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# Copper-Catalyzed Cross-Dehydrogenative Coupling (CDC) of Alkynes and Benzylic C–H Bonds

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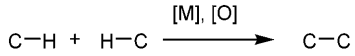
**Abstract:** The activation of benzylic C–H bonds and subsequent coupling with terminal alkynes in the presence of 2,3-dichloro-5,6-dicyanoquinone (DDQ) and a catalytic amount of copper(I) triflate is presented. Good to moderate yields of disubstituted alkynes are obtained for this cross-dehydrogenative coupling (CDC) reaction between a variety of aromatic alkynes and diphenylmethane derivatives.

**Keywords:** alkynes; C–C coupling; C–H activation; copper; diphenylmethanes

Disubstituted acetylenes are traditionally synthesized through elimination[1] or substitution reactions under harsh conditions. The metal-catalyzed substitution reactions generally employ a palladium catalyst and a highly active metal acetylide,[2] all of which have the disadvantage of generating a stoichiometric amount of metal waste. Another widely utilized method is the Sonagashira reaction in which the terminal C–H bond of the alkyne is activated in the presence of a catalytic amount of copper.[3] This method reduces the amount of metal waste due to the *in-situ* generated copper acetylide but it is still performed under rigorous conditions. Alternatively, there is growing interest in the direct substitution of benzylic alcohols owing to them being more environmentally friendly, readily available and less costly than benzylic halides. Initial studies in this field involved the use of highly functional alkynylsilane[4] and alkynylboron[5] reagents. More recently Jiao reported the $Fe(OTf)_3$/TfOH co-catalyzed cross-coupling of terminal alkynes and benzylic alcohols.[6] In the light of this, we envisioned the reaction being accessed through a cross-dehydrogenative coupling of the *sp* C–H bond of a terminal alkyne and a benzylic $sp^3$ C–H bond.

Metal-catalyzed C–H functionalization remains one of the most efficient but challenging areas for C–C bond formation in organic chemistry.[7] With the need for highly functionalized groups eliminated, the number of steps in the synthetic process and consequently the amount of toxic waste is reduced, making the overall process greener.[8] In the past, we[9] and others[10] have been involved in the synthesis of complex molecules *via* metal-catalyzed oxidative reactions which directly couple two C–H bonds in the starting materials; a reaction we termed cross-dehydrogenative coupling (CDC) (Scheme 1). In our continued effort to find novel CDC reactions, we wish to report the unprecedented copper-catalyzed alkynylation of benzylic C–H bonds.

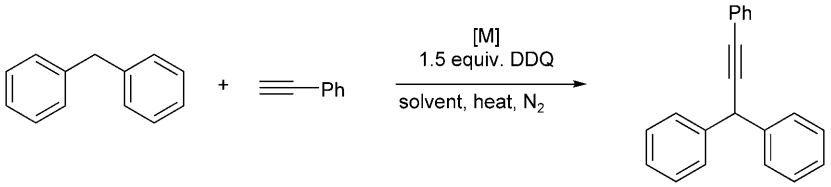



**Scheme 1.** Cross-dehydrogenative coupling.

One of the well known oxidizing agents in organic chemistry is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[11] Previously we[12] and others[13] have reported the efficient use of DDQ for C–C bond formations through activation of benzylic C–H bonds. The benzylic C–H bond lacking an adjacent heteroatom is more difficult to activate;[14] however, Shi recently disclosed the use of DDQ for the arylation of diphenylmethane derivatives.[15]

With this in mind, we began our study using the copper/indium system that we previously reported for the alkylation of benzylic ethers[16] but with DDQ as the oxidant in chlorobenzene ($C_6H_5Cl$). We were pleased to note that the reaction provided us with a 34% yield of product (Table 1, entry 1); the removal of indium increased the yield (Table 1, entry 2). Other Lewis acid metal salts were screened (Table 1, entries 3–6) but copper(II) triflate was found to be the best. Reduction of the amount of copper(II) triflate

**Table 1.** Optimization of the alkynylation of diphenylmethane with phenylacetylene.




| Entry[a] | Catalyst (mol%) | Solvent (mL) | Yield[b] [%] |
|---|---|---|---|
| 1 | $Cu(OTf)_2/In(OTf)_3$ (5/5) | $C_6H_5Cl$ (0.2) | 34 |
| 2 | $Cu(OTf)_2$ (5) | $C_6H_5Cl$ (0.4) | 52 |
| 3 | Cu(benzoate) (5) | $C_6H_5Cl$ (0.2) | NP |
| 4 | InCl (5) | $C_6H_5Cl$ (0.2) | 21 |
| 5 | $FeCl_2$ (5) | $C_6H_5Cl$ (0.2) | Trace |
| 6 | CuI (5) | $C_6H_5Cl$ (0.2) | NP |
| 7 | $Cu(OTf)_2$ (2.5) | $C_6H_5Cl$ (0.2) | 57 |
| 8 | CuOTf·toluene (2.5) | $C_6H_5Cl$ (0.4) | 64 |
| 9 | CuOTf·toluene (2.5) | DCE (0.2) | 49 |
| 10 | CuOTf·toluene (2.5) | DMF (0.2) | NP |
| 11 | CuOTf·toluene (2.5) | $MeNO_2$ (0.2) | 18 |
| 12 | CuOTf·toluene (1) | $C_6H_5Cl$ (0.4) | 71 |
| 13[c] | CuOTf·toluene (1) | $C_6H_5Cl$ (0.4) | 78 |
| 14 | none | $C_6H_5Cl$ (0.4) | NP |
| 15[d] | CuOTf·toluene (1) | $C_6H_5Cl$ (0.4) | 67 |
| 16[e] | CuOTf·toluene (1) | $C_6H_5Cl$ (0.4) | 70 |

[a] *Reaction conditions:* 0.2 mmol phenylacetylene, 5 equiv. diphenylmethane, 1.5 equiv. of DDQ at 105 °C and under nitrogen unless otherwise noted.
[b] NMR yields using mesitylene as an internal standard.
[c] Reaction run for 24 h at 120 °C.
[d] Reaction run for 24 h at 125 °C.
[e] Reaction run for 24 h at 120 °C and 2 equiv. DDQ.

was found to be beneficial to the reaction (Table 1, entry 7). Increasing the amount of chlorobenzene allowed for better stirring of the reaction mixture and likewise increased the yield (entry 8). The reaction did not proceed as efficiently in dichloroethane (DCE), dimethylformamide (DMF) or nitromethane ($MeNO_2$) (Table 1, entries 9–11).[17] During these investigations we noticed that copper(I) triflate was more active than copper(II) triflate for this reaction (Table 1, entry 12). Increasing the reaction time to 24 h and the temperature to 120 °C proved to be our best reaction conditions (Table 1, entry 13). The metal catalyst was critical for the reaction and its removal provided no product (entry 14). Further increasing the temperature or the amount of DDQ did not aid the reaction (Table 1, entries 15 and 16).[18] With our optimized conditions in hand (Table 1, entry 13) we then turned our attention to the scope of the reaction.

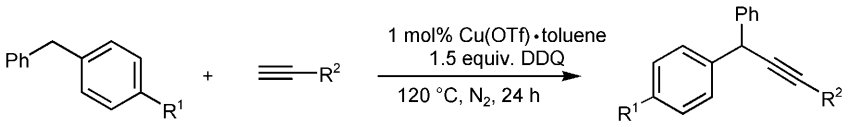
Phenylacetylene was found to be the most effective alkyne for this reaction providing the desired product in good yields. The reaction was sensitive to electronic changes on the phenyl group of the alkyne (Table 2, entries 2–8). It is thought that the electron-rich alkynes were more prone towards the competing oxidative dimerization, whereas the very low yield of 3-flourophenylacetylene (Table 2, entry 4) can be attributed to the lower nucleophilicity of an electron-deficient alkyne.[19] Aliphatic alkynes such as *n*-hexyne were not amenable to this system (Table 2, entry 9). Substitutions on the phenyl ring of diphenylmethane were well tolerated (Table 2, entries 10–14). 1,3-Diphenylpropene (**4**) was also found to be a feasible starting material for this reaction (Scheme 2).

A tentative mechanism for this reaction is proposed in Scheme 3. The benzylic radical (**6**) could be formed through single-electron transfer (SET) with DDQ and copper. This radical can be further oxidized to the benzylic cation (**8**) through a second SET. The reduced hydroquinone would then have the ability to abstract the acidic proton from the alkyne forming the copper acetylide (**7**) which adds to the benzylic carbocation (**8**) forming the desired product (**3a**).

In summary, we have developed a novel copper-catalyzed CDC method for the synthesis of disubstituted alkynes. To the best of our knowledge this is the first report of the metal-catalyzed alkynylation of the more challenging benzylic C–H bonds which are not adjacent to nitrogen atom.[20] This method provides a greener alternative to the nucleophilic substitution of diphenylmethanol since there is no need for pre-func-

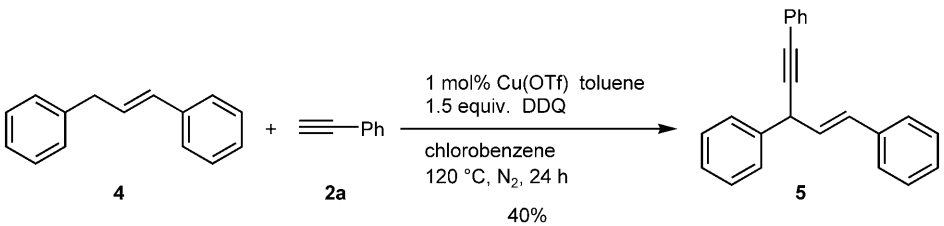
**Table 2.** Cross-dehydrogenative coupling of various alkynes and diphenylmethane derivatives.[a]




**1** **2** **3**

| Entry | $R^1$ | $R^2$ | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 | **1a** H | **2a** $C_6H_5$ | **3a** | 74 |
| 2 | **1a** H | **2b** 4-Me-$C_6H_4$ | **3b** | 62 |
| 3 | **1a** H | **2c** 4-*t*-Bu-$C_6H_4$ | **3c** | 54 |
| 4 | **1a** H | **2d** 3-F-$C_6H_4$ | **3d** | 29 |
| 5 | **1a** H | **2e** 4-$C_6H_5O$-$C_6H_4$ | **3e** | 45 |
| 6 | **1a** H | **2f** 4-*n*-Bu-$C_6H_4$ | **3f** | 57 |
| 7 | **1a** H | **2g** 4-$C_6H_5$-$C_6H_4$ | **3g** | 44 |
| 8 | **1a** H | **2h** 4-alkynyl-$C_6H_4$ | **3h** (mono) & **3i** (di) | 62 (1.6:1) |
| 9 | **1a** H | **2i** *n*-Hex | **3j** | 0 |
| 10 | **1b** $C_6H_5$ | **2a** $C_6H_5$ | **3k** | 71 |
| 11 | **1c** Cl | **2a** $C_6H_5$ | **3l** | 69 |
| 12 | **1d** *t*-Bu | **2a** $C_6H_5$ | **3m** | 61 |
| 13 | **1e** Me | **2a** $C_6H_5$ | **3n** | 83 |
| 14 | **1f** F | **2a** $C_6H_5$ | **3o** | 56 |

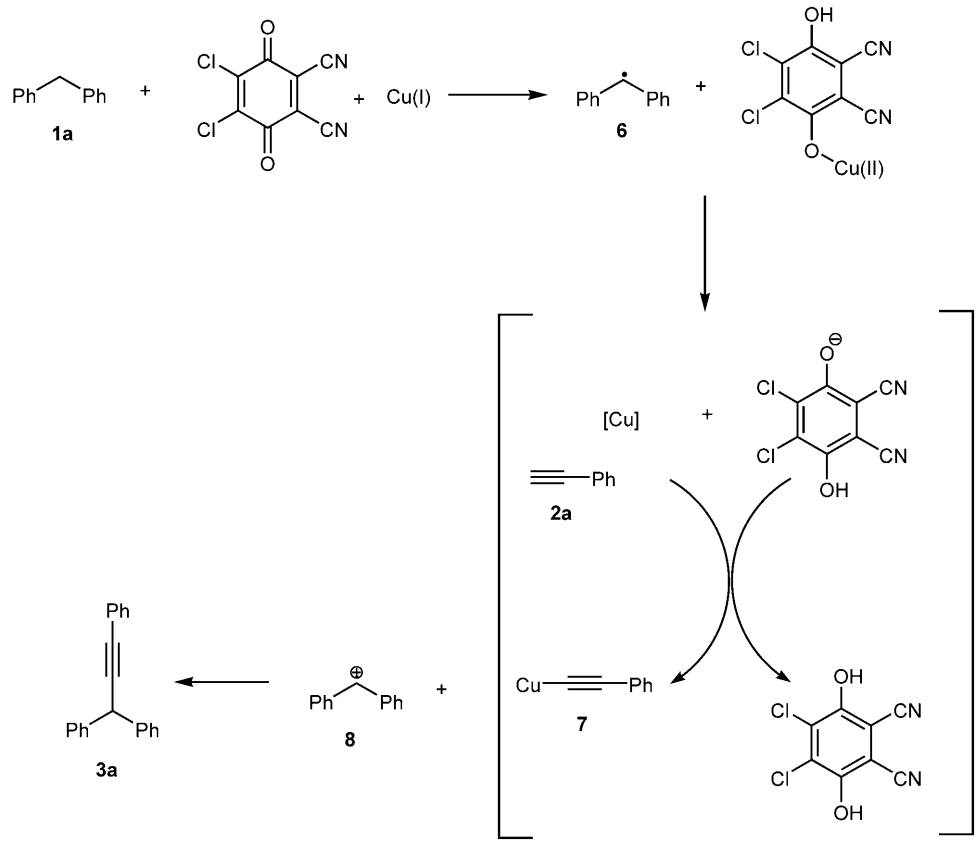
[a] *Reaction conditions:* 0.1 mmol **2**, 5 equiv. **1**, 1.5 equiv. of DDQ, 1 mol% CuOTf·toluene, 0.2 mL chlorobenzene under nitrogen at 120 °C unless otherwise noted.
[b] Isolated yield.




**4** **2a** **5**

**Scheme 2.** Alkynylation of diphenylpropene.




**Scheme 3.** Proposed mechanism for the CDC reaction.

tionalization. Further investigations into the mechanism, scope and application of this chemistry are in progress.

## Experimental Section

### Typical Procedure

CuOTf·toluene (0.001 mol) and DDQ (0.15 mmol) were placed in a sealable tube. To this 0.2 mL chlorobenzene, phenylacetylene (**2a**) (0.1 mmol) and diphenylmethane (**1a**) (0.5 mmol) were then added. The tube was sealed and flushed with nitrogen, then the contents were stirred for 24 h at 120 °C. The reaction mixture was cooled to room temperature and flushed through a short column of silica gel with ethyl acetate then the solvent was removed under vacuum. The product (**3a**) was isolated from the dark purple crude mixture by flash column chromatography (the eluent used was 10:1 petroleum ether:dichloromethane).

## Acknowledgements

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[17] We found that benzene evaporated too quickly under these conditions making stirring difficult. In addition, toluene was also tested but it was less effective than chlorobenzene.

[18] An 8% NMR yield was obtained when the reaction was performed without DDQ.

[19] The crude reaction mixture showed approximately 30% of unreacted 3-flourophenylacetylene remaining after the reaction. Increasing the reaction time to 30 h did not improve the yield.

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