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Synthesis of Highly Functionalized 9,10-Phenanthrenequinones by Oxidative Coupling Using $MoCl_5$

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ABSTRACT

The strong oxidative power of molybdenum pentachloride gives rise to an efficient oxidative C−C bond formation of benzil derivatives to the corresponding 9,10-phenanthrenequinones. A highly complementary method to previous approaches was developed. The required derivatives are accessible in a modular fashion and in excellent yields. By this approach the orchid-derived natural product cypripediquinone A was synthesized for the first time.

9,10-Phenanthrenequinones are important moieties and building blocks for a variety of current research efforts such as in light-emitting or conducting polymers,[1] as precursors for macromolecular architectures like blue light emitting polytriphenylene dendrimers,[2] or for synthesis of medicinally relevant phenanthro[9,10-*d*]imidazoles.[3] Furthermore, 9,10-phenanthrenequinones turned out to be key intermediates for the scaffold of dicotic and columnar liquid crystalline phenazine derivatives,[4] highly functionalized 2,2′-diacyl-1,1′-biaryls,[5] and fluorenone derivatives.[6] Phenanthrenequinones can be used as receptors for urea or amines[7] or as inhibitors for the protein tyrosin phosphatase CD45.[8]

Phenanthrenequinones were isolated from several orchids. Bulbophyllanthrone (2-hydroxy-3,4,7-trimethoxy-9,10-phenanthrenequinone) is a cytotoxic compound found in the orchids *Bulbophyllum odoratissimum* as well as in *Earina autumnalis* and exhibits high activity toward P388 murine leukemia and BSC cell lines.[9,10] Another naturally occurring 9,10-phenanthrenequinone, which was isolated from *Cypripedium macranthum* (orchid), is cypripediquinone A.[11]

Common synthetic strategies to 9,10-phenanthrenequinones are based on the oxidation of corresponding phenanthrenes with strong oxidizers like CrO_3[12] or iodic

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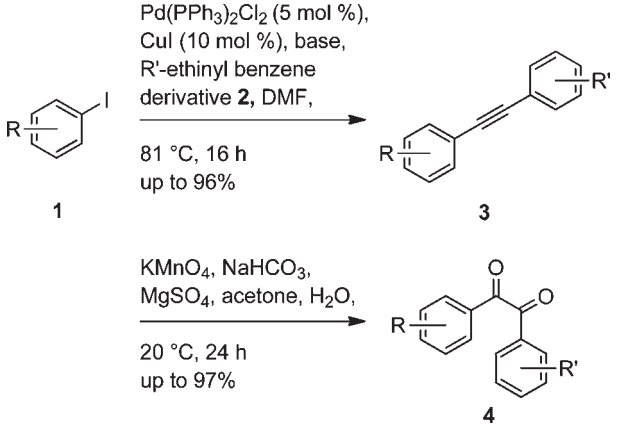
acid.[13] The oxidative coupling of benzil derivatives was previously demonstrated using highly toxic and relatively expensive thallium and vanadium reagents.[14] The closure of the central ring can be reductively accomplished by potassium graphite[15] or under drastic Scholl-type conditions using aluminum chloride.[16] The scope of these methods is quite limited, and only a few derivatives could be obtained in acceptable yields. The initial biaryl formation by a Suzuki coupling followed by an electrophilic cyclization of a glyoxylic moiety was successfully demonstrated by Yoshikawa and co-workers.[17] However, the method requires a donor functionality in position 3 of the phenanthrenequinone. The formation of six-membered rings by oxidative aryl−aryl coupling can be accomplished by many methods[18] and usually involves no electron-withdrawing moiety in the tether.[19,20] More sophisticated reagents are extremely powerful and can use fluoroarenes as substrates.[21] For the oxidative coupling reaction, $MoCl_5$ is a versatile and readily available reagent.[20] Because of the fast coupling process several labile moieties are tolerated.[22] The performance of this reagent can be enhanced if Lewis acids are added for intercepting hydrogen chloride formed in the course of the reaction.[23] The oxidative power of $MoCl_5$ is often compared to the commonly used hypervalent iodine reagents.[20] In several examples $MoCl_5$ exhibits a better performance.[24] The molybdenum salts generated during the transformation can direct the stereoselectivity of the oxidative coupling[25] or induce subsequent reductions by a redox procedure.[26]

Scheme 1. Synthesis of Starting Materials



Here, we report an alternative and modular approach to highly functionalized phenanthrenequinones which is complementary to the existing methods. The key step employs a $MoCl_5/TiCl_4$ mixture as an efficient oxidative coupling reagent to yield 9,10-phenanthrenequinones. The modular synthesis of the starting materials is based on the method of Vasilevsky and co-workers[27] and commences with the formation of tolanes **3** (Scheme 1). Here, standard conditions for the Sonogashira coupling ($Pd(PPh_3)_2Cl_2$, CuI, amine, DMF, 81 °C, 16 h) provided these intermediates in excellent yields up to 96%. When two iodo substituents are present in the component **1**, the less hindered leaving functionality cleanly undergoes the coupling process. Installation of the 1,2-dicarbonyl moiety was best accomplished by oxidation using $KMnO_4$ at room temperature using a pH buffer system based on $MgSO_4/NaHCO_3$ in an aqueous acetone solution.[28] Without the buffered reagent mixture,[27] the oxidation was unreliable and labile substrates were mostly decomposed. The elaborated protocol is easy to perform and provides very good yields for the benzil derivatives **4** in the range of 83 and 97%. The next step, the oxidative cyclization reaction, was not observed with $KMnO_4$ since this particular oxidant is not electrophilic enough.[18] For details, see the Supporting Information.

The oxidative cyclization of the benzil substrates **4** to the 9,10-phenanthrenequinones **5** is very efficiently performed by the $MoCl_5/TiCl_4$ mixture (Scheme 2). In the protocol, $TiCl_4$ does not only bind the formed hydrogen chloride but also induces a reactive conformation by complex formation with the 1,2-dicarbonyl moiety. Therefore, the $TiCl_4$ is

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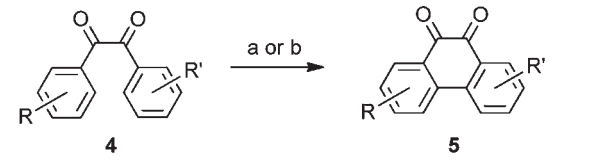
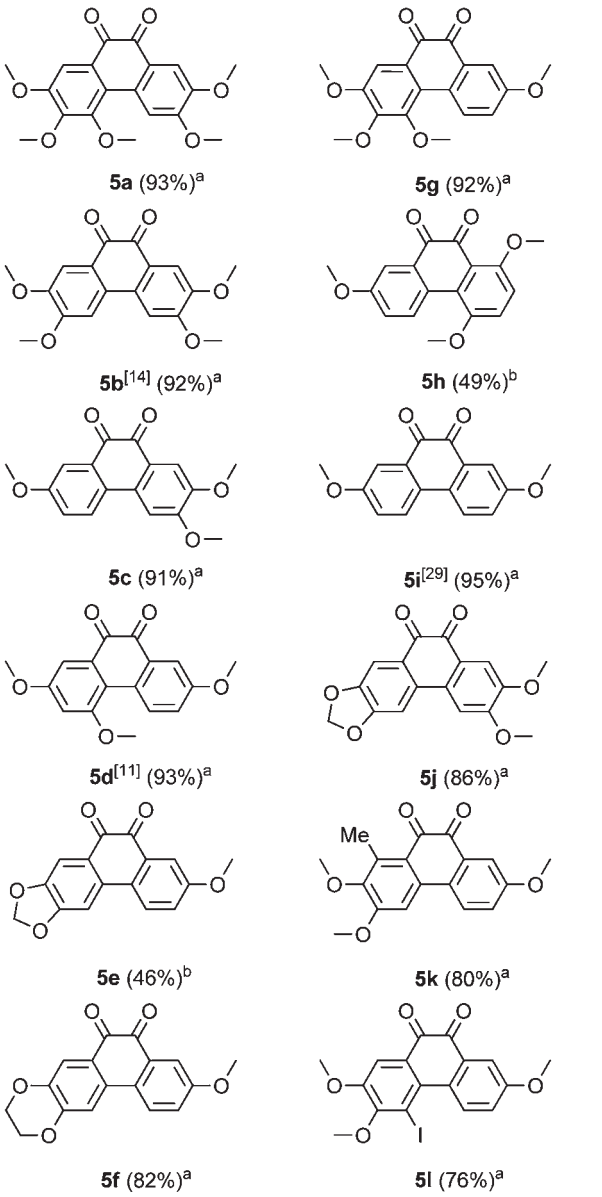
Scheme 2. Synthesis of the Phenanthrenequinones[a]





[a] $TiCl_4$ (2.2 equiv), $MoCl_5$ (2.2 equiv), CH_2Cl_2, 0 °C, 4 min. [b] $TiCl_4$ (2.2 equiv), $MoCl_5$ (2.2 equiv), CH_2Cl_2, 0 °C, 40 min.

added first, whereupon the solution turns intensively red. Then, the oxidant $MoCl_5$ enters the reaction scene. Because of the high oxidative power of the molybdenum(V) reagent, the conversion is brought to completion within a few minutes. Under the conditions described, neither the DDQ/$MeSO_3H$ mixture, mentioned as a strong reagent for oxidative intramolecular coupling reactions by Rathore and co-workers,[19] nor ferrous chloride[30] could form the desired product as effectively as the $MoCl_5/TiCl_4$ mixture (e.g., **5k**, Table 1). This underlines the unique character of $MoCl_5$ as oxidant.

Table 1. Comparison of Different Oxidative Reagents[a]

oxidant	temp (°C)	reaction time (min)	yield of **5k** (%)
DDQ/$MeSO_3H$	0	5	0
$FeCl_3$	20	10	6
$MoCl_5$	0	4	47
$TiCl_4$	0	10	0
$MoCl_5/TiCl_4$	0	4	80

[a] All reactions were performed in CH_2Cl_2 under inert atmosphere.

In general, activating groups in positions 2 and 7 of the phenanthrene guarantee the coupling reaction. If the aryl moiety is sufficiently electron rich, e.g., by two methoxy groups in position 1 and 4, the formation of **5h** is still possible in acceptable yields. Substrates with trimethoxyaryl moieties are coupled in excellent yields when the other aryl component exhibits one or two methoxy groups (**5a** and **5g**). *o*-Dimethoxy-substituted benzenes are usually the preferred substrates for $MoCl_5$ since a coordination to the molybdenum center occurs.[20] The 3,3′-dimethoxybenzil **4i** is still oxidatively cyclized since these donors are not compensated by the electron-withdrawing carbonyl groups. Consequently, **5i** is isolated in 95% yield. Substituents in position 4 or 5 on the phenanthrenequinones **5** should lead to a steric strain which should disfavor the formation of these products. This is not observed with methoxy substituents since **5a**, **5d**, and **5g** are formed in very good yield and **5h** in moderate yield, respectively. Even product **5l** with an iodine substituent at position 4 can be obtained in 76%. Here, the protodeiodination reaction is negligible since the oxidative coupling occurs much faster than the side reaction and the transformation is stopped after 4 min. The position of the iodo moiety was verified by X-ray analysis of a suitable single crystal (Figure 1). The molecule is twisted by an unusual torsional angle of 29.9° at the central carbon−carbon bond (for details, see the Supporting Information). A methyl group in position 1 of phenanthrenequinone **5k** leads to a slightly decreased yield compared to the parent compound **5c**. The molecular structure of **5k** was elucidated by X-ray analysis of a suitable single crystal (Figure 1). Interestingly, **5k** crystallizes as a hydrate forming a unique type of packing in the solid state (Supporting Information). If benzodioxoles are involved as substrates, the coupling partner should be electron rich, providing a good yield of 86% for **5j**, whereas less donor groups require prolonged reaction times and result in a significantly reduced yield (**5e**). This is attributed to the lability of the methylene moiety toward overoxidation.[31] We are pleased to find that the oxidative

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coupling reaction via $MoCl_5$ allows the formation of phenanthrenequinone **5f** with a benzo-1,4-dioxane subunit. The naturally occurring product cypripediquinone A (**5d**) was one of the examples synthesized with an overall yield of 74% in three steps from the corresponding aryl iodide (1-iodo-3,5-methoxybenzene **1d**). Remarkably, this compound was not previously synthesized.

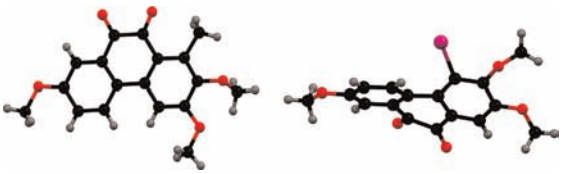
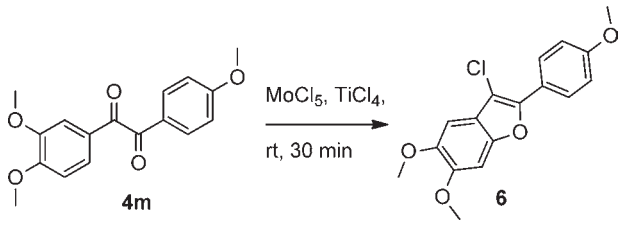


Figure 1. Molecular structure of phenanthrenequinone **5k** (left) and **5l** (right) by X-ray analysis.

The necessity for activating groups in the respective positions for the oxidative arylation reaction is demonstrated if **4m** is treated with the $MoCl_5/TiCl_4$ mixture (Scheme 3). Instead of a 9,10-phenanthrenequinone, the benzofuran **6** was isolated in 85% yield. The molecular structure was determined by X-ray analysis of a suitable single crystal (Figure 2). We anticipate that this particular cyclization occurs via a Nazarov-type reaction. Installation of the chloro function occurs subsequently by the oxophilic transition metal chlorides. Cremlyn and coworkers published a similar reaction sequence mediated by chlorosulfonic acid.[32]

Scheme 3. Limitation of This Method



Several 9,10-phenanthrenequinones with the substitution pattern obtainable by the method of Yoshikawa and co-workers are not accessible by this established method.[17] Conversely, most of our phenanthrenequinones are not feasible by their method. Consequently, these synthetic approaches are highly complementary. Furthermore, if no donor is present on an aryl moiety the method fails as well. Prolonged reaction times do not help since degradation by the strong electrophilic media takes over (Supporting Information).

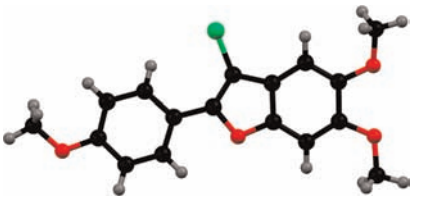


Figure 2. Molecular structure of benzofuran **6** by X-ray analysis.

In conclusion, a reliable and broad synthetic access to highly functionalized 9,10-phenanthrenequinones was established. The construction is highly modular and requires three synthetic steps which are easy to perform. The carbon skeleton is based on readily available iodobenzene derivatives and ethynylbenzene components. Our method requires donor functions in positions 2 and 7 of the final phenanthrene or sufficiently activated aryl moieties in the starting material. The oxidative coupling reaction represents the key step of the sequence and was conducted with the very strong oxidizing mixture $MoCl_5/TiCl_4$. This oxidative cyclization reaction is usually accomplished within a few minutes and is compatible with acid labile groups, e.g., iodo moieties. The total yield for the whole sequence is for most examples in the range of 70−80%. By this strategy, the naturally occurring product cypripediquinone A was synthesized for the first time. Application of this method in the construction of more complex naturally occurring and bioactive architectures exhibiting a highly functionalized phenanthro subunit will be reported in due course.

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Supporting Information Available. Experimental details, analytical data for all tolanes, benzils, and phenanthrenequinones, and crystallographic data for **5k**, **5l**, and **6** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.