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# Impregnated Copper on Magnetite as Recyclable Catalyst for the Addition of Alkoxy Diboron Reagents to C−C Double Bonds

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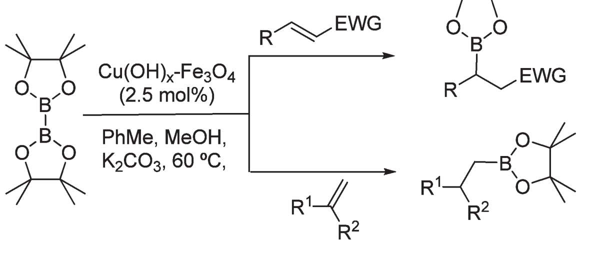
*Received February 22, 2010*



A simple protocol for the borylation with use of impregnated copper on magnetite is described. The reactions showed a very broad scope and all type of olefins could be used with similar results. The catalyst could be easily removed by a magnet and it could be reused several times, showing similar activity.

Organoboronic acid derivatives are of great importance in organic synthesis, not only for their own special characteristics and activities but also as organometallic key reagents in many syntheses, such as in the well-established cross-coupling protocols. Classically, they are prepared by the treatment of trialkyl borates with a magnesium or lithium organometallic reagent. However, this approach is restricted to substrates either without additional functional groups or with those compatible with the highly nucleophilic carbanionic center. These limitations have forced the development of new approaches to prepare this type of compound with highly reactive functionalities, such as Brønsted acid or electrophilic functionalities.[1]

Among the different ways to prepare organoboronate derivatives, the catalytic addition of diboron reagents to alkenes (or alkynes) via metal−boryl intermediates has shown its high potential and versatility in organic synthesis, providing a great variety of useful functionalized compounds.[2] A special case is the hydroborylation of simple olefins,[3] as well as of electron-deficient ones,[4] using alkoxy diboron reagents. This conjugate borylation has been carried out with either an organocatalyzed approach[5] or different metal complexes, such as nickel,[6] rhodium,[7] palladium,[6b] and platinum,[8] with copper complexes being the most employed ones.[9,10] Besides of the indisputable success of the copper complexes some aspects of this reaction still remain which could be improved, including the high catalyst loading (3−110 mol %), narrow substrate scope, high reaction temperatures, presence of labile phosphine ligands, and overall, the nonrecyclability of catalyst in known protocols.

In the course of our studies on the use of magnetite as catalyst[11] or as privileged support[12] in organic synthesis, we

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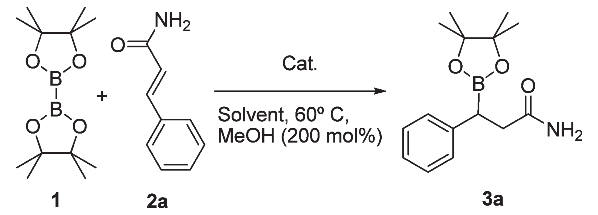
DOI: 10.1021/jo100325e

**TABLE 1. Screening of the Reaction Conditions**



| entry | cat. (mol %) | base (mol %) | solv. | *t* (h) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $Fe_3O_4$ (86) | *t*BuOK (9) | THF | 168 | 0 |
| 2 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | THF | 4 | 85 |
| 3 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | THF[b] | 48 | 0 |
| 4 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | THF[c] | 4 | 75 |
| 5 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | THF[d] | 4 | 85 |
| 6 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | MeOH | 4 | 70 |
| 7 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | DMSO | 4 | 40 |
| 8 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | MeCN | 4 | 60 |
| 9 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | PhMe | 4 | 86 |
| 10[e] | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (9) | PhMe | 4 | 30 |
| 11 | $Cu(OH)_x$-$Fe_3O_4$ (5) | *t*BuOK (90) | PhMe | 0.5 | 90 |
| 12 | $Cu(OH)_x$-$Fe_3O_4$ (5) |  | PhMe | 24 | 20 |
| 13 | $Cu(OH)_x$-$Fe_3O_4$ (5) | KOH (90) | PhMe | 0.5 | 93 |
| 14 | $Cu(OH)_x$-$Fe_3O_4$ (5) | $(NH_4)_2CO_3$ (90) | PhMe | 0.5 | 40 |
| 15 | $Cu(OH)_x$-$Fe_3O_4$ (5) | $Na_2CO_3$ (90) | PhMe | 0.5 | 64 |
| 16 | $Cu(OH)_x$-$Fe_3O_4$ (5) | $K_2CO_3$ (90) | PhMe | 0.5 | 95 |
| 17 | $Cu(OH)_x$-$Fe_3O_4$ (5) | $Cs_2CO_3$ (90) | PhMe | 0.5 | 82 |
| 18 | $Cu(OH)_x$-$Fe_3O_4$ (2.5) | $K_2CO_3$ (90) | PhMe | 0.25 | 99 |
| 19 | $Cu(OH)_x$-$Fe_3O_4$ (0.5) | $K_2CO_3$ (90) | PhMe | 0.5 | 55 |
| 20 |  | $K_2CO_3$ (90) | PhMe | 48 | 0 |

[a] Isolated yield after crystallization from $CH_2Cl_2$−hexane. [b] Reaction performed in the absence of MeOH. [c] Reaction performed at 25 °C. [d] Reaction performed at 110 °C. [e] Reaction performed with only 20 mol % of MeOH.

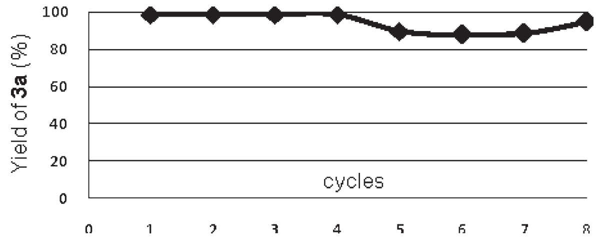
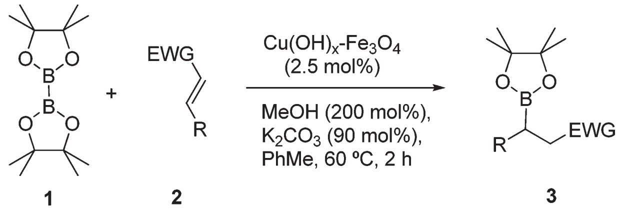


**FIGURE 1.** Yields of compound **3a** after several cycles.

**TABLE 2. Impregnated Copper Catalyzes the Michael-Type Borylation Process**



| entry | R | EWG | compd | yield (%)[a] |
|---|---|---|---|---|
| 1 | Ph | $CONH_2$ | **3a** | 99 |
| 2 | H | $CONH_2$ | **3b** | 99[b] |
| 3 | Ph | COOEt | **3c** | 91 |
| 4 | Ph | CN | **3d** | 99 |
| 5 | Ph | COMe | **3e** | 99 |
| 6 | Ph | COPh | **3f** | 98 |
| 7 | $CH_2OCO$ |  | **3g** | 93 |
| 8 | $(CH_2)_3CO$ |  | **3h** | 99 |

[a] Isolated yield. [b] Reaction performed for 16 h.

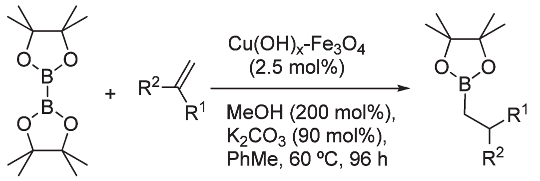
investigated the reaction of bis(pinacolato)diboron (**1**) with cinnamamide (**2a**) to give the corresponding benzyl boronic derivatives **3a** (Table 1). We decided to start our study using amides as the electrophilic partner since this type of substrate has been scarcely used in similar reactions. In fact, there is only one example with cinnamamide as substrate and equimolecular amounts of CuCl and 1,2-bis(diphenylphosphino)-benzene as the catalytic system.[9k] Moreover, this substrate is a very bad Michael-acceptor compared with other α,β-unsaturated compounds and has two acid protons, which could impede the nucleophilic attack of basic substrates. The initial reaction with a small excess of compound **1** (140 mol %) failed after 1 week at 60 °C in THF with use of only magnetite. However, the reaction performed with impregnated copper on magnetite gave the expected product in good yield (Table 1, entry 2). It should be pointed out that a similar protocol but with pinacolborane failed, recovering the starting amide **2a** unchanged. The catalyst was easily prepared by a basic precipitation−adsorption of an aqueous solution of copper chloride on the surface of commercially available magnetite (powder < 5 μm) leading to the incorporation of 1.37−1.62% of Cu according to X-ray fluorescence (BET area: 9.15 $m^2\ g^{-1}$).[12d]

Once the activity of the catalyst was demonstrated, different parameters of the reaction were optimized. The reaction failed in the absence of methanol (Table 1, entry 3), and the results at higher or lower temperatures did not change significantly (compare entries 2, 4, and 5). Other solvents used such as MeOH, DMSO, or MeCN did not improve the previous results, with toluene giving only a marginal improvement (see entries 6−9). Under these new reaction conditions, whereas the reduction of the amount of either MeOH or base decreased the yield, the increase of the amount of base had a beneficial effect (compare entries 9−12). After that, the nature of base was tested, finding that potassium carbonate gave the best result (compare entries 13−17). Finally, the amount of catalyst was tested, finding that a 50% reduction had a beneficial effect, obtaining the expected compound **3a** in practically quantitative yield after only 15 min of reaction. Meanwhile, a further decrease of the catalyst amount produced lower yield, even in longer reaction times (see entries 18 and 19). Finally the reaction in the absence of catalyst failed after 2 days of reaction time (entry 20).

Once the catalytic activity of the impregnated copper on magnetite was demonstrated, we faced the problem of its reuse, finding that the chemical yields were practically constant in a range between 88% and >99%, after 8 cycles of reaction, for the preparation of compound **3a** (Figure 1), with the catalyst being maintained inside the flask only by the help of a magnet.

Once the catalytic activity and its recyclability was proved, the scope of the reaction was tested (Table 2), finding excellent results for the reaction independently of the nature of substituents in the alkene **2**. The reaction could be performed with substituted and unsubstituted α,β-unsaturated carboxamides (entries 1 and 2), with other acid derivatives such as an ester and a nitrile (entries 3 and 4), even with ketones (entries 5 and 6) giving similar results. The

**SCHEME 1. Impregnated Copper Catalyzes the Borylation of Olefins**



**1** **4**

**5a**: $R^1$ = H, $R^2$ = Ph (99 %)
**5b**: $R^1$ = H, $R^2$ = 2-naphthyl (99 %)
**5c**: $R^1$ = H, $R^2$ = 4-$ClC_6H_4$ (56 %)
**5d**: $R^1$ = Me, $R^2$ = Ph (85 %)
**5e**: $R^1$ = $(CH_2)_3Me$, $R^2$ = H (95 %)

yields obtained for cyclic compounds **2** were similar to those obtained for acyclic ones (entries 7 and 8). In all cases yields were higher than 90%.

Finally, we faced the problem of using simple olefins **4**, and gratifyingly the reaction gave selectively only (or mainly, > 95%) one regioisomer **5** (see Scheme 1). In the case of product **5c**, the low yield was due to the presence of a small amount of the diborylation product (< 15%) and the starting chlorinated compound **4**, with dehalogenated byproduct not being detected. The above protocol could be used only by increasing the reaction time from a few hours to days.

Although the possible mechanism for this process is not clear, we believe that the reaction goes through the formation of the corresponding copper–boryl intermediate, as was pointed out earlier.[9g] This intermediate adds to the olefin to give the most stable anionic intermediate in both cases, with the protonation of enolic or benzylic intermediate liberating the copper salt.

In conclusion, impregnated copper on magnetite is an excellent catalyst for the borylation of any type of olefin in the absence of expensive and difficult to handle phosphines, and with one of the lowest catalyst loadings. The catalyst is easily removed from the reaction media just by the use of a simple magnet, and it could be reused several times without losing its initial activity. The reaction conditions implied the use of a soft base in clear contrast with the previous bases used. All these facts, together with the simplicity of the protocol, the wide scope of substrates, and their simple recycling permitted us to anticipate a good future for the process shown in this paper not only in the laboratory but also in industry.

## Experimental Section

To a stirred solution of bis(pinacolato)diboron (**1**, 0.7 mmol, 178 mg) in toluene (0.5 mL) under argon atmosphere were added $Cu(OH)_x/Fe_3O_4$ (50 mg), $K_2CO_3$ (0.45 mmol, 62 mg), the $\alpha,\beta$-unsaturated compound or olefin (0.5 mmol) and MeOH (1 mmol, 40 $\mu$L). The resulting mixture was stirred at 60 °C until the end of the reaction. The catalyst was removed by a magnet and the resulting mixture was quenched with a saturated solution of $NH_4Cl$ and extracted with AcOEt. The organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. The product was usually purified by chromatography on silica gel (hexane/ethyl acetate). Physical and spectroscopic data for the representative compound **3b** follow:

**3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (3b):** mp 184–188 °C; IR (KBr) $\nu$ 3418, 1676, 1549, 1315, 1115 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.05 (t, $J$ = 7.5 Hz, 2H), 1.25 (s, 12H), 2.37 ppm (t, $J$ = 7.4 Hz, 2H), 5.3–5.5, 5.5–5.7 (2 br s, 1 and 1H, respectively); $^{13}C$ NMR (300 MHz, $CDCl_3$, C attached to quadrupole B not observed) $\delta$ 24.8, 30.2, 83.3, 176.3 ppm; EI-MS $m/z$ 184 (10), 141 (94), 140 (100), 139 (197), 100 (25), 99 (15), 84 (20), 83 (16), 55 (10). Anal. Calcd for $C_9H_{18}BNO_3$: C, 54.30; H, 9.11; N, 7.04. Found: C, 54,32; H, 9.09; N, 6.98.

**Acknowledgment.** This work was supported by the Spanish Ministerio de Ciencia y Tecnología (Consolider Ingenio 2010 CSD2007-00006, CTQ2007-65218/BQU) and by Generalitat Valenciana (G.V. PROMETEO/2009/039). R.C. thanks to G.V. for a fellowship through the PROMETEO program.

**Supporting Information Available:** Characterization and copies of $^1H$ and $^{13}C$ for all compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.