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COMMUNICATIONS

Published on Web 03/14/2006

DDQ-Mediated Direct Cross-Dehydrogenative-Coupling (CDC) between Benzyl Ethers and Simple Ketones

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The development of various transition-metal-catalyzed coupling reactions has greatly advanced state-of-art synthetic methodologies.[1] On the other hand, there has been enormous interest in developing metal-free coupling reactions.[2] Among the various "newer" synthetic methodologies, the direct formations of C−C bonds from C−H bonds have attracted great attention recently.[3] Such synthetic methodologies will provide *the intrinsic advantages such as higher atom-economy, shorter synthetic routes*, and *requiring more economical feedstock, which leads to "benign by design"* (Green Chemistry).[4] Toward the utilization of C−H bonds for forming C−C bonds, recently, we and others have developed various Cross-Dehydrogenative-Coupling (CDC) reactions for forming new C−C bonds by utilizing two different C−H bonds (Figure 1).[5] In these cases, one or two metal catalysts are used together with an oxidizing reagent that can serve as a hydrogen acceptor. Despite the great advantages of these reactions, there are still certain limitations: (1) one or two metal catalysts are still required for the reaction (metal catalysts are sometimes undesirable); (2) less reactive nucleophiles, such as simple ketones, cannot react under these conditions. To overcome these limitations, herein we report *a highly efficient CDC reaction between benzyl ethers and simple ketones mediated by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) without using any metal catalyst* (Scheme 1).

To begin this study, we chose isochroman (**1a**) and acetophenone (**1b**) as the standard substrates to search for potential catalysts and suitable reaction conditions (Table 1). DDQ is a well-known oxidant in organic chemistry.[6] For many years, it has been used for the oxidation of allylic alcohol[7] and allylic ethers[8] to α,β-unsaturated carbonyl compounds. Recently, we reported a In(III)−Cu(II)-catalyzed reaction of bis-activated methylene compounds with benzyl ethers in methylene chloride, toluene, or acetonitrile.[9] However, simple ketones are unreactive under those conditions. In our initial experiment, using the ion liquid [BMIM]PF_6 as a solvent, the desired product **1c** was obtained in about 5% yield at room temperature (rt) in the presence of $InCl_3$ and $Cu(OTf)_2$ as catalysts. After extensive unsuccessful optimizations, it was found that the desired product could be generated in low yield under neat conditions at 50 °C (no reaction was observed at rt, entry 2) in the absence of any metal catalyst (entry 3). Various solvents were tested. No desired product was detected when CH_2Cl_2, 1,4-dioxane, or DMSO were used as solvents (entries 4, 5, and 6). The reaction could proceed in toluene, $MeNO_2$, H_2O, DCE, THF, hexane, and MeCN with varied efficiency (entries 7−13). Subsequent investigations revealed that the desired product could be obtained in 76% yield without using any solvent at 100 °C (entry 14). Further increase in the reaction temperature (entry 15) resulted in a slight decrease in yield. Switching the ratio of ether/ketone diminished the yield (entry 16). Both increase and decrease the amount of DDQ reduced the yield (entries 17 and 18). No product was detected without DDQ.

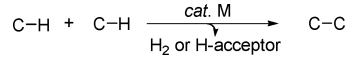


Figure 1. CDC reaction for the formation of C−C bonds.

Scheme 1. CDC Reaction of Ethers with Ketones

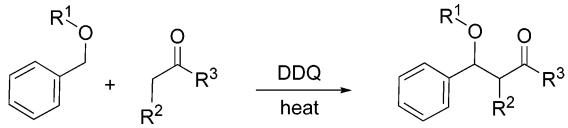
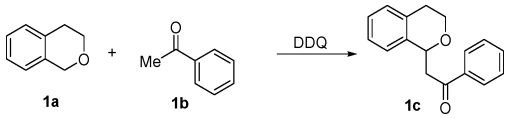


Table 1. CDC Reaction of Isochroman with Acetophenone[a]



entry	ether/ketone/DDQ (mmol)	solvent[b]	temp (°C)	yield (%)[c]
1[d]	0.2/0.4/0.24	[BMIM]PF_6	rt	5
2[e]	0.2/0.4/0.24	neat	rt	nd[f]
3	0.2/0.4/0.24	neat	50	10
4	0.2/0.4/0.24	CH_2Cl_2	reflux	nd[f]
5	0.2/0.4/0.24	1,4-dioxane	reflux	nd[f]
6[g]	0.2/0.4/0.24	DMSO	100	nd[f]
7	0.2/0.4/0.24	PhMe	reflux	40
8	0.2/0.4/0.24	$MeNO_2$	reflux	60
9	0.2/0.4/0.24	H_2O	reflux	45
10	0.2/0.4/0.24	DCE	reflux	38
11	0.2/0.4/0.24	THF	reflux	10
12	0.2/0.4/0.24	hexane	reflux	10
13	0.2/0.4/0.24	MeCN	reflux	35
14	0.2/0.4/0.24	neat	100	76
15	0.2/0.4/0.24	neat	125	71
16[h]	0.4/0.2/0.24	neat	100	37
17	0.2/0.4/0.2	neat	100	66
18	0.2/0.4/0.3	neat	100	62

[a] Reaction time: 2 h. [b] Solvent (0.5 mL) was used. [c] ^{1}H NMR yields using an internal standard. [d] Reaction time: overnight, $InCl_3/Cu(OTf)_2$ as catalyst. [e] Reaction time: overnight. [f] Not detected by ^{1}H NMR. [g] Isochroman (60%) remained after the reaction. [h] Yield was based on ketone.

Thus, under the optimized neat conditions, various ketones were reacted with isochroman, 3-methylisochroman, and benzyl methyl ether, and the corresponding results are listed in Table 2. Both aliphatic and aromatic ketones are effective for the current reaction. Benzyl ether is found to be less reactive than isochroman (compare entries 2, 10, 14, and 15). There is little difference in the reactivity between aliphatic ketones and aromatic ketones (compare entries 1−6, 10, and 11). When unsymmetrical 2-pentanone was reacted with isochroman (Scheme 2), a 1:1.5 mixture of the coupling products was obtained with the major isomer corresponding to the coupling at the more substituted carbon.

A tentative mechanism for the coupling is proposed in Scheme 3. A single electron transfer from the benzyl ether to DDQ generates a radical cation and a DDQ radical anion. The radical oxygen of the DDQ radical anion then abstracts a H-atom from the radical cation

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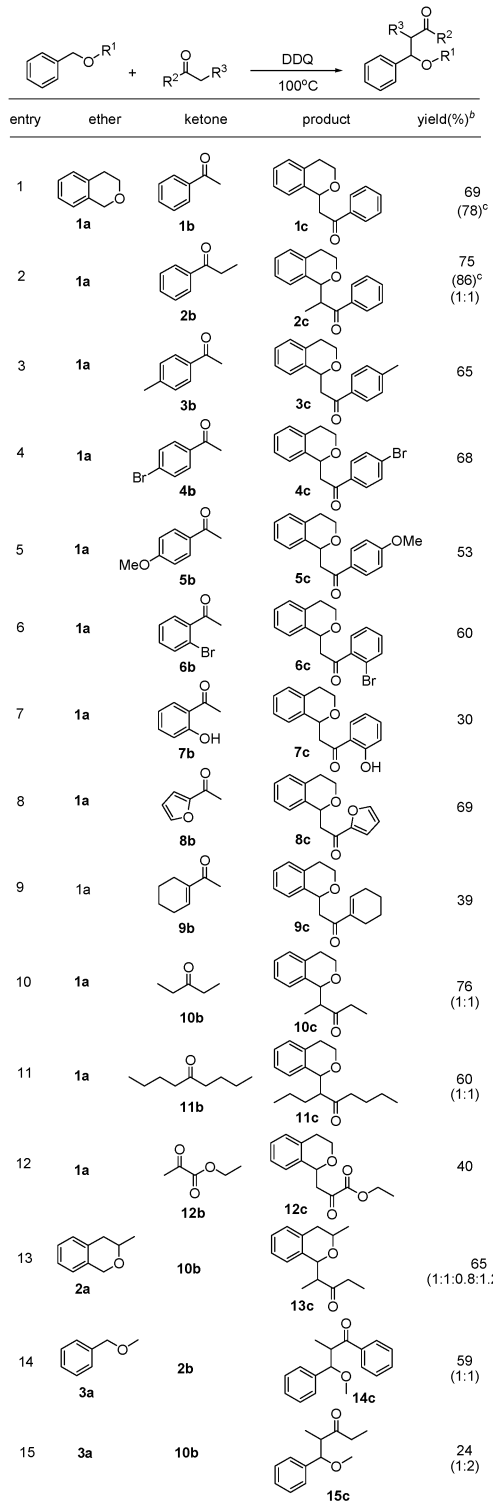
10.1021/ja060050p CCC: $33.50

Table 2. CDC Reaction of Benzyl Ethers with Ketones[a]

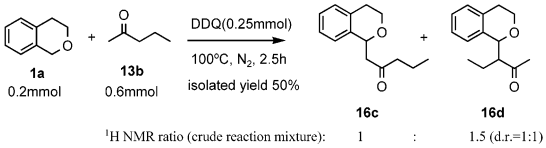


[a] Reaction conditions: ether (0.2mmol), ketone (0.6 mmol), DDQ (0.24 mmol), N_2, 100 °C, 2.5 h. [b] Isolated yield; the ratios of diastereomers measured prior to purification are given in parentheses. [c] ^{1}H NMR yield with internal standard.

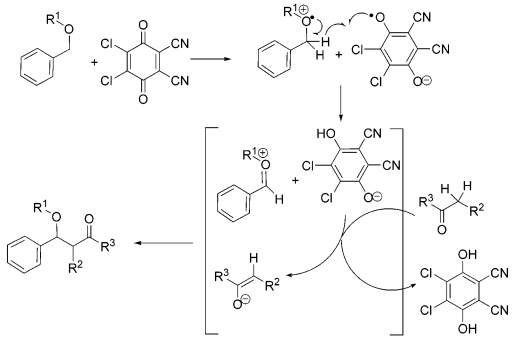
and generates a benzoxy cation, and the anionic oxygen of DDQ radical anion then abstracts an α-hydrogen from the ketone to generate an enolate. Finally, the attack of the enolate on the benzoxy cation generates the CDC product and the quinone derivative.

In summary, a novel direct Cross-Dehydrogenative-Coupling (CDC) between benzyl ethers and simple ketones was developed

Scheme 2. CDC Reaction of Isochroman with 2-pentanone



Scheme 3. Tentative Mechanism for the CDC Reaction of Benzyl Ethers with Ketones Mediated by DDQ



by using DDQ as a dehydrogenating reagent and an organomediator. The new method has several advantages: (1) simple benzyl ethers and ketones can be used directly; (2) no metal is needed for the reaction; (3) no additional reagent is required. The scope, mechanism, and application of this method are under investigation.

Acknowledgment. We are grateful to Canada Research Chair (Tier I) foundation (to C.J.L.) and the NSF-EPA joint program for a Sustainable Environment for support of our research. Y.Z. thanks McGill University for the hospitality during the aftermath of Hurricane Katrina.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

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JA060050P