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Versatile Biaryls and Fused Aromatics through Oxidative Coupling of Hydroquinones with (Hetero)Arenes

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Hydroquinones bearing an electron-withdrawing group at the C2-position can effectively underwent oxidative coupling with (hetero)arenes (e.g., indoles, electron-rich benzene derivatives) in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and $FeCl_3$ to produce the corresponding biaryl products. In the present reactions, the DDQ-mediated oxidation of hydroquinone derivatives produce benzoquinone intermediate, which subsequently underwent $FeCl_3$-catalyzed nucleophilic addition of (hetero)arenes to the α,β-unsaturated carbonyl moiety to give the biaryl product in a one-pot manner. Especially, the indole-based biaryl products were further converted into tetracyclic aromatics through DDQ-mediated oxidation followed by $FeCl_3$-catalyzed intramolecular cyclization. Thiophene derivatives were also applicable to give the tetracyclic aromatics. Moreover, the photophysical properties of the indole- and thiophene-based tetracyclic aromatics in the solution and the solid states were investigated.

Introduction

Biaryls (compounds with benzene-benzene, benzene-indole, etc. units) and multi-fused aromatic heterocycles are the basic backbones of biologically active substances, natural products, and functional materials such as organic light-emitting diodes (OLEDs) (Figure 1).[1–4] For example, fluvastatin[1] (a HMG-CoA reductase inhibitor that is used to treat hypercholesterolemia) and azilsartan[2] (an angiotensin II receptor blocker used to treat hypertension) have a biaryl moiety in their structure. Azonazine,[3] isolated from a fungus in the Hawaiian marine sediments, has a tetracyclic fused dihydrobenzofuran-indoline moiety. Benzofuran-indole-fused tetracycle A[4] is expected to be a raw material for OLEDs. Therefore, it is important to

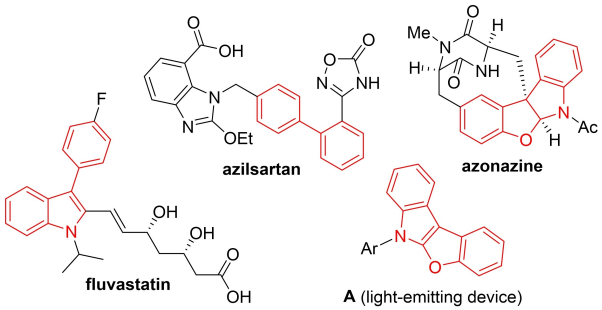

Figure 1. Structures of some useful compounds bearing biaryl and multi-fused aromatic backbones.

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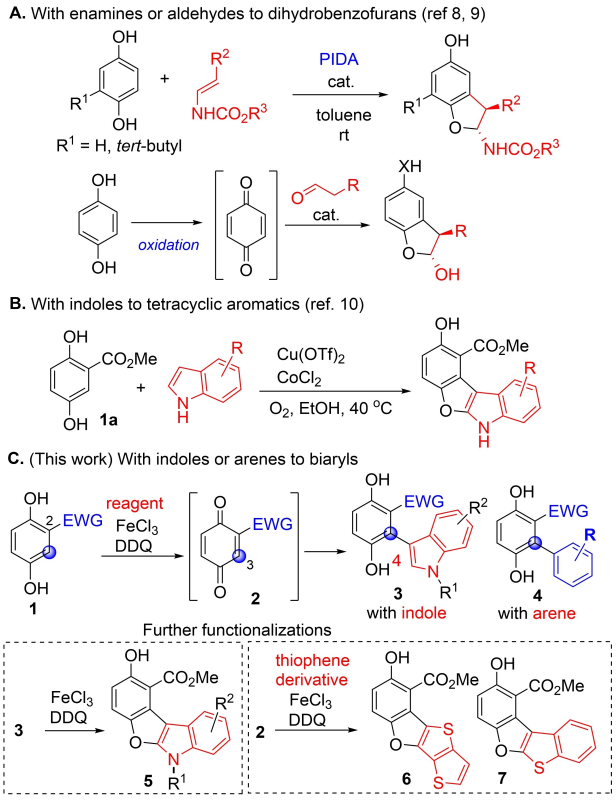
develop efficient and systematic synthetic methods to construct these highly functionalized aromatic derivatives.

Hydroquinone can be easily modified by the Friedel–Crafts type reaction to the corresponding C2-functionalized hydroquinone (e.g., electron-withdrawing group substituted at the C2 position; **1**, Scheme 1C).[5] Moreover, benzoquinones (**2**), which are the oxidized forms of hydroquinones, can undergo nucleophilic addition on their α,β-unsaturated carbonyl moieties to give the corresponding benzene-fused products in a stepwise manner from hydroquinone.[6] On the other hand, tandem reactions are valuable as environmentally friendly methods, as they do not require isolation and purification of reaction intermediates, thereby reducing the amount of wastes generated during the isolation of these intermediates.[7] Particularly, one-pot oxidative functionalizations of hydroquinones can be a powerful and straightforward tool to synthesize versatile aromatic products. Masson[8] and Jørgensen[9] have reported the asymmetric and oxidative one-pot reactions of hydroquinones with enamines and aliphatic aldehydes to construct dihydrobenzofuran derivatives (Scheme 1A). Furthermore, Zhong have recently developed the one-pot synthesis of tetracyclic aromatics from 2-methoxycarbonyl hydroquinone (**1a**) and indoles, without the isolation of any reaction intermediates, in the presence of copper and cobalt co-catalysts under atmospheric molecular oxygen (Scheme 1B).[10] This transformation is realized by well-designed co-catalytic system, and thus considerably environmentally benign method to obtain cyclic compounds. However, to the best of our knowledge, there are no reports on the oxidative one-pot synthesis of biaryls from hydroquinones, bearing some electron-withdrawing groups (2-methoxycarbonyl, 2-acetyl, 2-formyl, 2-cyano and 2-nitro).

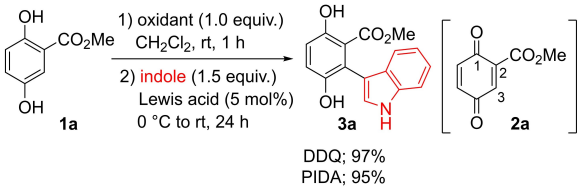
Herein, we report a novel oxidative coupling reaction of hydroquinones (**1**) with indole and electron-rich benzene derivatives to construct highly functionalized biaryls **3** and **4** in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and $FeCl_3$ as an oxidant and Lewis acid, respectively (Scheme 1C). Benzene-indole type biaryls **3** underwent further oxidative cyclization to benzofuran-indole-fused tetracyclic aromatics **5** in a stepwise manner. Benzofuran-thiophene derivative-fused tetracycles **6** and **7** could be directly constructed from benzoquinone (**2**) in a one-pot manner. Additionally, tetracyclic products **5–7** exhibited luminescence.



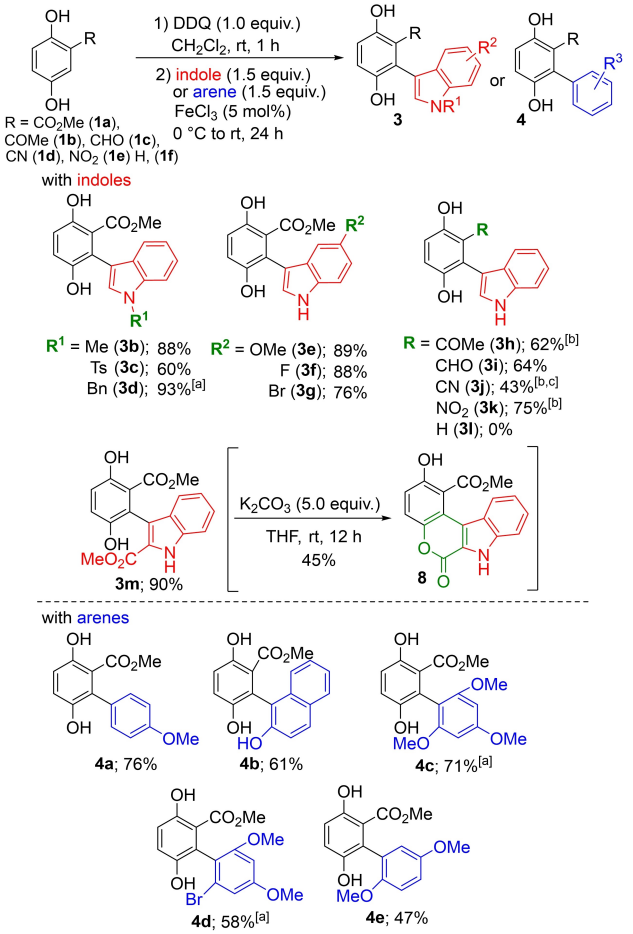
Scheme 1. Oxidative couplings of hydroquinones.

Results and Discussion

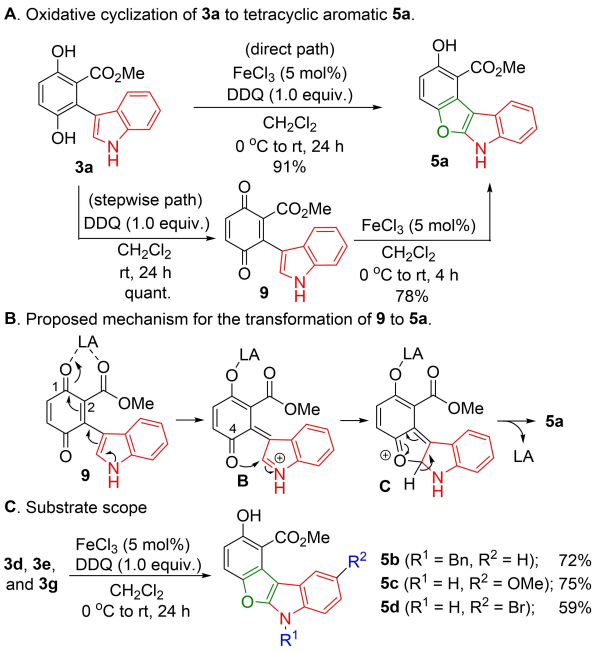
First, the oxidative coupling of **1a** with indole was investigated (eq. 1). The oxidation of **1a** with DDQ produced the corresponding 2-methoxycarbonyl benzoquinone intermediate **2a**, which underwent the $FeCl_3$-catalyzed site-selective nucleophilic addition of indole at the C3 position of **2a** to give the desired biaryl product **3a** in 97% yield. This site-selectivity was attributed to the increased electrophilicity at the C3 position of **2a** owing to the electron-withdrawing ester group substituted at the C2 position. Phenyliodine (III) diacetate (PIDA) also acted as an effective oxidant to give **3a** in 95% yield. The effects of other Lewis acids and oxidants are described in Table S1.



Next, the substrate scope of the indole nucleophiles and hydroquinones was investigated in the presence of DDQ (or PIDA)[11] and $FeCl_3$ (Scheme 2). When using *N*-methyl-, *N*-tosyl-, *N*-benzyl-, 5-methoxy-, 5-fluoro-, and 5-bromo indoles as nucleophiles with **1a**, the corresponding biaryl products **3b–3g** were obtained in good to excellent yields. 2-Methoxycarbonyl indole was also applicable to this reaction, affording biaryl **3m** that could be transformed into indole-fused 2-chromanone **8** as an important skeleton bearing bioactivity[12,13] by intramolecular cyclization between a hydroxy group and ester moiety under basic conditions. Furthermore, 2-acetyl-, 2-formyl, 2-cyano- and 2-nitro-hydroquinones **1b–1e** underwent oxidative coupling with indole to give the corresponding biaryls **3h–3k**, respectively. On the other hand, hydroquinone **1f** was not converted to biaryl **3l** because of the poor electrophilicity at the C3 position. Notably, electron-rich benzene derivatives could also be used instead of indole in the present oxidative coupling of **1a**. Anisole, 2-hydroxynaphthalene, 1,3,5-trimethoxybenzene, 1-bromo-3,5-dimethoxybenzene, and 1,4-dimethoxybenzene acted as nucleophiles to afford biaryls **4a–4e** in moderate to



Scheme 2. Investigation of substrate scope. [a] PIDA (1.0 equiv.) was used instead of DDQ. [b] THF was used instead of CH_2Cl_2. [c] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.



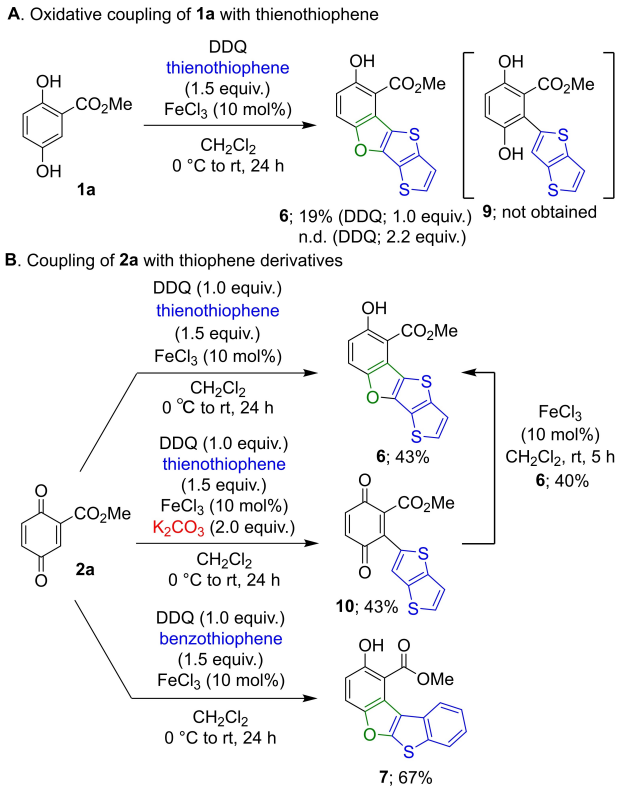
Scheme 3. Transformation of **3** to tetracyclic arene **5**. LA denotes Lewis acid.

good yields. *N*,*N*-dimethylaniline and thiophene were inapplicable as nucleophiles.

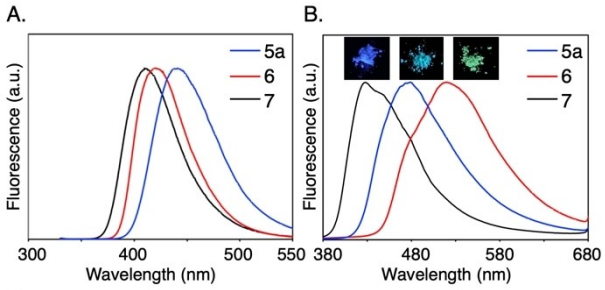
Indole-based biaryl **3a** was successfully converted to tetracyclic aromatic product **5a** in 91% yield in the presence of DDQ and catalytic $FeCl_3$ (Scheme 3A; direct path). This transformation can proceed via the oxidation of **3a** to benzoquinone **9**, followed by the $FeCl_3$-catalyzed cyclization of **9** to **5a** (stepwise path). The transformation of **9** to **5a** can be facilitated by the coordination of $FeCl_3$ as a Lewis acid to the two carbonyl moieties at the C1 position and the ester moiety at the C2 position of **9** (Scheme 3B). Reaction intermediate **B** was formed subsequently by the donation of the lone pair of electrons on the N atom of indole. The subsequent intramolecular nucleophilic attack of the carbonyl oxygen at the C4 position of **B** to the iminium moiety produced **C**. Finally, aromatization of **C** gave **5a**. Compounds **3d**, **3e**, and **3g** were also applicable as substrates in this reaction, affording the corresponding tetracyclic aromatic products **5b**–**5d** in good yields (Scheme 3C). Using the present oxidative coupling methods, versatile biaryls and tetracyclic aromatics could be constructed. Although **5a**–**5d** could be directly constructed by Zhong's method in Scheme 1-B,[10] our methodology has the advantage of applying the coupling reaction using thiophene derivatives instead of indoles, as shown in the next section.

The developed method was next applied for coupling using thiophene derivatives. The oxidative coupling of **1a** with thieno[3,2-*b*]thiophene in the presence of 1.0 equiv. of DDQ and catalytic $FeCl_3$ directly gave tetracyclic product **6**[14] in 19% yield, without the generation of biaryl **9**, unlike the case using indole (Scheme 4A). When the DDQ increased to 2.2 equiv., a complex mixture was obtained (Scheme 4B). Meanwhile, the reaction using benzoquinone **2a** as a substrate furnished **6** in 43% yield. The addition of K_2CO_3 suppressed the cyclization to give 3-thienothiophene-substituted benzoquinone **10** in 43% yield. This is because K_2CO_3 lowered the Lewis acidity of $FeCl_3$. The cyclization of **10** was catalyzed by $FeCl_3$ to afford **6** in 40% yield. Furthermore, the use of benzothiophene gave another type of tetracyclic aromatic product **7**[15] in 67% yield. Although low to moderate yields were obtained, novel tetracyclic aromatics bearing a thiophene skeleton could be synthesized using the developed oxidative coupling reactions.

Because Zhong have reported that a solution of **5** (2×10^{-5} M in toluene) shows blue-light emission at a wavelength of *ca.* 426 nm,[10] we also turned our attention to the photophysical properties of newly prepared compounds **6** and **7** (Figure. 2). Therefore, we investigated the photophysical properties of **5a**, **6** and **7** in the solution ($CHCl_3$ and toluene) and solid states. Figure 2A shows the fluorescence spectra in $CHCl_3$ as a representative (the fluorescence spectra in toluene are shown in Fig. S3). The fluorescence maximum decreased in the order **5a** (λ_{fl} = 441 nm) > **6** (λ_{fl} = 420 nm) > and **7** (λ_{fl} = 410 nm). The relative fluorescence quantum yields of **5a**, **6**, and **7** in $CHCl_3$ were 47%, 26%, and 6%, respectively (see absorption spectra of **5a**, **6**, and **7** in CH_2Cl_2 in Figure S4). Among the three compounds, the longest fluorescence maximum wavelength



Scheme 4. Oxidative coupling with thiophene derivatives. n.d denotes 'not detected.'



C.

	λ_{fl} [nm] Solution			Φ_{fl} [%] Solution[a]		
Entry	$CHCl_3$	Toluene	Solid	$CHCl_3$	Toluene	Solid
5a	441	425	479	47	53	12
6	420	416	521	26	31	8
7	410	404	428	6	6	9

Figure 2. (A) Normalized fluorescence spectra of **5a**, **6**, and **7** in $CHCl_3$. (B) Solid-state fluorescence spectra of **5a**, **6**, and **7**. Insets show the photographs of **5a**, **6**, and **7** under 365-nm irradiation. (C) Photophysical data of **5a**, **6**, and **7** in solution and solid state. [a]The relative fluorescence quantum yield (Φ_{fl}) was measured upon excitation at 366 nm using quinine sulfate (Φ_{fl} = 55% in 0.1 M H_2SO_4) as a reference material.

was observed for **6** in the solid state. Compound **6** exhibited green fluorescence, with a fluorescence maximum at 520 nm (Figure 2B). The photophysical data of these compounds are summarized in Figure 2C. The results indicate that the incorporation of thienothiophene units into benzofuran extends the π-conjugation, endowing unique optical properties in the solid state.

Conclusions

We have developed the oxidative coupling of hydroquinones bearing an electron-withdrawing group at the C2 position with (hetero)aromatics to afford biaryl products as pharmaceutically useful backbones. Furthermore, tetracyclic aromatics derived from indole and thiophene derivatives were constructed. The developed synthetic methodology can be a powerful tool for the flexible design of various polycyclic aromatics that have applications as functional luminescent materials.

Supporting Information

The authors have cited additional references within the Supporting Information.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article. Crystallographic coordinates of the compound **6** are deposited to CCDC (ID 2294744) and COD (3000464). MicroED raw diffraction images are available at XRDa (ID 162).

Keywords: Benzoquinones · Biaryls · Heterocycles · Lewis acids

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[14] The substitution position of thienothiophene to form **6** was determined from its nanocrystals by MicroED (see SI), because a single crystal of **6** large enough for our in-house X-ray diffractometer could not be obtained. The microcrystals of **6** were bent and plate-like, and the data quality was limited by streaking of the diffraction spots and twinning. Nonetheless, the resulting map showed the structure of **6** unambiguously. The assignment by MicroED was also supported by chemical modification of thienothiophene to di-deuterated thienothiophene and the following similar reaction as shown in Scheme 5 (see SI). Nucleophilicity of the C2 position on a thiophene is known to be higher than that of the C3 position. Probably, the nucleophilic properties of thienothiophene and those of thiophene are similar to each other.
[15] The structure was determined by NOE experiments (SI). Nucleophilicity of the C3 position on benzothiophene is known to be high, similar to the case of indole.

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