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Highly Convenient Amine-Free Sonogashira Coupling in Air in a Polar Mixed Aqueous Medium by *trans*- and *cis*-[$(NHC)_2PdX_2$] (X = Cl, Br) Complexes of *N*/*O*-Functionalized N-Heterocyclic Carbenes

Lipika Ray,[a] Samir Barman,[a] Mobin M. Shaikh,[b] and Prasenjit Ghosh*[a]

Abstract: Two new *trans*- and *cis*-[$(NHC)_2PdX_2$] (X = Cl, Br) complexes of *N*/*O*-functionalized N-heterocyclic carbenes employed in a highly convenient amine-free Sonogashira cross-coupling reaction in air in a polar mixed aqueous medium are reported. Specifically, the *trans*-[{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}$_2$PdBr$_2$] (**3**) and *cis*-[{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}$_2$PdCl$_2$] (**4**) complexes effectively catalyzed the Sonogashira cross-coupling reaction of aryl iodides with substituted acetylenes in air in a mixed solvent (DMF/H_2O, 3:1 v/v) under amine-free conditions. Interestingly, these *trans*- and *cis*-[$(NHC)_2PdX_2$] (X = Cl, Br) complexes, with two N-heterocyclic carbene ligands, exhibited superior activity compared with the now popular PEPPSI (pyridine enhanced precatalyst preparation, stabilization and initiation)-themed analogues, *trans*-[(NHC)Pd(pyridine)X_2] (X = Cl, Br), **3a** and **4a**, with one N-heterocyclic carbene ligand and a "throw away" pyridine ligand in a *trans* disposition to each other. The higher activities of **3** and **4** compared with PEPPSI analogues **3a** and **4a** are attributed to more-electron-rich metal centers, as revealed by DFT studies, in the former complexes and is in concurrence with a more electron-rich metal center being effective in facilitating the oxidative addition of aryl halide, often a rate-determining step in palladium-mediated cross-coupling reactions. Complexes **3** and **4** were prepared from the corresponding silver analogues by transmetalation with [(cod)$PdCl_2$], whereas the corresponding PEPPSI analogues **3a** and **4a** were obtained directly from the imidazolium halide salts by reaction with $PdCl_2$ in pyridine in the presence of K_2CO_3 as base.

Keywords: carbenes · cross-coupling · heterocycles · palladium · Sonogashira reaction

Introduction

The Sonogashira cross-coupling reaction provides an all important answer to the direct alkynation of aryl and alkenyl halides[1] and, not surprisingly, it has been effectively utilized over the years to construct conjugated enyne and arylalkyne frameworks in, for example, natural products,[2,3] pharmaceuticals,[4] biologically active molecules,[5] and molecular electronics.[6] The very popular Sonogashira cross-coupling reaction is catalyzed by palladium in a basic medium in the presence of copper as a co-catalyst. A copper–acetylide species is generated in situ, which transfers the acetylide moiety on to the palladium center for the desired sp^2–sp coupling by a reductive elimination pathway.[7] Note, despite its critical role in catalysis, upon exposure to air or any oxidizing agents the copper–acetylide species also yields an unwanted homocoupled side-product by the so-called Glaser coupling reaction,[8] thereby seriously undermining the cross-coupling reaction. The extremely high reactivity and the explosive nature of the copper–acetylide species makes the Sonogashira reaction sensitive to air and moisture.[7,8] Consequently, a formidable challenge in this area lies in broadening the scope of the reaction by designing suitable catalysts that enable the reaction to be carried out under mild conditions without the need for any additional stringent measures, such as the exclusion of air and moisture. In this regard it is worth mentioning that a report of the Sonogashira cross-

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Supporting information for this article is available on the WWW under http://www.chemeurj.org or from the author. It contains the CIF file with crystallographic data for **3** and **4** and the B3LYP coordinates of the optimized geometries of **3**, **3a**, **4**, and **4a**.

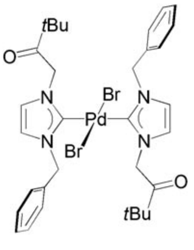
coupling reaction in air and in water has appeared only recently.[9] The other approach towards circumventing the difficulties associated with this reaction had been to develop a copper-free Sonogashira[10] cross-coupling reaction that focuses on enhancing the reactivity of the catalytic system so as to make the presence of copper unnecessary. However, this strategy was of limited success because these copper-free methods often involve the use of excess amines (even as solvents), which is not deemed to be environmentally friendly, and so the ultimate goal lies in developing a copper- and amine-free Sonogashira coupling reaction.[11]

Our objective was to advance the chemistry of nonfunctionalized and *N*/*O*-functionalized N-heterocyclic carbenes[12,13] for their use in biomedical applications[14] and in chemical catalysis.[15,16] Of special interest to us are palladium-mediated cross-coupling reactions, and in this regard we recently reported a highly efficient palladium precatalyst[17] that exhibits ultrahigh turnover numbers and also a series of convenient-to-handle air-stable PEPPSI (pyridine-enhanced precatalyst preparation, stabilization and initiation)-themed precatalysts[18] for the Suzuki–Miyaura cross-coupling reaction. During the design of these catalysts for cross-coupling reactions, we became particularly interested in knowing which of the two types of complexes, that is, the $[(NHC)_2PdX_2]$ (X = Cl, Br) complexes with two NHC ligands or the newly popular PEPPSI-themed *trans*-$[(NHC)Pd(pyridine)X_2]$ (X = Cl, Br) complexes[19] with one NHC ligand, would make a better catalyst? We rationalized that the NHCs, which are extremely good σ-donating ligands,[12,13,16b,18,20] would make the metal center in $[(NHC)_2PdX_2]$ more electron-rich, thereby assisting the aryl halide oxidative addition step compared with the corresponding PEPPSI analogues. Our other objective was to design highly efficient and robust catalysts that would be air-, moisture-, and functional-group-tolerant, which would facilitate cross-coupling reactions under ambient aerobic conditions.

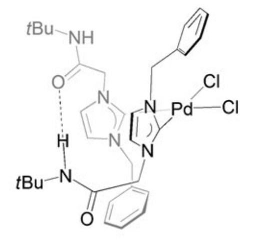
Herein we report two new *trans*- and *cis*-$[(NHC)_2PdX_2]$ (X = Cl, Br) complexes of *N*/*O*-functionalized N-heterocyclic carbenes, namely, *trans*-[{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}$_2$PdBr$_2$] (**3**) and *cis*-[{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}$_2$PdCl$_2$] (**4**), for highly convenient Sonogashira coupling of aryl iodides with substituted acetylenes in air in a mixed solvent (DMF/H_2O, 3:1 v/v) under amine-free conditions. More interestingly, complexes **3** and **4** were found to exhibit superior activity compared with the corresponding PEPPSI counterparts **3a** and **4a**, which implies that a more electron-rich metal center yields a better catalyst.

Results and Discussion

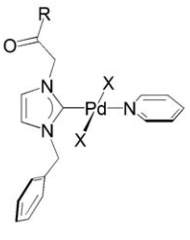
Despite being phenomenally successful in the catalysis of many important transformations,[21–23] the application of N-heterocyclic carbenes in Sonogashira cross-coupling reactions has remained surprisingly unexplored.[24,25] With our aim being to explore the utility of N-heterocyclic carbenes in palladium-mediated cross-coupling reactions, we became interested in designing N-heterocyclic carbene based precatalysts for Sonogashira coupling reactions. In particular, we were looking to develop highly efficient and robust catalysts that were tolerant to air, moisture, and various functional groups so as to allow Sonogashira cross-coupling reactions in mild aerobic conditions. With regards to the design of NHC-based catalysts for the cross-coupling reaction, we also wanted to know whether the more electron-rich $[(NHC)_2PdX_2]$ (X = Cl, Br)-type complexes with two NHC ligands would make better catalysts than the newly popular PEPPSI-themed *trans*-$[(NHC)Pd(pyridine)X_2]$ (X = Cl, Br)-type complexes containing one NHC ligand, and hence, to address this issue we set out to synthesize both these types of complexes to perform a comparative study.



3 (*trans*)

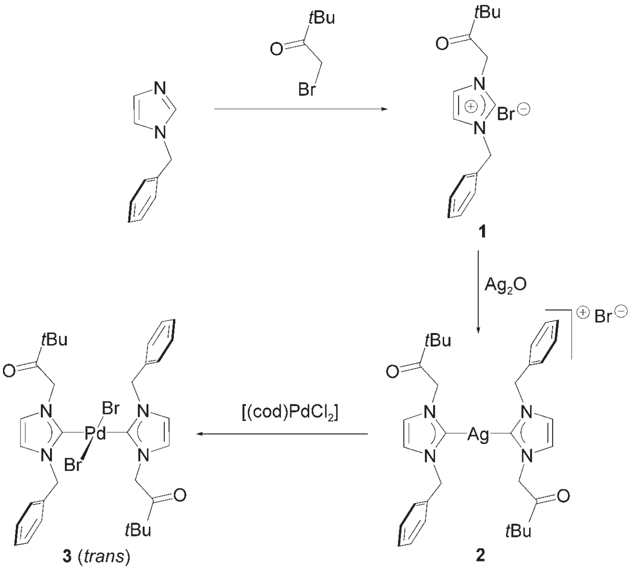


4 (*cis*)

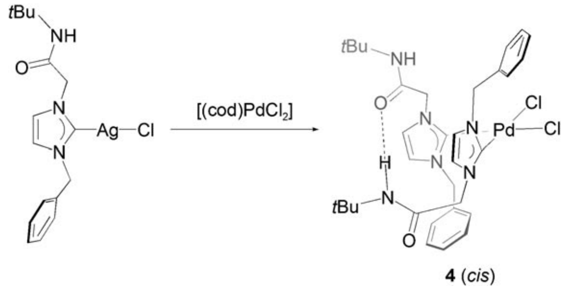


3a [R = *t*Bu, X = Br]
4a [R = -NH(*t*Bu), X = Cl]

The two new *trans*- and *cis*-$[(NHC)_2PdX_2]$ (X = Cl, Br) complexes **3** (Scheme 1) and **4** (Scheme 2) were synthesized from the corresponding silver complexes by a transmetalation reaction with $[(cod)PdCl_2]$ in yields of 80–87 %, whereas the corresponding PEPPSI analogues **3a** and **4a**[18] were synthesized directly from the corresponding imidazolium

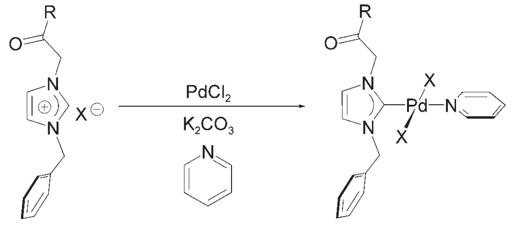


Scheme 1.



4 (*cis*)

Scheme 2.



3a [R = *t*Bu, X = Br]
4a [R = -NH(*t*Bu), X = Cl]

Scheme 3.

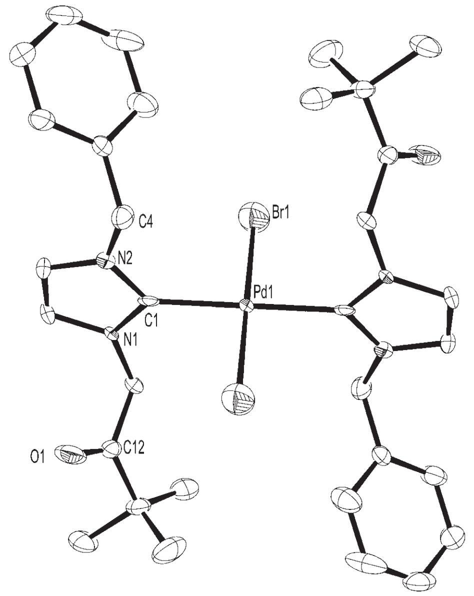


Figure 1. ORTEP drawing of **3** with thermal ellipsoids drawn at the 50% probability level. Selected bond lengths [Å] and angles [°]: N1–C1 1.365(12), N2–C1 1.359(12), Pd1–C1 2.018(9), Pd1–Br1 2.3750(13); C1-Pd1-Br1 90.8(2), C1-Pd1-C1 180.0(7).

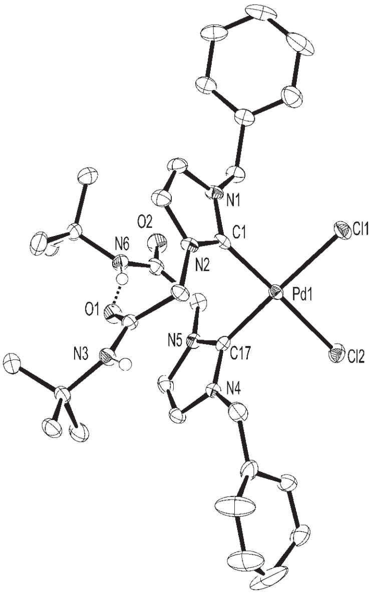


Figure 2. ORTEP drawing of **4** with thermal ellipsoids drawn at the 50% probability level. Selected bond lengths [Å] and angles [°]: N1–C1 1.355(2), N2–C1 1.357(2), N5–C17 1.349(2), N4–C17 1.346(2), Pd1–C17 1.975(2), Pd1–C1 1.998(2), Pd1–Cl1 2.3615(5), Pd1–Cl2 2.3541(5); C17-Pd1-C1 92.50(8), C1-Pd1-Cl1 90.00(6). The phenyl group is disordered and for clarity one set of disordered atoms is not shown.

halide salts (Scheme 3) by reaction with PdCl$_2$ in pyridine in the presence of K$_2$CO$_3$ as base.

Remarkably, two different molecular geometries were obtained for **3** and **4** even though they were synthesized under very similar conditions. Specifically, the molecular structures of these complexes revealed that, whereas **3** (Figure 1) exhibited the expected *trans* geometry around the metal center, a unique hydrogen-bonded *cis* arrangement was observed in the case of **4** (Figure 2). In particular, a hydrogen-bonding interaction was seen between the amido N–H proton of the functionalized side-arm of one NHC ligand and the amido oxygen atom of the functionalized side-arm of the other displaying a close N–H···O contact of 3.061 Å, which is shorter than the sum of the van der Waals radii of nitrogen and oxygen (3.27 Å).[26] Such a *cis* arrangement is a rare consequence of a hydrogen-bonding interaction between the amido-functionalized side-arms of the NHC ligands in **4**, in the absence of which the *trans* geometry would be sterically preferred. The hydrogen-bonding interaction in *cis* complex **4** seriously highlights the rare and interesting structural possibility that emerges as a result of *N*/*O*-functionalization of the *N*-substituted side-arms of the N-heterocyclic carbene ligand. To the best of our knowledge, complex **4** represents the only structurally characterized example of a *cis*-[(NHC)$_2$PdX$_2$] (X = halide)-type complex in which the two NHC ligands are not conjoined by any covalent linker.

Barring the hydrogen-bonding interaction, the other structural aspects of complexes **3** and **4** are similar, including the square-planar metal centers. The metal–carbene (Pd–C$_{carb}$) distance in **3** (2.018(9) Å) is slightly longer than in **4** (1.975(2) and 1.998(2) Å), but compares well with the sum of the individual covalent radii of palladium and carbon (2.055 Å)[27] and also falls well within the range (2.10–1.93 Å) observed in other structurally characterized examples.[28] The two imidazolyl rings in **3** are coplanar, similar to that observed in another related *trans*-(NHC) complex, [{1-(*o*-methoxybenzyl)-3-*tert*-butylimidazol-2-ylidene}$_2$PdCl$_2$].[17] Significantly, complex **3** also represents the only example of a structurally characterized palladium bromide derivative of the type [(NHC)$_2$PdX$_2$] (X = halide).

To obtain a better understanding of the nature of the NHC–Pd interaction in the *trans* and *cis* complexes **3** and **4,** detailed density functional theory (DFT) studies were carried out by computing the geometry-optimized structures of **3** and **4** at the B3LYP/SDD level of theory with the 6-31G(d) basis set using the atomic coordinates determined by X-ray analysis. Subsequently a single-point calculation was performed at the same level of theory for a detailed prediction of the electronic properties of these complexes. Further insights into the carbene–metal bond came from a post-wavefunction analysis using the natural bond orbital (NBO) method,[29] which was performed on these complexes as well as on the corresponding ligands and metal-ion fragments. Specifically, both natural and Mulliken charge analyses revealed that upon binding of the two NHC ligands to the PdX$_2$ (X = Cl, Br) fragment, the metal center in **3** and **4** becomes more electron-rich compared with the free ion and the PdX$_2$ (X = Cl, Br) fragment (see Tables S4–S7, S12, and S13 of the Supporting Information). Consequently, the electron density at the carbene carbon atom in **3** and **4** is lower relative to that of the free NHC ligand upon coordination to the PdX$_2$ (X = Cl, Br) fragment. Comparison of the electronic configurations of the metal centers in **3** and **4** with that of the PdX$_2$ (X = Cl, Br) fragment reveals that electron donation from the free NHC ligand to the unfilled 5s orbital of palladium occurs in these complexes (see Tables S14 and S15 of the Supporting Information).

Further insights into the nature of the NHC–metal interaction were obtained from correlation diagrams depicting the fragment molecular orbital contribution of the free NHC ligand and the PdX$_2$ (X = Cl, Br) fragments to the frontier molecular orbitals (MOs) of complexes **3** and **4**. Of particular interest are the molecular orbitals that represent the NHC–Pd σ interactions, which were found to be low-lying in **3** (HOMO-37) and **4** (HOMO-35 and HOMO-36). Specifically, the NHC–Pd σ-bonding orbital, HOMO-37 (53% NHC, 29% PdBr$_2$), in *trans* complex **3** showed an interaction of the carbene lone-pair (HOMO-1 of the free-NHC fragments) with a metal-based vacant LUMO (75% palladium with 33% s and 40% d character) of the PdBr$_2$ fragment (Figure 3 and Figure S1 of the Supporting Information). The corresponding NHC–Pd σ interactions in *cis* complex **4** consist of two adjacent interactions, HOMO-35 (47% NHC, 38% PdCl$_2$) and HOMO-36 (37% NHC, 38% PdCl$_2$). In HOMO-35, the carbene lone-pairs (HOMO (11%) and HOMO-1 (31%)) of the two free NHC fragments were seen to interact with another metal-based vacant LUMO+1 orbital (92% palladium with 69% s and 18% p character) of the PdCl$_2$ fragment (Figures 4 and 5 and Figure S2 of the Supporting Information). Likewise, the other NHC–Pd σ-bonding orbital, HOMO-36 (37% NHC, 38% PdCl$_2$), showed an interaction of the carbene lone-pairs (HOMO (11%) and HOMO-1 (31%)) of the two free NHC fragments with the vacant LUMO (51% Pd, 49% Cl with 39% d character) of the PdCl$_2$ fragment.

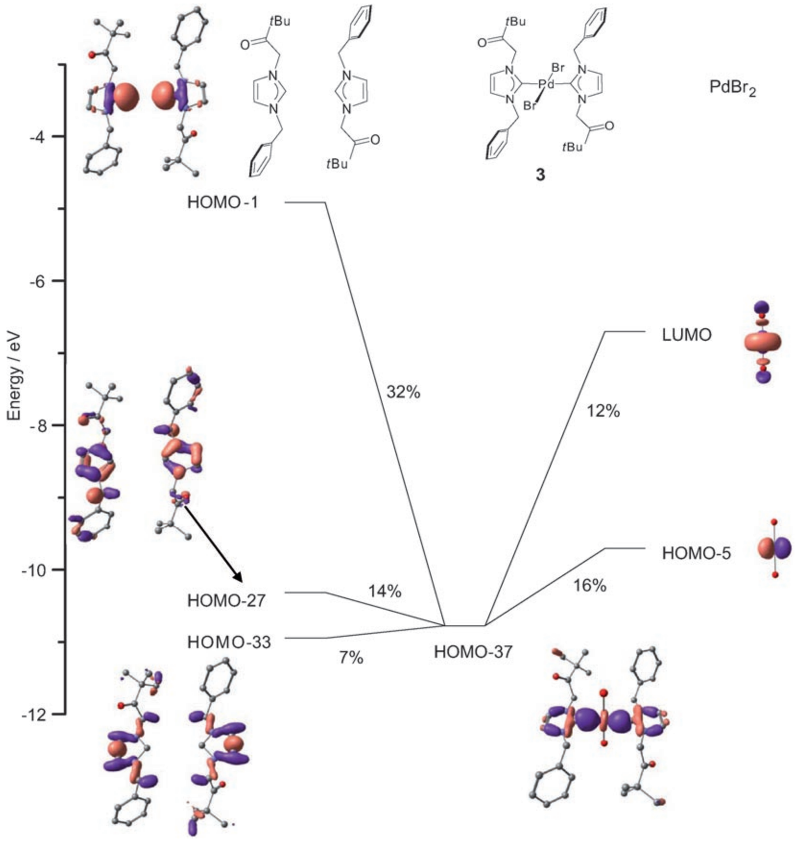


Figure 3. Simplified orbital interaction diagram showing the major contributions of the NHC–palladium bond in **3**.

A charge decomposition analysis (CDA) of **3** and **4** highlighted the relative extent of the [NHC$\xrightarrow{\sigma}$PdX$_2$] forward donation (X = Br, Cl), designated *d*, and the [NHC$\xleftarrow{\pi}$PdX$_2$] backward donation (X = Br, Cl), designated *b*, that occurs in these complexes. The *d*/*b* ratio, a measure of the forward σ donation relative to the backward π donation, for **3** (2.90) and **4** (2.98) suggests the predominance of the σ-bonding interaction in concurrence with the greater σ-donating abilities of the NHC ligands, and the values compare well with those reported for other Pd–NHC complexes, namely, *trans*-[{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}Pd(pyri-

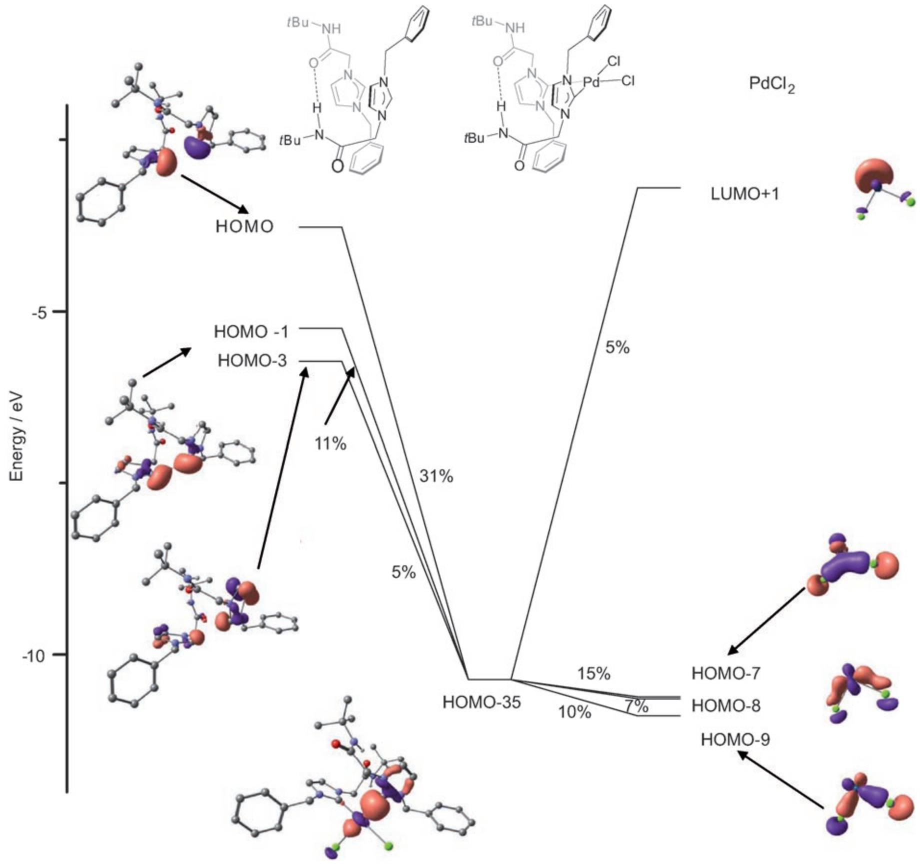


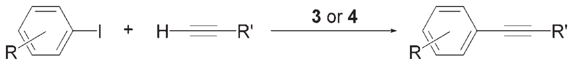
Figure 4. Simplified orbital interaction diagram showing the major contributions of the NHC–Pd σ-bonding orbital HOMO-35 in **4**.

dine)Cl$_2$] (2.59),[18] *trans*-[1-(2-hydroxycyclohexyl)-3-benzylimidazol-2-ylidene]Pd(pyridine)Cl$_2$ (2.79),[18] and *trans*-[1-(*o*-methoxybenzyl)-3-*tert*-butylimidazol-2-ylidene]Pd(pyridine)Br$_2$ (3.99)[18] (see Table S17 of the Supporting Information).

Lastly, the strength of the NHC–Pd interactions in **3** and **4** were computed at the B3LYP/SDD level of theory with the 6-31G(d) basis set and NHC–Pd bond energies (D_e) of 74.8 kcal mol^{-1} in **3** and 75.1 kcal mol^{-1} in **4** are suggestive of a strong interaction comparable to those reported for *trans*-[{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}Pd(pyridine)Cl$_2$] (81.9 kcal mol^{-1}),[18] *trans*-[{1-(2-hydroxycyclohexyl)-3-benzylimidazol-2-ylidene}Pd(pyridine)Cl$_2$] (82.4 kcal mol^{-1}),[18] and *trans*-[{1-(*o*-methoxybenzyl)-3-*tert*-butylimidazol-2-ylidene}Pd(pyridine)Br$_2$] (77.6 kcal mol^{-1}).[18] The stronger NHC–Pd interactions in **3** and **4** imply tighter binding of the ancillary NHC ligand to the metal center, which imparts greater stability to these complexes.

Significantly, both complexes **3** and **4** enabled highly convenient amine-free Sonogashira coupling reactions to take place in ambient aerobic conditions in a polar mixed aqueous medium (Scheme 4 and Tables 1 and 2). Specifically, when substituted terminal acetylenes were treated with aryl iodides in the presence of precatalysts **3** or **4** along with the co-catalyst CuBr, and Cs$_2$CO$_3$ as the base in a mixed DMF/H$_2$O (3:1 v/v) medium in air, Sonogashira cross-coupled products were obtained in high yields. A rapid rate of conversion to products within two hours was observed for most of the substrates, which reflects the high performances of **3** and **4**.

Also remarkable is the robust nature of precatalysts **3** and **4** because the coupling reactions were successfully carried out in air in a polar DMF/H$_2$O (3:1 v/v) mixed medium. Thus, the present catalysis by **3** and **4** under aerobic mixed aqueous conditions marks a significant improvement against the backdrop of the fact that Sonogashira reactions are traditionally air- and moisture-sensitive owing to the formation of a highly reactive copper–acetylide intermediate in the catalytic cycle.[7,8] Another very important feature of **3** and **4** is their high selectivity with regards to the formation of the desired cross-coupled product along with the negligible formation of the homocoupled product (up to 15 % for **3** and 21 % for **4**).



Scheme 4.

Note that the homocoupled products arise from an unwanted side-reaction of the reactive copper–acetylide intermediate by the so-called Glaser coupling reaction upon exposure to trace amounts of air or any oxidizing agent (Tables 1 and 2).[8] Lastly, these coupling reactions were carried out in amine-free conditions with Cs$_2$CO$_3$ as the base instead of the more frequently used amines, which is of considerable importance given the fact that amines are not considered environmentally benign and substantial efforts, at present, are being directed towards the development of amine-free Sonogashira cross-coupling reactions.

Note that the Sonogashira cross-coupling reaction can be extended to heterocyclic terminal alkynes, which has much potential, particularly from a synthetic perspective, because many heterocyclic compounds are known to exhibit important biological properties.[30] Another notable aspect of the two precatalysts **3** and **4** is their selectivity towards the iodo derivative. This is evident from the reactions of the *p*-bromoiodobenzene substrate; Sonogashira coupling was seen to occur at the iodo end and not at the bromo end, which remained intact.

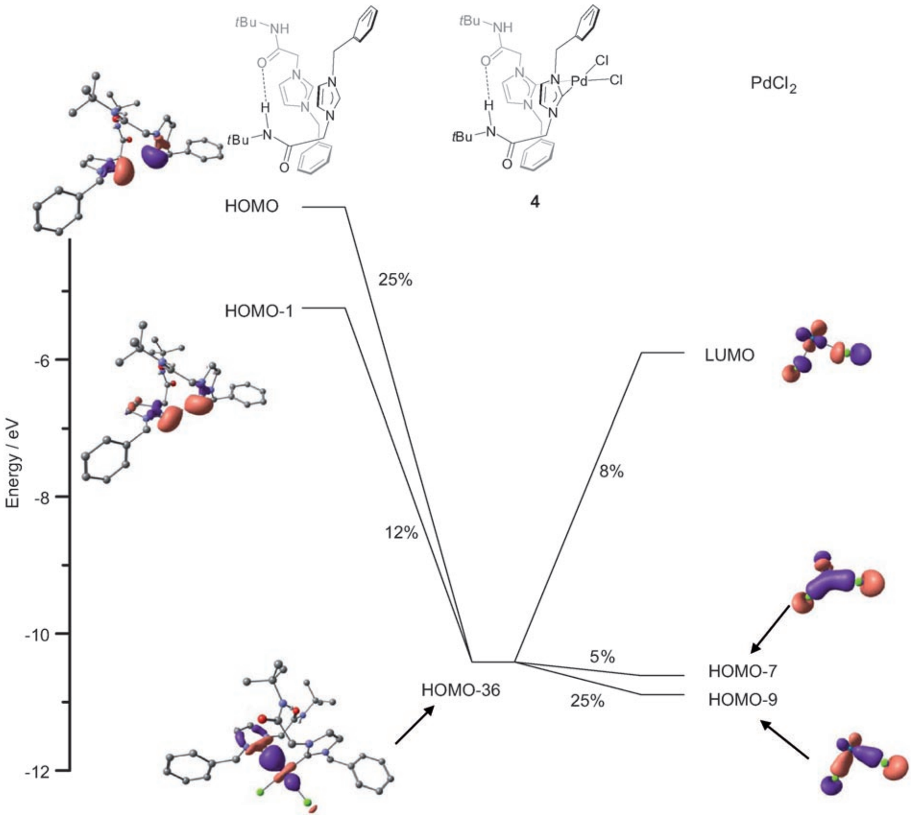


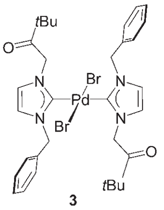
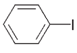
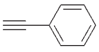
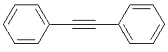
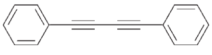
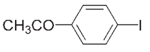
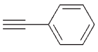
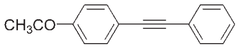
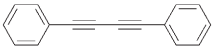
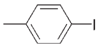
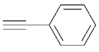
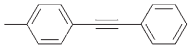
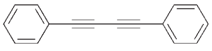
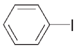
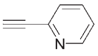
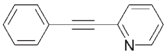
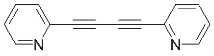
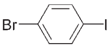
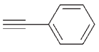
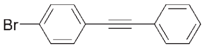
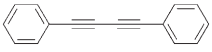
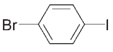
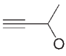
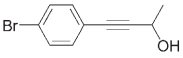
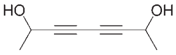
Figure 5. Simplified orbital interaction diagram showing the major contributions of the NHC−Pd σ-bonding orbital HOMO-36 in **4**.

Despite the existence of numerous phosphine-based catalysts for the Sonogashira reaction,[10] few N-heterocyclic carbene-based catalysts are known.[24,25] Also, in the light of the extraordinary successes enjoyed by NHCs in various catalytic reactions in general, and in palladium-mediated cross-coupling reactions in particular, the dearth of NHC-based catalysts for Sonogashira reactions prompted us to undertake the current study. Against this backdrop, complexes **3** and **4** assume importance because they represent the handful of examples of well-defined N-heterocyclic carbene-based palladium precatalysts known for homogeneous Sonogashira cross-coupling reactions.

With regards to our initial objective of finding out whether mono- or di-NHC-substituted palladium complexes would exhibit greater activity, a detailed comparative study of the *trans*- and *cis*-[(NHC)$_2$PdX$_2$] (X = Cl, Br)-type complexes **3** and **4** were performed with the corresponding PEPPSI analogues **3a** and **4a**. Interestingly, complexes **3** and **4**, which have two NHC ligands, were found to exhibit superior activity compared with **3a** and **4a** (Tables 1–4). The better performances of **3** and **4** can be correlated to more-electron-rich metal centers in these complexes. For example, a comparison of both the natural and Mulliken charges reveal that the palladium centers in **3** and **4**, which contain two strongly σ-donating NHC ligands, are more electron-rich than those of the PEPPSI analogues **3a** and **4a** stabilized by a single NHC ligand (see Tables S4–S13 of the Supporting Information). In this regard, the more electron-rich metal centers would greatly promote the oxidative addition of the aryl halide, which represents a key step in the palladium-mediated cross-coupling reaction.

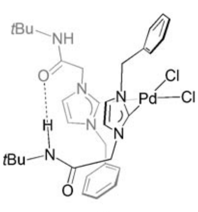
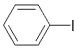
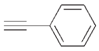
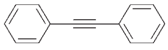
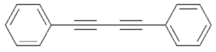
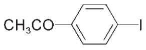
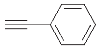
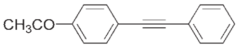
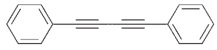
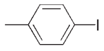
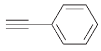
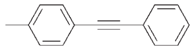
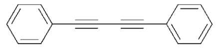
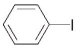
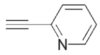
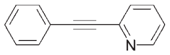
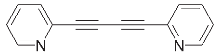
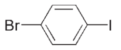
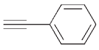
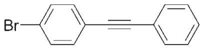
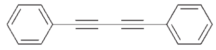
A comparison of the N-heterocyclic carbene-based palladium precatalysts **3** and **4** with the related phosphine-based precatalysts is important.[10] The NHC precatalysts **3** and **4**

Table 1. Selected results of the Sonogashira cross-coupling reaction of aryl halides (ArX, X = I) catalyzed by **3**.[a]

Catalyst	Reagent	Reagent	Desired cross-coupled product	Yield[b] [%]	Time [h]	Unwanted homocoupled product	Yield[b] [%]
 **3**				98	2		2
				80	2		3
				75	2		4
				97	2		0
				85	2		15
				68	2		0

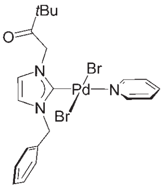
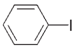
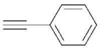
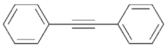
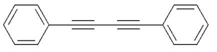
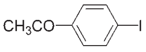
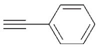
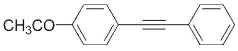
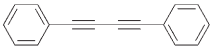
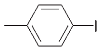
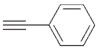
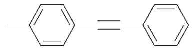
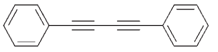
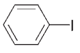
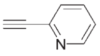
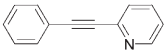
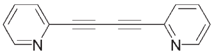
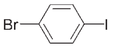
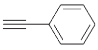
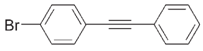
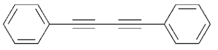
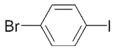
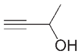
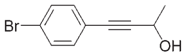
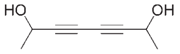
[a] Reaction conditions: aryl halide (ArX, X = I; 0.49 mmol), phenylacetylene (0.98 mmol), Cs_2CO_3 (2 mmol), catalyst (3 mol %), CuBr (10 mol %), DMF/H_2O (3:1; 10 mL), at 100 °C. [b] The yields were determined by GC using diethyleneglycol-di-*n*-butyl ether as the internal standard.

Table 2. Selected results of the Sonogashira cross-coupling reaction of aryl halides (ArX, X = I) catalyzed by **4**.[a]

Catalyst	Reagent	Reagent	Desired cross-coupled product	Yield[b] [%]	Time [h]	Unwanted homocoupled product	Yield[b] [%]
 **4**				84	12		0
				88	2		9
				94	2		6
				81	2		0
				90	2		21

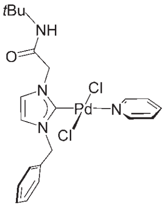
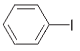
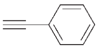
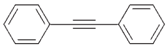
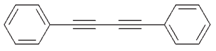
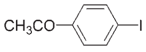
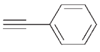
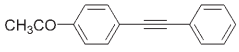
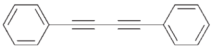
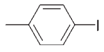
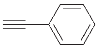
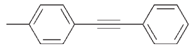
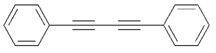
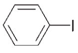
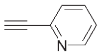
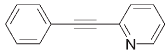
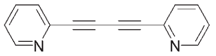
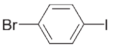
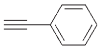
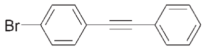
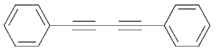
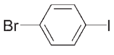
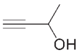
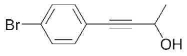
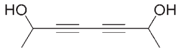
[a] Reaction conditions: aryl halide (0.49 mmol) (ArX, X = I), phenylacetylene (0.98 mmol), Cs_2CO_3 (2 mmol), catalyst (3 mol %), CuBr (10 mol %), DMF/H_2O (3:1; 10 mL), at 100 °C. [b] The yields were determined by GC using diethyleneglycol-di-*n*-butyl ether as the internal standard.

Table 3. Selected results of the Sonogashira cross-coupling reaction of aryl halides (ArI) catalyzed by **3a**.[a]

Catalyst	Reagent	Reagent	Desired cross-coupled product	Yield[b] [%]	Time [h]	Unwanted homocoupled product	Yield[b] [%]
 **3a**				4	2		5
				76	2		5
				42	2		0
				no reaction	2		0
				28	2		14
				no reaction	2		0

[a] Reaction conditions: aryl halide (0.49 mmol) (ArX, X = I), phenylacetylene (0.98 mmol), Cs_2CO_3 (2 mmol), CuBr (10 mol %), catalyst (3 mol %), DMF/H_2O (3:1; 10 mL) at 100 °C. [b] The yields were determined by GC using diethyleneglycol-di-*n*-butyl ether as the internal standard.

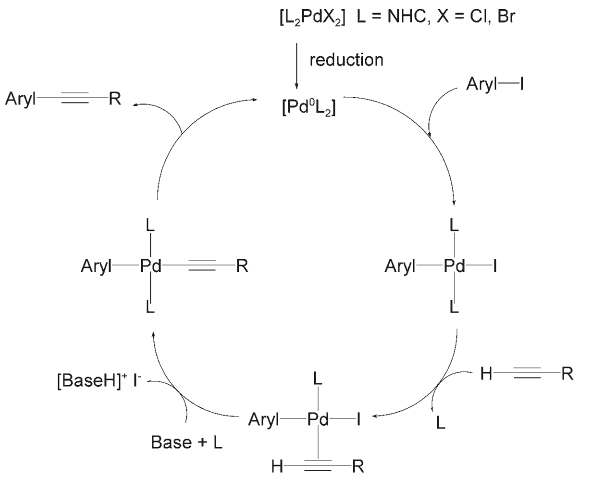
Table 4. Selected results of the Sonogashira cross-coupling reaction of aryl halides (ArX, X = I) catalyzed by **4a**.[a]

Catalyst	Reagent	Reagent	Desired cross-coupled product	Yield[b] [%]	Time [h]	Unwanted homocoupled product	Yield[b] [%]
 **4a**				27	2		13
				66	2		6
				11	2		12
				no reaction	2		0
				24	2		0
				no reaction	2		0

[a] Reaction conditions: aryl halide (ArX, X = I; 0.49 mmol), phenylacetylene (0.98 mmol), Cs_2CO_3 (2 mmol), CuBr (10 mol %), catalyst (3 mol %), DMF/H_2O (3:1; 10 mL) at 100 °C. [b] The yields were determined by GC using diethyleneglycol-di-*n*-butyl ether as the internal standard.

were found to be comparable to many of the phosphine-based precatalysts. Note that the latter are usually air- and moisture-sensitive and hence require anaerobic conditions, higher catalyst loading,[11] and also a longer reaction time (up to 48 h)[10] at higher temperatures (up to 140 °C).[9]

A tentative mechanism for the Sonogashira cross-coupling reaction is proposed in Scheme 5. Note that the mechanism excludes the formation of a copper–acetylide intermediate in view of the fact that very little or almost negligible amounts of Glaser-type homocoupled products were observed despite the coupling reactions being performed in air



Scheme 5.

in a mixed aqueous solvent. The copper–acetylide species is extremely sensitive to air and moisture, and its formation under these reaction conditions seems highly unlikely. Thus, the role of the CuBr co-catalyst is restricted to the reduction of the Pd^{II} center in **3** and **4** to the corresponding catalytically active Pd^0 species, which undergoes oxidative addition of the aryl iodide followed by the coordination and deprotonation of the terminal acetylene in the presence of a base, which leads to the desired cross-coupled product by a final reductive elimination step. In this regard, note that our attempt to independently synthesize and isolate the $[(NHC)_2Pd^0]$ species for a direct entry to the catalytic cycle was not successful.

Conclusions

In summary, two new precatalysts, namely, *trans*-[{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}$_2$PdBr$_2$] (**3**) and *cis*-[{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}$_2$PdCl$_2$} (**4**), have been designed and used in a highly convenient Sonogashira cross-coupling reaction of aryl iodides with substituted acetylenes in air in a mixed solvent (DMF/H_2O, 3:1 v/v) under amine-free conditions. More importantly, these complexes, which have two strong σ-donating NHC ligands, were found to exhibit superior activity compared with their corresponding PEPPSI counterparts, **3a** and **4a**, which support a single NHC ligand. Thus, a more electron-rich metal center acts as a better catalyst for the cross-coupling reaction.

Experimental Section

General procedures: All manipulations were carried out by using standard Schlenk techniques. Solvents were purified and degassed by standard procedures. Ag_2O was purchased from SD-Fine Chemicals (India) and used without any further purification. [(cod)PdCl$_2$],[31] benzylimidazole,[32] 1-benzyl-3-(*N*-*tert*-butylacetamido)imidazolium chloride,[18] [{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}AgCl],[13] and *trans*-[{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}Pd(pyridine)Cl$_2$] (**4a**)[18] were prepared according to reported literature procedures. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$ on a Varian 400 MHz NMR spectrometer. ^1H NMR signals are labeled as singlet (s), doublet (d), and multiplet (m). Infrared spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer with samples as KBr pellets. Mass spectrometry measurements were performed on a Micromass Q-Tof spectrometer. GC was carried out on a Shimadzu GC-15A gas chromatograph equipped with a FID detector. X-ray diffraction data for **3** and **4** were collected on an Oxford Diffraction Excaliber-S diffractometer. The crystal data collection and refinement parameters are summarized in Table 5. The structures were solved by using direct methods and standard difference map techniques and were refined by full-matrix least-squares procedures on F_2 with SHELXTL (Version 6.10).[33]

Table 5. X-ray crystallographic data for **3** and **4**.

Compound	3	4
lattice	monoclinic	monoclinic
formula	$C_{16}H_{20}BrN_2O\cdot0.5\,Pd$	$C_{32}H_{42}Cl_2N_6O_2Pd$
formula weight	389.45	720.02
space group	P_{21}/a	C_2/c
a [Å]	7.4702(2)	24.2317(5)
b [Å]	27.2734(7)	15.2987(4)
c [Å]	7.9624(2)	17.7705(4)
α [°]	90.00	90.00
β [°]	94.639(3)	91.655(2)
γ [°]	90.00	90.00
V [Å^3]	1616.93(7)	6585.0(3)
Z	4	8
temperature [K]	120(2)	120(2)
radiation (λ [Å])	0.71073	0.71073
ρ_{calcd} [g cm^{-3}]	1.600	1.453
$\mu(Mo_{K\alpha})$ [mm^{-1}]	3.079	0.765
θ [°]	2.97–25.00	3.05–25.00
no. of data	2848	5775
no. of parameters	190	421
R_1	0.0830	0.0226
wR_2	0.2354	0.0559
GOF	1.060	0.922

CCDC-643953 (**3**) and 637065 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of 1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazolium bromide (1): A mixture of benzylimidazole (0.889 g, 5.50 mmol) and α-bromopinacolone (1.00 g, 5.50 mmol) was dissolved in toluene (ca. 50 mL) and the reaction mixture was heated at reflux at 110 °C for 12 h until a white solid separated out. The solid was isolated by decanting off the solvent and washed with hot hexane (3×ca. 10 mL) to give **1** as a white solid (1.12 g, 61 %). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C, TMS): $\delta = 10.07$ (s, 1H; NCHN), 7.56 (brs 1H; NCHC*H*N), 7.42–7.38 (m, 5H; C_6H_5), 7.24 (brs 1H; NCHC*H*N), 5.93 (s, 2H; CH_2), 5.47 (s, 2H; CH_2), 1.28 ppm (s, 9H; $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta = 206.2$ (CO), 136.9 (NCN), 132.5 (*ipso*-C_6H_5), 128.9 (*m*-C_6H_5), 128.2 (*p*-C_6H_5), 124.1 (*o*-C_6H_5), 120.6 (NCHCHN), 54.2 (CH_2), 52.7 (CH_2), 42.9 ($C(CH_3)_3$), 25.8 ppm ($C(CH_3)_3$); IR (KBr): $\tilde{\nu} = 1717$ cm^{-1} (ν_{CO}); HRMS (ES): *m/z* calcd: 257.1654 [NHC-ligand]$^+$; found: 257.1643.

Synthesis of [{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}$_2$-Ag]Br (2): A mixture of 1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazolium bromide (**1**) (0.500 g, 1.49 mmol) and Ag_2O (0.171 g, 0.740 mmol) in dichloromethane (ca. 60 mL) was stirred at room temperature for 6 h. The reaction mixture was filtered and the solvent was removed under vacuum to give **2** as a brown solid (0.412 g, 80 %). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C, TMS): $\delta = 7.34–7.31$ (m, 5H; C_6H_5), 6.92 (brs, 1H;

NCHC*H*N), 6.89 (brs, 1H; NCHC*H*N), 5.39 (s, 2H; CH_2), 5.29 (s, 2H; CH_2), 1.30 ppm (s, 9H; $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta = 208.6$ (CO), 183.9 (NCN-Ag), 135.7 (*ipso*-C_6H_5), 128.6 (*m*-C_6H_5), 127.9 (*p*-C_6H_5), 127.5 (*o*-C_6H_5), 122.8 (N*C*HCHN), 120.4 (NCH*C*HN), 55.1 (CH_2), 50.5 (CH_2), 43.1 ($C(CH_3)_3$), 26.0 ppm ($C(CH_3)_3$); IR (KBr): $\tilde{\nu} = 1719\ cm^{-1}$ (ν_{CO}); HRMS (ES): *m*/*z* calcd: 619.2202 $[(NHC)_2Ag]^+$; found: 619.2212; elemental analysis calcd (%) for $C_{32}H_{40}N_4O_2AgBr$: C 54.87, H 5.76, N 8.00; found: C 55.23, H 6.53, N 8.16.

Synthesis of [{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}$_2$-PdBr$_2$] (3): A mixture of [{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}$_2$Ag}Br (**2**) (0.151 g, 0.236 mmol) and [(cod)$PdCl_2$] (0.030 g, 0.107 mmol) was heated at reflux in acetonitrile (ca. 30 mL) at 85 °C for 6 h until the formation of an off-white AgBr precipitate was observed. The reaction mixture was filtered and the solvent was removed under vacuum to give **3** as a yellow solid (0.067 g, 81 %). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C, TMS): $\delta = 7.37$–7.31 (m, 5H; C_6H_5), 6.92 (brs, 1H; NCHC*H*N), 6.86 (brs, 1H; NCHC*H*N), 5.38 (s, 2H; CH_2), 5.21 (s, 2H; CH_2), 1.32 ppm (s, 9H; $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta = 207.1$ (CO), 172.2 (NCN-Pd), 134.8 (*ipso*-C_6H_5), 129.0 (*m*-C_6H_5), 128.7 (*p*-C_6H_5), 127.9 (*o*-C_6H_5), 122.8 (N*C*HCHN), 120.3 (NCH*C*HN), 55.0 (CH_2), 54.9 (CH_2), 43.6 ($C(CH_3)_3$), 26.2 ppm ($C(CH_3)_3$); IR (KBr): $\tilde{\nu} = 1721\ cm^{-1}$ (ν_{CO}); elemental analysis calcd (%) for $C_{32}H_{40}Br_2N_4O_2Pd \cdot 2(CH_3CN)$: C 50.22, H 5.38, N 9.76; found: C 49.98, H 5.82, N 10.15.

Synthesis of *trans*-[{1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene}Pd(pyridine)Br$_2$] (3a): A mixture of 1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazolium bromide (0.306 g, 0.908 mmol), $PdCl_2$ (0.193 g, 1.09 mmol), and K_2CO_3 (0.627 g, 4.54 mmol) were heated at reflux in pyridine (ca. 5 mL) for 16 h. The reaction mixture was filtered and the solvent was removed under vacuum. Then the residue was washed with aqueous $CuSO_4$ solution and the aqueous layer was extracted with dichloromethane (3 × ca. 10 mL). Then the organic layer was collected and the solvent was removed under vacuum to give **3a** as a light-yellow crystalline solid (0.182 g, 67 %). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C, TMS): $\delta = 8.96$ (d, $^3J_{HH} = 8$ Hz, 2H; *o*-NC_5H_5), 7.77 (t, $^3J_{HH} = 8$ Hz, 1H; *p*-NC_5H_5), 7.50 (t, $^3J_{HH} = 8$ Hz, 2H; *m*-NC_5H_5), 7.39–7.35 (m, 5H; C_6H_5), 6.99 (brs, 1H; NCHC*H*N), 6.77 (brs, 1H; NCHC*H*N), 5.84 (s, 2H; CH_2), 5.71 (s, 2H; CH_2), 1.40 ppm (s, 9H; $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta = 206.8$ (CO), 153.3 (NCN-Pd), 151.9 (*o*-NC_5H_5), 151.1 (*m*-NC_5H_5), 138.0 (*ipso*-C_6H_5), 137.9 (*p*-NC_5H_5), 129.0 (*o*-C_6H_5), 128.9 (*m*-C_6H_5), 128.4 (*p*-C_6H_5), 121.2 (NCH*C*HN), 121.1 (N*C*HCHN), 54.7 (CH_2), 54.4 (CH_2), 43.7 ($C(CH_3)_3$), 26.5 ppm ($C(CH_3)_3$); IR (KBr): $\tilde{\nu} = 1718\ cm^{-1}$ (s, ν_{CO}); elemental analysis calcd (%) for $C_{21}H_{25}Br_2N_3OPd \cdot \frac{1}{3}(NC_5H_5)$: C 43.35, H 4.28, N 7.43; found: C 43.85, H 4.15, N 8.02.

Synthesis of [{1-benzyl-3-(N-*tert*-butylacetamido)imidazol-2-ylidene}$_2$-PdCl$_2$] (4): A mixture of [{1-benzyl-3-(*N*-*tert*-butylacetamido)imidazol-2-ylidene}AgCl] (0.261 g, 0.631 mmol) and [(cod)$PdCl_2$] (0.090 g, 0.315 mmol) was heated at reflux in acetonitrile (ca. 30 mL) at 85 °C for 6 h when the formation of an off-white AgCl precipitate was observed. The reaction mixture was filtered and the solvent was removed under vacuum to obtain **4** as a yellow solid (0.197 g, 87 %). ^1H NMR ($CDCl_3$, 400 MHz, 25 °C, TMS): $\delta = 7.43$–7.29 (m, 10H; $2C_6H_5$), 7.04 (brs, 1H; NCHC*H*N), 6.99 (brs, 1H; NCHC*H*N), 6.79 (brs, 1H; NCHC*H*N), 6.76 (brs, 1H; NCHC*H*N), 5.77 (s, 2H; CH_2), 5.61 (s, 2H; CH_2), 5.17 (s, 2H; CH_2), 4.99 (s, 2H; CH_2), 1.35 (s, 9H; $C(CH_3)_3$), 1.25 ppm (s, 9H; $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta = 164.9$ (CO), 160.2 (NCN-Pd), 134.3 (*ipso*-C_6H_5), 128.9 (*m*-C_6H_5), 128.5 (*p*-C_6H_5), 128.4 (*o*-C_6H_5), 122.0 (N*C*HCHN), 121.8 (NCH*C*HN), 55.1 (CH_2), 54.4 ($C(CH_3)_3$), 51.9 (CH_2), 28.5 ppm ($C(CH_3)_3$); IR (KBr): $\tilde{\nu} 1626\ cm^{-1}$ (ν_{CO}); elemental analysis calcd (%) for $C_{32}H_{42}N_6O_2PdCl_2$: C 53.38, H 5.88, N 11.67; found: C 53.75, H 5.96, N 11.15.

Computational methods: Density functional theory calculations were performed on the two palladium complexes **3** and **4** using the Gaussian 03[34] suite of quantum chemical programs. The Becke three-parameter exchange functional in conjunction with the Lee–Yang–Parr correlation functional (B3LYP) was employed in this study.[35,36] The Stuttgart–Dresden effective core potential (ECP), which represents 19 core electrons, along with valence basis sets (SDD) were used for palladium.[37,38] All other atoms were treated with the 6-31G(d) basis set.[39] The metal–ligand donor–acceptor interactions were inspected by using charge decomposition analysis (CDA).[40] CDA is a valuable tool for analyzing the interactions between molecular fragments on a quantitative basis, with an emphasis on electron donation.[41] The orbital contributions in the $[(NHC)_2PdX_2]$ ($X = Br$, Cl)-type complexes **3** and **4** can be divided into three parts: 1) σ donation from the $[NHC \xrightarrow{\sigma} PdX_2]$ fragment, 2) π back donation from the $[NHC \xleftarrow{\pi} PdX_2]$ fragment, and 3) a repulsive interaction between the occupied MOs of these two fragments.

The CDA calculations were performed by using the AOMix program[42] with the B3LYP/SDD, 6-31G(d) wavefunction. Molecular orbital (MO) compositions and the overlap populations were calculated by using the AOMix program.[43] Analysis of the MO compositions in terms of occupied and unoccupied fragment orbitals (OFOs and UFOs, respectively), construction of orbital interaction diagrams, and the charge decomposition analysis (CDA) were performed by using AOMix-CDA.[44] Natural bond orbital (NBO) analysis was performed by using the NBO 3.1 program implemented in the Gaussian 03 package.[34]

General procedure for the Sonogashira coupling reaction: In a typical run, performed in air, a 25 mL vial was charged with a mixture of aryl iodide, arylalkyne, Cs_2CO_3, and diethyleneglycol-di-*n*-butyl ether (internal standard) in a molar ratio of 1:2:4:1. Complexes **3**, **3a**, **4**, or **4a** (3 mol %) and CuBr (10 mol %) were added to the mixture (Tables 1–4). Finally, a mixed solvent (DMF/H_2O, 3:1 v/v, 10 mL) was added to the reaction mixture and heated at 100 °C for an appropriate period of time, after which it was filtered and the product was analyzed by gas chromatography using diethyleneglycol-di-*n*-butyl ether as the internal standard.

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