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# An Enantioselective Organocatalytic Oxidative Dearomatization Strategy

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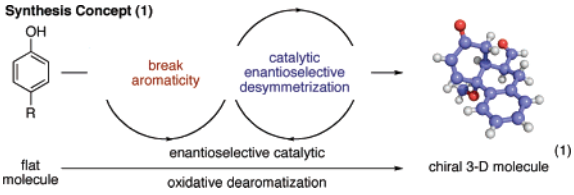
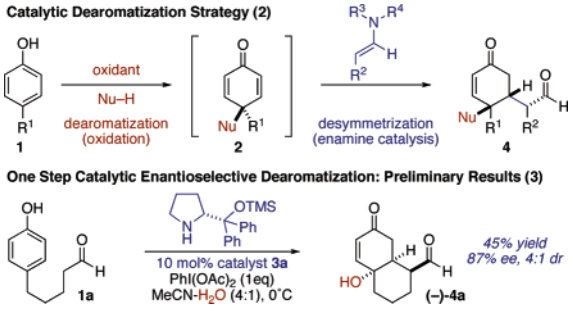
The inherent reactivity and functionality stored within aromatic systems provide numerous possibilities for the synthesis of 3-D organic structures via dearomatization processes.[1,2] Under oxidizing conditions, the dearomatization of ortho- and para-substituted phenols forms cyclohexadienones,[3] and these products have found widespread use in the chemical synthesis of natural products.[4] Additionally, the groups of Feringa,[5a] Hayashi,[5b] and Rovis[5c] have developed catalytic desymmetrization methods to convert the cyclohexadienone motif into useful enantioenriched molecules. The elegance of these stepwise tactics leads us to speculate that a catalytic asymmetric process that can directly transform an aromatic motif into the nonracemic structure would provide a powerful strategy for the rapid chemical synthesis of complex molecules (eq 1).[6,7]

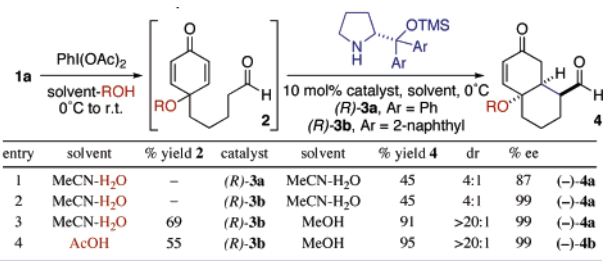



In this Communication, we report a process that directly converts a para-substituted phenol to a highly functionalized chiral molecule via oxidative deraromatization and amine-catalyzed enantioselective desymmetrizing Michael reaction (eq 2). This one-step transformation reveals a complex structure formed with exquisite control of three new stereogenic centers and an array of exploitable orthogonal functionality directly from a flat molecule that is devoid of architectural complexity.[8]

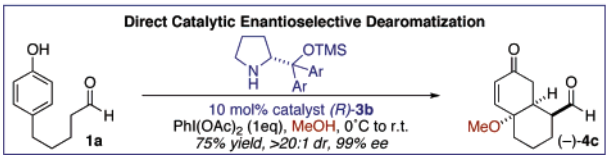



Central to the implementation of this strategy was the realization of a rapid method to oxidize the phenol ring that would not affect the sensitive aldehyde function. Hypervalent iodine reagents such as $PhI(OAc)_2$ facilitate fast oxidation of phenols to *meso*-cyclohexadieneones in the presence of protic nucleophiles suggesting that oxidation by this method could be suitable for our proposed dearomatization process.[3,9] Moreover, the fast oxidation of the phenol would minimize contact between oxidant and the amine catalyst or enamine intermediate that could lead to deleterious side reactions. Consequently, in considering the catalyst parameters we reasoned that a sterically bulky catalyst such as **3a**, instead of a simple proline catalyst, might shield the *N*-atom of the pyrrolidine ring from potential oxidation with any residual $PhI(OAc)_2$. Moreover, pyrrolidine **3a** also possesses tunable stereocontrolling elements and has demonstrated a versatile enamine reactivity profile in a range of organocatalytic enantioselective reactions.[10] In testing this catalytic enantioselective dearomatization strategy we were delighted to find that treatment of phenol **1a** with 1 equiv of $PhI(OAc)_2$ and 10 mol% of catalyst (*R*)-**3a** in $MeCN-H_2O$ at 0 °C afforded decalin (−)-**4a** in 45% yield with an enantiomeric excess (ee) of 87% as a 4:1 mixture of diastereomers (eq 3).

***Table 1.*** Reaction Optimization




| entry | solvent | % yield **2** | catalyst | solvent | % yield **4** | dr | % ee | |
|---|---|---|---|---|---|---|---|---|
| 1 | $MeCN-H_2O$ | – | (*R*)-**3a** | $MeCN-H_2O$ | 45 | 4:1 | 87 | (–)-**4a** |
| 2 | $MeCN-H_2O$ | – | (*R*)-**3b** | $MeCN-H_2O$ | 45 | 4:1 | 99 | (–)-**4a** |
| 3 | $MeCN-H_2O$ | 69 | (*R*)-**3b** | MeOH | 91 | >20:1 | 99 | (–)-**4a** |
| 4 | AcOH | 55 | (*R*)-**3b** | MeOH | 95 | >20:1 | 99 | (–)-**4b** |




With this promising lead in hand we next sought to improve the ee of the reaction. By increasing the size of the aryl groups (Ph **3a** to 2-naphthyl **3b**) we anticipated that the larger 2-naphthyl moiety would offer better facial discrimination in the desymmetrization step. Indeed, using 10 mol % of catalyst (*R*)-**3b** under the same conditions resulted in an increase in ee to 99% although the diastereomeric ratio (dr) and yield of the reaction remained moderate (Table 1, entries 1,2). To assess the influence of the reaction media we isolated the *meso*-cyclohexadienone **2** (R = H) and subjected this substrate to the desymmetrization reaction with catalyst (*R*)-**3b** in a range of solvents. To our surprise and delight the reaction in MeOH proceeded in excellent yield, ee and dr. This result highlights an important role of the protic reaction media in controlling the stereoselectivity in the desymmetrization step.[11] A similar outcome was observed with AcOH as the nucleophile in the oxidation step followed by cyclization in MeOH to afford (−)-**4b** with >20:1 dr, 99% ee in 52% yield over the two steps (entry 4).

In applying these optimizations and with MeOH as solvent and nucleophile the catalytic enantioselective dearomatization of **1a** using 1 equiv of $PhI(OAc)_2$ and 10 mol % of (R)-**3b** delivers (−)-**4c** in 75% yield for the one-step process with exquisite control of stereochemistry (>20:1 dr and 99% ee) (vide supra).

Having demonstrated the viability of this catalytic enantioselective dearomatization strategy we next investigated the scope of the transformation. To assess the impact of the structural and functional motifs on the reaction we tested a range of linking units between the phenol and aldehyde motifs using MeOH as the oxidation


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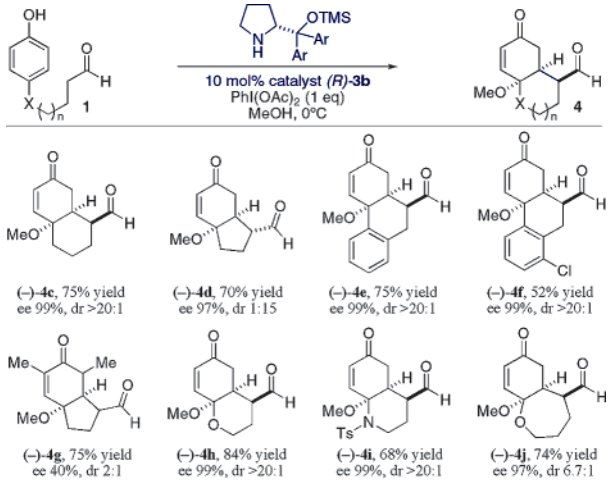
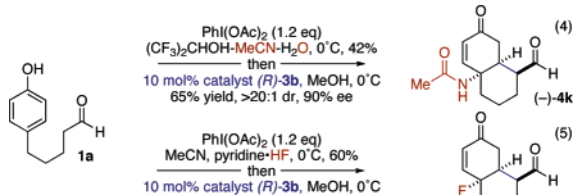
***Table 2.*** Catalytic Enantioselective Dearomatization

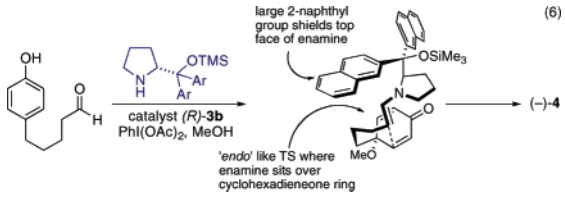



nucleophile (Table 2). In addition to the formation of the [4.4.0]-ring system (−)-**4c** we also found that a [4.3.0]-bicycloalkanone (−)-**4d** could be generated with excellent dr and ee.[11,12a] Biarylphenols were smoothly converted to polycyclic enones products (−)-**4e**,**f**, again in good yield and very high selectivity from the direct process.[12b] Substitution on the phenolic ring was not well tolerated, and a poor ee was observed for (−)-**4g** when a 2,6-dimethyl phenol was tested. However, heteroatoms can be incorporated to the tether unit and they produced highly functionalized enantiopure products (−)-**4h**,**i** in high yield and with excellent stereocontrol. It was noticeable that these substrates were more reactive than the carbon analogues, and this was highlighted by the successful cyclization to the more challenging seven-membered oxacene ring (−)-**4j** with excellent ee.

These scope studies demonstrate the flexibility of the catalytic asymmetric dearomatization process to efficiently generate a range of useful, architecturally complex, enantio-enriched molecules. In extending this potentially useful transformation, we also found that non-oxygen nucleophiles can participate in this reaction. For example, reaction of **1a** in HFIPA-MeCN allowed the -CN function to act as a nucleophile through a Ritter-type reaction to afford amide (−)-**4k** in high ee (eq 4).[13a] Moreover, oxidation in the presence of HF·pyridine complex formed the fluorinated *meso*-cyclohexadiene that,[13b] on catalytic desymmetrization, afforded decalin (−)-**4l** in excellent ee (eq 5). This example represents a simple method for the installation of a tertiary C−F bond within a complex chiral molecule using enantioselective catalysis.




The stereocontrolling elements of catalysts **3a** and **3b** have been well documented for enamine reactions involving intermolecular C−X bond forming processes;[10] however, their use in intramolecular reactions is less common. On the basis of the absolute configuration obtained from the crystal structure of a derivative of (−)-**4e** we suggest that the stereochemistry can be rationalized via a transition state (vide infra) that involves an endo-like attack onto the *Si* face of the *meso*-cyclohexadienone (eq 6).




In summary, we have developed a catalytic enantioselective strategy for chemical synthesis wherein substituted phenols are directly converted to complex nonracemic molecular architectures. The process involves oxidative dearomatization of substituted phenols followed by a desymmetrizing secondary amine catalyzed asymmetric intramolecular Michael addition and forms a range of highly functionalized polycyclic molecules with excellent selectivity. We are currently investigating the application of this process in the synthesis of natural products, in particular with carbon nucleophiles, and these results will be reported in due course.

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**Supporting Information Available:** Experimental data and procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The oxidation is the "yield limiting" factor and the cyclization proceeds almost quantitatively in the stepwise case. See Supporting Information for further details.

(12) (a) The dr is 3:1 after reaction, but equilibration at room temp gives 1:15 (−)-**4d**. (b) Absolute stereochemistry was confirmed by X-ray diffraction.

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