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Synthesis and Simple Immobilization of Palladium(II) Acyclic Diaminocarbene Complexes on Polystyrene Support as Efficient Catalysts for Sonogashira and Suzuki–Miyaura Cross-Coupling

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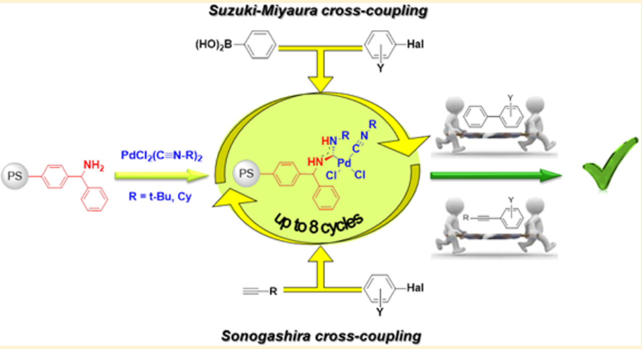
Supporting Information



ABSTRACT: Immobilization of palladium(II) acyclic diaminocarbene (Pd(II)-ADC) complexes on a resin support surface has been easily performed by metal-mediated addition of amino groups of benzhydrylamine-polystyrene to the coordinated isocyanide ligand of *cis*-$PdCl_2(CNR)_2$ (R = *t*-Bu, Cy). The investigation of the benzhydrylamine reaction with palladium-coordinated isocyanides in solution has revealed that, depending on the reaction conditions, two carbene-type complexes can be obtained as a result of the addition to the CN triple bond, as well as a third complex which is formed via substitution of the isocyanide ligand by benzhydrylamine. Nucleophilic addition of an amino group to the isocyanide ligand has led to a cis-acyclic diaminocarbene complex or a cationic diaminocarbene complex with trans configuration and an intramolecular hydrogen-bonded chloride anion (the nature of this noncovalent interaction was analyzed by DFT calculations, including AIM analysis). The unsupported and resin-supported palladium catalysts have demonstrated high catalytic activity in both Sonogashira and Suzuki–Miyaura cross-coupling. The supported catalyst can be recovered and repeatedly reused without a significant loss in efficiency. The degree of the palladium binding with polystyrene, the oxidation state, and the palladium leaching level were investigated by XPS and XRF analyses.

INTRODUCTION

Nowadays it is hard to imagine the development of synthetic organic chemistry without Pd-catalyzed reactions. A large number of reports and reviews published in the last decades have proved the efficiency of Pd catalysts in various significant reactions:[1−7] for example, the hydrogenation of C−C bonds,[8−14] C−heteroatom bond formation,[15−25] including the asymmetric reaction,[8,11,12,26,27] the synthesis and functionalization of heterocycles,[28−35] etc.

Among palladium-catalyzed reactions, great attention has been paid to C−C bond formation, which is regarded as a convenient methodology that simplifies the synthesis of complex organic molecules, natural product precursors, pharmaceuticals and advanced materials.[36−42] The importance, scope, and potential of cross-coupling chemistry for both academia and industry were marked by the Nobel Prize for Chemistry in 2010, which was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki "for palladium-catalyzed cross couplings in organic synthesis".[7,43−48]

A broad spectrum of new available palladium complexes have been proposed as precatalysts in homogeneous organic catalysis, most of which contain phosphane ligands.[49,50] Recent advances in this area relate to the creation and application of efficient phosphane-free catalysts,[51−54] among which palladium complexes with N-heterocyclic carbenes (NHCs)[55−62] and acyclic diaminocarbene (ADC) ligands are very promising.[54,63−66]

Homogeneous conditions, however, do not allow catalyst recovery; consequently they cannot be applied to technological processes. By comparison, heterogeneous catalysis offers a number of advantages such as the ease of handling, stability, the possibility of catalyst recycling, continuous processing, and ease of separation. Because of these, there is an ongoing interest in the development of stable heterogeneous systems containing palladium species, which exhibit long-lasting catalytic activity and could be rapidly reused without a significant loss in activity.[67−71]

Given the significance of palladium-mediated catalysis in organic synthesis, numerous reports have been published focusing on the excellent properties of phosphanes[72] or NHCs[73−101] containing Pd catalysts attached to polymeric materials, including their recyclability. However, recently reported procedures of palladium complex immobilization are

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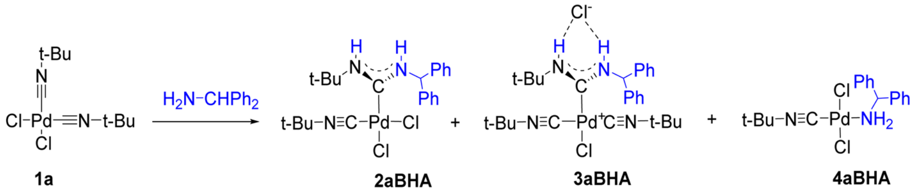
Table 1. Influence of Reaction Conditions on the Outcome of 2aBHA



entry	solvent	time, h	T, °C	ratio of products[a] 2aBHA	3aBHA	4aBHA
1	THF	12	20	0	1	1
2	$CHCl_3$	12	20	0	1	1
3	THF	12	−15 to 20	0	1	1
4	$CHCl_3$	5	50	0	1	1
5	CH_2Cl_2	12	20	0	1	1
6	C_6H_6	16	20	0	1	1
7[b]	$CHCl_3$	6	20	0	1	0
8[c]	$CHCl_3$	24	20	1	0	0
9[c]	$CHCl_3$	1	50	1	0	0

[a] According to ^{1}H NMR. [b] *t*-BuN≡C (1 equiv) was introduced into the reaction mixture. [c] NEt_3*HCl (1 equiv) was introduced into the reaction mixture.

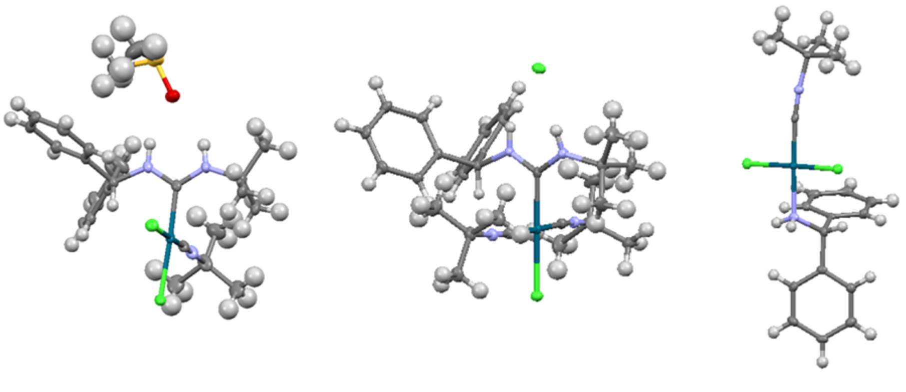

2aBHA+DMSO 3aBHA 4aBHA

Figure 1. Molecular structures of Pd complexes **2aBHA**, **3aBHA**, and **4aBHA**.

generally complicated, involve multiple steps, and are nonselective (Pd black formation during Pd(II) immobilization processes),[97,102] which are regarded as additional challenges to finding simpler and more convenient methods.

In the past few years, the catalytic properties of Pd(II)-ADC complexes in homogeneous catalysis and their application in organic synthesis have been investigated and assessed.[64,103] Their great potential as strong donors and flexible ligands in palladium-mediated catalysis due to the absence of a rigid backbone has been revealed. As an additional advantage, the desired Pd(II)-ADC complexes can be synthesized by a simple pathway of nucleophilic addition of readily available N-nucleophiles to palladium-activated isocyanides in good to quantitative yields.[104−107]

However, despite the keen interest in Pd(II)-ADC complexes and active research in this field, there have been no reports to date concerning the immobilization of palladium(II) acyclic diaminocarbene complexes on supports.

Herein we report the results of our investigation of the metal-mediated reactions of isocyanide palladium(II) complexes with benzhydrylamine in homogeneous and heterogeneous conditions.

We have found that, in contrast to the previously reported[66] direction of the homogeneous metal-mediated reaction, which involved a direct attack of an amine moiety on the coordinated isocyanide to give a Pd(II)-ADC complex, the reaction of benzhydrylamine occurs with a simultaneous formation of two different types of complexes: cationic and neutral.

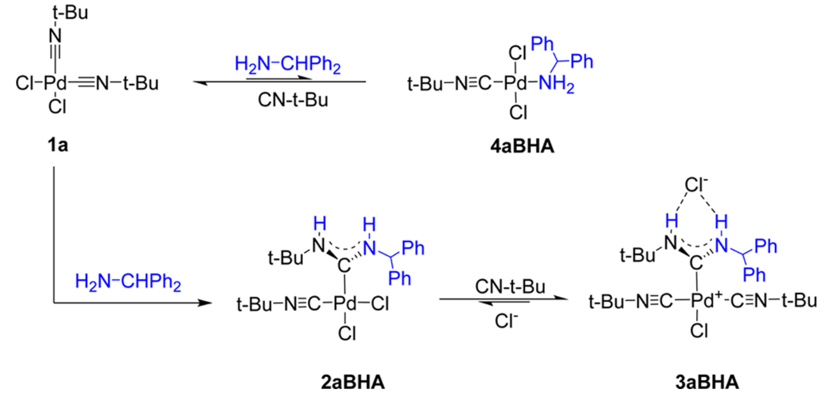
We have successfully extended this reaction to heterogeneous conditions and also report herein the synthesis of the first example of a Pd(II)-ADC catalytic system on a polystyrene support.

■ RESULTS AND DISCUSSION

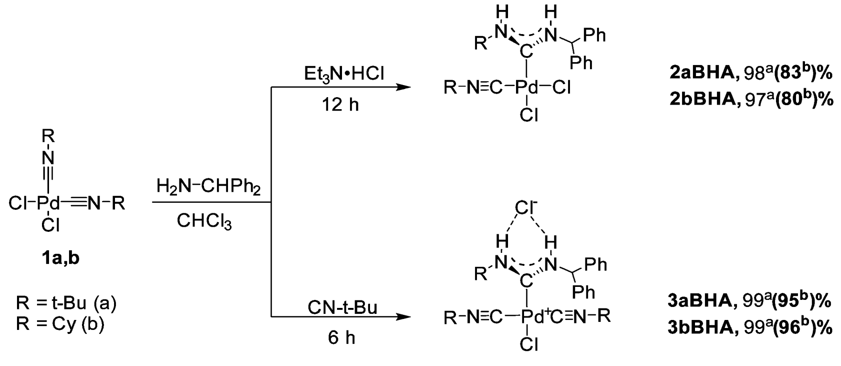
Synthesis of Unsupported Palladium(II) Acyclic Diaminocarbene Complexes. The efficient method for the preparation of unsymmetrically substituted palladium(II) acyclic diaminocarbene complexes from amines and Pd-activated isocyanides previously reported[66] by Hashmi et al. prompted us to choose commercially available benzhydrylamine-polystyrene with primary amino groups (BHA-polystyrene) as a support for the immobilization of the Pd(II)-ADC complex.

Since primary amines, in particular benzhydrylamine, have not been previously investigated as nucleophiles, we decided to

Scheme 1. Possible Mechanism of the Formation of 3aBHA and 4aBHA



Scheme 2. Synthesis of Palladium(II) Acyclic Diaminocarbene Complexes 2aBHA, 2bBHA, and 3aBHA



[a] NMR yield
[b] isolated yield

verify their reactivity in the nucleophilic addition to Pd-coordinated *tert*-butyl isocyanide and catalytic activity of the expected product of the reaction: Pd(II)-ADC complex **2aBHA** (Table 1).

For the initial studies of this reaction we chose the conditions described in the aforementioned work (THF as a solvent at 20 °C). To our surprise, after a full conversion of the starting materials an equimolar mixture of the complexes **3aBHA** and **4aBHA** was obtained instead of the desired Pd(II)-ADC complex **2aBHA.** A change in solvent or temperature did not significantly affect the outcome of the reaction (see Table 1, entries 1–6).

The structures of the complexes **3aBHA** and **4aBHA** were determined by ^{1}H and ^{13}C NMR, ESI-MS, and IR spectral data and were unambiguously proven by X-ray structure analysis (Figure 1). It was found that the cationic complex **3aBHA** has a trans configuration with the intramolecularly hydrogen bonded chloride in the outer coordination sphere. The IR spectra of complexes **3aBHA** and **4aBHA** both have a strong stretching vibration band at 2227 and 2240 cm^{-1}, respectively.

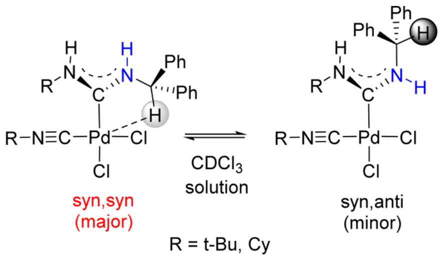
The fact that **3aBHA** and **4aBHA** always exist in the reaction mixture in equimolar amounts led us to assume that the conversion of **2aBHA,** which is obviously an intermediate for **3aBHA** formation, proceeds more quickly than the formation of **2aBHA** from the starting materials (Scheme 1). In order to prove the existence of an equilibrium between **1a** and **4aBHA,** an additional amount of *tert*-butyl isocyanide was introduced into the reaction mixture (Table 1, entry 7) and the complex **3aBHA** was obtained as the only product in the 95% isolated yield. Since we aimed at the synthesis of easily obtained polymer-supported Pd(II)-ADC complexes, the use of an extra amount of *t*-BuN≡C made the procedure complex and more expensive. Therefore, we decided to identify reaction conditions under which the conversion of **2aBHA** to **3aBHA** could be suppressed.

The analysis of the proposed transformation scheme (Scheme 1) led us to assume that the presence of extra chlorine anions can shift the equilibrium toward **2aBHA** formation. To prove our hypothesis, a source of chlorine anions ($Et_3N·HCl$) was introduced into the reaction mixture (Table 1, entry 8). ^{1}H NMR was used to follow the reaction process. According to ^{1}H NMR at room temperature, directly after the addition (approximately 5 min) of the complex **1a** into a mixture of benzhydrylamine (1 equiv) with $Et_3N·HCl$ (2 equiv) in $CDCl_3$, the formation of **2aBHA** along with **3aBHA** and **4aBHA** in the ratio 1.7:1:1 was detected at 53% conversion of the starting material. During the next 30 min, the amount of **3aBHA** and **4aBHA** remained constant and the reaction proceeded toward **2aBHA** formation. Within 30 min, the conversion of the starting material was estimated as 92% and the ratio of the products was 4:1:1. After 3.5 h, almost a full conversion (96%) of the starting material was achieved and the ratio of products was 10:1:1. The last ^{1}H NMR spectrum was recorded after 12 h, when **2aBHA** was found to be the only product. The presence of $Et_3N·HCl$ did not make the purification procedure complex. After the evaporation of $CHCl_3$, the precipitate was washed with an Et_2O/EtOH mixture to remove $Et_3N·HCl$. Then the crude product was recrystallized by a slow diffusion of pentane into the CH_2Cl_2 solution to give the compound **2aBHA** in a good isolated yield. The complex **2bBHA** was also obtained under the same conditions in a good yield (Scheme 2). The IR spectra of complexes **2aBHA** and **2bBHA** both have a strong stretching vibration band at 2223 and 2225 cm^{-1}, respectively. As a result, we found the conditions for the selective formation of complexes **2aBHA, 2bBHA**, and **3aBHA**.

The structures of Pd(II)-ADC complexes **2aBHA, 3aBHA**, and **4aBHA** were confirmed by X-ray single-crystal analysis (Figure 1 and Supporting Information).[108]

According to the X-ray data, complexes **2aBHA** and **3aBHA** both have a diaminocarbene nature with equivalent N−C−N bonds: 1.328, 1.329 Å and 1.325, 1.326 Å, respectively. Furthermore, N−C−N bond angles of the palladium-bonded diaminocarbene are 115.7° for **2aBHA** and 116.1° for **3aBHA**, significantly larger than the typical angles of 104−107° known for N-heterocyclic carbenes.[109] The substituents at the nitrogen atoms in **2aBHA** and **3aBHA** are arranged in a syn,syn configuration, where both *tert*-butyl and benzhydryl groups are pointing toward the same side of the palladium atom. The X-ray diffraction studies of **2aBHA** and **3aBHA** revealed an interaction of the methanetriyl group C*H*(Ph)$_2$ hydrogen with palladium with relatively short M···H distances (Pd···H-[C*H*(Ph)$_2$] = 2.56 Å for **2aBHA** and Pd···H[C*H*(Ph)$_2$] = 2.62 Å for **3aBHA**) and relatively small M···H−C bond angles (117° for **2aBHA** and 121° for **3aBHA**).

It is well-known that ADCs and related acyclic carbene ligands can adopt different conformations, denoted as syn or anti, relative to the Pd−$C_{carbene}$-NHR bond, depending on the nature and bulkiness of these groups.[66,110] However, in the NMR spectra of both **2aBHA** and **2bBHA,** only one rotamer is observed. In order to determine the conformation of the diaminocarbene fragment in solution ($CDCl_3$), NOE experiments were performed. The NOESY spectrum of **2bBHA** obtained in $CDCl_3$ at room temperature revealed an interaction between the N*H* atoms of the diaminocarbene fragment, which is only possible in the syn,syn conformation (see the Supporting Information). Moreover, the signals of the methanetriyl group hydrogens in ^{1}H NMR of the major syn,syn conformer for both **2aBHA** and **2bBHA** complexes are shifted downfield (7.26 and 7.09 ppm, respectively) in comparison with the uncoordinated methanetriyl group hydrogen atoms in the minor syn,anti conformations of complexes **2aBHA** and **2bBHA** (5.67 and 5.80 ppm, respectively) (eq 1). The bulkier substituents on the N atom (*t*-Bu vs Cy) led to an increase in the syn,syn/syn,anti isomeric ratio. This observation is in accordance with the hydrogen-bonded description of the interaction and could be described as an anagostic interaction.[111] These results are consistent with the solid-state structure.



(1)

Theoretical DFT Calculations for Bifurcated Hydrogen Bonding and Anagostic Interactions in 3aBHA. A study of the crystallographic data showed the presence of three-centered (bifurcated) hydrogen bonding (N−H···Cl···H−N) and anagostic interactions (C(Ph)$_2$H···Pd and CH_3···Pd) in **3aBHA**. In order to confirm the existence of these noncovalent interactions in the solid state and $CHCl_3$ solution and to quantify their energies, we carried out theoretical DFT calculations and performed a topological analysis of the electron density distribution within the formalism of Bader's theory (AIM method).[112] The results of this theoretical study are summarized in Tables 2 and 3; a contour line diagram of the Laplacian distribution $\nabla^2\rho(\mathbf{r})$, the bond paths, and selected zero-flux surfaces for **3aBHA** are shown in Figure 2.

The geometry optimization of **3aBHA** in the $CHCl_3$ solution indicates that the H···Cl, C(Ph)$_2$H···Pd, and CH_3···Pd distances in the isolated cluster are even shorter than those in the crystal (2.26−2.23 Å vs 2.45−2.32 Å, 2.48 Å vs 2.62 Å, and 2.54 Å vs 2.55 Å, respectively). The AIM analysis demonstrates the presence of two bond critical points (BCPs) (3, −1) for the three-centered hydrogen bonds N−H···Cl···H−N and two BCPs for the anagostic interactions C(Ph)$_2$H···Pd and CH_3···Pd in **3aBHA** in both the solid state and $CHCl_3$ solution (Tables 2 and 3). The low magnitude of the electron density, the positive values of the Laplacian, and the zero or very close to zero energy density in these BCPs are typical of noncovalent interactions.[115,116] We defined the energies for three-centered hydrogen bonds N−H···Cl···H−N according to the procedures proposed by Espinosa et al.[113] and Vener et al.,[114] and one can maintain that these interactions can be formally classified as hydrogen bonds from weak to moderate strength (4−5 kcal/mol for solid state and 5−6 kcal/mol for $CHCl_3$ solution) mainly due to electrostatics following the classification of Jeffrey[117] ("strong" H bonds, 40−15 kcal/mol; "moderate" H bonds, 15−4 kcal/mol; "weak" H bonds, <4 kcal/mol). The balance between the Lagrangian kinetic energy $G(\mathbf{r})$ and potential energy density $V(\mathbf{r})$ at the bond critical points (3, −1) reveals the nature of these interactions: if the ratio $-G(\mathbf{r})/V(\mathbf{r}) > 1$ is satisfied, then the nature of the appropriate interaction is purely noncovalent; in the case of $-G(\mathbf{r})/V(\mathbf{r}) < 1$ some covalent component is observed.[118] On the basis of this criterion, we can argue that the covalent component for the bifurcated hydrogen bond N−H···Cl···H−N in **3aBHA** is absent for the solid state and negligible for the $CHCl_3$ solution and the anagostic interactions C(Ph)$_2$H···Pd and CH_3···Pd in **3aBHA** are clearly noncovalent for both the solid state and the $CHCl_3$ solution. The negligible nonzero values of the Wiberg bond indices for N−H···Cl···H−N, C(Ph)$_2$H···Pd, and CH_3···Pd contacts in the optimized structure of **3aBHA** (0.08, 0.02, and 0.02, respectively) computed by using the natural bond orbital (NBO) partitioning scheme[119] additionally confirm the electrostatic nature of these noncovalent interactions.

In addition, according to the NMR data (^{1}H and ^{13}C) in the presence of triethylamine hydrochloride, only syn,syn conformers of **2aBHA** and **2bBHA** exist in solution (the minor isomer is not detected) due to an intermolecular three-centered hydrogen bond (N*H*···*Cl*$^-$···*H*N) formation, which demonstrates the stabilizing effect of the chloride ion. It is remarkable that **2aBHA** is insoluble in neat $CHCl_3$ and soluble in $CHCl_3$ with the $Et_3N·HCl$ additive or DMSO because of the destruction of intermolecular hydrogen bond interactions in the solid state of the complex. The intermolecular bifurcated hydrogen bond interaction N*H*···<u>O</u>(DMSO)···*H*N between

Table 2. Values of the Density of All Electrons ($\rho(\mathbf{r})$), Laplacian of Electron Density ($\nabla^2\rho(\mathbf{r})$), Energy Density (H_b), Potential Energy Density ($V(\mathbf{r})$), and Lagrangian Kinetic Energy ($G(\mathbf{r})$) (hartree) at the Bond Critical Points (3, −1), Corresponding to the Bifurcated Hydrogen Bonding N−H···Cl···H−N in 3aBHA for the Solid State and $CHCl_3$ Solution, Appropriate Bond Lengths d(H···Cl) (Å), and Energies of These Interactions (E_{int}) (kcal/mol), Defined by Two Approaches

$\rho(\mathbf{r})$	$\nabla^2\rho(\mathbf{r})$	H_b	$V(\mathbf{r})$	$G(\mathbf{r})$	E_{int}[a]	E_{int}[b]	d(H···Cl)
			Solid State				
0.017	0.058	0.001	−0.012	0.013	3.77	3.50	2.45
0.021	0.068	0.000	−0.016	0.017	5.02	4.58	2.32
			$CHCl_3$ Solution				
0.024	0.065	−0.001	−0.018	0.017	5.65	4.58	2.26
0.026	0.068	−0.001	−0.019	0.018	5.96	4.85	2.23

[a] $E_{int} = -V(\mathbf{r})/2$.[113] [b] $E_{int} = 0.429[G(\mathbf{r})]$.[114]

Table 3. Values of the Density of All Electrons ($\rho(\mathbf{r})$), Laplacian of Electron Density ($\nabla^2\rho(\mathbf{r})$), Energy Density (H_b), Potential Energy Density ($V(\mathbf{r})$), and Lagrangian Kinetic Energy ($G(\mathbf{r})$) (hartree) at the Bond Critical Points (3, −1), Corresponding to Anagostic Interactions $C(Ph)_2H$···Pd and CH_3···Pd in 3aBHA for the Solid State (Normal Text) and $CHCl_3$ Solution (in Parentheses), Appropriate Bond Lengths d(H···Pd) (Å), Bond Angles C−H−Pd (deg), and Energies of These Interactions (E_{int}) (kcal/mol), Defined by Two Approaches

	$\rho(\mathbf{r})$	$\nabla^2\rho(\mathbf{r})$	H_b	$V(\mathbf{r})$	$G(\mathbf{r})$	E_{int}[a]	E_{int}[b]	d(H···Pd)	C−H−Pd
$C^1{}_2H$···Pd	0.015 (0.019)	0.052 (0.058)	0.001 (0.000)	−0.011 (−0.015)	0.012 (0.015)	3.45 (4.71)	3.23 (4.04)	2.62 (2.48)	121 (121)
CH_3···Pd	0.016 (0.016)	0.053 (0.051)	0.001 (0.000)	−0.012 (−0.012)	0.013 (0.012)	3.77 (3.77)	3.50 (3.23)	2.55 (2.54)	129 (123)

[a] $E_{int} = -V(\mathbf{r})/2$.[113] [b] $E_{int} = 0.429[G(\mathbf{r})]$.[114]

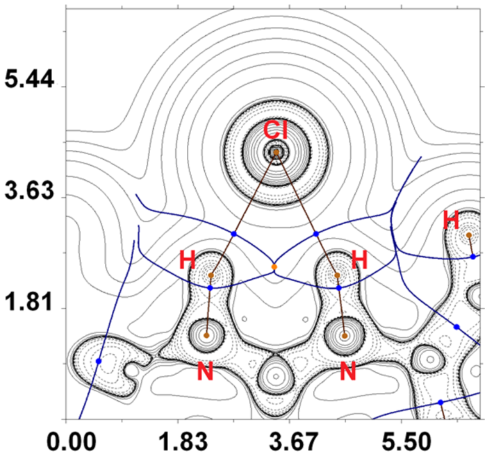


Figure 2. Contour line diagram of the Laplacian distribution $\nabla^2\rho(\mathbf{r})$, bond paths, and selected zero-flux surfaces for **3aBHA** (optimized structure in $CHCl_3$ solution). Bond critical points (3, −1) are shown in blue, ring critical point (3, +1) in orange, and nuclear critical points (3, −3) in pale brown. Lengths are given in Å.

DMSO and **2aBHA** molecules was also revealed in the solid state of **2aBHA** (crystallization from DMSO/$CHCl_3$) by X-ray crystallography.

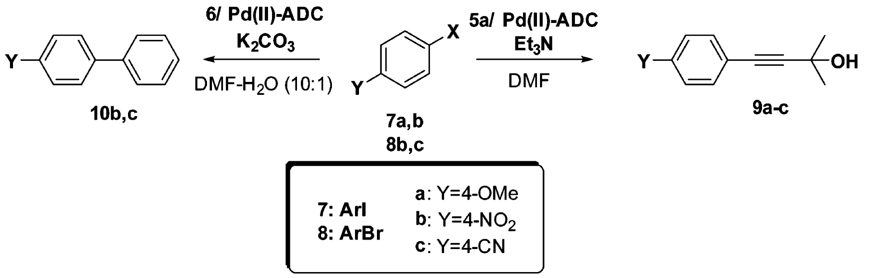
Thus, the formation of the three-centered hydrogen bond determines the formation of **3aBHA** in the reaction of benzhydrylamine with **1a** (Scheme 1), as well as the shift of equilibrium from **3aBHA** toward **2aBHA** by the addition of an external chloride ion ($Et_3N{\cdot}HCl$).

Catalytic Activity of Unsupported Pd(II)-ADC Complexes 2aBHA, 2bBHA, and 3aBHA in Sonogashira and Suzuki Coupling Reactions. It is well-known that ADC ligands have the following unique properties: strong σ-donor ability, conformational flexibility (adjustment to the specific catalytic cycle stage), and a large NCN angle that can favor the stability of the active catalytic Pd species. Pd(II)-ADC complexes demonstrate competitive advantages over phosphane and N-heterocyclic palladium(II) diaminocarbene complexes in catalytic applications in transition-metal-catalyzed organic transformations.[103,106,120] Thus, we turned to the evaluation of catalytic activity of the Pd(II)-ADC complexes **2aBHA, 2bBHA**, and **3aBHA** in cross-couplings. In our recent studies we found that the addition of PPh_3 promoted a higher rate of Sonogashira coupling when Pd(II)-ADC species were used as precatalysts.[121] Therefore, the PPh_3 additive was used for the Sonogashira coupling of 2-methyl-3-butyn-2-ol (**5a**) with iodo- and bromoarenes **7** and **8** (Table 4, entries 1−9).

Our first studies of the catalytic activity in Sonogashira coupling were carried out with a fixed time (3 h) and revealed a high efficiency of all of the complexes **2aBHA**, **2bBHA**, and **3aBHA** as precatalysts. With the use of 0.5 mol % catalyst loading, the coupling proceeded smoothly, with iodoarene **7a** having an electron-donating MeO group and aryl bromides **8b**,**c**, and led to cross-coupling products **9a−c** (Table 4, entries 3−6). We did not find any significant difference in the catalytic activities of the complexes **2aBHA** and **3aBHA** (Table 4, entries 3 and 4). In order to estimate the TONs, the catalysts **2aBHA** and **3aBHA** were used in extremely low concentrations (0.002 and 0.01 mol %) (Table 4, entries 8 and 9). It was found that TONs of up to 17000 for aryl iodides and up to 1200 for aryl bromides could be achieved with the use of the Pd(II)-ADC complexes **2aBHA** and **3aBHA** as precatalysts at 70 °C. We also tested the initial complex **1a** in Sonogashira coupling using the conditions of entry 1 (Table 4) and found a comparable but somewhat lower catalytic activity (the yield of **9a** was 21% with 0.1 mol % catalyst **1a** loading).

An analysis of recently published papers showed that the complexes obtained are among the best catalysts for the Sonogashira reaction. Thus, Valishina and co-workers[122] reported TONs of up to 3.7 × 10^4 for the selected acyclic diaminocarbene palladium(II) catalyst (the average value among the series of catalysts tested in this paper is 1× 10^4). In another paper,[123] the authors reported TONs for the palladium complexes of 2-formylpyridine thiosemicarbazone of around 1 × 10^4 for both Sonogashira and Suzuki couplings. The

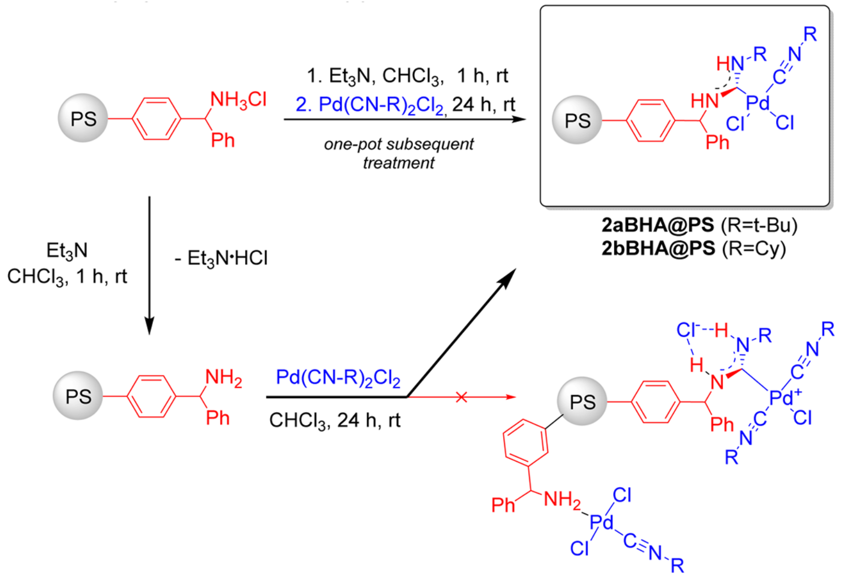
Table 4. Sonogashira and Suzuki–Miyaura Cross-Couplings Catalyzed by 2aBHA, 2bBHA, and 3aBHA



entry[a]	halide	Pd(II)-ADC	base	catalyst, mol %	temp, °C	time, h	product	yield,[b] %	TON	TOF
1	**7a**	**2bBHA**	Et_3N	0.1	50	3	**9a**	30	300	100
2	**7a**	**3aBHA**	Et_3N	0.1	50	3	**9a**	35	350	117
3	**7a**	**2aBHA**	Et_3N	0.5	50	3	**9a**	98	196	65
4	**7a**	**3aBHA**	Et_3N	0.5	50	3	**9a**	97	194	65
5	**8b**	**2aBHA**	Et3N	0.5	70	3	**9b**	75	150	50
6	**8c**	**2aBHA**	Et_3N	0.5	70	3	**9c**	27	54	18
7	**7b**	**2aBHA**	Et_3N	0.01	70	3	**9b**	58	5800	1933
8	**7a**	**2aBHA**	Et_3N	0.002	70	96	**9a**	34	17000	177
9	**8c**	**3aBHA**	Et_3N	0.01	70	96	**9c**	12	1200	13
10	**8c**	**2aBHA**	K_2CO_3	0.5	70	4	**10c**	75	150	32
11	**8b**	**2aBHA**	K_2CO_3	0.5	70	4	**10b**	99	198	42
12[c]	**8c**	**2aBHA**	K_2CO_3	0.5	70	4	**10c**	52	104	22

[a] Conditions unless specified otherwise: entries 1–9, aryl halide 1 equiv, alkyne 1.5 equiv, CuI 5 mol %, PPh_3 8 mol %, Et_3N 4 equiv, DMF; entries 10–12, aryl halide 1 equiv, phenylboronic acid 1.2 equiv, base 4 equiv, DMF/H_2O (10/1). [b] GCMS yield with dodecane as internal standard. [c] PPh_3 8 mol % was added.

Scheme 3. Preparation of Polystyrene-Supported Pd(II)-ADC Complexes 2aBHA@PS and 2bBHA@PS

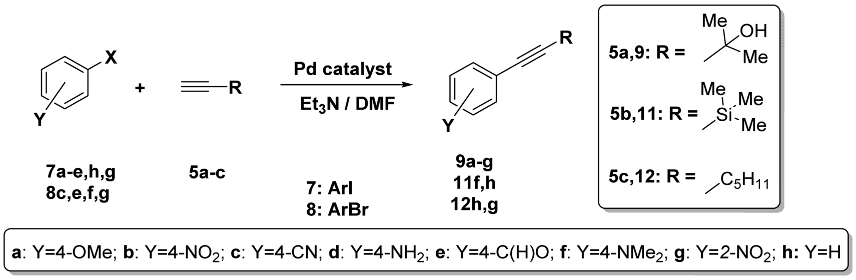


Pd-NHC catalysts reported by Dahm[124] and John[125] also exhibited similar catalytic activity in the Sonogashira coupling reaction, but the amount of catalyst used was noticeably larger, in the range of 1–4%.

The Pd(II)-ADC complex **2aBHA** was also tested in the Suzuki–Miyaura coupling of aryl bromides **8b,c** with phenylboronic acid (**6**) (Table 4, entries 10–12). After 4 h, substituted biphenyls **10b,c** were obtained in high to quantitative yields. These results led us to assume that the BHA-polystyrene-supported Pd(II)-ADC complex could exhibit relatively high and quite stable catalytic activity for both cross-coupling reactions.

Preparation of Polystyrene-Supported Pd(II)-ADC Complexes 2aBHA@PS and 2bBHA@PS. At the next step we investigated the scope of metal-mediated addition of the amine moiety of benzhydrylamine-polystyrene (BHA@PS) to palladium-coordinated isocyanides. Commercially available polystyrene resin modified with benzhydrylamine hydrochloride (0.6–0.9 mmol/g loading) was first sustained in $CHCl_3$ for 30 min and then treated with an equimolar amount of Et_3N to unlock the amino groups on the support. The resulting suspension containing triethylamine hydrochloride was used for further modification.

Table 5. Evaluation of the Catalytic Properties of 2aBHA@PS, 2bBHA@PS in Sonogashira Cross-Coupling[a]



entry	substrate	Pd catalyst/amt mol %	temp, °C	time, min	product	yield,[b] %	cycles[c]
1	**7a**	**2aBHA@PS**/10	40	55	**9a**	99	3
2	**7a**	2bBHA@PS/10	40	55	**9a**	98	2
3[d]	**7a**	**2aBHA@PS**/10	40	40	**9a**	98	2
4	**7b**	**2aBHA@PS**/10	40	5	**9b**	99	6
5	**8c**	**2aBHA@PS**/10	70	70	**9c**	97	3
6	**8c**	2bBHA@PS/10	70	80	**9c**	98	1
7	**7h**	**2aBHA@PS**/10	40	45	**11h**	94	2
8	**7d**	**2aBHA@PS**/10	40	60	**11f**	95	1
9	**7b**	**2aBHA@PS**/10	16	20	**9b**	99	8
10	**7b**	2bBHA@PS/10	20	20	**9b**	99	3
11	**7g**	2bBHA@PS/10	20	45	**9g**	99	2
12	**7g**	2bBHA@PS/10	20	50	**9g**	99	5
13	**7c**	2bBHA@PS/5	40	55	**9c**	97	1
14[d]	**7c**	2bBHA@PS/5	40	45	**9c**	96	1
15	**8f**	**2aBHA@PS**/10	70	90	**9f**	92	2
16	**8g**	**2aBHA@PS**/10	70	55	**12g**	95	2
17	**8g**	2bBHA@PS/10	70	50	**12g**	96	2
18	**7h**	**2aBHA@PS**/10	40	50	**12h**	93	2
19	**7h**	2bBHA@PS/10	40	55	**12h**	95	2
20[d]	**7a**	**2aBHA@PS**/1	40	180	**9a**	98	1
21[d]	**7b**	**2aBHA@PS**/1	40	120	**9b**	99	1
22[d]	**7c**	**2aBHA@PS**/1	40	80	**9c**	99	1
23[d]	**7e**	**2aBHA@PS**/1	40	90	**9e**	99	1
24[d]	**8e**	**2aBHA@PS**/1	70	150	**9e**	99	1
25	**7b**	**2aBHA@PS**/0.5	40	60	**9b**	99	2

[a] Reaction conditions unless specified otherwise: arylhalide 1 equiv, alkyne 1.5 equiv, CuI 10 mol %, Et$_3$N 4 equiv. [b] ^{1}H NMR yield, average per cycle. [c] A number of reactions carried out continuously with the appropriate substrate with the same sample of catalyst. [d] With PPh$_3$ (5 mol %).

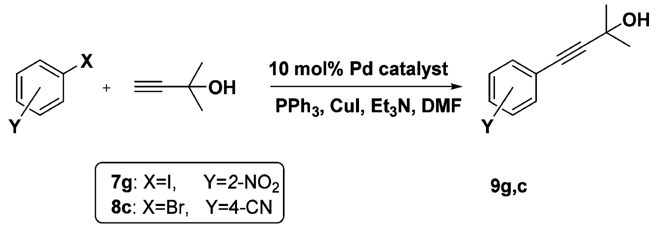
The suspension was mixed with *cis*-PdCl$_2$(CN-R)$_2$ (**1a**, R = *t*-Bu; **1b**, R = Cy) in chloroform (Scheme 3). The reactant ratio was chosen in such a way as to provide a 10-fold excess of surface amino groups in relation to *cis*-PdCl$_2$(CN-R)$_2$. The degree of palladium bonded to polystyrene was quantitative and was determined by X-ray fluorescence analysis (XRF) of the filtrate cross-checked with ^{1}H NMR after the immobilization. The yield of surface complexes was estimated as 0.075 mmol of Pd/g.

Curiously, in contrast to the homogeneous conditions, the reaction of benzhydrylamine bonded to resin with *cis*-PdCl$_2$(CN-*t*-Bu)$_2$ both in the presence and in the absence of triethylamine hydrochloride occurred with the formation of **2aBHA** immobilized on the polystyrene support. The formation of Pd(II)-ADC complexes on the surface of BHA-polystyrene (**2aBHA@PS, 2bBHA@PS**) was confirmed by IR studies of the samples obtained. While the starting *cis*-PdCl$_2$(CNR)$_2$ complexes display two overlapping stretches (2257 and 2243 cm^{-1} for **1a**, 2252 and 2233 cm^{-1} for **1b**), after the modification of the isocyanide ligand via the nucleophilic addition of amine moiety of the resin, strong new stretching vibration bands appeared at 2224 and 2225 cm^{-1} for **2aBHA@PS** and **2bBHA@PS**, respectively, which proves the presence of only one isocyanide ligand in the surface complexes. The C≡N stretching frequencies in IR spectra of the supported and unsupported Pd(II)-ADC complexes are similar.

Moreover, the data obtained are consistent with the spectral characteristics of nonsupported species **2aBHA** and **2bBHA** (see the Supporting Information).

Catalytic Activity of Polystyrene-Supported Pd(II)-ADC Complexes Pd(II)-ADC@PS in Sonogashira and Suzuki–Miyaura Cross-Coupling Reactions. To elucidate the scope of applications of Pd(II)-ADC@PS (**2aBHA@PS, 2bBHA@PS**) for catalysis, their activity was tested in Sonogashira and Suzuki–Miyaura cross-coupling in DMF in air. The outcome of the experiments of Sonogashira coupling is given in Table 5. Taking into account that nonsupported analogues **2aBHA** and **2bBHA** have relatively low TOF values but outstanding TON values and that the overall reaction rate in heterogeneous processes is generally limited by the diffusion rate to catalytically active centers, we decided to use 10 mol % of the catalyst (according to the weight concentration of Pd(II) complexes) as the initial conditions.

Table 6. Dependence of Palladium Leaching on PPh_3 Concentration in Sonogashira Coupling[a]



entry	substrate	Pd catalyst	PPh_3, mol %	temp, °C	time, min	product	yield, %	Pd leached, %[b]
1	**7g**	**2aBHA@PS**	0	40	25	**9g**	97	0.34
2	**7g**	**2bBHA@PS**	0	40	25	**9g**	96	0.41
3	**8c**	**2aBHA@PS**	0	70	70	**9c**	98	1.02
4	**8c**	**2bBHA@PS**	0	70	70	**9c**	96	1.19
5	**7g**	**2aBHA@PS**	5	40	15	**9g**	97	0.26
6	**7g**	**2bBHA@PS**	5	40	15	**9g**	94	0.24
7	**8c**	**2aBHA@PS**	5	70	70	**9c**	95	1.13
8	**8c**	**2bBHA@PS**	5	70	70	**9c**	97	1.08
9	**8c**	**2aBHA@PS**	5	80	70	**9c**	12	15.60
10	**8c**	**2bBHA@PS**	5	80	70	**9c**	9	14.90
11	**7g**	**2aBHA@PS**	10	40	15	**9g**	95	0.12
12	**7g**	**2bBHA@PS**	10	40	15	**9g**	98	0.08
13	**8c**	**2aBHA@PS**	10	70	65	**9c**	94	0.91
14	**8c**	**2bBHA@PS**	10	70	65	**9c**	96	1.00

[a] Reaction conditions: aryl halide 1 equiv, alkyne 1.5 equiv, CuI 10 mol %, Et_3N 4 equiv, catalyst 10 mol %, PPh_3 0−10 mol %, DMF 5.5 mL. [b] The relative uncertainty of the XPS method was estimated as 10%.

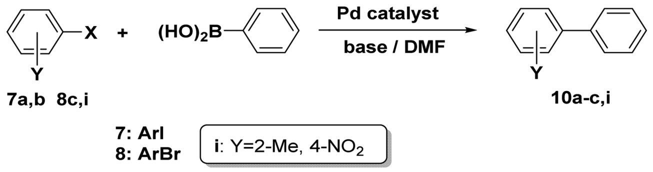
For the synthesis of aryl-substituted alkynes, we tested a wide range of aryl halides containing both electron-donating and electron-withdrawing groups. To determine the time of full conversion of the starting aryl halides, the reactions were monitored by TLC. We found that the common conditions for Sonogashira coupling (DMF, 4 equiv of Et_3N, 10 mol % CuI) were effective in this case for the preparation of arylacetylenes. It is also worth noting that a fairly high solubility of all the starting materials, products, and byproducts in DMF provided us with a very simple procedure for catalyst regeneration. Thus, the sequentially applied sample of the catalyst (which was recovered and reused six times in a row) yielded a sufficient amount of the coupling product in a very short time, 5 min (Table 5, entry 4).

As expected, the coupling of the bromo-substituted substrates proceeded at a higher temperature in comparison with that for iodo-substituted substrates (Table 5, entries 5, 6, and 15−17), which is usually attributed to the strength of the C−X bond.[126] As a consequence, the resistance of aryl bromides to oxidative addition to active Pd centers at the critical first step of the catalytic cycle results in a reduction in the reaction rate. Hence, heating the reaction mixtures to 70 °C for 50−90 min with 10 mol % catalyst loading was sufficient to obtain cross-coupling products in high yields (up to 98%) even in the case of the electron donor substituted bromide **8f** (Table 5, entry 15). In order to reduce the conversion time of bromoarenes, we attempted to increase the temperature. However, it was found that at 80 °C **2aBHA@PS** turned black in the same way as for **2bBHA@PS**, which was apparently caused by the decomposition of the palladium complexes on the surface. Further experiments demonstrated that the Pd(II)-ADC@PS catalytic system remained effective for synthetic purposes with lower catalyst loadings (Table 5, entries 13, 14, and 20−25). Thus, the aryl halide **7b** smoothly reacted with 2-methyl-3-butyn-2-ol (**5a**) even at 0.5 mol % catalyst loading of **2aBHA@PS** to give the product **9b** in a 99% yield (Table 5, entry 25). We did not find significant differences in the catalytic activities of **2aBHA@PS** and **2bBHA@PS**: the conversion time as well as yields remained almost the same with identical catalyst loadings.

Next we decided to examine the stability of the supported catalysts **2aBHA@PS** and **2bBHA@PS** by measuring the palladium concentration in the solution using X-ray photoelectron spectroscopy (XPS) upon completion of the reactions for the samples of **2aBHA@PS**. In all experiments, the percentage of palladium leached is given with respect to the amount of catalyst introduced. Blank experiments with the catalyst **2aBHA@PS** were accomplished without addition of substrates (Et_3N, DMF, 1 h) and demonstrated that palladium leaching caused by thermal decomposition is very low at 40 °C (0.03%) and tended to be more notable upon heating to 70 °C (0.82%). The analysis of the product mixture obtained after the separation and washing of Pd-containing resin indicated that palladium leaching from the support remained constant after each cycle, 0.46−0.53% (**2bBHA@PS**) and 0.71−0.98% (**2aBHA@PS**) in the 20−40 °C range, and increased up to 1.20% and 1.38% for **2bBHA@PS** and **2aBHA@PS**, respectively, at 70 °C. Such a low palladium leaching level showed that our initial conditions of 10 mol % of the catalyst (according to the weight concentration of Pd(II) complexes) is not a disadvantage for synthetic purposes.

In our recent study we found that the addition of PPh_3 caused a higher rate of the Sonogashira cross-coupling when Pd(II)-ADC species were used as precatalysts.[121,127] In the case of polystyrene-supported catalytic systems containing Pd(II)-ADC complexes, we also found that presence of PPh_3 accelerated the reaction rate. Thus, PPh_3 supplement resulted in an ∼20% decrease of the reaction time for aryl iodides (Table 6, entries 1, 3, 13, and 14).

Table 7. Evaluation of the Catalytic Properties of 2aBHA@PS and 2bBHA@PS in Suzuki–Miyaura Cross-Coupling[a]



entry	substrate	Pd catalyst/ mol %	DMF/H_2O, v/v	temp, °C	time, min	product	yield,[b] %	catalytic cycles[c]	Pd leached, %
1	**7a**	2aBHA@PS/5	100/0	65	120	**10a**	96	2	n/d[e]
2	**7b**	2aBHA@PS/5	100/0	65	120	**10b**	95	1	n/d[e]
3	**7b**	2aBHA@PS/5	100/0	65	90	**10b**	98	1	n/d[e]
4	**8c**	2aBHA@PS/5	100/0	75	150	**10c**	97	2	n/d[e]
5	**8c**	2aBHA@PS/5	95/5	70	50	**10c**	98	3	0.57
6	**8c**	2bBHA@PS/5	95/5	70	55	**10c**	97	2	0.64
7	**8c**	2aBHA@PS/5	90/10	70	60	**10c**	93	3	0.63
8	**8c**	2bBHA@PS/5	90/10	70	60	**10c**	95	3	0.38
9	**8i**	2aBHA@PS/5	95/5	70	50	**10i**	98	2	0.80
10	**8i**	2bBHA@PS/5	95/5	70	50	**10i**	96	2	0.50
11	**8c**	2aBHA@PS/5	80/20	70	50	**10c**	65	2	0.13
12	**8i**	2aBHA@PS/5	80/20	70	55	**10i**	71	3	0.16
13[d]	**8i**	2aBHA@PS/5	95/5	70	50	**10i**	98	3	0.05
14[d]	**8i**	2aBHA@PS/5	95/5	70	50	**10i**	96	3	0.03

[a] Reaction conditions unless specified otherwise: aryl halide 1 equiv, phenylboronic acid 1.2 equiv, base (Et_3N for entries 1, 2 and 4; K_2CO_3 for entries 3 and 5–14) 4 equiv, catalyst 0.5–5 mol %. [b] ^{1}H NMR yield, average per cycle. [c] The number of consequent reactions carried out with the same substrate. [d] With PPh_3 (5 mol %). [e] Not detected. [f] The relative uncertainty of the XRF method was estimated as 10%.

An analysis of the triphenylphosphine additive effect on the palladium leaching level indicated a sufficient drop of palladium concentration in stock solutions in the case of aryl iodides accompanied by a noticeable cut in the conversion times. Encouraged by these results, we turned our attention to the exploration of this intriguing effect. The dependence of palladium leaching on the PPh_3 concentration in solution was examined by X-ray fluorescence analysis (Table 6). For this purpose, we employed the reactions of bromide **8c** and iodide **7g** with 2-methyl-3-butyn-2-ol (**5a**) as a coupling partner. Unexpectedly, the addition of PPh_3 significantly decreased (up to 8 times) palladium leaching in the cross-coupling with iodides. The best results were obtained when 10 mol % of PPh_3 was used (Table 6, entries 11 and 12). In contrast to the reactions with iodoarenes and PPh_3, the additive did not affect palladium leaching when Sonogashira coupling was performed with aryl bromides at 70 °C.

It is noteworthy that recent experiments have demonstrated that, in the presence of an excess of a soft ligand (PPh_3, $AsPh_3$ etc.), the bimetallic (Pd,Cu-containing) complex formed during the transmetalation step rapidly undergoes decomposition to give the actual transmetalation complex [Pd(η^3-allyl)(alkynyl)-L].[128] In addition, the aforementioned effect cannot be obtained by amines, which are commonly used as bases in Sonogashira cross-coupling. The data are in full agreement with the rate acceleration observed, as demonstrated on the donor-substituted aryl iodide **7a,** which was fully converted to **9a** in 40 min in the presence of 10 mol % of the catalyst **2aBHA@PS** and 5 mol % of PPh_3 (Table 5, entry 3) in comparison with the PPh_3-free experiment (Table 5, entry 1: 10 mol % of **2aBHA@PS**, 55 min).

The ability of the polymer-bonded Pd(II)-ADC species **2aBHA@PS** and **2bBHA@PS** to catalyze Suzuki–Miyaura coupling was also examined (Table 7). The initial experiments demonstrated that commonly used conditions (Et_3N/DMF) are not favorable even in the case of the activated iodide **7b**. However, using K_2CO_3 as a base instead of Et_3N caused a decrease in the coupling time (Table 7, entries 2 and 3). Thus, a full conversion of the starting 1-iodo-4-nitrobenzene (**7b**) at 65 °C was observed within 120 min in the case of Et_3N and within 90 min when K_2CO_3 was employed. For a further optimization, we attempted to use a DMF/H_2O mixture as the solvent due to the higher solubility of K_2CO_3 in aqueous media. The results obtained indicated that the coupling of phenylboronic acid and aryl halides proceeded much more quickly (50–60 min) in the presence of 5–10% (vol) of water as a cosolvent and 4 equiv of K_2CO_3 as a base, giving cross-coupling products in quantitative yields (Table 7, entries 5–14). Under these conditions, a variety of differently substituted aryl bromides smoothly underwent cross-coupling with a 1.2 equiv excess of phenylboronic acid to afford biphenyls **10a–c,i** in excellent yields.

Using X-ray fluorescence analysis, we found that palladium leaching is noticeably less in the Suzuki–Miyaura coupling in comparison with the Sonogashira coupling even at 75 °C. The addition of PPh_3 also decreased palladium leaching in this case (Table 7, entries 13 and 14).

Thus, these results suggest that the catalytic system developed appears to be relatively stable in the 20–70 °C range and can be successfully applied to Sonogashira and Suzuki–Miyaura cross-coupling with a wide range of iodo- as well as bromoarenes.

XPS Studies. Previously, some heterogeneous NHC-based catalysts were characterized by the X-ray photoelectron spectroscopy (XPS) method.[75,76,80,82,89,91,97,102,129–132] However, Pd-NHC-containing polystyrene has only been investigated once by XPS prior to our work.[82]

To evaluate the applicability of the XPS analysis method, we used a freshly prepared sample of **2aBHA@PS**, containing 30% of modified amino groups. This degree of modification was found to provide a good signal intensity, suitable even for quantitative analysis.

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The presence in the XPS spectrum of two signals at 342.4 and 337.2 eV with good resolution and intensity corresponding to the binding energies of Pd $3d_{5/2}$ and Pd $3d_{3/2}$ electrons, respectively, proved that the freshly prepared **2aBHA@PS** precatalyst contains only Pd(II) species. The results obtained have demonstrated the possibility of the successful use of XPS analysis for the study of the surface composition of the catalyst developed. The samples of the polystyrene-supported catalysts **2aBHA@PS** were also analyzed by XPS before and after the Sonogashira and Suzuki–Miyaura coupling reactions (Figures 3 and 4). Some interesting differences were obtained.

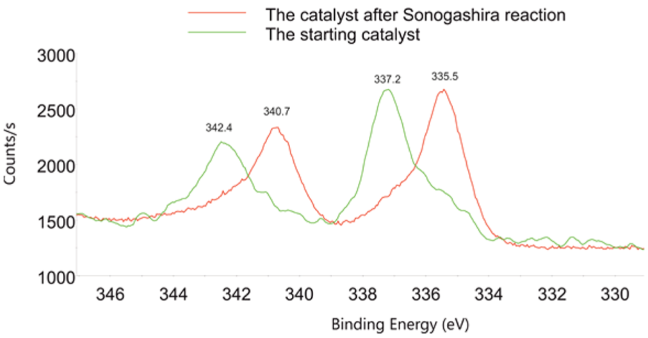

Figure 3. XPS spectra of the Pd-containing support **2aBHA@PS** before and after the Sonogashira reaction.

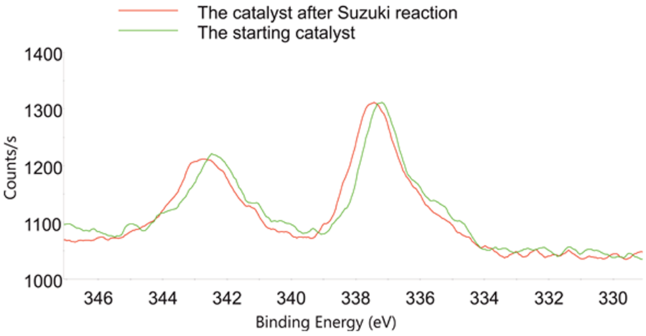

Figure 4. XPS spectra of the Pd-containing support **2aBHA@PS** before and after the Suzuki–Miyaura reaction.

To determine the surface composition and oxidation state of the catalyst after the Sonogashira coupling, we performed the reaction of 4-iodoanisole (**7a**) with 1.5 equiv of 2-methylbut-3-yn-2-ol (**5a**) in the presence of **2aBHA@PS** (1 mol % according to weight concentration of Pd(II) complexes), 5 mol % of PPh_3, 10 mol % of CuI and 4 equiv of Et_3N in DMF under air conditions at 40 °C. After the Sonogashira coupling the XPS spectrum of **2aBHA@PS** displayed two peaks of the binding energies of Pd $3d_{5/2}$ and Pd $3d_{3/2}$ electrons at 340.7 and 335.5 eV, respectively (Figure 3), which indicated the presence of Pd(0) and the absence of any Pd in the 2+ oxidation state in the recovered catalyst.

To determine the structural changes that occurred, **2aBHA@PS** was characterized by IR after Sonogashira coupling (Table 5, entry 23). In the IR spectrum of the recovered sample of the heterogeneous catalyst, the band of the isocyanide ligand was observed with a slight long-wavelength shift (see Figure S17 in the Supporting Information). This indicates that Pd species remain connected to the support with a change in their ligand environment under the reaction conditions.

It was found that palladium leaching is noticeably lower in the case of Suzuki–Miyaura coupling in comparison with the Sonogashira reaction (compare Tables 6 and 7). We attribute this tolerance of the Suzuki–Miyaura coupling to the fact that the starting Pd(II) complex on the surface of **2aBHA@PS** most likely did not convert to the less stable Pd(0) complex at the end of the reaction. In addition, the XPS analysis of the **2aBHA@PS** catalyst recovered after the Suzuki–Miyaura coupling (4-iodoanisole, 1.2 equiv of phenylboronic acid, 4 equiv of K_2CO_3, and 1 mol % of **2aBHA@PS**) confirmed that the oxidation state of Pd is +2 (Figure 4), which is in agreement with the data reported earlier.[133]

■ CONCLUSION

Depending on the reaction conditions, the nucleophilic addition of the primary amino group of benzhydrylamine to the isocyanide ligand of *cis*-$PdCl_2(CN\text{-}t\text{-}Bu)_2$ complexes has led to a cis-acyclic diaminocarbene complex or a trans-acyclic diaminocarbene cationic complex. It has been found that the formation of a three-centered hydrogen bond (NH···Cl···HN) is crucial for the formation and stabilization of the cationic complex. Both of the complexes exhibited high catalytic activity in Sonogashira and Suzuki–Miyaura coupling.

A very simple and convenient method of one-pot preparation and bonding of palladium(II) acyclic diaminocarbene complexes with polymer support via nucleophilic addition of the amine moiety to Pd-activated isocyanides has been developed.

Using this approach, new catalytic systems for palladium-catalyzed organic transformations have been prepared. The heterogeneous catalytic system developed has displayed high and stable activity in Sonogashira and Suzuki–Miyaura cross-couplings with aryl iodides and aryl bromides containing both electron-donating and electron-withdrawing groups. The addition of triphenylphosphine has been found to accelerate the Sonogashira coupling reaction rate, decrease palladium leaching, and reduce the amount of catalyst loading.

■ EXPERIMENTAL SECTION

General Remarks. Solvents and all reagents for catalytic studies were obtained from commercial sources and used as received, unless stated otherwise. Benzhydrylamine resin·HCl (2% cross-linked, 200–400 mesh, ca. 0.6–0.9 mmol/g, Bachem) was used as received. Chloroform was dried and purified by washing with concentrated sulfuric acid and distilled. DMF was purified via azeotropic distillation with benzene and water, distilled under reduced pressure, and stored under molecular sieves 4 Å. Infrared spectra (4000–200 cm^{-1}) were recorded on a Bruker Tensor 27 instrument as KBr pellets. NMR spectra were recorded at ambient temperature with a Bruker 400 Avance spectrometer at 400.13 (^1H) and 100.61 (^{13}C) MHz. Chemical shifts (δ) are given in ppm relative to the resonances of solvents (^1H, δ 7.26 for $CDCl_3$; ^{13}C, δ 77.16 for $CDCl_3$). Coupling constants (J) are given in Hz. Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, m = multiplet. The XPS spectrum of **2aBHA@PS** was analyzed by X-ray photoelectron spectroscopy (XPS) using a Thermo Fisher Scientific Escalab 250Xi spectrometer equipped with a monochromatic Al X-ray source. XPS analysis of the resin was performed in the Pd 3d region with a 20 eV pass energy, a 0.05 eV step, and a 0.5 s dwell time. Charge compensation was used, as each sample was nonconductive. All of the binding energy values are calibrated by using C(1s) = 284.6 eV as a reference. A graphical representation of XPS analysis data was performed with Thermo Avantage 5.52 (Avantage software). Mass spectra were recorded with a BrukerMicroTOF instrument (ESI). The instrument was operated in positive ion mode using an m/z range of 50–3000. The capillary voltage of the ion source was set at −4500 V (ESI^+-MS) and the capillary exit at 50−100 V. The nebulizer gas flow was 0.4 bar and drying gas flow was 4.0 L/min. For ESI, species were dissolved in MeOH. In the isotopic pattern, the most intense peaks are reported. Mass calibration for data system acquisition was achieved using CsI. Elemental analyses were performed on EURO EA3000 vectro model instrument. Thin-layer chromatography (TLC) was performed using Polygram precoated plastic sheets SIL G/UV254 (SiO_2, 0.20 mm thickness) from Macherey-Nagel. Column chromatography was performed using silica gel (40.0−63.0 nm particle size) from Macherey-Nagel. The complexes $PdCl_2(CNCy)_2$ and $PdCl_2$(CN-*t*-Bu)$_2$ were synthesized according to the literature procedure.[134]

Computational Details. The full geometry optimization of **3aBHA** and single-point calculations have been carried out at the DFT level of theory using the M06 functional (this functional reasonably describes weak dispersion forces and noncovalent interactions)[135] with the help of Gaussian-09 program package.[136] The experimental X-ray geometry was used as the starting point. The calculations were performed using the quasi-relativistic Stuttgart pseudopotential that described 28 core electrons and the appropriate contracted basis sets[137] for the palladium atoms and the 6-31+G* basis set for other atoms. No symmetry restrictions have been applied during the geometry optimization. The solvent effects were taken into account using the SMD continuum solvation model by Truhlar et al.[138] with $CHCl_3$ as solvent. The Hessian matrix was calculated analytically in order to prove the location of correct minima (no imaginary frequencies). The topological analysis of the electron density distribution with the help of the atoms in molecules (AIM) method developed by Bader has been performed by using the Multiwfn program (version 3.3.4).[139] The Cartesian atomic coordinates of the calculated equilibrium structure of **3aBHA** are presented in Table 21S in the Supporting Information.

Synthesis of $C_{23}H_{31}Cl_2N_3Pd$ (2aBHA). $PdCl_2$(CN-*t*-Bu)$_2$ (0.069 g, 0.2 mmol), $Et_3N{\cdot}HCl$ (0.069 g, 0.5 mmol), and $CHCl_3$ (2 mL) were placed together in a screw-cap vial. After homogenization of the resultant reaction mixture a solution of benzhydrylamine (BHA; 0.038 g, 0.2 mmol) in 1 mL of $CHCl_3$ was then added. The vial equipped with a magnetic stir bar was then placed in a steel bath, and the mixture was stirred at room temperature for 12 h. Then the organic solvent was evaporated under reduced pressure. A solvent mix (C_2H_5OH/Et_2O 2 mL/2 mL) was then added to the obtained residue and the resulting suspension filtered. The precipitate was washed with diethyl ether (2 × 3 mL) and dried at room temperature to give the corresponding Pd(II)-ADC complex **2aBHA** (colorless solid). Yield: 0.087 g (83%). Anal. Calcd for $C_{23}H_{31}Cl_2N_3Pd$ (526.84): C, 52.44; H, 5.93; N, 7.98. Found: C, 52.48; H, 5.83; N, 7.87. According to NMR data, the product was obtained as a mixture of two isomers (isomer ratio is 19:1), Major syn,syn isomer: ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 10/1) δ 8.37 (d, *J* = 8.8 Hz, 1H, N*H*), 7.78 (s, 1H, N*H*), 7.34−7.10 (m, 11H, Ar-*H* and C*H*), 1.55 (s, 9H, NH-C(C*H*$_3$)$_3$), 1.04 (s, 9H, C≡N- C(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$:DMSO-d_6 10:1) δ 184.36 (C_{carbene}), 141.79 (*C*(Ar)), 141.28 (*C*(Ar)), 128.65 (CH(Ar)), 128.59 (CH(Ar)), 128.29 (CH(Ar)), 127.61 (CH(Ar)), 127.52 (CH(Ar)), 127.21 (CH(Ar)), 66.36 (CH), 58.29(NH-*C*(CH$_3$)$_3$) 54.17(C≡N-*C*(CH$_3$)$_3$), 31.61(NH-C (*C*H$_3$)$_3$), 29.45(C≡N−C(*C*H$_3$)$_3$) (isocyanide carbon atom were not detected); IR (KBr, selected bands, cm^{-1}): ν 3241, 3064, 3030, 2980, 2223(C≡N), 1559, 1454, 1371, 1199, 702; HRMS (ESI+,70 V, MeCN) found 490.1216 [M − Cl], calcd for $C_{23}H_{31}ClN_3Pd$ 490.1241. X-ray-quality crystals of **2aBHA** were obtained by slow evaporation of a saturated solution (DMSO/$CHCl_3$ mixture).

Synthesis of $C_{27}H_{35}Cl_2N_3Pd$ (2bBHA). The compound was prepared by a procedure similar to that for **2aBHA**. A mixture of $PdCl_2$(CN-Cy)$_2$ (0.079 g, 0.2 mmol), $Et_3N{\cdot}HCl$ (0.069 g, 0.5 mmol), and BHA (0.038 g, 0.2 mmol) was used. A colorless solid was obtained. Yield: 0.093 g (80%). Anal. Calcd for $C_{27}H_{35}Cl_2N_3Pd$ (578.92): C, 56.02; H, 6.09; N, 7.26. Found: C, 56.01; H, 6.04; N, 7.19. According to NMR data, the product was obtained as a mixture of two isomers (isomer ratio is 13:1), Major syn,syn isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.9 Hz, 1H, N*H*), 7.98 (d, *J* = 8.9 Hz, 1H, N*H*), 7.54 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.35−7.29 (m, 5H, Ar-*H*), 7.22−7.05 (m, 4H, Ar-*H* and C*H*), 4.44 (m, 1H, C*H*(Cy)-NH), 3.26 (m, 1H, C*H*(Cy)-N≡C), 2.14 (d, *J* = 9.2 Hz) and 1.88−1.05(m, 20H, Cy-*H*); ^{13}C NMR (101 MHz, DMSO-d_6) δ 180.99 (C_{carbene}), 142.07 (*C*(Ar)), 141.02 (*C*(Ar)), 128.62 (CH(Ar)), 128.57 (CH(Ar)), 128.36 (CH(Ar)), 128.30 (CH(Ar)), 127.40 (CH(Ar)), 127.07 (CH(Ar)), 66.90 (CH), 59.17 (CH(Cy)-NH), 54.92 (CH(Cy)-N≡C), 33.40 (CH$_2$), 33.13 (CH$_2$), 31.72 (CH$_2$), 31.67 (CH$_2$), 25.22 (CH$_2$), 24.93 (CH$_2$), 24.87 (CH$_2$), 24.58 (CH$_2$), 22.94 (CH$_2$) (isocyanide carbon atom were not detected); IR (KBr, selected bands, cm^{-1}) ν 3246, 3054, 2929, 2855, 2225 (C≡N), 1588, 1573, 1451, 744, 700; HRMS (ESI+,70 V, MeCN) found 542.1618 [M − Cl], calcd for $C_{27}H_{35}ClN_3Pd$ 542.1554.

Synthesis of $C_{28}H_{40}Cl_2N_4Pd$ (3aBHA) and $C_{18}H_{22}Cl_2N_2Pd$ (4aBHA). $PdCl_2$(CN-*t*-Bu)$_2$ (0.069 g, 0.2 mmol) and $CHCl_3$ (2 mL) were placed in a screw-cap vial. After homogenization and cooling to 0 °C of the resultant reaction mixture a solution of benzhydrylamine (0.038 g, 0.2 mmol) in 1 mL of $CHCl_3$ was added. The vial equipped with a magnetic stir bar was placed in a steel bath, and the mixture was stirred at room temperature (20 °C) for 12 h. The organic solvent was removed under reduced pressure. Then THF (5 mL) was added to the obtained residue and the resulting suspension filtered. The precipitate was washed with diethyl ether (2 × 3 mL) and dried at room temperature to give the corresponding cationic complex **3aBHA** in 47% (0.057 g) yield. The filtrate was then concentrated to 1 mL, and hexane was added to afford a yellow solid. Recrystallization of the obtained residue from a dichloromethane/pentane mixture gave complex **4aBHA** in 45% (0.040 g) yield.

3aBHA: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (d, *J* = 10.3 Hz, 1H, N*H*), 10.33 (s, 1H, N*H*), 7.50 (d, *J* = 7.5 Hz, 4H, Ar-*ortho-H*), 7.29 (t, *J* = 7.6 Hz, 4H, Ar-*meta-H*), 7.19 (t, *J* = 7.4 Hz, 2H, Ar-*para-H*), 6.65 (d, *J* = 10.3 Hz, 1H, C*H*), 1.57 (s, 9H, NH-C (C*H*$_3$)$_3$), 1.24 (s, 18H, C≡N- C (C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.32 (C_{carbene}), 141.48 (*C*(Ar)), 129.04 (*C-meta*-H(Ar)), 127.71 (*C-para*-H(Ar)), 127.16 (*C-ortho*-H(Ar)), 69.92 (CH), 59.78(NH-*C*(CH$_3$)$_3$), 54.12(C≡N-*C*(CH$_3$)$_3$), 31.37 (NH-C(*C*H$_3$)$_3$), 29.52 (C≡N−C (*C*H$_3$)$_3$) (isocyanide carbon atom was not detected); IR (KBr, selected bands, cm^{-1}) ν 3191, 2979, 2228 (C≡N), 1589, 1568, 1453, 1186, 765, 702; HRMS (ESI+,70 V, MeCN) found 573.1990 [M − Cl], calcd for $C_{28}H_{40}ClN_4Pd$ 573.1976. Anal. Calcd for $C_{28}H_{40}Cl_2N_4Pd$ (609.98): C, 55.13; H, 6.61; N, 9.19. Found: C, 55.18; H, 6.75; N, 9.20. X-ray-quality crystals of **3aBHA** were obtained by slow evaporation of a saturated solution (pentane/CH_2Cl_2 mixture).

4aBHA: light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 4.3 Hz, 8H, Ar-*H*), 7.32 (m, 2H, Ar-*H*), 5.66 (t, *J* = 7.5 Hz, 1H, C*H*), 3.47 (d, *J* = 7.0 Hz, 2H, N*H*$_2$), 1.48 (s, 9H, C≡N-C(C*H*$_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.65 (*C*(Ar)), 129.12 (*C-meta*-H(Ar)), 128.28 (*C-para*-H(Ar)), 127.51 (*C-ortho*-H(Ar)), 60.78(C≡N-*C*(CH$_3$)$_3$), 30.08 (C≡N−C(*C*H$_3$)$_3$) (isocyanide carbon atom was not detected); IR (KBr, selected bands, cm^{-1}) ν 3311, 3246, 2984, 2240 (C≡N), 1585, 1573, 707, 337; HRMS (ESI+,70 V, MeCN) found 407.0491 [M − Cl], calcd for $C_{18}H_{22}ClN_2Pd$ 407.0506. Anal. Calcd for $C_{18}H_{22}Cl_2N_2Pd$ (443.71): C, 48.73; H, 5.00; N, 6.31. Found: C, 48.65; H, 5.09; N, 6.24. X-ray-quality crystals of **4aBHA** were obtained by slow evaporation of a saturated solution (pentane/CH_2Cl_2 mixture).

Synthesis of Complexes $C_{28}H_{40}Cl_2N_4Pd$ (3aBHA) and $C_{34}H_{46}Cl_2N_4Pd$ (3bBHA). $PdCl_2$(CN-R)$_2$ (R = *t*-Bu, Cy; 0.2 mmol) and $CHCl_3$ (2 mL) were placed in a screw-cap vial. After homogenization of the resultant reaction mixture a solution of benzhydrylamine (0.038 g, 0.2 mmol) and *tert*-butyl isocyanide (0.017 g, 0.2 mmol) in 1 mL of $CHCl_3$ was added. The vial equipped with a magnetic stir bar was placed in a steel bath, and the mixture was stirred at the appropriate temperature for 6 h. The organic solvent was removed under reduced pressure. Recrystallization of the obtained residue from a dichloromethane/hexane mixture gave complexes **3aBHA** and **3bBHA** in 95% (0.116 g) and 96% (0.132 g) yields, respectively.

3bBHA: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (d, *J* = 8.7 Hz, 1H, N*H*), 10.23 (d, *J* = 9.2 Hz, 1H, N*H*), 7.48 (d, *J* = 7.6 Hz, 4H, Ar-*ortho-H*), 7.31 (t, *J* = 7.5 Hz, 4H, Ar-*meta-H*), 7.20 (t, *J* = 7.3

Hz, 2H, Ar-*para-H*), 6.45 (bs, 1H, C*H*), 3.98 (m, 1H, C*H*(Cy)-NH), 3.69−3.44 (m, 2H, C*H*(Cy)-N≡C), 1.90−1.13 (m, 30H, Cy-*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.46 ($C_{carbene}$), 141.35 (*C*(Ar)), 129.04 (*C-meta*-H(Ar)), 127.71 (*C-para*-H(Ar)), 127.23 (*C-ortho*-H(Ar)), 68.61 (CH), 58.9417 (CH(Cy)-NH), 55.67 (CH(Cy)-N≡C), 33.59 (CH_2), 31.60 (CH_2), 31.56 (CH_2), 25.01 (CH_2), 24.41 (CH_2), 24.33 (CH_2), 22.65 (CH_2) (isocyanide carbon atom was not detected); IR (KBr, selected bands, cm^{-1}) ν 3168, 2933, 2856, 2232(C≡N), 1591, 1578, 1450, 1352, 753, 700; HRMS (ESI+,100 V, MeOH) found 651.2423 [M − Cl], calcd for $C_{18}H_{22}ClN_2Pd$ 651.2446. Anal. Calcd for $C_{34}H_{46}Cl_2N_4Pd$ (688.09): C, 59.35; H, 6.74; N, 8.14. Found: C, 59.47; H, 6.65; N, 8.20.

Preparation and Characterization of Supported Pd(II)-ADC Complexes. Benzhydrylamine hydrochloride resin (1 g, 200−400 mesh; BHA resin·HCl), Et_3N (55 mg, 0.55 mmol), and $CHCl_3$ (20 mL) were placed in a screw-cap vial equipped with a magnetic stir bar. The resulting suspension was vigorously stirred for 10 min. After this, *cis*-$PdCl_2(CNR)_2$ (R = *t*-Bu, 20.6 mg, 0.06 mmol; R = Cy, 23.7 mg, 0.06 mmol) was added and stirring was continued for 24 h. The obtained **2aBHA@PS** (R = *t*-Bu) or **2bBHA@PS** (R = Cy) was filtered off, washed with 10 mL of $CHCl_3$, and dried under reduced pressure. The filtrate was then concentrated and analyzed by NMR and XRF, which showed the starting complex completely bonded to the surface: white solid, estimated concentration of Pd 0.075 mmol/g.

2aBHA@PS: IR (KBr, cm^{-1}) 3082, 3060, 3024, 3002, 2919, 2851, 2224 (C≡N), 1944, 1874, 1807, 1745, 1720, 1671, 1600, 1583, 1562, 1493, 1449, 1371, 1330, 1314, 1279, 1217, 1199, 1182, 1155, 1067, 1028, 906, 843, 744, 697, 667, 621, 541.

2bBHA@PS: IR (KBr, cm^{-1}) 3082, 3059, 3025, 2920, 2849, 2225 (C≡N), 1943, 1872, 1803, 1663, 1600, 1492, 1451, 1365, 1181, 1154, 1068, 1027, 906, 842, 754, 695, 536.

General Procedure for Sonogashira Cross-Coupling. The polymer-supported palladium catalyst (**2aBHA@PS** or **2bBHA@PS**; 100 mg, 0.0075 mmol, 10 mol % according to weight concentration of surface complexes) in a 10 mL round-bottom flask was first sustained in 2 mL of DMF for 10 min, followed by 2 mL of a DMF solution of aryl halide (0.075 mmol), alkyne (0.113 mmol), Et_3N (30 mg, 0.3 mmol), and PPh_3 (5−10 mol %, if required). The flask then was placed in a preheated oil bath and CuI (1.4 mg, 0.0075 mmol, 10 mol %) was added at once. The resulting heterogeneous system was stirred for the required time, cooled to room temperature, and filtered. The supported catalyst was washed with an additional portion of DMF (10−15 mL). A 5 mL portion of the combined filtrate (20 mL in total) was sampled and analyzed by XRF, and the residual DMF solution was poured into 30 mL of water, followed by extraction with ethyl acetate. The extract was evaporated under reduced presser, dissolved in $CDCl_3$, and analyzed by ^{1}H NMR.

General Procedure for Suzuki−Miyaura Cross-Coupling. The polymer-supported palladium catalyst (**2aBHA@PS** or **2bBHA@PS**; 50 mg, 0.0036 mmol, 5 mol % according to weight concentration of surface complexes) in a 10 mL round-bottom flask was first sustained in 2 mL of DMF for 10 min, followed by 2 mL of a DMF solution of aryl halide (0.075 mmol), phenylboronic acid (11 mg, 0.09 mmol), aqueous K_2CO_3 or Et_3N (0.3 mmol), and PPh_3 (5−10 mol %, if required). The flask then was placed in a preheated oil bath and the resulting heterogeneous system was stirred for the required time, cooled to room temperature, and filtered. The supported catalyst was washed with an additional portion of DMF (10−15 mL). A 5 mL portion of the combined filtrate (20 mL in total) was sampled and analyzed by XRF, and the residual DMF solution was poured into 30 mL of water, followed by extraction with ethyl acetate. The extract was evaporated under reduced pressure, dissolved in $CDCl_3$, and analyzed by ^{1}H NMR.

General Procedure for Supported Catalyst Recycling. After separation of the product mixture and washing with an additional portion of DMF, the supported catalyst was washed with 10 mL of CH_2Cl_2 and dried at room temperature under reduced pressure. In some cases, when K_2CO_3 as a base was used, the catalyst was first washed with 10 mL of water followed by 5 mL of DMF and the required amount of CH_2Cl_2.

X-ray Fluorescence Analysis. XRF analysis was performed with a Rigaku NANOHUNTER benchtop total reflection X-ray fluorescence (TXRF) spectrometer. A Cu anode X-ray tube was used for excitation at 50 kV and 0.6 mA. X-ray fluorescence was detected using an Si/Li dispersive detector in a coplanar, right angle geometry to the X-ray source. Spectra were acquired over a 300 s acquisition period. Each solution of palladium was sampled (100 μL) three times on sodium glass plates as specified by the manufacturer and dried at 70 °C and each sample was measured twice; an average of six runs is reported. For quantitative analysis the palladium fluorescence was measured against an internal standard of known concentration (KI, 56 μg K/probe for Sonogashira coupling; *p*-TsOH, 101 μg S/probe for Suzuki−Miyaura coupling). The exact amount of Pd in solution was determined using the linear area of the calibration curve $I_{Pd}/I_{standard} = f([Pd])$. Standard solutions of known concentrations of palladium were prepared as follows: bis(acetonitrile)palladium(II) dichloride (2 mg) was dissolved in absolute acetone (10 mL), and the desired amounts of the resulting solution were transferred to glass vials using a microsyringe. Vials were dried at 50 °C for 10 min, cooled to room temperature, and filled with 5 mL of an internal standard solution in DMF (47.6 mg/L of KI corresponding to 56 μg of potassium/probe or 108.5 mg/L of TsOH corresponding to 101 μg of sulfur/probe).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00144.

Crystallographic data and bond lengths and angles for complexes **2aBHA**, **3aBHA**, and **4aBHA**, NMR and IR spectra of all complexes, details of XRF analysis, and theoretical studies (PDF)

Crystallographic data for complexes **2aBHA**, **3aBHA**, and **4aBHA** (CIF)

Cartesian coordinates for the calculated structures (XYZ)

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Notes

The authors declare no competing financial interest.

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