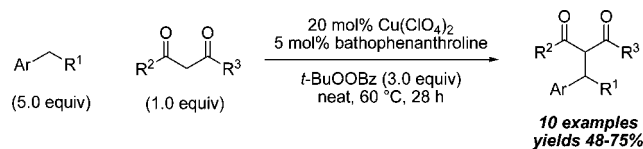# Copper-Catalyzed Oxidative Coupling of Benzylic C−H Bonds with 1,3-Dicarbonyl Compounds

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Received June 19, 2008

A copper-catalyzed oxidative coupling of benzylic C−H bonds with 1,3-dicarbonyl compounds is described. The reaction utilizes an inexpensive copper catalyst−oxidant system that is suitable for the coupling of a range of benzylic C−H bonds with various 1,3-dicarbonyl compounds. Kinetic isotope studies support a mechanism involving a benzylic hydrogen abstraction.

The direct functionalization of carbon−hydrogen bonds to carbon−carbon bonds remains an arduous challenge compounded by issues of selectivity, functional group compatibility, and susceptibility toward overoxidation.[1] Achieving selectivity among a range of C−H bonds, including sp³ and sp² hybridized C−H bonds, is of particular significance. While new metal catalyst systems have been developed for the direct coupling of aromatic and heteroaromatic C−H bonds,[2] fewer advances has been made within the realm of sp³ C−H bond functionalization. Despite notable progress,[3] most methodologies estab-

SCHEME 1. Direct Oxidative Coupling[a]
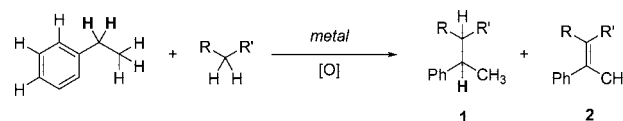
[a] Issues: C−H bond selectivity, further oxidation of products.

lished for the oxidative coupling of sp³ C−H bonds require carbene precursors,[4] directing groups,[5] and stoichiometric metal reagents[6] or remain limited to α-heteroatomic hydrocarbons.[7−9]

We were intrigued by the possibility of directly functionalizing a benzylic C−H bond with concomitant formation of a new C−C bond (Scheme 1). Realization of such a methodology would require overcoming the various issues of C−H bond selectivity and minimizing further functionalization of the coupling product **1** via competing oxidation (e.g., **2**). Our experience in the copper-catalyzed amidation of allylic and benzylic C−H bonds established an initial starting point in where to begin our investigations.[10] Recently, Li has reported a conceptually similar, iron-catalyzed, selective C−C bond formation by oxidative activation of benzylic C−H bonds.[11] Herein we describe our own efforts and proof of principle that a copper catalyst can effect the selective oxidative functional-

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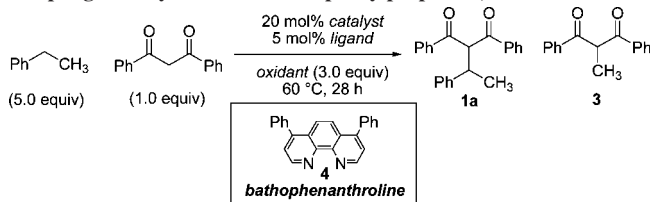
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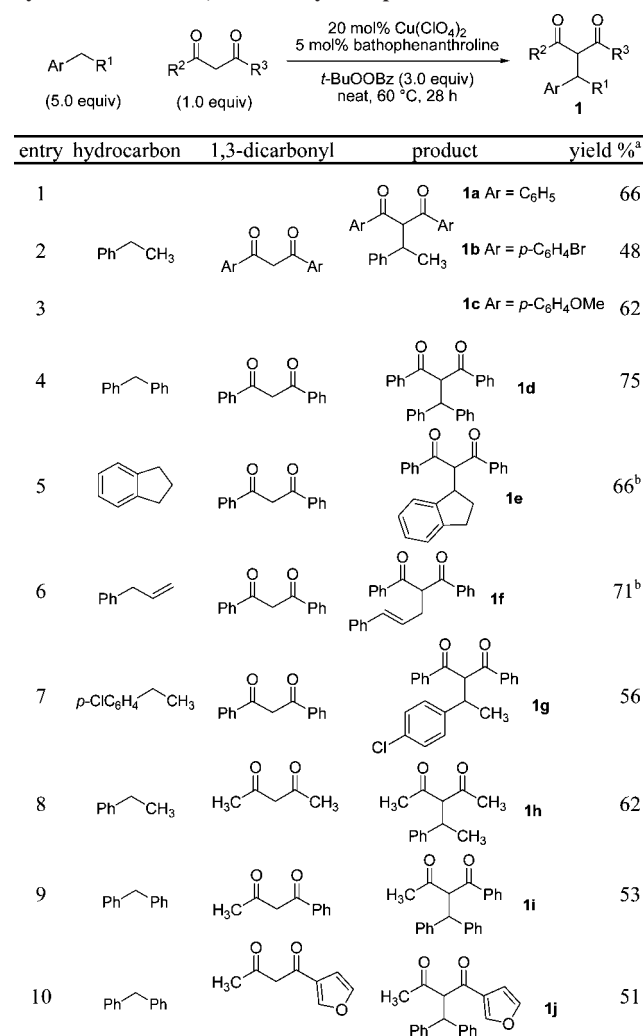**TABLE 1. Exploration of Reaction Parameters on the Oxidative Coupling of Ethylbenzene with Diphenylpropane-1,3-dione**

Ph–CH₃ (5.0 equiv) + Ph(C=O)CH₂(C=O)Ph (1.0 equiv) → [20 mol% catalyst, 5 mol% ligand, oxidant (3.0 equiv), 60 °C, 28 h] → **1a** + **3**

ligand 4: *bathophenanthroline* (Ph-substituted phenanthroline)

entry	reaction conditions (catalyst, ligand, oxidant, solvent)	yield (%)[a] 1a	yield (%)[a] 3
1	no catalyst, ligand **4**, *t*-BuOOBz, neat	<5	<5
2	Cu(ClO₄)₂, ligand **4**, *t*-BuOOBz, neat	47	22
3	Cu(ClO₄)₂, ligand **4**, *t*-BuOOBz, 1,2-dichloroethane	37	<5
4	Cu(ClO₄)₂, no ligand, *t*-BuOOBz, hexafluoroisopropanol	<5	40[b]
5[c]	**Cu(ClO₄)₂, ligand 4, *t*-BuOOBz, neat**	**71**	**6**
6[c]	Cu(OTf)₂, ligand **4**, *t*-BuOOBz, neat	61	<5
7[c]	Cu(ClO₄)₂, no ligand, *t*-BuOOBz, neat	57	<5
8[c]	Cu(ClO₄)₂, ligand **4**, *t*-BuOOH, neat	<5	<5
9[c,d]	Cu(ClO₄)₂, ligand **4**, *t*-BuOOBz, neat	52	<5

[a] Yield determined by ¹H NMR analysis of the unpurified reaction mixture versus an internal standard. Average of two runs. [b] Isolated yield; 10 mol % copper catalyst was used. [c] Diphenylpropane-1,3-dione was added after 6 h. [d] 2.5 equiv of ethylbenzene was used.

ization of benzylic C–H bonds, leading to the generation of a new carbon–carbon bond with a 1,3-dicarbonyl compound.

Our initial explorations focused on the oxidative coupling of ethylbenzene with diphenylpropane-1,3-dione (Table 1). Investigations on a variety of reaction conditions established that in the presence of copper(II) perchlorate, ligand **4**, and *tert*-butylperoxybenzoate (*t*-BuOOBz) oxidant at 60 °C, the desired coupling product **1a** could be obtained in 47% yield (entry 2). Despite our efforts, initial attempts to further improve the yield of **1a** were thwarted by the increased production of side product **3**. Interestingly, methylation product **3** could be formed predominately through the judicious choice of solvent (entry 4). We reasoned that competitive methyl transfer from the *tert*-butylperoxybenzoate oxidant to the 1,3-dicarbonyl reaction partner was contributing to the formation of **3** at the expense of the desired product **1a**.[12] It should be noted that a related palladium-catalyzed methylation of aryl C–H bonds using *tert*-butylperoxides as the methylating agent has recently been disclosed.[13] Fortunately, by adding the dicarbonyl component to the preheated reaction mixture after a period of 6 h, formation of the methylated product **3** could be suppressed, and reasonable yields of oxidative coupling product **1a** were obtained (entry 5). Overall, we found this procedure to be more convenient and equally effective, compared to the use of a syringe pump.

Copper(II) triflate (entry 6) was less effective than copper(II) perchlorate, and other copper salts such as CuCl₂ or Cu(OAc)₂ gave <5% yield of the desired coupling product. Slightly lower yields were obtained in the absence of ligand **4** (entry 7), which we suspect plays a role in increasing the solubility of the copper catalyst. In general, bidentate nitrogen-based ligands proved to be superior to other types of ligands, including phosphine ligands. Other oxidants were ineffective (entry 8),[14] while reduced quantities of the hydrocarbon component led to lower yields (entry 9). In contrast to other oxidative coupling

TABLE 2. Copper-Catalyzed Oxidative Coupling of Benzylic Hydrocarbons with 1,3-Dicarbonyl Compounds

Ar–R¹ (5.0 equiv) + R²(C=O)CH₂(C=O)R³ (1.0 equiv) → [20 mol% Cu(ClO₄)₂, 5 mol% bathophenanthroline, *t*-BuOOBz (3.0 equiv), neat, 60 °C, 28 h] → **1**

entry	hydrocarbon	1,3-dicarbonyl	product	yield %[a]
1	Ph–CH₃	Ar(C=O)CH₂(C=O)Ar	**1a** Ar = C₆H₅	66
2	Ph–CH₃		**1b** Ar = *p*-C₆H₄Br	48
3			**1c** Ar = *p*-C₆H₄OMe	62
4	Ph–CH₂–Ph	Ph(C=O)CH₂(C=O)Ph	**1d**	75
5	indane	Ph(C=O)CH₂(C=O)Ph	**1e**	66[b]
6	Ph–CH₂–CH=CH₂	Ph(C=O)CH₂(C=O)Ph	**1f**	71[b]
7	*p*-ClC₆H₄CH₂CH₃	Ph(C=O)CH₂(C=O)Ph	**1g**	56
8	Ph–CH₃	H₃C(C=O)CH₂(C=O)CH₃	**1h**	62
9	Ph–CH₂–Ph	H₃C(C=O)CH₂(C=O)Ph	**1i**	53
10	Ph–CH₂–Ph	H₃C(C=O)CH₂(C=O)(2-furyl)	**1j**	51

[a] Isolated yield. [b] Reaction was conducted at room temperature for 5 days.

methodologies,[6c] no significant quantities of the phenethylidene compound **2**, resulting from further oxidation of **1a**, was detected.

Having established reaction conditions suitable for the oxidative coupling of ethylbenzene with diphenylpropane-1,3-dione, we proceeded to investigate the range of 1,3-dicarbonyl and benzylic hydrocarbon coupling partners that could be employed (Table 2).

A variety of diketone substrates of varying electronic properties underwent oxidative coupling under our copper-catalyzed reaction protocol (entries 1–3, 8–10). In addition to ethylbenzene and derivatives, diphenylmethane (entries 4, 9, and 10), indane (entry 5) and allylbenzene (entry 6) are also capable hydrocarbon reaction components, with the latter substrate yielding the less sterically hindered terminal phenylpropenyl product. Attempts to utilize toluene as a hydrocarbon component have been unsuccessful to date, resulting in the formation of products in low yields (<20%). Aryl halides (entries 2 and 7),

(12) See Supporting Information for details.
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(14) Significantly lower yields were observed with other oxidants including CAN and PhI(OAc)₂. Use of *tert*-butylperoxyacetate gave slightly lower yields than *tert*-butylperoxybenzoate.

including arylbromides, are suitable reaction partners, allowing for further functionalization through a cross-coupling manifold. Finally, a heterocycle-containing dicarbonyl compound could also be employed in the oxidative coupling reaction (entry 10). This methodology compliments the iron-catalyzed oxidative coupling of Li,[11a] allowing for the coupling of the more challenging ethylbenzene derivatives and overall reducing the hydrocarbon stoichiometry required.

Based on the copper-catalyzed amidation protocol[10a] and the well-established Kharasch−Sosnovsky reaction,[15] we propose a mechanism that involves initial formation of a benzylic radical **A** (Figure 1) followed by reaction with the copper(II) species to generate a phenylalkyl benzoate **B**. Conversion to **1** may proceed through a Lewis or Brønsted acid catalyzed nucleophilic displacement of the benzylic benzoate intermediate **B** with the 1,3-dicarbonyl nucleophile,[16] although alternative mechanisms cannot be ruled out at this time. Of note, significant quantities of 1-phenylethyl benzoate **B** (R[1] = CH[3]) were observed in the initial stages of the reaction as determined by ^{1}H NMR analysis of the unpurified reaction mixture.

Phenylethyl benzoate **B** (R[1] = CH[3]) was synthesized independently and demonstrated to be a competent reagent, leading to the formation of **1a** under the copper-catalyzed conditions (eq 1).[12]

To provide further insight into the mechanism, a competitive kinetic isotope experiment was conducted using an excess of a 1:1 mixture of ethylbenzene and d_2-ethylbenzene (eq 2). A kinetic isotope effect of 1.6 was observed (based on the ratio of remaining starting material), consistent with a mechanism involving a benzylic hydrogen abstraction.[17]
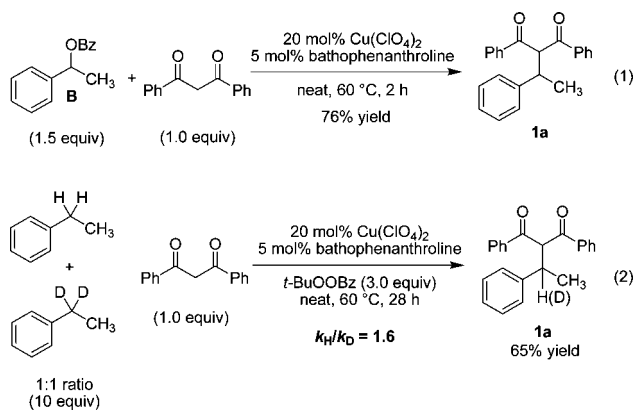
In summary, we have developed a copper-catalyzed oxidative functionalization of benzylic C−H bonds with 1,3-dicarbonyl compounds that results in the formation of a new C−C bond. The reaction utilizes an inexpensive copper catalyst−oxidant system[18] in the absence of added solvent, is suitable for the coupling of a range of benzylic C−H bonds with various 1,3-
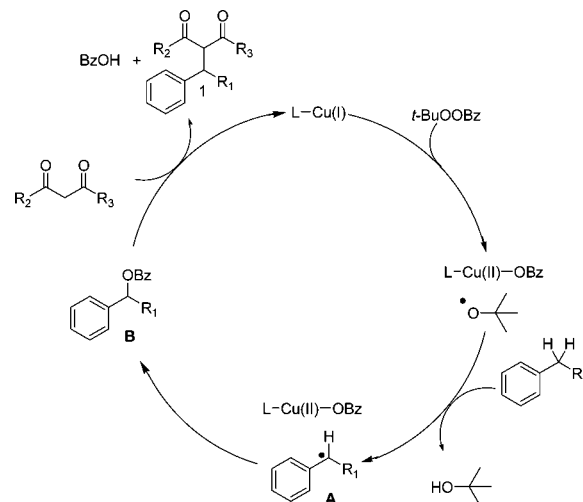

FIGURE 1. Proposed mechanistic pathway for the copper-catalyzed oxidative coupling reaction.

dicarbonyl compounds, and yields no significant quantities of over oxidized products.

Experimental Section

Representative Procedure for the Copper-Catalyzed Oxidative Coupling of Benzylic C−H bonds with 1,3-Dicarbonyl Compounds. Preparation of 1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione (1a). [*CAUTION: Care should be taken when heating a metal with a peroxide. use of a pressure flask with a blast shield in a well-ventilated fumehood is recommended. However, no issues were reported by the authors during the course of these experiments.*] Into a 15 mL sealable pressure flask equipped with a magnetic stir bar and under nitrogen was weighed copper(II) perchlorate (158 mg, 0.60 mmol, 20 mol%) and bathophenanthroline (50 mg, 0.15 mmol, 5 mol%). The solids were suspended in ethylbenzene (1.84 mL, 15.0 mmol, 5 equiv), and *tert*-butylperoxybenzoate (1.68 mL, 9.0 mmol, 3 equiv) was added dropwise over 5 min. The vial was sealed, stirred at room temperature for 5 min, and then heated to 60 °C in an oil bath for 6 h. After this time, the vial was removed from the oil bath and cooled to room temperature, and 1,3-diphenylpropane-1,3-dione (673 mg, 3.0 mmol, 1.0 equiv) was added. The vial was resealed and heated at 60 °C for an additional 22 h. The resulting mixture was cooled to room temperature and poured into a 125 mL separatory funnel containing aqueous sodium carbonate (75 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO[4], filtered, and concentrated under reduced pressure. Purification by column chromatography through silica gel, eluting with a gradient of 100% hexanes to 10% ethyl acetate in hexanes, afforded the desired product **1a** as a white solid (651 mg, 66% yield). Mp 126−127 °C; ^{1}H NMR (400 MHz, CDCl[3]) δ 8.06 (2H, d, J = 7.5 Hz), 7.76 (2H, d, J = 7.5 Hz), 7.59 (1H, t, J = 7.5 Hz), 7.49−7.43 (3H, m), 7.32−7.28 (4H, m), 7.20 (2H, t, J = 7.5 Hz), 7.10 (1H, t, J = 7.5 Hz), 5.63 (1H, d, J = 10.0 Hz), 4.10 (1H, dq, J = 10.0, 7.0 Hz), 1.37 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl[3]) δ 195.0, 194.6, 143.8, 137.2, 136.9, 133.6, 133.0, 128.9, 128.8, 128.52, 128.46, 128.42, 127.8, 126.6, 64.9, 41.2, 20.2; IR (KBr) ν 1694, 1595, 1447, 1267, 1197, 972, 756 cm^{−1}; HRMS (ESI+) m/z calcd for C[23]H[21]O[2] [M + H]+ 329.1536, found 329.1529.

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(18) Copper(II) perchlorate hexahydrate: $0.33 per gram (Aldrich). *tert*-Butylperoxybenzoate: $0.13 per gram (Aldrich).

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

JO801322P