

METAL-FREE OXIDATIVE C–C BOND FORMATION OF ACTIVE METHYLENIC SP³ C–H BONDS WITH BENZYLIC SP³ C–H AND ALLYLIC SP³ C–H BONDS MEDIATED BY DDQ

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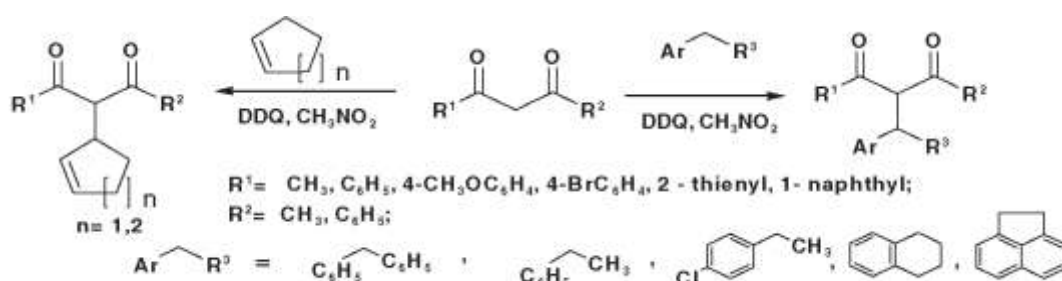
ABSTRACT

An efficient and simple method for the oxidative coupling of benzylic and allylic sp³ C–H bonds with active methylenic sp³ C–H bonds under metal-free conditions was developed by employing 2,3- dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant. The reaction was shown to proceed smoothly for various 1,3-dicarbonyl compounds with a range of benzylic and allylic substrates in good to excellent yields.

Keywords: Carbene, Dicarbonyl, Bathophenanthroline, Cross-coupling, DDQ (2,3 dichloro-5,6-dicyano benzoquinone)

Carbon–carbon bond construction¹ is a very important step in organic synthesis and is the foundation for the formation of complex structures from simple precursors. Transition-metal-catalyzed coupling reactions of various reactive functional groups are among the most useful protocol for the C–C bond formation,² the reaction may be further enhanced from the view point of atom-efficiency³ and green chemistry.⁴ The development of direct C–C bond-forming reactions of prior unmodified C–H substrates is an important task and attracted more interest in recent years.⁵ Such transformations will avoid the pre-functionalization of C–H bonds and make the synthetic scheme shorter and atom-economical. In this context, important progress has been made toward direct utilization of allylic and benzylic sp³ C–H bond rather than pre-functionalization. Most of the strategies based on cross-coupling reactions of sp³C–H bonds limited to a-hetero aromatic compounds^{6,7} or require carbene precursors,⁸ directing groups⁹, and stoichiometric metal reagents.¹⁰ However, only a few methods are available for forming new C–C bonds by utilizing two different C–H bonds, among them Trost's group reported C–C bond formation directly from an allylic sp³ C–H bond in two steps in the late 1970s.¹¹ Recently, some methods have been reported for the direct coupling of active methylenic sp³ C–H

bonds with simple allylic sp^3 C–H bonds in the presence of CuBr/CoCl₂/ t BuOOH (Scheme 1) catalyst system,¹² similarly with simple benzylic sp^3 C–H bonds using FeCl₂/ t BuOOt Bu catalyst system¹³ and Cu(ClO₄)₂/ t BuOOBz/bathophenanthroline ligand system.¹⁴ Despite great advantage of these reactions, there are still certain limitations such as the use of one or two transition metals in these transformations and use of peroxide as an oxidizing reagent under heating conditions. There are some general problems with metal-catalyzed reactions, such as cost of transition-metal catalyst and difficulty in the preparation of ligand or catalyst. Some metals are toxic in nature and heavy metal residues may present in the preparation of the compounds. Additionally, in view of the increased attention to environmental problems, transitionmetal-free methods are preferable for the coupling reactions.¹⁵



Scheme 1. Oxidative C–C bond formation of active methylenic sp^3 C–H bonds with benzylic sp^3 C–H and allylic sp^3 C–H bonds.

Table 1 Optimization of reaction conditions Reactions=?

Entry	Solvent	Temp (C)	Time (h)	Yieldb (%)
1	THF	Reflux	8	10
2	CH ₃ CN	Reflux	8	25
3	Dioxane	Reflux	8	20
4	CH ₂ Cl ₂	Reflux	8	75
5	CHCl ₃	Reflux	8	62
6	CCl ₄	Reflux	8	65
7	DCE	Reflux	6	78
8	Hexane	Reflux	6	NR ^c
9	Neat	80	6	51
10	CH ₃ NO ₂	rt	6	10
11	CH ₃ NO ₂	50	6	71
12	CH ₃ NO ₂	80	6	84
13	CH ₃ NO ₂	80	6	77 ^d
14	CH ₃ NO ₂	80	6	60 ^e

^a Conditions: 1a (0.2 mmol), 2a (1 mmol), and DDQ (0.24 mmol) in neat or the presence of indicated solvent and temperature.

^b Isolated yield.

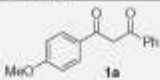

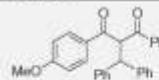



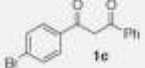

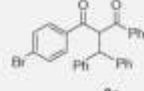
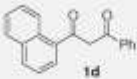

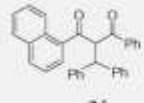
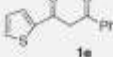

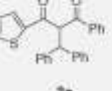
^c No reaction based on TLC analysis.

^d Compound 2a (0.5 mmol).

^e Compound 2a (0.2 mmol)

Table 2



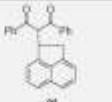
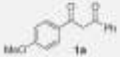

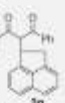





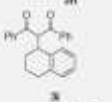
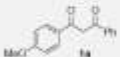


Oxidative coupling between diarylbenzylic C–H bond and various 1,3-dicarbonyl compounds^a

Entry	Substrate 1	Substrate 2	Product 3	Time (h)	Yield ^b (%)
1				6	84
2				6	79
3				8	78
4				8	72
5				8	60

$$\frac{a_{\text{Condition}}}{b_{\text{isolated yield}}} = ?$$

Table 3

Oxidative coupling between cyclic benzylic C–H bonds and various 1,3-dicarbonyl compounds^a

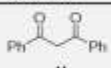

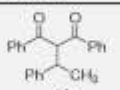
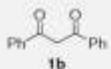

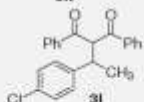
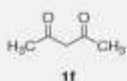

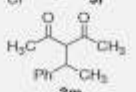
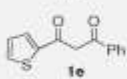

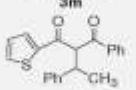
Entry	Substrate 1	Substrate 2	Product 3	Time (h)	Yield ^b (%)
1				6	60
2				6	42
3				6	58
4				6	64
5				6	61

^a Conditions: 0.2 mmol of 1, 1 mmol of 2, and 0.24 mmol of DDQ in nitromethane at 80 C.
^b Isolated yield.

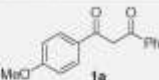

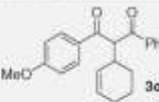
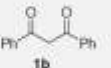

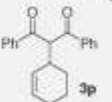
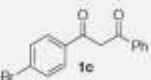

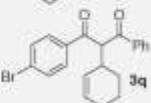
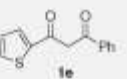

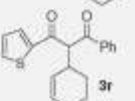
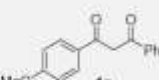

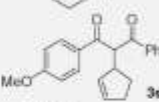
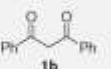

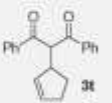
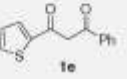

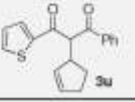
Although excellent results are available for C–C bond-forming reactions involving an oxidative coupling between sp^3 C–H and sp^3 C–H bonds, reactions under metal-free conditions are rare. Furthermore, there is no protocol for the direct coupling of the two types of sp^3 C–H bonds (allylic and benzylic) with active methylenic sp^3 C–H bonds by using single oxidizing reagent or catalyst system. Herein, we report a simple and highly efficient oxidative coupling of active methylenic sp^3 C–H bonds with two types of sp^3 C–H bonds such as simple allylic sp^3 C–H and benzylic sp^3 C–H bonds promoted by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) without using any metal catalyst. DDQ is a commercially available and important oxidation reagent in organic chemistry.¹⁶

The initial studies were carried out by reacting 1a with 2a as a prototype reaction under various reaction conditions using DDQ as dehydrogenating reagent to bring about this transformation and the results are summarized in Table 1. The reaction was examined by using various solvents to facilitate this transformation. When the reaction was performed in tetrahydrofuran, acetonitrile, and dioxane it afforded the desired product in low yields (Table 1, entries 1–3). However, the corresponding product was obtained in high yield in dichloromethane, chloroform, carbon tetrachloride, and dichloroethane (Table 1, entries 4–7). No product was observed when the reaction was performed in hexane (Table 1, entry 8). However, in the absence of solvent the reaction afforded the corresponding product in moderate yield (Table 1, entry 9). When the reaction was carried out in nitromethane at room temperature, the yield of the product was 10% (Table 1, entry 10). Perceptibly increased yields were observed at elevated reaction temperatures in nitromethane (Table 1, entries 11 and 12). Decreasing the equivalents of 2a resulted in reduced yield (Table 1, entries 12–14). When the reaction was carried out between 1a (0.2 mmol) and 2a (1 mmol) using DDQ (0.24 mmol) in nitromethane at 80 C, the reaction proceeded smoothly and afforded the desired product in excellent yield (Table 1, entry 12). To define the scope of the reaction mediated by DDQ under metal-free conditions, we have carried out various benzylic and allylic sp^3 C–H bonds with 1,3-dicarbonyl compounds.

Table 4**Oxidative coupling between acyclic benzylic C–H bonds and various 1,3-dicarbonyl compounds^a**

Entry	Substrate 1	Substrate 2	Product 3	Time (h)	Yield ^b (%)
1	 1b	 2d	 3k	8	68
2	 1b	 2e	 3l	8	57
3	 1f	 2d	 3m	8	51
4	 1e	 2d	 3n	8	56

^a Conditions: 0.2 mmol of 1, 1 mmol of 2, and 0.24 mmol of DDQ in nitromethane at 80 °C.^b Isolated yield.

Entry	Substrate 1	Substrate 2	Product 3	Time (h)	Yield ^b (%)
1	 1a	 2f	 3o	8	48
2	 1b	 2f	 3p	6	64
3	 1c	 2f	 3q	8	58
4	 1e	 2f	 3r	8	60
5	 1a	 2g	 3s	6	65 ^c
6	 1b	 2g	 3t	8	63 ^c
7	 1e	 2g	 3u	8	59 ^c

^a Conditions: 0.2 mmol of 1, 1 mmol of 2, and 0.24 mmol of DDQ in nitromethane at 80 °C.^b Isolated yield.^c At 50 °C.

The benzylic C–H bond of diphenylmethane was reacted efficiently with a range of 1,3-dicarbonyl compounds and the corresponding products were obtained in excellent yields (Table 2, entries 1–5). 1,3-Dicarbonyl compounds bearing aromatic ring with both electron-donating and electron-withdrawing groups in para position afforded excellent yields (Table 2, entries 1 and 3). Comparatively a low yield was obtained with 1,3-dicarbonyl substrates bearing a naphthalene group (1d) (Table 2, entry 4), probably because of the steric effect of the naphthalene group. Hetero aryl such as thienyl substrate (1e) was also found to react with diphenylmethane to give the desired product in good yield (Table 2, entry 5).

Substrates with less activated cyclic benzylic sp^3 C–H bond such as 1,2,3,4-tetrahydronaphthalene and acenaphthene were reacted with various 1,3-dicarbonyl compounds and the desired products were obtained in good yields (Table 3, entries 1–5). To explore the generality of the reaction, we also examined the reactions of less activated acyclic benzylic sp^3 C–H bond substrates such as ethylbenzene and para-ethylchlorobenzene with various 1,3-dicarbonyl compounds and found that the reactions proceeded well and gave the respective products in good yields (Table 4, entries 1–4). Substrates with allylic sp^3 C–H bond such as cyclohexene (2f) and cyclopentene (2g) were subjected to alkylation with various 1,3-dicarbonyl compounds and afforded the desired products in good yields (Table 5, entries 1–7). 1,3-Dicarbonyl compounds bearing aromatic ring with both electron-donating and electron-withdrawing groups in para position afforded good yields (Table 5, entries 1, 3, and 5). Furthermore, hetero aryl dicarbonyl compound (1e) also gave the desired products in good yields (Table 5, entries 4 and 7).

In summary, we have developed an efficient method for the direct oxidative coupling of active methylenic sp^3 C–H bonds with benzylic sp^3 C–H and allylic sp^3 C–H bonds by using DDQ as a dehydrogenating reagent.¹⁹ This method has several advantages: (1) no metal is required for the reaction. (2) It proceeds without additional reagent. (3) Simple benzylic and allylic substrates can be used directly without pre-functionalization. (4) It gives the desired products in good to excellent yields.

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19. A typical experimental procedure and spectral data of some representative compounds. Typical experimental procedure: To a solution of 1,3-dicarbonyl compound 1 (0.2 mmol), allylic, or benzylic sp^3 C–H compound 2 (1 mmol) in CH_3NO_2 was added DDQ (0.24 mmol) and the resulting mixture was stirred at 80° C for the indicated time. After completion of the reaction as noticed by TLC, the reaction mixture was cooled to room temperature and filtered. The filtrate was diluted with water (10 mL) and extracted into ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude residue, which was purified on silica gel column chromatography using hexane and ethyl acetate as the eluent to give the pure product. 2-Benzhydryl-1-(4-methoxyphenyl)-3-phenylpropane-1,3-dione (3a): IR (KBr): ν 3058, 2928, 2855, 1685, 1598, 1507, 1451, 1266, 1173, 1028, 975, 837, 700 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.89–7.81 (4H, m), 7.50–7.01 (13H, m), 6.84–6.77 (2H, m), 6.27 (1H, d, $J = 11.5$ Hz), 5.33 (1H, d, $J = 11.5$ Hz), 3.81 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3, 192.2, 163.6, 141.88, 141.83, 137.0, 133.1, 131.0, 128.55, 128.51, 128.4, 128.2, 126.5, 113.7, 62.2, 55.4, 52.3; MS (ESI) m/z : 443 $[M+Na]^+$; HRMS (ESI) m/z calcd for $C_{29}H_{24}O_3Na$: 443.1623, found: 443.1627. 2-Benzhydryl-1-(naphthalen-1-yl)-3-phenylpropane-1,3-dione (3d): IR (KBr): ν 3055, 2922, 2853, 1689, 1591, 1495, 1448, 1359, 1249, 1200, 1074, 1026, 969, 779, 744, 699 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 7.88–7.86 (2H, m), 7.80–7.73 (3H, m), 7.62 (1H, d, $J = 7.5$ Hz), 7.45–6.99 (16H, m), 6.42 (1H, d, $J = 12.0$ Hz), 5.39 (1H, d, $J = 12.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 194.0, 141.9, 141.4, 137.1, 136.5, 133.6, 133.1, 132.6, 130.0, 128.6, 128.52, 128.50, 128.3, 128.2, 127.9, 127.8, 126.6, 126.5, 126.4, 125.4, 123.9, 65.9, 52.6; MS (ESI) m/z : 463 $[M+Na]^+$; HRMS (ESI) m/z calcd for $C_{32}H_{24}O_2Na$: 463.1673, found: 463.1667. 2-(Cyclohex-2-enyl)-1,3-diphenylpropane-1,3-dione (3p): IR

(Neat): m 3062, 3025, 2926, 2856, 1696, 1665, 1596, 1448, 1270, 1192, 1075, 1001, 802, 760, 690 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): d 8.02–7.96 (4H, m), 7.58–7.39 (6H, m), 5.77–5.69 (1H, m), 5.55–5.47 (1H, m), 5.28 (1H, d, $J = 10.0$ Hz), 3.55–3.43 (1H, m), 2.05–1.97 (2H, m), 1.83–1.34 (4H, m); ^{13}C NMR (75 MHz, CDCl_3): d 194.9, 194.5, 137.2, 137.0, 133.4, 133.3, 132.3, 129.2, 129.15, 128.7, 128.66, 62.8, 37.1, 27.4, 25.1, 21.1; MS (ESI) m/z : 327 $[\text{M}+\text{Na}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{20}\text{O}_2\text{Na}$: 327.1360, found: 327.1348.