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Sonogashira Coupling Using Bulky Palladium-Phenanthryl Imidazolium Carbene Catalysis

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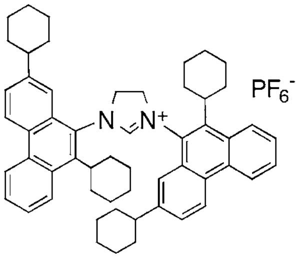
ABSTRACT



Bulky phenanthracenyl imidazolium-derived carbene ligands were investigated for copper-free Sonogashira coupling with terminal acetylenes. Aryl bromides and iodides gave coupled products in excellent yields from the $Pd(PPh_3)_2Cl_2$ complex with potassium *t*-butoxide and 18-crown-6 in THF. A remarkable dependence on the size of the ligand was found. The highest yields were obtained with the bulky 2,9-dicyclohexyl-10-phenanthryl ligand 5.

The use of palladium catalysts for the coupling of aryl and vinyl halides with terminal acetylenes is a powerful transformation for the production of substituted acetylenes.[1] Typical conditions include various palladium(0) and palladium(II) catalysts with copper cocatalysts and amine bases.[2] Often, excess acetylene is needed in order to obtain good yields, especially when electron-deficient substrates are used. Solvent polarity can also be a critical consideration. Polar aprotic solvents, DMF or NMP for example, allow for higher reaction temperatures with less reactive substrates. Solvents of intermediate polarity, ethyl acetate in particular, can often produce higher yields at lower temperatures with less diacetylene formation.[3] In an effort to reduce the amount of diacetylene formation, various copper-free conditions have recently been developed.[4] We now report a study of bulky phenanthrylimidazolium N-heterocyclic carbene (NHC) ligands for palladium catalysis of the Sonogashira reaction under copper-free conditions.[5] A dramatic dependence on the structure of the ligand is noted.

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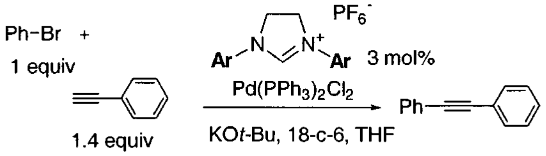
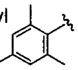
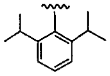
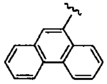
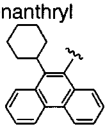
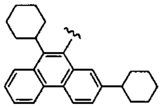
NHC ligands, due to their enhanced stability and reactivity, have been successfully applied to palladium and other transition metal-catalyzed reactions.[6] These include Heck,[7] Suzuki–Miyaura,[8] Stille, and Kumada couplings,[6] hydrogenation reactions,[9] and ring-closing metathesis reactions.[10] We recently reported base-free conditions with NHC catalysts for Heck and Suzuki couplings using reactive aryl diazonium ions.[11] Imidazolium carbene ligands provide strong σ-bond donation to the metal, together with attenuated back-bonding due to donation of the N1 and N3 lone pair electrons.[12] This arrangement renders the metal more electron-rich, allowing for a more favorable oxidative insertion step. Typical NHC–palladium complexes, formed by treatment of an imidazolium salt with base, are air stable and can be chromatographed in some cases. Alternatively, the NHC–Pd complex can be formed in situ without added base. Comparisons with substituted NHC ligands have been previously made between bis-mesityl and the 2,6-diisopropylimidazolium ligands and between the aromatic 4,5-dehydro and the saturated, non-aromatic 4,5-dihydro versions.[13] A dramatic effect is now demonstrated with the novel phenanthrenyl NHC ligands, where the most sterically hindered, extended aromatic ligand produces Sonogashira coupling product in high yields at moderate temperatures and short reaction times.

Shown in Table 1 are the effects of ligand substitution and reaction conditions. The known NHCs, *N,N*-bis-mesityl **1** and 2,6-diisopropylimidazolium hexafluoro phosphate **2**, were reacted with Pd(PPh$_3$)$_2$Cl$_2$ (3 mol %) and used in situ.[14] Other forms of palladium, were found to be less effective in this case, including Pd(OAc)$_2$, Pd(PPh$_3$)$_4$, PdCl$_2$, and Pd(dba). The optimal base was potassium *t*-butoxide (1.5 equiv) used with 18-crown-6 in THF heated at reflux for 12 h using bromobenzene as a test substrate. Other bases explored included K$_2$CO$_3$, Et$_3$N, Cs$_2$CO$_3$, and CsF, which proved to be inferior. When the solvent was changed to DMF or toluene, a comparable yield was obtained, while dioxane and methanol gave much lower yields. When the ligand is left out, a low yield was obtained following a 24 h reaction.

The most significant improvement was found when the new extended aromatic phenanthryl NHC ligands were explored.[15] Bis-9-phenanthryl ligand **3** gave only a slightly improved 51% yield under similar conditions. 10-Cyclohexyl-9-phenanthryl NHC **4**, a significantly more hindered variation, gave a 61% yield after only 3 h of reaction time. When used at room temperature, ligand **4** gave a modest 48% yield with bromobenzene. Finally, the more hindered 2,9-dicyclohexyl-10-phenanthryl ligand **5** gave a 90% yield of product after only 2 h of reaction time at 65 °C. After 12 h at room temperature, a 67% yield was obtained. Other variations, including Pd(OAc)$_2$ or the use of the chloride salt of **5**, gave lower yields. Use of Pd(dba)$_2$ gave a lower 71% yield under these conditions. The aromatic 4,5-dehydro analogue of **5** gave a reduced 82% yield after 2 h at reflux and a 51% yield at room temperature.

Table 1. Effect of Ligand and Conditions



lig.	Ar	time, h	temp. °C	yield, %^{a}
1	Mesityl 	12	65	17
2	2,6-di-*i*-PrPh 	12	65	47
-	no ligand	24	65	21
3	9-phenanthryl 	12	65	51
4	10-*c*-hexyl-9-phenanthryl 	3	65	61
4		12	rt	48
5	2,9-di-*c*-hexyl-10-phenanthryl 	2	65	**90**
5		12	rt	67
5		2	65	77^b
5		2	65	57^c

^{a} All yields are for isolated, chromatographed materials. ^{b} Pd(OAc)$_2$ was used for catalyst formation. ^{c} Chloride salt of dihydroimidazolium **5** was used.

The optimal coupling conditions with phenanthryl ligand **5** were used with numerous aryl bromides at 65 °C and iodides, reacted at room temperature, with terminal acetylenes to produce substituted alkynes (Table 2).[16] The iodides in general gave higher yields even when reacted at the lower temperature. Electron-rich and -deficient substrates were coupled with equal success with this system. Ortho substituents were well tolerated, including 2,6-dimethyl bromobenzene. 2-Bromothiophene also reacted with success. 1-Bromocyclohexene was investigated to demonstrate potential for

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(5) For previous NHC-catalyzed Sonogashira reactions, see: (a) McGuiness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741. (b) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411. (c) Hukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.

(6) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

(7) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511.

(8) (a) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290–292. (b) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077–1080.

(9) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.

(10) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.

(11) (a) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761. (b) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079.

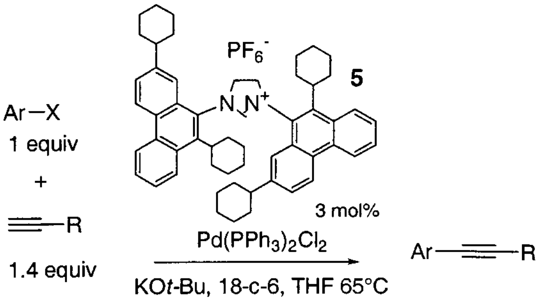
(12) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162.

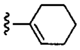
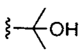
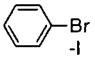
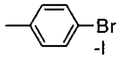
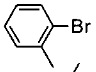
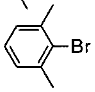
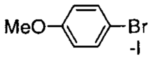
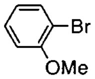
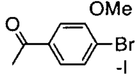
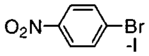
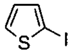
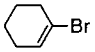
(13) Ref 8a and: Furstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343.

(14) Ligands **1** and **2** were formed following the known method: Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913.

(15) New bis-phenanthryl ligands **3**–**5** were formed using the method of Arduengo (ref 14) from the corresponding phenanthrylamines. See Supporting Information.

Table 2. Sonogashira Coupling with Bis-phenanthrenyl **5**



Ar−X	R= Ph yield, % (time, h)	*n*-hexyl		
 -I -Cl	91 (2)[a] 94 (3) trace (24)	87 (4)[a] 86 (4)	85 (4 h)[a] 90 (3.5)	86 (2.5) 76 (4)[b]
 -I	92 (2) 96 (3)	80 (4) 88 (3.5)	85 (4h) 91 (3.5)	88 (2.5) 81 (4)[b]
	87 (2)	76 (4)	82 (4)	84 (3)
	87 (2.5)	63 (5.5)	43 (5.5)	80 (3)
 -I	88 (2.5) 93 (3)	80 (5.5) 87 (3.5)	67 (5) 89 (4.5)	80 (3.5) 82 (5)[b]
	72 (2.5)	72 (5.5)	42 (5)	71 (4.5)
 -I	81 (2.5) 87 (3)	74 (5) 89 (3.5)	65 (5) 90 (3.5)	68 (5) 80 (4)[b]
 -I	88 (2.5) 98 (3)	78 (5.5) 91 (3.5)	78 (4) 93 (3)	81 (4) 87 (4)[b]
	88 (3)	80 (3.5)	87 (5)	71 (6)[b]
	74 (4)	56 (4.5)	71 (6.5)	72 (3)

[a] Reaction was conducted on 1 mmol scale. [b] Aryliodide reactions were conducted at room temperature.

applications with other vinyl halides. Chlorobenzene, in contrast, gave only a trace amount of product under these copper-free conditions.

There are two factors that may contribute to the success of the more bulky ligands in this case: dimer inhibition and enhancement of the rate of the reductive elimination step. The more bulky aryl groups may disfavor palladium complex dimerization, allowing for a higher concentration of the reactive palladium carbene monomer. Known crystal structures of palladium−NHC complexes are μ^2-bridged dimers.[17]

In summary, a dramatic dependence on the steric bulk of extended aromatic phenanthrylimidazolium carbene ligands for palladium-catalyzed Sonogashira coupling has been demonstrated. A wide range of substrates are coupled with high yields in THF at reflux using *t*-butoxide as base under copper-free conditions. Hindered NHC ligands of this type may be found to possess enhanced activity with related catalytic processes.

Acknowledgment. We are grateful to The NIH (GM57275, M.B.A.) and BYU for funding and The Chemistry College of Shandong University (Y.M.).

Supporting Information Available: Experimental procedures and characterization for all compounds, including the synthesis of ligand **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **General Procedure.** Aryl halide (0.100 mmol), terminal alkyne (0.140 mmol), $PdCl_2(PPh_3)_2$ (2.1 mg, 0.003 mmol, 3 mol %), dihydroimidazolium hexafluorophosphate salt (0.85 mg, 0.006 mmol, 6 mol %), and 18-c-6 (39 mg, 0.150 mmol) were treated with KO-*t*-Bu (16.8 mg, 0.150 mmol) in anhydrous THF (5 mL). The resulting suspension was stirred at room temperature for the aryl iodides or at reflux for the bromides, for the time indicated. The reaction mixture was washed (water, 5 mL) and extracted with ethyl acetate (3 mL, two times). Following drying with $MgSO_4$, concentration, and silica gel chromatography (EtOAc/hexanes, 0−10%), the known acetylene products, characterized by ^1H and ^{13}C NMR and MS, with the isolated yields indicated, were obtained. See Supporting Information.

(17) Flat, μ^2-bridged chloride, Pd−NHC X-ray complex formed from the free unsaturated carbene **2** is known: (a) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229. For a hindered 2:1 NHC−Pd complex, see: (b) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363.