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Polymer-Supported Copper Complex for C–N and C–O Cross-Coupling Reactions with Aryl Boronic Acids

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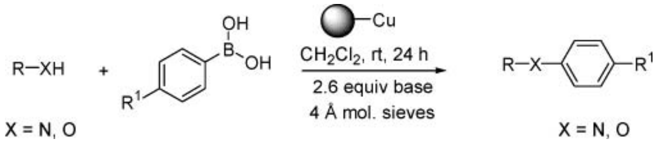
ABSTRACT



Immobilization of copper onto modified Wang resin provided a polymer-supported copper catalyst, which is effective in cross-coupling reactions between N- or O-containing substrates and arylboronic acids. The copper catalyst is air stable and can be recycled with minimal loss of activity.

In recent years, the formation of C(aryl)−N and C(aryl)−O bonds using copper-mediated processes has emerged as one of the most significant classes of cross-coupling reactions.[1] The initial reports of Chan[2], Evans,[3] and Lam[4] illustrated that arylamines, *N*-aryl heterocycles, and biaryl ethers can be prepared using boronic acids and cupric acetate [Cu(OAc)$_2$] as the catalyst. The advantage of this method was that the coupling reaction could be performed under milder conditions (room temperature, weak base, and in air) compared to that of the classical Ullmann and Goldberg arylation protocols.[5] Extensions to the cupric acetate method have included other organometalloid partners such as hypervalent siloxanes,[6] hypervalent diaryliodonium salts,[7] and arylstannanes.[2b] However, one limitation with the use of these coupling partners (including boronic acids) was that they require stoichiometric amounts of Cu(OAc)$_2$. More recently, Collman reported the first catalytic version of this reaction.[8] In this system, [Cu(OH)·TMEDA]$_2$Cl$_2$ was used as the source of copper, but this method worked for only a limited number of substrates. Two other catalytic systems have since been reported by Buchwald[9] and Lam.[10] Buchwald's system employed Cu(OAc)$_2$, myristic acid as an additive, and 2,6-lutidine as the stoichiometric base, and a number of amines were shown to cross couple with boronic acids efficiently. Lam's system also employed Cu(OAc)$_2$ as the catalyst along with an additional co-oxidant such as pyridine *N*-oxide.

We sought to develop a polymer-supported copper catalyst based upon the cupric acetate method in a way similar to the development of polymer-supported catalysts for palladium-catalyzed cross-coupling processes such as in the Heck[11] and Suzuki couplings.[12] The method would benefit from lower costs and the improved workup procedure that is often associated with the polymer-supported palladium catalysts.[13] This would inevitably improve its application in

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[1] Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed*. **2003**, *42*, 5400−5449.

[2] Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933−2936.

[3] Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett*. **1998**, *39*, 2937−2940.

[4] (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941−2944. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674−676.

[5] (a) Ullman, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2389−2391. (b) Goldberg, I. *Ber. Dtsch. Chem. Ges*. **1906**, *39*, 1691−1696.

[6] Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R. H.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc*. **2000**, *122*, 7600−7601.

[7] Kang, S. K.; Lee, S. H.; Lee, D. *Synlett* **2000**, 1022−1024.

[8] (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236. (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem*. **2001**, *66*, 1528−1531

[9] Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077−2079.

[10] Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett*. **2001**, *42*, 3415−3418

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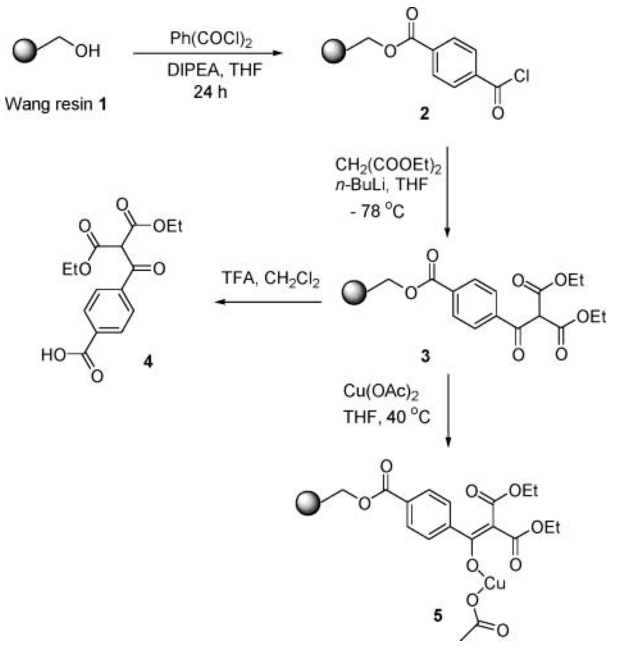
the parallel synthesis of libraries requiring this type of transformation.

Herein we report the synthesis of a polymer-supported copper catalyst and illustrate its application in a number of cross-coupling reactions between boronic acids and N-containing substrates or phenols. Our strategy was to attach a ligand to a polymer support and then allow it to bind to copper through ligand exchange. The resulting binding interaction also needs to be strong enough to prevent the copper from dissociating from the polymer support under the reaction conditions. To realize this strategy, we believed that a polystyrene support with a β-ketoester terminus would be ideal. Hence, using $Cu(OAc)_2$ as the source of copper, displacement of acetate would provide a copper-bound polymer-supported catalyst.[14]

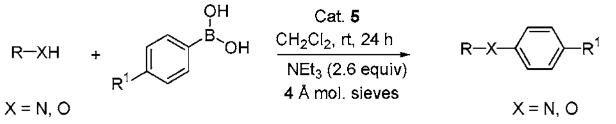
Starting from Wang resin (1.2 mmol/g), esterification with terephthaloyl chloride gave **2** (Scheme 1). Treatment of **2** with diethyl malonate provided a tricarbonyl-functionalized resin **3**. Confirmation of the tricarbonyl moiety was achieved by cleavage of the resin with trifluoroacetic acid (TFA) to give the ester **4**. With the identity of the resin confirmed, immobilization of copper onto the solid support was accomplished by adding $Cu(OAc)_2$ in THF at 40 °C, thus revealing a strongly colored dark green resin of proposed structure **5** (0.8 mmol/g).

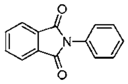
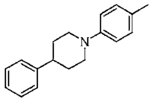
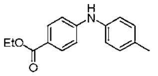
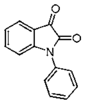
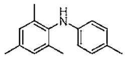
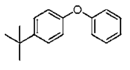
Scheme 1. Synthesis of the Solid-Phase Copper Catalyst



Our initial experiment using catalyst **5** was performed with phthalimide. We found that, using the conditions outlined in Table 1, the yield obtained for this substrate was comparable to the literature value of the homogeneous system (entry 1). Moreover, we noticed a significant improvement in the reaction time, taking 24 h compared to 48 h.[2] Using these conditions, we tested whether the reaction could be performed catalytically. With 0.25 equiv of catalyst, the coupling between 4-phenylpiperidine and *p*-tolylboronic acid (entry 2) gave a 35% isolated yield of the coupled product over 24 h, thus showing that our system was catalytic since the yield was greater than 25%. With 1.5 equiv of catalyst, the isolated yield was 51% after 24 h, indicating that the reaction time is slower using substoichiometric amounts. This deduction was further supported by the coupling reaction of ethyl 4-amino benzoate with *p*-tolylboronic acid (entry 3). The results show that with 0.25 equiv of catalyst, a 33% isolated yield was obtained after 24 h. With 1.5 equiv of catalyst, the isolated yield was 54%. With a 48 h reaction

Table 1. Copper-Mediated Coupling of N- and O-Containing Compounds with Aryl Boronic Acids[a]



entry	R^1	cat. 5 (equiv)	product	isolated yield (%)
1	H	1.5		72, 70,[b] 87[b]
2	Me	0.25 1.5		35 51
3	Me	0.25 1.5		33, 58,[c] 54
4	H	1.5		62, 67,[b] 54[b]
5	Me	1.5		51[b] 54[b, d]
6	H	1.5		81[e] 99[b,d, e]

[a] All reactions were performed with 3 equiv of boronic acid. [b] Recycled catalyst. [c] Reaction time was extended to 48 h, and an extra 3 equiv of boronic acid was added after the first 24 h. [d] Pyridine was used as the base. [e] Performed with 4 equiv of boronic acid.

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(11) (a) Andersson, C. M.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* **1985**, *50*, 3891−3895. (b) Zhang, Z. Y.; Pan, Y.; Hu, H. W.; Kao, T. Y. *Synth. Commun.* **1990**, *20*, 3563−3574. (c) Liao, Y.; Zhang, Z. Y.; Hu, H. W. *Synth. Commun.* **1995**, *25*, 595−601. (d) Kaneda, K.; Terasawa, M.; Imanaka, T.; Teranishi, S. *J. Organomet. Chem.* **1978**, *162*, 403.

(12) (a) Jang, S. B. *Tetrahedron Lett.* **1997**, *38*, 1793−1796. (b) Fenger, I.; Le Drian, C. *Tetrahedron Lett.* **1998**, *39*, 4287−4290.

(13) (a) Atrash, B.; Reader, J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 4779−4782. (b) Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412−3413. (c) Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 2871−2873.

(14) For examples of other copper catalysts on solid supports, see: Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467−3494 and references therein.

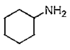
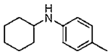
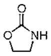
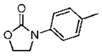
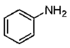
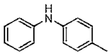
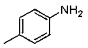
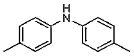
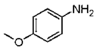
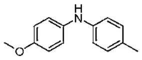
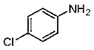
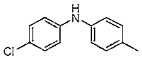
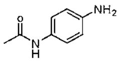
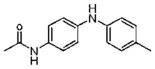
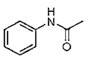
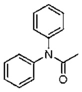
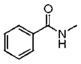
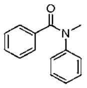
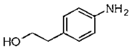
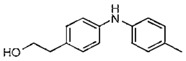
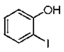
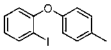
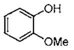
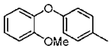
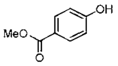
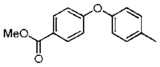
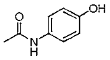
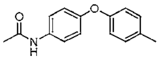
time and 0.25 equiv of catalyst, the isolated yield was 58%, but additional boronic acid (3 equiv) had to be added after 24 h, as all the boronic acid had been consumed.[15] From these results, we decided that larger amounts of catalyst, which benefit the reaction time, would be better for the purposes of developing a general method.

The reusability of catalyst **5** was assessed with both phthalimide and isatin (entries 1 and 4). The catalyst **5** was recycled twice to give isolated yields of 72, 70, and 87% with phthalimide and 62,, 67, and 54% with isatin. This showed that the catalyst retained activity through recycling, and it was also surprising to see that in the case of phthalimide, the yield actually improved in the third cycle. It was necessary to carry out a control experiment to confirm that the copper catalyst **5** promoted the cross-coupling reaction as opposed to leached copper in solution. After suspending **5** in CH_2Cl_2 overnight and then filtering off the catalyst, the cross-coupling reaction of isatin and phenylboronic acid was performed in the same reaction solvent. After 24 h, no conversion to product was detected by thin-layer chromatography or liquid chromatography/mass spectroscopy. The catalyst **5** was then added to the reaction mixture, and complete conversion to product was effected within 24 h. This illustrates that the cross-coupling reaction is indeed promoted by the polymer-supported copper catalyst **5**.

We also briefly explored the effect of changing the base from NEt_3 to pyridine. It has been shown that pyridine can be used to improve the low yields in reactions with NEt_3. It is hypothesized that pyridine plays a dual role in the reaction, one as a base and the other as a ligand to copper.[4b] We tested the effect of the base change to pyridine by looking at a phenol and an aniline example (entries 5 and 6). With trimethylaniline, coupling to phenylboronic acid gave isolated yields of 51 and 54% for NEt_3 and pyridine, respectively. With *tert*-butylphenol, the yields were 81 and 99%. Although the yields appear to be better with pyridine, they were still comparable, and therefore we decided that NEt_3 would be the better choice for a general method due to toxicity reasons.

Under our generalized conditions, a series of N-containing substrates and phenols were tested using both fresh and recycled batches of catalyst **5** (Table 2).[16] We were pleased to find that for all the N-containing substrates tested, the reactions were complete after 24 h, with yields varying between 48 and 93%. The reaction also appeared to work well with both electron-donating and electron-withdrawing groups in the para position of the anilines (entries 4−7). However, it appears that the reaction is not general for amides, and only starting material was recovered (entries 8 and 9). Nevertheless, we were able to use this chemoselectivity to account for the reaction of an amine in the presence of an amide (entry 7), and functional groups such as alcohols were well tolerated (entry 10). With phenols, we found that the reactions were complete after 24 h/ 4 equiv of boronic acid were required, and yields ranged between 50 and 83%. Both electron-withdrawing and -donating phenols worked well (entries 11−13). Furthermore, the phenolic OH group can be arylated in the presence of an amide group (entry 14).

Table 2. Copper-Mediated Coupling of N- and O-Containing Compounds with Aryl Boronic Acids Using the Generalized Conditions[a]

entry	starting material	R'	product	isolated yield (%)
1		Me		54
2		Me		48
3		Me		66[b]
4		Me		93[b]
5		Me		78
6		Me		54[b]
7		Me		55[b]
8		H		0
9		H		0
10		Me		75[b]
11		Me		56[b,c]
12		Me		83[b,c]
13		Me		67[c]
14		Me		50[c]

[a] All reactions were run using conditions outlined in Table 1 with 1.5 equiv of catalyst **5**, 3 equiv of arylboronic acid, and NEt_3 as the base. [b] Recycled catalyst. [c] Performed with 4 equiv of boronic acid.

A possible mechanism for N- or O-arylation is outlined in Scheme 2. The mechanism is based upon those proposed by Collman,[8a] Lam,[17] and Demir.[18] Coordination of the

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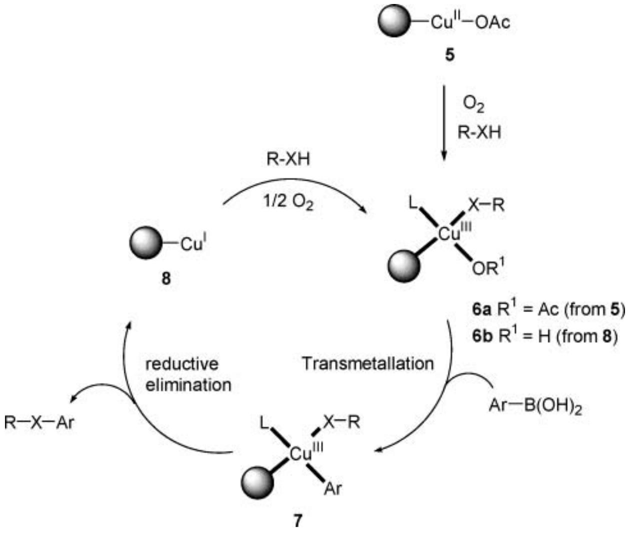
[15] Competing side reactions convert the excess boronic acid into the homocoupled biaryl products, but these are easily removed by flash chromatography.

[16] General procedure for the copper-catalyzed coupling of arylboronic acids with N- or O-containing substrates. The amine or phenol (0.34 mmol) was placed in a 25 mL round-bottomed flask (RBF). The catalyst **5** (0.64 g, 0.8 mmol/g, 0.52 mmol), aryl boronic acid (1 mmol), 4 Å crushed molecular sieves, NEt_3 (0.88 mmol), and dichloromethane (8 mL) were added. The RBF was equipped with a vacuum adaptor, and the reaction mixture was agitated vigorously for 24 h, open to air. The reaction mixture was diluted with methanol (4 mL) and filtered to remove the catalyst and sieves. Purification was accomplished by flash chromatography to give the desired product.

Scheme 2. Possible Mechanism of Catalysis



phenol/amine and oxidation by oxygen gives a copper(III) intermediate (**6a**). Transmetalation of (**6a**) with the arylboronic acid gives (**7**), which undergoes reductive elimination to product and also provides the copper(I)-bound catalyst **8**. Since our earlier experiments have shown that the reaction is catalytic, the copper catalyst **8** should also be able to effect the transformation to product. Hence, regeneration of the copper(III) intermediate **6b** can possibly be achieved by coordination of the phenol/amine and oxidation by oxygen. This suggests that, after one cycle, the actual catalyst is copper(I) in nature.[19] We believe that a copper(I)/copper(III) catalytic system is in place because reductive elimination of a copper(II) intermediate to copper(0) would dissociate the copper from the polymer resin, rendering it nonrecyclable.

In summary, we have developed a solid-phase variant for $Cu(OAc)_2$ and have shown that it can be successfully applied in a number of cross-coupling reactions between N-containing compounds or phenols and boronic acids. The solid-phase catalyst **5** can be recycled with minimal loss of activity and was able to promote the reaction catalytically. The easy workup procedure provides a method that is well suited toward the synthesis of parallel libraries based upon this type of transformation. Further assessment of the scope and limitations are currently underway.

Supporting Information Available: Experimental procedures and characterization for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048943E

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(17) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett*. **2003**, *44*, 1691−1694.

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(19) We have independently synthesized the copper(I) catalyst **8** by reacting CuI with resin **3**. The coupling reaction of isatin and phenylboronic acid was subsequently tested with this catalyst, and the yield obtained was 66%, comparable to the results given in Table 1.