

Synthesis, Characterization, and Catalytic Activity of *N*-Heterocyclic Carbene (NHC) Palladacycle Complexes

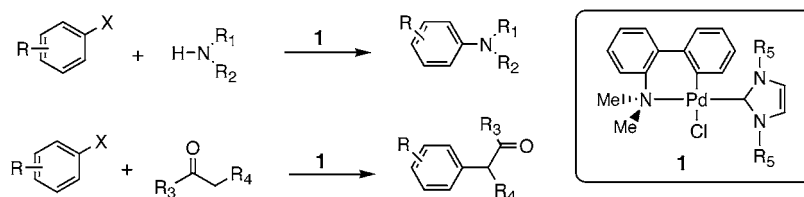
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ABSTRACT



Palladacycle dimers possessing bridging halides can be easily cleaved by using *N*-heterocyclic carbenes (NHCs) to generate novel monomeric complexes. The structure of one of these was determined by single-crystal diffraction study and consists of a square-planar coordination around the palladium center where the NHC ligand is trans to the amine of the palladacycle. The complex was found to be equally active in aryl amination and α -arylation of ketones even at very low catalyst loading (0.02 mol %). Primary and secondary alkyl/arylamines are equally active partners in coupling reactions.

Rapid developments in the area of metal-mediated cross-coupling reactions involving unactivated substrates, especially aryl chlorides, have highlighted both the positive and negative properties of phosphines as supporting ligands.¹ The high price associated with bulky tertiary phosphines and/or difficulties associated with removal of the ligands and their degradation byproducts, phosphine oxides, have encouraged researchers to explore alternative catalytic systems. To this end *N*-heterocyclic carbenes² (NHCs) and metallacycle³ scaffolds have been used as ancillary ligands.

The NHCs have the general advantage of being better σ -donors than tertiary phosphines rendering the oxidative

addition of the aryl halide to palladium facile. In addition, the significant steric demand brought about by the presence of bulky substituents on the NHC facilitates elimination of the product. The strong interaction between metal and carbenic carbon of the imidazole moiety inhibits the dissociation, thereby minimizing the need for excess ligand.⁴ The second class of alternative catalysts focuses on palla-

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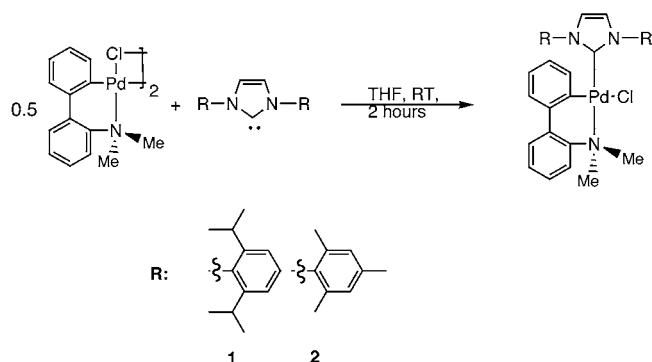
dacycles. Pioneering work by the Herrmann group and others³ has shown these catalysts to be very robust and capable of high turnover numbers, especially in Heck coupling reactions. Conceptually, some of these catalysts can be viewed as oxidative addition products of an aryl halide to palladium. The use of these catalysts on unactivated substrates usually requires long reaction times.

Recently, a combination of a palladacycle framework with highly donating, sterically demanding secondary phosphines has been reported.⁵ These catalysts combine the stability induced by the presence of a palladacycle framework with the high activity commonly associated with palladium/phosphine complexes. The mechanism of activation and the exact nature of the active catalytic species are still in question in this system. We were interested in an approach that would combine the important donating properties of NHC with the stability imparted by the palladacycle framework.

Recently, we reported the synthesis of monomeric NHC-Pd(allyl)Cl species⁶ by the reaction of NHC and $[(\eta^3\text{-allyl})\text{-PdCl}]_2$. We speculated that a similar reactivity pattern between palladacycle dimers and NHC could be applied to generate monomeric palladium complexes.

Herein, we describe the synthesis, characterization, and catalytic activity of a novel class of palladacycle/NHC complexes (NHC is IPr [*N,N'*-bis((2,6-diisopropylphenyl)-imidazol)-2-ylidene], IMes [*N,N'*-bis((2,4,6-trimethylphenyl)-imidazol)-2-ylidene]). Scheme 1 depicts the reaction between

Scheme 1. Synthetic Protocol Leading to NHC Modified Palladacycles



IPr and a palladacycle dimer. The reaction was performed in THF at room temperature for 2 h and afforded **1** in 67% yield after recrystallization. The product is a 16-electron species that is air and moisture stable. Crystals suitable for single-crystal X-ray diffraction were obtained from hexanes/

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CH₂Cl₂ solutions. The X-ray data confirmed the complex to have a distorted square-planar geometry with the NHC ligand trans to the amino group. The biphenyl geometry is twisted probably to accommodate the steric bulk of the IPr ligand. (Figure 1).

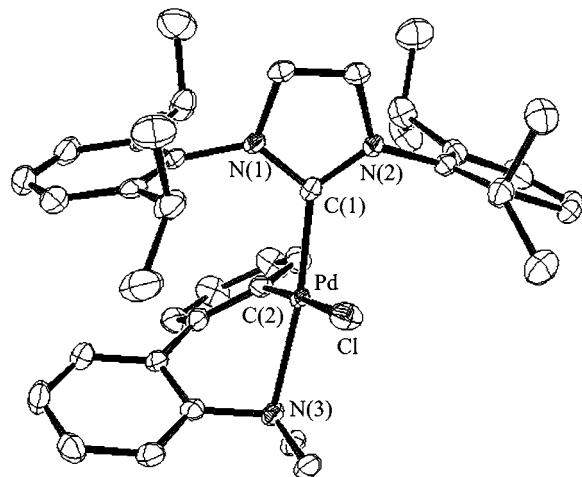


Figure 1. ORTEP drawing of **1**. Hydrogens are omitted for clarity. Selected bond distances (Å) and angles (deg): Pd–Cl, 2.403; Pd–C(1), 1.992; Pd–C(2), 1.981; Pd–N(3), 2.195; C(2)–Pd–Cl, 176.8; C(1)–Pd–N(3), 172.62.

We investigated the catalytic activity of NHC modified palladacycles (**1** and **2**) in the aryl amination⁷ using 4-chlorotoluene and morpholine as standard substrates. When **2** was used as the catalyst the reaction reached completion in 1.5 h at 70 °C. On the other hand, aniline is completely inert under these conditions. However, the use of **1** in this reaction involving aniline leads to quantitative product formation. It should be noted here that the secondary phosphine congeners to **1** and **2** perform arylation of amines but require much harsher conditions.⁵ Considering the existence of similar electronic effects in both catalysts (**1** and **2**), we suspect the difference in reactivity must be associated with a different rate of reductive elimination. Faster rates were observed for the more bulky ligand, IPr. Among bases, NaO^tBu was found to be the most effective in terms of conversion and price. Cs₂CO₃ and K₃PO₄ were completely ineffective, supporting the hypothesis of Hartwig that two different mechanisms can operate in arylation of amines.⁸

A survey of catalytic cross-coupling of aryl halides with a wide range of amines performed at 70 °C is provided in Table 1.

Aryl chlorides were used as coupling partners in most reactions. Despite the unreactive nature of the C–Cl bond these reactions required low catalyst loading and reaction times ranging from 20 min to a maximum of 4 h. It was

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Table 1. Cross-Coupling of Aryl Halides and Amines Mediated by **1**^a

substrates	product	time (h)	yield(%) ^a
		0.5	100 (92)
		0.5	100 (98)
		2	87 (80) ^b
		2	100 (95) ^b
		2	100 (88)
		2	100 (94)
		4	94 (90)
		3	97 (88)
		0.6	100 (83)
		0.6	87 (84)
		2	100 (89) ^b
		2	100 (96)
		2	95 (90)
		1	100 (87)
		0.5	100 (99)
		2	100 (92)
		4	92 (82)
		2	85 (75)
		2	100 (96)
		2	100 (88)
		1	100 (68)
		2	100 (98)

^a Conditions: 1.1 mmol of NaOtBu, 1 mol % of **1**, 1 mmol of ArX.; (a) Unless otherwise stated reactions were carried out with 3 mL of dioxane. (b) Reaction carried out with 3 mL of toluene. Yields were determined by GC. Isolated yields are bracketed and are an average of two runs.

interesting to observe that varying the nature of aryl group substituents had minimal influence on reaction rates. Sterically hindered aryl chlorides such as 2-methoxychlorobenzene or 2-methylchlorobenzene have rates slightly lower than nonhindered relatives. We were pleased to find that a large variety of substrates—heterocyclic alkylamines, dialkylamines, aryl-alkylamines and primary amines—are all efficient coupling partners. Furthermore, it should be pointed out that substrates such as aniline, hexylamine, and other primary amines have oftentimes been found to undergo a second arylation under catalytic conditions. This is not

Table 2. α -Arylation of Ketones^a

substrates	product	time (h)	yield(%)
		2	100 (89) ^a
		2	85 (78) ^b
		2	99 (90) ^a
		2	100 (97) ^a

^a Conditions: 1.1 mmol of NaO^tBu, 1 mol % of **1**, 1 mmol of ArX. (a) 3 mL of dioxane. (b) 3 mL of toluene. GC yields. Isolated yields are bracketed and are an average of two runs.

observed with this system. The reactivity of the present system compares favorably to that displayed by systems reported by Buchwald.⁹

We were interested in the activity of the catalyst at lower catalyst loadings. For this facet of the study, the reaction between *p*-chloroanisole and aniline was chosen as it involves a coupling of an electron-rich aryl with a poorly activated amine. The experiments showed that the TON can be nearly doubled by increasing the temperature of the reaction from 70 (TON = 160) to 110 °C (TON = 305). Under the more forcing conditions no formation of palladium black was observed. Harsher conditions were tested with use of 0.05 mol % of catalyst **1** and TON of up to 460 were obtained. Further studies in this direction are presently ongoing and are aimed at understanding the fate of the catalytic species.

While reaction conditions are still being optimized, initial results show that reactions involving 4-methoxychlorobenzene or 4-chlorotoluene and morpholine can be carried out at room temperature. These reactions reach completion within 2 h.

An attractive alternative to the use of aryl chlorides as a substrate in cross-coupling chemistry is the use of aryl triflates which are easily synthesized from phenols.¹⁰ We found that an important factor enabling the use of triflates is solvent selection. Standard reaction conditions involving dioxane as solvent led to no significant amount of products. The use of toluene led to conversions similar to those involving aryl chlorides.

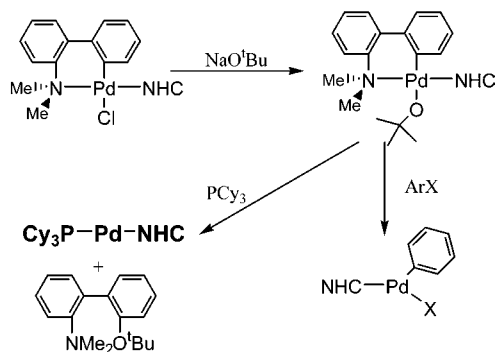
We investigated the use of palladacycle-NHC complexes as catalysts in the arylation of simple ketones with aryl halides and pseudohalides at 70 °C. The NaO^tBu base plays a dual role, it generates the active catalytic species (as described above) and it deprotonates the ketone. In our initial studies multiple arylations are not observed probably due to steric constraints.

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Indolese and co-workers recently reported a similar catalytic system but the palladacycle was stabilized and activated by the presence of a secondary phosphine.⁵ The reaction of **1** and tricyclohexylphosphine in the presence of NaO^tBu was monitored by ³¹P NMR spectroscopy. The appearance of a peak at 52.6 ppm, similar to the reported values for mixed NHC phosphine palladium(0) complexes synthesized by Cloke and co-workers,¹¹ was observed.¹² On the basis of this spectroscopic information, we speculate an activation mechanism that is initiated by an attack of alkoxide on palladium resulting in the formation of a palladium alkoxide. Aryl palladium alkoxide complexes have been shown to be susceptible to thermal reductive elimination.¹³ Alternatively, under catalytic conditions, a palladacycle-NHC aryl complex could form and subsequently eliminate the arylated aminoaryl fragment thereby generating the “Pd-NHC” fragment. We are now exploring which of these two activation modes is operating in the present system. In either case the generated electron-rich palladium(0) species stabilized by the presence of a NHC ligand then enters the catalytic cycle performing the oxidative addition of aryl halides (Scheme 2).

Scheme 2. Proposed Catalyst Activation Pathway



In summary, a new class of catalysts with a broad spectrum of activity in cross-coupling chemistry has been synthesized and fully characterized. The catalysts consist of a palladacycle scaffold stabilized by the presence of a highly donating, sterically demanding NHC ligand. The catalysts are well-defined, air stable, and very active in cross-coupling of aryl chlorides or triflates with amines and/or ketones. Their synthesis is simple and is achieved by mixing a NHC with a palladacycle in THF at room temperature. The large number of palladacycles and carbenes reported in the literature leaves open the possibility of discovering even more active catalysts. The proposed mechanism of activation is based on the generation of aryl-alkoxy palladium species that are subject to thermal elimination of ethers. The palladium(0) species formed upon elimination of the ether is stabilized by coordination to an electron-rich, sterically demanding NHC. Currently, we are expanding the scope and use of of NHC-palladacycle complexes to other cross-coupling and related reactions.

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Supporting Information Available: Experimental details for the synthesis of NHC/palladacycle complexes, catalysis protocol, and product isolation, as well as crystallographic tables. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) The general biaryl product depicted in Scheme 2 is a proposed product as GCMS (EI) results indicate the presence of a peak at 197 (269 less the alkoxide moiety). This in conjunction with a stable species indicated by the GC peak lends indirect support to such a species. Further studies aimed at unequivocally identifying and characterizing this product are ongoing.

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