## Sonogashira Reaction of Aryl Halides with Terminal Alkynes Catalyzed by Cobalt Hollow Nanospheres

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Abstract: Sonogashira reaction catalyzed by cobalt hollow nanospheres has been developed. Coupling of alkynes with aryl iodide or aryl bromide in the presence of potassium carbonate, triphenylphosphine, and cuprous iodide provides the corresponding products with moderate to good yields, which reveals obvious advantages such as low-cost catalyst, the recyclability of the catalyst, and simple experimental operation.

Key words: cobalt hollow nanospheres, catalysis, Sonogashira reaction, cross-coupling, alkynes

As a well-known sp<sup>2</sup>–sp coupling reaction between aryl or alkenyl halides and terminal alkynes, the Sonogashira reaction has become the most important method to prepare arylalkynes and conjugated enynes,<sup>1</sup> which are precursors for many natural products, pharmaceuticals, and molecular organic materials.<sup>2</sup> The Sonogashira reaction is usually performed using a palladium-phosphine ligand complex as the catalyst in the presence of a catalytic amount of a copper(I) salt and an amine (as a solvent or in large excess) under homogeneous conditions. The traditionally used catalysts are triphenylphosphine-related complexes,  $Pd(PPh_3)_4$ , with the more stable and soluble  $Pd(PPh_3)_2Cl_2$ being the most common. Although catalysts with bidentate ligands such as Pd(dppe)Cl<sub>2</sub>, Pd(dppp)Cl<sub>2</sub>, or Pd(dppf)Cl<sub>2</sub> have also been employed. Most frequently, rather high loadings of palladium (usually up to 5 mol%) and larger amounts of the copper(I) salt are required when these palladium species are employed. Numerous palladium complexes have been employed to catalyze this transformation in recent years, in which palladium-N complexes,<sup>3</sup> palladium–P,N complexes<sup>4</sup> and palladium– P,O complexes,<sup>5</sup> as well as palladium–NHC (N-heterocyclic carbene) complexes<sup>6</sup> were successfully used in these procedures.

Transition-metal nanoparticles are especially active catalytic systems due to their large surface area. In recent years, there has been growing interest in the fabrication of Pd nanoparticles and their applications in organic reactions, especially the formation of carbon–carbon bonds.<sup>7</sup> For example, ligand-free Pd nanoparticles of about 3.3 nm in size stabilized by tetraalkylammonium salts bearing long alkyl chains were obtained and used as heteroge-

SYNLETT 2008, No. 9, pp 1415–1417 Advanced online publication: 07.05.2008 DOI: 10.1055/s-2008-1072615; Art ID: W01008ST © Georg Thieme Verlag Stuttgart · New York neous catalysts for the Suzuki and Stille cross-coupling reactions of aryl halides carried out in ionic liquids.8 Hyeon and co-workers9 synthesized Pd/Ni bimetallic nanoparticles with a cheap metal core (Ni) and a noblemetal shell (Pd), which can be used in Sonogashira coupling reactions. In our previous works, bimetallic hollow palladium-cobalt nanoparticles have been prepared and successfully used as catalysts in aqueous media for the coupling of aryl iodides or bromides and phenylacetylene.<sup>10</sup> Instead of the costly palladium, nickel-catalyzed Sonogashira couplings of activated aryl iodides and aromatic terminal alkynes were also reported in recent years.<sup>11</sup> To our knowledge, as a well-established partner of nickel, especially as an inexpensive and relatively nontoxic metal, metallic cobalt has not been as a catalyst used in Sonogashira reaction.

In our recent research, cobalt hollow nanospheres were firstly prepared by a wet chemical method and used to catalyze the Heck reaction with a good result.<sup>12</sup> The high surface area of the hollow spheres resulting from the nanoparticulate nature of the shell, which is much larger than that of dense spheres of the same diameter, is responsible for the high catalytic activity. In this paper, these hollow nanospheres were further successfully applied as catalyst in the Sonogashira reaction (Scheme 1).

ArX + R 
$$\longrightarrow$$
 Ar  $\xrightarrow{\text{nano-Co, Ph_3P, Cul}}$  Ar  $\xrightarrow{\text{rano-R}}$  Ar  $\xrightarrow{\text{rano-R}}$ 

Scheme 1

The preparation of cobalt hollow nanospheres was described in our previous report. It was found that the average diameter of the hollow spheres was about 50 nm with mainly ranging from 50 nm to 60 nm, and the shell thickness was about 10 nm. The ICP-MS analyses showed that no palladium was detected in these hollow spheres, as well as in  $K_2CO_3$  and triphenylphosphine, which were used in this coupling reaction. For investigating the reaction conditions of these nanospheres-catalyzed Sonogashira reaction, the coupling of phenylacetylene and piodotoluene was chosen as a model reaction. The reaction was carried out under a nitrogen atmosphere to avoid the oxidative coupling of terminal alkynes which generally takes place in the presence of oxygen.<sup>13</sup> The experiment indicated that 3 mol% of catalyst could catalyze the reaction sufficiently. The reaction took place at 120 °C, and

solvents such as DMF or N-methyl-2-pyrrolidone (NMP) was chosen as the reaction media. In DMF, it gave a lower yield than in NMP. So NMP was adopted as the solvent of the reaction. As co-catalyst and ligand, cuprous iodide and triphenylphosphine were essential to the reaction. Without them, the reaction gave only traces of product. However, the addition of copper salt as cocatalyst in this crosscoupling reaction also has drawbacks. The in situ generation of copper acetylides under the reaction conditions could generate homocoupling products of the terminal alkyne (the so-called Glaser coupling),<sup>14</sup> so the quantity of cuprous iodide should be limited. The appropriate quantity of cuprous iodide in this reaction was 2 mol%. The yield of the reaction did not change significantly when the amount of triphenylphosphine was at the range of 10 mol% to 20 mol%. As described previously in the literature, a basic environment was also important for the Sonogashira reaction. As general bases, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, NaOH, and KOH were tested, and K<sub>2</sub>CO<sub>3</sub> was found to be the best. Potassium carbonate was therefore selected as the base for our research. Another notable advantage of this reaction was the recyclability of the Co catalyst. The catalyst could be reused after being separated from the solution and washed thoroughly with methanol and diethyl ether. After being reused three times, the catalytic activity did not decrease significantly.

**Table 1**The Coupling of Aryl Halides with Terminal Alkynes Using Cobalt Hollow Nanospheres as Catalyst

Entry	ArX	R	Time (h)	Yield (%) <sup>a</sup>
1	PhI	Ph	20	90
2	4-MeC <sub>6</sub> H <sub>4</sub> I	Ph	20	85 (83, 83, 80) <sup>t</sup>
3	3-MeC <sub>6</sub> H <sub>4</sub> I	Ph	22	86
4	2-MeC <sub>6</sub> H <sub>4</sub> I	Ph	24	80
5	4-ClC <sub>6</sub> H <sub>4</sub> I	Ph	20	87
6	2-ClC <sub>6</sub> H <sub>4</sub> I	Ph	24	82
7	PhBr	Ph	28	65
8	PhCl	Ph	30	Trace
9	PhI	Bu	20	85
10	4-MeC <sub>6</sub> H <sub>4</sub> I	Bu	20	88
11	3-MeC <sub>6</sub> H <sub>4</sub> I	Bu	20	86
12	2-MeC <sub>6</sub> H <sub>4</sub> I	Bu	24	82
13	4-ClC <sub>6</sub> H <sub>4</sub> I	Bu	20	88
14	3-ClC <sub>6</sub> H <sub>4</sub> I	Bu	24	82
15	PhBr	Bu	30	33

<sup>a</sup> Isolated yields. All products are known compounds, their structures were characterized by <sup>1</sup>H NMR, IR, and MS spectra.

<sup>b</sup> The catalyst was reused three times.

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Under the selected reaction conditions, the cobalt-catalyzed Sonogashira coupling of a series of aryl halides with terminal alkynes was studied.<sup>15</sup> The results are shown in Table 1. The reactions of aryl halides with electron-withdrawing or electron-donating groups did not show obvious differences. This means that the reaction was relatively insensitive to the electronic characteristics of the substituents. The reaction of aryl iodides with aromatic or aliphatic terminal alkynes gave the corresponding coupling products in higher yields than that of aryl bromides, while the reaction of aryl chloride gave only trace desired product. Furthermore, the reaction of aliphatic alkynes with low boiling points proceeded at a lower temperature to avoid the volatilization of alkynes. A possible mechanism of this cobalt-catalyzed Sonogashira reaction is shown in Scheme 2.



Scheme 2

In conclusion, we have successfully used hollow cobalt nanospheres in the Sonogashira reaction of aryl iodides with alkynes. The obvious advantages of this method are that the catalyst is much cheaper and easy to prepare as compared to the conventional palladium catalysts, and the catalyst can be reused for several times. The application of this new catalyst in organic synthesis is under way in our laboratory.

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- (15) Typical Experimental Procedure

To NMP (2 mL) were added aryl halide (1 mmol) and terminal alkyne (1 mmol), then cobalt nanoparticles (0.03 mmol, 3 mol%), Ph<sub>3</sub>P (0.1 mmol, 10 mol%), CuI (0.02 mmol, 2 mol%), and K<sub>2</sub>CO<sub>3</sub> (1.5 mmol) were added in turn. The mixture was heated at 120 °C (for aromatic alkyne) or 80 °C (for aliphatic alkyne) with stirring under a nitrogen atmosphere for the appropriate time (see Table 1, monitored by TLC) until the reaction was complete, then centrifuged. The solution was separated and the precipitate was washed with Et<sub>2</sub>O ( $3 \times 5$  mL). The solutions were combined and washed with H<sub>2</sub>O, dried over anhyd Na<sub>2</sub>SO<sub>4</sub>, and purified by column chromatography on SiO2 with hexane-EtOAc (100:1) as eluent to yield the products. The precipitate was further washed sufficiently with MeOH and Et<sub>2</sub>O, then dried, and the cobalt nanoparticles were recovered. After being reused three times, the yield of the product did not obviously decrease.

1-Methyl-4-phenylethynylbenzene: mp 71 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53–7.56 (m, 2 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.35–7.38 (m, 3 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 2.39 (s, 3 H). IR (KBr): v = 3018, 2235, 1630, 1547 cm<sup>-1</sup>. MS: *m/z* (%) = 192 (100) [M<sup>+</sup>], 101 (32).

Hex-1-ynyl-benzene: light yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.42 (d, *J* = 8.0 Hz, 2 H), 7.28–7.32 (m, 3 H), 2.41 (t, *J* = 6.9 Hz, 2 H), 1.47–1.62 (m, 4 H), 0.95 (t, *J* = 6.9 Hz, 3 H). IR (neat): v = 3025, 2988, 2225, 1620, 1526 cm<sup>-1</sup>. MS: *m*/*z* (%) = 158 (27) [M<sup>+</sup>], 115 (100), 129 (59), 143 (44).

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