#### Accepted Manuscript

Sonogashira reactions catalyzed by a new and efficient copper(I) catalyst incorporating *N*-benzyl DABCO chloride

Abdol R. Hajipour, Fatemeh Mohammadsaleh

PII:	S0040-4039(14)00552-8
DOI:	http://dx.doi.org/10.1016/j.tetlet.2014.03.120
Reference:	TETL 44442
To appear in:	Tetrahedron Letters
Received Date:	10 December 2013
Revised Date:	7 March 2014
Accepted Date:	27 March 2014



Please cite this article as: Hajipour, A.R., Mohammadsaleh, F., Sonogashira reactions catalyzed by a new and efficient copper(I) catalyst incorporating *N*-benzyl DABCO chloride, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.03.120

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Graphical Abstract** To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.

Sonogashira reactions catalyzed by a new and efficient copper(I) catalyst incorporating <i>N</i> -benzyl DABCO chloride Abdol R. Haijpour*, Eatemeh Mohammadsaleh	Leave this area blank for abstract info.
$R \xrightarrow{\qquad } X + = \xrightarrow{\qquad } \frac{5 \text{ mol}\% \text{ catalyst } A}{\text{DMF, K}_2 \text{CO}_3, 135 \text{ CC}}$	
Catalyst A $\left[ \begin{array}{c} & & \\ & &$	JUS



Tetrahedron Letters

journal homepage: www.elsevier.com

# Sonogashira reactions catalyzed by a new and efficient copper(I) catalyst incorporating *N*-benzyl DABCO chloride

Abdol R. Hajipour<sup>a,b\*</sup>, Fatemeh Mohammadsaleh<sup>a</sup>

<sup>a</sup> Pharmaceutical Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156, IR of Iran 🧹

<sup>b</sup> Department of Pharmacology, University of Wisconsin, Medical School, 1300 University Avenue, Madison, 53706-1532, WI, USA

#### ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: Coupling reactions Sonogashira reaction N-Benzyl DABCO chloride Copper(I) chloride Catalyst A new and effective catalytic system using [*N*-benzyl DABCO]<sup>+</sup>[Cu<sub>4</sub>Cl<sub>5</sub>]<sup>-</sup> was developed for the palladium-free Sonogashira cross-coupling reactions of phenylacetylene with a variety of aryl halides. In this homogeneous catalytic system, 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride, a quaternary ammonium salt containing a coordinating centre, plays an important role and increases the efficiency of Cu(I) species during the reaction. A number of internal alkynes were produced in moderate to excellent yields, in short reaction times in DMF at 135 °C.

2009 Elsevier Ltd. All rights reserved.

A variety of useful methods for the formation of arylnucleophile bonds using various sources of C-, O-, N-, P-, and Snucleophiles have been developed in cross-coupling chemistry.<sup>1-6</sup> Combinations of transition metals and ligands have been reported as highly efficient catalytic systems for the synthesis of C-C, C-N, and C-O bonds.<sup>1-6</sup> High catalytic activity and selectivity are important parameters for new catalytic systems.

The formation of carbon-carbon bonds is important in the synthesis of pharmaceuticals, and natural and industrial products.<sup>7-10</sup> The Sonogashira coupling reaction is a powerful synthetic procedure for the construction of  $C(sp)-C(sp^2)$  bonds by the introduction of a triple bond into aromatic systems via cross-coupling of aryl/alkyl halides and terminal alkynes.<sup>11,12</sup> Alkynes are building blocks for a wide range of pharmaceuticals, natural products and materials.<sup>13</sup> The original and general catalytic systems for Sonogashira coupling reactions involve the use of palladium-ligand (often a phosphine ligand) complexes as catalysts and a copper(I) salt as a co-catalyst.<sup>14,15</sup> The role of the copper co-catalyst is to generate a copper-acetylide intermediate that subsequently transmetallates at the palladium centre. In view of modern organic synthesis, the use of expensive palladium catalysts and the requirement for a copper(I) salt as a co-catalyst is less attractive, in particular, for industrial scale synthesis. A number of important studies have focused on the development of new catalytic systems with high catalytic activity including phosphineand palladium-free conditions. Numerous catalytically active metals have been developed for the Sonogashira coupling reactions.

Salts or nanoparticles of iron,<sup>16</sup> cobalt,<sup>17</sup> nickel,<sup>18</sup> silver,<sup>19</sup> gold<sup>20</sup> and ruthenium<sup>21</sup> in combination with various ligands have

been reported as catalysts for Sonogashira-type coupling reactions. Copper-based catalysts are powerful in C-N, C-O, C-S, and some C-C bond-forming reactions.<sup>22</sup> Recent attention has been concerned with employing copper-only catalytic systems in coupling reactions, in particular, for Sonogashira-type couplings. A number of copper-based catalytic systems have been proposed, including nanoparticles,<sup>23</sup> supported copper complexes,<sup>24</sup> a bis(µiodo)bis[(-)-sparteine]dicopper(I) catalyst,<sup>25</sup> Cu(I)/amino acid,<sup>26</sup> CuI/DABCO<sup>27</sup> and Cu(I)/diamine.<sup>28</sup> Miura and co-workers suggested a Cu(I)/Cu(III) mechanistic pathway for coppercatalyzed coupling reactions.<sup>29</sup> The development of a new catalytic system that is eco-friendly, readily available, mild and easily separable would be useful in modern synthesis.

Quaternary ammonium and phosphonium salts  $(Q^+ X^-)$  have been highly successful in enhancing the reactivity and selectivity of metal-catalyzed organic reactions.<sup>30-32</sup> The efficiency of these systems is due to the involvement of metal nanoparticles stabilized by quaternary salts and/or the formation of new catalytic systems.

In continuation of our studies on the synthesis and development of catalysts containing quaternary ammonium and phosphonium salts,<sup>32-34</sup> we introduce the new and interesting catalytic system of [*N*-benzyl DABCO]<sup>+</sup>[Cu<sub>4</sub>Cl<sub>5</sub>]<sup>-</sup> as an efficient catalyst for Sonogashira-like reactions of aryl halides with phenylacetylene giving quantitative yields.

Dimeric palladium(II) ammonium and phosphonium complexes have been previously reported as catalysts for chemical reactions;<sup>35-37</sup> however, only a few reports are available for the preparation of copper(I) complexes containing ammonium salts and  $Cu_4Cl_5$ .<sup>38-40</sup>

\* Corresponding author: Tel.: + 98 311 391 3262; fax: + 98 311 391 2350; e-mail: haji@cc.iut.ac.ir.

Tetrahedron Letters

Our first goal was the synthesis and characterization of [Nbenzyl DABCO]<sup>+</sup>[Cu<sub>4</sub>Cl<sub>5</sub>]<sup>-</sup> (Catalyst A).<sup>41</sup> The preparation of 1benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride ([N-benzyl DABCO]Cl) has been reported in our previous work.<sup>42</sup> [N-Benzyl DABCO]Cl was reacted with freshly recrystallized CuCl in methanol at reflux temperature under an N<sub>2</sub> atmosphere to give the catalyst A. The compound synthesized was characterized by elemental analysis (CHN), inductively coupled plasma analysis (ICP), UV-vis spectroscopy and thermogravimetric analysis (TGA). In 2003, Mys'kiv et al. reported the [Cu<sub>4</sub>Cl<sub>5</sub>] species as a counteranion for the quaternary ammonium cation, N,Ndiallylmorpholinium.<sup>38</sup> Also, Flonani et al. have introduced a structure for the anion [Cu<sub>4</sub>Cl<sub>5</sub>].<sup>40</sup> These reports, and also the results obtained from the CHN and ICP analysis of our compound helped us to suggest the formula, [N-benzyl  $DABCO]^{+}[Cu_4Cl_5]^{-}$ , for catalyst A. This compound is stable in air for several months and is insoluble in common organic solvents such as methanol, ethanol, acetonitrile and ethyl acetate, but is soluble in DMF.

The optical absorption properties of the catalyst **A** were investigated by UV–vis spectroscopy in DMF solution at room temperature. Figure 1 shows the absorbance spectra of [*N*-benzyl DABCO]Cl, CuCl and the catalyst **A**.



Figure 1. UV-vis absorption spectra

The UV–vis spectrum of [*N*-benzyl DABCO]Cl shows a sharp absorption band at 270 nm. In the spectrum of CuCl and catalyst **A** two absorption bands at around 276 nm and 284 nm were observed. The band in the 436-434 nm wavelength range also appeared in the UV–vis spectrum of catalyst **A**.

The thermal stability of catalyst **A** was investigated by thermogravimetric analysis with a heating rate of 10 °C min<sup>-1</sup> under an N<sub>2</sub> atmosphere. Figure 2 shows TGA thermograms of weight loss as a function of temperature for pure [*N*-benzyl DABCO]Cl and catalyst **A**. TGA results indicate that the catalyst **A** is stable up to 200 °C; and a total of 45.8% weight loss occurred by 800 °C.

The efficiency of this catalytic system was evaluated in the Sonogashira cross-coupling reactions of aryl halides and phenylacetylene.<sup>43</sup> In order to optimize the reaction conditions, we examined the effect of various reaction parameters such as solvent, base and temperature on the yields and reaction times of a series of screening experiments carried out for the cross-coupling of 4-iodonitrobenzene with phenylacetylene as a model reaction (Table 1).





Screening of different bases such as  $K_2CO_3$ , KOH and *t*-BuOK revealed  $K_2CO_3$  as the most effective base (Table 1, entries 7, 8, 11). The concentration of  $K_2CO_3$  was also found to be important in this reaction system (Table 1, entry 6). Among the different solvents tested such as  $H_2O$ , MeCN, DMF, NMP and DMSO, DMF gave the best result. It is noteworthy that the reaction temperature plays an important role in this reaction. The yield of the model reaction increased when the reaction was conducted at 135 °C (Table 1, entries 3 and 9).

We also examined catalyst loadings for the title reaction (Table 1), employing various amounts under optimized conditions. A catalyst loading of 5 mol% was found to be optimal with respect to the yield and short reaction times (Table 1, entries 3, 10, 11). A lower catalyst concentration usually led to slow reactions, and increasing the amount of catalyst shortened the reaction time. However, increasing the catalyst concentration to 10 mol% did not have any further significant effect on the yield or reaction time.

As shown in Table 1 (entries 13 and 14), we also investigated the efficiency of CuCl as the catalyst in this reaction. Without the aid of any ligands, treatment of 4-iodonitrobenzene with phenylacetylene, CuCl (10 mol%), and  $K_2CO_3$  (2 equiv) in DMF afforded only a trace amount of the corresponding Sonogashira product (5%). Under the same reaction conditions, adding [*N*-benzyl DABCO]Cl (5 mol%) to the reaction mixture improved the yield slightly (up to 10%).

According to the experimental results, the optimized conditions were obtained using N,N-dimethyl formamide (DMF) as solvent and K<sub>2</sub>CO<sub>3</sub> (2 eq) as a base at 135 °C. Under these conditions 4-nitro-1-phenylethynylbenzene was obtained as the desired product in 99% yield with only a trace amount of 1,4-diphenylbuta-1,3-diyne as a by-product formed via the homo-coupling of phenylacetylene.

Having optimized the reaction conditions, catalyst **A** was applied to the Sonogashira coupling of various aryl halides with phenylacetylene. We examined electronic effects on the resulting yields and conversion times. This catalytic system was compatible with a wide range of functional groups such as nitro, cyano, methoxy, halogen, and carbonyl on the aryl halides. Electron-poor aryl halides, in comparison to electron-rich aryl halides, gave better conversions in shorter reaction times. As shown in Table 2, all the aryl iodides were rapidly converted into the corresponding Sonogashira products in excellent yields. Aryl bromides also reacted with phenylacetylene to afford the corresponding Sonogashira products (Table 2. entries 7–11). However, the reactivity of aryl bromides was lower than that of the aryl iodides and they required longer times giving lower yields.

	O_2^	√ + ≡			
			solvent, base, Temp (°C), N <sub>2</sub>		
Entry	Solvent	Base	Catalyst (mol%)	Temp (°C)	$\frac{\text{Conversion}}{(\%)^{b}}$
1	H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	<b>A</b> , (5)	100	-
2	MeCN	$K_2CO_3$	<b>A</b> , (5)	80	-
3	DMF	$K_2CO_3$	<b>A</b> , (5)	135	99
4	NMP	$K_2CO_3$	<b>A</b> , (5)	135	48
5	DMSO	$K_2CO_3$	<b>A</b> , (5)	135	50
6 <sup>c</sup>	DMF	$K_2CO_3$	<b>A</b> , (5)	135	50
7	DMF	t-BuOK	<b>A</b> , (10)	135	90
8	DMF	KOH	<b>A</b> , (10)	135	85
9	DMF	$K_2CO_3$	<b>A</b> , (5)	115	7
10	DMF	$K_2CO_3$	<b>A</b> , (2.5)	135	25
11	DMF	$K_2CO_3$	<b>A</b> , (10)	135	99
12	DMF	$K_2CO_3$	-	135	0
13	DMF	$K_2CO_3$	CuCl, (10)	135	5
14	DMF	$K_2CO_3$	CuCl, (10) / [N-benzyl DABCO]Cl, (5)	135	10

**Table 1.** Optimization of the reaction conditions for the Sonogashira-like coupling <sup>a</sup>

<sup>a</sup>Reaction conditions: 4-nitroiodobenzene (0.1 mmol), phenylacetylene (0.12 mmol), 30 min.

<sup>b</sup>GC conversion.

<sup>c</sup>0.15 mmol K<sub>2</sub>CO<sub>3</sub>.

Substituent effects in the aryl iodides were less significant than those in the aryl bromides, and the reactivities of aryl bromides with electron-withdrawing substituents were higher than those of aryl bromides with electron donating substituents. For example, coupling of 4-bromoanisole with phenylacetylene (Table 2, entry 8) was slow. Aryl chlorides were inactive in this system.

Table 2. Sonogashira-like coupling reactions of aryl halides with phenylacetylene using catalyst A<sup>a</sup>



.





<sup>a</sup>Reaction conditions: aryl halide (0.2 mmol), phenylacetylene (0.22 mmol), K<sub>2</sub>CO<sub>3</sub> (0.4 mmol), DMF, 135 °C, 5 mol% catalyst A, N<sub>2</sub> atmosphere.

<sup>b</sup>GC conversion.

<sup>c</sup>Isolated yield.

<sup>d</sup>In DMSO solvent

The selectivity of the procedure was examined using 1-bromo-4-iodobenzene and 1,4-diiodobenzene. In these reactions iodide acted as the better leaving group (Scheme 1).

The absence of Pd contamination in the starting materials, including the bases ( $K_2CO_3$ , KOH, *t*-BuOK) and the Cu complex

was investigated by inductively coupled plasma (ICP) analysis, and no Pd-impurity was observed in any of the samples.



Scheme. 1. Reaction selectivity of 1-bromo-4-iodobenzene and 1,4-diiodobenzene with phenylacetylene.

In conclusion, we have synthesized [*N*-benzyl DABCO]<sup>+</sup>[Cu<sub>4</sub>Cl<sub>5</sub>] and employed it as an efficient and stable catalyst in Sonogashira-like cross-coupling reactions. Using this palladium-free catalytic system, a variety of substituted aromatic alkynes were prepared in good to excellent yields.

#### Acknowledgments

We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR of Iran, and Isfahan Science and Technology Town (ISTT), IR of Iran. Further financial support from the Center of Excellence in Sensor and Green Chemistry Research (IUT) is gratefully acknowledged.

#### **References and notes**

- 1. Ranu, B. C.; Dey, R.; Chatterjee, T.; Ahammed, S. *ChemSusChem.* **2012**, *5*, 22.
- 2. Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. Angew. Chem. Int. Ed. 2011, 50, 3904.
- Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Angew. Chem. Int. Ed. 2012, 51, 5062.
- 4. Furuya, T., Klein, J. E. M. N., Ritter, T. Synthesis 2010, 1804.
- 5. Meijere, A. In Metal-Catalysed Cross-Coupling Reactions; Diederich, F., Ed., 2nd ed.; Wiley-VCH: Weinheim, 2004.
- Beletskaya, I. P.; Cheprakov, A. V. Coord. Chem. Rev. 2004, 248, 2337.
- Ghasemi, H.; Antunes, L. M.; Organ, M. G. Org. Lett. 2004, 6, 2913.

- Hansen, T. M.; Engler, M. M.; Forsyth, C. J. Bioorg. Med. Chem. Lett. 2003, 13, 2127.
- Hiroya, K.; Matsumoto, S.; Sakamoto, T. Org. Lett. 2004, 6, 2953.
- 10. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Angew. Chem. 2005, 117, 4516.
- 11. Chinchilla, R.; Najera, C. Chem. Rev. 2007, 107, 874.
- 12. Doucet, H.; Hierso, J.-C. Angew. Chem. 2007, 119, 850.
- 13. Tykwinski, R. R. Angew. Chem. Int. Ed., 2003, 42, 1566.
- Sonogashira, K. In Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon Press: Oxford, 1999; Vol. 3, p 521.
- Prabakaran, K.; Khan, F. N.; Jin, S. *Tetrahedron Lett.* 2011, 52, 2566.
- Carril, M.; Correa, A.; Bolm, C. Angew. Chem. 2008, 120, 4940.
- 17. Feng, L.; Liu, F.; Sun, P.; Bao, J. Synlett 2008, 1415.
- 18. Wang, L.; Li, P.; Zhang, Y. Chem. Commun. 2004, 514.
- 19. Li, P.; Wang, L. Synlett 2006, 2261.
- GonzKlez-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. Angew. Chem. 2007, 119, 1558.
- 21. Park, S.; Kim, M.; Koo, D. H.; Chang, S. Adv. Synth. Catal. 2004, 346, 1638.
- 22. Monnier, F.; Taillefer, M. Angew. Chem. 2008, 120, 3140.
- Tang, B. X.; Wang, F.; Li, J. H.; Xie, Y. X.; Zhang, M. B. J. Org. Chem. 2007, 72, 6294.
- Biffis, A.; Scattolin, E.; Ravasio, N.; Zaccheria, F. Tetrahedron Lett. 2007, 48, 8761.
- Priyadarshini, S.; Joseph, P. J. A.; Srinivas, P.; Maheswaran, H.; Kantam, M. L.; Bhargava, S. *Tetrahedron Lett.* 2011, *52*, 1615.
- 26. Liu, F.; Ma, D. J. Org. Chem. 2007, 72, 4844,
- 27. Li, J. H.; Li, J. L.; Wang, D. P.; Pi, S. F.; Xie, Y. X.; Zhang, M. B.; Hu, X. C. J. Org. Chem. 2007, 72, 2053.
- Wang, Y. F.; Deng, W.; Liu, L.; Guo, Q. X. Chin. Chem. Lett. 2005, 16, 1197.
- Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. J. Org. Chem. 1993, 58, 4716.
- Calo, V.; Nacci, A.; Monopoli, A.; Ieva, E.; Cioffi, N. Org. Lett. 2005, 7, 617.
- 31. Jeffery, T. Tetrahedron. 1996, 52, 10113.
- Hajipour, A. R.; Azizi, G.; Ruoho, A. E. Synlett 2013, 24, 254.
- 33. Hajipour, A. R.; Najafi, N.; Rafieea, F. Appl. Organomet. Chem. 2013, 27, 228.
- Hajipour, A. R.; Mahboobi Dehbane, I.; Rafiee, F. Appl. Organomet. Chem. 2012, 26, 743.
- Zawartka, W.; Gniewek, A.; Trzeciaka, A.M.; Zilkowski, J.J.; Pernak, J. J. Mol. Catal. A: Chem. 2009, 304, 8.
- Zawartka, W.; Trzeciak, A.M.; Ziłkowski, J.J.; Lis, T.; Ciunik, Z.; Pernak, J. Adv. Synth. Catal. 2006, 348, 1689.

- Baig, S.; Richard, B.; Serp, P.; Mijoule, I.; Hussein, K.; Guihe'ry, N.; Barthelat, J.; Kalck, P. *Inorg. Chem.* 2006,45, 1935.
- Goreshnik, E. A.; Mys'kiv, M. G. Russ. J. Coord. Chem. 2003, 29, 505.
- Jeannin, Y.; Sécheresse, F.; Bernès, S.; Robert, F. Inorg. Chim. Acta. 1992, 198–200, 493.
- 40. Angelis, S. D.; Solan, E.; Flonani, C.; Chiesi-Villa, A.; Rizzoli, C. J. Am. Chem. Soc. **1994**, *116*, 5702.
- 41. Procedure for the synthesis of [N-benzyl DABCO]<sup>+</sup>[Cu<sub>4</sub>Cl<sub>5</sub>]<sup>-</sup>: In a round-bottom flask, CuCl (1 mmol, 0.099 g), freshly recrystallized from HCl, was mixed with MeOH (10 mL). The resulting mixture was treated with [N-benzyl DABCO]Cl (2 mmol, 0.47 g in 10 mL of MeOH). A yellow solid formed immediately. The mixture was stirred for 30 min at room temperature and then heated at 65 °C with stirring for about 4 h under an N<sub>2</sub> atmosphere. The yellow solid product was isolated by filtration and washed with methanol. Anal. Calcd for C<sub>13</sub>H<sub>19</sub>Cl<sub>5</sub>Cu<sub>4</sub>N<sub>2</sub>: Cu, 40.04; C, 24.60; H, 3.02; N, 4.41. Found: C, 24.59; H, 3.50; N, 4.37. The copper content of a 100 ppm solution of C<sub>13</sub>H<sub>19</sub>Cl<sub>5</sub>Cu<sub>4</sub>N<sub>2</sub> is 40.07% as analyzed by the ICP technique.
- 42. Hajipour, A.R.; Mahboubghah, N., J. Chem. Research (S), **1998**, 122.
- 43. General Procedure for Sonogashira Cross-Coupling: Aryl halide (0.2 mmol) and  $K_2CO_3$  (0.4 mmol) were added to a mixture of DMF (2 mL) and catalyst A (5 mol%) in a round-bottom flask equipped with a condenser and under an N2 atmosphere. The mixture was heated in an oil bath at 135 °C and then phenylacetylene (0.22 mmol) was added in two portions. The mixture was stirred continuously during and monitored by the reaction thin-layer chromatography (TLC) and gas chromatography (GC). After the reaction was complete, the mixture was cooled to room temperature and diluted with EtOAc and H<sub>2</sub>O. The product was extracted with EtOAc and the organic phase dried over MgSO4, filtered and concentrated. The arylalkynes obtained could be purified by silica gel column chromatography (hexane:EtOAc). The arylalkyne products were known compounds and were characterized from their IR, <sup>1</sup>H NMR and GC-MS. 1-Methoxy-(4phenylethynyl)benzene (Table 2, entry 2): FT-IR (KBr, cm<sup>-1</sup>): 3052, 2214, 1593, 1509, 1245, 1137,1028. <sup>1</sup>H-NMR (400 MHz, ppm, CDCl<sub>3</sub>):  $\delta$  = 7.42 (m, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.25 (m, 3H), 6.79 (d, J = 8.8 Hz,2H), 3.73 (s, 3H). MS (EI): *m*/*z* (%): 208 [M]<sup>+</sup> (100), 193 (57), 165 (60).

Click here to remove instruction text...