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Copper-Catalyzed Suzuki Cross-Coupling Using Mixed Nanocluster Catalysts

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Cross-coupling of aryl halides with arylboronic acids (the Suzuki−Miyaura reaction[1]) is one of the most useful synthetic protocols in organic chemistry.[2−5] It is used extensively in the synthesis of polymers, agrochemicals, and pharmaceutical intermediates. The catalyst of choice is almost invariably a palladium(0) complex, in the presence of (phosphorus) ligands, although for aryl chlorides nickel[6,7] catalysis has also been reported.

The accepted catalytic cycle begins with oxidative addition of the aryl halide to a homogeneous Pd(0) complex, followed by transmetalation and reductive elimination of the product. However, investigations by Reetz et al.[8,9] and Hyeon and co-workers[10] have shown that another reaction pathway is possible wherein the active moieties are nanosized palladium colloids or hollow shells. We have also shown that such palladium clusters can exhibit similar activity in Ullmann-type reactions.[11]

The catalytic activity evidenced by monometallic[12−19] and bimetallic[20] colloids prompted us to search for alternative colloid catalysts for C−C cross-coupling reactions. Copper and copper-based alternatives are particularly attractive, being orders of magnitude cheaper and also less harmful to the environment than any noble metal. Moreover, Cu(I) salts and Cu_2O have recently been reported as co-reagents[21−23] (albeit in stoichiometric amounts) and cocatalysts[24] in C−C and C−N[25] coupling reactions.

A mixture design[26] assuming no prior knowledge was applied to test the singular and the combined catalytic effects of copper with three noble metals (palladium, platinum, and ruthenium, see Figure 1). The fifteen cluster combinations **1**−**15** were prepared by mixing predetermined quantities of the appropriate homogeneous stock solutions of the metal chloride precursors, followed by reduction with tetraoctylammonium formate (TOAF) in dimethylformamide (DMF). XR diffraction analysis showed that the metal cluster cores were between 1.6 and 2.1 nm in size, depending on the metal precursors, with a distribution of ±0.1 nm (see Supporting Information for full experimental details).

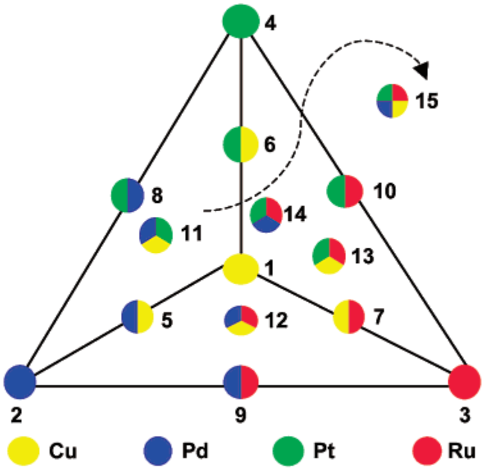


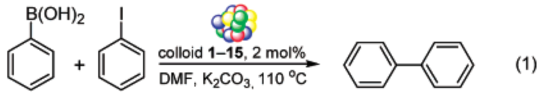
Figure 1. Experimental design for preparing colloid catalyst mixtures of copper, palladium, platinum, and ruthenium.

Table 1. Biphenyl Yields and Second-Order Reaction Rate Constants Obtained Using Various Nanocolloid Catalysts[a]

entry	catalyst[b] (composition)	yield/%[c]	k_{obs} (L/mol min^{-1})	r^2 (five observations)
1	**1** (Cu)	62	3.2×10^{-3}	0.985
2	**2** (Pd)	100	5.9×10^{-2} [d]	0.990
3	**3** (Ru)	40	2.0×10^{-3}	0.938
4	**5** (Cu/Pd)	100	6.1×10^{-2} [d]	0.992
5	**8** (Pd/Pt)	94	9.7×10^{-3}	0.934
6	**9** (Pd/Ru)	100	2.9×10^{-2}	0.985
7	**11** (Cu/Pd/Pt)	92	2.5×10^{-2}	0.991
8	**12** (Cu/Pd/Ru)	100	3.8×10^{-2} [d]	0.996
9	**14** (Pd/Pt/Ru)	81	7.3×10^{-3}	0.923
10	**15** (Cu/Pd/Pt/Ru)	62[e]	2.8×10^{-3}	0.992

[a] Standard reaction conditions: 0.50 mmol iodobenzene, 0.75 mmol phenylboronic acid, 1.5 mmol K_2CO_3, 0.01 mmol catalyst (2 mol % total metal nanoclusters relative to PhI), 12.5 mL DMF, N_2 atmosphere, 110 °C. [b] No conversion was observed with catalysts **4**, **6**, **7**, **10**, and **13**. [c] GC yield after 6 h, corrected for the presence of internal standard. [d] Value is the average of two repeated experiments. [e] 100% yield obtained after 24 h.

The coupling of phenylboronic acid and iodobenzene to give biphenyl (eq 1) was used as a model reaction. The results are shown



(1)

in Table 1 and in Figure 2. As expected, palladium **2** displayed the highest activity of the monometallic catalysts, affording quantitative yields after 4 h at 110 °C. No reaction was observed with the platinum clusters, but ruthenium and, surprisingly, copper clusters were found to be both active and stable (see Figure 2). Of the bimetallic combinations, Cu/Pd **5** was the most active, on par with pure Pd **2** (cf. Table 1, entries 4 and 2). The activity trends continued with the trimetallic clusters, with **12** > **11** > **14**. The tetrametallic combination **15** was less active but stable, reaching 100% conversion after 24 h. The lower activity of **15** when compared to that of the trimetallic catalysts **12**, **11**, and **14** may reflect structural differences caused by the presence of Pt.

Repeated experiments (broken lines in Figure 2) confirmed that the results are reproducible and that the nanoclusters retain their activity for at least 4 weeks (all duplicate experiments were performed using the same stock solution).

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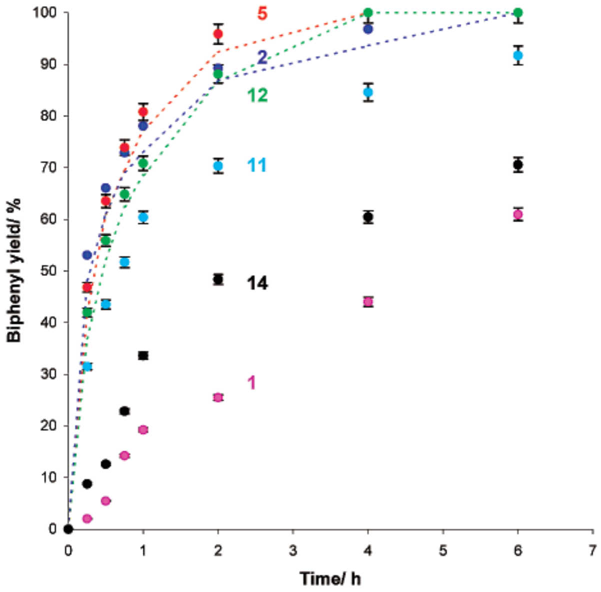
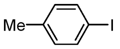
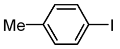
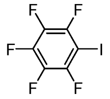
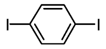
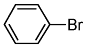
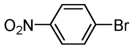
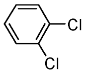


Figure 2. Time-resolved reaction profiles observed for the Suzuki coupling of phenylboronic acid and iodobenzene using various colloid catalysts. Broken lines represent duplicate reactions. Standard reaction conditions: 0.50 mmol iodobenzene, 0.75 mmol phenyl boronic acid, 1.5 mmol K_2CO_3, 0.01 mmol catalyst (2 mol % total metal nanocluster relative to PhI), 12.5 mL of DMF, 110 °C, N_2 atmosphere.

Table 2. Colloid-Catalyzed Suzuki Coupling with Various Substrates[a]

Entry	Substrate	Catalyst (composition)	Time /h	Conversion /%[b]
1		**1** (Cu)	8	100
2		**5** (Cu/Pd)	2	100
3		**5** (Cu/Pd)	2	100[c]
4		**5** (Cu/Pd)	24	100[d]
5		**12** (Cu/Pd/Ru)	24	62
6		**5** (Cu/Pd)	2	100[e]
7		**12** (Cu/Pd/Ru)	24	25[f]

[a] See Table 1 for reaction conditions. [b] GC yield, corrected for the presence of an internal standard. Only the cross-coupling product was observed, unless otherwise noted. [c] Biphenyl (12%) as byproduct. [d] 100% conversion to 1,4-diphenylbenzene (terphenyl) was observed, plus 10−12% biphenyl. [e] 4-Phenyl-1-nitrobenzene was formed in 100% yield after 4 h, and then reduced in ca. 50% yield to 4-phenyl-aniline after a further 20 h. [f] 2-Chlorobiphenyl (25%) and biphenyl (10%) were observed.

Further reactions confirmed that these novel cross-coupling catalysts are active over a range of aromatic substrates (see Table 2). In three of the experiments (Table 2, entries 3, 4, and 7), ca. 10% biphenyl is also observed. The amount of copper in these experiments is too small to account for this biphenyl forming via the stoichiometric Ullmann[27] reaction, and in any case no 4,4′-dimethylbiphenyl was observed when *p*-iodotoluene was used as the substrate. It is more likely that some homocoupling of phenylboronic acid occurs in these cases.[28,29] In the case of *p*-nitrobromobenzene a remarkable one-pot cross-coupling followed by reduction occurs, to yield first 100% 4-phenyl-nitrobenzene that is subsequently hydrogenated to 4-phenyl-aminobenzene. This surprising reaction may be due to the presence of the formate ions, that can give H_2 in the presence of palladium and water.[30]

We have shown here that designed copper and copper-based nanocolloids can catalyze the Suzuki reaction, and may eventually present an inexpensive and eco-friendly alternative to noble metal catalysts. Further studies on the structure and activity scope of these new materials are now in progress.

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Supporting Information Available: Detailed experimental procedures for the synthesis of catalysts **1**−**15**; procedures for performing the cross-coupling reactions; graphs showing time-resolved reaction profiles and kinetic analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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