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Selective Nucleophilic Oxygenation of Palladium-Bound Isocyanide Ligands: Route to Imine Complexes That Serve as Efficient Catalysts for Copper-/Phosphine-Free Sonogashira Reactions

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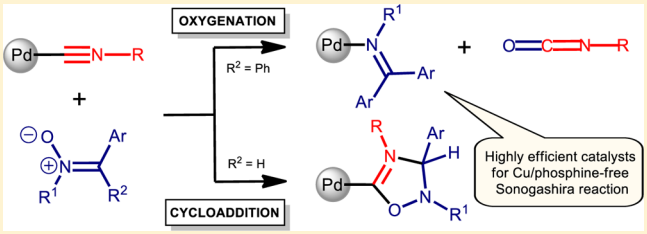
Supporting Information

ABSTRACT: Metal-mediated reactions between *cis*-$[PdCl_2(CNR)_2]$ (R = Xy (**1**), Cy (**2**), *t*Bu (**3**), C_6H_3(Cl-2)Me-6 (**4**)) and the *keto*nitrones $Ph_2C{=}N(O)C_6H_4R'$ (R′ = Me (**5**), Cl (**6**)) proceed in a 1:1 molar ratio as selective nucleophilic oxygenations and provide the imine−isocyanide complexes $[PdCl_2\{N(C_6H_4R'){=}CPh_2\}(CNR)]$ (**7**−**14**: R′ = Me, R = Xy (**7**), Cy (**8**), *t*Bu (**9**), C_6H_3(Cl-2)Me-6 (**10**); R′ = Cl, R = Xy (**11**), Cy (**12**), *t*Bu (**13**), C_6H_3(Cl-2)Me-6 (**14**)) in excellent yields (90−94%), while the reaction of the *cis*-$[PdCl_2(CNR)_2]$ complexes with *aldo*nitrones proceeds as 1,3-dipolar cycloaddition, giving carbene adducts which then convert to the imine complexes. Theoretical calculations at the DFT level indicate that, in the case of aldonitrones, formation of the imine complexes occurs preferably via a cycloaddition/splitting pathway, including the generation of a cycloadduct, while, in the case of ketonitrones, both the cycloaddition/splitting route and the direct oxygen atom transfer pathway are equally plausible from a kinetic viewpoint. Complexes **7**−**14** were characterized by elemental analyses (C, H, N), by high-resolution ESI$^+$-MS, IR, and ^{1}H and $^{13}C\{^1H\}$ NMR spectroscopy, and also by X-ray diffraction (for **8**). The catalytic activity study conducted for **7**−**14**, taken as the catalysts in the Cu-/phosphine-free Sonogashira reaction, was evaluated for a typical model system comprising 4-methoxyiodobenzene and phenylacetylene and affording 1-methoxy-4-(phenylethynyl)benzene. The obtained data indicate that **7**−**14** exhibit a high catalytic activity (yields up to 95%, TONs up to 15000), and these catalysts are among the best studied so far.



INTRODUCTION

In carbonyl chemistry, the nucleophilic oxygenation of carbon monoxide is a classic issue, and it has been thoroughly studied under both metal-mediated[1] and metal-free conditions.[2] Many of these oxidations proceed as a nucleophilic oxygenation (see reviews[3] and recent works[1f,4]), and they are particularly useful in synthetic chemistry for conducting oxidative substitution of metal-bound CO,[3b] liberation of organic ligands,[1a,3b] oligomerization of mononuclear metal carbonyl derivatives,[5] intramolecular ligand displacement,[6] and deinsertion reactions.[7]

Isocyanides are isoelectronic with the CO molecule, and it would seem that they have to undergo the same type oxidation. Surprisingly, despite the wealth of isocyanide chemistry, the conversion of RNC to RNCO has still been much less investigated than similar oxygenations of CO. The reported examples of such reactions include the nucleophilic oxygenation of an isocyanide by amine *N*-oxides,[8] N_2O,[9] DMSO,[10] and ozone.[11] In the vast majority of cases, these processes require an activation of the isocyanide C atom toward attack by an O-nucleophile that can be achieved by (i) application of *metal-free electrophiles* (sulfur tetrafluoride,[10a] halogen, acid,[12] and trifluoracetic anhydride catalyzed[10b] oxidations by DMSO, iodine catalyzed oxygenation by amine *N*-oxides[13]) or (ii) a *metal-mediated route* when metal centers bind the isocyanide C atom and act as electrophilic activators, thus facilitating nucleophilic oxygenations of RNC ligands (e.g., Au^0,[8] Mo^{IV}, or W^{IV} catalyzed[9] and Cu^I-mediated nucleophilic oxygenations[14]).

Previously, two of us reported that *aldo*nitrones, Ar(H)C=N(O)Alk, react with one isocyanide in *cis*-$[PdCl_2(CNR)_2]$ to form a cyclic carbene ligand formed via 1,3-dipolar cycloaddition (Scheme 1).[15] The reactions of such poorly studied dipoles as *keto*nitrones,[16] $Ar_2C{=}N(O)Ar$, with isocyanide ligands in their metal complexes were not studied, although we recently

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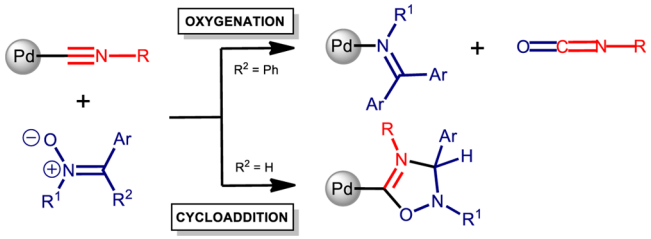
Scheme 1. Different Reactivity of Aldo- and Ketonitrones toward Pd^{II}-Bound Isocyanides



verified their reactivity toward various platinum- and palladium-activated nitrile, RCN, species.[16,17] In contrast to the previous cycloaddition study involving aldonitrones,[15] we now observe that an isocyanide ligand in *cis*-$[PdCl_2(CNR)_2]$ reacts with the ketonitrones $Ph_2C{=}N(O)C_6H_4R'$ (R′ = Me, Cl) and undergoes facile and selective oxygenation to give free isocyanates and mixed imine−isocyanide palladium(II) complexes (Scheme 1).

In this work (i) we compare the reactivity of the RNC ligands in *cis*-$[PdCl_2(CNR)_2]$ toward aldo- and ketonitrones and suggest an efficient route to oxygenate metal-activated RNC species by ketonitrones, (ii) as a result of the observed oxygenation we synthesize and characterize a series of mixed imine−isocyanide palladium(II) complexes, and (iii) we test these species as catalysts in copper-/phosphine-free Sonogashira cross-coupling and it appears that they exhibit a great efficiency in this reaction. All these results are consistently disclosed in this work.

RESULTS AND DISCUSSION

Palladium(II)-Mediated Nucleophilic Oxygenation of Isocyanide Ligands by Ketonitrones. In the current work, the isocyanide complexes *cis*-$[PdCl_2(CNR)_2]$ (R = Xy (**1**), Cy (**2**), *t*Bu (**3**), C_6H_3(Cl-2)Me-6 (**4**)), on one hand, and the ketonitrones $Ph_2C{=}N(O)C_6H_4R'$ (R′ = Me (**5**), Cl (**6**)), on the other hand, were employed as the partners for the reactivity study (Scheme 2 and Table 1).

Scheme 2. Studied Oxygenations

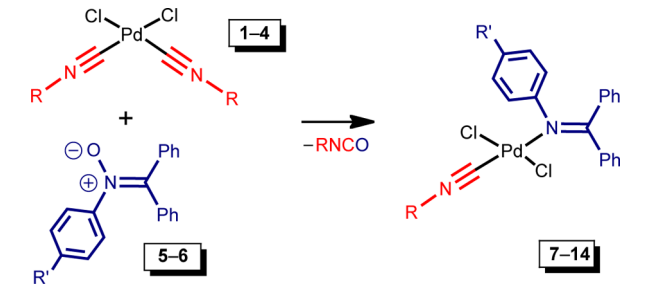


Table 1. Compound Numbering for Scheme 2

R		5, R′ = Me	6, R′ = Cl
Xy	1	7	11
Cy	2	8	12
*t*Bu	3	9	13
C_6H_3(Cl-2)Me-6	4	10	14

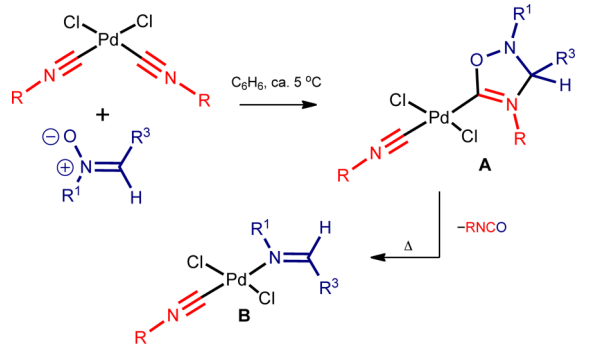
The reactions between **5** and **6** and the isocyanide ligands RNC in their palladium(II) complexes **1**−**4** were performed in dichloromethane or benzene solutions, and they lead to the generation of imine−isocyanide palladium(II) complexes **7**−**14**. These reactions were studied at different temperatures, in different solvents, and using various ratios of the reactants. The obtained results are disclosed in sections that follow.

When the reactions between **5** (or **6**) and **1**−**4**, in all possible combinations, in CH_2Cl_2 or C_6H_6 in molar ratios ranging from 1:1 to 1:2 were performed at ca. 5 °C for 4 h and then the reaction mixtures were stirred at room temperature for 5 h, we observed a selective oxygenation of the isocyanide ligands to give the corresponding uncomplexed isocyanates and generation of imine−isocyanide complexes **7**−**14**; the latter were isolated in excellent yields (90−94%). The formation of the RNCO isocyanates was unambiguously established by (i) the IR monitoring of the reaction mixtures (ca. 2260 cm^{-1}; lit.[10b] 2257 cm^{-1} ν(C═N═O))) and (ii) by the treatment of the reaction mixtures with Et_2NH followed by isolation of the substituted ureas $Et_2NC(O)NHR$ generated via the reported addition of Et_2NH to the isocyanates.[10b] Identification of $Et_2NC(O)NHR$ was based on comparison of their melting points with those for the known species.[18]

When the reactions between **5** (or **6**) and **1**−**4**, in 1:1 or 1:2 ratios, in CH_2Cl_2 were performed at −30 °C, only the decrease of the reaction rate was observed. At room temperature in either CH_2Cl_2 or C_6H_6, the reaction lost its selectivity, resulting in a broad mixture of products, where we detected imine−isocyanide complexes **7**−**14** (ca. 20−25% based on the ^1H NMR integration of the meta protons of the *p*-R′C_6H_4 group) and the corresponding isocyanates RNCO (identified by HRESI-MS) along with many other as yet unidentified species.

It has previously been reported[15] (Scheme 3) that the acyclic aldonitrones $R^3C(H){=}N(O)R^1$ (R^3 = 4-$CH_3C_6H_4$; R^1 = Me,

Scheme 3. Reaction of Pd^{II}-Bound Isocyanides with Aldonitrones



CH_2Ph) react with **1**−**4** (molar ratio 1:1, at ca. 5 °C in C_6H_6) to give stable carbene−isocyanide complexes **A** (ca. 60%), which are formed via 1,3-dipolar cycloaddition; they decompose only upon heating (C_6H_6, 60 °C; $CHCl_3$, room temperature) to give the corresponding isocyanates RNCO and imine−isocyanide complexes **B**.

In contrast to the cycloaddition study,[15] no evidence for generation of the carbene cycloadducts originating from **1**−**4** and ketonitrones **5** (or **6**) were detected by both HRESI-MS and ^1H NMR spectroscopy, even at −30 °C. Furthermore, imine−isocyanide complexes **7**−**14** originating from the deoxygenation of the *keto*nitrones, proved to be stable even in refluxing toluene (24 h), while imine−isocyanide species **B** (Scheme 3) are unstable and were not isolated in analytically

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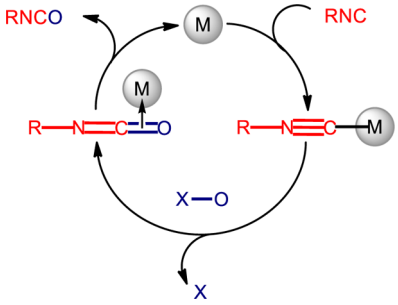
pure form and were characterized in their $CDCl_3$ solutions by HRESI-MS and ^1H NMR.

It should be pointed out that nitrones **5** and **6** do not react with the uncomplexed isocyanides RNC even under drastic conditions (125 h, reflux in the RNC media). The latter observation means that the oxygenation of the isocyanides by the ketonitrones is palladium(II)-mediated. The processes involving metal-mediated oxygenations of isocyanides to give isocyanates (Scheme 4) have been poorly studied, and they are

Scheme 4. Metal-Catalyzed Oxygenations



represented by amine *N*-oxide Au^0-catalyzed oxygenation[8] and Mo^{II}- or W^{II}-catalyzed oxidation by N_2O.[9] Plausible mechanisms of these transformations include the nucleophilic addition of R_3NO or N_2O to metal-coordinated isocyanides followed by formation of R_3N or N_2, respectively, and generation of π-coordinated isocyanate, which is then substituted by RNC (Scheme 4).

With regard to noncatalytic metal-mediated processes, only one example of oxidation of an isocyanide ligand to furnish isocyanate was reported, and it includes the reaction of $(RNC)Cu^I$ species with $t\text{-}BuCO_3^-$. It is believed that this transformation also proceeds via the nucleophilic oxygenation of the isocyanide ligand by $t\text{-}BuCO_3^-$.[14]

Theoretical Mechanistic Study. With the aim of understanding the reasons for the different chemical behaviors of ketonitrones and aldonitrones toward Pd^{II}-bound isocyanides, quantum chemical calculations of the reaction mechanisms have been performed. There are two plausible routes leading to imines and isocyanates upon the reaction between nitrones and isocyanides. The first involves the initial formation of the cycloadduct, via 1,3-dipolar cycloaddition (CA), which then splits into the imine and the isocyanate (route A, Scheme 5). This route is operating in the case of aldonitrones, as was proved by previous experimental[15] and theoretical[19] studies. The second route includes the direct oxygen atom transfer from the nitrone to the isocyanide ligand (route B, Scheme 5), which may occur either in a concerted or in a stepwise manner. The experimentally observed imine complex **IV** and free isocyanate are formed as a result of the substitution of OCNR for the imine in the coordination sphere of complex **III**.

1. Route A. The mechanism of generation of complex **IV** via route A was previously theoretically studied in detail by one of us for the reaction of the aldonitrone PhC(H)=N(O)Me with the complex $[PdCl_2(CNMe)_2]$ (**I**).[19f] It was shown that the cycloadduct $\mathbf{II}_{aldo}$ is formed in a stepwise manner via the acyclic intermediate $\mathbf{INT}_{aldo}$. Cycloadduct $\mathbf{II}_{aldo}$ then undergoes splitting via the concerted cleavage of the N(2)−C(3) and N(4)−O(5) bonds. This process is accompanied by the spontaneous recoordination of the isocyanate and formation of complex **III**, featuring the O-bound OCNMe ligand. Subsequent ligand substitution affords final product $\mathbf{IV}_{aldo}$ via a dissociative mechanism with a small activation barrier of 8.4 kcal/mol, while the rate-determining step of the whole reaction is the first CA.

Taking into account that in this work CH_2Cl_2 was employed as a solvent instead of the benzene applied previously,[15] we recalculated the activation and reaction energies of the reaction between PhC(H)=N(O)Me and **I** along route A with dichloromethane as the solvent (Table 2) (previously published values[19f] were obtained for a benzene solution).

Within this work, the same mechanistic route A was calculated for the reaction between the ketonitrone Ph_2C=N(O)Ph and **I**. The calculations demonstrated that in this case CA also occurs via the stepwise pathway, including the formation of acyclic intermediate $\mathbf{INT}_{keto}$. The first step, viz. the formation of $\mathbf{INT}_{keto}$ via $\mathbf{TS1}_{keto}$ (Figure 1), is the rate-determining step, while the energy of $\mathbf{TS2}_{keto}$ of the second step is 5.8 kcal/mol lower than the energy of $\mathbf{TS1}_{keto}$. The overall activation barrier of CA involving the ketonitrone is higher by 1.7 kcal/mol in comparison to that involving the aldonitrone (Figure 2).

CA of the aldonitrone is slightly exoergonic with a ΔG_s value of −0.8 kcal/mol, whereas the reaction with the ketonitrone is clearly endoergonic by 3.0 kcal/mol. This difference in the

Scheme 5. Mechanisms of Formation of Imine Complexes and Isocyanates upon the Reaction of Nitrones with Palladium-Bound Isocyanides

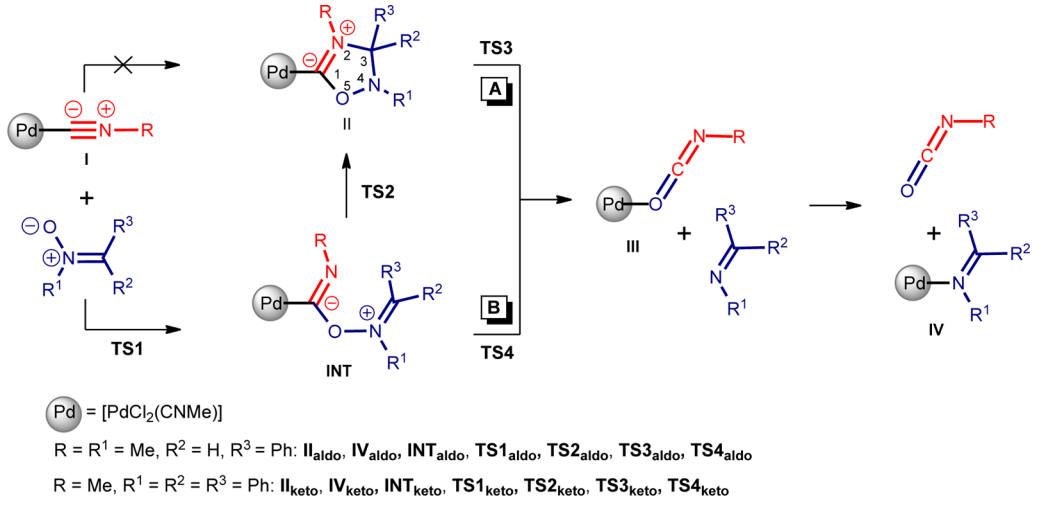


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Table 2. Calculated Gibbs Free Energies of Activation and Reaction for CH_2Cl_2 Solution (in kcal/mol)

reaction	$\Delta G_s^{\ddagger}$	ΔG_s
PhC(H)=N(O)Me + **I** → $\mathbf{INT}_{aldo}$ via $\mathbf{TS1}_{aldo}$	26.0	21.7
$\mathbf{INT}_{aldo}$ → $\mathbf{II}_{aldo}$ via $\mathbf{TS2}_{aldo}$	3.7	−22.5
$\mathbf{II}_{aldo}$ → **III** + MeN=C(H)Ph via $\mathbf{TS3}_{aldo}$	25.7	−36.0
$\mathbf{INT}_{aldo}$ → **III** + MeNC(H)Ph via $\mathbf{TS4}_{aldo}$	7.1	−58.6
III + MeN=C(H)Ph → $\mathbf{IV}_{aldo}$ + OCNMe		−14.2
Ph_2C=N(O)Ph + **I** → $\mathbf{INT}_{keto}$ via $\mathbf{TS1}_{keto}$	27.7	20.2
$\mathbf{INT}_{keto}$ → $\mathbf{II}_{keto}$ via $\mathbf{TS2}_{keto}$	1.7	−17.2
$\mathbf{II}_{keto}$ → **III** + PhN=CPh_2 via $\mathbf{TS3}_{keto}$	22.3	−47.8
$\mathbf{INT}_{keto}$ → **III** + PhN=CPh_2 via $\mathbf{TS4}_{keto}$	5.1	−65.0
III + PhN=CPh_2 → $\mathbf{IV}_{keto}$ + OCNMe		−8.1

thermodynamic stabilities of the CA products is crucial for the comparison of the reactivity of these two types of nitrones toward isocyanide ligands (see below).

Splitting of $\mathbf{II}_{keto}$ to furnish **III** and Ph_2C=NPh occurs in a concerted mode via $\mathbf{TS3}_{keto}$. The calculated activation energy of the $\mathbf{II}_{keto}$ splitting is lower by 3.3 kcal/mol than that of the $\mathbf{II}_{aldo}$ splitting (the $\Delta G_s^{\ddagger}$ values are 22.3 and 25.7 kcal/mol, respectively; Figure 2).

2. Route B. Route B starts with the formation of the intermediate **INT**, which then is directly converted to **III** via **TS4**. In the case of the aldonitrone PhCH=N(O)Me, the rate-limiting step for route B is the second one (decomposition of $\mathbf{INT}_{aldo}$), while for the ketonitrone Ph_2C=N(O)Me the rate-determining step is the first one (formation of $\mathbf{INT}_{keto}$). The activation barrier of the $\mathbf{INT}_{keto}$ decomposition into **III** is lower than that of $\mathbf{INT}_{aldo}$ (5.1 vs 7.1 kcal/mol, respectively). However, the conversion of both $\mathbf{INT}_{keto}$ and $\mathbf{INT}_{aldo}$ into the CA product requires an even smaller activation energy (1.7 and 3.7 kcal/mol, respectively).

An inspection of Figure 2 indicates three principal differences in the energy profiles for the reactions of the aldonitrone and the ketonitrone with **I**, i.e., (i) the rate-limiting step of route B is the $\mathbf{INT}_{aldo}$ → **III** step for the aldonitrones, while it is the Ph_2C=N(O)Ph + **I** → $\mathbf{INT}_{keto}$ step for the ketonitrone, (ii) cycloadduct $\mathbf{II}_{aldo}$ is slightly exoergonic relative to the starting reactants, whereas the cycloadduct $\mathbf{II}_{keto}$ is endoergonic, and (iii) the activation barrier of the **II** decomposition into **III** is lower for the ketonitrone than for the aldonitrone by 3.3 kcal/mol. Considering these features, the following conclusions may be formulated. First, for the aldonitrone, the generation of the oxygen atom transfer product $\mathbf{IV}_{aldo}$ occurs via formation of cycloadduct $\mathbf{II}_{aldo}$ as the intermediate (route A), while route B is clearly less favorable. This conclusion is coherent with the experiment,[15] where the cycloadducts were isolated. Second, for the ketonitrone, both routes of the $\mathbf{IV}_{keto}$ formation (A and B) are equally plausible. The generation of the cycloadduct $\mathbf{II}_{keto}$ is also expected. However, its accumulation should be less efficient compared to that of $\mathbf{II}_{aldo}$ due to the positive ΔG_s values of $\mathbf{II}_{keto}$ formation and a lower activation barrier to its decomposition. Note that the difference of 3.3 kcal/mol between the activation barriers of the $\mathbf{II}_{aldo}$ and $\mathbf{II}_{keto}$ decompositions corresponds to the difference in the reaction rates by a factor of ca. 280.

Additionally, an extensive search of the potential energy surface was carried out with the aim of locating transition states for the one-step concerted **I** → **III** oxygen transfers. However, we were unable to find TSs that would allow the rejection of the possibility of this route.

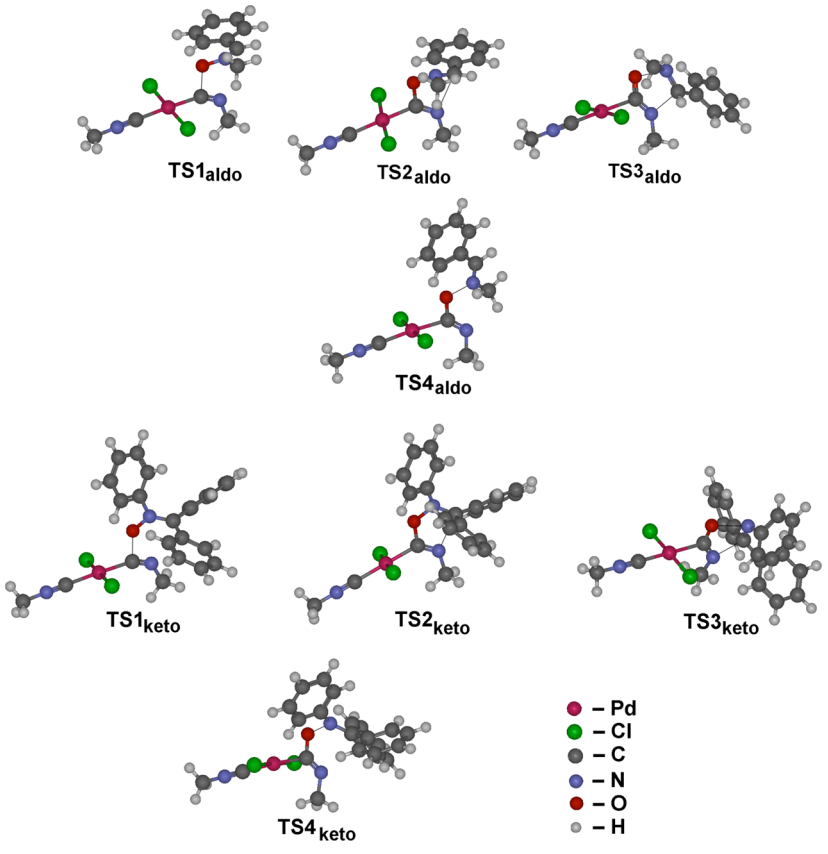

Figure 1. Equilibrium structures of transition states.

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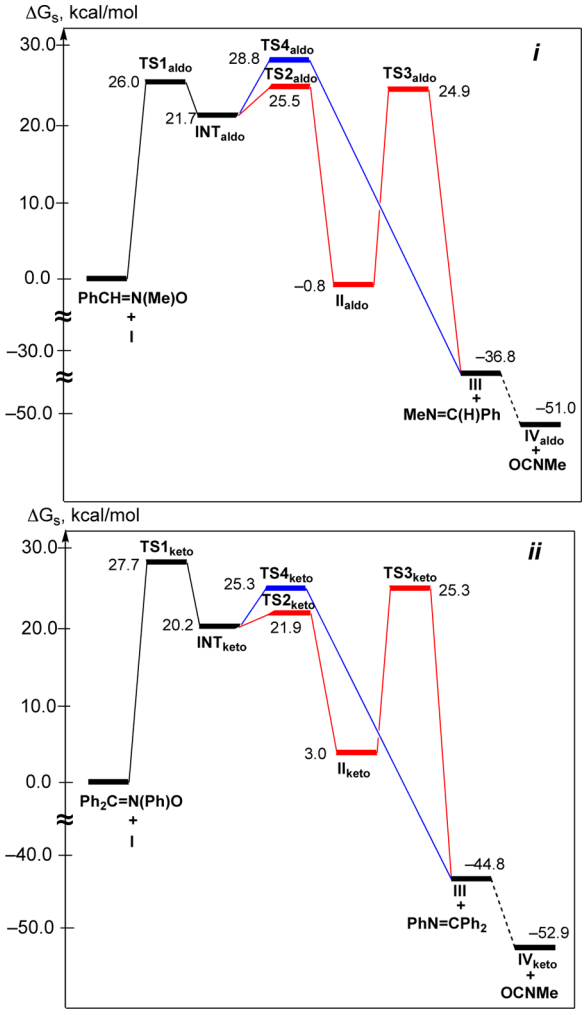

Figure 2. Energy profiles of the reactions of the aldonitrone PhC(H)═N(O)Me (i) and the ketonitrone Ph_2C═N(O)Ph (ii) with complex **I**. Relative energies are indicated in kcal/mol; route A is shown in red and route B in blue.

Characterization of 7–14. Complexes **7–14** were obtained as yellow solids and characterized by elemental analyses (C, H, N), by HRESI$^+$-MS, IR, and ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, and also by X-ray diffraction (for **8**). All palladium species gave satisfactory microanalyses. In the ESI$^+$-MS, the typical ions that were detected were $[M + H]^+$, $[M + Na]^+$, and $[M + K]^+$ with the characteristic isotopic distribution. A comparison of the IR spectra of the products with those of starting **1–4** indicated intense ν(C═N) vibrations in the range between 1630 and 1639 cm^{-1} along with ν(C≡N) bands at ca. 2240 cm^{-1}.

In the ^{1}H NMR spectra of **7–14**, signal integrations give evidence that the reaction between any of the *cis*-$[PdCl_2(CNR)_2]$ complexes and any of the ketonitrones proceeds in a 1:1 ratio. Both ^{1}H and ^{13}C{^{1}H} NMR spectra of **7–14** exhibit signals from the imine and the isocyanide ligands; the resonances of the isocyanide ligands are shifted slightly to low field in comparison to those in starting **1–4**. In the ^{13}C{^{1}H} NMR spectra, peaks from the imine C atom (163.0–165.3 ppm) were recognized.

Complex **8** was characterized by a single-crystal X-ray diffraction study (Figure 3). In **8**, the chlorides are mutually trans (Cl1–Pd–Cl2 = 175.30(3)°) and the C1 atom of the isocyanide and the N2 atom of the imine ligand complete a slightly distorted

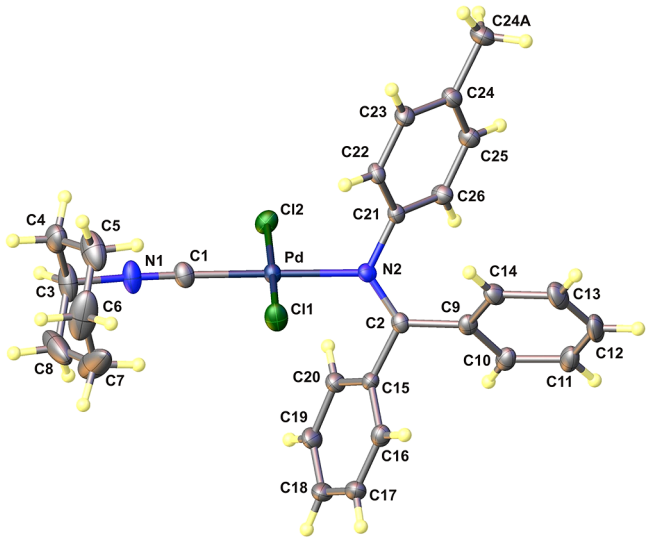

Figure 3. Molecular structure of **8** with the atomic numbering scheme. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (deg): Pd–C(1) = 1.922(4), Pd–N(2) = 2.053(3), Pd–Cl(1) = 2.3003(9), Pd–Cl(2) = 2.3052(9), C(1)–N(1) = 1.147(5), N(1)–C(3) = 1.465(5), N(2)–C(2) = 1.302(4), N(2)–C(21) = 1.434(4); C(1)–Pd–N(2) = 176.64(13), C(1)–Pd–Cl(1) = 86.98(11), N(2)–Pd–Cl(1) = 89.82(7), Cl(1)–Pd–Cl(2) = 175.30(3), C(2)–N(2)–C(21) = 120.3(3), C(2)–N(2)–Pd = 123.2(2), C(21)–N(2)–Pd = 116.41(19), N(1)–C(1)–Pd = 175.6(3), C(1)–N(1)–C(3) = 170.7(4).

square planar environment around the metal center. The C═N bond length (N2–C2 = 1.302(4) Å) is in the range that is typical of double-bond values and agrees with that reported for the related complex $[PdCl_2\{N(Me)$═$C(H)C_6H_4Me\text{-}4\}(CNC_6H_4OMe\text{-}4)]$.[15] In the isocyanide moiety, the C≡N triple-bond length (C1–N1 = 1.147(5) Å) is equal, within 3σ, to those in *cis*-$[PdCl_2(CNR)_2]$ (R = Cy, 1.128–1.142 Å; R = 2,6-$Me_2C_6H_3$, 1.128–1.142 Å; R = *t*Bu, 1.108–1.149 Å).[20]

Application of 7–14 as Catalysts for Sonogashira Coupling. The Sonogashira reaction has been proven to be a very powerful method for carbon–carbon bond formation. It has been widely employed in fine chemical synthesis: in particular, in medicinal chemistry and natural product preparation.[21−25] The conventional protocol for Sonogashira cross-coupling runs under anaerobic conditions and requires a homogeneous palladium catalyst and copper(I) cocatalyst.[26] However, the latter can lead to undesired side reactions (e.g., oxidative homocoupling of the terminal acetylene to give a diyne) and to a drop in the selectivity of the main cross-coupling process.

Numerous modifications to the Sonogashira reaction,[27−31] aiming at increasing the selectivity of the process, have been reported to date. Despite the success of some systems, the vast majority of them still require anaerobic conditions, high catalyst loadings (up to 5 mol %), and long reaction times (up to 24 h), hence the search for new alternative, more efficient systems for Sonogashira coupling.

In this work, we evaluated the catalytic activity of **7–14** in Cu-/phosphine-free Sonogashira reactions. For this study we addressed the reaction of 4-methoxyiodobenzene (4-iodoanisole) with phenylacetylene, affording 1-methoxy-4-(phenylethynyl)-benzene, a typical model reaction for studying Sonogashira coupling.

We conducted the preliminary optimizations of the catalytic system and found that the most appropriate are the conditions described previously by some of us for palladium–aminocarbene

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Table 3. Catalytic Properties of 7−14 in the Model Sonogashira System

	1×10^{-8} mol of catalyst				1×10^{-9} mol of catalyst			
catalyst	entry	yield, %	TON	TOF, min^{-1}	entry	yield, %	TON	TOF, min^{-1}
7	1	94	9400	157	9	14	14000	233
8	2	92	9200	153	10	14	14000	233
9	3	94	9400	157	11	13	13000	217
10	4	93	9300	155	12	12	12000	200
11	5	90	9000	150	13	12	12000	200
12	6	95	9500	158	14	12	12000	200
13	7	92	9200	153	15	15	15000	250
14	8	93	9300	155	16	12	12000	200

complexes: viz., nondistilled ethanol as a solvent, potassium carbonate as a base, in air. The reaction proceeds in refluxing EtOH, and full conversion of the starting materials is achieved within 1 h. The obtained results are summarized in Table 3.

With 1×10^{-8} mol of **7**−**14** as catalysts, the yields of the target product were nearly quantitative (90−95%, entries 1−8 of Table 3). Decreasing the concentration of any of **7**−**14** to 10^{-9} resulted in a drop in the yield of the cross-coupling system to 12−15% (entries 9−16 of Table 3). In contrast to the iodides, when aryl bromides and chlorides were used as the substrates, the yields of the cross-coupling product were less that 20% (for chlorides) or 44% (for bromides) under any of the attempted conditions (temperature 80−110 °C, time 1−48 h, catalyst loading 10^{-8}−10^{-5} mol, bases Cs_2CO_3, Et_3N, and *t*-BuOK, cocatalysts CuI and PPh_3).

In conclusion, all imine−isocyanide palladium(II) complexes **7**−**14** exhibit high catalytic activity in the model cross-coupling system. The yields of the cross-coupling product were up to 95%, with TONs up to 15000 and TOFs up to 250 min^{-1}. These results are among the best reported so far[32b,33] in the field of Cu-/phosphine-free Sonogashira coupling. To the best of our knowledge, the most efficient Cu-/phosphine-free systems that provide ca. 90% yields of the coupling products are based on palladium complexes, and they are characterized by TONs that range from 8600 to 9950.[32b,33]

Final Remarks. The results obtained in this work could be considered from a few perspectives. First, we found that the isocyanide ligands in their palladium(II) complexes undergo rapid and selective metal-mediated nucleophilic oxygenation by ketonitrones. The interaction of palladium(II)-bound isocyanides with *ketonitrones* proceeds as at least overall nucleophilic oxygenation of RNC ligands independent of the molar ratio of reactants and the solvent employed, while the interactions of Pd^{II}-bound isocyanides with *aldonitrones* provide cycloadducts, which only after upon heating convert to corresponding imine−isocyanide complexes. The theoretical calculations indicate that, in the case of aldonitrones, formation of the imine complexes occurs preferably via a CA/splitting pathway, including the generation of a cycloadduct, while in the case of ketonitrones both the CA/splitting route and the direct oxygen atom transfer pathway are equally plausible from a kinetic viewpoint. In addition, the cycloadduct derived from CA of the ketonitrone is less stable and more easily splits into the imine and the isocyanate, in comparison with the cycloadduct derived from the aldonitrone. These features allow the explanation of the experimentally observed difference in the behavior of keto- and aldonitrones toward the metal-bound isocyanides.

Second, the obtained imine−isocyanide complexes **7**−**14** were found to be unexpectedly stable and were isolated in an analytically pure form, in contrast to similar species derived from aldonitrones, which were unstable and were characterized only in $CDCl_3$ solutions by HRESI-MS and ^1H NMR spectroscopy.

Third, complexes **7**−**14** were tested as catalysts in copper-/phosphine-free Sonogashira reactions and demonstrated high catalytic activity in the model coupling of 4-methoxyiodobenzene (4-iodoanisole) with phenylacetylene (yields 90−95%, TONs up to 15000, and TOFs up to 250 min^{-1}), and these results are among the best so far reported in the field of Cu-/phosphine-free Sonogashira coupling. As a continuation of this work, we intend to enhance the range of nucleophilic oxygen donors, which could convert isocyanide ligands in their palladium(II) complexes into isocyanate followed by substitution of RNCO by other ligands; this project is underway in our group.

EXPERIMENTAL SECTION

Materials and Instrumentation. Solvents, $PdCl_2$, and all isocyanides were obtained from commercial sources and used as received, with the exception of benzene and chloroform, which were purified by conventional distillation over sodium/benzophenone and calcium chloride, respectively. Complexes **1**−**4** were prepared as previously reported.[34] Ketonitrones **5** and **6** were obtained according to the previously described protocol by the reaction of aryl nitroso compounds with diphenyldiazomethane in diethyl ether at room temperature (60−85%).[35] C, H, and N elemental analyses were carried out by the Department of Organic Chemistry of Saint Petersburg State University on a Hewlett-Packard 185B Carbon Hydrogen Nitrogen Analyzer. Electrospray ionization mass spectra were obtained on a Bruker micrOTOF spectrometer equipped with an electrospray ionization (ESI) source. The instrument was operated in both positive and negative ion modes 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 ±(70−150) V. For ESI species were dissolved in MeCN; $NaBF_4$ or formic acid was used as an additional ionization agent. In the isotopic pattern, the most intense peak is reported. TLC was performed on Merck 60 F_{254} SiO_2 plates. Infrared spectra (4000−400 cm^{-1}) were recorded on a Shimadzu FTIR-8400S instrument as KBr pellets. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker Avance II+ 400 MHz (UltraShield Magnet) and Avance II+ 500 MHz (UltraShield Plus Magnet) spectrometers at ambient temperature in CD_2Cl_2.

X-ray Diffraction Study. Crystals of **8** suitable for an X-ray study were obtained by slow evaporation of a CH_2Cl_2 solution at room temperature. For the single-crystal X-ray diffraction experiment, a crystal of **8** was fixed on a micro mount, placed in a Bruker Kappa APEX II DUO diffractometer, and measured at 100 K using monochromated microfocused Mo Kα radiation. The unit cell parameters (Table S1; see the Supporting Information) were refined by least-squares techniques using 24619 reflections in the 2θ range of 3.28−70.16°. The structure was solved by direct methods and refined to R1 = 0.052 (wR2 = 0.122) for 8558 unique reflections with $|F_o| \geq 4\sigma_F$ by means of the SHELXL-97 program[36] incorporated in the OLEX2 program package.[37] Positions of H atoms were modeled using the

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"riding" model. Absorbance correction was applied using the SADABS program.[38] Positions of H atoms were modeled using the "riding" model, except for OH, where the H atoms were localized objectively and kept fixed during refinement. Supplementary crystallographic data for this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC 921202) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Computational Details. A full geometry optimization of all structures and transition states (TS) has been carried out at the DFT/HF hybrid level of theory using Becke's three-parameter hybrid exchange functional in combination with the gradient-corrected correlation functional of Lee, Yang, and Parr (B3LYP)[39] with the help of the Gaussian-03 program package. No symmetry operations were applied. The geometry optimization was carried out using a quasi-relativistic Stuttgart pseudopotential that described 60 core electrons and the appropriate contracted basis set[40] for the palladium atoms and the 6-31G(d) basis set for other atoms. Then, single-point calculations were performed on the basis of the equilibrium geometries found using the 6-311+G(d,p) basis set for nonmetal atoms. As was shown by some of us previously,[19a−e] this approach is sufficiently accurate for the description of the nucleophilic additions and cycloadditions to the C≡N bond, providing results close to those obtained by such methods as MP2, MP4, CCSD(T), CBS-Q, and G3B3.

The Hessian matrix was calculated analytically for the optimized structures in order to prove the location of correct minima (no imaginary frequencies) or saddle points (only one imaginary frequency) and to estimate the thermodynamic parameters, the latter being calculated at 25 °C. The nature of all transition states was investigated by the analysis of vectors associated with the imaginary frequency and by the calculations of the intrinsic reaction coordinates (IRC) using the Gonzalez−Schlegel method.[41] Sometimes, the IRC calculations failed due to the low imaginary frequency of a transition state. In these cases, the analysis of the TS nature was performed in accord with the following procedure. First, the atoms of TS were shifted from the equilibrium positions along the vectors corresponding to the imaginary frequency, in both directions. Then, geometry optimization with small size of an optimization step was carried out.

Solvent effects (δE_s) were taken into account in the single-point calculations on the basis of gas-phase geometries at the CPCM-B3LYP/6-311+G(d,p)//gas-B3LYP/6-31G(d) level of theory using the polarizable continuum model in the CPCM version[42] with CH_2Cl_2 as solvent. The UAKS model was applied for the molecular cavity. The entropic term in solution (S_s) was calculated according to the procedure described by Wertz[43] and Cooper and Ziegler[44] using eqs 1−4,

$$\Delta S_1 = R \ln V^{s}_{m,liq}/V_{m,gas} \quad (1)$$

$$\Delta S_2 = R \ln V^{\circ}_{m}/V^{s}_{m,liq} \quad (2)$$

$$\alpha = \frac{S^{os}_{liq} - (S^{os}_{gas} + R \ln V^{s}_{m,liq}/V_{m,gas})}{(S^{os}_{gas} + R \ln V^{s}_{m,liq}/V_{m,gas})} \quad (3)$$

$$\begin{aligned} S_s &= S_g + \Delta S_{sol} \\ &= S_g + [\Delta S_1 + \alpha(S_g + \Delta S_1) + \Delta S_2] \\ &= S_g + [(-11.80 \text{ cal/(mol K)}) - 0.21(S_g - 11.80 \text{ cal/(mol K)}) \\ &\quad + 5.45 \text{ cal/(mol K)}] \end{aligned} \quad (4)$$

where S_g is the gas-phase entropy of the solute, ΔS_{sol} is the solvation entropy, S^{os}_{liq}, S^{os}_{gas}, and $V^{s}_{m,liq}$ are the standard entropies and molar volume of the solvent in liquid and gas phases, respectively (173.84 and 270.28 J/(mol K) and 64.15 mL/mol, respectively, for CH_2Cl_2), $V_{m,gas}$ is the molar volume of the ideal gas at 25 °C (24450 mL/mol), and V°_{m} is the molar volume of the solution corresponding to the standard conditions (1000 mL/mol). The enthalpies and Gibbs free energies in solution (H_s and G_s) were estimated using eqs 5 and 6,

$$\begin{aligned} H_s &= E_s(\text{6-311+G(d, p)}) - E_g(\text{6-311+G(d, p)}) \\ &\quad + H_g(\text{6-31G(d)}) \end{aligned} \quad (5)$$

$$G_s = H_s - TS_s \quad (6)$$

where E_s, E_g, and H_g are the total energies in solution and in the gas phase and the gas-phase enthalpy calculated at the corresponding level, respectively.

Synthetic Work. *Synthesis of Imine−Isocyanide Complexes 7−14 (General Procedure).* A solution of any of **1**−**4** (0.1 mmol) in CH_2Cl_2 (1 mL) was added at ca. 5 °C to a solution of ketonitrone **5** or **6** (0.1 mmol) in $CHCl_3$ (1 mL). The system was kept at this temperature for approximately 4 h, whereupon it was gradually heated to 20−25 °C (ca. 15 min) and stirred at room temperature for 5 h. The yellow solution that formed was evaporated under vacuum at room temperature, and the oily residue obtained was extracted with Et_2O (three 3 mL portions). The solvent was evaporated under vacuum at 20−25 °C to give yellow powders of **7**−**14**, which were dried in air at room temperature.

7 (54 mg, 94%). Anal. Found: C, 60.03; H, 4.56; N, 4.85. Calcd for $C_{29}H_{26}N_2Cl_2Pd$: C, 60.07; H, 4.52; N, 4.83. High-resolution ESI$^+$: m/z 601.0403 ([M + Na]$^+$ requires 601.0406); R_f = 0.37 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2933 m (C−H), 2247 m (C≡N), 1630 s (N═C). δ_H (400.130 MHz, CD_2Cl_2): 2.30 (3H, s, CH_3 from *p*-tol), 2.43 (6H, s, CH_3 from Xyl) 7.11−8.25 (17H, 5 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 16.2 (CH_3 from *p*-tol), 21.3 (CH_3 from Xyl), 127.2−140.2 ($C_{aromatic}$), 165.0 (C═N); the C≡N carbon was not detected. Complex **7** has no specific melting point. On heating it gradually decomposes starting from 155 °C to furnish a dark brown residue.

8 (51 mg, 92%). Anal. Found: C, 58.10; H, 5.02; N, 5.02. Calcd for $C_{27}H_{28}N_2Cl_2Pd$: C, 58.13; H, 5.06; N, 5.05. High-resolution ESI$^+$: m/z 557.0744 ([M + H]$^+$ requires 557.0743). R_f = 0.41 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2939 m (C−H), 2244 m (C≡N), 1633 s (N═C). δ_H (400.130 MHz, CD_2Cl_2): 1.14−1.80 (10H, m, CH_2 from Cy), 2.31 (3H, s, CH_3 from *p*-tol), 3.93 (1H, br m, CH from Cy), 7.13−8.28 (14H, 4 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 20.4 (CH_3 from *p*-tol), 24.4, 31.3, and 34.0 (CH_2 from Cy), 127.7−140.0 ($C_{aromatic}$), 163.0 (C═N); the C≡N carbon was not detected. Complex **8** has no specific melting point. On heating it gradually decomposes starting from 148 °C to furnish a dark brown residue.

9 (48 mg, 90%). Anal. Found: C, 56.50; H, 4.91; N, 5.25. Calcd for $C_{25}H_{26}N_2Cl_2Pd$: C, 56.46; H, 4.93; N, 5.27. High-resolution ESI$^+$: m/z 553.0408 ([M + Na]$^+$ requires 553.0406). R_f = 0.36 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2933 m (C−H), 2244 m (C≡N), 1639 s (N═C). δ_H (400.130 MHz, CD_2Cl_2): 1.44 (9H, s, CH_3 from *t*Bu), 2.31 (3H, s, CH_3 from *p*-tol), 7.15−8.28 (14H, 5 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 16.2 (CH_3 from *p*-tol), 31.3 and 30.4 (C from *t*Bu), 127.5−140.0 ($C_{aromatic}$), 164.0 (C═N); the C≡N carbon was not detected. Complex **9** has no specific melting point. On heating it gradually decomposes starting from 153 °C to furnish a dark brown residue.

10 (54 mg, 94%). Anal. Found: C 56.06; H, 3.84; N, 4.66. Calcd for $C_{28}H_{23}N_2Cl_3Pd$: C, 56.02; H, 3.86; N, 4.67. High-resolution ESI$^+$: m/z 620.9855 ([M + Na]$^+$ requires 620.9859). R_f = 0.33 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2929 m (C−H), 2244 m (C≡N), 1637 s (N═C). δ_H (100.613 MHz, CD_2Cl_2): 2.31 (3H, s, CH_3 from *p*-tol), 2.52 (3H, s, CH_3 from $C_6H_3(Cl)CH_3$) 7.10−8.22 (17H, 5 m, $H_{aromatic}$). δ_C (75.5 MHz, CD_2Cl_2): 18.2 (CH_3 from *p*-tol), 22.6 (CH_3 from $C_6H_3(Cl)CH_3$), 127.2−140.8 ($C_{aromatic}$), 165.1 (C═N); the C≡N carbon was not detected. Complex **10** has no specific melting point. On heating it gradually decomposes starting from 155 °C to furnish a dark brown residue.

11 (56 mg, 93%). Anal. Found: C, 56.03; H, 3.90; N, 4.66. Calcd for $C_{25}H_{23}N_2Cl_3Pd$: C, 56.02; H, 3.86; N, 4.67. High-resolution ESI$^+$: m/z 584.9862 ([M + Na]$^+$ requires 584.9859). R_f = 0.35 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2932 m (C−H), 2243 m

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(C≡N), 1636 s (N=C). δ_H (400.130 MHz, CD_2Cl_2): 2.43 (6H, s, CH_3 from Xyl) 7.14−8.31 (17H, 5 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 21.4 (CH_3 from Xyl), 128.0−141.3 ($C_{aromatic}$), 165.2 (C=N); the C≡N carbon was not detected. Complex **11** has no specific melting point. On heating it gradually decomposes starting from 155 °C to furnish a dark brown residue.

12 (52 mg, 90%). Anal. Found: C, 54.02; H, 4.39; N, 4.88. Calcd for $C_{26}H_{25}N_2Cl_3Pd$: C, 54.00; H, 4.36; N, 4.84. High-resolution ESI$^+$: m/z 559.0012 ($[M + Na]^+$ requires 559.0016). R_f = 0.39 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2933 m (C−H), 2241 m (C≡N), 1635 s (N=C). δ_H (400.130 MHz, CD_2Cl_2): 1.14−1.81 (10H, m, CH_2 from Cy), 3.93 (1H, br m, CH from Cy), 7.15−8.32 (14H, 4 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 24.4, 31.3, and 34.1 (CH_2 from Cy), 127.5−142.3 ($C_{aromatic}$), 164.5 (C=N); the C≡N carbon was not detected. Complex **12** has no specific melting point. On heating it gradually decomposes starting from 141 °C to furnish a dark brown residue.

13 (48 mg, 93%). Anal. Found: C, 52.17; H, 4.19; N, 5.05. Calcd for $C_{24}H_{23}N_2Cl_3Pd$: C, 52.20; H, 4.20; N, 5.07. High-resolution ESI$^+$: m/z 551.0044 ($[M + H]^+$ requires 551.0040). R_f = 0.38 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2931 m (C−H), 2244 m (C≡N), 1633 s (N=C). δ_H (400.130 MHz, CD_2Cl_2): 1.43 (9H, CH_3 from *t*Bu), 7.19−8.32 (14H, 5 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 31.3 and 30.4 (C from *t*Bu), 127.3−142.5 ($C_{aromatic}$), 164.7 (C=N); the C≡N carbon was not detected. Complex **13** has no specific melting point. On heating it gradually decomposes starting from 150 °C to furnish a dark brown residue.

14 (59 mg, 90%). Anal. Found: C, 52.28; H, 3.28; N, 4.52. Calcd for $C_{27}H_{20}N_2Cl_4Pd$: C, 52.25; H, 3.25; N, 4.51. High-resolution ESI$^+$: m/z 642.9285 ($[M + Na]^+$ requires 642.9284). R_f = 0.37 (eluent $CHCl_3$/*n*-hexane, 5/1, v/v). ν_{max}(KBr)/cm^{-1}: 2921 m (C−H), 2238 m (C≡N), 1633 s (N=C). δ_H (400.130 MHz, CD_2Cl_2): 2.54 (3H, s, CH_3 from $C_6H_3(Cl)CH_3$), 7.14−8.24 (17H, 5 m, $H_{aromatic}$). δ_C (100.613 MHz, CD_2Cl_2): 18.0 (CH_3 from *p*-tol), 22.6 (CH_3 from $C_6H_3(Cl)$-CH_3), 127.4−142.2 ($C_{aromatic}$), 165.2 (C=N); the C≡N carbon was not detected. Complex **14** has no specific melting point. On heating it gradually decomposes starting from 155 °C to furnish a dark brown residue.

Catalytic Studies: General Procedure for the Catalytic Sonogashira Cross-Coupling. A 10 mL vial was charged with potassium carbonate (2.5×10^{-4} mol, 2.5 equiv), the aryl iodide (1.0×10^{-4} mol, 1.0 equiv), phenylacetylene (1.5×10^{-4} mol, 1.5 equiv), and a solution of the catalyst (1×10^{-8} mol) in EtOH (1 mL) and equipped with a Teflon-coated magnetic bar. The vial was closed with a septum and an aluminum crimp seal and kept in the oil bath at 80 °C for 1 h with vigorous stirring. After it was cooled to room temperature, the reaction mixture was evaporated to dryness under a stream of dinitrogen and 1,2-dimethoxyethane (1 equiv; used as a NMR internal standard) was added. The content of the vial was extracted with three 0.20 mL portions of $CDCl_3$; all fractions were combined and analyzed by ^{1}H NMR spectroscopy. The product peak assignments were based on the published data,[45] while quantifications were performed upon integration of the selected peaks of the product with those of the standard.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables and a CIF file giving crystallographic data for **8** and additional computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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