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General Approach for the Synthesis of Chiral Perylenequinones via Catalytic Enantioselective Oxidative Biaryl Coupling

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Cercosporin, phleichrome, and the calphostins belong to a class of natural products[1] that contain an extended oxidized aromatic unit known as a perylenequinone (Figure 1). These potent protein kinase C inhibitors with unique binding to the regulatory domain[2] are promising agents for photodynamic cancer therapy due to the photochemical properties of perylenequinones.[3]

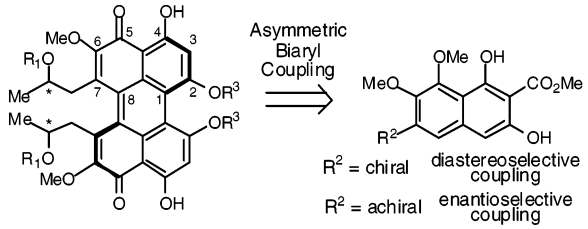
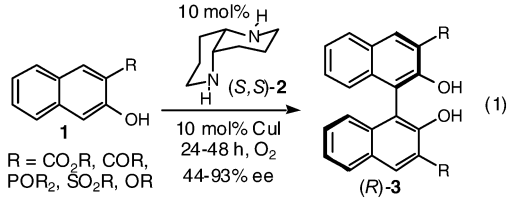


Figure 1. Perylenequinone natural products.

The perylenequinone substitution renders these interesting structures helical (naphthalene dihedral ~20°),[4] introducing axial chirality and contributing to their complexity. The biosynthetic pathways to these compounds likely involve oxidative phenolic coupling.[1a] Prior approaches[5] by Broka,[6] Coleman,[7] and Merlic[8] have utilized this concept by employing diastereoselective oxidative couplings of chiral 2-naphthols (Figure 1). Typically, these couplings yield the undesired diastereomer. Additional steps involving separation, isomerization, or Mitsunobu inversion are needed to obtain the required diastereomer.

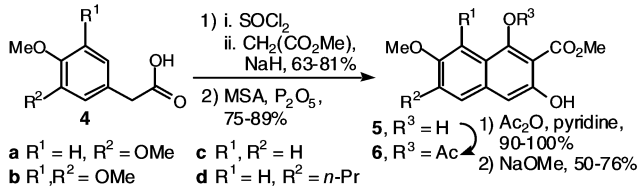
Utilizing the catalytic asymmetric oxidative phenolic coupling method that we have developed (eq 1),[9] we propose that this series of compounds could be generated by an *enantioselective* coupling of a functionalized 2-naphthol (Figure 1). The C7/C7′ side-chain stereogenic centers could then be introduced separately. Such a versatile approach would allow the selective and convergent synthesis of the complete diastereomeric series.



(1)

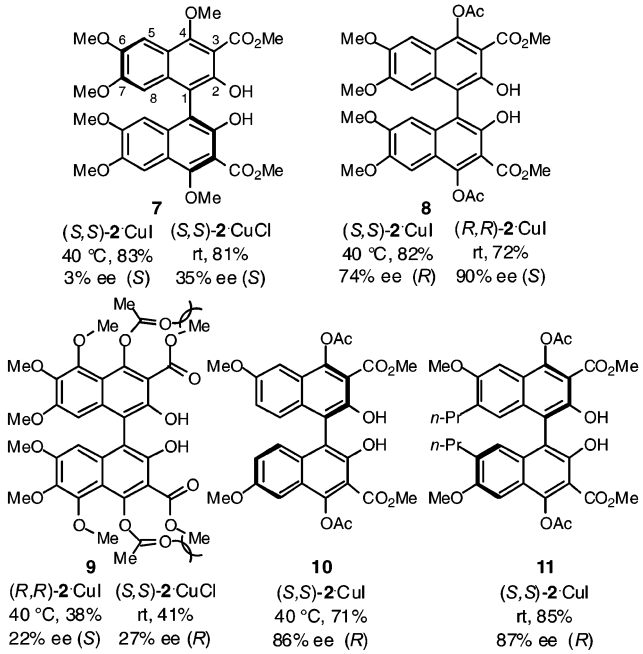
Since enantioselective oxidative binaphthol couplings have only been reported for naphthalenes with a low degree of substitution,[9,10] we began this effort by assessing the ability of our catalyst to form highly functionalized chiral binaphthols. Installation of the majority of the substituents found in perylenequinone natural products in the 2-naphthol would obviate the need for multiple late-stage functionalization. The substituted 2-naphthols required for this study were generated[11] by utilizing the optimized protocol outlined in Scheme 1 for **6a**−**d**.

Scheme 1



Application of the copper catalysts derived from **2** to the biaryl coupling of **5a** led to only trace amounts of the corresponding binaphthol. Presumably, the unprotected C4 OH competes with the C2 OH for catalyst or facilitates *p*-quinone formation. With protection of the C4 OH as the methyl ether, these problems were alleviated as seen by the formation of **7** in good yield (Chart 1).

Chart 1. Couplings with 10 mol % Catalyst under O_2



The enantioselectivity of **7**, however, was low (3% ee) under the same conditions used to obtain **3a** (eq 1, R = CO_2Me) with high enantioselectivity and yield (85%, 93% ee).[9] The three methoxy groups in the substrate leading to **7** introduce additional electron density which reduces the naphthalene oxidation potential and stabilizes the intermediate 2-keto-1-radical. As a result, the reaction was considerably more rapid than that leading to **3a**. Milder reaction conditions were therefore examined (CuCl cat., rt; Chart 1); the yield (81%) was again high, but the enantioselectivity remained low (35% ee). Due to the high degree of similarity between **3a** and **7**, this result was unexpected. Analysis of the enantiomeric

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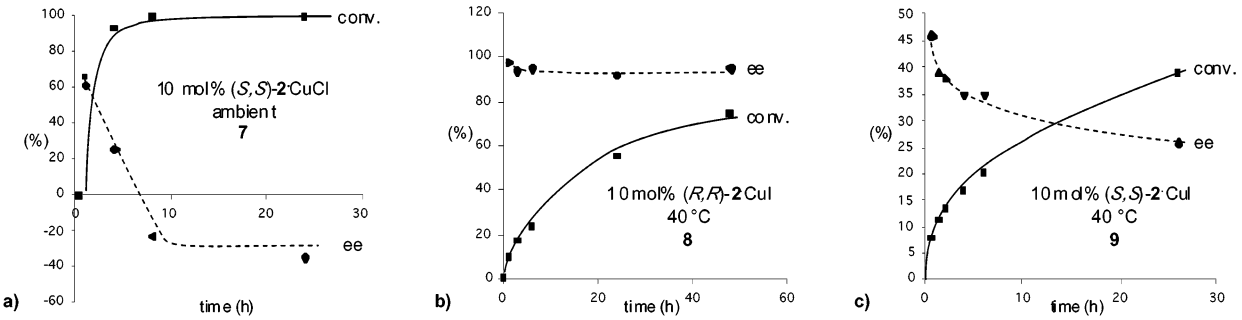
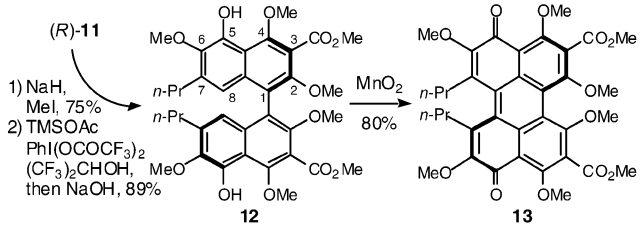


Figure 2. Conversion vs time and enantiomeric excess vs time (monitored by CSP HPLC) for the formation of **7**−**9**.

Scheme 2



excess and conversion vs time proved key to understanding these results (Figure 2a).

While conversion to **7** was very rapid, the enantiomeric excess also eroded rapidly during the early stages of the reaction. After initially observing 61% ee (*R*), the selectivity dropped and stabilized at 35% ee (*S*). Enantioselective formation of the (*R*)-product under kinetic control from the chiral catalyst accompanied by enantiomerization of **7** to a thermodynamic endpoint explains this trend. The predominance of the (*S*)-enantiomer at the conclusion may arise from a more stable catalyst−product complex with the (*S*)- vs (*R*)-enantiomer.[12]

We attribute the rapid enantiomerization of **7** to the electron-rich nature of the naphthalene.[13] This effect, and hence the resultant enantiomerization, should be attenuated by replacing the C4 OMe with OAc.[14] To our delight, this pentasubstituted naphthalene (**6a**) provided the highly functionalized binaphthol **8** (Chart 1) in good yield (72%) and high selectivity (90% ee). Enantiomerization was largely suppressed as the enantiomeric excess remained almost constant over the reaction course (Figure 2b). As expected, the rate of formation of **8** was slower than that of **7** but substantially faster than that of **3a**. This correlates with the ability of the substituents to stabilize the putative electron-deficient radical intermediate.[9d]

Next, an even more highly substituted naphthalene (**6b**) matching the perylenequinone natural product substitution pattern was examined. The introduction of even one additional electron-donating group (C5 OMe) facilitated enantiomerization, albeit more slowly than with **7** (Figure 2a vs 2c), so that the selectivity of **9** was low (27% ee). The reaction rate was also slow, which is not consistent with the electron-rich nature of this substrate. We hypothesize that substituent gearing effects prevent the substrate from adopting the conformation needed for catalyst coordination (coplanar C3 C═O and C2 OH, Chart 1).

For the purpose of synthesis of perylenequinone natural product analogues, the best compromise between substitution, reactivity, and selectivity is found in **10** and **11** (Chart 1) which form in good yield (71−85%) and high selectivity (86−87% ee) from **6c** and **6d**. To determine if such analogues, which lack the C5 OH, could be transformed to chiral perylenequninones, **11** was protected as the hexamethyl ether. Direct oxidation then proceeded surprisingly smoothly using TMSOAc and $PhI(OCOCF_3)_2$ in $(CF_3)_2CHOH$[15] (Scheme 2) to yield **12**. MnO_2 oxidation[7b] of **12** generated **13** with retention of axial chirality. This represents the first asymmetric synthesis of a perylenequinone containing only an axial chirality element.

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Supporting Information Available: Full experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Twenty mole percent of catalyst is employed relative to the product.

(13) Enantiomerization may occur via C1 protonation or via product oxidation (C1 radical). Both are more favorable with more electron-rich systems.

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