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Suzuki Cross Coupling followed by Cross Dehydrogenative Coupling: An Efficient One Pot Synthesis of Phenanthrenequinones and Analogues

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Abstract: An efficient one pot protocol has been developed towards the synthesis of substituted phenanthrenequinone and analogous derivatives *via* Suzuki cross coupling followed by copper catalyzed cross dehydrogenative coupling.

Keywords: Phenanthrenequinone, One pot reaction, Suzuki coupling, Cross dehydrogenative coupling.

9,10-Phenanthrenequinones are important structural confirmations found in a plethora of natural, metabolic, or synthetic products and other biologically active molecules. For example Biruloquinone,[1a,b] isolated from *Cladonia macilenta*, a lichen forming fungus, has been found to display inhibition capacity towards acetylcholinase. Bulbophyllanthrone[1c] has been analyzed to exhibit antiproliferative activity towards P388 murine leukemia as well as BSC cell lines. Phenanthrenequinones have also been explored as elementary unit in many research works such as in electron accepting polymers,[2a] polytriphenylene dendrimers emitting blue light,[2b] phenazine derivatives in liquid crystalline form,[2c] 2,2' -diacyl-1,1' –biaryls with high functionalizations[2d] and fluorenone derivatives.[2e] They have also been studied for sensing urea and amides[2f] and also for the inhibition for tyrosin phosphatase CD45.[2g] The metal complexes of 9,10-phenanthrenequinone diimine displays sequence-specific recognition of DNA[2h] and have been studied for the development of artificial nucleases for shape-selective DNA photo cleavage.[2i] Phenanthrenequinone thiosemicarbazone itself and its metal complexes of have been investigated as potential anticancer agents.[2j]

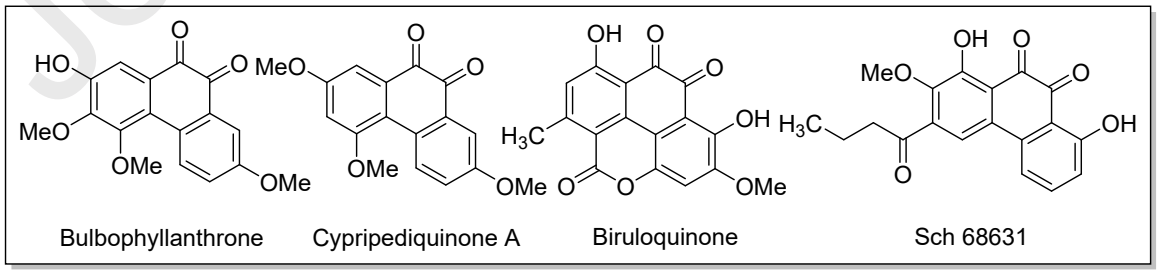


Figure 1: Some promising bioactive molecules containing phenanthrenequinone

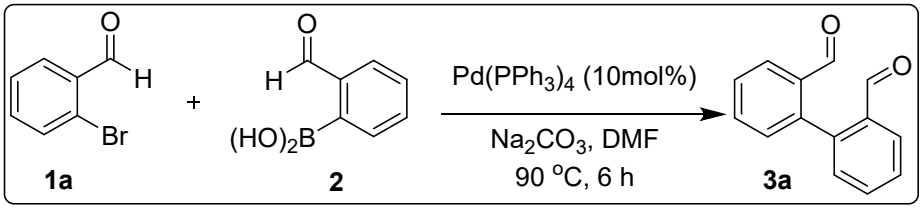
Due to such tremendous applications synthesis of 9,10-phenanthrenequinone has attracted attention of synthetic chemists from early decades to modern age. Traditional approach for the synthesis of 9,10-phenanthrenequinone depends upon oxidation of different phenanthrenes with various oxidizing agents.[3,4] Oxidation of phenanthrene based molecules such as 10-hydroxyphenanthren-9(10H)- ones,[5] 9,10- dihydrophenanthrenes,[6] phenanthrene-9,10-diol[7] and 9-phenanthrenols[8] has also been explored as an alternative method. Intramolecular oxidative coupling of benzils by different oxidants e.g. thallium (III) oxide and vanadium (V) oxyfluoride,[9] $MoCl_5/TiCl_4$ mixture,[10] potassium-graphite intercalation compound,[11] C_8K[12] etc has also been studied by different groups. Imidazolides were subjected towards intramolecular Friedel−Crafts reaction by $TiCl_4$ to produce the corresponding phenanthroquinones as reported by Yoshikawa and co-workers.[13] Other nonphenanthrene-based resources such as 2- acetylbiphenyls,[14] benzoins,[12,15] benzils,[11,16] dimethyl biphenyl-2,2′-dicarboxylate[17] or 2,2′-dilithiobiphenyl[18] have also been examined to construct the phenanthrenequinone skeleton. One of the most recent transformation includes Cu(0)-Selectflour catalyzed synthesis from *o*-aryl chalcones.[19]

Most of the synthetic strategies include use of toxic reagents, relatively expensive catalysts, harsh reaction conditions and prolonged reaction time. Other drawbacks are employment of multistep operations, strain in the preparation of substrates with various functionalities and low yields of the products.

Now one pot technique has manifested as a robust procedure in terms of resource and energy efficiency as well as environmental sustainability as several synthetic transformations can be performed within a single pot. The one pot strategy reduces chemical waste and rationalizes practical aspects.

Herein we have reported an efficient one pot synthesis of 9,10-Phenanthrenequinones from easily accessible starting materials within a very fast reaction time. The technique described here allows the construction of 9,10-Phenanthrenequinones with a diverse range of functionalities in good to excellent yields.

Initially 2-bromobenzaldehyde (**1a**) was selected as the model structure for our study. First **1a** was subjected towards Suzuki coupling with 2-formylphenylboronic acid (**2**) under standard Pd(0) conditions (Scheme 1). Formation of **3a** was observed under standardized Suzuki reaction condition and confirmed by data in accordance with literature reports.



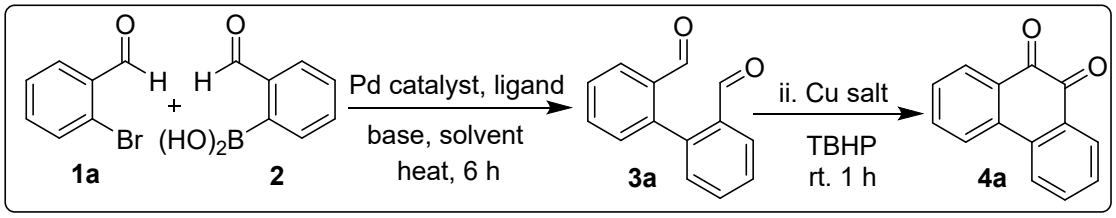
Scheme 1: Suzuki cross coupling reaction

Next our target was to find a suitable reaction condition for cyclization of the Suzuki coupled product to form the desired quinone skeleton. After thorough survey of recent literature reports it was found that cross-dehydrogenative coupling (CDC) is a powerful method to transform two less reactive C-H bonds into C-C bond in a selective manner in presence of various functional groups.[20] This coupling can be carried out in presence of cheap catalysts e.g. copper and iron salts as well as different oxidizing agents e.g. *tert*-butylhydroperoxide, hydrogen peroxide, dioxygen 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Moreover this technique does not require pre-functionalization or preactivation of C-H bonds. So we envisioned that our Suzuki coupled product (**3a**) which contains two C-H bonds in close proximity should undergo cyclization when subjected towards reaction conditions for CDC coupling. For this purpose after the completion of the Suzuki coupling, monitored by TLC, **3a** formed in the reaction mixture was treated with Cu salt and TBHP. To our much delight we observed the formation of 9,10-Phenanthrenequinone (**4a**) along with the consumption of the starting material in a rapid and fast process within 1 hr.

Next our task was to determine the optimal condition for the one pot operation. A series of reaction conditions was established and scrutinized to attain the optimized reaction condition for the one pot analysis.

To study the optimization for the one pot method different set of Pd, Cu catalysts, bases and solvents were introduced and investigated under the reaction condition. Different palladium complexes such as $Pd(PPh_3)_4$, $PdCl_2$, $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ were analyzed. $Pd(PPh_3)_2Cl_2$ was found to be the most promising one for the one pot technique along with K_3PO_4 as the base among different bases such as Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOAc etc. Next for the CDC reaction an array of various Cu catalysts i. e. CuCl, CuBr, CuI, $Cu(OAc)_2$ and even $CuCl_2$ were employed one by one and examined to find CuCl as the most effective catalyst. After that different types and amount of oxidants were also varied for the investigation. Among TBHP, H_2O_2 and m-CPBA TBHP in 3 equivalent gave the highest yield of the product. Effect of solvent was also studied. Under standard Suzuki coupling carried out in DMF solvent when Cu catalyst and the additive were added the CDC coupling did not take place efficiently. Other solvents like acetonitrile or dioxane when employed the yield was a little better but also not satisfactory. An excellent result was furnished when DMSO was incorporated as the solvent and explored. Final inspection was done to obtain the amount of the Cu catalyst and it was observed that in presence of CuCl in 5 mol% the reaction produced the product in highest yield. When the reaction was performed in absence of any catalyst, the reaction did not take place which indicates the subsistence nature of the Cu catalyst.

Table 1: Optimal condition determination for the one –pot cyclization[a, b]



Entry	Pd Catalyst	Ligand	Base	Cu Catalyst	Oxidant	Solvent	Yield (%)[c]
1	$Pd(PPh_3)_4$	-	Na_2CO_3	CuCl (10)	TBHP (3)	DMF	<10
2	$Pd(PPh_3)_4$	-	K_2CO_3	CuCl (10)	TBHP (3)	DMF	<10
3	$Pd(PPh_3)_4$	-	Cs_2CO_3	CuCl (10)	TBHP (3)	DMF	<10
4	$Pd(PPh_3)_4$	-	NaOAc	CuCl (10)	TBHP (3)	DMSO	40
5	$Pd(PPh_3)_4$	-	K_3PO_4	CuCl (10)	TBHP (3)	DMSO	55
6	$PdCl_2$	PPh_3	K_3PO_4	CuCl (10)	TBHP (3)	DMSO	58
7	$Pd(OAC)_2$	PPh_3	K_3PO_4	CuCl (10)	TBHP (3)	DMSO	65
8	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (10)	TBHP (3)	DMSO	80
9	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (10)	TBHP (3)	CH_3CN	55
10	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (10)	TBHP (3)	Dioxane	25
11	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuBr (10)	TBHP (3)	DMSO	58
12	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuI (10)	TBHP (3)	DMSO	<10
13	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	$Cu(OAc)_2$ (10)	TBHP (3)	DMSO	24
14	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	$CuCl_2$ (10)	TBHP (3)	DMSO	42
15	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (10)	m-CPBA (3)	DMSO	40
16	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (10)	H_2O_2 (3)	DMSO	24
17	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (20)	TBHP (3)	DMSO	75
18	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (30)	TBHP (3)	DMSO	70
19	**$Pd(PPh_3)_2Cl_2$**	-	**K_3PO_4**	**CuCl (5)**	**TBHP (3)**	**DMSO**	**85**
20	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	-	TBHP (3)	DMSO	N. R.

Entry	Pd Catalyst	Ligand	Base	Cu Catalyst	Oxidant	Solvent	Yield (%)[c]
21	**$Pd(PPh_3)_2Cl_2$**	**-**	**K_3PO_4**	**CuCl (5)**	**TBHP (5)**	**DMSO**	**85**
22	$Pd(PPh_3)_2Cl_2$	-	K_3PO_4	CuCl (10)	TBHP (1)	DMSO	75

[a] Reagents and conditions: **1a** (1 mmol), **2** (1.2 mmol), Pd catalyst (10 mol%), base (1.5 mmol), in 5 mL DMSO at 90 °C for 6 h. (ii) Cu salt, oxidant, 1 h at rt.

[b] Reaction was done in a two-necked round-bottomed flask under N_2 atmosphere.

[c] Yields refer to the isolated yields after purification through column chromatography.

N. R. = no reaction

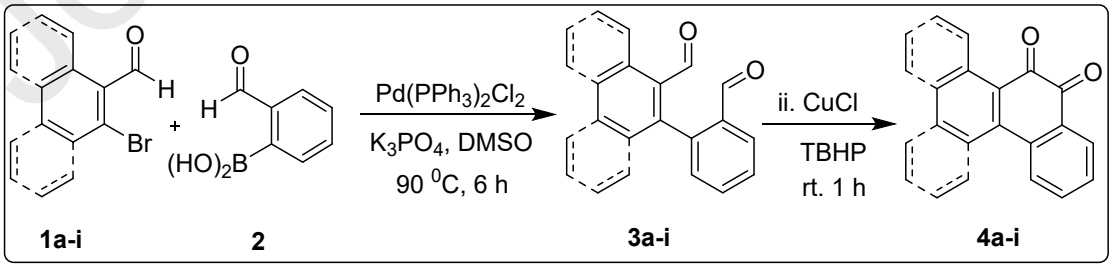
Next to evaluate the scope of this assessment further, various 2-bromobenzaldehydes (**1a-i**) were tested under the optimized reaction conditions established above (entry 21 in Table 1).

It was perceived that the protocol prosecuted smoothly to furnish different 9,10-Phenanthrenequinones with diverse functionalities **(4a-i)** in moderate to good yields (Table 2).

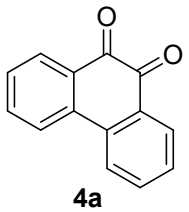
Table 2 illustrates the extension of the methodology to the formation of different 9,10-Phenanthrenequinones containing various substituents. Products containing electron donating groups were furnished in higher yields whereas electron withdrawing group $–NO_2$ drastically decrease the yield of the product.

The reaction is believed to proceed through radical pathway. As TBHP is well known to produce *t*-Butyloxy radical and hydroxyl radical in presence of metal catalysts.[21] The ^tBuO radical thus produced can abstract the acyl hydrogen from the substrate to form acyl radical.[22] Next the acyl radical is responsible for the next transformations.

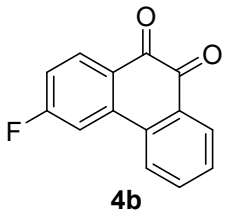
Table 2: Exploration of substrates scope [a,b]



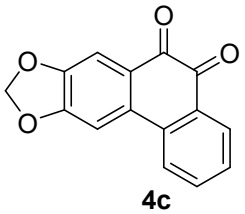
Scheme 2: Synthesis of assorted 9,10-Phenanthrenequinones



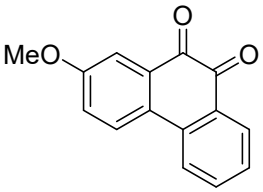
4a
(85%)



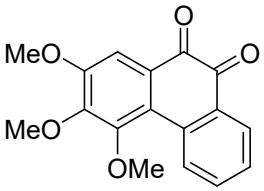
4b
(80%)



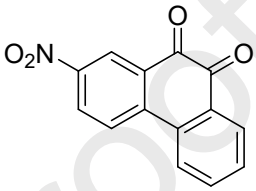
4c
(85%)



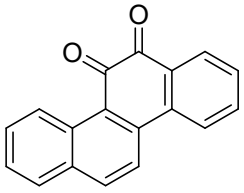
4d
(90%)



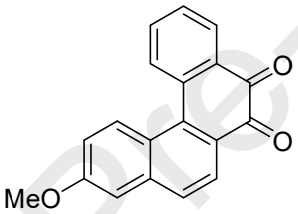
4e
(86%)



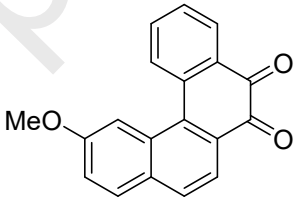
4f
(75%)



4g
(85%)



4h
(86%)



4i
(88%)

[a]All the reactions were carried out with (i) **1a-i** (1 mmol), **2** (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%), K_3PO_4 (1.5 mmol), in 5 mL DMSO at 90 ^oC for 6 h. (ii) CuCl (5 mol%), TBHP (3 equivalent), 1 h at rt.

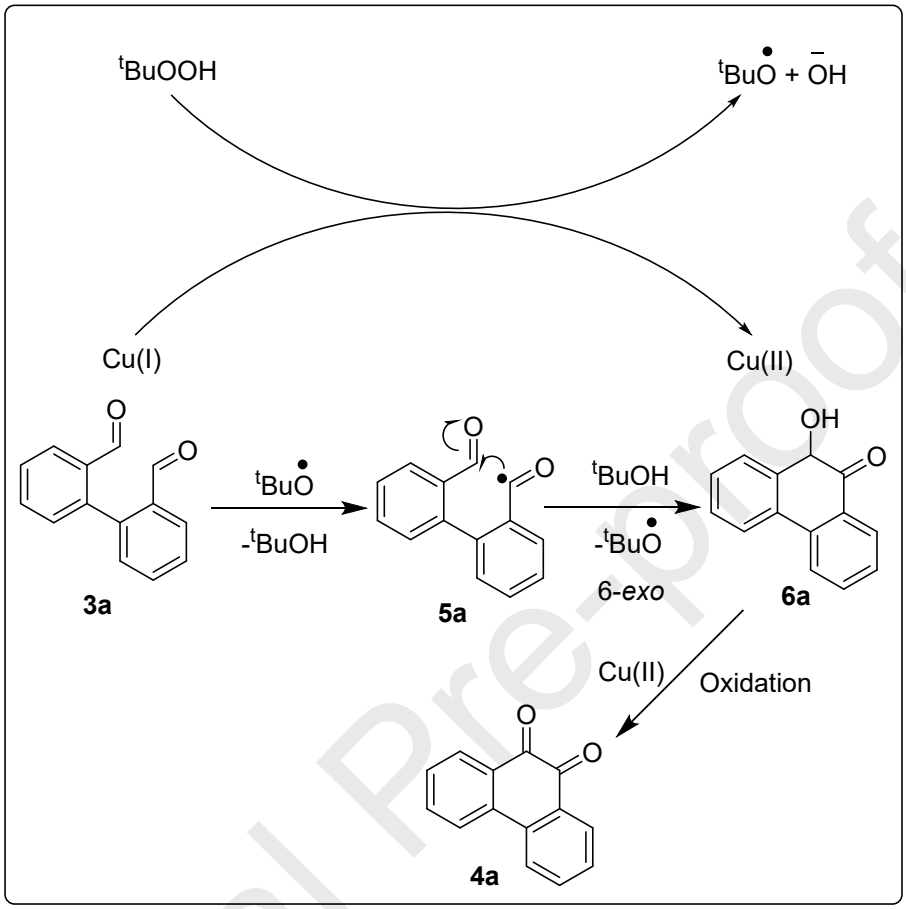
[b]Isolated yields.

However this two step one-pot methodology was found restricted for β-bromo carbaldehydes containing chromene or thiochromene skeletons as they produced inseparable mixture of various products under this described reaction condition.

Proposed Mechanism

A proposed mechanism is illustrated in Scheme 3. At first TBHP produces *t*-Butyloxy radical and hydroxyl radical in presence of Cu(I). Then the formyl hydrogen of the substrate (**3a**) is abstracted by ^tBuO radical to form the acyl radical **5a**. Next this acyl radical will undergo 6-exo

cyclization to form the intermediate **6a**. The final step is the oxidation by Cu(II) to afford the final phenathrenequinone **4a**.



Scheme 3: Proposed mechanism

Conclusion

Thus we were able to open up an interesting and feasible avenue for the formation of 9,10-Phenanthrenequinones from easily accessible starting materials. The construction is highly adaptive and customizable. Also this strategy includes fewer synthetic steps which are simple and trouble-free to perform. The one pot synthesis of 9,10-Phenanthrenequinone which includes Suzuki cross coupling followed by cross dehydrogenative coupling has been well established and it diminishes total number of actions in the overall synthetic procedures along with maximum transfer of mass from the substrate to the product.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedure and spectral data for the final compounds **4a-i**) associated with this article can be found, in the online version, at

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23. **General procedure for the synthesis of phenanthrenequinone:** 2-bromobenzaldehyde (1 mmol), 2-formylphenylboronic acid (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (10 mol%) and K_3PO_4 (1.5 mmol) was taken in a two neck round bottomed flask. 5 mL DMSO was added to it and the reaction mixture was degassed properly with N_2. Next the reaction was allowed to stir at 90^oC for 6h. After the completion of the reaction, the reaction mixture was cooled to room temperature and to it were added CuCl (5 mol %) and TBHP (3 equivalent). It was stirred for another 1 h at rt. Then it was diluted with water and extracted with ethyl acetate several times. The organic parts were collected together and concentrated under vacuum after drying over Na_2SO_4. Products were purified by column chromatography using 60-120 mesh silica gel and 5:1 pet ether : ethyl acetate as the eluent.

24. **Spectral data of representative compound, phenanthro[3,2-d][1,3]dioxole-5,6-dione (4c):** orange solid, yield 85%, m.p. greater than 200 ^oC.^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.54 (s, 1H), 7.42-7.38 (m, 1H), 7.36 (s, 1H), 6.11 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.40, 178.38, 154.88, 149.10, 136.07, 135.74, 134.78, 130.44, 130.37, 129.24, 126.97, 124.80, 109.14, 104.82, 102.75. HRMS (ESI-TOF): $[M + Na]^+$ calculated for $C_{15}H_8O_4Na$: 275.0320; found: 275.0316.

- An effective one pot technique has been designed to afford 9,10-phenanthrenequinones.

- Suzuki cross coupling and cross dehydrogenative coupling are the two key steps.
- Precursors are simple and readily accessible.
- Reaction conditions are mild, short and very easy to perform.

Graphical Abstract

Suzuki Cross Coupling followed by Cross

Dehydrogenative Coupling: An Efficient One Pot Synthesis of

Phenanthrenequinones and Analogues

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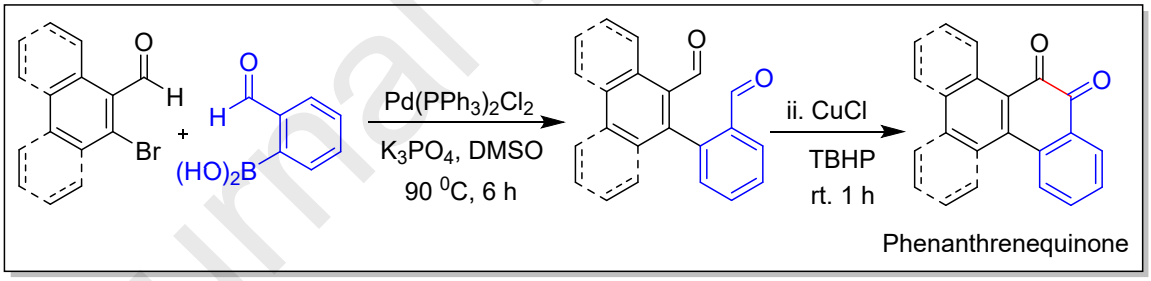

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.