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Carbamoyl-Substituted *N*-Heterocyclic Carbene Complexes of Palladium(II): Application to Sonogashira Cross-Coupling Reactions

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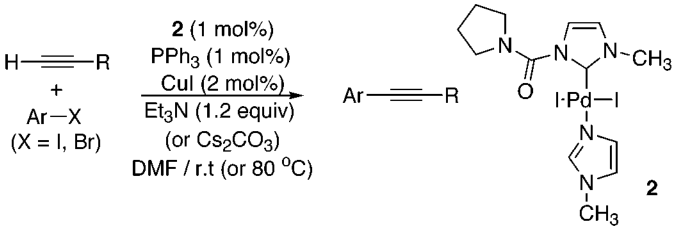
ABSTRACT



The first examples of *N*-carbamoyl-substituted heterocyclic carbene Pd(II) complexes are described. These thermal and hydrolytically stable complexes are readily prepared from carbamoyl imidazolium salts and efficiently promote Sonogashira cross-coupling reactions under mild conditions. Cesium carbonate is also shown to be an effective base for the coupling of aryl bromides.

Since the first isolation of free carbene species by Arduengo,[1] nucleophilic *N*-heterocyclic carbenes, especially imidazol-2-ylidenes, have attracted considerable attention as possible alternatives for the widely used phosphine ligands in homogeneous catalysis.[2] The primary advantage of these ligands is that they do not readily dissociate from the metal center and have strong σ-donor character. These “phosphine mimics” are less toxic and can be synthesized more readily than many conventional phosphine ligands. The synthesis of palladium complexes of heterocyclic carbene ligands and their use in cross-coupling reactions was initially reported by Herrmann.[3] Recently, the combination of $Pd(dba)_2$ or $Pd(OAc)_2$ with electron-rich and sterically demanding versions of carbene ligand precursors, imidazolium salts, has been demonstrated to effectively mediate the coupling of aryl halides with amines,[4] amides,[5] alkenes (Heck coupling),[6] organomagnesium,[7] organosilicon,[8] organoboron,[9] and organostannane reagents.[10]

We have recently demonstrated the utility of carbamoyl imidazolium salts as *N*,*N*′-disubstituted carbamoyl cation equivalents for the formation of tri- and tetrasubstituted ureas,

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[†] To whom correspondence concerning the crystallographic data should be addressed.

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carbamates, and thiocarbamates.[11] The H-2 proton on the imidazolium salts of these compounds undergoes H/D exchange in deuterated solvents under mildly basic conditions, presumably via a carbene (imidazol-2-ylidene) intermediate.[12] The stronger acidity of the H-2 proton relative to other imidazolium salts encouraged us to investigate the formation of metal carbene complexes derived from carbamoyl imidazolium salts. In addition, whereas most of the *N*-heterocyclic carbene ligands or their metal complexes contain either alkyl- or aryl-substitution on the nitrogen atoms, to our knowledge there are no examples of catalytic usage of metal complexes containing electron-withdrawing *N*-substituents on the carbene. Indeed, only gold(I) carbene complexes with electron-withdrawing *N*-substituents (e.g., *N*-tosyl, benzoyl, and COOEt) on the imidazol-2-ylidene ring have been reported in the literature.[13] Complexes having such substitution would certainly be expected to have different electronic properties compared to the commonly used *N*-alkyl- or *N*-aryl-substituted heterocyclic carbene complexes. We were particularly interested to determine whether catalytic activity in cross-coupling reactions would be retained for complexes with electron-withdrawing *N*-substituents, since these would be anticipated to have poorer σ-donor character. We now report the first synthesis of *N*-carbamoyl-substituted, *N*-heterocyclic carbene complexes of palladium(II) derived from carbamoyl imidazolium salts and a systematic study of their catalytic activity in Sonogashira cross-coupling reactions.

The palladium complex **2** of the *N*-carbamoyl-substituted heterocyclic carbene was prepared from Pd(OAc)$_2$ and 2 equiv of carbamoyl imidazolium salt **1** in refluxing THF.[3a,14] Orange-yellow crystals of **2** were obtained after purification via flash chromatography. Complex **2** is both air- and moisture-stable, and consequently special handling precautions are unnecessary. Although the exact mechanism of formation of this unique palladium complex is not known, formation of the palladium-bound carbamoyl imidazol-2-ylidene is accompanied by the release of acetic acid, which rapidly reacts with a second equivalent of carbamoyl imidazolium salt to form *N*-acetyl-pyrrolidine.[15] The byproduct of this nucleophilic attack, *N*-methylimidazole, then coordinates to the palladium center to form the palladium complex **2**. The X-ray crystal structure analysis of the complex **2** (Figure 1) revealed an expected square-planar core geometry and showed that the Pd−C bond length (1.970(5) Å) lies in the range of those known carbene complexes (1.948−2.074 Å).[16] The carbene and *N*-methylimidazole are in a *trans* arrangement reflecting the known order of *trans* influences of carbene > iodide > amine. Coordination between the carbamoyl oxygen and palladium is not apparent in the solid state (Pd−O distance = 3.466 Å). The torsion angle between the carbonyl group and imidazol-2-ylidene ring is approximately 60°, indicating relatively little π-orbital overlap between these two groups in the complex. The plane defined by the square planar core geometry around the Pd is almost orthogonal to that of the imidazol-2-ylidene ring (as found in other Pd−carbene complexes) but is coplanar with that of the *N*-methylimidazole ligand.

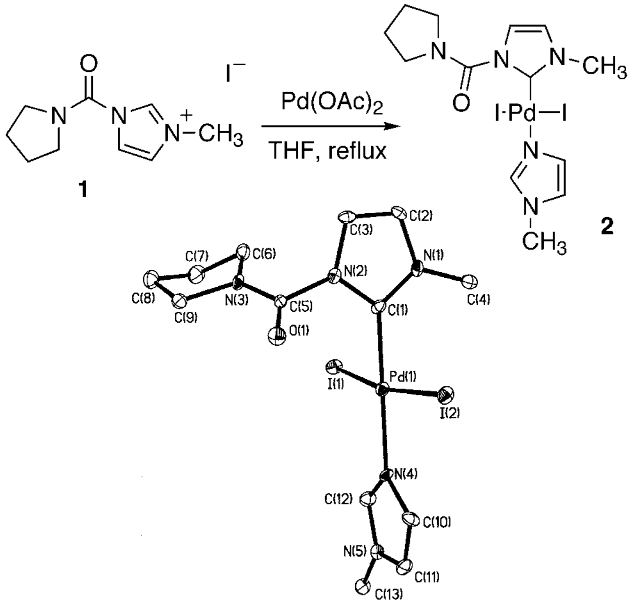

Figure 1. Synthesis and ORTEP diagram of palladium(II) complex **2** with 30% thermal ellipsoids.

Palladium-catalyzed cross-coupling reactions between terminal alkynes and aryl halides have been used extensively in natural products chemistry and materials science for the synthesis of substituted and conjugated alkynes.[17] This reaction, known as the Sonogashira reaction,[18] is generally carried out in the presence of a catalytic amount of palladium complex and copper iodide with an amine serving as both solvent and base. Several improved procedures to promote the coupling of aryl halides with alkynes without the use of harsh conditions have also been reported.[19] Although *N*-heterocyclic carbene based metal complexes have been successfully used in several cross-coupling reactions,[3−10] their application in Sonogashira reactions has not yielded promising results.[3b,20] In Herrmann's[3b] and Cavell's[20a] catalyst

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(11) (a) Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267−6270. (b) Batey, R. A.; Yoshina-Ishii, C.; Taylor, S. D.; Santhakumar, V. *Tetrahedron Lett.* **1999**, *40*, 2669−2672.

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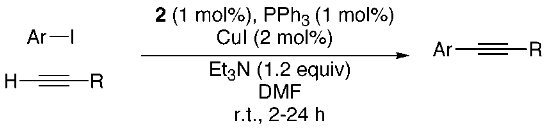
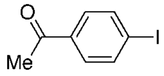
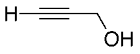
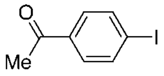
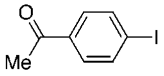
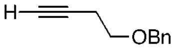
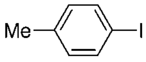
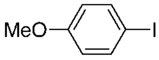
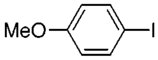
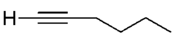
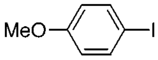
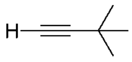
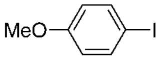
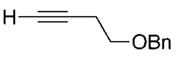
systems, triethylamine had to be employed as solvent and even with activated aryl bromide substrates reaction occurred at elevated temperature (90 °C). Herrmann's mixed palladium(II) complex bearing an *N*-heterocyclic carbene and triphenylphosphine[20b] failed to promote Sonogashira cross-coupling, instead providing diyne and enyne products, formed through alkyne self-coupling.

Because of the possibility of byproduct generation and other functional group tolerance, instead of applying the standard reaction conditions with amine as solvent, we investigated several other organic solvents in the palladium–carbene complex **2** catalyzed Sonogashira reaction of 4-bromoacetophenone with phenylacetylene. The reaction was carried out at elevated temperature with Et_3N as the base. The use of DMF as solvent gave excellent yields, particularly with a 1:1 ratio of complex **2**:PPh_3 (97% conversion was achieved after 1 h, whereas with just **2** alone only 50% conversion was achieved after 48 h). Sonogashira coupling of a wide array of aryl iodides with terminal alkynes could be achieved at room temperature using the optimized conditions (Table 1). For example, 4-iodoacetophenone reacted with terminal alkynes in good to excellent yields (Table 1, entries 1–3). Less reactive 4-iodoanisole and 4-iodotoluene also reacted cleanly at room temperature and with high efficiency (Table 1, entries 4–8).

Table 1. Room Temperature Sonogashira Reactions Catalyzed by Palladium–Carbene Complex **2**[a]

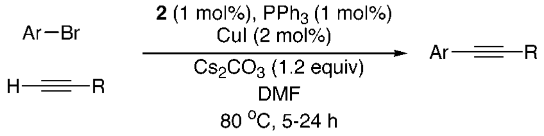


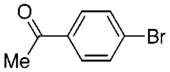
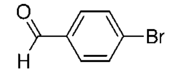
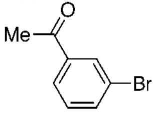
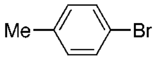
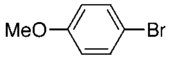
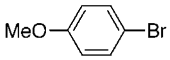
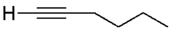
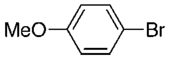
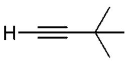
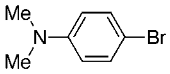
Entry	Aryl Iodide	Alkyne	Yield (%)[b]
1			87%
2		H—≡—Ph	95%
3			92%
4		H—≡—Ph	quant.
5		H—≡—Ph	98%
6			91%
7			93%
8			90%

[a] The reaction was carried out in degassed DMF (1 M) with 1 mol % palladium carbene complex **2** as catalyst, 1 mol % PPh_3 as ligand, 2 mol % of CuI as cocatalyst, and 1.2 equiv of base at rt for 2–24 h. [b] Isolated yields.

For activated aryl bromides reaction was complete within 6 h at 80 °C (Table 2, entries 1–3). Deactivated aryl bromides with electron-donating substituents on the aromatic ring are less reactive substrates in Sonogashira reactions. Using the optimized conditions for activated aryl bromides, i.e., with Et_3N as base, the reaction of 4-bromoanisole with phenylacetylene proceeded very slowly. Several organic and inorganic bases were tested to improve the rate of the reaction. The use of Cs_2CO_3 achieved almost complete conversion within 1 day, the fastest among all organic and carbonate bases tested. For example, Et_3N, $^{i}Pr_2NH$, and K_2CO_3 gave only 27%, 25%, and 4% conversion, respectively, after 24 h at 80 °C. The use of Na_2CO_3[21] or

Table 2. Sonogashira Reactions Catalyzed by Palladium Carbene Complex **2**[a]



Entry	Aryl Bromide	Alkyne	Yield (%)[b]
1		H—≡—Ph	99%[c]
2		H—≡—Ph	89%[c]
3		H—≡—Ph	97%[c]
4		H—≡—Ph	90%
5		H—≡—Ph	85%
6			74%
7			97%
8		H—≡—Ph	95%

[a] The reaction was carried out in degassed DMF (1 M) with 1 mol % palladium–carbene complex **2** as catalyst, 1 mol % PPh_3 as ligand, 2 mol % of CuI as cocatalyst, and 1.2 equiv of base at 80 °C for 5–24 h. [b] Isolated yields. [c] Et_3N as base.

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K_2CO_3 [22] as a base have also been reported by several research groups as modified procedures for Sonogashira reactions. However, this is the first time to our knowledge that Cs_2CO_3 has been used as a base to increase the rate of Sonogashira reactions, although it is now widely used in other Pd-catalyzed cross-coupling reactions. Other deactivated aryl bromide substrates were also coupled efficiently using Cs_2CO_3 as base (Table 2, entries 4−8). The use of a 1:1 ratio of complex **2**·PPh_3 was critical for coupling of deactivated aryl bromides, with none of the desired products formed using **2** alone.

As mentioned above, the addition of ligands improved the rate of cross-coupling reactions. Palladium complex **3**, which is believed to be the functioning precatalyst in the optimized conditions, was isolated by mixing complex **2** with 1 equiv of triphenylphosphine. The X-ray crystal structure analysis (Figure 2) showed a typical square-planar core geometry and Pd−carbene C bond length (1.990(3) Å).[16]

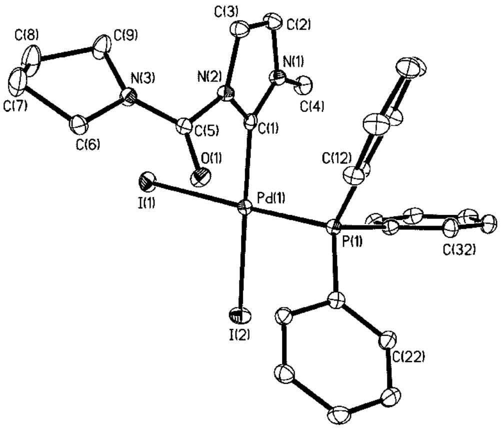

Figure 2. ORTEP diagram of palladium(II) complex **3** with 30% thermal ellipsoids.

The structure analysis also showed a *cis* arrangement of the carbene ligand and triphenylphosphine. The Pd−I bond distances are essentially identical (Pd−I(1) = 2.6467(3) Å and Pd−I(2) = 2.6482(3) Å), contrasting with those obtained by Herrmann in a similar *cis*-Pd-carbene-PPh_3I_2 complex[23] that had corresponding Pd−I bond distances of (2.6370(5) and 2.6519(5) Å). Even in the presence of excess triphenylphosphine, displacement of the *N*-heterocyclic carbene does not occur. Cross-coupling reactions catalyzed by complex **3** gave results identical to those obtained with complex **2** and 1 equiv of triphenylphosphine.

In conclusion, the first *N*-carbamoyl-substituted heterocyclic carbene complexes of palladium(II) have been developed. The complexes are readily synthesized, show good thermal and hydrolytic stability, and can be stored for extended periods without decomposition or loss of activity. Both the **2**/PPh_3 and **3** precatalyst systems have been shown to efficiently cross-couple a variety of aryl halides with terminal alkynes under relatively mild reaction conditions, a feature that may be advantageous over methods that employ air-sensitive phosphines or palladium complexes. Cs_2CO_3 is also shown to be an effective base for the cross-coupling of deactivated aryl bromides and terminal alkynes. The employment of *N*-carbamoyl-substituted heterocyclic carbenes affects both the steric environment and electron density at the metal center. The desirable σ-donor character of the carbene ligand is not eliminated by such substitution, with catalytic viability of the complexes being retained. The use of carbamoyl or other electron-withdrawing substituents (such as acyl, COOR, SO_2R, imidoyl, imidate, etc.) may be useful for the design of future catalytic systems employing *N*-heterocyclic carbene ligands. Further investigations of these *N*-heterocyclic carbene palladium(II) complexes in other palladium catalyzed organic transformations[24] are ongoing.

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Supporting Information Available: Experimental procedures and characterization data for new compounds and products and X-ray crystallographic data for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[24] In preliminary experiments we have demonstrated that this complex can also be used for Suzuki−Miyaura, Heck, and hydrostannation reactions.