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An Approach to 3,6-Disubstituted 2,5-Dioxybenzoquinones via Two Sequential Suzuki Couplings. Three-Step Synthesis of Leucomelone

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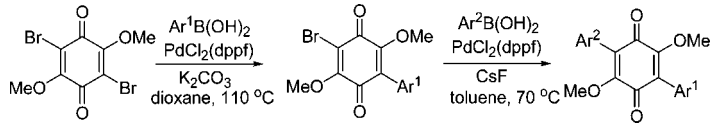
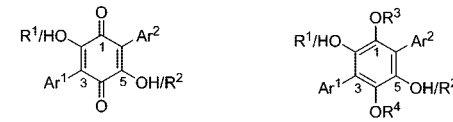
ABSTRACT



Two sequential Suzuki coupling reactions have been developed for efficient synthesis of synthetically and biologically important 3,6-disubstituted 2,5-dioxybenzoquinone architectures in a highly chemoselective controlled manner. The method serves as a key step in the total synthesis of leucomelone in three steps and in 61% overall yield.

The 3,6-disubstituted 2,5-dioxybenzoquinone framework and its reductive phenol form are widely distributed in a large collection of natural products (Figure 1).[1−7] Significantly, they display a broad spectrum of intriguing biological activities including potent immunosuppressant,[1] antioxidative,[2] neuroprotective,[3] anticogulant,[4] antidiabetic,[5] anticancer,[6] and specific 5-lipoxygenase inhibitory activities.[7]



3,6-disubstituted 2,5-dioxybenquinone (**1**) **2**

Figure 1. Naturally occurring 3,6-disubstituted 2,5-dioxybenzoquinone architecture (**1**) and its reduced phenol form (**2**).

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(1) Xie, C.; Koshino, H.; Esumi, Y.; Onose, J.; Yoshikawa, K.; Abe, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5424.
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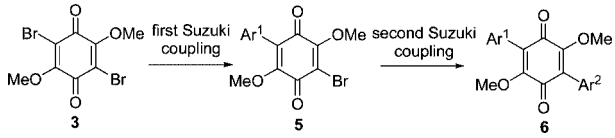
Moreover, notably, most of the terphenyls are plentiful in edible mushrooms, indicating their relatively low toxicity profile.[2] Accordingly, these molecules serve as attractive leads for the development of new therapeutic agents.

As a result of a wide range of bioactivities of this class of compounds,[5] in the recent past, their syntheses have received increasing interest. The terphenylquinone nucleus was generally built up via substitution with diazonium salt but in low yield.[8] The alumina/potassium carbonate-promoted condensation was developed as a key step for the synthesis of asterriquinones.[9a−c] An improved protocol using cesium carbonate was disclosed.[9d] However, these approaches were limited to the preparation of symmetric asterriquinones. Recently, Pirrung and co-workers reported a Pd-catalyzed Heck reaction, which enabled introduction of different indole moieties in a chemoselective controlled mode.[10] Nevertheless, toxic mercuric indole reagents were employed with a limited scope.

We were interested in developing a general approach to unsymmetrical 3,6-disubstituted 2,5-dioxybenzoquinones. A convergent strategy is particularly attractive in medicinal chemistry since it is a more efficient way of generating structural diversity from readily available common late-stage intermediates. We envisioned that Suzuki cross-coupling reaction with 3,6-dibromo-2,5-dimethoxybenzoquinone (**3**) was an ideal solution as a result of a large number of boronic acids available (Scheme 1).[11] Furthermore, the intermediate

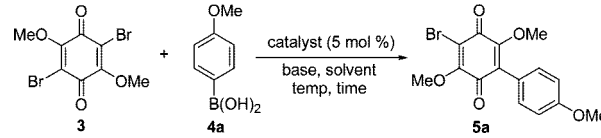
Scheme 1. Convergent Approach to Unsymmetrical 3,6-Disubstituted 2,5-Dimethoxybenzoquinone via Two Sequential Suzuki Cross-Coupling Reactions



3 can be conveniently prepared in a large scale in two steps from commercially available starting matereial.[12] However, the challenges were also realized. Examples of Suzuki cross-couplings of quinones with boronic acids were extremely rare. To the best of our knowledge, only a single study involved reaction of dihalobenzoquinone with indolylboron was described.[13] However, highly toxic Tl_2CO_3 as base was used, and the approach failed to react with aromatic boronic acids.[14] Moreover, controlled chemoselective introduction of two different aromatic moieties into the central quinone unit was a challenging task. Herein, we wish to report an efficient protocol enabling to construct the differentially 3,6-disubstituted 2,5-dioxybenzoquinones via two sequential Suzuki-coupling reactions in high efficiency. We also successfully applied the strategy for three-step synthesis of natural product leucomelone in 61% overall yield.

Initial efforts focused on the optimization of the first Suzuki coupling reaction conditions aimed at improving the reaction yield and controlled generation of monosubstituted product without forming bis-aryl product. A model reaction of **3** (1.0 equiv) with 4-methoxyphenylboronic acid (**4a**, 1.4 equiv) was carried out in dixoane in the presence of K_2CO_3 as base at 110 °C (Table 1). It was found the reaction

Table 1. Optimization of Suzuki Coupling of 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (**3**) with 4-Methoxyphenylboronic Acid (**4a**)[a]



entry	catalyst	base	solvent	*T* (°C)	time (h)	SM[b] (%)	yield[c] (%)
1	$Pd(PPh_3)_4$	K_2CO_3	dioxane	110	18	8	52
2	$Pd(OAc)_2/PCy_3$	K_2CO_3	dioxane	110	18	2	44
3	$PdCl_2(PPh_3)_2$	K_2CO_3	dioxane	110	18	11	73
4	$PdCl_2$(dppf)	K_2CO_3	dioxane	110	18	8	78
5	$PdCl_2$(dppf)	K_2CO_3	THF	70	18	14	73
6	$PdCl_2$(dppf)	K_2CO_3	toluene	120	18	11	48
7	$PdCl_2$(dppf)	K_2CO_3	DMF	110	18	0	0
8	$PdCl_2$(dppf)	K_2CO_3	dioxane/ water	100	18	0	0
9	$PdCl_2$(dppf)	Na_2CO_3	dioxnae	110	18	63	20
10	$PdCl_2$(dppf)	Cs_2CO_3	dioxane	110	12	0	50
11	$PdCl_2$(dppf)	Cs_2CO_3	dioxane	rt	16	0	68
12	$PdCl_2$(dppf)	K_2CO_3	dioxane	110	24	4	80
13	$PdCl_2$(dppf)	K_2CO_3	dioxane	110	30	2	76

[a] 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (**3**, 0.10 mmol), 4-methoxyphenylboronic acid (**4a**, 0.14 mmol), catalyst (0.005 mmol), base (0.20 mmol), solvent (1 mL). [b] Calculated based on recovered starting material (SM) **3**. [c] Isolated yield.

efficiency was highly catalyst dependent (entries 1−4). Among the catalysts probed, $PdCl_2$(dppf) was most effective. In this case, monosubstituted product **4a** was generated in 78% yield (entry 4). Importantly, under the reaction conditions, a very small amount of bis-substitution product (<5%) was observed. The effect of solvents on the reaction was

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(11) For recent reviews of Suzuki cross-couplings, see: (a) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(12) 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (**3**) can be prepared in two steps from cheap and commercially available 2,5-dimethoxy-1,4-benzoquinone in high yields; see the Supporting Information for details.

(13) (a) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett.* **1993**, *34*, 7637. (b) Kasahara, T.; Kondo, Y. *Chem. Commun.* **2006**, *37*, 891.

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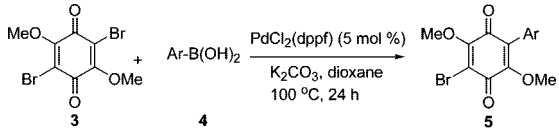
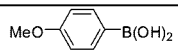
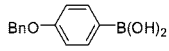
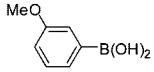
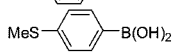
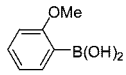
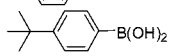
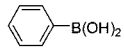
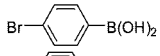
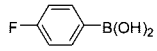
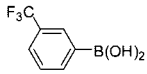
significant (entries 4−8). Clearly, the optimal reaction yield was achieved in dioxane (entry 4). No reaction occurred when DMF was used (entry 7) and water dramatically hindered reaction (entry 8). We found that the substantial decomposition of the substrate **3** was observed under these reaction conditions. Survey of bases revealed that K_2CO_3 was of choice (entries 4, 9, and 10). Finally, the reaction time was also optimized. It was found that 24 h reaction time was optimal using $PdCl_2$(dppf) as catalyst and K_2CO_3 as base in dioxane at 110 °C with obtaining the best yield (80%) (entries 4, 12, and 13).

Having established the optimal reaction conditions of the Suzuki coupling reaction, we next probed the scope of the process. As revealed in Table 2, a variety of boronic acids

Table 2. Suzuki Monocoupling of 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (**3**) with Boronic Acids (**4**)



3 **4** **5**

entry	boronic acid	product	yield (%)[b]
1		**5a**	80
2		**5b**	28 (62)[c] 80[d]
3		**5c**	82
4		**5d**	70
5		**5e**	78
6		**5f**	75
7		**5g**	74
8		**5h**	66
9		**5i**	59 59[e]
10		**5j**	62 62[e]
11		**5k**	67

[a] Reaction conditions, unless specified, boronic acid (1.4 equiv), 5 mol % of $PdCl_2$(dppf), K_2CO_3 (2.0 equiv), dioxane, 110 °C, 24 h. [b] Isolated yield. [c] Recovered starting material. [d] Boronic acid (1.4 equiv), 5 mol % of $PdCl_2$(dppf), Cs_2CO_3 (2.0 equiv), dioxane, rt, 16 h. [e] Boronic acid (1.4 equiv), 5 mol % of $PdCl_2$(dppf), K_2CO_3 (2.0 equiv), Ag_2O (1.2 equiv), dioxane, 110 °C, 24 h.

bearing electron-donating, neutral, and withdrawing substituents could participate in the process and generally good to high yields for products **5** were obtained. The relatively higher yields were achieved with boronic acids containing electron-donating (entries 1−6) and -neutral groups (entry 7). Interestingly, the reaction proceeded very poorly (28%) with *p*-benzyloxyphenylboronic acid under the standard reaction conditions (entry 2). It was found that switching the base from K_2CO_3 to Cs_2CO_3 and lowering reaction temperature to rt led to a significant improvement of yield (80%). Longer reaction times did not help in enhancing reaction yields for boronic acids possessing electron-withdrawing moieties (entries 9 and 10). In contrast, a considerable amount (ca. 10%) of monoreduction and dicoupling reduction phenol products were obtained as byproducts. Addition of Ag_2O did not result in improved reaction yields but instead suppressed the formation of the byproduct.[15] Probing steric effects indicated that the impact was limited (entry 5). Finally, the catalytic system worked smoothly for the heterocylic boronic acid substrate as well (entry 11).

Having successfully established the protocol for producing a monocoupling product, we shifted our focus to the second Suzuki coupling process with the aim of further diversifying the 2-arylbenzoquinones (**5**). After extensive exploration of reaction conditions including catalyst screening and loading, solvents, and bases using **5a** reacting with 4-methoxyphenylboronic acid as a model system, we found that the cross-coupling process could be accomplished in high yield (84%) with the same catalyst $PdCl_2$(dppf) (2 mol %) but in toluene and CsF as base (Table 3, entry 1). It is noteworthy that higher catalyst loading (e.g., 5 mol %) gave rise to a pronounced amount of reduction phenol product. As demonstrated, the optimized reaction conditions served as a general approach to the preparation of the corresponding unsymmetrical 3,5-diarylbenzoquinones (**6**). Various boronic acids with different electronic and steric features could be tolerated in the process. High to excellent yields were achieved (entries 1−8, 84−96%). Heterocyclic susbtrate could also participate in the process despite relatively low reaction yield (entry 9).

To further demonstrate the versatility of the synthetic strategy, we also investigated a one-step bis-Suzuki reaction of 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone (**3**) with boronic acids (Scheme 2). During the course of our study of these Suzuki coupling reactions, we found that the major side reaction was the reduced phenol of bromosubstrates. This insight prompted us to add Ag_2O to suppress the formation of reductive products.[15] Indeed, it was shown that one-pot process was successfully developed for efficient preparation of the symmetrical disubstituted benzoquinones in good yields (64% and 72%, respectively).

Finally, we demonstrated the synthetic utility of the powerful strategy for three-step synthesis of natural product

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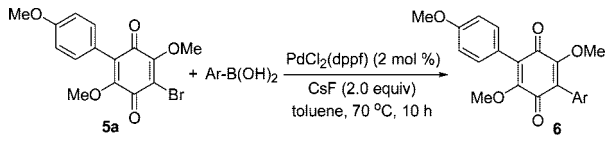
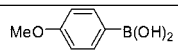
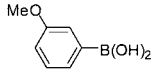
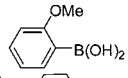
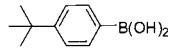
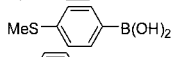
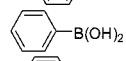
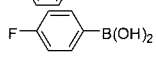
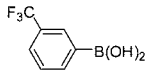
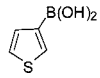
Table 3. Suzuki Monocoupling of 5-Aryl-2-bromo-3,6-dimethoxy-1,4-benzoquinone (**5a**) with Boronic Acids



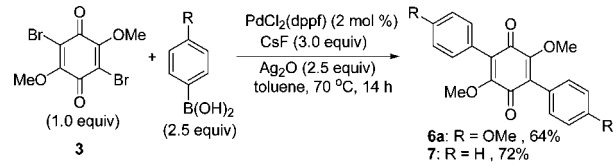
bntry	boronic acid	product	yield (%)[b]
1		**6a**	84
2		**6b**	84
3		**6c**	92
4		**6d**	95
5		**6e**	96
6		**6f**	95
7		**6g**	87
8		**6h**	86
9[c]		**6i**	53

[a] Unless specified, reaction conditions: 1.5 equiv of boronic acid, 2 mol % of $PdCl_2$(dppf), CsF (2.0 equiv), toluene, 70 °C, 10 h. [b] Isolated yields. [c] Conditions: 1.5 equiv of boronic acid, 5 mol % of $PdCl_2$(dppf), CsF (2.0 equiv), toluene, 70 °C, 10 h.

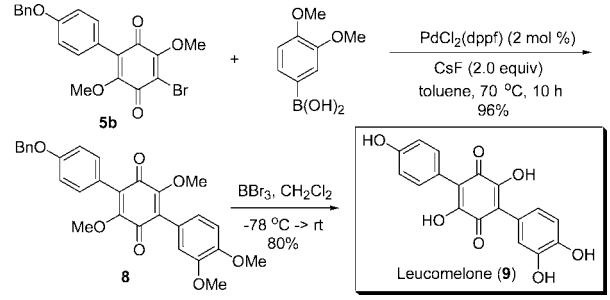
leucomelone (**9**) in 61% overall yield from readily available **3** (Scheme 3).[16]

In conclusion, we have developed a new, convergent, and versatile synthetic strategy for efficient synthesis of 2,5-disubstituted 3,6-methoxy-1,4-benzoquinones from readily available molecules. By careful manipulation of the Suzuki cross-coupling reaction conditions, it is possible to chemoselectively introduce aromatic components into dihalogenated benzoquinone scaffolds. This approach can be used to rapidly construct the medicinally interesting, structurally diversified terphenylquinones or terphenylhydroquinones for biological studies.

Scheme 2. Suzuki Dicoupling of 2,5-Dibromo-3,6-dimethoxy-1,4-benzoquinone (**2**) with Boronic Acids



Scheme 3. Total Synthesis of Leucomelone (**9**)



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Supporting Information Available: Experimental procedures; ^{1}H NMR and ^{13}C NMR data and spectra of **5a**−**k**, **6a**−**i**, and **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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