Synthesis of Aryl-Substituted 1,4-Benzoquinone via Palladium(II)-Catalyzed Decarboxylative Coupling of Arene Carboxylate with 1,4-Benzoquinone

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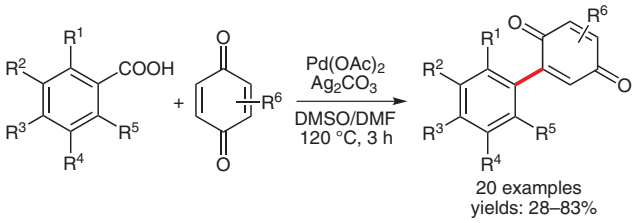
Abstract: Various aryl-substituted 1,4-benzoquinone derivatives have been prepared via a palladium-catalyzed decarboxylative cross-coupling of electron-rich aromatic acids with 1,4-benzoquinones.

Key words: palladium-catalysis, decarboxylative coupling, C–C bond formation, arene carboxylate, benzoquinone

The development of direct carbon–carbon bond formation that uses safe, environmentally benign, and low-cost starting materials remains a critical challenge for modern synthetic organic chemists. Recently, some efficient metal-catalyzed decarboxylative systems have been explored for C–C bond couplings by using simple carboxylic acids as the active coupling partners.[1] These interesting studies show that acids can replace both halides and organometallic reagents. An efficient Heck-type reaction which was believed to be a milestone in palladium-catalyzed decarboxylative cross-coupling using *ortho*-substituted arene carboxylates alternative to aromatic halides with olefins was developed by Myers et al.[2] On the other hand, carboxylic acids are proved to be efficient surrogates to organometallic reagents in Suzuki–Miyaura coupling reaction.[3] Although most of these reactions suffer from limited substrate scope, relatively high additive loading, and high reaction temperature, it remains very attractive since it would be safe, convenience, and high selectivities. We wish to report herein a palladium-catalyzed direct decarboxylative coupling of carboxylic acids with 1,4-benzoquinone to give various aryl-substituted benzoquinones. Substituted 1,4-benzoquinone derivatives show versatile biological activities.[4] In the past decades, many methods have been explored to produce these useful structures.[5] However, most of these methods suffer from unstable starting materials and relatively low selectivities. Taking advantage of safety, low-cost, and commercial availability of carboxylic acids, we successfully accomplished a decarboxylative cross-coupling procedure by using arene carboxylates as the coupling substrates (Scheme 1). To the best of our knowledge, this is the first example of Pd-catalyzed synthesis of aryl-substituted benzoquinones via a direct decarboxylative coupling reaction by using aromatic acids and 1,4-benzoquinone.



Scheme 1 Synthesis of aryl-substituted 1,4-benzoquinones using arene carboxylates and 1,4-benzoquinone

As the initial research, we select 2,4,5-trimethoxybenzoic acid and 1,4-benzoquinone as standard substrates to optimize suitable conditions for this reaction (Table 1). The desired decarboxylative coupling product was obtained in 37% yield using 20 mol% of $Pd(O_2CCF_3)_2$ and 3 equivalents of Ag_2CO_3 at 120 °C in a mixed solution of 5% DMSO–DMF (Table 1, entry 1). Interestingly, the isolated yield of the product increased to 72% by using 20 mol% of $Pd(OAc)_2$ as catalyst (Table 1, entry 2). However, the yield was not improved by using other palladium catalysts (Table 1, entries 3–5) and other additives (Table 1, entries 6–8). Further investigation of solvent effect showed that DMF is a more effective solvent (Table 1, entries 9–12). Decrease of the catalyst and additive dosage was less efficient (Table 1, entries 13–16). In the present Pd(II)-catalyzed decarboxylative C–C bond formation, excess amount of Ag_2CO_3 was required. It acts not only as an oxidant which is believed to reoxidize Pd(0) to Pd(II), but also as a base which might react with carboxylic acid to form ArCOOAg followed by transmetalation with $Pd(OAc)_2(DMSO)_2$. Other bases such as Na_2CO_3, K_2CO_3, and Cs_2CO_3 cannot replace the role of Ag_2CO_3.

It is seen from Table 2 that aromatic acids bearing electron-donating groups gave moderate to good yields of the desired products (Table 2, entries 1–5).[6] However, 2,3,4-trimethoxybenzoic acid only gave 28% yield (Table 2, entry 6), it might be attributed to buttressing effect of the vicinal methoxyl groups. 2,4,6-Trimethyl benzoic acid gave 43% yield (Table 2, entry 7). The yield of the product decreased as the acid bearing an electron-withdrawing group. For example, 2,6-dimethoxy-3-bromobenzoic acid and 2-methoxyl-4-amino-5-chlorobenzoic acid gave 36% and 31% yields of the corresponding products, respective-

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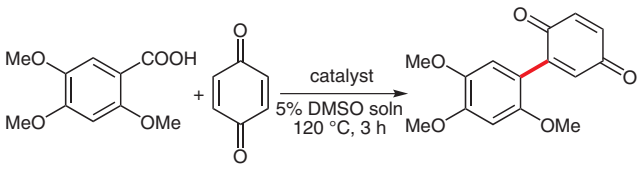
Table 1 Optimization of the Typical Reaction Conditions[a]



Entry	Catalyst	Solvent	Additive	Yield (%)[b]
1	$Pd(TFA)_2$	DMF	Ag_2CO_3	37
2	$Pd(OAc)_2$	DMF	Ag_2CO_3	72
3	$PdCl_2$	DMF	Ag_2CO_3	53
4	$Pd(PPh_3)_2Cl_2$	DMF	Ag_2CO_3	35
5	$Pd(PPh_3)_4$	DMF	Ag_2CO_3	44
6	$Pd(OAc)_2$	DMF	AgOAc	44
7	$Pd(OAc)_2$	DMF	$Cu(OAc)_2$	22
8	$Pd(OAc)_2$	DMF	$Cu_2(OH)_2CO_3$	53
9	$Pd(OAc)_2$	benzene	Ag_2CO_3	35
10	$Pd(OAc)_2$	toluene	Ag_2CO_3	38
11	$Pd(OAc)_2$	DMA[c]	Ag_2CO_3	46
12	$Pd(OAc)_2$	diglyme[d]	Ag_2CO_3	53
13[e]	$Pd(OAc)_2$	DMF	Ag_2CO_3	53
14[f]	$Pd(OAc)_2$	DMF	Ag_2CO_3	47
15[g]	$Pd(OAc)_2$	DMF	Ag_2CO_3	36
16[h]	$Pd(OAc)_2$	DMF	Ag_2CO_3	22

[a] Reaction conditions: 2,4,5-trimethoxybenzoic acid (0.2 mmol), 1,4-benzoquinone (0.3 mmol), additive (0.6 mmol), catalyst (0.04 mmol), DMSO (0.5 mL) in solvent (10 mL), 120 °C, 3 h, unless otherwise specified.
[b] Isolated yields.
[c] DMA = *N*,*N*-dimethylacetamide.
[d] Diglyme = 2-methoxyethyl ether.
[e] Ag_2CO_3 (0.4 mmol).
[f] Ag_2CO_3 (0.2 mmol).
[g] $Pd(OAc)_2$ (0.02 mmol).
[h] $Pd(OAc)_2$ (0.01 mmol).

ly (Table 2, entries 8 and 9). It is noteworthy that some heterocyclic acids also gave the desired products in 34% to 52% yields (Table 2, entries 10–12). On the other hand, 1,4-naphthoquinone and some substituted benzoquinones were investigated as substrates for cross-coupling of aromatic acids under the typical conditions (Table 2). Various aryl-substituted 1,4-naphthoquinones were obtained in moderate yields by using electron-rich benzoic acids and 1,4-naphthoquinone (Table 2, entries 13–16). It is hard to evaluate the reactivity between 2,4,6-trimethoxylbenzoic acid and 2,4,6-trimethylbenzoic acid in this system. For arylation of 1,4-benzoquinone, the former showed higher reactivity than the later (entries 2 and 7), nevertheless in the case of 1,4-naphthoquinone, 2,4,6-trimethoxybenzoic acid showed lower reactivity than 2,4,6-trimethylbenzoic acid (entries 15 and 16). 2-Methyl-1,4-benzoquinone and 2-bromo-1,4-benzoquinone gave a mixture of 5- and 6-aryl-substituted benzoquinones in moderate yields (entries 17–19).[5] No products were obtained using more sterically hindered 2,6-dimethyl 1,4-benzoquinone (entry 20). Many other experiments show that at least one electron-donating *ortho*-positioned group in the acid is necessary for this reaction. In addition, the steric effect of benzoquinones is obvious but the electronic effect is not clear which is just opposite to carboxylic acids.

A possible mechanism of this Pd(II)-catalyzed decarboxylative Heck-type cross-coupling is proposed as followed. Decarboxylation of the acid which might be catalyzed by silver(I) salt[7] occurs to form an arylsilver intermediate, which is then transmetalated to give an arylpalladium(II) intermediate followed by Heck addition to benzoquinone, and β-hydride elimination gives the C–C bond-coupling product.

Table 2 Synthesis of Aryl-Substituted 1,4-Benzoquinone Using Carboxylic Acids with 1,4-Benzoquinone[a]

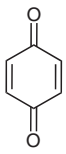
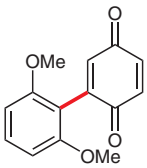
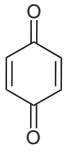
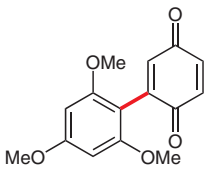
Entry	Benzoquinone	Product	Yield (%)[b]
1			83
2			78

Table 2 Synthesis of Aryl-Substituted 1,4-Benzoquinone Using Carboxylic Acids with 1,4-Benzoquinone[a] (continued)

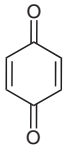
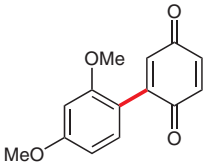
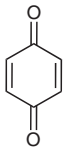
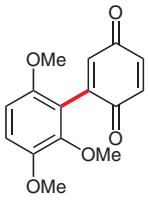
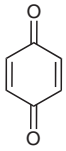
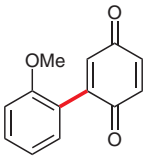
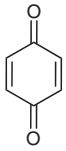
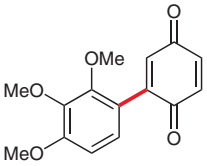
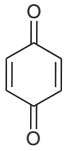
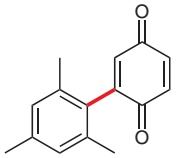
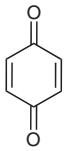
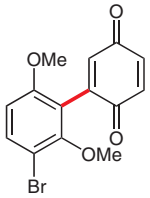
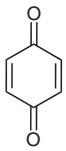
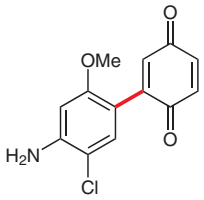
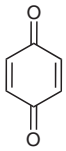
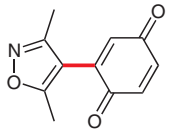
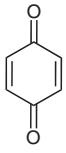
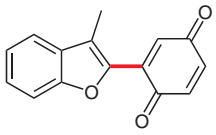
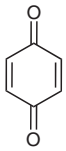
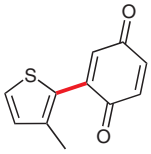
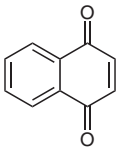
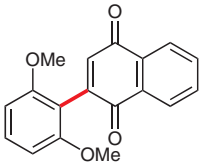
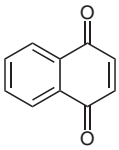
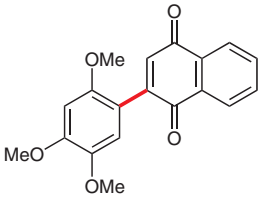
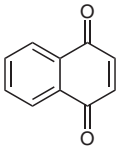
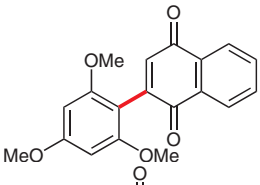
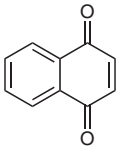
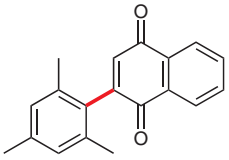
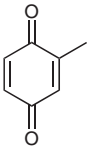
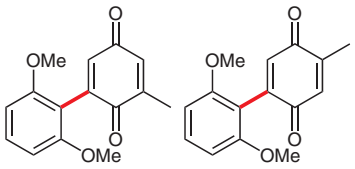
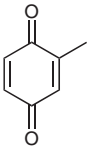
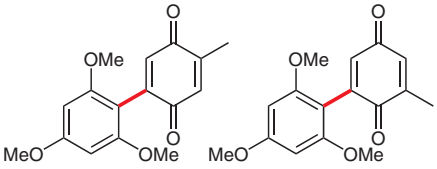
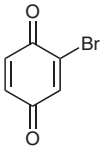
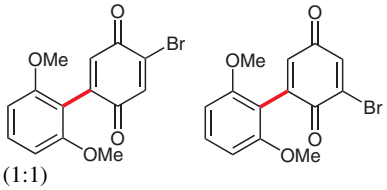
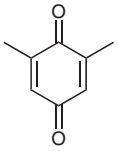
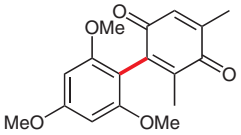
Entry	Benzoquinone	Product	Yield (%)[b]
3			55
4			71
5			44
6			28
7			43
8			36
9			31
10			34
11			52

Table 2 Synthesis of Aryl-Substituted 1,4-Benzoquinone Using Carboxylic Acids with 1,4-Benzoquinone[a] (continued)

Entry	Benzoquinone	Product	Yield (%)[b]
12			39
13			63
14			41
15			49
16			55
17		 (1:1)	68
18		 (1:1)	55
19		 (1:1)	41
20			0

[a] Reaction conditions: acid (0.2 mmol), 1, 4-benzoquinone (0.3 mmol), Ag_2CO_3 (0.6 mmol), $Pd(OAc)_2$ (0.04 mmol), DMSO (0.5 mL) in DMF (10 mL), 120 °C, 3 h, unless otherwise specified.
[b] Isolated yield.

In summary, this work demonstrates a palladium(II)-catalyzed decarboxylative cross-coupling method to prepare aryl-substituted 1,4-benzoquinone derivatives by using electron-rich arene carboxylates and 1,4-benzoquinones. Although electron-rich acid is necessary and hindered benzoquinone is not effective, carboxylic acids involving heterocyclic carboxylic acids as substrates, direct coupling with benzoquinone, and short reaction time makes this procedure attractive. Further investigation including more efficient catalytic systems and expansion of the substrate scope is under way in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) **Representative Procedure**
2,6-Dimethoxybenzoic acid (36 mg, 0.2 mmol, 1.0 equiv), 1,4-benzoquinone (32 mg, 0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.02 equiv), and Ag_2CO_3 (165 mg, 0.6 mmol, 3 equiv) were added in DMF (10 mL) and DMSO (0.5 mL). The mixture was heated at 120 °C for 3 h, then was cooled and poured into EtOAc (50 mL). The mixture was filtered; the filtrate was washed sequentially with aq HCl (1 M, 2 × 40 mL) and brine (20 mL), then was dried over $MgSO_4$, filtered, and concentrated. Chromatographic separation gave the pure product **1** (40 mg, 0.164 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 10.0 Hz, 1 H), 6.81–6.71 (m, 2 H), 6.61 (d, *J* = 8.4 Hz, 2 H), 3.73 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.80, 185.54, 157.80, 142.73, 137.13, 136.32, 135.99, 130.89, 110.03, 103.96, 55.83. MS (EI): *m/z* (%) = 244 (100) [M^+], 213 (22), 162 (56), 161 (54), 131 (35), 91 (39), 54 (60), 39 (29). ESI-HRMS: *m/z* calcd for $C_{14}H_{12}O_4$ [M + H]$^+$: 245.0808; found: 245.0803, error: 2.0 ppm.

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