Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 8761–8764
Tetrahedron Letters

# Supported copper precatalysts for ligand-free, palladium-free Sonogashira coupling reactions

Andrea Biffis,[a,*] Elena Scattolin,[a] Nicoletta Ravasio[b,*] and Federica Zaccheria[c]

[a]Dipartimento di Scienze Chimiche, Università di Padova, Via Marzolo 1, I-35131 Padova, Italy
[b]CNR-ISTM, Via Golgi 19, I-20133 Milano, Italy
[c]Dipartimento di Chimica Inorganica, Metallorganica e Analitica, Università di Milano, Via Venezian 21, I-20133 Milano, Italy

Received 30 July 2007; revised 25 September 2007; accepted 1 October 2007

**Abstract**—Copper(II) oxide and Cu metal, highly dispersed on inert oxides (silica, alumina), have been employed as precatalysts in ligand-free, palladium-free Sonogashira coupling reactions. Best results were obtained with highly dispersed Cu metal on alumina, which exhibited high reactivity with aryl iodides. Electron-rich alkynes, in particular arylacetylenes, act as the most effective alkyne substrates. The present catalytic system appears attractive in view of its ease of application and low cost, due to the use of a readily available non-noble metal catalyst combined with the absence of ligands.

Metal-catalyzed carbon–carbon and carbon–heteroatom cross-coupling reactions have nowadays become one of the most important reaction classes in chemical synthesis, having been developed to reach a very high degree of synthetic usefulness.[1] However, since most of these reactions need a noble metal catalyst (albeit in extremely low amount in some cases[2]), the cost of the catalyst may become an issue for their technological application. Therefore, a flourishing area of research is the quest for catalysts made out of less noble metals, which exhibit comparable catalytic efficiency.

Copper-based catalysts have been occasionally proposed as an alternative to the more commonly employed palladium-based catalysts for technologically relevant C–C coupling reactions, such as Heck,[3] Suzuki,[4] and most notably for Sonogashira couplings.[5–8] The latter reaction is routinely performed using a palladium-based catalyst and a copper(I) salt as a cocatalyst.[9] The role of the copper cocatalyst is to form an intermediate copper acetylide that subsequently transmetallates to the palladium centre. In recent years, many different copper-free, palladium-based catalytic systems have been proposed for this reaction,[10] but on the other hand efficient palladium-free systems would obviously be much more interesting for economical reasons, related both to the higher cost of palladium as well as to the difficulties in removing the metal (and its ligands) from the reaction product. Indeed, it is a common industrial practice to avoid, whenever possible, the use of Pd catalysts in the last steps of the synthesis of a complex molecule.

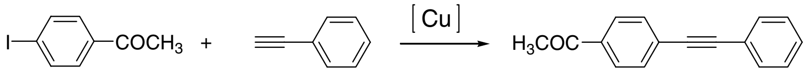
Although it was early recognized that copper(I) acetylides could effectively react with organic halides in a stoichiometric fashion,[11] only a limited number of copper-based catalysts for the Sonogashira reaction has been described up to now. Most reports deal with copper(I) complexes containing phosphine ligands, which are quite effective catalysts with aryl iodide substrates; however, such catalysts have to be employed in quite large amounts (usually 10 mol %), which causes difficulties in the subsequent purification of the reaction product from the catalyst and especially from the phosphine ligand.[5] More recently, alternative nitrogen-containing ligands,[6] supported copper complexes,[7] as well as ligand-free copper nanoparticles[8] have been described as effective catalysts for this reaction. In this contribution, we wish to report on a novel class of solid, easy to handle copper-based catalysts for ligand-free, palladium-free Sonogashira coupling reactions.

As previously shown by some of us, pre-reduced CuO/$SiO_2$ and CuO/$Al_2O_3$ materials with a copper loading of 5–8% are very effective catalysts for a series of organic

---

[*] Corresponding authors. Tel.: +39 049 8275216; fax: +39 049 8275223 (A.B.); tel.: +39 02 50314382; fax: +39 02 50313927 (N.R.); e-mail addresses: andrea.biffis@unipd.it; n.ravasio@istm.cnr.it

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.005



**Scheme 1.**

synthesis transformations.[12] These two materials, both in oxidized and reduced form,[13], were therefore used as catalyst in preliminary tests run on a standard Sonogashira reaction, namely the coupling of iodoacetophenone with phenylacetylene (Scheme 1).

Using this test reaction, an optimization of the reaction conditions for the silica-supported catalyst in oxidized form was carried out. We started by investigating the standard reaction conditions described in the works of Venkantaraman and co-workers (toluene, 110 °C, $K_2CO_3$ as the base)[5c] and of Rothenberg and co-workers (DMF, 110 °C, tetrabutylammonium acetate, TBAA as the base).[8] The results are reported in Table 1.[14]

It is apparent from the reported results that the reaction conditions employed by Rothenberg for copper nanoparticles turned out to be the best also in the case of our catalysts. Using them, yields up to 48% could be achieved, while only 17% yield was obtained under the conditions of Venkantaraman et al. Quite remarkably, using TBAA in toluene or $K_2CO_3$ in DMF no product formation at all was observed, which highlights the importance of choosing the right solvent/base pair for this reaction. We also found that the nature of the catalyst support had a marked influence on the reaction outcome. Switching from silica to alumina significantly increased the catalytic efficiency of the catalyst, allowing to obtain an almost quantitative yield (entry 5). Furthermore, determination of the conversion curve (Fig. 1) made it clear that in the latter case 8 h of reaction is already sufficient to reach 90% yield. The existence of an induction period was also apparent from the sigmoidal shape of the curve, which suggests that CuO/Al acts in fact as a precatalyst generating the true catalytically active species in situ (see below).

**Table 1.** Optimization of the reaction conditions

| | Catalyst | Solvent | Base | Yield (%) |
|---|---|---|---|---|
| 1 | CuO/Si | Toluene | $K_2CO_3$ | 17 |
| 2 | CuO/Si | Toluene | TBAA | 0 |
| 3 | CuO/Si | DMF | TBAA | 48 |
| 4 | CuO/Si | DMF | $K_2CO_3$ | 0 |
| 5 | CuO/Al | DMF | TBAA | 95 |

Reaction conditions: 1 equiv iodoacetophenone, 1.2 equiv phenylacetylene, 1 equiv base, 20 mol % Cu, 110 °C, 24 h.

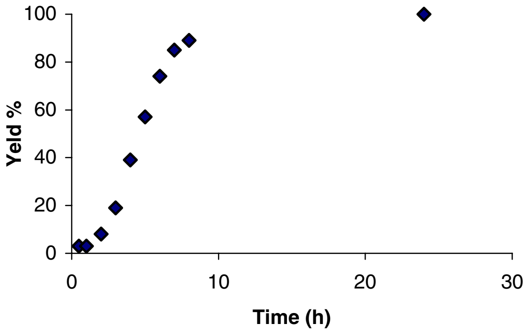


**Figure 1.**

Catalyst CuO/Al was subsequently employed to perform a systematic evaluation of the generality of the reaction with respect to the aryl halide, the alkyne and the metal oxidation state. Reduction of the CuO phase under mild experimental conditions ($H_2$, 270 °C) leads to well-formed Cu(0) crystallites very active in catalytic reactions.[12] Therefore, we also examined the activity of the fully reduced material (Cu/Al) under the same experimental conditions.

As can be derived from the results reported in Table 2, the reaction appears to be limited to aryl iodides. Reactions with aryl bromides or chlorides gave poor yields (entries 4–7) with both catalysts, whereas deactivated aryl iodides turned out to be much more active in the presence of the pre-reduced Cu/Al (entries 8–11).

Remarkably, in no case we obtained evidence for the formation of significant quantities of the alkyne head-to-head homocoupling product (Hay coupling),[15] that was reportedly produced in substantial amounts using other catalytic systems.[6] Concerning the alkyne, best results were obtained with phenylacetylene. Alkynes with more electron-donating substituents gave lower yields (entry 13) whereas no reaction was observed with electron-poor alkynes such as ethyl propiolate (entry 14). Therefore, the scope of our supported copper

**Table 2.** Sonogashira reactions with reduced and unreduced copper on alumina catalysts

| | Catalyst | Aryl halide | Alkyne | Yield (%) |
|---|---|---|---|---|
| 1 | CuO/Al | Iodoacetophenone | Phenylacetylene | 95 |
| 2 | Cu/Al | ” | ” | 100 |
| 3 | Cu/Al[a] | ” | ” | 90 |
| 4 | CuO/Al | Bromoacetophenone | ” | 15 |
| 5 | Cu/Al | ” | ” | 10 |
| 6 | CuO/Al | Chloroacetophenone | ” | 5 |
| 7 | Cu/Al | ” | ” | 0 |
| 8 | CuO/Al | Iodotoluene | ” | 80 |
| 9 | Cu/Al | | | 100 |
| 10 | CuO/Al | Iodoanisole | ” | 5 |
| 11 | Cu/Al | ” | ” | 70 |
| 12 | CuO/Al | Iodopentafluorobenzene | ” | 95[b] |
| 13 | CuO/Al | Iodoacetophenone | 1-Octyne | 50 |
| 14 | CuO/Al | ” | Ethyl propiolate | 0 |

Reaction conditions: 1 equiv iodoacetophenone, 1.2 equiv alkyne, 1 equiv TBAA, 20 mol % Cu, DMF, 110 °C, 24 h.

[a] 10 mol % Cu.

[b] Isolated yield.

catalyst appears to be similar to that of most soluble copper-based catalysts reported to date, whose application is generally limited to aryl iodides and arylacetylenes as substrates.

In the case of activated iodoarenes such as iodoacetophenone, it is possible to lower the amount of catalyst to 10 mol % while maintaining a very high yield by using the pre-reduced catalyst (entry 3). Remarkably, supported copper metal appears to be oxidized in the course of the reaction (the color of the catalyst turns from dark brown to yellow) even upon working with a carefully deoxygenated solvent. This is in contrast with the observation of Rothenberg et al.,[8] who claimed stability of their copper nanocluster catalysts under reaction conditions, and may indicate that the reaction mechanism is similar both with oxidized and reduced catalyst.

An unexpected activity of copper(0)-containing catalysts has already been observed by some of us in the oxidative coupling of 2,6-dimethylphenol.[16] This reaction is homogeneously catalyzed by a copper(II) complex prepared by autooxidation of CuCl, but replacement of cuprous chloride by the corresponding copper(II) salt under the same conditions results in an inactive system, indicating that the oxidation of CuCl must yield a product, which cannot be described in the usual terms[17] as far as the oxidation state is concerned. In a similar way, the CuO/Si catalyzed oxidative coupling takes place only in the presence of the pre-reduced catalyst.[16] The higher catalytic activity observed in Sonogashira couplings when using the pre-reduced material may suggest that also in this case interaction of the catalyst with the substrate and other reactants triggers its evolution to a more suitable configuration concerning both geometry and oxidation state with respect to the unreduced catalyst. Indeed, a heterogeneous catalyst containing almost exclusively supported Cu(I) as isolated copper ions[18] was found to exhibit poor activity, reaching as the best result 18% yield in the coupling between iodoacetophenone and phenylacetylene under the optimized reaction conditions for the CuO-based catalysts.

The active catalytic species in the reaction investigated in this work was found to be actually a soluble one, released into solution from the supported catalyst. In fact, separation of the heterogeneous catalyst by filtration at the reaction temperature after the first 2.5 h of reaction pointed out that the reaction continued unaltered in the solution. Metal leaching at the end of the reaction was found to amount to 62.7% of the total copper present, determined by ICP-AAS spectroscopy. Consequently, the catalyst was not reusable; however, a simple filtration on Celite afforded a solution containing only the product, the eventual unreacted substrate and the base.

Summarizing the results obtained in this work, we can state that highy dispersed copper(II) oxide and, most notably, Cu metal on alumina act as efficient precatalysts for Sonogashira coupling reactions of aryl iodides. The use of a readily available non-noble metal catalyst and the absence of ligands, allowing a simpler product recovery, make this reaction attractive from the synthetic point of view. We are currently aiming at optimizing the catalytic performance with different electron-rich alkynes as well as at extending the application of catalysts of this kind to other coupling reactions.

## References and notes

1. de Meijere, A. In *Metal-Catalysed Cross-Coupling Reactions*; Diederichs, F., Ed., 2nd ed.; Wiley-VCH: Weinheim, 2004.
2. Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553.
3. (a) Declerck, V.; Martinez, J.; Lamaty, F. *Synlett* **2006**, 3029, and references cited therein; (b) Calò, V.; Nacci, A.; Monopoli, A.; Ieva, E.; Cioffi, N. *Org. Lett.* **2005**, *7*, 617.
4. (a) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 11858; (b) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Adv. Synth. Catal.* **2003**, *345*, 979.
5. (a) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716; (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843; (c) Saejueng, P.; Bates, C. G.; Venkantaraman, D. *Synthesis* **2005**, 1706, and references cited therein.
6. (a) Ma, D.; Liu, F. *Chem. Commun.* **2004**, 1934; (b) Deng, C.-L.; Xie, Y.-X.; Yin, D.-L.; Li, J.-H. *Synthesis* **2006**, 3370.
7. Zhang, L. Y.; Li, P. H.; Wang, L. *Lett. Org. Chem.* **2006**, *3*, 282.
8. Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Green Chem.* **2004**, *6*, 215.
9. Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1999; Vol. 3, pp 521.
10. See for example (a) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679; (b) Ruiz, J.; Cutillas, N.; Lopez, F.; Lopez, G.; Bautista, D. *Organometallics* **2006**, *25*, 5768; (c) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365.
11. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 2163.
12. (a) Zaccheria, F.; Ravasio, N.; Fusi, A.; Psaro, R. *Tetrahedron Lett.* **2005**, *46*, 3695; (b) Zaccheria, F.; Ravasio, N.; Rodondi, M.; Fusi, A.; Psaro, R. *Adv. Synth. Catal.* **2005**, *347*, 1267; (c) Zaccheria, F.; Ravasio, N.; Fusi, A.; Psaro, R. *Chem. Eur. J.* **2006**, *12*, 6426; (d) Ravasio, N.; Zaccheria, F.; Fusi, A.; Psaro, R. *Appl. Catal. A: Gen.* **2006**, *315*, 114.
13. *Catalyst preparation*. The employed catalysts (8% w/w Cu) were prepared as already reported[12] starting from a $[Cu(NH_3)_4]^{2+}$ aqueous solution. $Al_2O_3$ (BET = 280 $m^2/g$, PV = 1.75 mL/g) and $SiO_2$ (BET = 313 $m^2/g$, PV = 1.79 mL/g) were kindly supplied by GRACE Davison (Worms, Germany). The obtained catalyst on $Al_2O_3$ was subsequently reduced at 270 °C with $H_2$ (1 atm), removing the formed water under reduced pressure.
14. *General procedure for the catalytic tests*. An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with 40 mg catalyst, heated under air for 15 min at about 200 °C, and then under vacuum for another 15 min. After cooling to room temperature, 0.25 mmol of aryl halide and 0.25 mmol of base were quickly added. The tube was closed with a rubber septum, evacuated and filled with argon. Alkyne (0.3 mmol) and solvent (3 mL) were subsequently injected, and the tube was placed in an oil bath preheated at 110 °C. The reaction mixture was stirred

at 110 °C for 24 h, after which it was cooled to room temperature and diluted with 5 mL dichloromethane. The resulting suspension was filtered and the solvent was removed under vacuum to give a brown solid. The reaction yield was determined by $^1$H NMR spectroscopy. In the case of iodopentafluorobenzene as reagent, the product was isolated by flash chromatography (eluent: *n*-hexane:diethylether 9:1).

15. Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320.
16. (a) Boccuzzi, F.; Martra, G.; Partipilo Papalia, C.; Ravasio, N. *J. Catal.* **1999**, *184*, 327; (b) Ercoli, M.; Fusi, A.; Psaro, R.; Ravasio, N.; Zaccheria, F. *J. Mol. Catal.* **2003**, *204–205*, 729.
17. Finkbeiner, F. H.; Hay, A. S.; Blanchard, H. S.; Endres, G. F. *J. Org. Chem.* **1966**, *31*, 549.
18. Gervasini, A.; Manzoli, M.; Martra, G.; Ravasio, N.; Sordelli, L.; Zaccheria, F. *J. Phys. Chem. B* **2006**, *110*, 7851.