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FULL PAPER

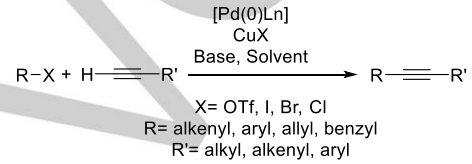
# A Novel, Sustainable, User-Friendly Protocol for the Pd-Free Sonogashira Coupling Reaction

Aggeliki A. Liori,[a] Ioannis K. Stamatopoulos,[a] Argyro T. Papastavrou,[a] Afroditi Pinaka,[a] and Georgios C. Vougioukalakis*[a]

**Abstract:** We herein present a new catalytic system for the palladium-free Sonogashira coupling reaction. The catalytically-active moiety is formed in situ, in a straightforward and user-friendly manner, by combining a widely-available low-cost copper salt and an N-heterocyclic carbene precursor. A series of N-heterocyclic carbene ligand precursors with variable structural features, some of which are novel, were tested and the reaction conditions were optimized. Using the catalytic system with the optimum performance, the scope of the alkyne and the aryl halide was probed. Aryl iodides readily react with terminal alkynes, providing the coupling products in high to excellent yields. The protocol is highly-efficient with alkynes bearing either alkyl or aryl substituents, the latter having either electron-donating or electron-withdrawing groups.

## Introduction

The Sonogashira reaction is known since 1975 and comprises a powerful synthetic approach for the construction of C(sp)-C($sp^2$) bonds.[1] Heck and Cassar independently reported the Pd-catalyzed arylation and alkenylation of alkynes in the presence of organic or inorganic bases in 1975.[2] Later on, Sonogashira and Hagihara showed that the addition of a catalytic amount of copper(I) iodide, as co-catalyst, induces a significant accelerating effect in the reaction rate.[1] In the early days, reaction conditions included Pd(0) as (pre)catalyst, triphenylphosphine as ligand and copper iodide as co-catalyst, in a basic medium at temperatures between 25°C and 100°C (Scheme 1). According to the generally-accepted mechanism, a copper-acetylide species is generated in situ, which then transfers the acetylide moiety to palladium for the desired coupling to occur, through a reductive elimination pathway. Sonogashira coupling approaches are widely-applied in the synthesis of pharmaceuticals, natural products and organic materials with technological applications.[3] In natural product synthesis, the Sonogashira reaction can be used as the key coupling step to synthesize conjugated enynes or enediynes. It can be also combined with transformations that convert the triple bond into other functionalities, or with regioselective hetero-annulation, leading to heterocyclic products.[4] Aryl-alkyne and conjugated alkenyne moieties are moreover contained in many intermediates or precursors used in the synthesis of non-linear optical materials and polymers utilized in applications such as molecular electronics.[5]




**Scheme 1.** The typical Sonogashira-Hagihara coupling reaction conditions.

Many modifications of the typical Sonogashira reaction have been developed, including the use of other transition metals, ligands, environmentally-friendly reaction media (ionic liquids, water, or solvent-less), phase-transfer or even photochemical reaction conditions.[5a] Microwave irradiation, combined with a phase-transfer agent, has been also applied to the Sonogashira reaction in the absence of a metal catalyst.[6] Successful examples using water as the solvent have been reported under palladium, copper, or iron catalysis.[7]

Numerous metal complexes, salts, or nanoparticles, based on iron, cobalt, nickel, copper, indium, silver, gold, manganese or ruthenium have been reported to catalyze the Sonogashira coupling reaction, besides palladium.[8] The straightforward and step-economical nature of some of these protocols makes them ideal for industrial applications. Along these lines, the replacement of noble transition metal catalysts with low-cost, environmentally benign and abundant transition metal catalytic systems is a highly-attractive strategy, increasing the sustainability of chemical transformations.[9,10]

The majority of ligands utilized in Pd-free, Cu(I)- or Cu(II)-catalyzed Sonogashira coupling reactions contain nitrogen, phosphorus, or oxygen donors. The most widely-used Cu-based catalytic systems employ ethylenediamine, 1,10-phenathroline, 1,4-diphenyl-1,4-diazabuta-1,3-diene, 1,4-diazabicyclo[2.2.2]octane (DABCO) or N,N'-dibenzyl-BINAM.[11] In most cases, a large excess (up to 30%) of the multi-dentate ligand is required.[12] Other synthetic protocols employ multinuclear copper complexes bridged by N-donor ligands, copper nanoparticles, microwave-assisted reactions, or Cu-catalyzed Sonogashira couplings under blue LED light irradiation.[13,14]

The use of N-heterocyclic carbenes (NHCs) in the rapidly-evolving field of copper-catalyzed Sonogashira reaction has not been investigated thoroughly, despite the wide utilization of this ligand family in other useful transformations, such as in Heck coupling and olefin metathesis.[15] This Cu-catalyzed approach

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has thus far resulted in only limited success, with only four recently published reports.[16-18] In 2009, Biffis and co-workers developed trinuclear NHC-coordinated copper complex **1** (Figure 1), compared its catalytic activity in the Sonogashira coupling reaction with [Cu(Cl)(IPr)] (**2**) and showed that **1** is more catalytically-efficient. A range of aryl iodides, bromides and chlorides were successfully transformed into the corresponding internal alkynes.[16,17] Whittlesey and co-workers have synthesized another tri-nuclear copper complex, bearing a tripodal NHC ligand and an isolated oxygen atom (**3**, Figure 1), which also shows Sonogashira coupling efficiency.[18] Shulka and co-workers prepared PS-Cu-NHC complex **4** (Figure 1), a recyclable heterogeneous catalyst, and successfully utilized it in Sonogashira coupling reactions as well.[19] In another recent work, Tahsini and co-workers investigated the catalytic activity of a series of copper bis-carbene mononuclear complexes (**5**, Figure 1) in Sonogashira couplings. These complexes efficiently catalyze the coupling of aryl iodides with phenyl acetylene derivatives in the presence of oxygen, while the reaction proceeds through a radical mechanism.[20]

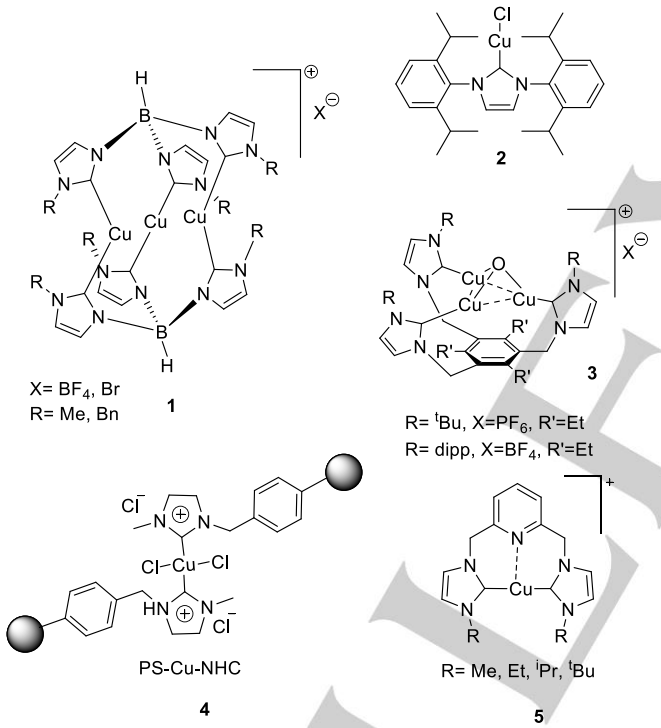



**Figure 1**: N-Heterocyclic carbene-based copper complexes as Sonogashira catalysts.

Considering the lack of a detailed study on the catalytic activity of simple, in-situ-prepared NHC/Cu-based catalytic systems in the Sonogashira reaction, along with the wide availability, low-cost and biocompatibility of copper, we herein report the development of a sustainable, inexpensive, straightforward and user-friendly protocol for this highly-useful transformation. This protocol can be easily followed in any synthetic laboratory and requires a very simple experimental setup, along with widely-available, stable (pre)catalytic components. The in-situ formation of this new catalytic system reduces the required effort, time and chemicals for the synthesis, purification and characterization of the (pre)catalysts. Besides screening a number of low-cost, widely-available copper sources, an extensive library of NHC precursors, some of which are new, having different steric and electronic properties, are evaluated. The most efficient catalytic system comprises $CuSO_4•5H_2O$ and a commercially-available NHC precursor salt. This system couples a wide variety of terminal alkynes (electron-poor aryl, electron-rich aryl, or alkyl) with both electron-poor and electron-rich aryl iodides, in a highly-efficient manner.

## Results and Discussion

Given that aerobic reaction conditions favor the Glaser/Hey alkyne homocoupling (by)products,[21] all experiments were conducted under an inert atmosphere. In order to probe and optimize the cross-coupling reaction conditions, we chose the coupling of *p*-iodonitrobenzene with phenylacetylene as the model reaction. Initially, we tested a number of widely-available copper sources (Table 1). Both copper(I) and copper(II) salts catalyze the reaction, with the catalytic activity and selectivity towards the desired Sonogashira coupling product being dependent on the nature of the copper salt. Among all tested salts, $CuSO_4•5H_2O$ afforded the optimum results under the herein studied conditions.

**Table 1.** Copper source optimization.


| Entry | Copper Source | Product (%)* | Homocoupling Product (%)* |
|---|---|---|---|
| 1 | $Cu(NO_3)_2•3H_2O$ | 26 | 6 |
| 2 | $Cu(OAc)_2•2H_2O$ | 38 | 6 |
| 3 | $Cu(OAc)_2$ | 52 | 7 |
| 4 | $CuCl_2•2H_2O$ | 48 | 5 |
| 5 | $CuSO_4•5H_2O$ | 59 | 8 |
| 6 | $CuCl_2$ | 44 | 5 |
| 7 | CuCl | 38 | 10 |
| 8 | CuI | 44 | 10 |

*Yields calculated by GC/MS analysis
Experimental conditions: Cu salt 12 mol%, NHC precursor **25** 12 mol%, 1-iodo-4-nitrobenzene 0.5 mmol, phenylacetylene 0.6 mmol, $K_2CO_3$ 1 mmol, solvent DMF (3 mL), temperature = 125°C, reaction time 8h.

**Table 2.** Base optimization.

| Entry | Base | Product (%)* | Homocoupling Product (%)* |
|---|---|---|---|
| 1 | $K_2CO_3$ | 59 | 8 |
| 2 | $Cs_2CO_3$ | 43 | 6 |
| 3 | KOH | 50 | 8 |
| 4 | *t*BuONa | 32 | 8 |

*Yields calculated by GC/MS analysis
Experimental conditions: $CuSO_4$•$5H_2O$ 12 mol%, NHC precursor **25** 12 mol%, 1-iodo-4-nitrobenzene 0.5 mmol, phenylacetylene 0.6 mmol, base 1 mmol, solvent DMF 3 mL, temperature = 125°C, reaction time 8h.

**Table 3.** Solvent optimization.

| Entry | Solvent | Product (%)* | Homocoupling Product (%)* |
|---|---|---|---|
| 1 | DMF | 59 | 8 |
| 2 | EtOH | 30 | 5 |
| 3 | Dioxane | 0 | 0 |
| 4 | DMAc | 54 | 6 |
| 5 | NMP | 38 | 7 |
| 6 | $Et_3N$ | 29 | 5 |
| 7 | DMSO | 36 | 8 |

*Yields calculated by GC/MS analysis
Experimental conditions: $CuSO_4$•$5H_2O$ 12 mol%, NHC precursor **25** 12 mol%, 1-iodo-4-nitrobenzene 0.5 mmol, phenylacetylene 0.6 mmol, base 1 mmol, solvent 3 mL, temperature = 125°C, reaction time 8h.

After determining the optimum copper source, we studied the effect of base. As shown in Table 2, the best results were obtained with $K_2CO_3$. With regards to the solvent, polar aprotic solvents are the most commonly-used media for the Sonogashira reaction. This was confirmed in the case of the herein-developed protocol as well, with the most efficient solvent being DMF (Table 3). Moreover, reaction temperatures in the range of 100°C are typical for the copper-catalyzed Sonogashira coupling reaction. Our studies showed that the herein-reported catalytic system exerts its highest efficiency at 125°C. Finally, we investigated the impact of the (pre)catalytic species' loading. The best results were obtained with 20 mol% copper and NHC precursor loading (copper/NHC precursor 1:1, entry 6, Table 4). Use of other copper/NHC precursor ratios does not improve the desired product yield (Table 4).

The in situ-generated NHC ligands' influence on the reaction outcome was then studied thoroughly, by employing a series of NHC precursors having variable steric and electronic characteristics. Besides the known from the literature NHC precursor salts **6**-**7**, **9** and **18**-**31** (Table 5), novel, unsymmetrical NHC precursors **10**-**17** (Table 5) were also synthesized and utilized.

**Table 4.** (Pre)catalytic species' loading optimization.

| Entry | $CuSO_4$•$5H_2O$ | NHC Precursor **25** | Sonogashira Product (%)* | Homocoupling Product (%)* |
|---|---|---|---|---|
| 1 | 5 | 15 | 33 | 9 |
| 2 | 10 | 10 | 41 | 7 |
| 3 | 10 | 20 | 36 | 5 |
| 4 | 20 | 10 | 56 | 16 |
| 5 | 12 | 12 | 59 | 8 |
| 6 | 20 | 20 | 81 | 15 |

*Yields calculated by GC/MS analysis
Experimental conditions: copper source $CuSO_4$•$5H_2O$, NHC precursor **25**, 1-iodo-4-nitrobenzene 0.5 mmol, phenylacetylene 0.6 mmol, $K_2CO_3$ 1 mmol, solvent DMF (3 mL), temperature = 125°C, reaction time 8h.

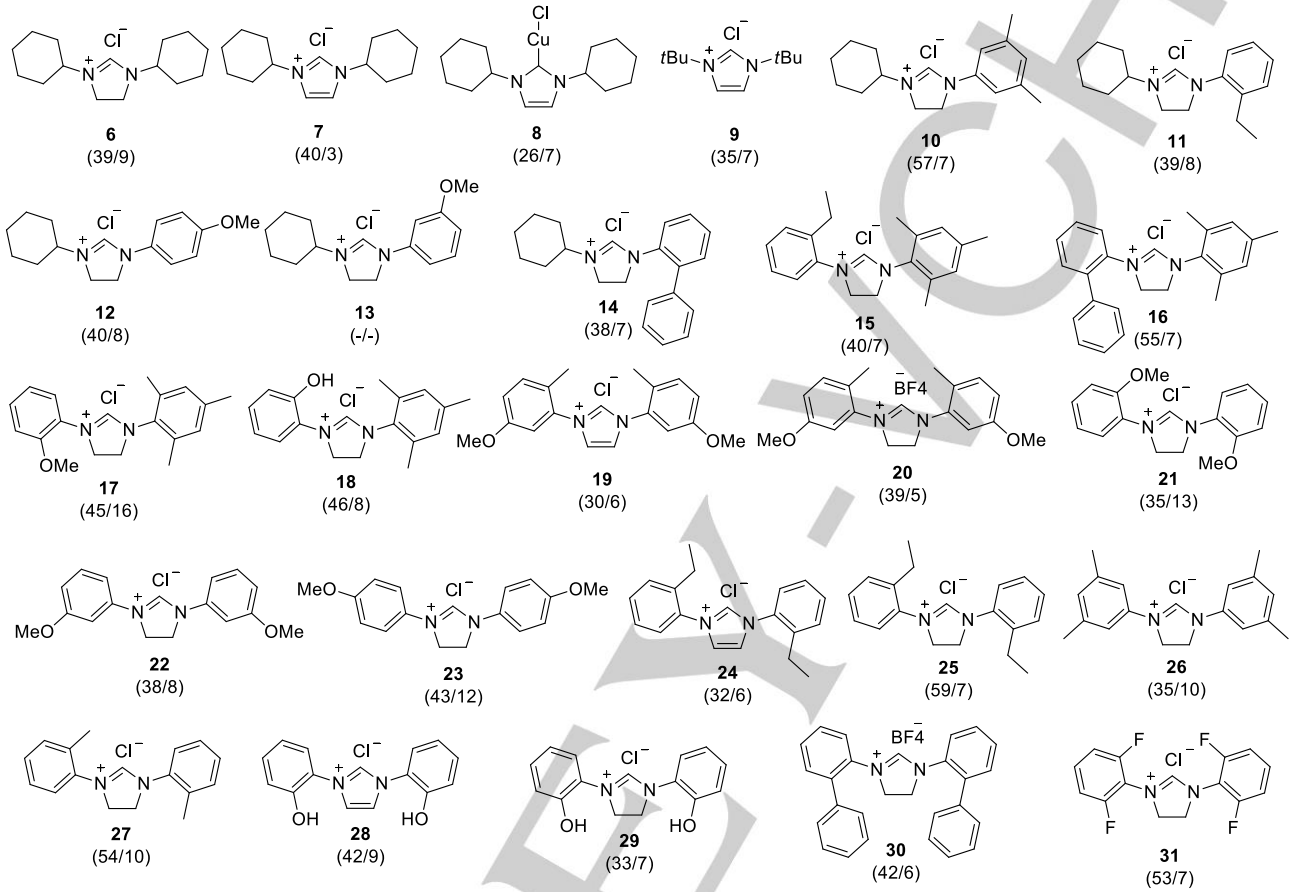
It is interesting to note that the preformed, well-defined copper complex **8** affords lower Sonogashira product yields and inferior product/byproduct (Glaser/Hey alkyne homocoupling) ratios in comparison to the in-situ formed analogous catalytic system based on NHC precursor **7** (Table 5) under identical conditions. This finding suggests the formation of different and/or additional, more active catalytic species in the case of the in-situ formed system, in comparison to the well-defined one.

With regards to the structural variation of the NHCs utilized, the increased yield of the homocoupling (by)product in the case of *ortho*- and *para*- MeO-substituted **21** and **23**, in comparison to the *meta*-substituted **22**, can be attributed to the increased electron density transfer to the nitrogen atom of the imidazolinium ring in the case of **21** and **23**. Moreover, the increased Sonogashira product yield in the case of *meta*- and *para*-substituted NHC salts **22** and **23**, in comparison to the *ortho*-substituted NHC precursor **21**, most probably originates from the decreased steric hindrance adjacent to the carbenic center of the NHCs in the case of NHC salts **22** and **23**. Furthermore, there is no clear correlation between the saturated or unsaturated backbone of the imidazolinium or imidazolium ring, respectively, as well as between the symmetrical or unsymmetrical nature of the NHC substituents with the corresponding catalytic activity. The highest Sonogashira product yield (59%) and optimum product/byproduct ratio (59/7) from all herein-studied NHC precursors were obtained with the symmetrical carbene **25** (Table 5). The corresponding NHC precursor having an unsaturated imidazolinium ring (**24**, Table 5) provides significantly lower product yield and product/byproduct ratio.

Finally, although the coupling of *p*-iodonitrobenzene with phenyl acetylene is feasible in the absence of an NHC precursor (Sonogashira/homocoupling product yield is 28%/7% under identical to the NHC screening reaction conditions), both the Sonogashira product yield and the Sonogashira/homocoupling product ratio is significantly inferior, in comparison to the conditions employing an NHC precursor as well. That is, in the reaction of *p*-iodonitrobenzene, the addition of NHC salts significantly improves the Sonogashira product yields and

decreases the yield of the alkyne dimer (byproduct). Even more importantly, no Sonogashira product was generated in the absence of an NHC precursor with the other organohalides studied (both aromatic and aliphatic).

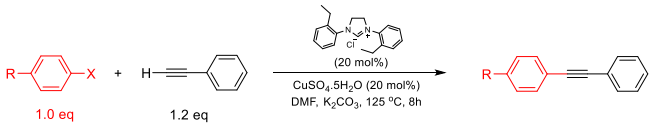
**Table 5.** NHC precursors and the well-defined Cu complex studied, along with the corresponding Sonogashira and homocoupling (by)product yields.

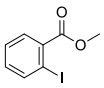



Experimental conditions: $CuSO_4 \cdot 5H_2O$ 20%, NHC precursor 20%, $K_2CO_3$ 1 mmol, 1-iodo-4-nitrobenzene 0.5 mmol, phenylacetylene 0.6 mmol, solvent DMF 3 mL, temperature =125°C, reaction time 8h.

Having determined the optimum catalytic system and reaction conditions, we examined the organohalide and alkyne reaction scope. Aryl iodides bearing electron withdrawing groups react with phenylacetylene affording the cross-coupling product in very good GC and isolated yields (entries 1 and 8, Table 6). Iodobenzene and aryl iodides having electron donating substituents react in low to very good yields (entries 4, 7 and 9, Table 6). Electron-poor aryl bromides are less reactive (entries 2 and 12, Table 6), while electron-rich aryl bromides are not reactive at all with phenylacetylene (entries 5 and 6, Table 6). Aryl chlorides do not react with phenylacetylene as well, even when they bear electron withdrawing substituents (entry 3, Table 6). Our protocol is highly-efficient with heterocyclic aryl iodides such as 3-iodopyridine (entry 11, Table 6).

**Table 6.** Aryl halide Sonogashira reaction scope.




| Entry | R | X | Sonogashira Coupling Product % GC Yield (Isolated Yield) |
|---|---|---|---|
| 1 | $NO_2$ | I | 81 (77) |
| 2 | $NO_2$ | Br | 32 |
| 3 | $NO_2$ | Cl | trace |
| 4 | OMe | I | 70 (67) |
| 5 | OMe | Br | trace |
| 6 | Me | Br | trace |
| 7 | H | I | 75 (71) |
| 8 | $CF_3$ | I | 65 |
| 9 | $NH_2$ | I | 19 |
| 10 |  | | 79* |
| 11 |  | | 87 (84) |
| 12 |  | | 9 monosubstituted |

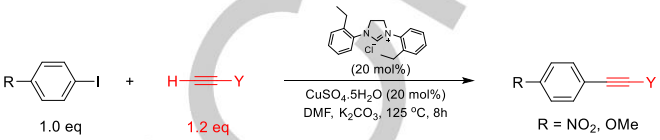
Experimental conditions: $CuSO_4$•$5H_2O$ 20 mol%, NHC precursor **25** 20mol%, aryl halide 0.5 mmol, phenylacetylene 0.6 mmol, $K_2CO_3$ 1 mmol, solvent DMF 3 mL, temperature =125 °C, reaction time 8h.

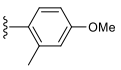
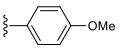
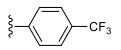
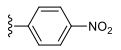
*Depending on the workup conditions, a small percentage gets hydrolyzed to the corresponding acid.

We then extensively studied the Sonogashira reaction scope with regards to the alkyne, by coupling *p*-iodonitrobenzene or *p*-iodoanisole with alkyl- or aryl-substituted terminal alkynes having variable steric and electronic characteristics (Table 7). The bulky, *tert*-butylacetylene reacts in very good to excellent yields (entry 2) with both *p*-iodonitrobenzene and *p*-iodoanisole, while 1-pentyne reacts in low to moderate yields (entry 1) most probably due to its low boiling point. Both *tert*-butylacetylene and 1-pentyne provide better yields with the electron-poor *p*-iodonitrobenzene. Aryl-substituted terminal alkynes bearing electron donating groups at the phenyl ring react in excellent to quantitative yields (entries 4-7, Table 7), against both *p*-iodonitrobenzene and *p*-iodoanisole, with the reactions of *p*-iodoanisole being slightly more efficient. It is worth mentioning that even the cross-coupling of an *ortho*-substituted, sterically-hindered alkyne proceeds efficiently, as shown in entry 6 (Table 7).

Terminal alkynes bearing aryl substituents with electron-withdrawing groups react almost quantitatively with *p*-iodonitrobenzene, whereas with *p*-iodoanisole they react in low yields (entries 8 and 9, Table 7). These low yields, in the case of *p*-iodoanisole, originate from the competing formation of the Glaser/Hey alkyne homocoupling product.

**Table 7.** Terminal alkyne Sonogashira reaction scope.




| Entry | Y | Cross-Product % NMR Yield (Isolated Yield) R=$NO_2$ | Cross-Product % NMR Yield (Isolated Yield) R=OMe |
|---|---|---|---|
| 1 |  | 41 | 28 |
| 2 |  | 97 | 84 |
| 3 |  | 81 (77) | 70 (67) |
| 4 |  | 82 | 99 |
| 5 |  | 89 | 99 |
| 6 |  | 56 (51) | 86 (80) |
| 7 |  | 99 | 99 |
| 8 |  | 98 (92) | 1 |
| 9 |  | 99 (94) | 16 |

Experimental conditions: $CuSO_4$•$5H_2O$ 20 mol%, NHC precursor **25** 20mol%, 1-iodo-4-nitrobenzene or *p*-iodoanisole 0.5 mmol, terminal alkyne 0.6 mmol, $K_2CO_3$ 1 mmol, solvent DMF 3 mL, temperature = 125 °C, reaction time 8h.

## Mechanistic Insights

An important issue concerning the use of copper salts as catalysts in palladium-free Sonogashira reactions is the possible presence of palladium impurities. In this regard, Novak and co-workers have published a work on the influence of palladium traces on the copper-catalyzed Sonogashira reaction.[22] More specifically, they showed that palladium concentration of even ppb levels can significantly increase the catalytic activity of a copper-based catalytic system. To verify copper catalysis in our system, we

examined the catalytic activity of four different $CuSO_4•5H_2O$ sources, from different producers, including a new batch having the highest possible commercially-available purity (99.999%), in the reaction of Table 1, entry 5. Our study afforded almost identical results in all cases, with variations within our protocol's experimental error.

On a different note, copper catalysis in the Sonogashira cross-coupling reaction is often associated with the presence of radical species. To probe the possible involvement of free radicals in our protocol, we performed two types of benchmark reactions. Experiments carried out in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), one of the most widely-utilized radical scavenger, showed only a very slight decrease of the coupling product yield, suggesting the absence of radical species in the main reaction pathway.[23] Moreover, experiments carried out in the presence of the radical initiator azobisisobutyronitrile (AIBN) did not show an enhanced catalytic activity of our system, again excluding the intervention of free radical species in the main cross-coupling route.[24]

Additionally, we performed a number of blank experiments in the reaction of phenylacetylene with aryl iodides (*p*-iodonitrobenezene and *p*-iodoanisole). All experiments carried out without a copper source showed that the reaction does not proceed in absence of copper. Finally, experiments carried out by using only the inorganic base did not afford any cross-coupled product at all.[25]

The generally-accepted copper(I)-catalyzed Sonogashira coupling mechanism involves formation of the copper acetylide, oxidative addition to the organohalide and, eventually, reductive elimination of the cross-coupled product.[26-28] The current mechanistic understanding concerning copper(II) catalytic systems involves reduction of copper(II) to copper(I) by the solvent or the ligand (usually amines), followed by the mechanism proposed for copper(I) systems.[29] The transient formation of yellow solids in the reaction mixture of copper-catalyzed Sonogashira couplings has been attributed to intermediate copper acetylides.[30] In the course of our experiments we observed that the reaction mixtures very often turned yellow, during the first minutes of the reaction, a fact we also believe is due to the transient formation of copper acetylides.

## Conclusions

A novel, sustainable, user-friendly catalytic protocol for the copper-based, palladium-free Sonogashira coupling reaction was developed. The catalytic system is formed in-situ in a straightforward manner, by using widely-available, low-cost, stable pre-catalytic species: a copper salt, an NHC ligand precursor and an inorganic base. The reaction conditions were optimized and the impact of the NHCs' stereochemical and electronic features influence on the reaction outcome was investigated by screening a series of NHC ligand precursors bearing a variety of functional groups. Some of the studied NHC precursors have not been reported in the literature before. The cross-coupling reaction scope with regards to both the organohalide and the alkyne was investigated thoroughly. Aryl iodides, bearing either electron-withdrawing or electron-donating substituents, react in good to excellent yields with phenylacetylene, while aryl bromides are less reactive and aryl chlorides do not react at all. With regards to the different terminal alkynes studied, the protocol is highly efficient with both alkyl- and aryl-substituted alkynes, bearing either electron donating or electron withdrawing moieties, in most cases providing excellent or quantitative yields with *p*-iodonitrobenezene and *p*-iodoanisole.

## Experimental Section

**General Remarks.** All chemicals were obtained from commercial sources and were used without any further purification. Solvents were purified according to published procedures,[31] distilled and stored under argon over 3Å molecular sieves. $^1H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded with a Varian Mercury 200MHz spectrometer. NMR spectroscopic data is given in the order: chemical shift, multiplicity (s: singlet, br. S: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet), coupling constant in Hertz (Hz), and number of protons. HRMS spectra were recorded in a QTOF maxis Impact (Bruker) spectrometer with Electron Spray Ionization (ESI). The GC-MS spectra were recorded with a Shimandzu R GCMS-QP2010 Plus Chromatograph Mass Spectrometer using a MEGAR (MEGA-5, F.T: 0.25μm, I.D.: 0.25mm, L: 30m, Tmax: 350 °C, Column ID# 11475) column. The course of the reactions and the separation of the formed products was followed with either GC-MS or thin layer chromatography (TLC), using aluminium sheets (0.2 mm) coated with silica gel 60 with fluorescence material that absorbs at 254 nm (silica gel 60 F254). The purification of the products was carried out by flash column chromatography, using silica gel 60 (230-400 mesh).

**General procedure for the Sonogashira coupling reactions.** A dry Schlenk tube equipped with a magnetic stirrer is loaded under argon with $CuSO_4•5H_2O$ (20 mol%, 0.1 mmol), the NHC precursor (20 mol%, 0.1 mmol), $K_2CO_3$ (2 mmol), the aryl halide (0.5 mmol) and dry DMF (3 mL). The terminal alkyne (0.6 mmol) is then added and the reaction mixture is sealed under an argon atmosphere. The Schlenk tube is transferred in a preheated oil bath (125°C) and the reaction mixture is stirred for 8h. Then, the reaction mixture is cooled to room temperature and transferred in a 250 mL separating funnel with 50 mL of $H_2O$. The mixture is extracted with ethyl acetate (3X15mL). The organic layers are combined, washed with brine (15 mL) and dried over $MgSO_4$. The dry organic layer is filtered and the solvent is removed in a rotary evaporator. Products are separated with column chromatography using a $CH_2Cl_2$/*n*-hexane 2/8 mixture.

The preparation of the novel NHC ligand precursors was carried out according to published procedures[32] and is discussed in the Supporting Information of the article.

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**Keywords:** copper • N-heterocyclic carbenes • catalysis • cross coupling • Sonogashira coupling • alkynes • organohalides

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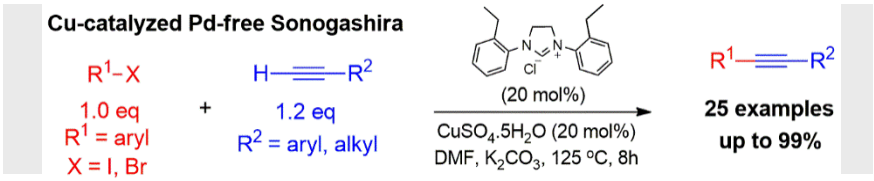


An efficient, user-friendly protocol for the Pd-free, Cu-catalyzed Sonogashira cross-coupling reaction was developed. The (pre)catalytic species utilized are low-cost, stable and widely available: $CuSO_4 \cdot 5H_2O$ as the copper source, an NHC salt precursor and $K_2CO_3$ as the base.

**Sustainable Catalysis**

*Aggeliki A.Liori, Ioannis K. Stamatopoulos, Argyro T. Papastavrou, Afroditi Pinaka, G. C. Vougioukalakis**

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**A Novel, Sustainable, User-Friendly Protocol for the Pd-Free Sonogashira Coupling Reaction**