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Domino Approach to Benzofurans by the Sequential Sonogashira/Hydroalkoxylation Couplings Catalyzed by New N-Heterocyclic-Carbene-Palladium Complexes

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A set of three different NHC-Pd-pyridine complexes (NHC = 1,2,4-trimethyltriazolyldiylidene, 1,3-dimethylimidazolylidene, and 1,4-dimethyltriazolylidene) have been prepared and fully characterized. The X-ray molecular structures of two of the complexes are reported. The three complexes have been tested in a series of reactions between *o*-hydroxyaryl halides and phenylacetylene to afford benzofurans, in a tandem process that comprises a Sonogashira coupling followed by a cyclic hydroalkoxylation. All three catalysts afforded excellent yields of the final products when the corresponding iodoarenes were used.

Introduction

In the search for efficient methods for the preparation of complex products with pharmaceutical interest, it is important to find ways for the replacement of multistep, salt-generating procedures with catalyzed reactions that strive for atom economy.[1] One-pot processes for multistep reactions not only are convenient from an economical point of view but also afford environmental benefits because they produce less contaminant residues. Substituted benzofurans can be found as the key structural unit of many biologically active compounds with pharmaceutical applications.[2] Although various methods for the preparation of benzofurans are known, those using palladium catalysts for coupling/cyclization reactions of alkynes with *o*-hydroxyaryl halides are the ones more widely used recently.[3−5] We have found it interesting that, although both the Sonogashira coupling of terminal alkynes and aryl halides and intramolecular alkyne hydroalkoxylation can be catalyzed by palladium complexes (Scheme 1), there are just a few examples in the literature reporting the reaction of *o*-hydroxyaryl halides and terminal alkynes to directly afford benzofurans.[5,6] A closer look at the overall process reveals that the two steps may find some incompatibilities regarding the nature of the catalyst, base, solvent, and additives used for each individual step, so in most cases the isolation of the alkynylbenzyl alcohol (or alkynylphenols) intermediate is needed prior to the cyclization process.[4,7−9]

We have recently been interested in the preparation of stable catalysts that may be compatible with a wide variety of organic transformations.[10] In our search, we found that the 1,2,4-trimethyltriazolyldiylidene ligand (*ditz*) provides a high versatility that makes it suitable for the coordination to different metals, such as Rh,[11,12] Ir,[11,12] Pd,[13] and Ru.[14] We have also used ditz for the preparation of Rh/Ir heterometallic complexes that we have used for tandem catalysis.[12] We also found that in some cases the coordination of the ligand to the dimetallic species provided activities that are enhanced compared to the monometallic analogues.[12,13]

In connection with our previous work, and in view of the recent results described by Ghosh and co-workers showing that a series of NHC-Pd-pyridine complexes are good catalysts for the Sonogashira coupling in amine-free conditions,[15]

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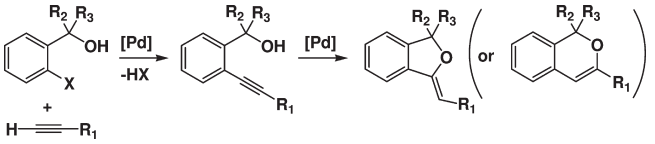
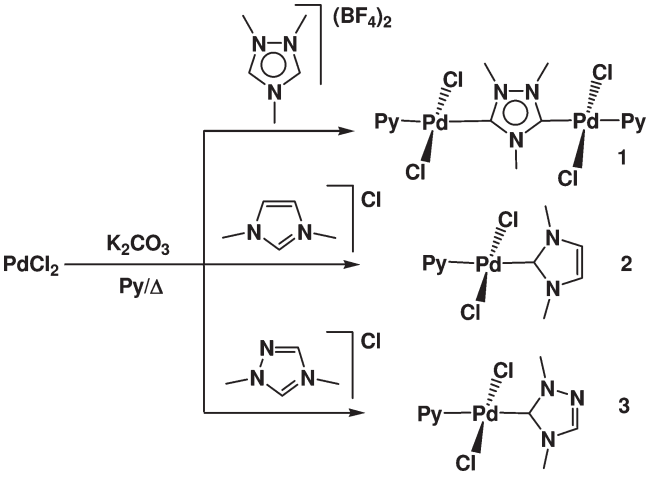
Scheme 1



Scheme 2



we have now obtained Pd-pyridine complexes with three different types of NHCs, namely, imidazolylidene, triazolylidene, and a dimetallic complex bridged by ditz. The new complexes have shown excellent efficiencies in the tandem reaction between *o*-hydroxyaryl halides and phenylacetylene to directly afford benzofurans.

Results and Discussion

Synthesis and Characterization of Compounds. The reactions of palladium dichloride with the corresponding azolium salts in refluxing pyridine in the presence of K_2CO_3, afford the NHC-Pd-Py complexes **1**, **2**, and **3** in high yield (Scheme 2). All three complexes were fully characterized by NMR spectroscopy and mass spectrometry and gave satisfactory elemental analyses. We thought that these three complexes constituted a good set of potential catalysts to study because the electronic density on the palladium center is modified by the nature of the ligands (σ-donor strength: 1,3-imidazolylidene > 1,3-triazolylidene > 1,2,4-trimetyltriazolyldiylidene), but the steric properties remain unmodified.

The ^{1}H NMR of **1** shows two distinctive signals for the three methyl groups of the triazolyl-diylidene ligand, confirming the binary symmetry for the molecule. The ^{13}C NMR provides direct evidence of the metalation of the ligand, as seen by the signal at 164.9 ppm assigned to the Pd−$C_{carbene}$. The dimetallic nature of the compound is confirmed by the data resulting from the electrospray mass spectrometry (ESI-MS), which shows a main peak at $m/z = 646.6$, due to $[M + Na]^+$. The most representative ^{13}C NMR signals of compounds **2** and **3** are those due to the metalated carbons at 153.9 and 143.4 ppm, respectively.

X-ray-Diffraction Studies. The molecular structures of **1** and **2** were determined by means of X-ray diffraction studies. The molecular diagrams of **1** and **2** are shown in Figures 1 and 2. The molecular structure of **1** consists of two $PdCl_2$(pyridine) fragments connected by a ditz bridge. The two metal fragments present a *trans* conformation related to the

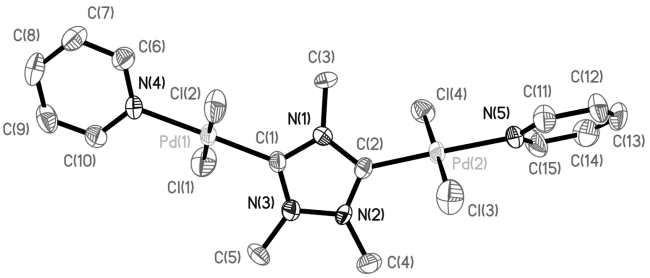


Figure 1. Molecular diagram of complex **1**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) 1.951(4), Pd(1)−N(4) 2.079(5), Pd(1)−Cl(1) 2.290(2), Pd(1)−Cl(2) 2.296(2), Pd(2)−C(2) 1.968(7), Pd(2)−N(5) 2.088(6), Pd(2)−Cl(3) 2.299(2), Pd(2)−Cl(4) 2.291(2), C(1)−Pd(1)−N(4) 178.9(3), C(1)−Pd(1)−Cl(1) 89.8(2), N(4)−Pd(1)−Cl(1) 90.58(17), Cl(1)−Pd(1)−Cl(2) 178.48(8), C(2)−Pd(2)−N(5) 178.1(3), C(2)−Pd(2)−Cl(4) 89.4(2), N(5)−Pd(2)−Cl(4) 89.8(2), Cl(4)−Pd(2)−Cl(3) 178.16(8).

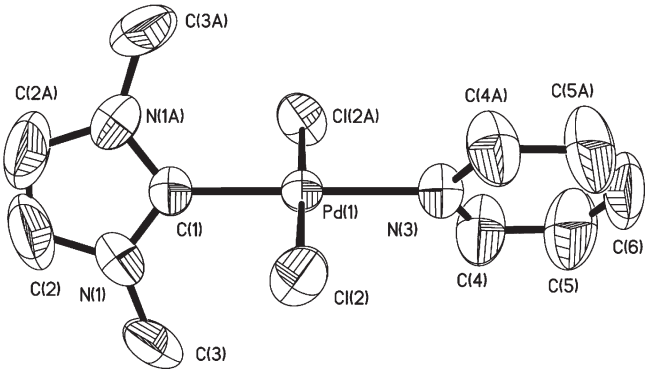
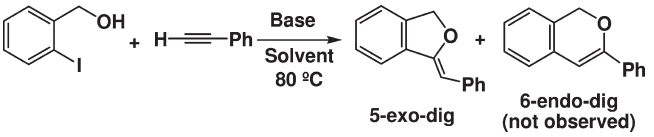


Figure 2. Molecular diagram of complex **2**. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) 1.972(8), Pd(1)−N(3) 2.084(8), Pd(1)−Cl(2) 2.3325(15), C(1)−Pd(1)−N(3) 180.0 (1), C(1)−Pd(1)−Cl(2) 89.43(5), N(3)−Pd(1)−Cl(2) 90.57(5).

chloro ligands. The two coordination planes about the metal centers are disposed at an angle of 47.6°, calculated as the average of the two torsion angles defined by Cl(1)−Pd(1)−Pd(2)−Cl(4) and Cl(2)−Pd(1)−Pd(2)−Cl(3). This angle is slightly higher than that shown for the related dipalladium complex [*trans*-$PdCl_2$(MeCN)]$_2$(μ-ditz) (32.3°).[13] The two metal centers are quasi-coplanar with the plane of the azole ring, with a small deviation of 1.60° shown by the torsion angle Pd(2)−C(2)−N(2)−N(3). The distance between the two palladium atoms is 6.03 Å, and the average Pd−C distance is 1.960 Å, similar to the same parameters shown by [*trans*-$PdCl_2$(MeCN)]$_2$(μ-ditz).[13]

The structure of **2** consists of a pseudo-square-planar molecule with a palladium center surrounded by 1,3-dimethylimidazolylidene, two chloro ligands in a *trans* configuration, and a pyridine. The azole plane deviates from the coordination plane of the molecule by an angle of 72.72° (according to the torsion angle defined by Cl(2)−Pd(1)−C(1)−N(1)). The Pd−C distance is 1.972 Å, similar to that shown by other palladium-related species[15] and by **1**. The Pd−N(pyridine) distance is 2.084 Å, almost identical to that shown by **1** for the same bond (2.080 Å), indicating a similar *trans* influence for ditz and the imidazolylidene ligand in **2**. These distances are longer than those shown for other related complexes with non-NHC ligands, indicating the high *trans*

Table 1. Base/Solvent Evaluation for the Formation of Benzofuran[a]



entry	base	solvent	yield (%)
1	Cs_2CO_3	DMSO	99
2	Cs_2CO_3	MeCN	59
3	Cs_2CO_3	toluene	30
4	K_2CO_3	DMSO	25
5	NaOH	DMSO	36
6	NaOAc	DMSO	5

[a] Reaction conditions: phenylacetylene (0.75 mmol), iodobenzyl alcohol (0.525 mmol), Cs_2CO_3 (1.57 mmol), catalyst (1% mol palladium), solvent (3 mL), and anisole as internal reference (0.525 mmol). Mixture heated at 80 °C for 3 h. Yields determined by GC.

influence of both NHCs in **1** and **2**.[16] All other distances and angles lie in the expected range.

Study of the Tandem Catalytic Process. Our studies on the tandem reaction between *o*-hydroxyaryl halides and phenylacetylene to afford benzofurans aimed to find the best conditions to achieve maximum yields under the mildest reaction conditions and minimum addition of additives. In order to optimize the reaction conditions, we first screened a series of solvents and bases using **1** as a catalyst in the reaction between *o*-iodobenzyl alcohol and phenylacetylene. As shown in Table 1, the best combination of solvent and base is obtained when using DMSO and Cs_2CO_3, for which full conversion to the final product is obtained. Remarkably, additives other than the base (CuI, amine, KI, etc.) were not needed in order to achieve high reaction outcomes, a result that is more relevant if we take into account that the overall reaction comprises two steps for which normally different additives are needed. For all the reactions tested, the 5-exo-dig product was the only one observed, and we never detected the formation of the 6-endo-dig cyclization product.

Then we performed an evaluation of the activities of our new three complexes and $PdCl_2(PPh_3)_2$ and $Pd(AcO)_2$ for comparison. All the reactions were carried out at 80 °C in DMSO and with Cs_2CO_3. The results are summarized in Table 2. All three NHC-Pd complexes achieved full conversions to the final product (**B**) when *o*-iodobenzyl alcohol was used (entries 3−5). Interestingly, only the *Z* isomer of **B** was obtained, and we never observed the formation of the *E* product. Under the same reaction conditions, $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ afforded poor yields, although the Sonogashira coupling seemed to have proceeded with quite good progress, a result that is not surprising if we take into account that $PdCl_2(PPh_3)_2$ is normally used for the preparation of the intermediate **A**.[8] This result clearly illustrates that a good catalyst for the Sonogashira coupling may not be good for the cyclic hydroalkoxylation, so that if we are pursuing good outcomes for the overall reaction, we have to finely tune the catalysts to make them active in the two consecutive transformations.

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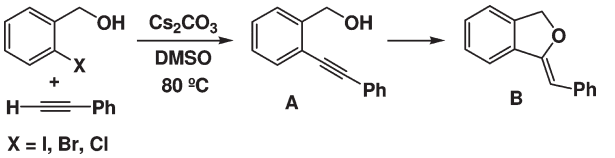
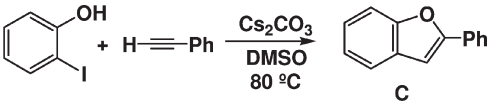
Table 2. Catalyst Evaluation of the Sonogashira/Cyclic Hydroalkoxylation Reaction[a]



				yield % (isolated)	
entry	X	catalyst	time (h)	**A**	**B**
1	I	$PdCl_2(PPh_3)_2$	1	68	28
2	I	$Pd(OAc)_2$	1	58	19
3	I	**1**	1	0	99 (85)
4	I	**2**	1	0	98 (80)
5	I	**3**	1	0	98 (84)
6	Br	**1**	12	0	43
7	Br	**2**	12	0	77
8	Br	**3**	12	0	45
9	Cl	**1**	12	0	7
10	Cl	**2**	12	0	5
11	Cl	**3**	12	0	3

[a] Reaction conditions: phenylacetylene (0.75 mmol), halobenzyl alcohol (0.525 mmol), Cs_2CO_3 (1.57 mmol), catalyst (1% mol palladium), DMSO (3 mL), and anisole as internal reference (0.525 mmol). The mixture was heated at 80 °C. Yields determined by GC (isolated yields in parentheses).

Table 3. Sonogashira/Cyclic Hydroalkoxylation Reaction between *o*-Iodophenol and Phenylacetylene[a]



entry	halophenol	cat.	time (h)	yield %
1	I	**1**	8	93
2	I	**2**	20	16
3	I	**3**	16	88

[a] Reaction conditions: phenylacetylene (0.75 mmol), halophenol (0.525 mmol), Cs_2CO_3 (1.57 mmol), catalyst (1% mol palladium), DMSO (3 mL), and anisole as internal reference (0.525 mmol). The mixture was heated at 80 °C. Yields determined by GC.

Catalysts **1**−**3** were tested for other halobenzyl alcohols (halo = bromo, chloro). The activation of *o*-bromobenzyl alcohol was moderate for **1** and **3** (yields 43% and 45%, respectively, entries 6 and 8) and very good for **2** (77%, entry 7). When *o*-chlorobenzyl alcohol was used, the formation of the final product **B** was almost negligible (entries 9−11). Despite the moderate to low yields displayed by the bromo and chloro derivatives of compound **B** (except for the result shown in entry 7), we did not detect any amount of intermediate **A**, meaning that the activation of the C−X bond is the rate-limiting step for these cases.

In order to widen the applicability of this tandem process, we decided to carry out a similar reaction between *o*-iodophenol and phenylacetylene using compounds **1**−**3** as catalysts. The results are summarized in Table 3. The dimetallic catalyst **1** afforded the best activity, with almost full conversion to the final product (2-phenylbenzofuran, **C**) in 8 h. The triazolylidene complex **3** also afforded an excellent conversion (88%) although in a longer reaction time (16 h, entry 3). The time-dependent reaction profiles of these three reactions

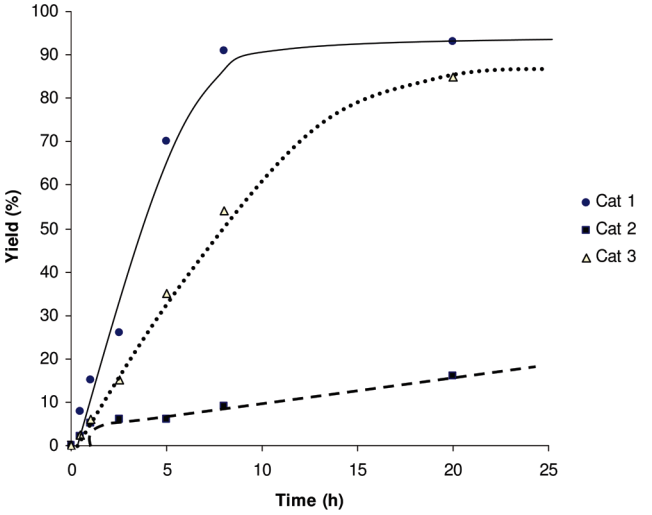


Figure 3. Time course of the formation of 2-phenylbenzofuran by the consecutive Sonogashira/cyclic hydroalkoxylation reactions between *o*-iodophenol and phenylacetylene.

are shown in Figure 3. As can be seen, catalyst **1** provides the best activity in terms of both overall conversion and reaction rate, while **3** affords a very poor outcome. It is worth mentioning that the catalyst that showed the best activation for the Sonogashira coupling (catalyst **2**) as seen for the activation of the C−Br bond in *o*-bromobenzyl alcohol (Table 2, entry 7) now provides the poorest yields in the formation of **C**, again illustrating that tuning the catalyst for a good performance in the Sonogashira coupling may result in its deactivation toward the cyclic hydroalkoxylation. The replacement of *o*-iodophenol by *o*-bromophenol in this reaction resulted in an important decrease of the reaction outcome, with yields below 20% (best yield: 19% for catalyst **3**; data not shown in Table 3).

Conclusions

In this work we have prepared a set of three different NHC-Pd-pyridine complexes that have been tested in the consecutive Sonogashira/cyclic hydroalkoxylation reactions between *o*-hydroxyaryl halides and phenylacetylene to directly afford benzofurans. All three catalysts provide excellent yields of the final products when *o*-iodobenzyl alcohol is used, while for *o*-iodophenol catalysts **1** and **3** are the ones to give the best outcomes. For other halosubstituted arenes, we obtained poor outcomes, except for the case of *o*-bromobenzyl alcohol, for which moderate to high yields were achieved. The same reactions performed with $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ stopped after the Sonogashira coupling, providing very low activity in the second reaction (cyclic hydroxyalkoxylation). Although more detailed studies are needed, our results seem to indicate that the palladium complex with the more basic NHC (**2**) is the one to provide better yields when *o*-bromobenzyl alcohol is used, probably as a consequence of its better efficiency in the activation of the Sonogashira reaction. On the contrary, for the reactions with *o*-iodophenol, the reaction outcome is favored for the complexes with the less basic NHC ligands, with a variation of the overall catalytic activity in the order **1** (NHC = ditz) > **3** (NHC = triazolylidene) > **2** (NHC = imidazolylidene). Assuming that for this latter process the cyclization is the rate-limiting reaction (the Sonogashira coupling is assumed to be fast for C−I activations), it seems that less basic NHCs favor this second reaction of the sequence. Although a wider set of substrates should be used in order to achieve a definitive conclusion, these preliminary results indicate that the electronic character of the ligand may be having an opposite effect on the trends of the catalytic activities for the two reactions comprising this overall process, so it is difficult to find an accurate balance of the electronic properties of the ligand to afford a catalyst that is active in both reactions at the same time.

This tandem process provides a clear benefit compared to the traditional methods for the preparation of benzofurans that implies the same sequence of reactions but with the isolation of the Sonogahira coupling intermediate followed by the cyclic hydroalkoxylation, which usually requires different reaction conditions including a different catalyst.

Table 4. Crystallographic Data and Structure Refinement for Complexes 1 and 2[a]

	1	**2**
empirical formula	$C_{15}H_{19}Cl_4N_5Pd_2$	$C_{10}H_{13}Cl_2N_3Pd$
mol wt	623.5	352.5
radiation	Mo Kα (monochr); 0.71073 λ (Å)	
T (K)	293	293
cryst syst	triclinic	hexagonal
space group	$P\bar{1}$	$P6(1)22$
a (Å)	8.4373(10)	9.0470(5)
b (Å)	9.2156(11)	9.0470(5)
c (Å)	14.2393(17)	29.203(3)
α (deg)	84.508(3)	90
β (deg)	80.142(2)	90
γ (deg)	88.531(3)	120
V (Å^3)	1085.8(2)	2070.0(3)
Z	2	6
D_{calcd} (Mg m^{-3})	1.909	1.697
μ(Mo Kα) (mm^{-1})	2.158	1.710
total, unique no. of rflns	7277, 4930	14 177, 1592
R_{int}	0.0396	0.0409
no. of params, restrictions	235, 0	76, 0
R, R_w ($I > 2\sigma$)	0.0381, 0.0887	0.0804, 0.2047
GOF	1.029	1.080
min., max. resid dens (e Å^{-3})	−0.909, 1.0804	−0.537, 0.750

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$, for all $I > 3\sigma(I)$. [b] $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$.

Experimental Section

General Procedures. 1,2,4-Trimethyltriazolium tetrafluoroborate, 1,3-bis(*N*-methyl)imidazolium chloride, and 1,4-bis(*N*-methyl)triazolium chloride were prepared according to literature procedures.[17] All other reagents and solvents were used as received from commercial suppliers. Synthesis and catalytic experiments were carried out under aerobic conditions and without solvent pretreatment. NMR spectra were recorded on Varian spectrometers operating at 300 or 500 MHz (^{1}H NMR) and 75 and 125 MHz (^{13}C NMR), respectively, and referenced to $SiMe_4$ (δ in ppm and J in hertz). NMR spectra were recorded at room temperature with $CDCl_3$ unless otherwise stated. A QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK) was used. Elemental analyses were carried out on a Euro-EA3000 Eurovector analyzer. A GC-2010 gas chromatograph (Shimadzu) equipped with a FID and a Teknokroma (TRB-5MS, 30 m × 0.25 mm × 0.25 μm) column was used.

Synthesis of 1. A mixture of 1,2,4-trimethyltriazolium tetrafluoroborate (60 mg, 0.21 mmol), $PdCl_2$ (75 mg, 0.42 mmol),

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and K_2CO_3 (221 mg, 1.6 mmol) was refluxed for 3 h in pyridine (3 mL). The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. Pure compound **1** was obtained as a light yellow solid after recrystallization from dichloromethane/*n*-hexanes (2 times). Yield: 95 mg (75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (d, $^3J_{H-H}$ = 6.0 Hz, 4H, Py), 7.78 (t, $^3J_{H-H}$ = 8.0 Hz, 2H, Py), 7.33 (t, $^3J_{H-H}$ = 6.8 Hz, 4H, Py), 4.69 (s, 3H, NCH_3), 4.46 (s, 6H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9 (NCN-Pd), 153.6, 151.6, 138.8, 125.2, 125.0 (Py), 40.9, 37.8 ($-CH_3$). Anal. Calcd for $C_{15}H_{19}N_5Pd_2Cl_4$ (624.0): C, 28.87; H, 3.07; N, 11.22. Found: C, 28.97; H, 3.28; N, 11.35. Electrospray MS cone 25 V (*m*/*z*, fragment): 646.6, $[M+Na]^+$.

Synthesis of 2. Compound **2** was obtained following the procedure described for **1** using 1,3-bis(*N*-methyl)imidazolium chloride (28 mg, 0.21 mmol). Yield: 61 mg (83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (d, $^3J_{H-H}$ = 4.8 Hz, 2H, Py), 7.74 (t, $^3J_{H-H}$ = 5.4 Hz, 2H, Py), 7.35 (t, $^3J_{H-H}$ = 6.6 Hz, 4H, Py), 6.92 (s, 2H, NC*H*C*H*N), 3.97 (s, 6H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (NCN-Pd), 152.4, 138.3, 124.9 (Py), 121.5 (N*C*H*C*HN), 40.5 ($-CH_3$). Anal. Calcd for $C_{10}H_{13}N_3PdCl_2$ (352.6): C, 34.10; H, 3.72; N, 11.92. Found: C, 34.23; H, 3.68; N, 11.35. Electrospray MS cone 25 V (*m*/*z*, fragment): 357.1, $[M-Cl+MeCN]^+$.

Synthesis of 3. Compound **3** was obtained following the procedure described for **1** using 1,4-bis(*N*-methyl)triazolium chloride (28 mg, 0.21 mmol). Yield: 50 mg (67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.97 (d, $^3J_{H-H}$ = 6.6 Hz, 1H, Py), 8.83 (d, $^3J_{H-H}$ = 6.6 Hz, 1H, Py), 7.94 (s, 1H, NC*H*N), 7.80−7.75 (m, 1H, Py), 7.40−7.31 (m, 2H, Py), 4.32 (s, 3H, NCH_3), 4.15 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (NCN-Pd), 153.6, 151.5, 138.8, 125.2, 124.8 (Py), 121.6 (N*C*HN), 40.3, 35.7 ($-CH_3$). Anal. Calcd for $C_9H_{12}N_4PdCl_2$ (353.6): C, 30.63; H, 3.42; N, 15.92. Found: C, 30.43; H, 3.48; N, 16.03. Electrospray MS cone 25 V (*m*/*z*, fragment): 358.0, $[M-Cl+MeCN]^+$.

Catalytic Study of the Consecutive Sonogashira/Cyclic Alkyne Hydroalkoxylation. In a typical run a capped vessel containing a stirrer bar was charged with the corresponding halobenzyl alcohol (0.53 mmol), phenylacetylene (0.75 mmol), Cs_2CO_3 (1.57 mmol), anisole as internal reference (0.525 mmol), catalyst (1% mol palladium), and DMSO (3 mL). The reaction mixture was stirred at 80 °C for the appropriate time. Yields and conversions were determined by GC chromatography. Isolated yields were determined by ^{1}H NMR spectroscopy after column chromatography purification. Catalytic reactions were carried out under air and with regular solvents. The confirmation of the nature of the products was performed by comparison with the literature data.[8,9]

X-ray Diffraction Studies. Single crystals of **1** and **2** were mounted on a glass fiber in a random orientation. Data collection was performed at room temperature on a Siemens Smart CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) with a nominal crystal to detector distance of 4.0 cm. Space group assignment was based on systematic absences, E statistics, and successful refinement of the structures. The structure was solved by direct methods with the aid of successive difference Fourier maps and were refined using the SHELXTL 6.1 software package.[18] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to ideal positions and refined using a riding model. Details of the data collection, cell dimensions, and structure refinement are given in Table 4. The diffraction frames were integrated using the SAINT package.[19]

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Supporting Information Available: Full crystallographic data are available as a CIF file free of charge via the Internet at http://pubs.acs.org.

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