Palladium(0)-Catalyzed Arylative Dearomatization of Phenols

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Supporting Information

ABSTRACT: The palladium-catalyzed arylative dearomatization of phenols to yield spirocyclohexadienone products in good to excellent yields has been developed. Preliminary results demonstrate that the formation of the spirocyclic all-carbon quaternary center can be accomplished with high levels of enantiocontrol (up to 91% ee).

The dearomatization of aromatic compounds has been widely recognized as a powerful transformation for the generation of high levels of molecular complexity from simple planar starting materials.1,2 Of particular interest is the dearomatization of phenols to cyclohexadienone derivatives. This is in part due to the fact that this process is involved in the biosynthesis of natural products.3 However, the development of synthetic methods to effect this transformation has been challenging because of the stability of the aromatic starting material, problems with a lack of chemoselectivity, and the potential for undesired product rearomatization. Previous reports have demonstrated that the dearomatization of phenols occurs in the presence of main group p-block arylating agents, providing mixtures of ortho- and para-arylated cyclohexadienones as well as diaryl ethers (Scheme 1a).4 While these transformations are important, the use of toxic arylating reagents in some cases and the product mixtures that are often obtained limit their synthetic utility. The oxidation of phenols using stoichiometric quantities of relatively strong oxidants in the presence of nucleophilic arenes can also lead to similar products.5 We felt that there remained a need to develop milder, catalytic conditions to effect this type of transformation in a highly chemoselective fashion.

While transition-metal catalysis offers an efficient route to diaryl ethers via phenol O-arylation and biaryls via direct C-arylation (Scheme 1b),6,7 complementary dearomatization via C-arylation remains underdeveloped.8,9 Herein we describe a Pd(0)-catalyzed protocol for the dearomatization of phenols10 that provides spirocyclic compounds, an important motif in natural products and material science (Scheme 1c).11 Notably, this transformation is mechanistically unique in comparison with traditional oxidative dearomatization processes involving attack of an “activated” electrophilic phenol by a nucleophile (Scheme 2).1c,13 Therefore, this system offers new opportunities for enantioinduction using asymmetric catalysis.12,13,14

The success of this dearomatization strategy relies on the ability to avoid diaryl ether formation arising from a competitive intermolecular C–O cross-coupling reaction and to favor reductive elimination of the product from palladacycle I over rearomatization processes (Scheme 2). With this in mind, we initially looked at catalyst systems that are inefficient for C–O cross-coupling and effective for C–C bond-forming processes. With Pd(dba)2 (3 mol %), XPhos (4.5 mol %), and KOt-Bu (1.5 equiv) in THF at 100 °C, product 2a was obtained in 6% yield (Table 1, entry 1). An evaluation of bases revealed a significant increase in yield to 23% when K2PO4 was employed (entry 2). A further improvement to 34% was obtained with K2CO3 (entry 3).14 Switching to [Pd(cinnamyl)Cl]2 as the palladium source led to an additional augmentation to 48%, and the yield was further enhanced to 77% when the reaction was performed at 120 °C in 1,4-dioxane (entries 4 and 5). Finally, an evaluation of biarylphosphine ligands (entries 5–8) revealed L1 to be optimal, providing 2a in 93% GC yield.

Illustrative examples of the scope of this dearomatization protocol with respect to substitution on the phenol and benzene rings and to the length of the tether are shown in Table 2. Submitting 1a to [Pd(cinnamyl)Cl]2 (1 mol %), L1 (3 mol %), and K2CO3 (1.5 equiv) in dioxane at 120 °C for 16 h provided 2a in 81% isolated yield. Additionally, this transformation could be performed on a 10 mmol scale, yielding 2a in 91%. Substitution at the position ortho to the hydroxyl group was well-tolerated, as exemplified by 2b and 2c, which were obtained in 91 and 90% yield, respectively. Also, substrates bearing substituents ortho to the carbon undergoing rehybridization were compatible, providing the corresponding

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cyclohexadienones 2d–f in good yields. It should be noted that because of the importance of its nucleophilic character in the reaction, substitution on the phenol ring is at present limited to electron-neutral or -donating groups. With respect to the aryl bromide reaction component, electron-neutral (2g and 2m) and -donating (2h) groups were well-tolerated. Substrates with electron-withdrawing substituents proved to be more challenging and required either higher dilution (2j) or increased catalyst loading (2k). Chlorine-containing products 2i and 2l were obtained in good yields, providing a useful synthetic handle for further functionalization of the spirocyclohexadienone product. The carbon tether between the two aromatic rings could be lengthened without affecting product formation, as seen with tetralin derivative 2n, which was isolated in 84% yield. Finally, the dearomatization of ortho-substituted phenol 1o was examined (eq 1).

We next focused our attention on the development of an asymmetric version of this reaction, the products of which would be cyclohexadienones bearing an enantioenriched all-carbon quaternary stereocenter. Despite the importance of this motif in natural product synthesis, few asymmetric methods for its formation are available. We were encouraged by the results of a recent study by Toste, in which spiropyrans were produced with low to moderate enantioselectivity using a rhodium catalyst.16

Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd (mol %)</th>
<th>ligand</th>
<th>base</th>
<th>T (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)₂ (3)</td>
<td>XPhos</td>
<td>KOt-Bu</td>
<td>THF 100</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)₂ (3)</td>
<td>XPhos</td>
<td>K₂PO₄</td>
<td>THF 100</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)₂ (3)</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>THF 100</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>[Pd(cinnamyl)Cl]₂ (1.5)</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>THF 100</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>[Pd(cinnamyl)Cl]₂ (1)</td>
<td>XPhos</td>
<td>K₂CO₃</td>
<td>dioxane 120</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>[Pd(cinnamyl)Cl]₂ (1)</td>
<td>SPhos</td>
<td>K₂CO₃</td>
<td>dioxane 120</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>[Pd(cinnamyl)Cl]₂ (1)</td>
<td>RuPhos</td>
<td>K₂CO₃</td>
<td>dioxane 120</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>[Pd(cinnamyl)Cl]₂ (1)</td>
<td>L1</td>
<td>K₂CO₃</td>
<td>dioxane 120</td>
<td>93</td>
</tr>
</tbody>
</table>

* Reaction conditions: Pd source (x mol %), ligand (1.5x mol %), base (1.5 equiv), and 1a (0.1 mmol) in solvent (0.2 M) at the indicated temperature for 16 h. GC yield using dodecane as an internal standard.

We next focused our attention on the development of an asymmetric version of this reaction, the products of which would be cyclohexadienones bearing an enantioenriched all-carbon quaternary stereocenter. Despite the importance of this motif in natural product synthesis, few asymmetric methods for its formation are available. We were encouraged by the results of a recent study by Toste, in which spiropyran deoxygenated with low to moderate enantioselectivity using a rhodium catalyst.16

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Scheme 3. Asymmetric Dearomatization of Phenols

| a | Reaction conditions: Pd(OAc)$_2$ (4 mol %), H$_2$O (16 mol %), L$_2$ or L$_3$ (12 mol %), K$_2$CO$_3$ (1.5 equiv), and phenol (0.10 mmol) in 1,4-dioxane (0.5 mL) at 80 °C for 16 h. GC yields using dodecane as an internal standard. ee values were determined by HPLC.

6 Correlation exist. 16 An evaluation of chiral ligands revealed that a catalyst system based on L$_3$ had been reported previously by our group in the enantioselective α-arylation and α-vinylation of oxindoles. 19,20 The use of a water-mediated catalyst activation protocol to form the active L*Pd(0) complex was found to be crucial for obtaining good ee’s in a reproducible manner. 18,21

Finally, studies revealed that the presence of a free hydroxyl group is essential for the observed reactivity. When methyl- or benzyl-protected derivatives of phenol 1a were submitted to the standard reaction conditions, little to no product was observed. These results suggest that deprotonation is required in order to induce nucleophilic attack at the Pd(H) center (Scheme 2).

In conclusion, we have developed a transition-metal-catalyzed arylative dearomatization of phenols to provide spirocyclohexadienones bearing all-carbon quaternary centers in good to excellent yields. Initial studies demonstrated that the development of a highly enantioselective variant of this reaction is practical, with ee’s of up to 91% currently being obtained using a catalyst system based on L$_3$. The scope of electron-rich arenes that may be dearomatized using this palladium-catalyzed protocol, with a focus on the development of asymmetric intermolecular processes, is currently under investigation.

**ACKNOWLEDGMENT**

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**REFERENCES**


(12) For the use of chiral hypervalent iodine reagents to mediate the oxidative asymmetric dearomatization of phenols, see: (a) Up to 86% ee: Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. Angew. Chem. Int. Ed. 2008,

(13) After the completion of this work, a paper by You and co-workers describing the Ir-catalyzed intramolecular asymmetric allylic dearomatization of phenols appeared (see ref 9b).

(14) The use of Li₂CO₃, Na₂CO₃, and Cs₂CO₃ did not promote the desired transformation.


(18) See the Supporting Information for additional details.

