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A Simple and Efficient Copper-Free Catalytic System Based on a Palladacycle for the Arylation of Alkynes

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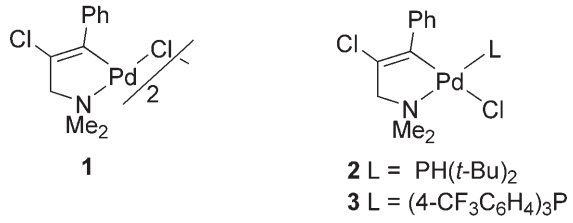
Abstract: The palladacycle [Pd(k^2-*C*,*N*-C=(C_6H_5)-C(Cl)CH_2NMe_2)(μ-Cl)]$_2$ (**1**) derived from the chloropalladation of 3-(dimethylamino)-1-phenyl-1-propyne and its phosphine adduct [Pd(k^2-*C*,*N*-C=(C_6H_5)C(Cl)-CH_2NMe_2)P(4-$CF_3C_6H_4$)$_3$(Cl)] (**3**) promote the alkynylation of bromo- and iodoarenes under relatively mild reaction conditions. The coupling of iodoarenes and activated bromoarenes with *terminal alkynes* can be conducted at room temperature. Turnover numbers have been achieved up to 10^5 with iodoarenes and up to 94 for deactivated bromoarenes but at higher temperatures (120 °C). Selective poisoning experiments (Hg, Collman and Crabtree tests) suggest that soluble Pd(0) species are the most probable catalytically active species involved in this Csp^2–Csp coupling reaction.

Keywords: arylation; C–C bond formation; cross-coupling; palladacycles; Sonogashira reaction

Introduction

The arylation (employing aryl halides) of alkenes (Heck coupling), arylboronic acids (Suzuki coupling) and alkynes (Sonogashira coupling or Heck alkynylation) are among the most investigated catalytic processes mediated by transition-metal complexes. Palladium-based complexes are by far the most used and effective catalyst precursors for the promotion of such coupling reactions.[1,2] Indeed, there is a legion of catalyst precursors and experimental protocols that allow the Heck and Suzuki coupling to be performed with almost any aryl halide, employing very low Pd loadings (down to ppbs) and under mild reaction conditions such as at room temperature.[3–8] In contrast, the current scope of the Pd-catalyzed alkynylations of aryl halides is still rather limited.[9] The classical experimental protocol involves, in most of the cases, the use of a palladium source such as [$PdCl_2(PPh_3)_2$] or [Pd(PPh_3)$_4$] in the presence of Cu salts, known as the Sonogashira reaction.[10–15] More active catalytic systems have been recently reported that employ in most of the cases the Pd complex associated with sterically hindered phosphines,[16,17] such as P(t-Bu)$_3$, but many more persuasive developments and examples are certainly needed to fully justify the use of structurally more elaborate and/or expensive phosphines. The pincer-type palladacycle [PdCl{C_6H_3-[OP(i-Pr)$_2$]$_2$-2,6}] catalyzes the coupling of aryl chlorides with phenylacetylene in the presence of $ZnCl_2$ as co-catalyst to give the products in modest to excellent yields.[18] The use of relatively high amounts of Pd (typically 5–10%) and copper or zinc salts (10–15%), and the use of amines as solvents render this method limited for practical applications.

The alkynylation of aryl halides can be also performed in the absence of Cu salts – the Heck protocol is inherently simpler than the Sonogashira reaction. However, in these cases more drastic reaction conditions must be employed (usually temperatures >70 °C). Moreover, generally this protocol is limited to vinyl halides, iodoarenes and bromoarenes substituted with electron-withdrawing groups and relative large quantities of palladium must be used (2–4%).[19] Relatively more efficient Pd catalytic systems can be formed by the use, for example, of [Pd_2dba_3/P(t-Bu)$_3$][20] or [Pd(η^3-alyl)-μ-Cl)$_2$]/P(t-Bu)$_3$[21] and other Pd compounds associated with phosphines.[22,23] However, large amounts of palladium and auxiliary ligands (5 mol % of Pd and 10% of the phosphines) must be employed. The Hermann–Beller PC-palladacycle is quite active for the coupling of bromoarenes with phenylacetylene and turnover numbers up to 8000 in the case of 4-bromoacetophenone have been reported.[24] However, this system is not active for other alkynes such as 1-hexyne and trimethylsilyl-



Scheme 1.

acetylene. A palladacycle derived from an oxime derivative is probably the most efficient Pd precursor to promote the arylation of various alkynes reported to date. This system typically operates with 0.1 mol % of palladium in the presence of stoichiometric amounts of base without the addition of phosphine ligands but the reaction has to be performed at 110 °C.[25] It is, however, surprisingly that little is known about the catalytically active species and reaction paths involved in these Pd-catalyzed alkynylation reactions if compared with the huge efforts devoted to the Heck and Suzuki couplings.

It is evident that there is a need for more efficient and simple palladium catalyst precursors that operate under milder reaction conditions for the arylation of alkynes. We have recently reported that the palladacycle $\{Pd[k^2\text{-}C,N\text{-}C{=}(C_6H_5)C(Cl)CH_2NMe_2](\mu\text{-}Cl)\}_2$ (**1**) derived from the chloropalladation of the 3-(dimethylamino)-1-phenyl-1-propyne is amongst the most effective catalyst precursors for the coupling of haloarenes with alkenes and in some cases this reaction can be conducted at room temperature.[26] We now report that palladacycle **1**[27] is also an effective catalyst precursor for the alkynylation of iodo- and bromoarenes at room temperature. For comparative purposes we have also investigated the electron-rich and electron-poor phosphine adducts **2** and **3** (Scheme 1).[28–30] Moreover, poisoning tests have been performed in order to get insight into the nature of the catalytically active species involved in this Csp^2-Csp coupling reaction.

Results and Discussion

Preparation and Characterization of Palladacycles 2 and 3

The phosphine adducts **2** and **3** were prepared in good yields by simple addition of di-*t*-butylphosphine or tris-*p*-trifluoromethane-phenylphosphine, respectively, to a dichloromethane solution of palladacycle **1** at room temperature. The monomeric palladacycles **2** and **3** were isolated as light yellow powders and characterized by C,H,N-analysis, ^1H and ^{13}C NMR. In particular the ^1H NMR spectra of **2** and **3** in $CDCl_3$ show a doublet for the NMe_2 group with a $^4J_{P,H} = 2.4$ Hz and $^4J_{P,H} = 2.9$ Hz, respectively. The methylene hydrogens also appear as doublet with $^4J_{P,H} = 1.4$ Hz and $^4J_{P,H} = 1.9$ Hz in the ^1H NMR spectra of **2** and **3**, respectively. These $^4J_{P,H}$ coupling constants are typical for P-ligands located *trans* to the Pd-N moieties as observed in analogous monomeric palladacycles. Moreover, the molecular structure of **2** has also been ascertained by means of X-ray studies. Two independent molecules were found for complex **2** showing only small deviations in the phosphine conformation. The structure of **2**, together with selected bond distances and angles is shown in Figure 1.

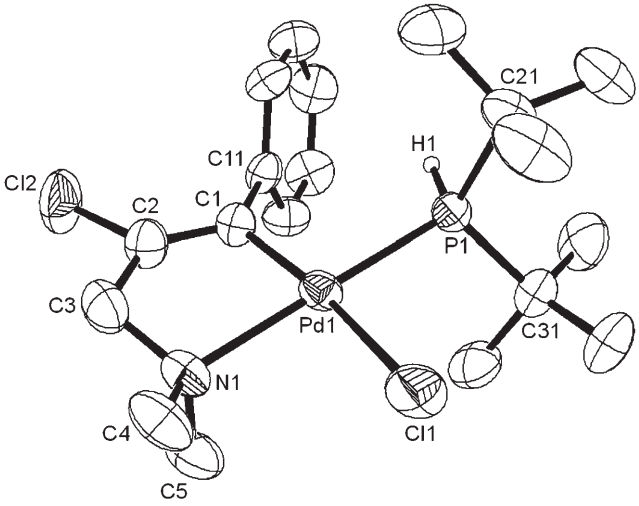


Figure 1. Molecular structure of **2**. Selected bond distances (A) and angles (°): **Molecule A:** Pd1–C1 2.050(3), Pd1–N1 2.186(3), Pd1–P1 2.2722(8), Pd1–Cl1 2.4013(9), C1–C2 1.331(5); C1–Pd1–N1 82.46(11), C1–Pd1–P1 93.55(9), N1–Pd1–P1 173.61(7), P1–Pd1–Cl1 93.13(3), N1–Pd1–Cl1 90.79(8). **Molecule B:** Pd1–C1 2.057(3), Pd1–N1 2.189(3), Pd1–P1 2.2613(8), Pd1–Cl1 2.4001(9), C1–C2 1.332(5), C1–Pd1–N1 83.11(13), C1–Pd1–P1 93.06(10), N1–Pd1–P1 175.76(9), P1–Pd1–Cl1 92.71(3), N1–Pd1–Cl1 91.18(9).

Crystallographic data and details of the structure determination are presented in Table 1 (see also Experimental Section). In compound **2** the Pd(II) center is coordinated in a distorted square-planar fashion by the N and the P donor groups, a C(sp^2) vinyl atom and a Cl atom. The C(vinyl)–Pd–Cl bond angle is 173.5° and the P and N donor groups are also in mutual *trans* positions with a bond angle of 174.6° showing an angular deviation of 5.4° from exact *trans* coordination. The location of the P-ligand *trans* to the NMe_2 group is reflected on the Pd–N bond distance of 2.187 Å in **2** that is larger than that observed in the dimeric palladacycle **1** (2.064 Å).[31] The σ Pd–C(vinyl) single bond in **2** (2.054 Å) is slightly larger than those observed in analogous compounds, where the distances fall in the range between 1.991 and 2.011 Å.

Table 1. Crystal data and structure refinement for **2**.

Empirical formula	$C_{19}H_{32}Cl_2NPPd$	
Formula weight	482.73	
Temperature	230(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1ū	
Z	4	
Unit cell dimensions	$a = 11.2665(1)$ Å	$\alpha = 87.573(1)^\circ$
	$b = 11.6317(1)$ Å	$\beta = 78.682(1)^\circ$
	$c = 18.0339(1)$ Å	$\gamma = 87.020(1)^\circ$
Volume	2312.98(3) $Å^3$	
Density (calculated)	1.39 g/cm^3	
Absorption coefficient	1.10 mm^{-1}	
Crystal shape	polyhedron	
Crystal size	$0.27 \times 0.25 \times 0.25$ mm^3	
Theta range for data collection	1.1 to 27.6 deg.	
Index ranges	$-14 \le h \le 14,\ -15 \le k \le 15,\ -23 \le l \le 23$	
Reflections collected	23933	
Independent reflections	10495 ($R(int) = 0.0312$)	
Observed reflections	7813 ($I > 2\sigma(I)$)	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.77 and 0.75	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	10495/0/447	
Goodness-of-fit on F^2	1.02	
Final R indices ($I > 2\sigma(I)$)	$R1 = 0.037$, $wR2 = 0.084$	
Largest diff. peak and hole	0.98 and -0.66 e $Å^{-3}$	

Catalytic Performance of Palladacycles 1–3 in the Alkynylation Reaction

The potential of compounds **1**–**3** as catalyst precursors was initially probed in the coupling of phenylacetylene with iodobenzene using various reaction conditions (solvent, base, temperature and Pd loadings). DMA (dimethylacetamide) is the solvent of choice and among the various bases [$NaOAc/NBu_4Br$, Na_2CO_3, pyrrolidine, HMTA (hexamethylenetetramine) and NEt_3] tested, NBu_4OAc gave the best results, although DABCO (diazabicyclo[2.2.2]octane) can be also used (Table 2, entries 1 and 8). Interestingly, the reaction can be performed at room temperature using 1% of **1** (Table 2, entries 1 and 2) or **3** (Table 2, entry 5), and relative short reaction times (4 h). The loadings of **1** and **3** can be reduced down to 0.00005% (Table 2, entries 7 and 10) giving good yield in the diphenylacetylene, but in these cases the temperature should be higher (120 °C) and longer reaction times are required.

It is clear that the alkynylation of iodobenzene can be performed with the phosphine-free palladacycle **1**. The presence of a bulky electron-rich phosphine has a detrimental effect on the yield (compare entries 2 and 4 of Table 2) although the presence of an electron-poor phosphine has no significant effect on the reaction yield (compare entries 6 and 9 of Table 2). Once the best reaction conditions were established the catalytic system was extended to aryl bromides (Table 3) and other alkynes (Table 4).

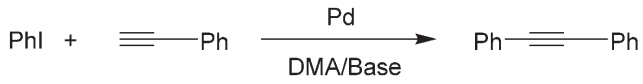
The experimental protocol using palladacycle **1** has been thus successfully extended to aryl bromides containing either electron-withdrawing of electron-donating groups affording disubstituted alkynes in good yields. Note the reaction involving bromoarenes substituted with electron-withdrawing groups can be performed at room temperature (see entries 2, 7 and 12, Table 3) in contrast to the bromo substrates containing electron-donating groups where the reaction should be performed at higher temperatures (entries 18 and 19, Table 3) and the phosphine adduct **3** must be used.

The same protocol can be used with other alkynes such 1-heptyne and 2-methyl-3-butyn-2-ol. (Table 4). However the reaction fails when acetylenes containing electron-withdrawing groups are used (Entry 10, Table 4).

Catalytically Active Species

It is now accepted that in most of the cases, the catalytically active species involved in C–C coupling reactions, in particular for Heck and Suzuki protocols, are based on Pd(0) and that the reaction proceeds through a Pd(0)/Pd(II) catalytic cycle whatever the nature of the catalyst precursor (ionic, molecular, colloidal, support-

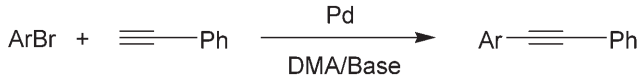
Table 2. Coupling of phenylacetylene with iodobenzene promoted by palladacycles **1**–**3**.[a]



Entry	Pd	[PhI]/[Pd]	Base	T [^{0}C]	t [h]	Conv. [%][b]	Yield [%][b]
1	1	1.0×10^2	DABCO	30	4	89	88
2	1	$1{,}0\times10^2$	NBu_4OAc	30	4	100	97 (91)
3	1	1.0×10^3	NBu_4OAc	30	4	32	22
4	2	1.0×10^2	NBu_4OAc	30	4	52	43
5	3	1.0×10^2	NBu_4OAc	30	4	100	97 (87)
6	1	5.0×10^4	NBu_4OAc	120	24	98	95 (80)
7	1	5.0×10^5	NBu_4OAc	120	24	82	80
8	1	5.0×10^4	DABCO	120	24	60	52
9	3	5.0×10^4	NBu_4OAc	120	24	100	97 (90)
10	3	5.0×10^5	NBu_4OAc	120	24	62	62

[a] *Reaction conditions:* DMA (3 mL), NBu_4OAc or DABCO (0.7 mmol), phenylacetylene (0.54 mmol), PhI (0.5 mmol).
[b] Yield and conversion obtained by GC (using methyl benzoate as internal standard). Isolated yield in parenthesis.

Table 3. Coupling of bromoarenes with phenylacetylene promoted by palladacycles **1** and **3**.[a]

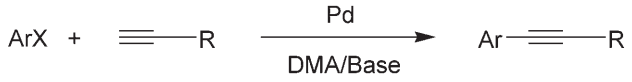


Entry	Pd	ArBr	[ArBr]/[Pd]	T [°C]	Conv. [%][b]	Yield [%][b]
1	1	2-BrPy	1.0×10^2	80	92	74
2	1	4-NCC_6H_4Br	1.0×10^2	30	95	95
3	1	4-NCC_6H_4Br	1.0×10^3	50	100	97 (90)
4	1	4-NCC_6H_4Br	1.0×10^4	120	87	82
5	1	4-NCC_6H_4Br	1.0×10^5	150	35	40
6[d]	1	4-NCC_6H_4Br	1.0×10^3	80	100	97
7[c]	1	4-$MeCOC_6H_4Br$	1.0×10^2	30	77	75
8	1	4-$MeCOC_6H_4Br$	1.0×10^2	80	99	95 (87)
9	1	4-$MeCOC_6H_4Br$	1.0×10^4	120	94	91
10	1	4-$MeCOC_6H_4Br$	1.0×10^5	150	42	40
11[d]	1	4-$MeCOC_6H_4Br$	1.0×10^3	80	47	50
12	3	4-CNC_6H_4Br	1.0×10^2	30	89	89
13	3	4-CNC_6H_4Br	1.0×10^3	50	100	98 (92)
14	3	4-CNC_6H_4Br	1.0×10^4	120	89	89
15	3	4-CNC_6H_4Br	1.0×10^5	150	38	39
16	3	4-$MeCOC_6H_4Br$	1.0×10^2	30	68	65
17	3	4-$MeCOC_6H_4Br$	1.0×10^4	120	100	98
18	3	4-$MeOC_6H_4Br$	1.0×10^2	130	89	78 (60)
19	3	4-MeC_6H_4Br	1.0×10^2	130	94	90 (80)

[a] *Reaction conditions:* 4 h, DMA (3 mL), NBu_4OAc (0.7 mmol), phenylacetylene (0.54 mmol), ArBr (0.5 mmol).
[b] Yield and conversions obtained by GC (using methyl benzoate as internal standard), Isolated yield in parenthesis.
[c] Reaction time 24 hours.
[d] DABCO (0.7 mmol) used as base instead of NBu_4OAc.

ed or "heterogeneous").[32–38] In this respect several approaches, such as poisoning experiments, intrinsic kinetics, and physical-chemical analysis can be used as probes to determine the nature of the "true" catalyst.[39,40] Although some of these approaches have been used to probe the species involved in the Heck reaction promoted by palladacycles only limited conclusions have appeared so far, most of them indicating that they are pre-catalysts of ill-defined Pd(0) catalytically active species. In the case of the alkynylation of aryl halides the sit-

Table 4. Coupling of aryl halides with alkynes promoted by palladacycles **1** and **3** under different reaction conditions.[a]



Entry	Pd	ArX	R	[ArX]/[Pd]	T [°C]	Conv. [%][b]	Yield [%][b]
1	1	PhI	n-C_4H_9	1.0×10^2	30	100	98(90)
2	1	PhI	n-C_4H_9	1.0×10^3	120	98	97
3	1	4-$MeCOC_6H_4Br$	n-C_4H_9	1.0×10^2	120	100	93(85)
4	3	PhI	n-C_4H_9	1.0×10^3	120	100	98
5	1	PhI	$C(Me_2)OH$	1.0×10^2	80	75	70
6	1	PhI	$C(Me_2)OH$	1.0×10^2	120	93	85
7	1	4-$MeCOC_6H_4Br$	$C(Me_2)OH$	1.0×10^2	120	92	45
8	3	PhI	$C(Me_2)OH$	1.0×10^2	80	72	68
9	3	PhI	$C(Me_2)OH$	1.0×10^2	120	100	97(90)
10	1	PhI	CO_2Et	1.0×10^2	30	0	0

[a] *Reaction conditions:* 4 h, DMA (3 mL), NBu_4OAc (0.7 mmol), acetylene (0.54 mmol), ArX (0.5 mmol).
[b] Yield and conversions obtained by GC (using methyl benzoate as internal standard), isolated yield in parenthesis.

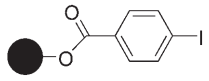
uation is much more complicated since no systematic investigation has been performed so far in order to identify the possible catalytic species involved in this process.

In order to characterize the involvement of homogeneous or heterogeneous components in the alkynylation of aryl halides by **1** we have performed the Hg poisoning test. This test relies on the formation of an amalgam with colloidal palladium although poisoning of molecular Pd(0) cannot be excluded.[41] Moreover, a Hg poisoning test can confirm a homogeneous catalytic system but not a heterogeneous one. The Hg(0) poisoning test was performed in the coupling of iodobenzene with phenylacetylene promoted by palladacycle **1** at room temperature. When compared to control reactions, a complete inhibition of the catalytic activity was observed after Hg (300 equivalents) addition, confirming the intervention of Pd(0) species.

Second, we have performed the Collman test that is based on the ability of substrates attached to cross-linked polymers in distinguishing homogeneous or heterogeneous catalytically active species.[42] In this system only soluble or highly solvated species are able to diffuse through the polymeric matrix and as a consequence only homogeneous catalytically active species are expected to show catalytic activity. The catalytic activity of the reaction of iodoarene attached to cross-linked polystyrene (Wang resin) promoted by palladacycle **1** is almost similar to those conducted with free substrates and quantitative yields of the coupling products can be obtained after resin cleavage.

Huge catalytic activities were obtained ([ArX]/[Pd] = 1.0×10^5) (entries 2 and 3, Table 5) even without low concentrations of free substrate (three phase test).[43] These results strongly suggest that homogeneous catalytically active species are responsible for the catalytic activity observed.

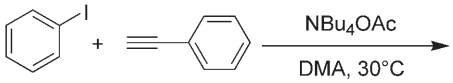
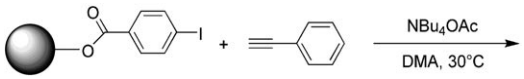
Table 5. Catalytic activity of palladacycle **1** with polymer-supported alkyne.[a]

Entry	Substrate	Acetylene	[ArX]/[Pd]	T [°C]	Yield[b] [%]
1			1.0×10^2	30	100
2			1.0×10^5	130	100
3			1.0×10^6	130	58

[a] *Reaction conditions:* 24 h, DMA (3 mL), resin (0.35 mmol), NBu_4OAc (0.7 mmol), phenylacetylene (0.5 mmol).
[b] Yield obtained by ^1H NMR (using 1,3,5-trihydroxybenzene as internal standard) after resin cleavage with TFA/CH_2Cl_2

Inasmuch as the Collman test indicates the involvement of homogeneous palladium species we decided to run the test with the homogeneous species selective inhibitor dibenzo[*a, e*]cyclooctatetraene (DCT). This test is based on the ability of this diene to form stable and inert homogeneous complexes with platinum metals.[44] However, the irreversibility of the DCT-Pd complex formation depends on the temperature and as a consequence, the test's validity also depends on the reaction temperature. The general experimental protocol includes the prior generation of the catalytically active species and the subsequent contact of the active species with DCT for at least two hours prior to the addition of substrates. With minor adaptation, the Crabtree test was applied to the reactions of iodobenzene and iodoarene attached to the Wang resin with phenylacetylene performed at room temperature (Table 6). After 15 minutes, aliquots were taken from the reactions for quantification and DCT (2 equivalents.) was added to one re-

Table 6. DCT inhibition tests.[a]

Reaction	[DCT]/[Pd]	Relative activity (%)
	0	100[b]
	2	100[b]
	0	100[c]
	2	100[c]

[a] *Reaction conditions:* DMA (5 mL), phenylacetylene (1.2 mmol) ArI (1 mmol), **1** (1.0×10^{-3} mmol) and NBu_4OAc (1.4 mmol). Experiment with Wang resin with coupled substrate: DMA (3 mL), resin (0.35 mmol), NBu_4OAc (0.5 mmol), phenylacetylene (0.5 mmol). DCT (2:1 DCT:Pd) added after reaction time of 15 minutes. Relative activities were calculated by the yields obtained at reaction times of 15 minutes and 24 h.
[b] Yields obtained by GC (using methyl benzoate as internal standard).
[c] Yields obtained by ^1H NMR (using 1,3,5-trihydroxybenzene as internal standard) after resin cleavage with TFA/CH_2Cl_2.

action vessel. After 24 hours, the reactions were stopped for conversion quantification and comparison. In both cases no inhibition of the catalytic activity was observed, suggesting that no Pd(0) molecular complex is involved in the process.

The combined Hg, Collman and Crabtree test results suggest that soluble non-monometallic Pd(0) species are the catalytically active species. Of note is that the involvement of Pd(0) nanoparticles as the catalytically active species, or as the source of Pd catalytically active species, similar to those proposed in Heck arylation of alkenes, cannot be ruled out at this stage of our studies but all attempts to identify Pd nanoparticles by transmission electron microscopy were unsuccessful. However, we propose that the reaction probably proceeds through the oxidative addition of the aryl halide to the Pd(0) catalytic species that generates homogenous Ar–Pd–X species. The coordination of the alkyne to the metal center followed based-assisted H–X elimination gave the Ar–Pd-C≡CR that by reductive elimination yields the coupling product and Pd(0), analogous to the recently proposed mechanism of Cu-free Sonogashira coupling.[21]

We do not have any significant information on the mechanism of formation of the Pd(0) catalytically active species starting from the palladacycles employed in this study. However, it is important to note that in all catalytic tests performed in this study small amounts of the homocoupling product of the terminal acetylene[45–49] were observed (1–4 mol %) even for those tests performed with low initial concentrations of palladium. Moreover, no experimental evidence was found to support the hypothesis of the reductive coupling of the terminal acetylene being responsible for the generation of Pd(0) species. The homocoupling product of the terminal acetylene was not observed when palladacycle **1** was reacted with a slight excess of phenylacetylene in the presence of the base NBu_4OAc. Neither the Sonogashira nor homocoupling products were observed in control experiment performed without the catalytic precursor.

Effect of Aromatic Substituent on Reaction Rate

To gain some insight into the electronic influence of the *p*-substituent of the iodoarene on the reaction rate, competitive experiments using seven aryl iodides were performed under pseudo-zero order conditions with respect to the iodoarenes. The reaction rates were determined in the competitive experiments by measuring the relative initial reaction rate of iodobenzene and substituted iodobenzene conversions (activated from deactivated aryl halides). The resulting Hammett plots are presented in Figure 2.

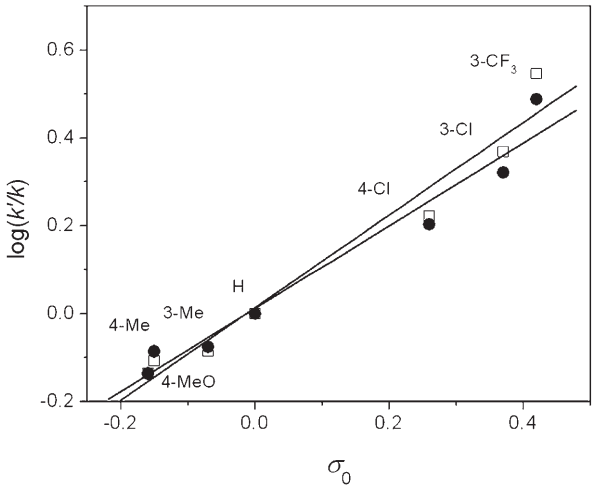


Figure 2. Hammett correlation for the Heck competitive reaction between iodo arenes and phenylacetylene at 80 °C in DMA promoted by **1** using the σ_0 constants. (□) DABCO ($\rho = 1.0$; $R = 0.98$) and (●) NBu_4OAc ($\rho = 0.96$; $R = 0.98$).

The use of σ_0 constants results in good fits and correlations yielding a value close to $\rho = 1.0$ independent of the base used, indicating that the electronic influence on the reaction rate is not so pronounced if compared with Heck or Suzuki coupling reactions where ρ values for iodoarenes can reach 1.8–2.0[50] that are close to the value of 2.0 observed for the oxidative addition reaction of iodoarenes with $[Pd(PPh_3)_4]$.[51,52] Therefore in case of aryl iodides the rate-determining step (which is sensitive to the electronic influence of aryl iodide) is most probably not the oxidative addition of the aryl halide to Pd(0) species for the alkynylation promoted by palladacycle **1**. This may also explain why the presence of an electron-rich phosphine in adduct **2** has a detrimental effect on the catalytic performance since it is expected that electron-rich ligands improve the oxidative addition of aryl halides. Therefore it is probably that in these cases the rate-determining step is related with the reductive elimination path involving Ar–Pd–C≡CR species.

Conclusion

In conclusion, we have established new catalysts based on palladacycles for the alkynylation reaction. From the view point of TON values the arylation of acetylenes ranks with the best in the literature for palladacycles and their phosphine adducts. The catalyst precursor **1** probably acts as reservoir of catalytically active Pd(0) species and the alkynylation reaction follows a Pd(0)/Pd(II) mechanism. The poisoning tests indicated the involvement of soluble Pd(0) species as the catalytically active species generated from the palladacycle **1**.

Experimental Section

General Remarks

All reactions involving organometallic compounds were carried out under an argon or nitrogen atmosphere in oven-dried Schlenk tubes. Solvents were dried with suitable drying agents and distilled under argon prior to use. The palladacycle **1** was prepared using the procedure reported previously.[26] All other chemicals were purchased from commercial sources (Acros or Aldrich) and used without further purification. NMR spectra were recorded on a Varian Inova 300 spectrometer. Infrared spectra were performed on a Bomem B-102 spectrometer. Gas chromatographic analyses were performed with a Hewlett-Packard 5890 Gas Chromatograph with an FID and 30 meter capillary column with a dimethylpolysiloxane stationary phase. Mass spectra were obtained using a GC/MS Shimadzu QP-5050 (EI, 70 eV).

Preparation of Adduct 2

A Schlenk flask was charged with palladacycle **1** (0.5 mmol, 168 mg) and CH_2Cl_2 (5 mL). Di-*t*-butylphosphine (175 mg, 1.2 mmol) dissolved in CH_2Cl_2 (1 mL) was added to the solution. After two hours stirring at room temperature, the CH_2Cl_2 was concentrated to 0.5 mL and hexane (10 mL) was added. The reaction mixture was filtered and after removal of volatiles complex **2** was obtained as a faint yellow solid; yield: 193 mg (80%). Elemental analysis: $C_{19}H_{32}Cl_2NPPd$ (482.77) requires: C 47.27, H 6.68, N 2.90; found: C 47.38, H 6.54, N 2.99; ^{1}H NMR ($CDCl_3$): $\delta = 7.33–6.93$ (m, 5H, H arom), 3.66 (d, 2H, CH_2N, $^4J_{P,H} = 1.4$ Hz), 2.86 [d, 6H, $N(Me)_2$, $^4J_{P,H} = 2.4$ Hz], 2.75 (d, 1H, HP, $J_{P,H} = 359.3$ Hz), 1.31 (d, 9H, *t*-Bu, $^3J_{P,H} = 14.6$ Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta =$ 146.1 (d, $^3J_{P,C} = 7.3$ Hz, C=C-Pd), 120.3 (d, $^2J_{P,C} = 4.4$ Hz, C=C-Cl), 147.3, 131.7, 127.9, 127.8, 125.3 (C arom), 73.1 (d, $^3J_{P,C} = 2.6$ Hz, CH_2N), 49.9 [d, $^3J_{P,C} = 2.6$ Hz, $N(Me)_2$], 34.9 [d, $^1J_{P,C} = 20.5$ Hz, $C(CH_3)_3$], 30.1 [d, $^2J_{P,C} = 4.0$ Hz, $C(CH_3)_3$].

Preparation of Adduct 3

A Schlenk flask was charged with palladacycle **1** (0.5 mmol, 168 mg) and CH_2Cl_2 (5 mL). Tris-*p*-trifluoromethane-phenylphosphine (560 mg, 1.2 mmol) dissolved in CH_2Cl_2 (1 mL) was added to the solution. After two hours stirring at room temperature, the CH_2Cl_2 was concentrated to 0.5 mL and hexane (10 mL) was added. The reaction mixture was filtered and after removing of volatiles complex **3** was obtained as a faint yellow solid; yield: 280 mg (70%). Elemental analysis: $C_{32}H_{25}Cl_2F_9NPPd$ (802.84) requires: C 47.87, H 3.14, N 1.74; found: C 47.88, H 3.04, N 1.53; ^{1}H NMR ($CDCl_3$): $\delta = 7.69–7.5$ (m, 12H, H arom, PPh*p*-CF_3), 6.87 + 6.52 (m, 5H, H arom, Ph), 3.88 (d, 2H, CH_2N, $^4J_{P,H} = 1.9$ Hz), 2.98 [d, 6H, $N(Me)_2$, $^4J_{P,H} = 2.9$ Hz]; $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 142.9$ (d, $^3J_{P,C} =$ 5.1 Hz, C=C), 134.2 (d, $J_{P,C} = 49.1$ Hz, C-P), 149.3 134.4, 127.9, 126.9, 125.4, 125.1 (C arom), 121.8 (d, $^2J_{P,C} = 3.7$ Hz, C=C), 132.5 (q, $^3J_{F,C} = 31.3$ Hz CCF_3), 123.5 (q, $^2J_{F,C} =$ 272.8 Hz CF_3), 74.8 (d, $^3J_{P,C} = 2.9$ Hz CH_2N), 50.4 [d, $^3J_{P,C} =$ 2.9 Hz, $N(Me)_2$].

Typical Experiment for the Alkynylation Reaction

A 10-mL resealable Schlenk flask was evacuated and back-filled with argon and charged with tetrabutylammonium acetate (0.7 mmol, 224 mg), *N,N*-dimethylacetamide (3 mL), iodobenzene (0.5 mmol, 56 μL, 102 mg), phenylacetylene (0.6 mmol, 66 μL) and methyl benzoate as internal standard (35 mg). After the addition of the palladacycle **1** in *N,N*-dimethylacetamide (1.6 mg, 5×10^{-3} mmol) the reaction mixture was stirred at 30 °C for 4 h. GC analysis indicated 98% yield in diphenylacetylene and 2% of homocoupling acetylene product. The solution was added to a 10 wt % HCl (20 mL) and the product extracted with hexane (2×10 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated under vacuum, to give diphenylacetylene; yield: 84 mg (95%); > 95% pure by ^{1}H NMR and GC. ^{1}H NMR ($CDCl_3$): $\delta = 7.23$ (m, 10H, CH arom); GC-MS (EI, 70 eV): *m/z* (%) = 178 (M^+, 30), 152 (10), 126 (15), 111 (6), 98 (15), 87 (16).

Attachment of 4-Iodobenzoic Acid to Wang Resin

Wang resin (2 g, OH loading: 1 mmol g^{-1}, 2 mmol of OH) was suspended in 9:1 (v/v) CH_2Cl_2/DMF in a Schlenk flask. The 4-iodobenzoic acid (6 mmol), dicyclohexylcarbodiimide (1.24 g, 6 mmol) and 4-dimethylaminopiridine (25 mg, 0.2 mmol) were added to the resin suspension and the reaction mixture was refluxed for 4 h. The resin was collected on a filter funnel, washed with $3\times$ DMF, $3\times H_2O$, $3\times$ DMF, $3\times CH_2Cl_2$, $3\times$ MeOH and dried under vacuum.

Estimation of resin loading: 300 mg of Wang resin modified with the4-iodobenzoic acid were suspended in trifluoroacetic acid:CH_2Cl_2 1:1 (v/v) and stirred for 2 h. The cleavage solution was dried under vacuum and the residual amount of free halobenzoic acid was employed to obtain the resin loading.

Hg(0) Poisoning Test

Two identical Sonogashira experiments consisting of phenylacetylene (0.6 mmol, 66 μL), iodobenzene (0.5 mmol, 56 μL, 102 mg), 3 mL of *N,N*-dimethylacetamide, tetrabutylammonium acetate (0.7 mmol, 224 mg) and palladacycle **1** in *N,N*-dimethylacetamide (1.6 mg, 5×10^{-3} mmol) were stirred at 30 °C. Aliquots were taken from both reactions and analyzed by GC. After two hours, Hg (0.3 mmol, 60 mg) was added to one reaction vessel.

Typical Experiment for the Alkynylation Reaction of Phenylacetylene Attached to the Wang Resin

A 10-mL resealable Schlenk flask was evacuated and back-filled with argon and charged with tetrabutylammonium acetate (0.5 mmol, 160 mg) and the Wang resin containing the attached 4-iodobenzoic acid (500 mg, I loading: 0.68 mmol g^{-1}, 0.35 mmol of I), DMA (3 mL), phenylacetylene (0.5 mmol, 55 μL) and palladacycle **1** (1.2 mg, 3.5×10^{-3} mmol). The reaction mixture was stirred at 30 °C for 24 h. The Wang resin was collected in a filter funnel, washed with 3 mL portions of $3\times$ DMF, $3\times H_2O$, $3\times$ DMF, $3\times CH_2Cl_2$, $3\times$ MeOH and dried under vacuum.

Determination of yield: The Wang resin was suspended in the cleavage solution [3 mL, trifluoroacetic acid:CH_2Cl_2, 1:1 (v/v)] and stirred for 2 h. The cleavage solution was dried under vacuum and 1,3,5-trihydroxybenzene utilized as internal standard for ^{1}H NMR quantification of the Sonogashira product.

DCT Inhibition Test

Two identical Sonogashira experiments consisting of phenylacetylene (0.6 mmol, 66 μL), iodobenzene (0.5 mmol, 56 μL, 102 mg), 3 mL of *N,N*-dimethylacetamide, tetrabutylammonium acetate (0.7 mmol, 224 mg) and palladacycle **1** in *N,N*-dimethylacetamide (1.6 mg, 5×10^{-3} mmol) were stirred at 30 °C. Aliquots were taken from both reactions and analyzed by GC. After two hours, DCT (2×10^{-2} mmol, 4 mg) was added to one reaction vessel. Aliquots were taken from both reactions and analyzed by GC.

Typical Experiment for the Hammet Competition Reaction

A 10-mL resealable Schlenk flask was evacuated and back-filled with argon and charged with tetrabutylammonium acetate (0.7 mmol, 224 mg), *N,N*-dimethylacetamide (3 mL), phenylacetylene (0.2 mmol, 22 μL), methyl benzoate, as internal standard (35 mg), 0.6 mmol of PhI and 0.6 mmol of one of the substrates: 4-$MeOC_6H_4I$, 4-MeC_6H_4I, 3-MeC_6H_4I, 4-ClC_6H_4I, 3-ClC_6H_4Br or 3-$CF_3C_6H_4Br$. After the addition of the palladacycle **1** in *N,N*-dimethylacetamide (1.6 mg, 5×10^{-3} mmol) the reaction mixture was stirred at 80 °C. The reaction was monitored by GC the initial relative rates were used to plot Hammett correlation.

X-Ray Crystallographic Study

Crystals of **2** were first prepared by slow diffusion of hexane into an acetone solution. A yellow crystal (polyhedron), dimensions $0.27\times0.25\times0.25$ mm^3, was mounted on a glass fiber with perfluoropolyether. The measurements were made on a Bruker SMART-CCD diffractometer with graphite monochromated Mo-K_α radiation, lambda = 0.71073 Å, crystal system triclinic, space group $P\bar{1}$, $Z=4$, $a=11.2665(1)$ Å, $b=11.6317(1)$ Å, $c=18.0339(1)$ Å, $\alpha=87.573(1)^\circ$, $\beta=78.682(1)^\circ$, $\gamma=87.020(1)^\circ$, $V=2312.98(3)$ Å^3, $\varrho=1.386$ g/cm^3, $T=230(2)$ K, $2\Theta_{max}=27.64^\circ$, 50 kV, 40 mA, 1116 0.5 deg omega-scans, 10 s each, covering a whole sphere in reciprocal space, 23933 reflections measured, 10495 unique (R(int) = 0.0312), 7813 observed ($I>2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[53] based on the Laue symmetry of the reciprocal space, $\mu=1.10$ mm^{-1}, $T_{min}=0.75$, $T_{max}=0.77$, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL-PLUS (5.10) software package,[54] 447 parameters refined, hydrogen atoms were treated using appropriate riding models except of atoms H1 at P1, which were refined isotropically, goodness of fit 1.02 for observed reflections, final residual values R1(F) = 0.037, wR(F^2) = 0.084 for observed reflections, residual electron density -0.66 to 0.98 e Å^{-3}. CCDC 279491 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk)

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