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Highly Efficient Metal-Free Cross-Coupling by C−H Activation between Allylic and Active Methylenic Compounds Promoted by DDQ

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Abstract: A metal-free very highly efficient and concise oxidative-coupling reaction promoted by 2,3-dichloro-5,6-dicyanoquinone (DDQ) between diarylallylic sp^3 C−H and active methylenic sp^3 C−H bonds is reported. The corresponding products are obtained in good to excellent yields.

Keywords: active methylenic compounds; allylic compounds; C−C bond formation; C−H activation; cross-coupling; DDQ; 2,3-dichloro-5,6-dicyanoquinone

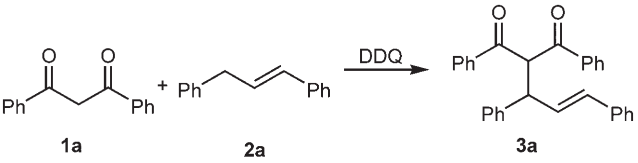
The formation of carbon-carbon bonds is one of the most useful and fundamental reactions since it represents a key step in the synthesis of complex molecules.[1] Metal-mediated cross-coupling of two pre-functionalized substrates is one of the most important synthetic tools for constructing the carbon-carbon bond.[2] With the emergence of the concepts of "atom economy"[3] and "green chemistry",[4] the cross-coupling reaction for C−C bond formation by transition metal-catalyzed C−H activation of one partner has attracted great interest because of its conciseness and atom economy and a number of excellent results have been obtained.[5] As a more challenging subject, oxidative intermolecular C−C bond formation by using two different C−H bonds was also developed, such as (i) sp^3 C−H with sp^3 C−H,[6] (ii) sp^2 C−H with sp^2 C−H,[7] (iii) sp^3 C−H with sp^2 C−H,[8] and (iv) sp^3 C−H with sp C−H.[9] In these transformations, both of the starting materials could be used directly in the C−H form without pre-functionalization. Among them, sp^3 C−H bonds that undergo the cross-coupling reaction are usually located at the α-position to a nitrogen or oxygen atom. The reason for this may lie in the fact that the nitrogen or oxygen atom activates the adjacent sp^3 C−H bond and further stabilizes the *in situ* formed intermediates. The C−H activation of the sp^3 C−H bond at the α-position of an aromatic ring or a vinyl group was also reported.[6a,d] For example, the allylic sp^3 C−H bond of cyclohexene was coupled with the methylenic sp^3 C−H bond *via* catalysis by copper(I) bromide and cobalt(II) chloride. Very recently, coupling of cyclohexane with methylene compounds catalyzed by the system of $FeCl_2/(t\text{-}Bu)_2O_2$ was reported.[6b] Although there were a lot of excellent results about C−C bond formation through C−H activation, examples of the reactions under metal-free condition are rare.

The palladium-catalyzed allylic alkylation (the Tsuji–Trost coupling reaction), usually employing an allylic acetate or its derivatives as the starting material, which have to be synthesized in several steps, represents one of the most common C−C bond formation methodologies in organic synthesis.[10] Progress has been made by the direct use of allylic alcohols and the overall process of allylation has become highly efficient and atom economical.[11] In fact, Trost's group tried to make an allylic alkylation directly from an allylic sp^3 C−H by palladating an olefin in the late 1970s.[12] Recently, Li's group has reported a first catalytic allylic alkylation reaction directly from allylic sp^3 C−H and methylenic sp^3 C−H bonds using Cu(I)/Co(II) and *t*-BuOOH as the catalyst-system.[6d]

Herein, we report that 2,3-dichloro-5,6-dicyanoquinone (DDQ) mediates a very highly efficient and concise oxidative-coupling reaction between diarylallylic sp^3 C−H and active methylenic sp^3 C−H bonds without any metal catalyst.

DDQ is a well-known oxidation reagent for organic synthesis.[13] The coupling reactions between some nucleophiles and benzylic substrates bearing a hetero atom at the α-position were reported in the presence

Table 1. Screening of reaction conditions.[a]



Entry	Solvent	T [°C]	Yield [%][b]
1	neat	r.t.	75[c]
2	neat	50	74[c]
3	neat	90	68[c]
4	NMP	r.t.	nd
5	hexane	r.t.	nd
6	THF	r.t.	53
7	$CHCl_3$	r.t.	61
8	CH_2Cl_2	r.t.	88
9	DCE	r.t.	82
10	CCl_4	r.t.	71
11	$MeNO_2$	r.t.	70
12	dioxane	r.t.	42
13	CH_2Cl_2	r.t.	73[d]
14	CH_2Cl_2	r.t.	80[e]

[a] 0.5 mmol of **1a**, 0.6 mmol of **2a**, 1.2 mL of solvent, 0.6 mmol of DDQ, 1 hour.

[b] Isolated yield.

[c] 0.5 mmol of **1a**, 4 mmol of **2a**, and 0.6 mmol of DDQ.

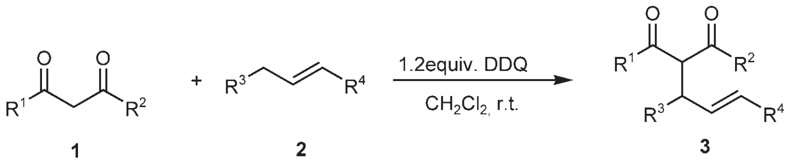
[d] 0.5 mmol of DDQ.

[e] 0.75 mmol of DDQ.

of DDQ.[14] In this paper, we initially examined the oxidative-coupling of **1a** and **2a** with DDQ in the absence of metal and solvent at room temperature. To our delight, the desired coupling product **3a** was obtained in 75% yield after an hour (Table 1, entry 1). It seemed that the reaction was not sensitive to temperature, since the results of the reaction did not change obviously when the temperature was raised to 50 °C or 90 °C (entries 2 and 3). Then a number of solvents were surveyed. No desired coupling product was observed when the reaction was carried out in NMP or hexane (entries 4 and 5). The reaction could proceed in THF, $CHCl_3$, CH_2Cl_2, DCE, CCl_4, $MeNO_2$, MeCN and dioxane (entries 6–13). However, considerable amounts of undesired products were formed in THF or dioxane and the rate of the reaction became slower when $CHCl_3$, CCl_4 or $MeNO_2$ were used as the solvents. Interestingly, the speed and yield of the reaction in DCE were comparable with those in CH_2Cl_2. Based on the above investigation, CH_2Cl_2 was preferred as the reaction media from the practical point of view. As for the influence of DDQ dosage on the reaction, it was found that decreasing the amount of the DDQ resulted in reduced yield, while increasing the amount to 1.5 equiv. did not make the reaction system complex and the yield was just a little lower.

With the optimized reaction conditions established, various substrates were subjected to this cross-coupling reaction (Table 2). The electronic effect of the

Table 2. Allylation of active methylenic compounds.[a]

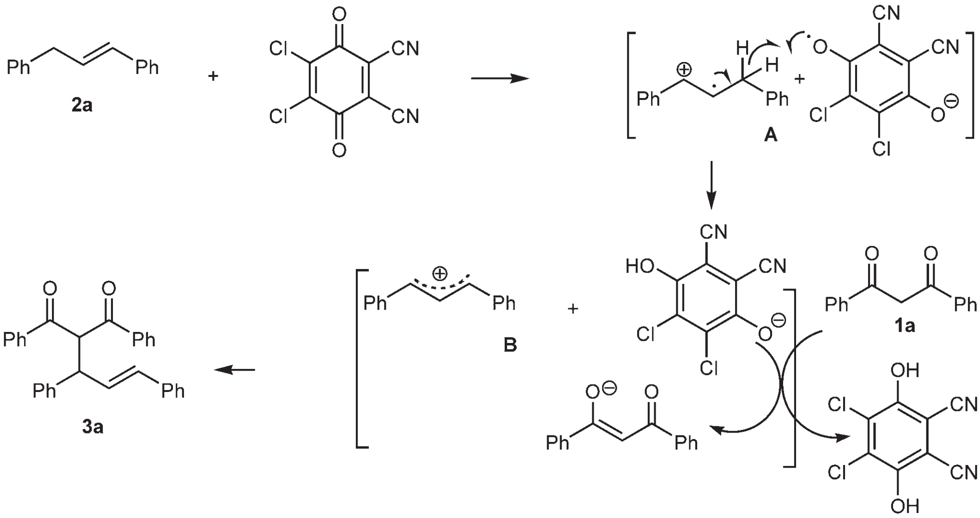


Entry	R^1, R^2	R^3, R^4	Time [h]	Product	Yield [%][b]
1	C_6H_5, C_6H_5	C_6H_5, C_6H_5	1	**3a**	88
2	2-$CH_3C_6H_4$, C_6H_5	C_6H_5, C_6H_5	0.5	**3b**	79
3	3-ClC_6H_4, C_6H_5	C_6H_5, C_6H_5	2	**3c**	84
4	3-$CH_3OC_6H_4$, C_6H_5	C_6H_5, C_6H_5	0.5	**3d**	96
5	4-ClC_6H_4, C_6H_5	C_6H_5, C_6H_5	4	**3e**	40
6	4-$CH_3OC_6H_4$, C_6H_5	C_6H_5, C_6H_5	0.5	**3f**	84
7	thienyl, C_6H_5	C_6H_5, C_6H_5	0.5	**3g**	98
8	furanyl, C_6H_5	C_6H_5, C_6H_5	0.5	**3h**	93
9	C_6H_5, CH_3	C_6H_5, C_6H_5	0.5	**3i**	90
10	CH_3, CH_3	C_6H_5, C_6H_5	0.5	**3j**	60
11[c]	CH_3, OEt	C_6H_5, C_6H_5	2	**3k**	70
12[c]	-$(CH_2)_4$-, OEt	C_6H_5, C_6H_5	3	**3l**	75
13	C_6H_5, C_6H_5	4-$CH_3C_6H_4$, C_6H_5	2.5	**3m**	92
14	C_6H_5, C_6H_5	4-CNC_6H_4, C_6H_5	3.5	**3n**	72
15	CH_3, CH_3	4-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$	2.5	**3o**	95
16	C_6H_5, C_6H_5	4-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$	3	**3p**	71

[a] 0.5 mmol of **1**, 0.6 mmol of **2**, 0.6 mmol of DDQ, and 1.2 mL of CH_2Cl_2 unless noted.

[b] Isolated yields.

[c] 0.5 mmol of **1**, 4 mmol of **2**, 0.6 mmol of DDQ, 90 °C.



Scheme 1. Possible reaction mechanism.

substituents on aromatic ring of **1** was observed. For example, the substrates bearing an electron-donating group on the aromatic ring (entries 2, 4, and 6) reacted rapidly and 79–96% yields were obtained, while that bearing a chloro group on the *para*-position reacted a little more slowly and a moderate yield was obtained (entry 5). Heteroaryl species such as furanyl, thienyl were compatible with the present procedure and excellent results were obtained (entries 7 and 8). Acetylacetone and benzoylacetone were also suitable substrates here (entries 9 and 10). Reactions of acyclic and cyclic β-keto esters were comparatively sluggish, so the reaction temperature was raised to 90 °C (entries 11 and 12). To expand the scope of the substrates, we further examined the mono- and disubstituted 1,3-diarylpropenes (entries 13–16) and obtained the expected products in satisfactory yields.

A possible mechanism for this coupling reaction may involve a single-electron transfer process in the first step.[6e,14a,15] But we cannot ascertain if DDQ abstracts an electron firstly from the arylallylic compound or the active methylene compound. When a solution of **2a** was combined with DDQ, we observed the immediate formation of a deep green color that is likely a charge-transfer complex **A**, whereas when a solution of **1a** was combined with DDQ, no obvious color change was observed.[16] So maybe the first step of the reaction is a single-electron transfer process between the arylallylic double bond and DDQ, which generates the radical ion pair **A**. A possible mechanism may be that shown in Scheme 1.

In summary, we have developed a highly efficient coupling reaction between arylallylic compounds and active methylene compounds using DDQ as a promoter. It provides a highly efficient approach to allylic alkylation by using allylic sp^3 C–H bonds directly. The reaction has several advantages: (i) it proceeds without a metal catalyst and additional reagent and (ii) it gives the products in good to excellent yields in a short time.

Experimental Section

General Procedure

A 10-mL, two-necked, round-bottom flask was charged with a mixture of the methylene compound (0.5 mmol) and the 1,3-diarylpropene (0.6 mmol) in CH_2Cl_2 (1.2 mL) and DDQ (0.6 mmol) was added. The resulting mixture was stirred for the indicated time at room temperature. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether and ethyl acetate as the eluent to give the pure product. For more details, see Supporting Information.

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