

# A very efficient, copper-free palladium catalyst for the Sonogashira reaction with aryl halides

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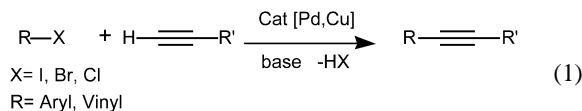
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Received (in Cambridge, UK) 13th May 2003, Accepted 16th June 2003

First published as an Advance Article on the web 1st July 2003

The new complex  $[\text{Pd}\{t\text{-Bu}_2\text{PCH}_2\text{N}(\text{CH}_2\text{Ph})\text{CH}_2\text{Pt-Bu}_2\}(\text{OAc})_2]$  is a very efficient catalyst for the Sonogashira cross-coupling reaction of aryl halides with acetylenes at room temperature, without co-catalyst.

The Sonogashira cross-coupling reaction is a useful straightforward synthetic strategy for the synthesis of aryl or vinyl acetylenes from aryl or vinyl halides and terminal alkynes (eqn. 1). The most usual procedure for this reaction uses Pd(0)/Cu(I)-catalysts and a base (often an amine as solvent).<sup>1,2</sup> Actually, Pd(II) catalysts generally exhibit greater long-term stability than Pd(0) species and can be stored under normal laboratory conditions for several months. In the Pd(II)/Cu(I)-catalytic system, the active 14-electron Pd(0) catalyst is formed by Cu(I)-catalyzed bis-alkynylation of the Pd complex followed by reductive elimination of diphenyldiacetylene.



Many applications of the Sonogashira coupling of aryl halides with terminal alkynes have been reported in the literature since 1975. For instance, Ryu recently described such a coupling in ionic liquids with the purpose of recycling the catalyst,<sup>3</sup> and Mori used TBAF/Ag<sub>2</sub>O system as co-catalyst reagents.<sup>4</sup> The use of aryl bromide or chloride, however, has only been recently explored owing to their poor reactivity.<sup>5</sup> Nevertheless, it is of great interest to extend the scope of this reaction to these aryl halides because of their low cost, especially for synthetic laboratory and industrial chemistry.

On the other hand, very few examples of single "palladium-only" catalysts have been reported to be active in this cross-coupling reaction without the presence of a co-catalyst. Recently, Böhm and Hermann proposed a copper-free procedure using  $[\text{Pd}_2(\text{dba})_3/\text{P}(t\text{-Bu})_3]$  as a catalyst for the Sonogashira reaction of aryl bromides at room temperature.<sup>6</sup> Pal *et al.* used  $[\text{PdCl}_2(\text{PPh}_3)_2]$  at 80 °C in a copper-free procedure to synthesize 4-substituted-aryl-1-butanones from aryl bromides.<sup>7</sup> The Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> mixture has been used by Fu *et al.* in a copper-free catalyzed cross-coupling reaction of vinyl tosylates with terminal acetylenes, and Nájera *et al.* described an amine-free and copper-free Sonogashira coupling procedure of aryl iodides and bromides catalyzed by oxime palladacycles with high TON's.<sup>8</sup> These improved procedures in the absence of a co-catalyst avoid the oxidative homo-coupling reaction of the acetylenic reagent that is observed in the presence of a Cu(I) co-catalyst. Some Cu(I) acetylides are formed *in situ* and can undergo oxidative dimerization to diphenyldiacetylenes if they are exposed to air (a reaction known as the Glaser coupling).<sup>9</sup> These by-products are generally not easy to separate from the desired products.

We now report the synthesis and the remarkable catalytic activity in Sonogashira cross-coupling of complex **1** in which a

bulky and electron-rich chelating bis-*tert*-butylphosphine ligand (Chart 1) is coordinated to Pd(II).

Bis(*tert*-butylaminomethylphosphine) has been synthesized by addition of benzylamine onto a bis-*tert*-butylhydroxymethylphosphonium salt prepared according to a known procedure.<sup>10</sup> The palladium complex was synthesized by treatment of bis(*tert*-butylaminomethylphosphine) with palladium acetate at room temperature for one hour. This Pd(II) complex **1** was purified by further precipitations from CH<sub>2</sub>Cl<sub>2</sub>/pentane, and was stored under nitrogen. It was isolated with 95% yield and was characterized by <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR.†

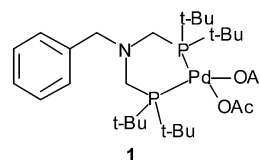
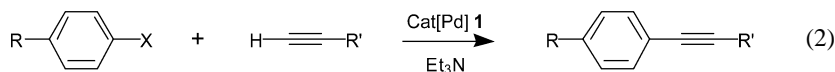


Chart 1

The ability of **1** to cross-couple acetylenes with aryl halides in a simple one-pot procedure without a co-catalyst and at low catalyst concentrations is summarized in Table 1 and eqn. 2. All reactions were carried out using triethylamine as both the base and solvent, and between -40 °C and 80 °C. The products were purified and analyzed by <sup>1</sup>H NMR. Isolated yields were determined after silica-gel column chromatography (Table 1). The cross-coupling reactions are quantitative, and very fast conversions are obtained at 1 mol% Pd loading for iodobenzene and bromobenzene (entries 1, 2, 10 and 11) even at room temperature. Note that the reaction also occurs at low temperatures in good yields (entries 3 and 4). The Pd complex **1** shows excellent activity, and we even obtained turnover numbers as high as 10<sup>5</sup> for entry 9. Trimethylsilylacetylene was cross-coupled with both iodobenzene and bromobenzene at room temperature in good but not quantitative yields (entries 5 and 13). Indeed, Nolan reported Sonogashira cross-coupling of aryl halides with the TMS group of substituted trimethylsilylacetylenes, giving substituted phenylacetylenes in good yields.<sup>11</sup> In our case dealing with trimethylsilylacetylene itself, however, products resulting from its dimerization are formed as indicated by mass spectral evidence, which lowers the cross-coupling yields (entries 5 and 13).

Substantial reactivity of aryl chlorides with acetylenes is found in our system even at room temperature (entries 14–21). For instance, activated aryl chlorides give the cross-coupling products in 30% yield (entry 20). The yields are low due to the low rates of the cross-coupling reactions compared to the faster homo-coupling of the alkyne that provides the by-product.

In summary, we have disclosed a very efficient Pd(II) catalyst for the Sonogashira cross-coupling of aryl halides with acetylenes in a simple one-pot procedure free of co-catalyst at room temperature. The yields are good to excellent with aryl bromide and iodide and, under these mild conditions, even aryl chlorides give significant results. Future work is directed towards further use of such a ligand, its late-transition-metal



**Table 1** Reactions conditions, conversions and turnover numbers (TON) for the Sonogashira coupling of aryl halides with alkynes using **1** as the sole catalyst<sup>a</sup>

Entry	X	R	R'	Catalyst <b>1</b>		React. time	Conv. (%) <sup>b</sup>	TON
				Temperature/°C	(mol%)			
1	I	H	C <sub>6</sub> H <sub>5</sub>	80	1	15 min	100	100
2	I	H	C <sub>6</sub> H <sub>5</sub>	25	1	30 min	100	100
3	I	H	C <sub>6</sub> H <sub>5</sub>	-20	1	1 d	70	70
4	I	H	C <sub>6</sub> H <sub>5</sub>	-40	1	2 d	51	51
5	I	H	Si(CH <sub>3</sub> ) <sub>3</sub>	25	1	8 h	76	76
6	I	H	C <sub>6</sub> H <sub>5</sub>	80	0.5	15 min	100	200
7	I	H	C <sub>6</sub> H <sub>5</sub>	80	0.1	2 h	100	1000
8	I	H	C <sub>6</sub> H <sub>5</sub>	80	0.01	1 d	87	8700
9	I	H	C <sub>6</sub> H <sub>5</sub>	80	0.001	7 d	71	71000
10	Br	H	C <sub>6</sub> H <sub>5</sub>	80	1	20 min	100	100
11	Br	H	C <sub>6</sub> H <sub>5</sub>	25	1	1 h	100	100
12	Br	Me	C <sub>6</sub> H <sub>5</sub>	80	1	3 h	96	96
13	Br	H	Si(CH <sub>3</sub> ) <sub>3</sub>	25	1	15 h	54	54
14	Cl	H	C <sub>6</sub> H <sub>5</sub>	80	1	50 min	4	4
15	Cl	H	C <sub>6</sub> H <sub>5</sub>	25	1	3 h	9	9
16	Cl	H	Si(CH <sub>3</sub> ) <sub>3</sub>	25	1	2 d	5	5
17	Cl	CN	C <sub>6</sub> H <sub>5</sub>	80	1	5 d	13	13
18	Cl	F	C <sub>6</sub> H <sub>5</sub>	80	1	5 d	14	14
19	Cl	COOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	25	1	3 d	15	15
20	Cl	COOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	80	2	3 d	30	30
21	Cl	COOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	40	1	3 d	22	22

<sup>a</sup> Reaction conditions: aryl halide (2 mmol), alkyne (3 mmol), Et<sub>3</sub>N (6 mL). <sup>b</sup> Unoptimized isolated yield.

complexes and their derivatives including the synthesis of complex molecules.

## Notes and references

† Selected data for **1**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 7.25 (m, 5H, Ph), 3.58 (s, 2H, NCH<sub>2</sub>), 2.66 (s, 4H, NCH<sub>2</sub>P), 1.89 (s, 6H, CH<sub>3</sub>), 1.39 (s, 18H, *t*-Bu), 1.32 (s, 18H, *t*-Bu). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz): δ (ppm) 31.8 (s, *t*-Bu), 33.2 (s, *t*-Bu), 36.3 (s, Me), 44.1 (s, NCH<sub>2</sub>P), 67.5 (s, CH<sub>2</sub>N), 128.6–135.1 (s, CH and C arom.), 176 (s, CO). <sup>31</sup>P{<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 27 ppm.

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