

Remarkable co-catalysis by copper(I) oxide in the palladium catalyzed cross-coupling of arylboronic acids with ethyl bromoacetate†

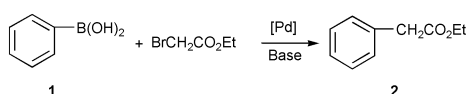
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Copper(I) oxide can effectively co-catalyze the Suzuki type cross-coupling reactions of arylboronic acids with ethyl bromoacetate. As an alternative protocol for introducing the methylenecarboxy group into functionalized molecules, this reaction occurs in the absence of highly toxic thallium compounds or special ligands and should be convenient and practical.



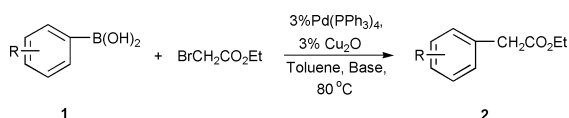
Scheme 1 The cross-coupling reaction of phenylboronic acid with ethyl bromoacetate.

Table 1 The cross-coupling reaction of phenylboronic acid **1** with ethyl bromoacetate **2^a**

| Entry | Catalyst | T(°C)/ t(h) | 2^b (%) | 3^b (%) | 4^b (%) | 5^b (%) |
|-----------------|--|----------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 1 ^c | Pd(PPh ₃) ₄ | 80/17 | 5 | 65 | 4 | 2 |
| 2 ^c | Ag ₂ O/Pd(PPh ₃) ₄ | 80/17 | 7 | 64 | 6 | 3 |
| 3 ^d | Pd/(PPh ₃) ₄ | 25/12 | 19 | 60 | 3 | 2 |
| 4 ^d | Cu ₂ O/Pd(PPh ₃) ₄ | 25/12 | 22 | 53 | 5 | 4 |
| 5 ^d | Cu ₂ O/Pd(PPh ₃) ₄ | 80/12 | 6 | 65 | 4 | 6 |
| 6 | Pd(PPh ₃) ₄ | 110/15 | 2 | 67 | 4 | 4 |
| 7 | Pd(PPh ₃) ₄ | 80/17 | 42 | 46 | 3 | 3 |
| 8 | CuI/Pd(PPh ₃) ₄ | 80/17 | 44 | 44 | 3 | 2 |
| 9 | Ag ₂ O/Pd(PPh ₃) ₄ | 80/17 | 46 | 40 | 4 | 3 |
| 10 | Ag ₂ CO ₃ /Pd(PPh ₃) ₄ | 80/18 | 43 | 41 | 4 | 4 |
| 11 | Ag ₂ O/PdCl ₂ (dppf) | 80/15 | 4 | 70 | 3 | 2 |
| 12 | Ag ₂ O/PdCl ₂ (MeCN) ₂ /(n-Bu) ₃ P | 80/15 | 5 | 68 | 4 | 2 |
| 13 | Cu ₂ O | 25/15 | 4 | 60 | 3 | 3 |
| 14 | Cu ₂ O/Pd(PPh ₃) ₄ | 25/15 | 3 | 68 | 3 | 2 |
| 15 | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 8 | 64 | 3 | 4 |
| 16 | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 87 | 9 | 0 | 0 |
| 17 ^e | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 86 | 8 | 0 | 2 |
| 18 ^f | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 84 | 10 | 3 | 2 |
| 19 ^g | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 66 | 29 | 0 | 1 |
| 20 ^h | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 42 | 55 | 0 | 3 |
| 21 ⁱ | Cu ₂ O/Pd(PPh ₃) ₄ | 80/17 | 41 | 56 | 0 | 3 |

^a All the reactions were carried out using a mixture of phenylboronic acids (1.1 mmol) and ethyl bromoacetate (1 mmol), 3 equiv. of ancillary catalyst (except for entries 1, 3, 6, 7, 13), 3.3 equiv. K₃PO₄·3H₂O (entry 15, 1 equiv.), and 3% catalyst (except for entry 13) in 4 ml of toluene under argon atmosphere. ^b GC yields based on the amount of ethyl bromoacetate used.

^c 1,4-Dioxane as the solvent and KOH as the base. ^d THF as the solvent. ^e K₂CO₃ as the base. ^f The amount of Cu₂O is 3% mmol. ^g The amount of Cu₂O is 1% mmol. ^h The amount of Cu₂O is 3% mmol, the amount of K₃PO₄·3H₂O is 2 equiv. ⁱ The amount of Cu₂O is 3% mmol, the amount of K₃PO₄·3H₂O is 1 equiv.



Scheme 2 Cross-coupling of various arylboronic acids with ethyl bromoacetate co-catalyzed by Cu₂O.

† Electronic supplementary information (ESI) available: general experimental procedure and NMR, IR, MS and elemental analysis for compounds **2a–i**. See <http://www.rsc.org/suppdata/cc/b1/b111355k/>

Pd-catalyzed C–C bond formation is one of the most fundamental and important reactions in organic synthesis.¹ It plays an important role in a wide range of preparative organic processes, from the synthesis of natural products² to supramolecular chemistry and material science.³ The widely used methods are the palladium-catalyzed coupling reactions of electrophiles with organomagnesium,⁴ -zinc,⁵ -tin,⁶ -aluminum,⁷ -zirconium⁸ and particularly organoboron⁹ reagents. The coupling reactions

Table 2 Cross-coupling of various arylboronic acids with ethyl bromoacetate co-catalyzed by Cu₂O^a

| Entry | Arylboronic acid | Product | Yield (%) ^b | |
|-------|------------------|-----------|------------------------|----------------|
| | | | A ^c | B ^d |
| 1 | 1a | 2a | 85 | 84 |
| 2 | 1b | 2b | 84 | 82 |
| 3 | 1c | 2c | 85 | 84 |
| 4 | 1d | 2d | 85 | 83 |
| 5 | 1e | 2e | 45 | 63 |
| 6 | 1f | 2f | 43 | 62 |
| 7 | 1g | 2g | 42 | 58 |
| 8 | 1h | 2h | 46 | 45 |
| 9 | 1i | 2i | 65 | 66 |

^a All the reactions were carried out using a mixture of arylboronic acids (1.1 mmol) and ethyl bromoacetate (1 mmol), 3% mmol of Cu₂O, 3.3 mmol base (based on boronic acids), and 3% mmol Pd(PPh₃)₄ in 4 ml of toluene at 80 °C under argon atmosphere for 14 ~ 17 h. All the products were identified by ¹H NMR, IR, mass spectral and elemental analysis. [†] ^b Isolated yields based on the amount of ethyl bromoacetate used. ^c Method A: using K₃PO₄·3H₂O as base. ^d Method B: using K₂CO₃ as base.

of organoboron compounds have many attractive features (such as high yields, mild conditions, with many tolerant functional groups and the ability to remain unaffected in the presence of water), which make the synthetic process very convenient.

Although the cross-coupling of aryl, alkenyl halides or triflates with organoboron compounds has been widely described, only a few studies to date have explored the coupling of haloacetate with organoboron compounds.¹⁰ In order to expand the scope of Suzuki type coupling reaction and develop a convenient and practical method for introducing methylenecarboxy group into molecules, we studied the cross-coupling reactions of arylboronic acids with ethyl bromoacetate focusing on the effects of bases, solvents and catalysts. Herein, we wish to report our experimental results.

Initially, to optimize the coupling conditions, phenylboronic acid and ethyl bromoacetate were used as the starting materials (Scheme 1).

It was found that under some conditions, the rate of the desired cross-coupling reaction is lower than the redox, homo-coupling reactions of phenylboronic acid and the reductive reaction of ethyl bromoacetate, which lead to biphenyl **3**, benzene **4**, and ethyl acetate **5**. The results are summarized in Table 1.

Table 1 shows that the use of solvent, base and catalyst (including co-catalyst) plays an import role in the coupling reactions. It was noticeable that the use of Cu₂O as a co-catalyst dramatically improved the coupling of phenylboronic acid with ethyl bromoacetate. And 3% equiv. Cu₂O is enough and necessary for accomplishing the desired coupling reaction. Moreover, the reaction temperature is also important.

Under the optimum conditions above-mentioned, the coupling reactions of various arylboronic acids with ethyl bromoacetate were explored (Scheme 2).

The desired coupling products were obtained in moderate to good yields. The results are shown in Table 2.

As illustrated in Table 2, the coupling reactions of various arylboronic acids with ethyl bromoacetate co-catalyzed by Cu₂O can proceed smoothly to give the desired coupling products in moderate to good yields without using highly toxic base or special ligands. Interestingly, in some cases, using

K₂CO₃ as base is better than K₃PO₄·3H₂O in the coupling reactions.

In conclusion, we first found that Cu₂O effectively co-catalyzed the Suzuki type coupling reactions of arylboronic acids with ethyl bromoacetate. Compared with the cross-coupling conditions reported,¹⁰ the reaction does not use highly toxic thallium carbonate or special ligands such as P(Nap)₃, and should be a convenient and practical method for introducing methylenecarboxy group into molecules. Further study on the exact role of Cu₂O and the scope of the reaction is currently underway in our laboratory.

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