# Palladium(II) Chloride and a (Dipyridin-2-ylmethyl)amine-Derived Palladium(II) Chloride Complex as Highly Efficient Catalysts for the Synthesis of Alkynes in Water or in NMP and of Diynes in the Absence of Reoxidant

**Juan Gil-Moltó[a] and Carmen Nájera*[a]**

**Keywords:** Palladium catalyst / N ligands / Alkynes / Diynes / Water chemistry

The (dipyridin-2-ylmethyl)amine-derived palladium chloride complex **1** and $PdCl_2$ are efficient catalysts for cross-coupling reactions between terminal alkynes and aryl iodides or bromides under modified Sonogashira–Cassar–Heck conditions. The alkynylation can be performed under copper-free conditions in water at reflux or at room temperature under air with pyrrolidine as base and tetra-*n*-butylammonium bromide (TBAB) as additive, with TONs of up to $7 \times 10^4$ and TOFs ($h^{-1}$) of up to 6666. Terminal alkynes can be arylated in NMP as well under copper- and amine-free conditions at 110 °C or room temperature, with tetra-*n*-butylammonium acetate (TBAA) acting as base with TONs up to $2 \times 10^5$ and TOFs ($h^{-1}$) up to 66666. In general, complex **1** displays a slightly higher efficiency than $PdCl_2$ as catalyst and maintains the same activity after five consecutive runs. Alternatively, these alkynylation processes can be carried out under microwave heating conditions. The homocoupling of terminal alkynes to the corresponding 1,3-diynes proceeds under phosphane-free conditions with the (dipyridin-2-ylmethyl)amine-derived palladium chloride complex **1** or with $PdCl_2$ as catalysts and with CuI as cocatalyst in NMP with use of either TBAA or pyrrolidine as bases. This Glaser-type reaction can be performed at 110 °C or at room temp. in the presence of air without the use of a reoxidant.

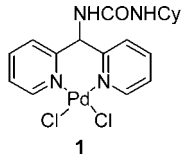

## Introduction

Palladium-catalysed homo-[1] and cross-coupling[2] reactions are very important processes in modern acetylene chemistry for the synthesis of natural products and biologically active molecules, and in materials science for the preparation of conjugated acetylenic oligomers and polymers, liquid crystals and other engineering materials.[3] These reactions are widely used for the synthesis of symmetrical 1,3-diynes and internal alkynes or enynes. Several important aspects have been improved in recent years, mainly concerning the elimination of the reoxidant in the case of the Pd–Cu co-catalysed homocoupling of terminal alkynes.[4] Palladium-catalysed cross-coupling reactions of aryl or vinyl halides and terminal alkynes were first reported by Cassar's,[5] Heck's[6] and Sonogashira's[7] groups. The first two of these groups worked under copper-free conditions using either sodium methoxide as base and DMF as solvent[5] or an amine as both base and solvent,[6] respectively. Later, it was found that the reaction was faster in pyrrolidine as solvent.[8] However, the copper-co-catalysed reaction conditions in an amine as solvent have became more popular over the years.[7] Recent improvements in the alkynylation reaction have been concentrated on the simpler Cassar–Heck protocol, the elimination of copper as co-catalyst and the amine as solvent, in order to avoid undesired homocoupling by-reactions, and the precipitation of catalytically inactive palladium black.[9]

The use of water as solvent represents one of the safest and economically and environmentally most advantageous alternatives to organic solvents for metal-catalysed reactions.[10] Aqueous-phase Sonogashira couplings have been performed with the aid of hydrophilic phosphines,[11] polymer-supported ligands,[12] palladium on carbon,[13] palladium zeolites[14] and other activating reagents such as prolinol,[15] potassium fluoride,[16] aqueous ammonia[17] and quaternary ammonium salts.[18] Sonogashira couplings in neat water with use of $(PPh_3)_2PdCl_2$,[19] $(PPh_3)_4Pd$[20] and palladium-phosphinous acid[21] as catalysts have been described. Microwave-assisted transition metal-free alkynylation reactions in water have been recently achieved, showing limited scope.[22] We reported the first cross-coupling reactions between terminal alkynes and aryl halides in neat water under copper-free conditions with use of a (dipyridin-2-ylmethyl)amine-derived palladium dichloride complex **1**[23] as catalyst.[24] We now report a full account of the catalytic activity of complex **1** and ligandless $PdCl_2$ in cross-coupling and homocoupling reactions of terminal alkynes in water and in NMP (*N*-methylpyrrolidone) as solvents.

[a] Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
Fax: +34-965903549
E-mail: cnajera@ua.es

 **DOI: 10.1002/ejoc.200500319**  

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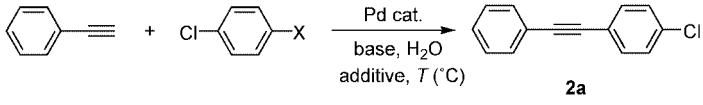
## Results and Discussion

### Cross-Coupling Reactions between Aryl Halides and Terminal Alkynes

The reaction conditions for the alkynylation of 4-chlorophenyl iodide and bromide with phenylacetylene in neat water were studied with the dipyridine–palladium dichloride complex **1**[25] and palladium dichloride as catalysts (Scheme 1 and Table 1). In a first round of screening, different bases and additives were essayed for the coupling between 4-chlorophenyl iodide and phenylacetylene to give alkyne **2a** in the presence of 0.1 mol-% of complex **1** as catalyst in water at reflux (Table 1, Entries 1–5). When $K_2CO_3$ was used as base in the presence of tetra-*n*-butylammonium acetate (TBAA, 1 equiv.) and with pyrrolidine (5 mol-%), the coupling had taken place in high yields after 7 h (Table 1, Entries 1 and 2), whereas a mixture of $K_2CO_3$ and 5 mol-% of pyrrolidine afforded a lower yield (Table 1, Entry 3). In all these cases the formation of small amounts of 1,4-diphenylbuta-1,3-diyne (**3a**) (up to 4%) and other secondary products such as enynes[26] from the excess of phenylacetylene (up to 19%) were observed. When the cross-coupling reaction was performed with only pyrrolidine (2 equiv.) as base the yield increased again, to 93% after 6 h, whereas in the presence of tetra-*n*-butylammonium bromide (TBAB, 0.5 equiv.) the reaction had taken place quantitatively after 1 h (Table 1, Entries 4 and 5). Under the last set of reaction conditions the formation of secondary products was almost inhibited, and the loading of complex **1** could be reduced to 0.01 mol-% with similar results (Table 1, compare Entries 5 and 7). Under these reaction conditions, complex **1** and ligandless palladium dichloride[24] (0.01 mol-% of Pd) gave the same results and the amount of enynes was less than 4% (Table 1, compare Entries 7 and 8). With a low loading of complex **1** (0.001 mol-%) the reaction was slower (4 d) and a 3:1 mixture of alkyne **2a** and enynes was obtained (Table 1, Entry 9). Alternatively, the alkynylation reaction could be performed at room temperature in ca. 1 d by increasing the loading of catalysts to 1 mol-%. Under these reaction conditions, complex **1** showed a higher efficiency than $PdCl_2$ (Table 1, compare Entries 10 and 11). Cross-coupling between phenylacetylene and 4-chlorophenyl bromide was performed in water at reflux with pyrrolidine as base and TBAB as additive in the presence of 0.2 mol-% of palladium. In this alkynylation process complex **1** was the best catalyst, $PdCl_2$ providing a lower yield together with a 6:1 mixture of alkyne **2a** and the *trans*/*cis*-enyne resulting from the head-to-head dimerization of phenylacetylene[27] (Table 1, compare Entries 12 and 13). Alternatively, alkynylation of 4-chloroiodobenzene and 4-chlorobromobenzene with phenylacetylene could also be carried out under microwave irradiation conditions at 120 °C, requiring 5 and 10 min, respectively (Table 1, Entries 6 and 14).




**2a**

Scheme 1.

Table 1. Optimization of the reaction conditions for the cross-coupling between phenylacetylene and 4-chlorophenyl iodide or bromide in water.

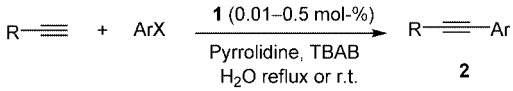
| Entry | X | Catalyst (mol-%) | Base (2 equiv.) | Additive | *T* [°C] | Time | Yield [%][a] | Product ratio[b] **2a**/**3a**/enynes |
|---|---|---|---|---|---|---|---|---|
| 1 | I | **1** (0.1) | $K_2CO_3$ | TBAA[c] | 100 | 7 h | 96 | 84:3:13 |
| 2 | I | **1** (0.1) | $K_2CO_3$ | TBAA[c][d] | 100 | 7 h | 100 | 90:0:10 |
| 3 | I | **1** (0.1) | $K_2CO_3$ | -[d] | 100 | 5 h | 69 | 80:1:19 |
| 4 | I | **1** (0.1) | pyrrolidine | - | 100 | 6 h | 93 | 90:1:9 |
| 5 | I | **1** (0.1) | pyrrolidine | TBAB[e] | 100 | 1 h | 100 (91) | 97:0:3 |
| 6 | I | **1** (0.1) | pyrrolidine | TBAB[e] | 120[f] | 5 min | 96 | 84:0:16 |
| 7 | I | **1** (0.01) | pyrrolidine | TBAB[e] | 100 | 1.5 h | 100 (93) | 96:0:4 |
| 8 | I | $PdCl_2$ (0.01) | pyrrolidine | TBAB[e] | 100 | 1.5 h | 100 | 97:0:3 |
| 9 | I | **1** (0.001) | pyrrolidine | TBAB[e] | 100 | 4 d | 70 | 76:0:24 |
| 10 | I | **1** (1) | pyrrolidine | TBAB[e] | 25 | 1 d | 94 (89) | 97:0:3 |
| 11 | I | $PdCl_2$ (1) | pyrrolidine | TBAB[e] | 25 | 1 d | 69 | 100:0:0 |
| 12 | Br | **1** (0.2) | pyrrolidine | TBAB[e] | 100 | 4 h | 96 (82) | 94:4:2 |
| 13 | Br | $PdCl_2$ (0.2) | pyrrolidine | TBAB[e] | 100 | 2.5 h | 73 | 86:0:14 |
| 14 | Br | **1** (0.1) | pyrrolidine | TBAB[e] | 120[f] | 10 min | 66 | 75:0:25 |

[a] GC yields for compound **2a** based on aryl halide (numbers in parenthesis are isolated yields of alkyne **2a** after column chromatography). [b] Determined by GC. [c] 1 equiv. [d] Pyrrolidine (5 mol-%) was added. [e] 0.5 equiv. [f] The reaction was carried out under microwave irradiation conditions.

The stability of the catalyst **1** in water at reflux and under aerobic conditions was evaluated by performing the cross-coupling between 4-chloroiodobenzene and phenylacetylene in the presence of 0.1 mol-% of complex over several cycles. After the completion of the first run (1 h, 100%), new reagents (phenylacetylene, 4-chloroiodobenzene and pyrrolidine) were added to the reaction mixture. Practically the same results were obtained after five consecutive runs.

These aqueous reaction conditions were then applied to cross-coupling reactions between terminal alkynes and electron-poor or electron-rich aryl iodides or bromides to give internal alkynes **2** (Scheme 2 and Table 2). Couplings of 4-chlorophenyl iodide with phenylacetylene, oct-1-yne and (triisopropylsilyl)acetylene took place in short times and with good yields in the presence of 0.01 to 0.1 mol-% of catalyst **1** (Table 2, Entries 1–3). In the case of an arylation-reluctant reagent, such as *N*,*N*-dimethylpropargylamine, the reaction proceed with a lower rate and yield (Table 2, Entry 4). When the deactivated 4-methoxyphenyl iodide was coupled with different terminal alkynes, the results were similar to those obtained with the activated 4-chlorophenyl iodide (Table 2, Entries 5–7). The diarylenediyne **4** was prepared in high yield through the very fast dialkynylation of *o*-diiodobenzene with phenylacetylene (Table 2, Entry 8). The alkynylation of *N*-acetyl-*o*-iodoaniline was faster with phenylacetylene than with oct-1-yne, affording the corresponding *o*-alkynylanilides **2h** and **2i** in 90 and 61% yields, respectively (Table 2, Entries 9 and 10). In the former case a concomitant indole cyclization (6% yield) was observed. In the reaction between *o*-iodophenol and phenylacetylene, however, the cyclization took place readily to provide benzofuran **5** as the sole product (Table 2, Entry 11).



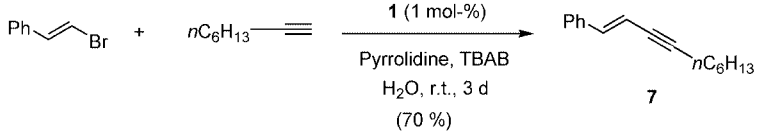

Scheme 2.

We then studied the cross-coupling reaction with aryl bromides, using 0.2 to 0.5 mol-% of palladium complex **1** to provide alkynes **2**–**6** (Table 2, Entries 12–21). In general these alkynylation reactions took place with lower rates and yields than those involving aryl iodides. In many cases an excess of terminal alkyne was added in order to increase the yield of the expected product **2**, due to partial dimerization of the terminal alkyne to the corresponding diyne and enyne. Alternatively, the coupling between phenylacetylene and 4-methoxyphenyl bromide was performed in a single-mode microwave cavity in 10 min at 120 °C, giving compound **2e**, but in lower yield than under conventional heating conditions (Table 2, compare Entries 16 and 17). The reaction between phenylacetylene and 2-bromothiophene gave place to afford compound **6** in 85% yield in only 2 h (Table 2, Entry 21). The cross-coupling between (*E*)-β-bromostyrene and oct-1-yne was performed at room temp. in water over 3 d to afford the enyne **7** stereospecifically in 70% yield (Scheme 3).

The alkynylation of aryl iodides and bromides under copper- and amine-free conditions in the presence of TBAA as base, NMP as solvent and an oxime-derived palladacycle as catalyst have been described by our group.[4a,9a] We applied these conditions to cross-couplings between different terminal alkynes and aryl iodides or bromides to prepare alkynes **2** in the presence of complex **1** or $PdCl_2$ as catalysts (Scheme 4 and Table 3). Coupling between 4-chloroiodobenzene and phenylacetylene was achieved with 0.1 to 0.0005 mol-% loadings of complex **1** in NMP at 110 °C in the presence of 2 equiv. of TBAA in good yields and with high rates (Table 3, Entries 1–3). Very high efficiency at these very low catalyst loadings was also achieved when $PdCl_2$ was used as catalyst but the reaction time increased from 3 to 19 h (Table 3, Entry 4). When this reaction was carried out at room temp. the loadings of both catalysts **1** and $PdCl_2$ needed to be increased to 1 mol-% to give **2a** in 94% and 95% yields, respectively (Table 2, Entries 5 and 6). In addition, when this coupling was carried out in the presence of 0.1 mol-% of complex **1** under microwave conditions at 120 °C, a quantitative yield was observed after 5 min reaction time (Table 3, Entry 7).

Cross-couplings between 4-chloroiodobenzene and (triisopropylsilyl)acetylene or *N*,*N*-dimethylpropargylamine, to give compounds **2c** and **2d**, respectively, were faster in NMP than in $H_2O$ (Table 3, Entries 8 and 9). When deactivated 4-methoxyiodobenzene was coupled with different terminal alkynes, higher rates were observed in NMP than in $H_2O$ (Table 3, Entries 10–12). In the case of *N*,*N*-dimethylpropargylamine the arylation with 4-methoxyiodobenzene took place only in NMP, to give product **2n** in moderate yield (Table 3, Entry 13). Similar results were observed in NMP and in $H_2O$ with *ortho*-substituted iodobenzenes, which were alkynylated very rapidly to furnish diyne **4**, *o*-alkynylated acetanilides **2h** and **2i** and benzofuran **5** in good yields (Table 3, Entries 14–17).

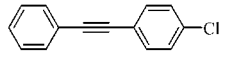
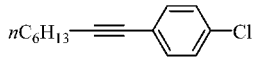
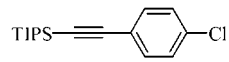
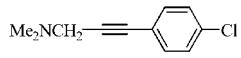
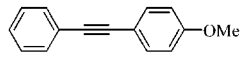
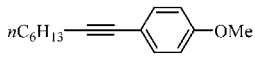
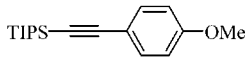
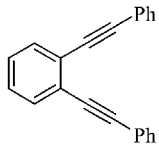
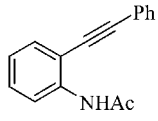
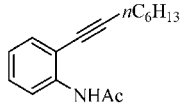
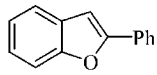
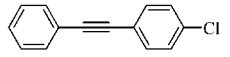
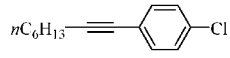
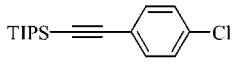
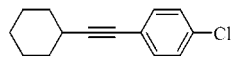
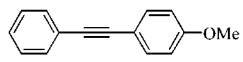
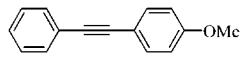
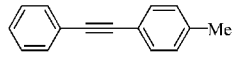
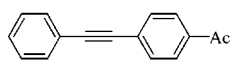
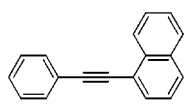
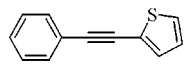
For cross-couplings of aryl bromides in NMP at 110 °C in the presence of TBAA as base, 0.1 to 0.2 mol-% loadings of catalyst **1** were used and the reactions were again faster than in $H_2O$ (Table 3, Entries 18–29). Coupling between phenylacetylene and 4-chlorobromobenzene to afford alkyne **2a** was performed with both catalysts for comparison, giving similar results after 1 h reaction time (Table 3, En-




Scheme 3.

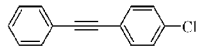
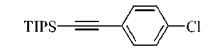
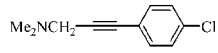
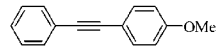
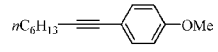
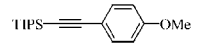
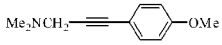
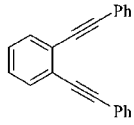
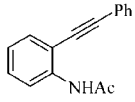
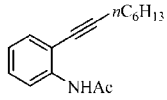
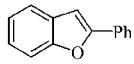
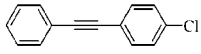
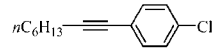
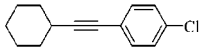
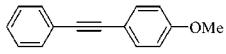
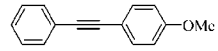
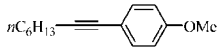
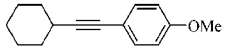
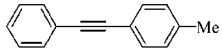
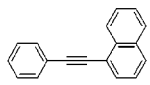
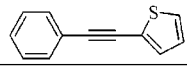
Table 2. Cross-coupling between terminal alkynes and aryl iodides or bromides in water.[a]

| Entry | R | ArX | **1** (mol-%) | Time [h] | No. | Product | Yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | 4-$ClC_6H_4I$ | 0.01 | 1.5 | **2a** |  | 100 (93) |
| 2 | $nC_6H_{13}$ | 4-$ClC_6H_4I$ | 0.1 | 23 | **2b** |  | 85 |
| 3 | $iPr_3Si$ | 4-$ClC_6H_4I$ | 0.1 | 6 | **2c** |  | 94 (81) |
| 4 | $Me_2NCH_2$ | 4-$ClC_6H_4I$ | 0.1 | 22.5 | **2d** |  | 55 |
| 5 | Ph | 4-$MeOC_6H_4I$ | 0.1 | 2 | **2e** |  | 91 (62) |
| 6 | $nC_6H_{13}$ | 4-$MeOC_6H_4I$ | 0.1 | 7 | **2f** |  | 100 |
| 7 | $iPr_3Si$ | 4-$MeOC_6H_4I$ | 0.1 | 17 | **2g** |  | 89 (65) |
| 8 | Ph[c] | 2-$IC_6H_4I$ | 0.1 | 0.5 | **4** |  | 100 (91) |
| 9 | Ph | 2-(AcNH)$C_6H_4I$ | 0.1 | 1 | **2h** |  | 100 (90)[d] |
| 10 | $nC_6H_{13}$ | 2-(AcNH)$C_6H_4I$ | 0.1 | 9 | **2i** |  | 61 |
| 11 | Ph | 2-$HOC_6H_4I$ | 0.1 | 1 | **5** |  | 100 (61) |
| 12 | Ph | 4-$ClC_6H_4Br$ | 0.2 | 4 | **2a** |  | 96 (82) |
| 13 | $nC_6H_{13}$ | 4-$ClC_6H_4Br$ | 0.2 | 23 | **2b** |  | 75 (65) |
| 14 | $iPr_3Si$ | 4-$ClC_6H_4Br$ | 0.2 | 6 | **2c** |  | 87 (79) |
| 15 | $cC_6H_{11}$ | 4-$ClC_6H_4Br$ | 0.2 | 22 | **2j** |  | 30 |
| 16 | Ph | 4-$MeOC_6H_4Br$ | 0.5 | 98 | **2e** |  | 95 |
| 17 | Ph | 4-$MeOC_6H_4Br$ | 0.5 | -[e] | **2e** |  | 30 |
| 18 | Ph | 4-$MeC_6H_4Br$ | 0.2 | 50 | **2k** |  | 100 (76) |
| 19 | Ph | 4-$MeCOC_6H_4Br$ | 0.2 | 2 | **2l** |  | 86 (81) |
| 20 | Ph | 1-naphthylBr | 0.2 | 6 | **2m** |  | 62 |
| 21 | Ph | 2-thienylBr | 0.2 | 2 | **6** |  | 90 (85) |

[a] Reaction conditions: alkyne (1.2 mmol), aryl halide (1 mmol), pyrrolidine (2 mmol), TBAB (0.5 mmol), complex **1** (0.01–0.5 mol-%), $H_2O$ (2.5 mL) reflux. [b] GC yields for alkynes **2** and **4–6**, based on starting aryl halide (numbers in parenthesis are isolated yields after column chromatography). [c] 2 equiv. were used. [d] A 6% yield of the corresponding indole derivative was obtained. [e] The reaction was performed under microwave heating conditions (10 min at 120 °C, 0.5 mmol scale).

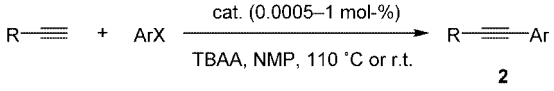
  

Table 3. Cross-coupling of terminal alkynes with aryl iodides and bromides in NMP.[a]

| Entry | R | ArX | **1** (mol-%) | Time [h] | No. | Product | Yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | 4-ClC$_6$H$_4$I | 0.1 | 1 | **2a** |  | 97 (88) |
| 2 | Ph | 4-ClC$_6$H$_4$I | 0.01 | 0.5 | **2a** | | 91 |
| 3 | Ph | 4-ClC$_6$H$_4$I | 0.0005[c] | 3 | **2a** | | 100 (85) |
| 4 | Ph | 4-ClC$_6$H$_4$I | 0.0005[d][e] | 19 | **2a** | | 91 |
| 5 | Ph | 4-ClC$_6$H$_4$I | 1[f] | 44 | **2a** | | 94 |
| 6 | Ph | 4-ClC$_6$H$_4$I | 1[e][f] | 20 | **2a** | | 95 |
| 7 | Ph | 4-ClC$_6$H$_4$I | 0.1 | –[g] | **2a** | | 100 |
| 8 | *i*Pr$_3$Si | 4-ClC$_6$H$_4$I | 0.1 | 0.5 | **2c** |  | 100 (92) |
| 9 | Me$_2$NCH$_2$ | 4-ClC$_6$H$_4$I | 0.1 | 1.5 | **2d** |  | 100 (73) |
| 10 | Ph | 4-MeOC$_6$H$_4$I | 0.1 | 0.5 | **2e** |  | 96 (71) |
| 11 | *n*C$_6$H$_{13}$ | 4-MeOC$_6$H$_4$I | 0.1 | 0.5 | **2f** |  | 95 |
| 12 | *i*Pr$_3$Si | 4-MeOC$_6$H$_4$I | 0.1 | 0.5 | **2g** |  | 100 (85) |
| 13 | Me$_2$NCH$_2$ | 4-MeOC$_6$H$_4$I | 0.1 | 4.5 | **2n** |  | 100 (42) |
| 14 | Ph[h] | 2-IC$_6$H$_4$I | 0.1 | 0.5 | **4** |  | 100 (93) |
| 15 | Ph | 2-(AcNH)C$_6$H$_4$I | 0.1 | 1 | **2h** |  | 100 (96) |
| 16 | *n*C$_6$H$_{13}$ | 2-(AcNH)C$_6$H$_4$I | 0.1 | 0.5 | **2i** |  | 100 (69) |
| 17 | Ph | 2-HOC$_6$H$_4$I | 0.1 | 0.5 | **5** |  | 100 (57) |
| 18 | Ph | 4-ClC$_6$H$_4$Br | 0.1 | 1 | **2a** |  | 80 (68) |
| 19 | Ph | 4-ClC$_6$H$_4$Br | 0.1[e] | 1 | **2a** | | 70 |
| 20 | Ph | 4-ClC$_6$H$_4$Br | 0.1 | –[g] | **2a** | | 88 |
| 21 | *n*C$_6$H$_{13}$ | 4-ClC$_6$H$_4$Br | 0.2 | 3.5 | **2b** |  | 92 (88) |
| 22 | *c*C$_6$H$_{11}$ | 4-ClC$_6$H$_4$Br | 0.1 | 1 | **2j** |  | 86 (69) |
| 23 | Ph | 4-MeOC$_6$H$_4$Br | 0.2 | 7 | **2e** |  | 45 |
| 24 | Ph | 4-MeOC$_6$H$_4$Br | 0.5 | –[g] | **2e** |  | 45 |
| 25 | *n*C$_6$H$_{13}$ | 4-MeOC$_6$H$_4$Br | 0.1 | 1 | **2f** |  | 67 (59) |
| 26 | *c*C$_6$H$_{11}$ | 4-MeOC$_6$H$_4$Br | 0.1 | 1 | **2o** |  | 70 (61) |
| 27 | Ph | 4-MeC$_6$H$_4$Br | 0.2 | 26 | **2k** |  | 36 |
| 28 | Ph | 1-naphthylBr | 0.2 | 2.5 | **2m** |  | 83 (77) |
| 29 | Ph | 2-thienylBr | 0.1 | 1.5 | **6** |  | 90 (83) |

[a] Reaction conditions: alkyne (1.2 mmol), aryl halide (1 mmol), TBAA (2 mmol), complex **1** (0.0005–1 mol-%), NMP (2 mL), 110 °C. [b] GC yields for alkynes **2**, **4**–**6** based on starting aryl halide (numbers in parenthesis are isolated yields after column chromatography). [c] The reaction was performed on a 4 mmol scale. [d] The reaction was performed on 15 mmol scale. [e] $PdCl_2$ was used as catalyst. [f] At room temp. [g] The reaction was performed under microwave heating conditions (5 min at 120 °C, 0.5 mmol scale). [h] 2 equiv. were used.




Scheme 4.

tries 18 and 19). Deactivated 4-methoxyphenyl bromide provided higher yields with alkylacetylenes than with phenylacetylene (Table 3, Entries 23, 25 and 26). For the coupling under microwave conditions to give compound **2e**, the loading of catalyst had to be increased to 0.5 mol-% in order to achieve the same yield as under conventional heating conditions (Table 3, compare Entries 23 and 24).

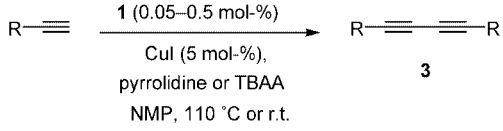
The catalytic activity of complex **1** (0.1 mol-%) under NMP/TBAA conditions was studied as described before in $H_2O$, but now for coupling between phenylacetylene and 4-methoxyiodobenzene, always giving quantitative yields of alkyne **2e** after five cycles of 30 min. The same behaviour was observed for coupling between 4-chlorobromobenzene and phenylacetylene in the presence of 0.1 mol-% of catalyst **1**, with yields between 77 and 81% being obtained during five consecutive cycles of 1 h.

The beneficial effect of TBAB as an additive in cross-couplings between terminal acetylenes and aryl halides in water can be attributed to the stabilization of palladium nanoparticles, which can be formed from palladium salts or complexes in water or in the presence of amines or alcohols.[28] The formation of palladium nanoparticles by treatment of a related PS-PEG-anchored dipyridin-2-ylamine–palladium(II) acetate complex with benzyl alcohol in water at reflux has been described.[29] A similar reducing process can take place in the case of complex **1**, with the aid of the amine. In addition, polar organic solvents such as propylene carbonate and NMP are also able to stabilize Pd nanoparticles in the absence of surfactants.[28b] We can therefore postulate that Pd nanoparticles may be formed in the case of the alkynylation reactions in NMP. It is worth noting that we never observed precipitation of palladium black under the conditions described here for these alkynylation reactions.

It can be concluded that, in general, cross-couplings between terminal alkynes, specially alkylacetylenes, and aryl iodides or bromides were more efficient and faster in NMP than in $H_2O$ either with heating or at room temp. Pyrrolidine was the base of choice for these alkynylation reactions in neat water, whereas TBAA was more appropriate for the NMP couplings. With respect to the palladium catalyst, both the (dipyridin-2-ylmethyl)amine-derived complex **1** and ligandless $PdCl_2$ can be used for these Sonogashira-type reactions, but the former catalyst was in general more efficient. Alternatively, these couplings can be run under microwave irradiation conditions in shorter reaction times.

## Homocoupling Reactions of Terminal Alkynes

For homocoupling of terminal alkynes to give diynes **3** (Scheme 5) we applied the same reaction conditions as we had found to be appropriate with oxime-derived palladacycles as catalyst.[4a] Homocoupling of alkynes in NMP in the presence of complex **1** as catalyst and CuI as co-catalyst in the absence of a reoxidant could be performed either at 110 °C or at room temp. in the presence either of pyrrolidine (1.1 equiv.) or of TBAA (1.5 equiv.) as bases, to afford diynes **3** in high yields (Scheme 5 and Table 4). In general,




Scheme 5.

Table 4. Homocoupling reactions of terminal alkynes to give diynes **3**.[a]

| Entry | X | Catalyst (mol-%) | Base (2 equiv.) | *T* [°C] | Time | Yield [%][b] | Product No. |
|---|---|---|---|---|---|---|---|
| 1 | PhC≡CH | **1** (0.05) | TBAA | 110 | 4 h | 100 (99) | **3a** |
| 2 | | $PdCl_2$ (0.05) | TBAA | 110 | 6 h | 94 | **3a** |
| 3 | | **1** (0.05) | pyrrolidine | 110 | 2 h | 100 | **3a** |
| 4 | | $PdCl_2$ (0.05) | pyrrolidine | 110 | 2 h | 100 | **3a** |
| 5 | | **1** (0.5) | TBAA | rt | 22 h | 100 | **3a** |
| 6 | | $PdCl_2$ (0.5) | TBAA | rt | 8 d | 28 | **3a** |
| 7 | | **1** (0.5) | pyrrolidine | rt | 2 h | 92 | **3a** |
| 8 | | $PdCl_2$ (0.5) | pyrrolidine | rt | 2 h | 98 | **3a** |
| 9 | $nC_6H_{13}C$≡CH | 0.05 | TBAA | 110 | 21.5 h | 100 (92) | **3b** |
| 10 | | 0.05 | pyrrolidine | 110 | 3 h | 100 | **3b** |
| 11 | | 0.5 | TBAA | rt | 19 d | 100 | **3b** |
| 12 | | 0.5 | pyrrolidine | rt | 9 d | 100 (92) | **3b** |
| 13 | $iPr_3SiC$≡CH | 0.05 | TBAA | 110 | 1 d | - | **3c** |
| 14 | | 0.05 | pyrrolidine | 110 | 3 h | 100 (82) | **3c** |
| 15 | | 0.5 | pyrrolidine | rt | 2.5 h | 63 | **3c** |
| 16 | $cC_6H_{11}C$≡CH | 0.05 | TBAA | 110 | 5 h | 99 (90) | **3j** |
| 17 | | 0.05 | pyrrolidine | 110 | 2 h | 98 | **3j** |
| 18 | | 0.5 | TBAA | rt | 4 d | 100 | **3j** |
| 19 | | 0.5 | pyrrolidine | rt | 3.5 h | 91 | **3j** |

[a] Reaction conditions: alkyne (1 mmol), pyrrolidine (1.1 mmol) or TBAA (1.5 mmol), complex **1** or $PdCl_2$, CuI (5 mol-%), NMP (2 mL) 110 °C or room temp. [b] GC yields for compounds **3** based on starting alkyne (numbers in parenthesis are isolated yields of diyne **3** after column chromatography).

the reaction was performed at 110 °C with 0.05 mol-% of complex **1** or $PdCl_2$ and with 0.5 mol-% loading of palladium at room temp. With regard to the use of pyrrolidine or TBAA as bases, the former gave higher rates, especially at room temp. In the case of (triisopropylsilyl)acetylene, homocoupling to give diyne **3c** took place only in the presence of pyrrolidine as base (Table 4, Entries 13–15). With respect to the catalyst, complex **1** and $PdCl_2$ displayed similar efficiencies with pyrrolidine as base (Table 4, Entries 3, 4 and 7, 8), but complex **1** proved to be the more efficient catalyst when TBAA was used as base (Table 4, Entries 1, 2 and 5, 6). Under aerobic conditions, the oxygen present in the reaction mixture was enough to act as an oxidant of $Cu^{I}$ to $Cu^{II}$.[30] However, these Glaser-type homocouplings failed in water as solvent. When the homocoupling of phenylacetylene was performed under microwave irradiation conditions at 120 °C, either in a sealed tube or in a open vessel, the corresponding enyne was mainly formed.

## Conclusions

In conclusion, both the (dipyridin-2-ylmethyl)amine-derived palladium(II) chloride complex **1** and $PdCl_2$ have been demonstrated to be very active and efficient catalysts for the copper-free alkynylation of aryl iodides and bromides in water at reflux and at room temp. in the presence of pyrrolidine as base and TBAB as additive. Complex **1** showed higher efficiency than $PdCl_2$, especially under room temp. conditions. Alternatively, cross-couplings between terminal alkynes and aryl iodides or bromides can be performed under copper- and amine-free conditions, either with complex **1** or $PdCl_2$, in NMP as solvent at 110 °C with TBAA as base. The efficiency of these cross-coupling processes was higher in NMP (TOFs up to 66666 $h^{-1}$) than in water (TOFs up to 6666 $h^{-1}$). Complex **1** showed very high stability in water and in NMP under aerobic conditions and no deactivation was observed after five consecutive cycles. These alkynylation reactions can also be performed under MW conditions at 120 °C, with reaction times of 5 to 10 min. For the homocoupling reaction to prepare diynes, NMP had to be used as solvent and complex **1** was the more efficient catalyst, especially at room temp., the reaction failing with water as solvent. These Glaser-type reactions must be carried out in the presence of CuI as co-catalyst but in the absence of a reoxidant, just working under aerobic conditions. The use of pyrrolidine as base afforded higher reaction rates than TBAA either at 110 °C or at room temp. All these results indicate that the designed pyridine ligand could be a good candidate for inmobilization on a solid support in order to recover the palladium after the coupling.

## Experimental Section

**General Methods:** The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin layer chromatography was performed on Polygram® SIL G/$UV_{254}$ plates. M.p.s were determined on a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on a HP-6890 instrument fitted with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophotometer in $cm^{-1}$. $^1H$ NMR spectra were recorded on a Bruker AC 300 instrument (300 MHz). Chemical shifts are reported in ppm with tetramethylsilane (TMS, 0.00 ppm) as internal standard. $^{13}C$ NMR spectra were recorded at 75 MHz with $CDCl_3$ as the internal reference. EI-MS were measured on an Agilent Technologies 5973N Mass Selective Detector G2579A in *m/z* (rel. intensity in % of base peak). HRMS were performed on a Finnigan MAT95S apparatus. Elemental analysis were carried out in a Carlo Erba EA 1108 (CHNS-O) by the corresponding services at the University of Alicante. The catalysts were weighed in an electronic microscale (Sartorius, XM1000P) with a precision of 1 μg. Microwave reactions were performed with a CEM Discover Synthesis Unit in glass vessels (10 mL) sealed with a septum under magnetic stirring at 120 °C and 120 W.

**General Procedure for Cross-Couplings of Aryl Halides with Alkynes in Water:** A 10 mL round-bottomed flask was charged with palladium catalyst **1** or $PdCl_2$ (see Tables 1 and 2), aryl halide (1 mmol), alkyne (1.5 mmol), pyrrolidine (2 mmol), tetrabutylammonium bromide (0.5 mmol) and water (2.5 mL). The mixture was stirred at 100 °C or room temp. for the reaction time indicated in Tables 1 and 2. The reaction progress was analysed by GLC. The mixture was extracted with EtOAc (3 × 15 mL), dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel.

**General Procedure for Cross-Couplings of Aryl Halides with Alkynes in NMP:** A mixture of palladium catalyst **1** or $PdCl_2$ (see Table 3), aryl halide (1 mmol), alkyne (1.5 mmol) and tetrabutylammonium acetate (2 mmol) in NMP (2 mL) was stirred at 110 °C or room temp. for the reaction time indicated in Table 3. The reaction progress was analysed by GLC. The reaction mixture was extracted with water and EtOAc, dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel.

Compounds **2a**, **2e**, **2h**, **2k**, **2l**, **2m**, **4**, **5** and **6** are commercially available, while compounds **2b**,[4a] **2c**,[4a] **2d**,[31] **2f**,[32] **2g**,[4a] **2n**[33] and **7**[34] have been reported previously and were characterized by comparison with their reported data. Physical, analytical and spectroscopic data of newly synthesized compounds follow:

***N*-[2-(1-Octynyl)phenyl]acetamide (2i):** Colourless solid, m.p. 62 °C. $R_f$ (Hex/AcOEt 9:1) = 0.25. $^1H$ NMR ($CDCl_3$): $\delta$ = 8.37 (d, $J$ = 8.3 Hz, 1 H,), 7.96 (br. s, 1 H), 7.37 (dd, $J_1$ = 1.2, $J_2$ = 7.6 Hz, 1 H), 7.29–7.24 (dt, $J_1$ = 1.23, $J_2$ = 8.8 Hz, 1 H), 6.99 (t, $J$ = 7.5 Hz, 1 H), 2.50 (t, $J$ = 6.9 Hz, 2 H), 2.20 (s, 1 H), 1.69–1.60 (m, 2 H), 1.53–1.44 (m, 2 H), 1.35–1.31 (m, 4 H), 0.91 (t, $J$ = 6.9 Hz, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 168 (C=O), 138.8, 313.4, 128.7, 123.1, 118.9, 112.5 (6 × C-Ar), 97.8, 75.9 (2 × C≡C), 31.3 ($CH_2$), 28.6 (2 × $CH_2$), 24.8 ($CH_3$), 22.5, 19.5 (2 × $CH_2$), 14.0 ($CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3259.34, 3050, 2962.06, 2930.66, 2856.06, 2235.51, 1663.94, 1576.69, 1536.55, 1447.37, 1365.88, 1304.44, 756.52, 725.6, 689.69 $cm^{-1}$. EIMS (70 eV): *m/z* (%) = 243 $[M]^+$ (18), 200 (29), 186 (33), 173 (33), 172 (36), 158 (23), 143.9 (29), 142.9 (23), 129.9 (100), 116.9 (18), 114.9 (15), 105.9 (27), 102.9 (21), 76.9 (21). HRMS calcd. 243.1623, found 243.1635. $C_{16}H_{21}NO$ (243.3): calcd. C 78.97, H 8.70, N 5.76; found C 79.05, H 8.76, N 5.73.

**1-(4-Chlorophenyl)-2-cyclohexylacetylene (2j):** Yellow oil, $R_f$ (Hex) = 0.61. $^1H$ NMR ($CDCl_3$): $\delta$ = 7.29 (d, $J$ = 8.6 Hz, 2 H), 7.21 (d, $J$ = 8.6 Hz, 2 H), 2.59–2.51 (m, 1 H), 1.87–1.72 (m, 4 H), 1.55–1.49 (m, 3 H), 1.33–1.29 (m, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 133.2, 132.7, 128.3, 122.6 (6 × C–Ar), 95.4, 79.4 (2 × C≡C), 32.5

($CH_2$), 29.5 (CH), 25.8 ($CH_2$), 25.3 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 2931.45, 2853.96, 2667.07, 2235.51, 1489.71, 1448.35, 1397.53, 1090.95, 1014.54, 827.29 $cm^{-1}$. EIMS (70 eV): *m*/*z* (%) = 220 [*M* + 2] (30), 219 (15), 218 $[M]^+$ (93), 190.9 (20), 189.9 (34), 183 (41), 176.9 (32), 175.9 (27), 174.9 (69), 163.9 (31), 161.9 (36), 155 (55), 154 (31), 153 (34), 152 (22), 150.9 (17), 148.9 (32), 142 (28), 141 (100), 138.9 (24), 137.9 (18), 135.9 (37), 129 (48), 128 (21), 126.9 (51), 126 (21), 124.9 (24), 115 (24). HRMS calcd.218.0862, found 218.0859.

**1-(2-Cyclohexyl-1-ethynyl)-4-methoxybenzene (2o):** Yellow oil, $R_f$ (Hex) = 0.24. $^1H$ NMR ($CDCl_3$): $\delta$ = 7.24 (d, *J* = 8.7 Hz, 2 H), 6.71 (d, *J* = 8.7 Hz, 2 H), 3.69 (s, 3 H), 2.51–2.43 (m, 1 H), 1.81–1.24 (m, 10 H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 158.9, 132.8, 116.2, 113.7 (6×C–Ar), 92.8, 80.1 (2×C≡C), 55.1 ($OCH_3$), 32.8 ($CH_2$), 29.6 (CH), 25.9 ($CH_2$), 24.9 ($CH_2$) ppm. IR (film): $\tilde{\nu}$ = 2931.04, 2853.42, 2235.5, 1606.29, 1509.29, 1447.8, 1286.84, 1250.96, 1172.02, 1105.21, 1033.83, 830.72 $cm^{-1}$. EIMS (70 eV): *m*/*z* (%) = 215 (16), 214 $[M]^+$ (100), 172 (25), 172 (78), 144.9 (19), 142.9 (17), 141 (17), 127.9 (24), 121 (16) 114.9 (30). HRMS calcd. 214.1358, found 214.1356.

**General Procedure for Homocouplings of Terminal Alkynes:** A mixture of palladium catalyst **1** or $PdCl_2$ (see Table 4), alkyne (1 mmol), tetra-*n*-butylammonium acetate (1.5 mmol) or pyrrolidine (1.1 mmol) in NMP (2 mL) was heated to 110 °C or at room temp. in air for the reaction time shown in Table 4. The reaction progress was analysed by GLC. The mixture was extracted with water and EtOAc, dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel. Compound **3a** is commercially available, and compounds **3b**,[4a] **3c**[4a] and **3j**[35] have been reported previously and were characterized by comparison with their reported data.

## Acknowledgments

This work was supported by the Dirección General de Investigación of the Ministerio de Educación y Ciencia (MEC) (grants: BQU2001–0724-CO2–01, CTQ2004–00808/BQU) and the University of Alicante. J. G.-M. thanks the MEC for a predoctoral fellowship.

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Received: May 5, 2005
Published Online: August 8, 2005

  