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Efficient Palladium-Catalyzed Oxidative Indolation of Allylic Compounds with DDQ *via* sp^3 C–H Bond Activation and Carbon-Carbon Bond Formation Under Mild Conditions

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Abstract: An efficient oxidative cross-coupling reaction between 1,3-diarylpropenes and indoles in the presence of palladium chloride was achieved with 2,3-dichloro-5,6-dicyanoquinone (DDQ) as oxidant. The reaction afforded 1,3-diphenylallylindoles in moderate to high yields under mild conditions, thus providing a novel methodology to synthesize the respective products.

Keywords: C–C bond formation; C–H bond activation; cross-dehydrogenative-coupling (CDC) reaction; indolation; palladium catalysis

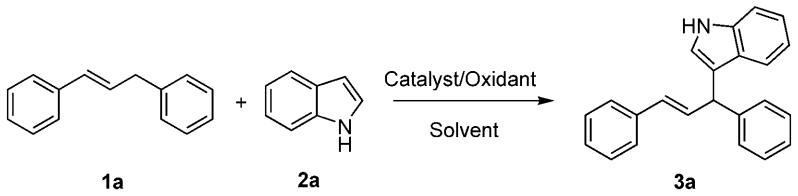
Indoles are key structural units in many natural products and important pharmaceuticals.[1] The development of new, efficient and selective synthetic methods for the functionalization of indoles continues to receive considerable attention.[2] With the emergence of the concepts of "atom economy"[3] and "green chemistry"[4] transition metal-catalyzed C–H bond activation directly to form C–C bond has attracted great attention recently and a number of excellent results have been obtained.[5] Various oxidative intermolecular cross-dehydrogenative-coupling (CDC) reactions by using two different C–H bonds have also been 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]

The palladium-catalyzed allylic alkylation (Tsuji–Trost coupling reaction), usually employing an allylic acetate or its derivatives, and later using allylic alcohols directly as the starting material, represents one of the most common C–C bond formation methodologies in organic synthesis.[10] 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.[11] 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.[6e] Our group has reported a metal-free allylic alkylation reaction by using the allylic sp^3 C–H bond.[6a] Herein, we report the first Pd(II)-catalyzed CDC reactions of allylic indolation directly using allylic sp^3 C–H bond and indoles with 2,3-dichloro-5,6-dicyanoquinone (DDQ) as the oxidant under mild conditions.

To begin our study, we chose 1,3-diphenylpropene **1a** and indole **2a** as the standard substrates to search for suitable reaction conditions. DDQ is a well-known oxidation reagent for organic synthesis.[12] The coupling reactions between some nucleophiles and benzylic substrates bearing a heteroatom at the α-position were reported in the presence of DDQ.[13]

We also applied a stoichiometric amount of DDQ as an oxidant in our allylic indolation reaction. However, the desired product was obtained only in less than 5% yield without catalyst (Table 1, entry 1). From the literature we found that CuBr may be an efficient catalyst in the indolation reaction.[8a] To improve the reaction yield, CuBr was used as a catalyst. The yield of the desired product was raised to 19% (Table 1, entry 2). After various transition metal catalysts were surveyed to optimize the reaction results (Table 1, entries 3, 4 and 5), $PdCl_2$ was found to be the most efficient catalyst and the yield of the product was far improved. Allylation had taken place at the 3-position of indoles and no *N*-allylation product was detected (Table 1, entry 6). In addition, we tried other oxidants such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl peroxide and benzoquinone (BQ), since they acted well as the oxidants in recent reports of C–C bond formation reactions *via* the C–H bond activation. Unfortunately, all these oxidants were not suitable for this CDC reaction (Table 1, entries 7–9). Then a number of solvents were screened and the re-

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

Entry	Catalyst	Oxidant	Solvent	Temp. [°C]	Yield [%][b]
1	None	DDQ	CH_2Cl_2	0	trace
2	CuBr	DDQ	CH_2Cl_2	0	19
3	$FeCl_3$	DDQ	CH_2Cl_2	0	trace
4	$NiCl_2$	DDQ	CH_2Cl_2	0	28
5	$ZrCl_4$	DDQ	CH_2Cl_2	0	39
6	$PdCl_2$	DDQ	CH_2Cl_2	0	67
7	$PdCl_2$	TBHP	CH_2Cl_2	0	N.D.
8	$PdCl_2$	*tert*-butyl peroxide	CH_2Cl_2	0	N.D.
9	$PdCl_2$	BQ	CH_2Cl_2	50	trace
10	$PdCl_2$	DDQ	toluene	0	75
11	$PdCl_2$	DDQ	CH_3NO_2	0	36
12	$PdCl_2$	DDQ	THF	0	66
13	$PdCl_2$	DDQ	DMF	0	52
14	$PdCl_2$	DDQ	CH_3CN	0	81
15	$PdCl_2$	DDQ	$CHCl_3$	0	51
16	$PdCl_2$	DDQ	CH_3CN	-10	79
17	$PdCl_2$	DDQ	CH_3CN	r.t	38
18	$PdCl_2$	DDQ	CH_3CN	70	20

[a] 0.5 mmol of **1a**, 0.6 mmol of **2a**, 1.5 mL of solvent, 0.6 mmol of oxidant.
[b] Isolated yield

action could proceed in CH_2Cl_2, toluene, CH_3NO_2, THF, DMF, CH_3CN and $CHCl_3$. However, considerable amounts of undesired products were formed in CH_3NO_2, DMF and $CHCl_3$ (Table 1, entries 11, 13 and 15). And the reaction performed best in CH_3CN (Table 1, entry 14). Further investigation showed that this CDC reaction was very sensitive to the temperature. The yield of the coupling product rapidly decreased when we increased the reaction temperature (Table 1, entries 17 and 18). Lower reaction temperatures also caused the yield of the desired product to go down slightly (Table 1, entry 16).

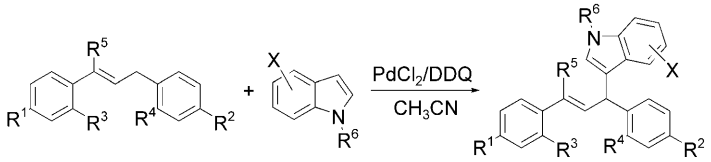
With the optimized reaction conditions established, various substrates were subjected to the CDC reactions and representative results are summarized in Table 2. Indoles with electron-withdrawing groups reacted well with the diarylpropenes under the standard reaction conditions (Table 2, entries 2 and 3). However, PPh_3 was required to achieve a moderate yield when indoles bearing electron-donating group were used (Table 2, entries 5–7). To expand the scope of the reaction, we further examined mono- and disubstituted 1,3-diarylpropenes. High yields in the coupling products were obtained with electron-donating groups on the aromatic ring of the 1,3-diarylpropenes, while moderate yields were found with electron-withdrawing-groups on the aromatic ring (Table 2, entries 9–13). Interestingly, no isomers were detected when **1g** reacted with indole (Table 2, entry 14), while α- and γ-indolated isomers were detected when the mono- or asymmetrically disubstituted 1,3-diarylpropenes reacted with indole (Table 2, entries 9, 12 and 13). The steric effect caused the yield of the coupling product to decrease (Table 2, entries 4 and 15).

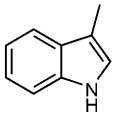
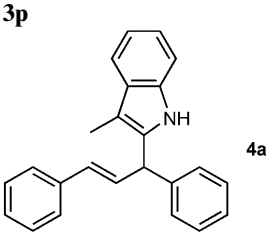
Interestingly, when the 3-position of indole was substituted, the C-2 alkylation product was also obtained (Table 2, entry 16).

On the basis of these observations, a tentative mechanism is proposed in Scheme 1. Firstly, DDQ abstracted a hydride from **1a** to form the conjugated intermediate **A**.[6a] Then **A** would undergo carbometalation with palladium chloride and indole to form π-allyl palladium intermediate **B**.[14] Subsequent elimination would produce intermediate **C**, which finally afforded the product **3a** after a proton was abstracted by the phenolic anion. The fact that isomers were detected when indole reacted with mono- or asymmetrically disubstituted 1,3-diarylpropenes implies the involvement of the π-allyl palladium intermediate **B** during the catalytic cycle.

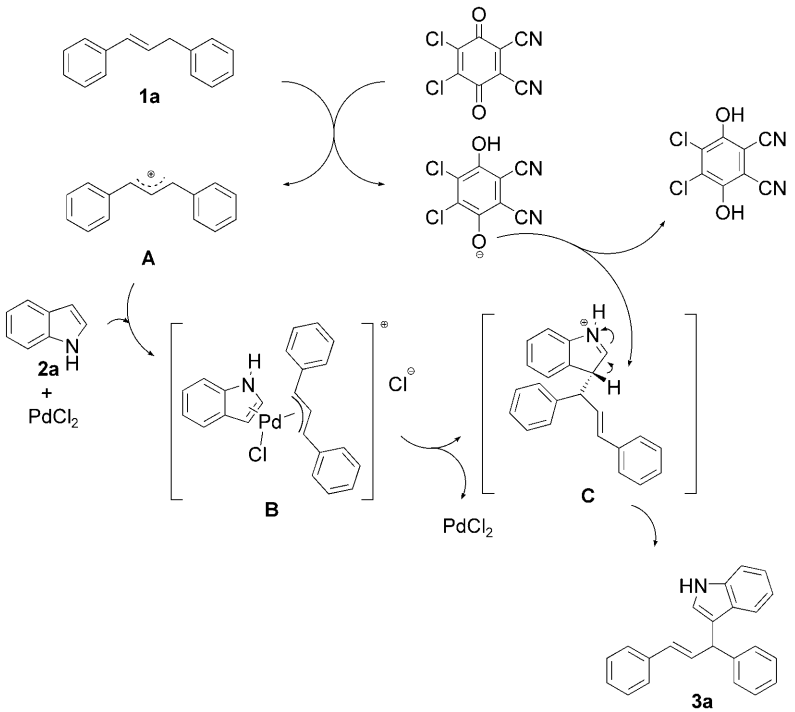
In summary, we have developed an efficient catalytic allylic indolation *via* a CDC reaction between allylic sp^3 C–H and the C-3 and/or C-2 position of indole catalyzed by palladium chloride under mild condi-

Table 2. CDC reaction of indoles with diarylpropenes.[a]



Entry	R^1, R^2, R^3, R^4, R^5	X, R^6	Product	Yield [%][b]
1	H, H, H, H, H **1a**	H, H **2a**	**3a**	81
2	**1a**	5-Br, H **2b**	**3b**	71
3	**1a**	5-CN, H **2c**	**3c**	83
4	**1a**	4-CO_2CH_3, H **2d**	**3d**	46
5	**1a**	5-CH_3, H **2e**	**3e**	53[c]
6	**1a**	5-OMe, H **2f**	**3f**	48[c]
7	**1a**	7-CH_3, H **2g**	**3g**	51[c]
8	**1a**	H, CH_3 **2h**	**3h**	77
9	H, Cl, H, H, H **1b**	**2a**	**3i**, **3j**	71
10	Cl, Cl, H, H, H **1c**	**2a**	**3k**	60
11	H, H, Br, Br, H **1d**	**2a**	**3l**	49
12	CH_3, H, H, H, H **1e**	**2a**	**3m**, **3n**	94
13	H, CH_3, H, H, H **1f**	**2a**	**3m**, **3n**	90
14	OMe, Cl, H, H, H **1g**	**2a**	**3o**	91
15	H, H, H, H, CH_3 **1h**	**2a**	**3p**	40
16	**1a**	 **2i**	 **4a**	55

[a] 0.5 mmol of diarylpropenes, 0.6 mmol of indole, 1.5 mL of CH_3CN, 0.6 mmol of DDQ, 5 mol% $PdCl_2$, 0 °C, 2 h.
[b] Isolated yield based on diarylpropene.
[c] 10 mol% PPh_3 were added.



Scheme 1. Possible mechanism.

tions. This novel methodology provides an efficient approach to directly use allylic sp^3 C–H bonds for the purpose of C–C bond formation. The scope, mechanism, and synthetic application of this reaction are under investigation.

Experimental Section

General Procedure for Products 3

To a mixture of $PdCl_2$ (0.025 mmol), 1,3-diarylpropene (0.5 mmol) and 1.5 mL of CH_3CN, DDQ (0.6 mmol) was added at 0 °C. After stirring for 5 min, indole (0.6 mmol) was added to the mixture dropwise. Then the reaction vessel was capped and the mixture stirred for 2 h. The resulting mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1), and the fraction with an $R_f = 0.3$ was collected to give the desired product (*E*)-3-(1,3-diphenylallyl)-1*H*-indole (**3a**) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (s, 1H), 7.50–7.17 (m, 14H), 7.09–7.03 (m, 1H), 6.92 (s, 1H), 6.81–6.73 (dd, $J = 7.2$, 15.6 Hz, 1H), 6.48 (d, $J = 15.6$ Hz, 1H), 5.16 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 46.1, 111.0, 118.7, 119.4, 119.8, 122.0, 122.5, 126.2, 126.3, 126.8, 127.1, 128.3, 128.4, 130.5, 132.5, 136.6, 137.4, 143.3; MS (70 eV, EI) $m/z = 309$.

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