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Sonogashira Couplings Catalyzed by Collaborative (*N*-Heterocyclic Carbene)-Copper and -Palladium Complexes

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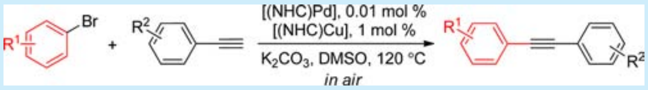
Supporting Information

ABSTRACT: A general protocol for the Sonogashira reaction using a 100:1 combination of (*N*-heterocyclic carbene)-Cu and (*N*-heterocyclic carbene)-Pd complexes is presented. Catalyst loadings of 1 mol % (NHC)-Cu and 0.01 mol % (NHC)-Pd allow for the coupling of aryl bromides and aryl alkynes, in air and in a non-anhydrous solvent, in high yields.



Transition-metal-catalyzed cross-coupling reactions have become one of the most prominent and reliable methods for the formation of carbon–carbon bonds.[1] Among them, the Sonogashira reaction, involving the coupling of a terminal alkyne and an aromatic halide to access arylated alkynes,[2,3] has been found useful in the synthesis of carbo- and heterocycles, natural products, polymers, and molecular nanostructures.[4] This C(sp)–C(sp^2) bond formation was first reported by the groups of Heck and Cassar using palladium complexes.[5,6] This discovery was soon followed by work from Sonogashira and coworkers, reporting that the addition of a copper co-catalyst could enhance the coupling.[7] The formation of reactive copper acetylides is often portrayed as a problem, thus rendering the reaction air- and moisture-sensitive. In addition, aerobic conditions tend to enhance the formation of undesired Glaser–Hay homocoupling products.[8−10] For these reasons, the development of copper-free systems has recently received significant attention.[11−21] On the other hand, efforts have also been made to carry out the coupling exclusively using copper,[22−27] as its significantly lower cost is advantageous to industrial applications. However, it has been shown that, very often, the presence of trace amounts of palladium has a significant effect on the "copper-catalyzed" Sonogashira reaction.[28,29] Similar phenomena have been reported for other cross-coupling reactions.[30]

Recently, Bolm and co-workers showed that copper-catalyzed reactions accelerate considerably in the presence of chelating diamines.[22,25] This was attributed to diamine ligation to copper, breaking down polymeric copper acetylides species and leading to more reactive monomeric copper acetylides. With these precedents in mind, it is surprising that the use of copper complexes bearing *N*-heterocyclic carbene ligands (NHC)[31,32] has been barely explored and, to the best of our knowledge, only two examples have been reported in the literature. In both cases, elaborated tris-copper tripodal NHC complexes were used for azole and phenol arylation, in addition to the coupling of aryl iodides and phenylacetylenes.[26,33] On the other hand, the use of (NHC)-Pd complexes for this reaction is more common, with or without the concurrence of a Cu salt.[34]

Because of our interests in the development of protocols for polymerizations using cross-coupling reactions,[35] we have recently turned our attention to the Sonogashira coupling. We reasoned that while an (NHC)-Pd catalyst could still be responsible for the catalytic cycle, the bulky nature of the most commonly used (NHC)-Cu complexes should be enough to inhibit the formation of the unreactive polymeric acetylide. In addition, the strong electron-donating properties of the NHC ligands should enhance the nucleophilicity of the copper acetylide, which is beneficial for the transmetalation step. Herein, we report the development of a novel protocol for Sonogashira couplings of arylacetylenes and aryl bromides that makes use of an (NHC)-Cu complex, in combination with submolar % amounts of an (NHC)-Pd complex, without the need of anhydrous conditions or inert atmosphere.

We first prepared a series of (NHC)CuCl complexes using a microwave synthesis protocol recently developed by our group (Figure 1).[36] To minimize the impact of other palladium

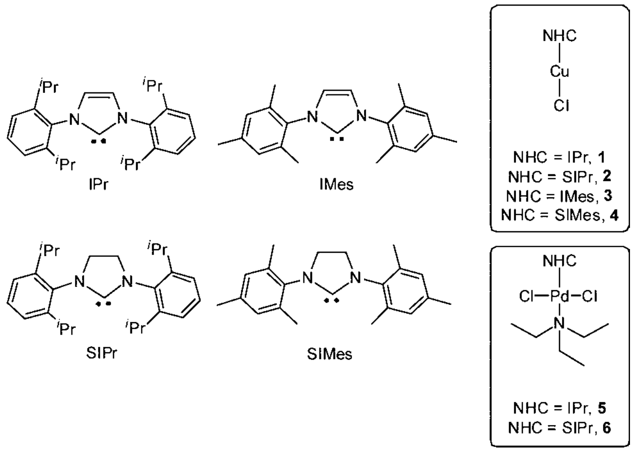


Figure 1. Complexes used in this study.

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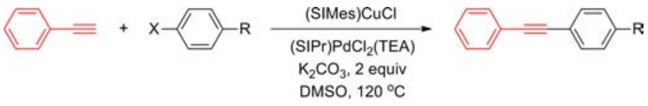
impurities, all of the coupling reactions were carried out in brand-new disposable screw-cap reaction vials and the magnetic stirring bars were washed in an acid bath before each use. The reaction vials were loaded in open air, and the solvent utilized (DMSO) was of technical grade. We began our investigation with the coupling of phenylacetylene and iodobenzene at 120 °C, in the presence of 1 mol % copper complex (SIMes)CuCl (**4**). After observing no further conversion to product after 21 h by gas chromatography, a 72% yield of the desired product was isolated (Table 1, entry 1). A dramatic change was observed when a very small amount (0.01 mol %) of palladium complex (SIPr)Pd(TEA)Cl_2 (**6**)[37] was added, driving the reaction to completion in only 30 min (Table 1, entry 2). On its own, the same amount of **6** afforded only 31% of phenylacetylene after 4 h. This preliminary catalytic system was also capable of coupling bromobenzene (Table 1, entry 4) in high yield after 21 h, although no product could be obtained when attempting to couple an activated chloride (4′-chloroacetophenone), even with a substantially higher palladium loading (Table 1, entry 5). Attempts to couple heterocyclic alkynes 2-ethynylpyridine and 2-ethynylthiophene were also unsuccessful. It is worth mentioning that less than 5% of the Glaser homocoupling product was observed in all of these experiments, which is significant given the high reaction temperature and aerobic atmosphere.

Table 1. Initial Studies

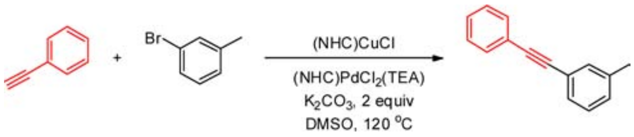


entry	R	X	[Cu] (mol %)	[Pd] (mol %)	*t* (h)	yield (%)[a]
1	H	I	1	0	21	72
2	H	I	1	0.01	0.5	99
3	H	I	0	0.01	4	31
4	H	Br	1	0.01	21	91
5	MeCO	Cl	1	1	24	nd

[a] Reaction conditions: aryl halide, 0.5 mmol; phenylacetylene, 0.75 mmol; K_2CO_3, 1 mmol; DMSO, 0.5 mL total; in air. See Supporting Information for details on (NHC)-Pd catalyst stock solution.

With a preliminary idea of the limitations of the protocol, we chose the coupling of 3-bromotoluene and phenylacetylene to further optimize our catalytic system. Keeping constant the (NHC)-Pd complex (**6**), we compared the activity of (NHC)CuCl complexes **1**−**4** (Table 2, entries 1−4). Complexes bearing saturated carbenes (**2** and **4**) gave considerably superior yields compared with those with unsaturated carbenes, with **2** affording the highest yield (94%). This trend in reactivity toward alkynes had been previously observed in A^3 coupling reactions.[38] Decreasing the loading of palladium catalyst by half did not affect the amount of product isolated (Table 2, entry 5), but changing **6** for IPr-bearing counterpart **5** decreased the yield considerably (Table 2, entry 6). Decreasing further the copper loading proved to be detrimental (Table 2, entry 7), as well as attempts to decrease the reaction time, even using a higher Pd loading (Table 2, entries 8 and 9). Having identified the combination of Pd complex **6** and Cu complex **2** as the most efficient, a series of experiments were carried out to ensure that the coupling was being catalyzed by the cooperation of the two (NHC)-metal complexes. The absence of the Cu complex in the reaction led to incomplete reactions (Table 2, entries 10 and 11), as well as the removal of the Pd complex (Table 2, entry 12). Finally, we examined the effect of the NHC ligands in this catalytic system. The use of CuCl in combination with (NHC)-Pd **6** afforded a considerably lower yield, along with an increase in Glaser byproduct (Table 2, entry 13). Similarly, when the (NHC)-Pd was switched to $Pd(OAc)_2$ and used in combination with (NHC)-Cu **2**, the yield of the desired coupling product was reduced by almost half (Table 2, entry 14).

Table 2. Reaction Optimization



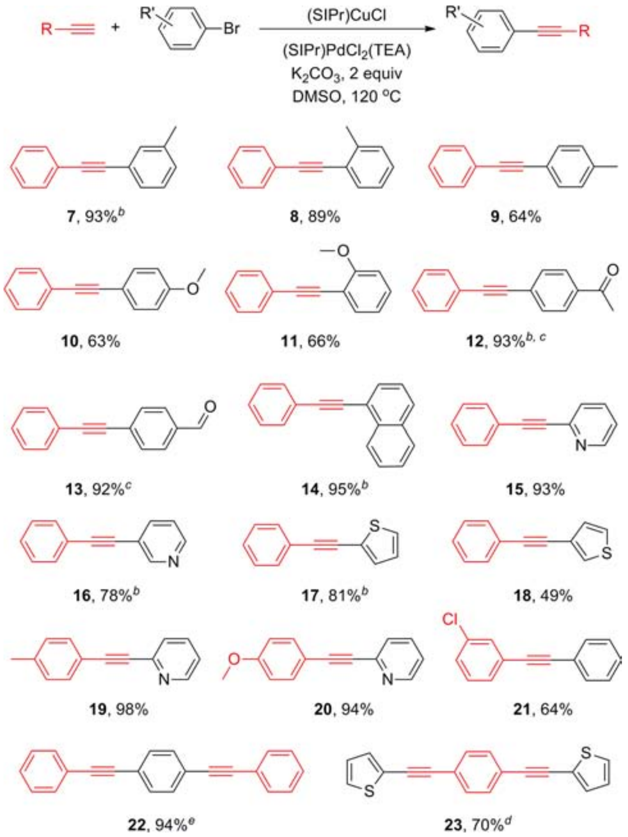
entry	[Cu] (mol %)	[Pd] (mol %)	*t* (h)	yield (%)[a]
1	**1** (1)	**6** (0.01)	24	16
2	**2** (1)	**6** (0.01)	24	94
3	**3** (1)	**6** (0.01)	24	34
4	**4** (1)	**6** (0.01)	24	67
5	**2** (1)	**6** (0.005)	24	93
6	**2** (1)	**5** (0.005)	24	79
7	**2** (0.5)	**6** (0.005)	24	83
8	**2** (1)	**6** (0.005)	16	78
9	**2** (1)	**6** (0.1)	6	86
10		**6** (0.005)	24	14
11		**6** (0.1)	24	27
12	**2** (1)		24	5
13	CuCl (1)	**6** (0.005)	24	51[b]
14	**2** (1)	$Pd(OAc)_2$ (0.005)	24	56

[a] Reaction conditions: 3-bromotoluene, 0.5 mmol; phenylacetylene, 0.75 mmol; K_2CO_3, 1 mmol; DMSO, 0.5 mL; in air. See Supporting Information for details on Pd catalyst stock solution. [b] 12% of homocoupling product observed by GC.

With the optimized conditions in hand, a variety of aryl bromides were coupled with aryl alkynes (Scheme 1). Phenylacetylene was coupled with a series of electron-rich (Scheme 1, **7**−**11**), electron-poor (Scheme 1, **12**, **13**), neutral (Scheme 1, **14**), and heterocyclic bromides (Scheme 1, **15**−**18**), in yields ranging from 49% to 95%. As expected, the coupling of activated bromides proceeded at a much faster rate, and the reactions were completed almost 1 order of magnitude faster (3 h vs 24 h). Excellent yields were obtained when aromatic acetylenes bearing electron-donating groups such as methyl and methoxy were used (Scheme 1, **19** and **20**). On the other hand, the presence of an electron-withdrawing chloride proved detrimental, and the coupled product was obtained in a moderate yield (Scheme 1, **21**). It is worth at this point mentioning that control experiments proved that stock solutions of (NHC)-Pd complex **6** in DMSO could be used for at least one month without detriment in activity in the coupling reactions.

Poly(*p*-phenyleneethynylene)s (PPEs) conjugated polymers have been widely applied in the area of sensor, solar cell, and display technologies and are usually prepared by Sonogashira coupling between an aryl diiodide and acetylenes.[39] To test the potential of our protocol for these polymerizations, we coupled 1,4-dibromobenzene with phenylacetylene, obtaining the desired coupling product in an excellent yield (Scheme 1, **22**). With the same purpose and to expand the scope to heterocycles, we were able to couple diacetylene with 2-

Scheme 1. Sonogashira Reactions of Aryl Bromides and Arylacetylenes Catalyzed by NHC-Bearing Catalysts 2 and 6[a]

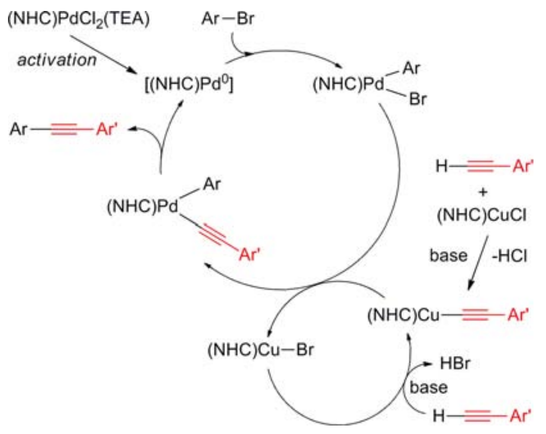


[a]Reaction conditions: 3-bromotoluene, 0.5 mmol; phenylacetylene, 0.75 mmol; K_2CO_3, 1 mmol; **6**, 0.01 mol %; **2**, 1 mol %; DMSO, 0.5 mL total; in air; 24 h. See Supporting Information for details on Pd catalyst stock solution. [b]**6**, 0.005 mol %. [c]Three hour reaction time. [d]Diacetylene, 0.5 mmol; bromothiophene, 1.1 mmol. [e]Dibromobenzene, 0.5 mmol; phenylacetylene, 1.1 mmol.

bromothiophene under the same reaction conditions, albeit with a lower yield (Scheme 1, **23**).

A plausible mechanism for the reaction is depicted in Scheme 2, based on the classical description of the Sonogashira reaction, involving two connected catalytic cycles.[40] The first one is a $Pd^0/Pd^{II}/Pd^0$ oxidative addition/transmetalation/reductive elimination process, promoted by the (NHC)$PdCl_2$(TEA) complex. Analogous (NHC)$PdCl_2$(3-Cl-pyridine) complexes have been shown to provide the catalytically active (NHC)-Pd(0) species (activation) after a sequential double transmetalation of the organometallic coupling partner, in this case the (NHC)Cu(acetylide) complex formed in the second catalytic cycle, followed by reductive elimination.[41]

Scheme 2. Proposed Mechanism



In summary, we have developed a user-friendly protocol for the Sonogashira coupling of a wide range of aryl bromides with aryl alkynes, making use of low loadings of a combination of (NHC)-Pd and (NHC)-Cu catalysts. To the best of our knowledge, these are the lowest (NHC)-Pd and (NHC)-Cu catalyst loadings reported in the literature for the Sonogashira coupling of aryl bromides. In addition, the reactions can be carried out in a non-anhydrous solvent and without the need for an inert atmosphere. Mechanistic studies as well as the application of this protocol for Sonogashira polymerizations are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and ^1H and $^{13}C\{^1H\}$ NMR spectra for products **7**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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