Copper-Free Sonogashira Reaction Using Gold Nanoparticles Supported on Ce_2O_3, Nb_2O_5 and SiO_2 under Microwave Irradiation

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Abstract: In the present communication we wish to report a copper-free Sonogashira reaction catalyzed by gold-supported catalysts under microwave irradiation. Aryl and alkyl acetylenes were used and good yields were obtained with short reaction times when DMF was used as solvent. Three different supported gold catalysts were used and Au/SiO_2 gave the best result for both aryl and alkyl acetylenes.

Key words: Sonogashira reaction, gold nanoparticles, supported catalyst

The Sonogashira reaction[1] is a carbon–carbon coupling reaction between terminal alkynes and aryl or vinyl halides. This reaction has been widely applied in different areas such as natural product synthesis and material science. The reaction generally proceeds in the presence of a palladium catalyst and a co-catalyst. The most widely employed co-catalysts are Cu(I) salts (Scheme 1). The original Sonogashira reaction was performed in the presence of large amounts of Pd(0) and Cu_2I_2 under inert conditions. These conditions of course are not presently acceptable from economic and environmental points of view.

The most significant improvement in this reaction[2] has been based on the omission of Cu_2I_2, not only because of environmental concerns but also because it can induce the formation of oxidatively homocoupled byproducts of acetylenes that are difficult to separate from the desired product and because Cu_2I_2 has also been shown to inhibit the Sonogashira reaction.

The use of gold in catalysis has received increased attention recently. Previously considered catalytically inactive,[3] gold is now widely used in catalytic processes and in organic synthesis.[4] Corma's group has successfully applied Au/Ce_2O_3 among other gold-supported catalysts in different processes, in particular in the Sonogashira coupling.[5] Corma's hypothesis that Au(I) can replace both Cu(I) and Pd(0) in the catalytic cycle is very attractive,[5a,b] particularly if these gold-supported catalysts act as sources of soluble species as widely demonstrated in Pd(0) chemistry by our[6] and other groups.[7]

$$R^1\!-\!\!\equiv\!\!-\!H \;+\; R^2\!-\!X \xrightarrow[\text{Cu}^+\ \text{Y}^-\text{, base}]{\text{Palladium catalyst}} R^1\!-\!\!\equiv\!\!-\!R^2$$

Scheme 1 The Sonogashira cross-coupling reaction

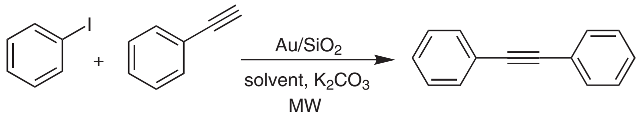
Since the conditions to carry out this reactions involved temperatures of about 130 °C and reaction times of 24–48 hours, the use of microwave irradiation emerged as a possibility to save time and increase yields.

Use of microwaves (MWs) as an alternative energy source is becoming widespread in organic chemistry, as demonstrated by the rapidly growing number of annual publications on this topic. Of course the main reason for using MW is related to the fact that it is a very fast way of energy transfer.[8] Moreover, the reaction temperature can easily go above the solvent boiling point and the effect on improving reaction rates is dramatic.[9]

Herein, we report copper-free Sonogashira reactions between aryl halides and phenylacetylene or 1-octyne catalyzed by gold under microwave irradiation.

We first investigated the effect of various solvents on the model reaction between iodobenzene (**1**) and phenylacetylene (**2**) catalyzed by 3 mol% of supported Au/SiO_2 in the absence of Cu_2I_2. K_2CO_3 was used as base in this reaction (Table 1).

Table 1 Effect of Different Solvents on the Reaction between Iodobenzene (**1**) and Phenylacetylene (**2**) Catalyzed by Supported Au/SiO_2 (3% mol) under Microwave Irradiation



1 2 3

Entry	Solvent[a]	Time	Yield[b]
1	THF	1 h	68% (59)[c]
2	H_2O	1 h	15%
3	DMF	1 h	87% (81)[c]
4	EtOH	1 h	no reaction

[a] The solvent volume used was 5 mL.
[b] Based on GC analysis.
[c] Isolated yield.

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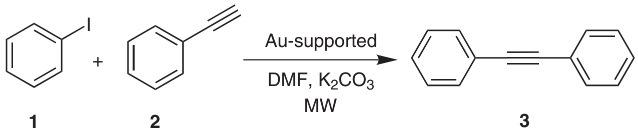
Table 2 The Use of Different Gold-Supported Catalysts in the Reaction between Iodobenzene (**1**) and Phenylacetylene (**2**) under Microwave Irradiation



Entry	Catalyst[a]	Time	Yield[b]	TONs
1	Au/SiO_2	1 h	87% (81%)[c]	29
2	Au/Nb_2O_5	1 h	66%	22
3	Au/Ce_2O_3	1 h	52%	17

[a] The amount of catalyst used was 3% mol.
[b] Based on GC analysis.
[c] Isolated yield.

As shown in Table 1, the use of DMF gave the highest yield (entry 3, 87%) after one hour under microwave irradiation in the reaction of iodobenzene (**1**) with phenylacetylene (**2**). The yield of the cross-coupled product was reduced in the presence of protic (entries 2 and 4) and low-polarity solvents (entry 1). This result can be related to the fact that as DMF is a dipolar aprotic solvent it is expected to be a very good absorber of MW irradiation.

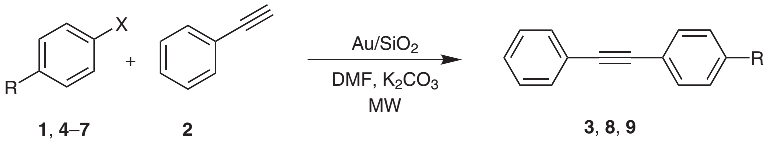
After selecting DMF as the optimal solvent, we investigated the effect of other gold-supported catalysts on the copper-free Sonogashira reaction of iodobenzene (**1**) with phenylacetylene (**2**), under microwave irradiation. According to the results shown in Table 2, Au/SiO_2 gave the best yield (entry 1, 87%), when compared to the other catalysts, Au/Ce_2O_3 and Au/Nb_2O_5 (entries 2 and 3, respectively). However, it is very important to emphasize that there is no significance difference in the turnover numbers (TONs), between these three catalytic sources. As the three catalytic sources tested, Au/SiO_2 (4.2 nm), Au/Nb_2O_5 (4.9 nm) and Au/Ce_2O_3 (5.9 nm) have approximately the same particle size, the slight difference in TONs can be attributed only to the difference in the surface area presented by the support, SiO_2 (200 m^2/g), Nb_2O_5 (49 m^2/g) and Ce_2O_3 (20 m^2/g).

We next investigated the copper-free Sonogashira reactions of a variety of aryl iodides and bromides **4–7** with phenylacetylene (**1**) in DMF under Au/SiO_2 catalysis and microwave irradiation. As summarized in Table 3, the reaction between 4-nitroiodobenzene (**4**) and phenylacetylene (**2**) led to the reaction product in 84% yield (entry 2). However, aryl iodides with electron-donating groups such as 4-OMe (entry 3), gave moderate yields after 3.5 hours of reaction. When less reactive aryl bromides were used in the copper-free reaction, the coupling products **10** and **11** were also obtained in moderate yields after a reaction time of 3.5 hours (entries 4 and 5) and no yield improvement was observed after this time.

Finally, we explored the reaction between aryl iodides and bromides **4–7** with 1-octyne (**12**) in DMF under Au/SiO_2 catalysis and microwave irradiation (Table 4). Iodobenzene (**1**) and 4-nitroiodobenzene gave good yields in short reaction times. The less activated aryl bromides and aryl iodides substituted with an electron-donating group led to moderate yields with longer reaction times.

In summary, in the present letter it has been shown that the use of gold-supported catalysts under microwave irradiation is a very convenient way to carry out copper-free Sonogashira coupling.[10] It has been demonstrated that, in contrast to the very long reaction times previously reported, one to 3.5 hours were needed under the present conditions with at least similar yields. The Au/SiO_2-supported catalyst provided the best yields, although similar TONs were obtained with all the three catalytic sources. The fact that reaction was carried out in DMF, a good MW absorber, perhaps contributed to the formation of soluble species, Au(III), upon oxidative addition and that of Au(I) after reductive elimination, perhaps also leading to the

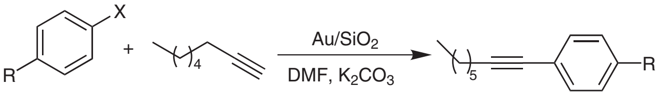
Table 3 Reaction of Aryl Iodides and Bromides **4–7** with Phenylacetylene (**1**) Catalyzed by Supported Au/SiO_2 (3 mol%) in DMF under Microwave Irradiation



Entry	R	X	Time[a]	Yield[b]
1	H	I	1 h	**3**, 87% (81)[c]
2	NO_2	I	1 h	**8**, 84% (80)[c]
3	OMe	I	3.5 h	**9**, 56% (50)[c]
4	H	Br	3.5 h	**3**, 61%
5	OMe	Br	3.5 h	**9**, 43%

[a] No further improvement was observed.
[b] Based on GC analysis.
[c] Isolated yield.

Table 4 Reaction of Aryl Iodides and Bromides **4–7** with 1-Octyne (**12**) Catalyzed by Supported Au/SiO$_2$ (3 mol%) in DMF under Microwave Irradiation



1, **4–7** **12** **13–15**

Entry	R	X	Time[a]	Yield[b]
1	H	I	1 h	**13**, 66% (60)[c]
2	NO$_2$	I	1 h	**14**, 78% (75)[c]
3	OMe	I	3.5 h	**15**, 59% (50)[c]
4	H	Br	3.5 h	**13**, 52%
5	OMe	Br	3.5 h	**15**, 32%

[a] No further improvement was observed.
[b] Based on GC analysis.
[c] Isolated yield.

formation of Au(I) acetylides, and very fast catalytic cycles in solution.

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(10) A mixture of the aryl halide (1.00 mmol), Au-supported catalyst (3 mol%), phenylacetylene or 1-octyne (1.00 mmol) and K_2CO_3 (138 mg, 1.00 mmol) was mixed in DMF (5.0 mL). Microwave-assisted syntheses were conducted with a CEM Discover focussed microwave oven (150 W). After the reaction, usual aqueous workup and column chromatographic purification process on silica gel (hexanes–EtOAc, 9:1) were carried out. The spectroscopic data of compounds **3**, **8**, **9**, **13**, **14** and **15** are as follows.

Compound 3: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.50 (m, 4 H), 7.20–7.25 (m, 6 H).

Compound 8: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (m, 2 H), 7.95 (m, 2 H), 7.49–7.53 (m, 2 H), 7.20–7.25 (m, 3 H).

Compound 9: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (m, 2 H), 7.46 (m, 2 H), 7.18–7.23 (m, 3 H), 6.84 (m, 2 H), 3.80 (s, 3 H).

Compound 13: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 1 H), 7.13 (m, 4 H), 2.38 (m, 2 H), 1.40 (m, 8 H), 0.89 (m, 3 H).

Compound 14: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (m, 2 H), 7.89 (m, 2 H), 2.35 (m, 2 H), 1.33 (m, 8 H), 0.85 (m, 3 H).

Compound 15: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 2 H), 6.79 (m, 2 H), 3.55 (s, 3 H), 2.40 (m, 2 H), 1.45 (m, 8 H), 1.11 (m, 3 H).

Commercial Nb_2O_5 (49 m^2/g^1) and SiO_2 (200 m^2/g), kindly provided by CBMM and DEGUSA, were used as received. CeO_2 (20m^2/g) was obtained by calcination of Ce(III) nitrate hexahydrate (ACROS, 99.5%) at 800 °C/h in a conventional oven. Gold was incorporated into the supports using the deposition–precipitation method at a constant pH of 8 by addition of Na_2CO_3 and using a $HAuCl_4$ (ACROS) solution as gold source. Characterization of the catalysts by small-angle X-ray scattering (SAXS) revealed gold particle sizes of 4.9, 5.9 and 4.2 nm for Nb_2O_5, CeO_2 and SiO_2 supports, respectively.