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CDC Reactions of *N*-Aryl Tetrahydroisoquinolines Using Catalytic Amounts of DDQ: C–H Activation under Aerobic Conditions**

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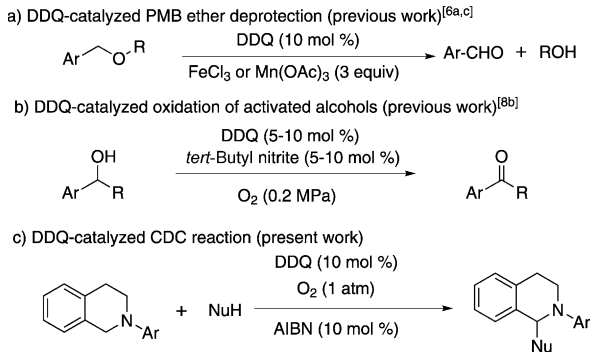
Dedicated to Professor Sosale Chandrasekhar on the occasion of his 60th birthday

C–C bond-forming reactions through oxidative cross-dehyrogenative coupling (CDC) reactions have been in the limelight recently,[1] mainly because CDC methods do not require pre-functionalized precursors prior to the coupling reactions, and are atom economical and environmentally benign.[1] Generally, CDC reactions are accomplished using transition-metal catalysts with co-oxidants such as *tert*-butylhydroperoxide (TBHP), H_2O_2, molecular oxygen, and so on.[1] Metal-free reactions have evoked a great deal of attention from the synthetic community because metal impurities can be detrimental in pharmaceutically important intermediates and final products.[2] Hence, there is a devoted effort to accomplish metal-free reaction. In this context, a considerable attempt has been made to perform CDC reactions in the absence of metal catalysts.[1e] As a result, there are number of reports on C–C bond formation using a stoichiometric amount of oxidants either in the presence or in the absence of metal catalysts (but in some cases metal catalysts are unavoidable).[3] DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is a well-known oxidant with a high oxidation potential;[4] it has been used in a stoichiometric amount in many reactions such as deprotection of ethers,[5a] benzylic oxidation,[5b] oxidation of activated alcohols,[5c] and C–C bond-forming reactions.[3] However, when DDQ is employed in a stoichiometric amount, the major difficulty is the removal of the resultant by-product 2,3-dichloro-5,6-dicyanohydroquinone ($DDQH_2$).[6] The additional impediments in using DDQ are the high cost and high molecular weight of this oxidant. Therefore, there are sustained efforts to address these issues by attempting to employ DDQ in a catalytic amount and regenerate DDQ from the resulting $DDQH_2$ by using various co-oxidants such as $FeCl_3$,[6a] $Mn(OAc)_3$,[6b,c] MnO_2,[7], and so forth (Scheme 1). However, most of these efforts resulted in using a large excess (3–6 equiv) of inorganic co-oxidants, which is one of the major setbacks due to toxicity and environmental concerns. Furthermore, the use of a catalytic amount of DDQ with a catalytic amount of co-oxidant remains largely an unexplored area. One of the practical ways to overcome such problem is to use DDQ in a catalytic amount and employ molecular oxygen as a co-oxidant;[8] this strategy has significant environmental and economic benefits due to the natural abundance of molecular oxygen, lower cost, and the production of water as the sole by-product in the reaction. To the best of our knowledge, C–C bond forming reactions mediated by a catalytic amount of DDQ is scarce.[7] Thus this is the first report of regenerating DDQ by using catalytic amount of azobisisobutyronitrile (AIBN) and molecular oxygen. Herein, we present C–C and C–P bond forming reactions by CDC method mediated by a catalytic amount of DDQ using molecular oxygen as the co-oxidant and AIBN as an additive.



Scheme 1. Reactions that use catalytic amounts of DDQ.

Mannich products such as β-amino ketones and aldehydes are versatile synthetic intermediate for numerous pharmaceuticals and natural products. β-Amino ketones and aldehydes can be converted in to 1,3-amino alcohols by reduction or to Michael acceptors by elimination of amine functionality.[9] Traditionally, the Mannich reaction involves the addition of carbonyl compounds to imines or iminium ion. Interestingly, similar Mannich products are synthesized by employing a CDC reaction of tertiary amines with carbonyl compounds, which proceed through the in situ activation of C–H bonds adjacent to the nitrogen to form an iminium ion. These CDC reactions are accomplished by using a varie-

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[**] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; CDC = cross-dehydrogenative coupling.

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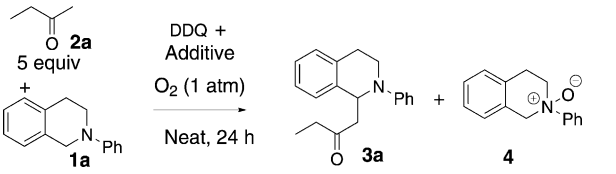
ty of reagents such as CuI/O_2/AcOH (Guo et al.),[10a] $VO(acac)_2$/TBHP/proline (Klussmann et al.),[10b] Ru/visible light/proline (Rueping et al.),[10c] and others.[10d–f] In all these cases, it is essential to activate ketones to their enolate form because ketones are less reactive pronucleophiles. Additionally, substituted ketones resulted in lower yields of the required product, and hence they are not studied in greater detail. In continuation of our studies in C–H functionalization,[11] herein we report an unprecedented Mannich-type reaction of THIQ (tetrahydroisoquinoline) with ketones by employing a catalytic amount of DDQ (10 mol%) in the presence of molecular oxygen and a catalytic amount AIBN as an additive. The additional advantage of this method is that it does not require the activation of ketones.

For the optimization studies, we chose *N*-phenyl tetrahydroisoquinoline (**1a**) and 2-butanone (**2a**) as model substrates. As shown in Table 1, the reaction of **1a** (1 equiv) with **2a** (5 equiv) in the presence of DDQ (10 mol%) as an oxidant and molecular oxygen as a co-oxidant at 60°C under solvent-free conditions furnished the expected product **3a** in 48% yield (Table 1, entry 1). It is worth noting

Table 1. Optimization of reaction conditions.



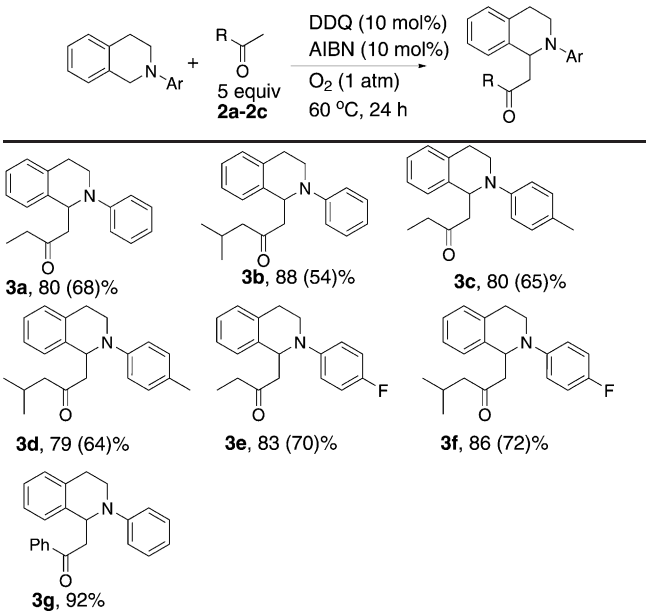
Entry	DDQ [mol%]	Additive [(mol%)]	*T* [°C]	*t* [h]	Yield [%][a]	
					3a	**4**
1	10	–	60	24	48	–
2	10	Fe powder (10)	60	24	56	–
3	10	MoO_3(10)	60	24	52	–
4	10	$Pd(OAc)_2$ (10)	60	24	56	–
5	10	V_2O_5(10)	60	24	80	–
6	10	AIBN (10)	60	24	80	6
7	10	AIBN (10)	RT	24	25	–
8	10	AIBN (30)	60	24	86	4
9	20	AIBN (20)	60	24	82	4
10	10	AIBN (5)	60	24	70	6
11	5	AIBN (5)	60	24	32	7
12	10	BPO (5)	60	24	74	12
13[b]	10	AIBN (10)	60	24	9	–
14	–	AIBN (10)	60	24	trace	–

[a] Conversion of yields based on tertiary amine and determined by NMR spectroscopy. [b] Reaction in the absence of O_2. AIBN = Azobisisobutyronitrile. BPO = Benzoyl peroxide.

that ketone **2a** underwent a facile coupling reaction with THIQ (**1a**) in the absence of activating reagents such as bases or acids.[10] Addition of metal catalysts (10 mol%) such as iron powder, MoO_3 and $Pd(OAc)_2$ as additives did not improve yields of the product (Table 1, entries 2–4). However, addition of V_2O_5 (10 mol%) as additive improved the yield of the product dramatically to 80% (Table 1, entry 5). As the DDQ-mediated reaction follows a free radical pathway, we thought that it is appropriate to use free-radical initiator as the additive and follow the reaction. Interestingly, the addition of azobisisobutyronitrile (AIBN, 10 mol%) induced a striking change in the outcome of results and furnished the expected product **3a** in 80% along with the corresponding *N*-oxide **4** in a trace amount (6%, Table 1, entry 6). However, performing the same reaction under ambient temperature resulted in lower yields of the product (25%, Table 1, entry 7). Increasing the oxidant (DDQ) loading as well as varying the amount of AIBN has brought out a marginal change in the yields of the products (Table 1, entries 8–11). Although the use of benzoyl peroxide (BPO) as a radical initiator furnished **3a** in 74%, it also gave the by-product **4** (12%, Table 1, entry 12). The control experiment of **1a** with **2a** in argon atmosphere (in the absence of molecular oxygen) furnished a trace amount of **3a** (9%, Table 1, entry 13), indicating that molecular oxygen is crucial for the reaction. Similarly, the reaction of **1a** with **2a** in the absence of DDQ furnished a trace amount of the product **2a** (Table 1, entry 14). These two control experiments clearly indicate that the reaction requires DDQ, AIBN, and molecular oxygen. Based on these optimization studies, further reactions were performed at 60°C using THIQ (1 equiv), ketone (5 equiv), DDQ (10 mol%), and AIBN (10 mol%) in molecular oxygen.

The scope and generality of this method was investigated using a variety of *N*-aryl tetrahydroisoquinolines and ketones (Table 2). Ethyl methyl ketone underwent a facile coupling with *N*-phenyl tetrahydroisoquinoline to furnish the expected product **3a** in good yield (80%, Table 2). Interestingly, reaction of sterically hindered ketone such as isobu-

Table 2. DDQ-catalyzed Mannich reaction of *N*-aryl tetrahydroisoquinolines.[a,b,c]



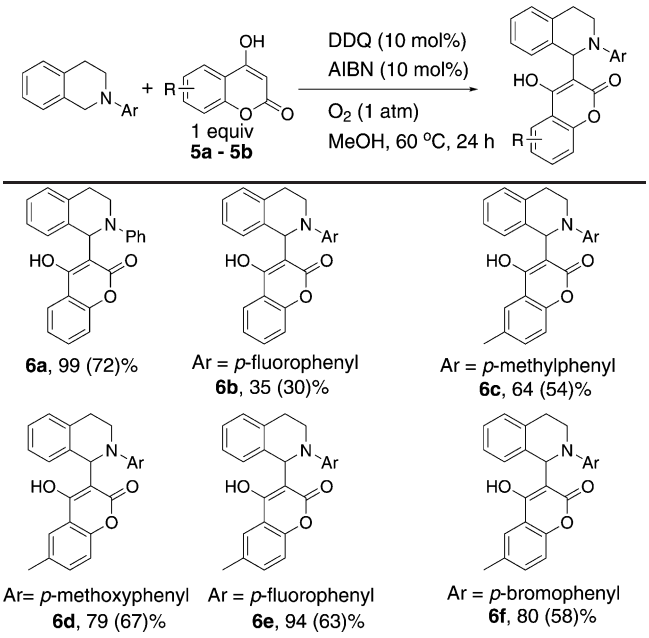
[a] Standard reaction conditions: **1a** (1 mmol), **2a** (5 mmol), DDQ (0.1 mmol), AIBN (0.1 mmol), neat, 60°C, 24 h. [b] Yields determined by NMR spectroscopy based on tertiary amine. [c] Isolated product yields are presented in parenthesis.

tyl methyl ketone with *N*-phenyl tetrahydroisoquinoline furnished the expected product **3b** in 88% yield (Table 2). However, it is documented that the similar reaction using $VO(acac)_2$/TBHP/L-proline catalytic system furnished the same product in lower yields and required an extended reaction time.[10b] *N*-(*p*-Methyl)phenyl and *N*-(*p*-fluoro)phenyl tetrahydroisoquinolines underwent facile CDC reactions with ethyl methyl ketone (**2a**) and isobutyl methyl ketone (**2b**) to afford the desired coupled products **3c**, **3d**, **3e**, and **3f** in 80, 79, 83, and 86% yields, respectively (Table 2). In addition, acetophenone (**2c**) with *N*-phenyl tetrahydroisoquinoline afforded the expected product in excellent yield (92%, Table 2). As seen from these examples, the coupling reaction of *N*-aryl tetrahydroisoquinoline with ketone occurred at the less-hindered side of the ketone, which may be due to steric hindrance.[12]

After successful oxidative Mannich reaction of THIQ with ketones, we turned our attention to apply this methodology for the alkylation of 4-hydroxycoumarins (at position 3) with *N*-aryl tetrahydroisoquinolines. Hydroxycoumarin derivatives are found to exhibit anti-HIV, anti-bacterial, anti-tumor, anti-inflammatory, anti-viral effects, antioxidant, anti-coagulant, antitubercular, and analgesic activities.[13] Owing to their remarkable and broad-ranging pharmacological activity, these compounds have aroused a great deal of synthetic interest.[13] To the best of our knowledge, hitherto there have been no reports on the utility of 4-hydroxycoumarin derivatives as nucleophiles in CDC reactions. Therefore, we document the first report of a DDQ-catalyzed CDC reaction of *N*-aryl tetrahydroisoquinolines with 4-hydroxycoumarin derivatives in the presence of molecular oxygen as the oxidant and AIBN as the additive (Table 3). As can be seen in Table 3, *N*-phenyl and *N*-(*p*-fluoro)phenyl tetrahydroisoquinolines underwent coupling reaction with 4-hydroxycoumarin (**5a**) to furnish the desired coupled products **6a** and **6b** (Table 3). Interestingly, 6-methyl-4-hydroxycoumarin (**5b**) with various *N*-aryl tetrahydroisoquinolines such as *N*-(*p*-methyl)phenyl tetrahydroisoquinoline, *N*-(*p*-methoxy)phenyl tetrahydroisoquinoline, *N*-(*p*-fluoro)phenyl tetrahydroisoquinoline, and *N*-(*p*-bromo)phenyl tetrahydroisoquinoline furnished the expected products **6c**, **6d**, **6e**, and **6f** in good yields (Table 3).

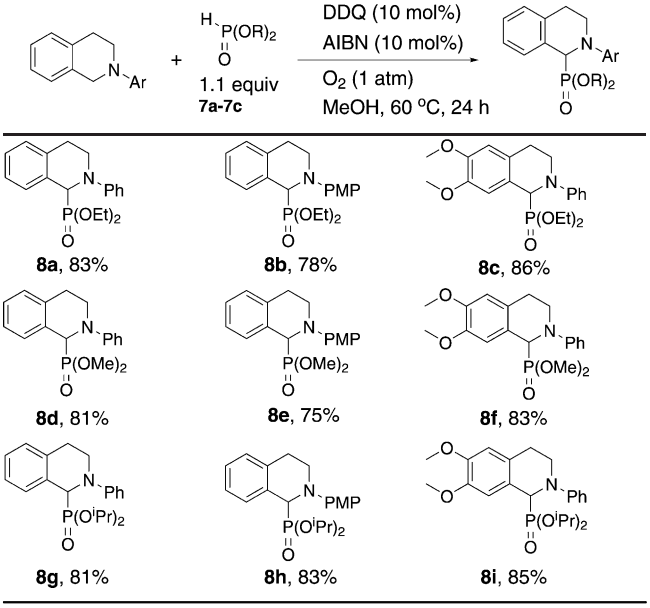
After alkylation of 4-hydroxycoumarins, we continued our investigation for the hydrophosphorylation of *N*-aryl tetrahydroisoquinolines using CDC reactions. α-Amino phosphonates are biologically active compounds and are a potential alternative to an amino acid moiety.[14] α-Phosphonation of tertiary amines through CDC methods are reported using Cu, Ir, Fe and Eosin Y as the catalysts.[14] In continuation of our pursuit on metal-free reactions,[15] herein, we report the α-phosphonation of *N*-aryl tetrahydroisoquinolines using same catalytic system (DDQ/O_2/AIBN) in MeOH at 60°C and the results are depicted in Table 4. Diethyl phosphite (**7a**) underwent a facile hydrophosphorylation reaction with a variety of *N*-aryl tetrahydroisoquinolines such as *N*-phenyl tetrahydroisoquinolines, *N*-(*p*-methoxy)phenyl tetrahydroisoquinoline, and *N*-phenyl-6,7-dimethoxy tetrahydroisoquinoline to furnish the corresponding phosphonated products such as **8a**, **8b**, and **8c** in good yields (Table 4). Interestingly, dimethyl phosphite (**7b**) and sterically hindered diisopropyl phosphite (**7c**) underwent smooth reaction with *N*-aryl tet-

Table 3. DDQ-catalyzed CDC reaction of *N*-aryl tetrahydroisoquinolines with hydroxycoumarins.[a,b,c]



[a] Standard reaction conditions: **1a** (1 mmol), **5a** (1 mmol), DDQ (0.1 mmol), AIBN (0.1 mmol), MeOH, 60°C, 24 h. [b] Yields based on tertiary amine and determined by NMR spectroscopy. [c] Isolated product yields are presented in parenthesis.

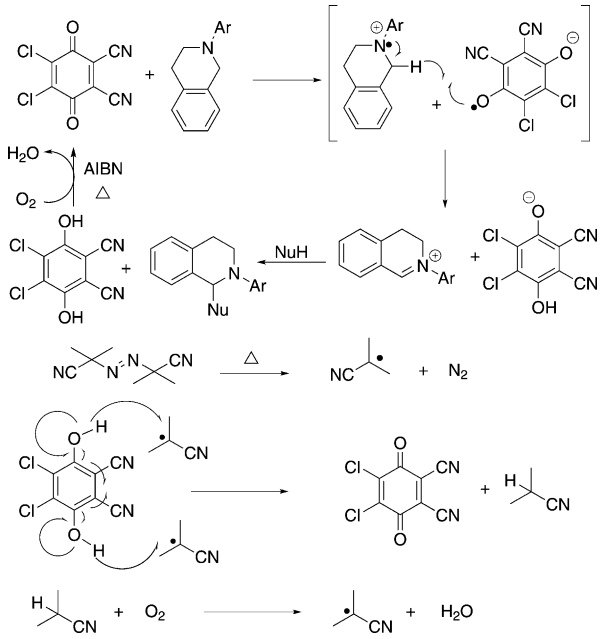
Table 4. DDQ-catalyzed α-phosphonation of *N*-aryl tetrahydroisoquinolines by a CDC method.[a,b]



[a] Standard reaction condition: **1a** (1 mmol), **5a** (1.1 mmol), DDQ (0.1 mmol), AIBN (0.1 mmol), MeOH, 60°C, 24 h. [b] Isolated product yields.

rahydroisoquinolines to furnish the desired α-phosphonated products **8d–8i**, which were isolated in good yields (Table 4).

The exact mechanism of the reaction is not clear at this stage, however the reaction did not proceed in the presence of radical scavenger BHT (2,6-bis(1,1-dimethylethyl)-4-methylphenol), which indicates that the reaction proceeds through the radical pathway (Scheme 2). We believe that in the presence of DDQ, *N*-aryl tetrahydroisoquinoline forms an iminium ion intermediate, which undergoes further reaction with various pronucleophiles to form the desired coupled product. With respect to the Mannich reaction, the DDQ anion abstracts the α proton from the ketones and generates the corresponding enolates.[3b,16] Further work is underway in our laboratory to exploit the utility of this new catalytic system, DDQ/O_2/AIBN in organic synthesis.



Scheme 2. Plausible mechanism for the α-functionalization of *N*-aryl tetrahydroisoquinolines.

In summary, we have exploited a catalytic amount of DDQ (10 mol%) to accomplish C–H functionalization of *N*-aryl tetrahydroisoquinolines by CDC method to form C–C, and C–P bonds. Furthermore, the catalytic use of DDQ to accomplish the CDC reaction is unprecedented. This CDC reaction is versatile and works well with a variety of *N*-aryl tetrahydroisoquinolines in combination with pronucleophiles. The highlight of the method is that it requires only a catalytic amount AIBN (10 mol%) as additive under aerobic conditions. Furthermore, for the first time 4-hydroxycoumarin is used as a pronucleophile in the CDC reaction with *N*-aryl tetrahydroisoquinolines. As hydroxycoumarin derivatives exhibit a broad-ranging pharmacological activity,[13] 4-hydroxycoumarin-derived *N*-aryl tetrahydroisoquinoline derivatives may also find an application as pharmaceuticals. Interestingly, the Mannich reaction does not require any extra reagent or co-catalyst to activate ketones to enolates. In addition, α-phosphonation of *N*-aryl tetrahydroisoquinolines employs only a stoichiometric amount of dialkyl H-phosphonates.

Experimental Section

A mixture of DDQ (10 mol%, 10.8 mg, 0.048 mmol), AIBN (7.8 mg, 0.048 mmol), *N*-phenyl tetrahydroisoquinoline (100 mg, 0.48 mmol) and 4-hydroxycoumarin (**5a**, 77.5 mg, 0.48 mmol) in MeOH (1 mL) were heated at 60°C under oxygen atmosphere (oxygen balloon) for 24 h. The solvent was removed under vacuo, added water and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1:4) to afford the desired product **6a** (72%) as a pale yellow solid in 72% yield. M.p. 138–140°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (dd, $J_1 = 1.2$ Hz, $J_2 = 7.9$ Hz, 1H), 7.45–7.38 (m, 4H), 7.34–7.30 (m, 2H), 7.25–7.12 (m, 6H), 6.16 (s, 1H), 3.69 (dd, $J_1 = 4.9$ Hz, $J_2 = 11.9$ Hz, 1H), 3.58–3.49 (m, 1H), 3.25 (td, $J_1 = 2.8$ Hz, $J_2 = 12.2$ Hz, $J_3 = 24.2$ Hz, 1H), 2.96 ppm (d, $J = 16.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.1$, 164.0, 153.3, 148.5, 135.6, 132.7, 131.9, 129.6, 128.2, 127.4, 126.9, 126.2, 123.6, 123.2, 122.3, 116.4, 104.7, 58.2, 54.9, 30.3 ppm; IR (neat): $\tilde{\nu} = 3712$, 2923, 2866, 2846, 2629, 2066, 1633 cm^{-1}; HRMS: *m/z*: calcd for $C_{24}H_{19}NO_3$: 392.1263 [*M*+Na]; found: 392.1261.

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Keywords: CDC reaction · C–H activation · DDQ · hydroxycoumarins · Mannich reaction · metal-free reaction

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[12] The regioselectivity obtained in this reaction can be explained on the basis of predictions of Mannich reactions with unsymmetrical ketones, see: H. O. House, *Modern Synthetic Methods*, 2nd ed., W. A. Benjamin Inc., Berlin, **1972**, p. 657. Additionally, Klussmann (ref. [10b]) and Huang (ref. [10f]) in their work on CDC reactions reported the sensitivity of Mannich reaction towards steric hindrance. Hence, the coupling generally occurs at the α carbon, which is unsubstituted in the case of unsymmetrical ketones. We believe that the regioselectivity observed in DDQ-catalyzed Mannich reaction also is due to steric hindrance. Therefore, the coupling always takes place at less-substituted side of the unsymmetrical ketones.

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[16] In a reaction of benzylic ethers with DDQ, a single electron transfer from benzylic ethers to DDQ generates a radical cation and DDQ radical anion. The radical oxygen of the DDQ radical anion thus generated abstracts a hydrogen atom from the radical cation to generate a benzoxy cation. Further, the anionic oxygen of the DDQ radical anion abstracts the α hydrogen from the ketone to generate an enolate. Finally, the attack of the enolate on the benzoxy cation generates the CDC product (see ref. [3b]). Based on this information, we have shown that DDQ anion can abstract the α hydrogen of the ketone to form the enolate. On the other hand, generally ketones are in equilibrium with their enol form to a lesser extent. Hence, we believe that the reaction may proceed through addition of the enol to the iminium ion to form the Mannich products.

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