M + H)$^+$. Anal. Calcd for $C_{13}H_{22}SiO$: C, 70.27; H, 9.91. Found: C, 70.18; H, 9.95.

1-(Trimethylsilyl)-5-methylhexa-1,3-diyn-5-ol (8) was prepared according to General Procedure B from 1-iodo-2-(trimethylsilyl)acetylene (**2**) and 3-methylbut-1-yn-3-ol to give an orange oil (57% yield): ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 1H, OH), 1.53 (s, 6H), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 87.6, 87.0, 81.8, 67.1, 65.4, 30.9, −0.6; TLC, R_f = 0.44 (CH_2Cl_2); GC/MS m/z 180 (M)$^{+\bullet}$, 165 (M − CH_3)$^+$, 107 (M − $SiMe_3$)$^+$. Anal. Calcd for $C_{10}H_{16}OSi$: C, 66.67; H, 8.89. Found: C, 67.01; H, 8.63.

1,1-Diethyl-6-hydroxyundec-2,4-ynylamine (9) was prepared according to General Procedure B starting from 1,1-diethyl-3-iodoprop-2-ynylamine (**3**) and oct-1-yn-3-ol to give an orange oil (65% yield): ^{1}H NMR ($CDCl_3$) δ 4.41 (t, J = 6.6 Hz, 1H), 1.85 (br s, 2H, NH_2), 1.61 (m, 4H), 1.52 (m, 4H), 1.37 (m, 2H), 1.25 (m, 4H), 0.95 (t, J = 7.4 Hz, 6H), 0.83 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 85.2, 79.2, 69.3, 66.6, 62.6, 53.3, 37.5, 34.2, 31.3, 24.7, 22.4, 13.9, 8.6; TLC, R_f = 0.31 (AcOEt/cyclohexane 4/1); IR (film) 3352 (ν(O−H)), 3300 (ν(N−H)), 2315, 2245 (ν(C≡C)), 1589 (δ(N−H)), 1051 (ν(C−O)) cm^{-1}; GC/MS m/z 234 (M − 1)$^+$; 220 (M − CH_3)$^+$; 206 (M − C_2H_5)$^+$; 178 (M − C_4H_9)$^+$; 150 (M − C_6H_{13})$^+$. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.60; H, 10.64; N, 5.96. Found: C, 76.75; H, 10.18; N, 5.71.

2-Butylindole (10)[30] **and 1-(2-aminophenyl)hex-1-yne (11)**[31] were obtained from 2-iodoaniline and hex-1-yne according to General Procedure C and separated by flash chromatography. **10**: 56% yield; ^{1}H NMR δ 7.80 (br s, 1H, NH), 7.40 (m, 2H), 7.2 (m, 2H), 6.25 (s, 1H), 2.80 (t, J = 7.4 Hz, 2H), 1.80 to 1.50 (m, 2H), 1.50 to 1.20 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 139.8, 135.7, 120.6, 119.4, 116.6, 114.0, 99.3, 30.9, 21.9, 19.2, 13.5; TLC, R_f = 0.45 (AcOEt/cyclohexane 1/5); IR (film) 3310 (ν(N−H)), 1620 (ν(C≡C)) cm^{-1}; GC/MS m/z 173 (M)$^{+\bullet}$, 144 (M − C_2H_5)$^+$, 130 (M − C_3H_7)$^+$. **11**: 19% yield; ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 2H), 6.72 (d, J = 7.8 Hz, 2H), 4.20 (br s, 2H, NH_2), 2.50 (t, J = 6.8 Hz, 2H), 1.70 to 1.30 (m, 4H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 139.8, 128.6, 122.4, 117.8, 114.0, 95.6, 76.9, 31.2, 27.8, 22.3, 13.7; TLC, R_f = 0.25 (AcOEt/cyclohexane 1/5); IR (film) 3312 (ν(N−H)), 2240 (ν(C≡C)) cm^{-1}; GC/MS m/z 173 (M)$^{+\bullet}$, 158 (M − CH_3)$^+$, 144 (M − C_2H_5)$^+$, 130 (M − C_3H_7)$^+$.

2-(1-Amino-1-ethylpropyl)benzofuran (13) was prepared according General Procedure C from 2-iodophenol and oct-1-yn-3-ol to give a clear oil (57% yield): ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.20 (m, 2H), 6.50 (s, 1H), 1.85 (q, J = 7.4 Hz, 4H), 1.70 (br s, 2H NH_2), 0.90 (t, J = 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.7, 154.6, 128.5, 123.2, 122.4, 120.4, 101.8, 102.0, 56.4, 32.7, 7.9; TLC, R_f = 0.1 (CH_2Cl_2/MeOH 1/1); IR (film) 3380, 3350 (ν(N−H)) cm^{-1}; GC/MS m/z 203 (M)$^{+\bullet}$, 174 (M − C_2H_5)$^+$. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.90. Found: C, 76.01; H, 8.14; N, 6.73.

1-(2-Benzofuryl)hexan-1-ol (14)[32] was prepared according General Procedure C starting from 2-iodophenol and oct-1-yn-3-ol to give an oil (60% yield): ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.25 (m, 2H), 6.60 (s, 1H), 4.8 (dt, J_{HC-OH} = 6.2 Hz and J_{HC-CH2} = 6.5 Hz, 1H), 2.2 (d, J = 6.2 Hz, 1H, OH), 1.95 (m, 2H), 1.35 (m, 6H), 0.9 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 154.6, 128.0, 123.9, 122.6, 120.9, 111.1, 102.3, 68.2, 35.4, 31.5, 25, 22.4, 13.9; TLC, R_f = 0.4 (CH_2Cl_2); IR (film) 3350 (ν(O−H)), 2980 (ν(H−C=)), 1450 (ν(C=C)) cm^{-1}; GC/MS m/z 218 (M)$^{+\bullet}$, 147 (M − C_5H_{11})$^+$, 91 ($PhCH_2$)$^+$.

2-(1-Hydroxy-1-methylethyl)-5-formylbenzofuran (15)[33] was prepared according General Procedure C from 3-iodo-4-hydroxybenzaldehyde and 2-methylbut-3-yn-2-ol to give a clear oil (99% yield): ^{1}H NMR ($CDCl_3$) δ 10.00 (s, 1H, CHO), 8.00 (d, J = 1.6 Hz, 1H), 7.80 (dd, J_{1-3} = 8.5 Hz and J_{1-4} = 1.6 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 6.80 (s, 1H), 2.75 (br s, 1H, OH), 1.7 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 191.9, 165.0, 158.0, 132.0,

128.8, 125.6, 124, 111.8, 100.8, 69.1, 28.6; TLC, R_f = 0.15 (CH_2Cl_2/MeOH 40/1); IR (film) 3403 (ν(O—H)), 2982 (ν(C=C) arom), 1692 (ν(C=O)) cm^{-1}; MS (EI, 70 eV) m/z 204 $(M)^{+\bullet}$, 189 $(M - CH_3)^+$, 173 $(M - 2CH_3 - 1)^+$, 159 $(M - CH_3 - CHO - 1)^+$, 128 $(M - CHO - C(OH)Me_2)^+$, 105 $(PhCHO - 1)^+$.

3-(3-Hydroxy-3-methylbut-3-ynyl)-4-(methoxymethoxy)benzaldehyde (17) was prepared according General Procedure C from 3-iodo-4-(methoxymethoxy)benzaldehyde (**16**) and 2-methylbut-3-yn-2-ol to afford a clear oil (99% yield): ^1H NMR ($CDCl_3$) δ 9.90 (s, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.80 (dd, ^3J = 8.6 Hz and ^4J = 2.1 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 5.30 (s, 2H), 3.50 (s, 3H), 2.35 (s, 1H, OH), 1.7 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 190.2, 162.1, 135.4, 131.2, 130.2, 114.4, 113.9, 99, 94.6, 77.6, 65.6, 56.5, 31.4; TLC, R_f = 0.15 (CH_2Cl_2/MeOH 40/1); IR (film) 3413 (ν(O—H)), 2979 (ν(H—C) arom), 2247 (ν(C≡C)) 1693 (ν(C=O)) cm^{-1}; MS (DCI/NH_3) m/z 266 $(M + NH_4^+)$, 249 $(M + 1)^+$, 248 $(M)^{+\bullet}$, 231 $(M - H_2O)^+$. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.63; H, 6.47.

4-(Methoxymethoxy)-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (18). In a flask equipped with a magnetic bar, 3-(3-hydroxy-3-methylbut-3-ynyl)-4-(methoxymethoxy)benzaldehyde (**17**, 325 mg, 1.3 mmol) was dissolved in 2 mL of anhydrous pyridine. The solution was cooled to 0 °C and after 5 min, $POCl_3$ (0.85 equiv, 102 μL, 1.1 mmol) was added dropwise under vigorous stirring. The mixture was allowed to warm to room temperature for 12 h. The reaction was then hydrolyzed with glacial water and extracted with diethyl ether (4 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel ($CHCl_3$/EtOH 99/1) to afford **18** as an oil (111 mg, 38% yield): ^1H NMR ($CDCl_3$) δ 9.90 (s, 1H, CHO), 8.00 (d, J = 0.8 Hz, 1H), 7.80 (dd, ^3J = 8 Hz and ^4J = 0.8 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 5.45 (s, 1H), 5.30 (s, 1H), (s, 2H), 3.50 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.2, 162.0, 135.3, 131.1, 130.9, 130.3, 122.5, 114.4, 113.9, 99.1, 83.0, 94.6, 56.4, 31.3; TLC, R_f = 0.65 (CH_2Cl_2/MeOH 40/1); IR (film) 2982 (ν(H—C) arom), 2220 (ν(C≡C)), 1693 (ν(C=O)), 1614 (ν(C=C)) cm^{-1}; GC/MS m/z 230 $(M)^{+\bullet}$, 215 $(M - CH_3)^+$, 199 $(M - OMe)^+$, 169 $(M - OMOM)^+$, 128 $(M - OMOM - H_2C{=}CCH_3)^+$. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.04; H, 6.09. Found: C, 73.57; H, 5.97.

4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (Eutypine, 19).[34] 4-(Methoxymethoxy)-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (**18**, 250 mg, 1.08 mmol) was hydrolyzed with 50 mL of aqueous 1% HCl at room temperature for 24 h. The mixture was then extracted with 4 × 30 mL of diethyl ether. The organic layer was washed with a saturated aqueous solution of Na_2SO_4, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel ($CHCl_3$/EtOH 99/1) to afford **19** (200 mg, 99% yield): ^1H NMR ($CDCl_3$) δ 9.80 (s, 1H), 8.60 (br s, 1H, OH), 7.90 (m, 1H), 7.70 (m, 1H), 7.20 (m, 1H), 5.40 (s, 1H), 5.30 (s, 1H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.2, 161.9, 140.0, 135.3, 131.2, 130.2, 126.6, 114.4, 113.9, 95.6, 83.0, 31.3; TLC, R_f = 0.15 (CH_2Cl_2/MeOH 40/1); IR (film) 3500 to 3200 (ν(O—H)), 2982 (ν(H—C) arom), 2197 (ν(C≡C)), 1700 (ν(C=O)), 1610 (ν(C=C)) cm^{-1}; GC/MS m/z 186 $(M)^{+\bullet}$, 157 $(M - CHO)^+$, 128 $(M - H_2O - MeC{=}CH_2 + 1)^+$.

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