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Highly Convenient, Clean, Fast, and Reliable Sonogashira Coupling Reactions Promoted by Aminophosphine-Based Pincer Complexes of Palladium Performed under Additive- and Amine-Free Reaction Conditions

Jeanne L. Bolliger[a] and Christian M. Frech[a,*]

[a] Department of Inorganic Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland
Fax: (+41)-44-635-6802; e-mail: chfrech@aci.uzh.ch

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Abstract: Sequential addition of 1,1′,1″-phosphinetriyltripiperidine and 1,3-diaminobenzene or resorcinol to toluene solutions of (cyclooctadiene)palladium dichloride [Pd(cod)(Cl)$_2$] under nitrogen in "one pot" almost quantitatively yielded the aminophosphine-based pincer complexes {[C$_6$H$_3$-2,6-(XP{piperidinyl}$_2$)$_2$]Pd(Cl)} (X=NH **1**; X=O **2**). Complex **1** (and to a minor extent **2**) proved to be efficient Sonogashira catalysts, which allow the quantitative coupling of various electronically deactivated and/or sterically hindered and functionalized aryl iodides and aryl bromides with several alkynes as coupling partners within very short reaction times and low catalyst loadings. Importantly, in contrast to most of the Sonogashira catalysts, which either are both air- and moisture-sensitive and/or require the addition of co-catalysts, such as copper(I) iodide [CuI], for example, or a large excess of an amine, the coupling reactions were carried out without the use of amines, co-catalysts or other aditives and without exclusion of air and moisture. Moreover, the desired products were exclusively formed (no side-products were detected) without employing an excess of one of the substrates. Ethylene glycol and potassium phosphate (K$_3$PO$_4$) were found to be the ideal solvent and base for this transformation. Experimental observations strongly indicate that palladium nanoparticles are not the catalytically active form of **1** and **2**. On the other hand, their transformation into another homogeneous catalytically active species cannot be excluded.

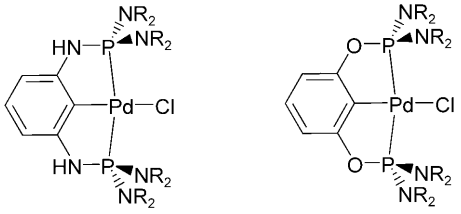
Keywords: C–C coupling; cross-coupling; palladium; pincer complexes

Introduction

The Sonogashira reaction (cross-coupling of aryl or vinyl halides with terminal alkynes) belongs nowadays to an indispensable set of palladium-catalyzed cross-coupling reactions and is the most important method for the synthesis of internal acetylenes,[1–3] which finds its application in a wide range of organic processes, such as the preparation of natural products,[5,6] pharmaceuticals,[7] biologically active molecules,[8] liquid crystalline materials and conducting polymers,[9] or molecular electronics in general.[10] Although recent developments have led to a considerable increase in the activity of Sonogashira catalysts, of which some efficiently couple sterically hindered substrates or occasionally even aryl chlorides,[11] their syntheses are often time-consuming, difficult, and/or require the use of expensive starting materials. Moreover, most of these catalysts are air- and moisture-sensitive, require either a co-catalyst (CuI, ZnCl$_2$ or FeCl$_3$) and/or the use of excess amines (sometimes even as solvents), prolonged reaction times (typically 12–24 h with aryl bromides), relatively high catalyst loadings (1–5 mol%), and/or the use of an excess of one of the substrates for efficient and high-yielding product formations.[12–17] Among other reasons, PdCl$_2$(PPh$_3$)$_2$, PdCl$_2$/PPh$_3$, and Pd(PPh$_3$)$_4$ therefore still are the most widely used catalysts in organic chemistry even though high catalyst loadings (typically 5 mol%), large amounts of copper(I) iodide [for the *in situ* generation of copper(I) acetylides],[18] and excess of an amine, such as diisopropylamine are required. Thus, the development of more efficient, but cheap and easily prepared catalysts, which allow the perfor-

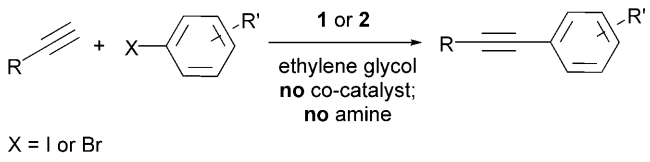
mance of Sonogashira cross-coupling reactions with low catalyst loadings under *additive- and amine-free* reaction conditions and without the need of exclusion of air and moisture, is of high general interest.

We report herein the catalytic activity of aminophosphine-based pincer complexes of palladium with the general formula of {[C_6H_3-2,6-(XP{piperidinyl}$_2$)$_2$]Pd(Cl)} (X = NH **1**; X = O **2**) in Sonogashira



1 R = piperidyl **2**

cross-coupling reactions, which fulfill most of the desired catalyst properties (Scheme 1).



Scheme 1. Sonogashira cross-coupling reactions of aryl halides with terminal acetylenes catalyzed by {C_6H_3-2,6-[XP(piperidinyl)$_2$]$_2$Pd(Cl)} (X = NH **1**; X = O **2**).

Results and Discussion

The aminophosphine-based pincer complexes **1** and **2** were recently shown to be extremely efficient Heck and Suzuki catalysts, which are prepared in excellent yields from very cheap starting materials in an extremely short and simple way {**1** and **2** can be isolated as analytically pure and colorless solids from "one-pot" reactions of [Pd(cod)(Cl)$_2$] (cod = cyclooctadiene), 1,1′,1″-phosphinetriyltripiperidine and 1,3-diaminobenzene (or resorcinol, respectively) in toluene under N_2 within less than one hour}.[21] Remarkably, the catalysts remain stable in solution for several months at room temperature and afford the coupling products at essentially the same conversion rates and yields as freshly prepared catalyst solutions from pure **1** and **2**, respectively.[22]

Both complexes exhibit high activity in the catalytic coupling of terminal acetylenes with aryl iodides without the use of co-catalysts or other additives, under amine-free reaction conditions, and lead to high conversion rates and excellent yields at very low catalyst loadings (0.005 mol%) even for electronically deactivated and/or sterically hindered and functionalized substrates. Ethylene glycol and K_3PO_4 were found to be the ideal solvent and base for this transformation. Ethylene glycol was neither degassed nor dried prior to use,[23] since these catalysts allow one to carry out Sonogashira coupling reactions without excluding air and moisture.[24] Furthermore, in contrast to most known catalysts, no excess of neither substrate is required for the quantitative yield of the coupling products.[25] Indeed, homocoupled products or other side reactions were *not* detected under these reaction conditions, which makes the product separation very easy. In sharp contrast, the inclusion of copper salts or other co-catalysts, such as $ZnCl_2$ and $FeCl_3$ and/or additives, for example, tetrabutylammonium bromide was found to promote the formation of side-products. Catalyst **1** was found to be generally more active when compared with complex **2** (see Table 1). For example, phenyl iodide and ethynylbenzene underwent complete C–C coupling into 1,1′-ethyne-1,2-diyldibenzene in the presence of K_3PO_4 and only 0.005 mol% of **1** within less than 15 min in ethylene glycol at 140 °C, whereas a reaction time of 1 hour was necessary with catalyst **2** (Table 1, entries 1 and 3). Similarly, when 1-ethynyl-2,4,5-trimethylbenzene was used as coupling partner complete C–C coupling was observed within a 15 min reaction time with catalyst **1** (Table 1, entry 4). Exclusive formation of 1-methoxy-4-(phenylethynyl)benzene and 4-(phenylethynyl)aniline, respectively, was observed with electronically deactivated substrates such as 4-iodoanisole or 4-iodoaniline. Only 15 min were required for quantitative product formation with **1** (Table 1, entries 5 and 7), whereas 1 hour was required to achieve a yield of 92% of 4-(phenylethynyl)aniline with catalyst **2** (Table 1, entry 9). The same yields and conversion rates were obtained with 1-ethynyl-2,4,5-trimethylbenzene as coupling partner (Table 1, entries 6 and 10). Excellent conversion rates and yields were also observed when 4-iodophenol was used as coupling partner (Table 1, entries 11 and 12). Full conversions were obtained within only 15 min with **1**. The same yields and conversion rates were noticed when sterically hindered 2-iodotoluene was coupled with ethynylbenzene or 1-ethynyl-2,4,5-trimethylbenzene, respectively (Table 1, entries 13 and 16). On the other hand, retarded conversion was observed when 2-iodobiphenyl was used as coupling partner (Table 1, entries 17 and 18). About 95% of the coupling products was obtained with catalyst **1**. While the product formation was complete within 30 min with ethynylbenzene as coupling partner, 90 min were required with 1-ethynyl-2,4,5-trimethylbenzene. Sonogashira reactions performed with sterically hindered and electronically deactivated 1-iodo-2-methoxybenzene yielded 100% of the coupling product within 30 min with catalyst **1**

Table 1. Sonogashira cross-coupling reactions of aryl iodides with ethynylbenzene and 1-ethynyl-2,4,5-trimethylbenzene (ethynyltrimethylbenzene) catalyzed by $\{C_6H_3\text{-}2,6\text{-}[XP(piperidinyl)_2]_2Pd(Cl)\}$ (X = NH **1**; X = O **2**).[a]

Entry	Aryl iodide	Alkyne	Cat. (ppm)	Conv. [%][b]	*t* [h]	TOF[c]	TON[d]
1	iodobenzene	ethynylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
2[e]	iodobenzene	ethynylbenzene	**1** (0.5)	100	6	333,333	2.0×10^6
3	iodobenzene	ethynylbenzene	**2** (50)	95	1	19,000	19,000
4	iodobenzene	ethynyltrimethylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
5	4-iodomethoxybenzene	ethynylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
6	4-iodomethoxybenzene	ethynyltrimethylbenzene	**1** (50)	94	0.33	56,400	18,800
7	4-iodoaniline	ethynylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
8[e]	4-iodoaniline	ethynylbenzene	**1** (0.5)	92	7	262,857	1.84×10^6
9	4-iodoaniline	ethynylbenzene	**2** (50)	92	1	18,400	18,400
10	4-iodoaniline	ethynyltrimethylbenzene	**1** (50)	92	0.5	36,800	18,400
11	4-iodophenol	ethynylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
12	4-iodophenol	ethynyltrimethylbenzene	**1** (50)	95	0.25	76,000	19,000
13	2-iodotoluene	ethynylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
14[e]	2-iodotoluene	ethynylbenzene	**1** (0.5)	97	8	242,500	1.94×10^6
15	2-iodotoluene	ethynylbenzene	**2** (50)	100	1	20,000	20,000
16	2-iodotoluene	ethynyltrimethylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
17	2-iodobiphenyl	ethynylbenzene	**1** (50)	96	0.5	38,400	19,200
18	2-iodobiphenyl	ethynyltrimethylbenzene	**1** (50)	92	1.5	12,267	18,400
19	2-iodomethoxybenzene	ethynylbenzene	**1** (50)	100	< 0.5	> 40,000	20,000
20	2-iodomethoxybenzene	ethynylbenzene	**2** (50)	48	1	9,600	9,600
21	2-iodomethoxybenzene	ethynyltrimethylbenzene	**1** (50)	100	0.5	40,000	20,000
22	4-iodo-3-methylaniline	ethynylbenzene	**1** (50)	100	0.33	60,000	20,000
23	2-iodo-*m*-xylene	ethynylbenzene	**1** (50)	100	0.25	80,000	20,000
24	2-iodo-*m*-xylene	ethynyltrimethylbenzene	**1** (50)	96	0.25	76,800	19,200
25	2-iodo-1,3-dimethoxybenzene	ethynylbenzene	**1** (50)	96	4	4,800	19,200
26	2-iodo-1,3-dimethoxybenzene	ethynyltrimethylbenzene	**1** (50)	75	6	2,500	15,000
27	2-iodothiophene	ethynylbenzene	**1** (50)	100	3	6,667	20,000
28	3-iodopyridine	ethynylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
29	3-iodopyridine	ethynyltrimethylbenzene	**1** (50)	100	< 0.25	> 80,000	20,000
30	2-iodopyridine	ethynylbenzene	**1** (50)	96	0.5	38,400	19,200

[a] *Reaction conditions:* 2.0 mmol aryl halide, 2.2 mmol ethynylbenzene or 2.0 mmol 1-ethynyl-2,4,5-trimethylbenzene, ~2.2 mmol K_3PO_4, 4 mL ethylene glycol, catalyst added in solution (dioxane), reaction performed at 140 °C.
[b] Determined by GC/MS, based on aryl halide.
[c] Defined as mol product per mol of catalyst per hour.
[d] Defined as mol product per mol of catalyst.
[e] Reactions were performed with 10 mmol of aryl halide and 10.5 mmol of ethynylbenzene in 12 mL of ethylene glycol.

(Table 1, entries 19 and 21). In contrast, only 48% of 1-methoxy-2-(phenylethynyl)benzene was obtained within 60 min when catalyst **2** was employed (Table 1, entry 20). Even when 4-iodo-3-methylaniline was coupled with ethynylbenzene, complete conversion was achieved within 20 min with catalyst **1** (Table 1, entry 22). Remarkably, 1,3-dimethyl-2-(phenylethynyl)benzene was exclusively and quantitatively formed within only 15 min when 2-iodo-*m*-xylene was coupled with ethynylbenzene or 1-ethynyl-2,4,5-trimethylbenzene, respectively (Table 1, entries 23 and 24). A prolonged reaction time was required with the sterically hindered and electronically deactivated 2-iodo-1,3-dimethoxybenzene. A reaction time of 4 h was needed to quantitatively convert 2-iodo-1,3-dimethoxybenzene into 1,3-dimethoxy-2-(phenylethynyl)benzene and 1-[(2,6-dimethoxyphenyl)ethynyl]-2,4,5-trimethylbenzene, respectively (Table 1, entries 25 and 26). Remarkably, even though a lower conversion rate was observed, complete product formation occurred within only 3 h with 2-iodothiophene as coupling partner (Table 1, entry 27). Quantitative formation of 3-(phenylethynyl)pyridine and 3-[(2,4,5-trimethylphenyl)ethynyl]pyridine, respectively, was achieved within only 15 min of reaction time, indicating that also substrates with ligating properties, such as pyridines, are compatible with the aminophosphine-based pincer-type Sonogashira catalysts (Table 1, entries 28 and 29). Indeed, complete conversion of 2-iodopyridine and ethynylbenzene into 2-(phenylethynyl)pyridine was achieved within only 30 min (Table 1, entry 30). The excellent performance of **1** was demonstrated further in exemplary coupling reactions of phenyl iodide, 2-iodotoluene and 4-iodoaniline with ethynylbenzene in the presence of only 0.00005 mol% of catalyst. Greater than 90% conversion was achieved in all

these reactions within less than 8 h of reaction time (Table 1, entries 2, 8 and 14).

In sharp contrast, when 2-ethynylpyridine was used as coupling partner the formation of 2-(phenylethynyl)pyridine was not observed. Instead, 2-(1,3-dioxolan-2-ylmethyl)pyridine was quantitatively formed. The dramatic difference in reactivity of seemingly similar substrate molecules was attributed to inductive effects of the functionalized alkyne: 2-ethynylpyridine is readily attacked in a first step at the terminal carbon atom of the ethynyl unit by ethylene glycol to yield 2-{[(*E*)-2-pyridin-2-ylethenyl]oxy}ethanol or 2-{[(*Z*)-2-pyridin-2-ylethenyl]oxy}ethanol, respectively, which react in a subsequent step selectively to 2-(1,3-dioxolan-2-ylmethyl)pyridine (see Table 3, entries 6–10).[26] Catalysts are not required for this transformation as shown by reactions of 2-ethynylpyridine with ethylene glycol and K_3PO_4, which quantitatively yielded 2-(1,3-dioxolan-2-ylmethyl)pyridine within 5 min at 140 °C,[22] implying that Sonogashira cross-coupling reactions with 2-ethynylpyridines are not possible with ethylene glycol as solvent under these reaction conditions. This is in contrast to 3-ethynylpyridine, which undergoes smooth product formations, since a nucleophilic attack on the terminal carbon atom is significantly slower.

In comparison with ethynylbenzene and 2,4,5-trimethylbenzene, essentially the same yields but generally lower conversion rates were noticed with 2-ethynyl-6-methoxynaphthalene as coupling partner (Table 2). For instance, whereas quantitative product formation was achieved with phenyl iodide within only 30 min of reaction time with 0.005 mol% of **1** (and 5 h with 0.5 ppm of catalyst **1**), product yields of ~90% were obtained after 120 min with the electronically deactivated substrates 1-iodo-4-methoxybenzene and 4-iodoaniline (Table 2, entries 1–4). On the other hand, quantitative formation of 2-methoxy-6-[(2-methylphenyl)ethynyl]naphthalene and 2-methoxy-6-[(2-methoxyphenyl)ethynyl]naphthalene occurred within only 30 and 90 min, respectively (Table 2, entries 5 and 6). A similar yield but prolonged reaction time was necessary with sterically hindered 2-iodobiphenyl as coupling partner (Table 2, entry 7). Reactions performed with 2-iodo-1,3-dimethylbenzene gave 78% of 2-[(2,6-dimethylphenyl)ethynyl]-6-methoxynaphthalene within 90 min (Table 2, entry 8). Quantitative product formations were achieved after 30 and 60 min with 3-iodopyridine as well as with 2-iodopyridine, respectively, as coupling partners (Table 2, entries 9 and 10). Remarkably, also reactions performed with 2-iodothiophene yielded 2-[(6-methoxynaphthalen-2-yl)ethynyl]thiophene quantitatively after 4 h (Table 2, entry 11).

Furthermore, >95% conversion was generally obtained within 1 hour when 5-ethynyl-1-methyl-1*H*-imidazole was coupled with iodobenzene, 2-iodotoluene, 2-iodobiphenyl and 2-iodo-*m*-xylene (Table 3, entries 1–4). Lower yields were noticed with 1-iodo-4-methoxybenzene as coupling partner (Table 3, entry 5). On the other hand, significantly higher conversion rates were realized with 3-ethynylpyridine (Table 3, entries 6–10).[26] In nearly all the reactions examined, >90% conversion was achieved within 30 min or less. Reactions performed with 4-iodoaniline only yielded 66% of the coupling product within 1 hour.

In comparison with aryl iodides, similar yields but generally lower conversion rates were observed when aryl bromides were used as coupling partners (Table 4).[27] For example, whereas product yields of only ~70% were obtained after 3 and 4 h when

Table 2. Sonogashira cross-coupling reactions of aryl iodides with 2-ethynyl-6-methoxynaphthalene catalyzed by {[C_6H_3-2,6-(NHP{piperidinyl}$_2$)$_2$]Pd(Cl)} (**1**).[a]

Entry	Aryl iodide	Alkyne	Cat. (ppm)	Conv. [%][b]	*t* [h]	TOF[c]	TON[d]
1	iodobenzene	2-ethynyl-6-methoxynaphthalene	**1** (50)	100	0.5	>40,000	20,000
2	iodobenzene	2-ethynyl-6-methoxynaphthalene	**1** (0.5)	100	5	400,000	2×10^6
3	4-iodoanisole	2-ethynyl-6-methoxynaphthalene	**1** (50)	91	2	9,100	18,200
4	4-iodoaniline	2-ethynyl-6-methoxynaphthalene	**1** (50)	86	2	8,600	17,200
5	2-iodotoluene	2-ethynyl-6-methoxynaphthalene	**1** (50)	92	0.5	36,800	18,400
6	2-iodoanisole	2-ethynyl-6-methoxynaphthalene	**1** (50)	97	1.5	12,933	19,400
7	2-iodobiphenyl	2-ethynyl-6-methoxynaphthalene	**1** (50)	97	3.5	5,543	19,400
8	2-iodo-*m*-xylene	2-ethynyl-6-methoxynaphthalene	**1** (50)	78	1.5	10,400	15,600
9	3-iodopyridine	2-ethynyl-6-methoxynaphthalene	**1** (50)	100	0.5	>40,000	20,000
10	2-iodopyridine	2-ethynyl-6-methoxynaphthalene	**1** (50)	100	1	20,000	20,000
11	2-iodothiophene	2-ethynyl-6-methoxynaphthalene	**1** (50)	100	4	5,000	20,000

[a] *Reaction conditions:* 2.0 mmol aryl halide, 2.0 mmol 2-ethynyl-6-methoxynaphthalene, 2.4 mmol K_3PO_4, 6 mL ethylene glycol, catalyst added in solution (dioxane), reaction performed at 140 °C.
[b] Determined by GC/MS, based on aryl halide.
[c] Defined as mol product per mol of catalyst per hour.
[d] Defined as mol product per mol of catalyst.

Table 3. Sonogashira cross-coupling reactions of aryl iodides with 5-ethynyl-1-methyl-1*H*-imidazole and 3-ethynylpyridine catalyzed by {[C_6H_3-2,6-(NHP{piperidinyl}$_2$)$_2$]Pd(Cl)] (**1**).[a]

Entry	Aryl iodide	Alkyne	Cat. (ppm)	Conv. [%][b]	*t* [h]	TOF[c]	TON[d]
1	iodobenzene	5-ethynyl-1-methyl-1*H*-imidazole	**1** (50)	100	1	20,000	20,000
2	2-iodotoluene	5-ethynyl-1-methyl-1*H*-imidazole	**1** (50)	100	1	20,000	20,000
3	2-iodobiphenyl	5-ethynyl-1-methyl-1*H*-imidazole	**1** (50)	97	1.5	13,333	20,000
4	2-iodo-*m*-xylene	5-ethynyl-1-methyl-1*H*-imidazole	**1** (50)	96	1	19,200	19,200
5	4-iodoanisole	5-ethynyl-1-methyl-1*H*-imidazole	**1** (50)	44	2	4,400	8,800
6	iodobenzene	3-ethynylpyridine	**1** (50)	97	0.25	77,600	19,400
7	4-iodoanisole	3-ethynylpyridine	**1** (50)	91	0.5	36,400	18,200
8	4-iodoaniline	3-ethynylpyridine	**1** (50)	66	1	13,200	13,200
9	2-iodotoluene	3-ethynylpyridine	**1** (50)	100	0.25	$>$80,000	20,000
10	2-iodoanisole	3-ethynylpyridine	**1** (50)	98	0.5	39,200	19,600

[a] *Reaction conditions:* 2.0 mmol aryl halide, 2.2 mmol 5-ethynyl-1-methyl-1*H*-imidazole or 2.2 mmol 3-ethynylpyridine, 2.4 mmol K_3PO_4, 6 mL ethylene glycol, catalyst added in solution (dioxane), reaction performed at 140 °C.
[b] Determined by GC/MS, based on aryl halide.
[c] Defined as mol product per mol of catalyst per hour.
[d] Defined as mol product per mol of catalyst.

Table 4. Sonogashira cross-coupling reactions of aryl bromides with different alkynes catalyzed by {[C_6H_3-2,6-(NHP{piperidinyl}$_2$)$_2$]Pd(Cl)} (**1**).[a]

Entry	Aryl bromide	Alkyne	Cat. (ppm)	Conv. [%][b]	*t* [h]	TOF[c]	TON[d]
1	bromobenzene	ethynylbenzene	**1** (100)	71	3	2,367	7,100
2	4-bromophenol	ethynylbenzene	**1** (100)	100	2	5,000	10,000
3	4-bromoaniline	ethynylbenzene	**1** (100)	68	4	1,700	6,800
4	2-bromotoluene	ethynylbenzene	**1** (100)	58	6	967	5,800
5	2-bromothiophene	ethynylbenzene	**1** (100)	100	6	1,667	10,000
6	3-bromopyridine	ethynylbenzene	**1** (100)	98	4	2,450	9,800
7	2-bromopyridine	ethynylbenzene	**1** (100)	100	4	2,500	10,000
8	bromobenzene	ethynyltrimethylbenzene	**1** (100)	83	3	2,767	8,300
9	4-bromoanisole	ethynyltrimethylbenzene	**1** (100)	58	4	1,450	5,800
10	4-bromoaniline	ethynyltrimethylbenzene	**1** (100)	93	6	1,550	9,300
11	4-bromophenol	ethynyltrimethylbenzene	**1** (100)	95	2	4,750	9,500
12	2-bromotoluene	ethynyltrimethylbenzene	**1** (100)	93	3	3,100	9,300
13	2-bromo-*m*-xylene	ethynyltrimethylbenzene	**1** (100)	84	3	2,800	8,400
14	3-bromopyridine	ethynyltrimethylbenzene	**1** (100)	100	2	5,000	10,000
15	2-bromopyridine	ethynyltrimethylbenzene	**1** (100)	93	2	4,650	9,300
16	2-bromothiophene	ethynyltrimethylbenzene	**1** (100)	98	2	4,900	9,800
17	bromobenzene	2-ethynyl-6-methoxynaphthalene	**1** (100)	100	3	3,333	10,000
18	4-bromoanisole	2-ethynyl-6-methoxynaphthalene	**1** (100)	81	4	2,025	8,100
19	4-bromoaniline	2-ethynyl-6-methoxynaphthalene	**1** (100)	79	4	1,975	7,900
20	2-bromotoluene	2-ethynyl-6-methoxynaphthalene	**1** (100)	100	4	2,500	10,000
21	2-bromo-*m*-xylene	2-ethynyl-6-methoxynaphthalene	**1** (100)	90	6	1,500	9,000
22	3-bromopyridine	2-ethynyl-6-methoxynaphthalene	**1** (100)	100	4	2,500	10,000
23	2-bromopyridine	2-ethynyl-6-methoxynaphthalene	**1** (100)	100	6	1,667	10,000
24	2-bromothiophene	2-ethynyl-6-methoxynaphthalene	**1** (100)	100	6	1,667	10,000

[a] *Reaction conditions:* 2.0 mmol aryl bromide, 3.0 mmol alkyne, 2.4 mmol K_3PO_4, 6 mL ethylene glycol, catalyst added in solution (dioxane), reaction performed at 140 °C.
[b] Determined by GC/MS, based on aryl halide.
[c] Defined as mol product per mol of catalyst per hour.
[d] Defined as mol product per mol of catalyst.

phenyl bromide and 4-bromoaniline, respectively, were coupled with ethynylbenzene, complete C–C bond formation was observed with functionalized aryl bromides, such as 4-bromophenol, 2-bromopyridine, 3-bromopyridine and 2-bromothiophene after 6 h and less (Table 4, entries 1–7). Clean product formation and excellent conversion rates and yields were generally observed with 1-ethynyl-2,4,5-trimethylbenzene

and 2-ethynyl-6-methoxynaphthalene as coupling partners (Table 4, entries 8–24). Greater than 80% yields of the coupling products were obtained within 6 h or less when bromobenzene, 4-bromoaniline, 4-bromophenol, sterically hindered 2-bromotoluene and 2-bromo-*m*-xylene as well as functionalized aryl bromides, such as 3-bromopyridine, 2-bromopyridine and 2-bromothiophene were coupled with 1-ethynyl-2,4,5-trimethylbenzene (Table 4, entries 8–16). Similarly, in almost all the reactions examined with 2-ethynyl-6-methoxynaphthalene clean, quantitative product formation was observed (Table 4, entries 17–24). Impressive examples are reactions performed with 2-bromotoluene and 2-bromo-*m*-xylene, as well as with 3-bromopyridine, 2-bromopyridine and 2-bromothiophene, respectively.[28] In contrast to the reactions examined with aryl halides, no product formation was noticed with trifluoromethanesulfonates as coupling partner.[29]

Overall, **1** and **2** belong nowadays to the most convenient Sonogashira catalysts, since their preparation is extremely simple, short and cheap. Moreover, **1** and **2** remain stable in solution for several months at room temperature and afford the coupling products at essentially the same conversion rates and yields as freshly prepared catalyst solutions from pure **1** and **2**, respectively. Complex **1** and to a minor extent **2** proved to be efficient and extremely reliable Sonogashira catalysts, which afford the coupling products without the formation of homocoupled products or other side-products within very short reaction times and at very low catalyst loadings with aryl iodides under *additive- and amine-free* reaction conditions. Furthermore, exclusion of air and moisture is not necessary. The catalysts remain highly active after the reaction is complete and catalysis is resumed at essentially the same rate upon addition of more substrates, a first piece of evidence that palladium nanoparticles are not the catalytically active forms of **1** and **2**, respectively. Moreover, in contrast to most known catalysts, no excess of either substrate is required for the quantitative yield of the coupling products.[25]

The performance of the Sonogashira cross-coupling reaction was found to be strongly temperature-dependent, resulting in a dramatic drop in activity when the reaction temperature was lowered. For instance, reactions performed with phenyl iodide and ethynylbenzene in ethylene glycol at 120 °C in the presence of 0.005 mol% of catalyst **1** quantitatively yield the coupling product within 2 h but only led to about 11% conversion after 3 h at 100 °C. 58% conversion into 1,1′-ethyne-1,2-diyldibenzene was observed after 20 h. Almost no activity was observed when the reactions were performed below 80 °C (~4% conversion was obtained after 20 h at 80 °C). Similarly, the change of solvent had a dramatic influence on the product formation and conversion rate of the Sonogashira cross-coupling reaction. Generally no or low product yields were observed when the reactions were performed in solvents of low polarity, such as dioxane, toluene or *p*-xylene. Low yields in combination with large amounts of various by-products were observed when highly polar solvents, such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), ethanol or hexanol were used as reaction medium for Sonogashira reactions. The use of mixed solvent media did not improve the performance of the Sonogashira cross-coupling. Significant sensitivity to base was noticed as well. Under otherwise identical reaction conditions the change of base, such as NEt_3, K_2CO_3, Na_2CO_3, $NaHCO_3$, NaOH, K_3PO_4, NaOAc and KO-*t*-Bu led to considerable variation in levels of conversion, isolated yields and by-product formation. However, only K_2CO_3 and K_3PO_4 gave acceptable results with ethylene glycol, of which the latter reveals the cleaner transformations, higher conversion rates and yields.

Even though sigmoidal-shaped kinetics with induction periods between 3 and 5 min were observed with **1**,[30] its transformation into palladium nanoparticles appears to be unlikely, since the addition of up to 5% water (in order to promote the formation of palladium nanoparticles) to the reaction mixtures of exemplary Sonogashira reactions with phenyl iodide and ethynylbenzene had no effect on the induction periods but led to lower conversion rates.[31] This is in line with the observation that the addition of tetrabutylammonium bromide, hexadecyltrimethylammonium bromide or benzyltriethylammonium chloride (~10 mol%) – salts known to stabilize palladium nanoparticles – to catalytic reaction mixtures neither had an influence on the conversion rates and the yields nor on the induction period.[30] Moreover, also the addition of mercury to catalytic reaction mixtures had no effect, thus suggesting that the catalytically active species has a homogeneous nature.[32,33] Indeed, no difference was noticed in either the conversion rates or product yields when up to an equimolar amount (relative to aryl iodide) of thiophene was added to the reaction mixtures.[34,35] Similarly, no effect was observed in the presence of up to an equimolar amount (relative to catalyst) of triphenylphosphine, a further indication that palladium nanoparticles are not the catalytically active form of **1** and **2**, respectively. On the other hand, (partial) conversion of **1** (or **2**) into another catalytically active species, such as phosphorous amidite- or phosphite-based Pd(II) or Pd(0) complexes (probably with the involvement of a Pd–C bond cleavage) most probably occurs under our catalytic reaction conditions,[36] as indicated by the following experiment. When the aryl iodide and the alkyne were added to preheated reaction mixtures (6 min at 140 °C) of ethylene glycol, catalyst and base, instant

product formation occurred without indication period.[29]

In conclusion, we have demonstrated that the aminophosphine-based pincer complexes {[C_6H_3-2,6-(XP{piperidinyl}$_2$)$_2$]Pd(Cl)} (X = NH **1**; X = O **2**) are convenient, efficient and extremely reliable Sonogashira catalysts, leading to very high conversion rates and excellent yields for a large variety of substrates with very low catalyst loadings (0.005 mol%). Lower catalyst loadings lead to the same yields but slower reactions. Ethylene glycol and K_3PO_4 were found to be the ideal solvent and base for this transformation. The catalyst preparation is extremely easy, short and cheap. Catalyst solutions remain stable for several months at room temperature and afford the coupling products at essentially the same conversion rates and yields as freshly prepared catalyst solutions from pure **1** and **2**, respectively. Most important, the Sonogashira reactions were carried out without exclusion of air and moisture and without the use of amines, co-catalysts, such as CuI, $ZnCl_2$ or $FeCl_3$ or other additives, such as tetrabutylammonium bromide. Moreover, since none of the starting materials are required in a large excess for quantitative coupling, the present system is very attractive for Sonogashira cross-coupling reactions.

Experimental Section

General Procedures

All synthetic operations for the catalyst preparation were carried out in oven-dried glassware using a combination of glove-box (M. Braun 150B-G-II) and Schlenk techniques under a dinitrogen atmosphere. Solvents were reagent grade or better, freshly distilled under an N_2 atmosphere by standard procedures, and degassed by freeze-thaw cycles before use. Deuterated solvents were purchased from Armar and used as received. All the chemicals were purchased from Aldrich Chemical Co., Acros Organics, or Fluka and used without further purification.

Analysis

^{1}H, and ^{13}C{^{1}H} NMR spectra were recorded at 300.00 and 75.42 MHz, respectively, on a Bruker ARX-300 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) coupling constants (*J*) are in Hz. The ^{1}H and ^{13}C NMR chemical shifts are reported relative to tetramethylsilane; the resonance of the residual protons of the solvent was used as internal standard for ^{1}H [$\delta = 5.32$ (CD_2Cl_2); 4.78 and 3.30 (CD_3OD)] and *all-d* solvent peaks for ^{13}C [$\delta =$ 53.8 (CD_2Cl_2); 49.0 (CD_3OD)]. All measurements were carried out at 298 K. Abbreviations used in the description of NMR data are as follows: s, singlet; d, duplet; t, triplet; m, multiplet. Elemental analyses were performed on a Leco CHNS-932 analysator at the University of Zurich, Switzerland.

Procedure for the "One-Pot" Synthesis of Catalyst Solutions of 1 and 2

In a Young Schlenk tube 100 mg (0.35 mmol) of [Pd(cod)$(Cl)_2$] were suspended with 50 mL of toluene. After the addition of toluene solutions (20 mL) containing two equivalents of 1,1′,1″-phosphinetriyltripiperidine (198.5 mg; 0.70 mmol), the reaction mixture was stirred for 10 min. Subsequently, an equimolar amount of resorcinol or 1,3-diaminobenzene, respectively, was added to these solutions. The reaction mixtures were heated up to 100 °C and stirred until decolorization occurred. After the mixtures had been cooled to room temperature and the insoluble reaction products had been precipitated, the reaction mixtures were filtered. Removal of the solvent and exctraction with diethyl ether afforded the complexes in very high yields.[21a]

General Procedure for Sonogashira Cross-Coupling Reactions of Aryl Iodides with Alkynes

All Sonogashira cross-coupling reactions were carried out without rigorous exclusion of air and moisture. Ethylene glycol was of reagent grade (98%) or better and used as received. A Schlenk tube was charged with powdered K_3PO_4 and appropriate amounts of the aryl halide and alkyne (if solid). The Schlenk tube was capped with a Teflon screw cap, evacuated and backfilled with nitrogen. After addition of ethylene glycol, the aryl halide and alkyne (if liquid), and 0.005 mol% of the catalyst (dissolved in dioxane) in a positive flow of nitrogen, the Schlenk tube was resealed and the contents vigorously stirred at 140 °C in an oil bath. Samples taken from the reaction mixture were quenched with water, extracted with ethyl acetate, and analyzed by GC/MS. At the end of catalysis the reaction mixtures were allowed to cool to room temperature, quenched with water (25 mL) and extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were washed with 20 mL of water (or 20 mL of 1 M Na_2CO_3 in reactions performed with 5-ethynyl-1-methyl-1*H*-imidazole), dried ($MgSO_4$) and evaporated to dryness. The crude material was purified by flash chromatography on silica gel.

1-[(4-Methoxyphenyl)ethynyl]-2,4,5-trimethylbenzene (Table 1, entry 6)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as a colorless powder. Yield: 84%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.47$ (d, $^3J =$ 8.9 Hz, 2H), 7.26 (s, 1H), 7.02 (s, 1H), 6.90 (d, $^3J = 8.9$ Hz, 2H), 3.83 (s, 3H), 2.44 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 160.2$, 137.7, 137.6, 134.4, 133.3, 133.0, 131.4, 121.0, 116.5, 114.6, 92.8, 87.8, 20.4, 19.9, 19.4; elemental analysis: calcd. for $C_{18}H_{18}O$: C 86.36, H 7.25; found: C 86.19, H 7.17.

4-[(2,4,5-Trimethylphenyl)ethynyl]aniline (Table 1, entry 10)

The title compound was obtained after flash chromatography on silica gel (toluene/diethyl ether; 1:1) as a colorless powder. Yield: 72%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.32$ (d, $^3J = 8.7$ Hz, 2H), 7.24 (s, 1H), 7.01 (s, 1H), 6.69 (d, $^3J =$ 8.7 Hz, 2H), 3.88 (broad s, 2H), 2.43 (s, 3H), 2.25 (s, 3H),

2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 147.2$, 137.3, 136.9, 134.1, 132.9, 132.6, 131.0, 121.0, 114.9, 113.1, 93.3, 86.6, 20.1, 19.6, 19.1; elemental analysis: calcd. for $C_{17}H_{17}N$: C 86.77, H 7.28, N 5.95; found: C 86.69, H 7.23, N 5.98.

4-[(2,4,5-Trimethylphenyl)ethynyl]phenol (Table 1, entry 12)

The title compound was obtained after flash chromatography on silica gel (diethyl ether/hexane; 1:2) as a colorless powder. Yield: 90%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.42$ (d, $^3J = 8.8$ Hz, 2H), 7.24 (s, 1H), 7.01 (s, 1H), 6.82 (d, $^3J = 8.8$ Hz, 2H), 5.16 (broad s, 1H), 2.42 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 156.0$, 137.5, 137.4, 134.1, 133.2, 132.7, 131.1, 120.6, 116.4, 115.7, 92.5, 87.4, 20.1, 19.6, 19.0; elemental analysis: calcd. for $C_{17}H_{16}O$: C 86.41, H 6.82; found: C 86.37, H 6.79.

1,2,4-Trimethyl-5-[(2-methylphenyl)ethynyl]benzene (Table 1, entry 16)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as a colorless powder. Yield: 99%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.59$–7.57 (m, 1H), 7.37 (s, 1H), 7.34–7.21 (m, 3H), 7.08 (s, 1H), 2.61 (s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 137.9$ (2 overlapping signals), 135.3, 131.9, 130.7, 129.7, 128.9, 127.5, 126.0, 123.6, 121.7, 118.4, 90.8, 89.3, 18.8, 18.1, 17.4, 16.8; elemental analysis: calcd. for $C_{18}H_{18}$: C 92.26, H 7.74; found: C 92.57, H 7.91.

2-[(2,4,5-Trimethylphenyl)ethynyl]biphenyl (Table 1, entry 18)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as a colorless powder. Yield: 84%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.75$–7.70 (m, 3H), 7.54–7.37 (m, 6H), 7.18 (s, 1H), 7.00 (s, 1H), 2.27 (2 overlapping s, 6H), 2.54 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 143.9$, 141.2, 137.7, 137.6, 134.1, 133.4, 133.0, 131.1, 129.9, 129.7, 128.6, 128.3, 127.8, 127.4, 122.5, 120.5, 92.3, 92.0, 20.0, 19.7, 19.1; elemental analysis: calcd. for $C_{23}H_{20}$: C 93.20, H 6.80; found: C 93.11, H 6.83.

1-[(2-Methoxyphenyl)ethynyl]-2,4,5-trimethylbenzene (Table 1, entry 21)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as an orange oil, which solidified upon standing. Yield: 91%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.52$–7.49 (m, 1H), 7.36–7.30 (m, 1H) overlapped with 7.30 (s, 1H), 7.05 (s, 1H), 7.00–6.93 (m, 2H), 3.92 (s, 3H), 2.49 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 160.3$, 137.8, 137.5, 134.2, 133.3, 132.8, 131.1, 129.8, 120.7, 113.3, 111.1, 93.0, 89.0, 56.0 20.1, 19.7, 19.1; elemental analysis: calcd. for $C_{18}H_{18}O$: C 86.36, H 7.25; found: C 86.41, H 7.29.

1-[(2,6-Dimethylphenyl)ethynyl]-2,4,5-trimethylbenzene (Table 1, entry 24)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as a colorless powder. Yield: 86%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.36$ (s, 1H), 7.20–7.11 (m, 3H), 7.07 (s, 1H), 2.59 (s, 6H), 2.53 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 140.3$, 137.5, 137.3, 134.2, 133.0, 131.2, 127.8, 127.0, 123.8, 121.1, 97.7, 90.3, 21.4, 20.5, 19.7, 19.1; elemental analysis: calcd. for $C_{19}H_{20}$: C 91.88, H 8.12; found: C 91.73, H 8.05.

1-[(2,6-Dimethoxyphenyl)ethynyl]-2,4,5-trimethylbenzene (Table 1, entry 26)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:1) as a colorless powder. Yield: 65%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.27$ (s, 1H) overlapped with 7.25 (t, $^3J = 8.4$ Hz, 1H), 7.03 (s, 1H), 6.59 (d, $^3J = 8.4$ Hz, 2H), 3.91 (s, 6H), 2.48 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 161.5$, 137.7, 137.2, 134.0, 132.5, 131.1, 129.7, 121.1, 103.9, 102.4, 97.3, 85.3, 56.3 20.0, 19.7, 19.0; elemental analysis: calcd. for $C_{19}H_{20}O_2$: C 81.40, H 7.19; found: C 81.30, H 7.11.

3-[(2,4,5-Trimethylphenyl)ethynyl]pyridine (Table 1, entry 29)

The title compound was obtained after flash chromatography on silica gel (diethyl ether) as a colorless powder. Yield: 98%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 8.78$ (dd, $^4J_{A'C} = 2.1$ Hz, $^5J_{A'B} = 0.9$ Hz, 1H), 8.53 (dd, $^3J_{AB} = 4.9$ Hz, $^4J_{AC} = 1.7$ Hz, 1H), 7.80 (ddd $^3J_{CB} = 7.9$ Hz, $^4J_{CA'} = 2.1$ Hz, $^4J_{CA} = 1.7$ Hz, 1H), 7.30 (s, 1H), 7.29 (ddd, $^3J_{BC} = 7.9$ Hz , $^3J_{BA} = 4.9$ Hz, $^5J_{BA'} = 0.9$ Hz, 1H), 7.04 (s, 1H), 2.47 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 158.1$, 154.4, 144.1, 143.7, 140.1, 138.9, 137.0, 129.1, 127.0, 125.6, 98.0, 95.0, 25.9, 25.6, 24.9; elemental analysis: calcd. for $C_{16}H_{15}N$: C 86.84, H 6.83, N 6.33; found: C 86.65, H 6.75, N 6.47.

2-(1,3-Dioxolan-2-ylmethyl)pyridine

A Schlenk tube charged with 1 mmol 2-ethynylpyridine, 1 mmol K_3PO_4, and 2 mL ethylene glycol was placed in an oil bath and the content stirred at 140 °C for 5 min. After addition of water (10 mL) the product was extracted with ethyl acetate (2×15 mL). The combined organic extracts were washed with water (20 mL), dried ($MgSO_4$) and evaporated to dryness giving the analytically pure 2-(1,3-dioxolan-2-ylmethyl)pyridine as a pale yellow oil. Yield: 77%. ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 8.52$–8.51 (m, 1H), 7.63–7.57 (m, 1H), 7.26–7.24 (m, 1H), 7.15–7.11 (m, 1H), 5.25 (t, $^3J = 5.0$ Hz, 1H), 3.96–3.92 (m, 2H), 3.84–3.79 (m, 2H), 3.12 (d, $^3J = 5.0$ Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): $\delta = 157.3$, 149.5, 136.3, 124.3, 121.8, 104.2, 65.2, 43.5; elemental analysis: calcd. for $C_9H_{11}NO_2$: C 65.44, H 6.71, N 8.48; found: C 65.25, H 6.61, N 8.71.

2-Methoxy-6-[(4-methoxyphenyl)ethynyl]naphthalene (Table 2, entry 3)

The title compound was obtained after flash chromatography on silica gel (hexane/diethyl ether; 2:1) as a pale yellow oil. Yield: 87%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.96$ (d, $^4J = 1.0$ Hz, 1H), 7.73 (2 overlapping dublets, $^3J = 8.5$ Hz, 2H), 7.56–7.50 (m, 3H), 7.18–7.14 (m, 2H), 3.92 (s, 3H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 160.1$, 158.7, 134.4, 133.3, 131.2, 129.6, 129.2, 128.9, 127.2, 119.7, 118.8, 115.7, 114.4, 106.1, 89.3, 88.8, 55.7 (2 overlapping signals); elemental analysis: calcd. for $C_{20}H_{16}O_2$: C 83.31, H 5.59; found: C 83.29, H 5.61.

4-[(6-Methoxynaphthalen-2-yl)ethynyl]aniline (Table 2, entry 4)

The title compound was obtained after flash chromatography on silica gel (hexane/ethyl acetate; 2:1) as a pale brown powder. Yield: 78%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.93$ (d, $^4J = 1.0$ Hz, 1H), 7.73–7.70 (m, 2H), 7.52 (dd, $^3J = 8.5$ Hz, $^4J = 1.7$ Hz, 1H), 7.36 (d, $^3J = 8.6$ Hz, 2H), 7.18–7.15 (m, 2H), 6.66 (d, $^3J = 8.6$ Hz, 2H), 3.92 (s, 3H, overlapped with broad s, 2H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 158.8$, 147.6, 134.4, 133.3, 131.0, 129.6, 129.4, 129.1, 127.3, 119.8, 119.3, 115.0, 112.9, 106.4, 90.3, 88.0, 55.8; elemental analysis: calcd. for $C_{19}H_{15}NO$: C 83.49, H 5.53, N 5.12; found: C 83.41, H 5.54, N 5.14.

2-Methoxy-6-[(2-methylphenyl)ethynyl]naphthalene (Table 2, entry 5)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as a colorless powder. Yield: 89%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.99$ (d, $^4J = 1.0$ Hz, 1H), 7.74 (2 overlapping dublets, $^3J = 8.1$ Hz, 2H), 7.56 (dd, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz, 1H), 7.53 (d, $^3J = 6.3$ Hz, 1H), 7.28–7.24 (m, 2H), 7.22–7.18 (m, 2H), 7.17 (s, 1H), 3.92 (s, 3H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 158.8$, 140.5, 134.5, 132.0, 131.3, 129.8, 129.6, 129.2, 128.9, 128.6, 127.2, 126.0, 123.5, 119.7, 118.7, 106.2, 94.3, 88.3, 55.6, 20.9; elemental analysis: calcd. for $C_{20}H_{16}O$: C 88.20, H 5.92; found: C 88.17, H 5.91.

2-[(6-Methoxynaphthalen-2-yl)ethynyl]biphenyl (Table 2, entry 7)

The title compound was obtained after flash chromatography on silica gel (diethyl ether) as a colorless powder. Yield: 94%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.82$ (broad s, 1H), 7.77–7.67 (m, 5H), 7.57–7.36 (m, 7H), 7.19–7.14 (m, 2H), 7.17 (s, 1H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 158.8$, 144.1, 141.0, 134.5, 133.1, 131.2, 129.8, 129.7, 129.5, 128.9, 128.8, 128.7, 128.3, 127.9, 127.5, 127.1, 122.0, 119.7, 118.5, 106.2, 93.0, 89.3, 55.6; elemental analysis: calcd. for $C_{25}H_{18}O$: C 89.79, H 5.43; found: C 89.88, H 5.48.

2-[(2,6-Dimethylphenyl)ethynyl]-6-methoxynaphthalene (Table 2, entry 8)

The title compound was obtained after flash chromatography on silica gel (toluene/hexane; 1:2) as a colorless powder. Yield: 66%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 8.03$ (d, $^4J = 0.9$ Hz, 1H), 7.76 (2 overlapping dublets, $^3J = 8.6$ Hz, 2H), 7.62 (dd, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz, 1H), 7.23–7.12 (m, 5H), 3.94 (s, 3H), 2.61 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 158.7$, 140.5, 134.5, 131.0, 129.5, 129.2, 128.9, 128.0, 127.2, 127.0, 123.4, 119.7, 119.0, 106.2, 98.8, 87.1, 55.6, 21.2; elemental analysis: calcd. for $C_{21}H_{18}O$: C 88.08, H 6.34; found: C 88.19, H 6.32.

3-[(6-Methoxynaphthalen-2-yl)ethynyl]pyridine (Table 2, entry 9)

The title compound was obtained after flash chromatography on silica gel (diethyl ether) as a colorless powder. Yield: 90%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 8.78$ (d, $^4J = 1.9$ Hz, 1H), 8.53 (dd, $^3J = 4.9$ Hz, $^4J = 1.6$ Hz, 1H), 8.01 (d, $^4J = 0.9$ Hz, 1H), 7.84 (dt, $^3J = 7.9$ Hz, $^4J = 1.9$ Hz, 1H) 7.74 (2 overlapping dublets, $^3J = 8.4$ Hz, 2H), 7.56 (dd, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz, 1H), 7.29 (ddd, $^3J = 7.9$ Hz , $^3J = 4.9$ Hz, $^5J = 0.6$ Hz, 1H), 7.20–7.16 (m, 2H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 159.0$, 152.5, 148.8, 138.5, 134.8, 131.8, 129.6, 129.0, 128.7, 127.3, 123.3, 120.8, 119.8, 117.7, 106.2, 93.3, 85.9, 55.6; elemental analysis: calcd. for $C_{18}H_{13}NO$: C 83.38, H 5.05, N 5.40; found: C 83.27, H 4.99, N 5.49.

2-[(6-Methoxynaphthalen-2-yl)ethynyl]pyridine (Table 2, entry 10)

The title compound was obtained after flash chromatography on silica gel (diethyl ether) as a pale yellow powder. Yield: 89%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 8.62$ (ddd, $^3J_{AB} = 4.9$ Hz, $^4J_{AC} = 1.8$ Hz, $^5J_{AB'} = 1.0$ Hz, 1H), 8.06 (d, $^4J = 0.8$ Hz, 1H), 7.75 (2 overlapping doublets, $^3J = 8.5$ Hz, 2H), 7.71–7.54 (m, 3H), 7.26–7.15 (m, 3H), 3.91 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 159.1$, 150.4, 143.9, 136.3, 134.9, 132.3, 129.7, 129.2, 128.7, 127.4, 127.3, 123.0, 119.8, 117.4, 106.2, 89.7, 88.9, 55.7; elemental analysis: calcd. for $C_{18}H_{13}NO$: C 83.38, H 5.05, N 5.40; found: C 83.21, H 5.17, N 5.31.

2-[(6-Methoxynaphthalen-2-yl)ethynyl]thiophene (Table 2, entry 11)

The title compound was obtained after flash chromatography on silica gel (hexane/diethyl ether 4:1) as a colorless powder. Yield: 94%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 7.98$ (d, $^4J = 0.8$ Hz, 1H), 7.74 (2 overlapping doublets, $^3J = 8.8$ Hz, $^3J = 8.4$ Hz, 2H), 7.55 (dd, $^3J = 8.4$ Hz, $^4J = 1.7$ Hz, 1H), 7.36–7.35 (m, 2H), 7.19 (dd, $^3J = 8.8$ Hz, $^4J = 2.6$ Hz, 1H), 7.16 (d, $^4J = 2.4$ Hz, 1H), 7.07–7.08 (m, 1H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): $\delta = 158.9$, 134.6, 132.2, 131.3 129.6, 128.9, 128.7, 127.6 (2 overlapping signals), 127.3, 123.7, 119.8, 118.0, 106.1, 93.9, 82.4, 55.7; elemental analysis: calcd. for $C_{17}H_{12}OS$: C 77.24, H 4.58; found: C 77.06, H 4.66.

1-Methyl-5-[(2-methylphenyl)ethynyl]-1*H*-imidazole (Table 3, entry 2)

The title compound was obtained after flash chromatography on silica gel (CH_2Cl_2/methanol 3:1) as a pale yellow powder. Yield: 95%. ^{1}H NMR (300 MHz, MeOH-d_4): $\delta =$ 7.49 (s, 1H), 7.28–7.26 (m, 1H), 7.08–6.96 (m, 4H), 3.53 (s,

3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, MeOH-d_4): δ = 140.8, 140.0, 133.6, 132.5, 130.6, 129.9, 126.8, 123.3, 117.9, 96.4, 81.5, 32.5, 21.0; elemental analysis: calcd. for $C_{13}H_{12}N_2$: C 79.56, H 6.16, N 14.27; found: C 79.42, H 6.13, N 14.19.

5-(Biphenyl-2-ylethynyl)-1-methyl-1*H*-imidazole (Table 3, entry 3)

The title compound was obtained after flash chromatography on silica gel (CH_2Cl_2 with 10% methanol) as a pale yellow oil. Yield: 79%. ^1H NMR (300 MHz, MeOH-d_4): δ = 7.49–7.38 (m, 4H), 7.32–7.19 (m, 6H), 7.00 (s, 1H), 3.21 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, MeOH-d_4): δ = 145.0, 141.9, 139.8, 133.6, 133.3, 130.6, 130.2, 129.9, 129.1, 128.6, 128.3, 122.1, 117.8, 97.3, 80.5, 32.3; elemental analysis: calcd. for $C_{18}H_{14}N_2$: C 83.69, H 5.46, N 10.84; found: C 83.54, H 5.52, N 10.87.

1-Methyl-5-[(2,6-dimethylphenyl)ethynyl]-1*H*-imidazole (Table 3, entry 4)

The title compound was obtained after flash chromatography on silica gel (CH_2Cl_2 with 10% methanol) as a pale yellow powder. Yield: 88%. ^1H NMR (300 MHz, MeOH-d_4): δ = 7.56 (s, 1H), 7.15 (s, 1H), 7.05–6.94 (m, 3H), 3.63 (s, 3H), 2.35 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, MeOH-d_4): δ = 140.9, 139.9, 133.4, 129.3, 127.8, 123.1, 118.1, 95.1, 85.9, 32.6, 21.3; elemental analysis: calcd. for $C_{14}H_{14}N_2$: C 79.97, H 6.71, N 13.32; found: C 79.89, H 6.69, N 13.40.

5-[(4-Methoxyphenyl)ethynyl]-1-methyl-1*H*-imidazole (Table 3, entry 5)

The title compound was obtained after flash chromatography on silica gel (CH_2Cl_2 with 10% methanol) as a yellow powder. Yield: 36%. ^1H NMR (300 MHz, MeOH-d_4): δ = 7.60 (s, 1H), 7.38 (d, ^3J = 8.9 Hz, 2H), 7.13 (s, 1H), 6.86 (d, ^3J = 8.9 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, MeOH-d_4): δ = 161.6, 139.7, 133.9, 133.2, 118.1, 115.5, 115.2, 97.4, 75.8, 55.8, 32.3; elemental analysis: calcd. for $C_{13}H_{12}N_2O$: C 73.57, H 5.70, N 13.20; found: C 73.51, H 5.72, N 13.26.

4-(Pyridin-3-ylethynyl)aniline (Table 3, entry 8)

The title compound was obtained after flash chromatography on silica gel (diethyl ether) as a colorless powder. Yield: 58%. ^1H NMR (300 MHz, CD_2Cl_2): δ = 8.70 (dd, $^4J_{A'C}$ = 2.1 Hz, $^5J_{A'B}$ = 0.9 Hz, 1H), 8.48 (dd, $^3J_{AB}$ = 4.9 Hz, $^4J_{AC}$ = 1.7 Hz, 1H), 7.77 (ddd, $^3J_{CB}$ = 7.9 Hz, $^4J_{CA'}$ = 2.1 Hz, $^4J_{CA}$ = 1.7 Hz, 1H), 7.34 (d, ^3J = 8.7 Hz, 2H), 7.26 (ddd, $^3J_{BC}$ = 7.9 Hz , $^3J_{BA}$ = 4.9 Hz, $^5J_{BA'}$ = 0.9 Hz, 1H), 6.65 (m, ^3J = 8.7 Hz, 2H), 3.99 (broad s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): δ = 152.2, 148.3, 147.9, 138.2, 133.3, 123.3, 121.3, 114.8, 111.6, 93.7, 84.2; elemental analysis: calcd. for $C_{13}H_{10}N_2$: C 80.39, H 5.19, N 14.42; found: C 80.22, H, 5.21, N 14.30.

3-[(2-Methoxyphenyl)ethynyl]pyridine (Table 3, entry 10)

The title compound was obtained after flash chromatography on silica gel (diethyl ether) as a colorless oil. Yield: 83%. ^1H NMR (300 MHz, CD_2Cl_2): δ = 8.75 (dd, $^4J_{A'C}$ = 2.1 Hz, $^5J_{A'B}$ = 0.9 Hz, 1H), 8.52 (dd, $^3J_{AB}$ = 4.9 Hz, $^4J_{AC}$ = 1.7 Hz, 1H), 7.82 (ddd, $^3J_{CB}$ = 7.9 Hz, $^4J_{CA'}$ = 2.1 Hz, $^4J_{CA}$ = 1.7 Hz, 1H), 7.52–7.49 (m, 1H), 7.39–7.32 (m, 1H), 7.28 (ddd, $^3J_{BC}$ = 7.9 Hz , $^3J_{BA}$ = 4.9 Hz, $^5J_{BA'}$ = 0.9 Hz, 1H), 6.99–6.94 (m, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): δ = 160.5, 152.4, 148.8, 138.4, 133.7, 130.7, 123.3, 120.9, 120.8, 112.0, 111.2, 90.0, 89.3, 56.1; elemental analysis: calcd. for $C_{14}H_{11}NO$: C 80.36, H 5.30, N 6.69; found: C 80.25, H 5.36, N 6.65.

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[24] Note that only recently reports on Sonogashira cross-coupling reactions in air and (mixed) aqueous media have appreared a) C. Wolf, R. Lerebours, *Org. Biomol. Chem.* **2004**, *2*, 2161; b) L. Ray, S. Barman, M. M. Shaikh, P. Ghosh, *Chem. Eur. J.* **2008**, *14*, 6646.
[25] Since the boiling point of ethynylbenzene is 142 °C and hence, only slightly above the reaction temperature (140 °C), reactions with ethynylbenzene were performed with 1.1 equiv. (relative to aryl iodide) to assure complete product formation within 15 min. Similarly, in reactions with 3-ethynylpyridine a slight excess (1.1 equiv. relative to aryl iodide) was added as well.[26]
[26] It should be mentioned that also 3-ethynylpyridine undergoes slow formation of 3-(1,3-dioxolan-2-ylmethyl)-pyridine with ethylene glycol under catalytic reaction conditions. This side-reaction, however, only lead to significant amounts of 3-(1,3-dioxolan-2-ylmethyl)pyridine in slow Sonogashira cross-coupling reactions, as it is for instance the case when 4-iodoaniline (see Table 3, entry 8) was used as coupling partner, explaining the relatively low product yield obtained.
[27] In contrast to reactions examined with aryl iodides, where no side-products were detectable, small amounts of homocoupling was observed in some of the reactions performed with aryl bromides. Thus, in order to maximize the product yields the reactions were generally performed with 1.5 equivalents (relative to aryl bromide) of alkyne.
[28] Coupling reactions performed with 3-ethynylpyridine and 5-ethynyl-1-methyl-1*H*-imidazole and aryl bromides as coupling partners were only of limited success, since the formation of side-products, such as 3-(1,3-dioxolan-2-ylmethyl)pyridine became dominant.
[29] Aryl trifluoromethanesulfonates are sensitive towards moisture and hence, are expected to be incompatible with our reaction protocol. Indeed, no coupling products were formed, clean conversions into their corresponding phenols occurred instead.
[30] See graph S1 in the Supporting Information.
[31] If palladium nanoparticles were the catalytically active form of **1** (and **2**), the presence of water in the reaction mixtures of the Sonogashira reaction should lead to shorter induction periods when compared with anhydrous reaction conditions.[21b] The reason for the effect of water on the induction period could be explained by a faster decomposition of the pincer core. However, no effect on the induction period was noticed. The addition of large amounts of water (~10%), however, could result in the partial decomposition of the catalyst and would provide an explanation for the slower conversions observed.
[32] For a comprehensive review article about the problem of distinguishing true homogeneous catalysis from soluble or other metal-particle heterogeneous catalysis under reducing conditions see: J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317 and references cited therein.
[33] a) K. Yu, W. Sommer, J. M. Richardson, M. Weck, C. W. Jones, *Adv. Synth. Catal.* **2005**, *347*, 161; b) K. Yu, W. Sommer, M. Weck, C. W. Jones, *J. Catal.* **2005**, *226*, 101; c) D. E. Bergbreiter, P. L. Osburn, J. D. Frels, *Adv. Synth. Catal.* **2005**, *347*, 172; d) M. R. Eberhard, *Org. Lett.* **2004**, *6*, 2125.
[34] This result was expected to be obtained, since 2-iodothiophene was successfully coupled with ethynylbenzene and 2-ethynyl-6-methoxynaphthalene (see Table 1, entry 24 and Table 2, entry 10).
[35] The addition of CS_2 to catalytic reaction mixtures is not appropriate, due to catalyst degradation involving P–N bond cleavage and (partial) formation of the bis(piperidine-1-carbodithioato)palladium complex $[Pd(S_2CNpiperidyl)_2]$.[21b]
[36] It should be noted that NMR investigations were not conclusive and the transformation of **1** (or **2**) into another, catalytically active species could not be confirmed by NMR spectroscopy.

