Palladium(0)-Catalyzed Arylative Dearomatization of Phenols

The MIT Faculty has made this article openly available. Please share how this access benefits you. Your story matters.
Palladium(0)-Catalyzed Arylative Dearomatization of Phenols

Sophie Rousseaux, Jorge García-Fortanet, Miguel Angel Del Aguila Sanchez, and Stephen L. Buchwald

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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. Of particular interest is the dearomatization of phenols to cyclohexadienone derivatives. This is in part due to this processes' involvement in the biosynthesis of natural products. However, the development of synthetic methods to effect this transformation has been challenging due to 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 to provide mixtures of ortho- and para-arylated cyclohexadienones, as well as diaryl ethers (Scheme 1a). While these transformations are important, the use of sometimes toxic arylating reagents, as well as 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. 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), complementary dearomatization via C-arylation remains underdeveloped. Herein, we describe a Pd(0)-catalyzed protocol for the dearomatization of phenols, providing spirocyclic compounds, an important motif in natural products and material science (Scheme 1c). Notably, this transformation is mechanistically unique compared to traditional oxidative dearomatization processes involving attack of a nucleophile onto an “activated” electrophilic phenol (Scheme 2). Therefore, this system offers new opportunities for enantioinduction using asymmetric catalysis.

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 product reductive elimination 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. Using Pd(dba)$_2$ (3 mol %), XPhos (4.5 mol %) and KOt-Bu (1.5 equivalents) 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 K$_3$PO$_4$ was employed (entry 2). A further improvement to 34% was obtained with K$_2$CO$_3$ (entry 3). Switching to [Pd(cinnamyl)Cl]$_2$ as the palladium source led to an additional augmentation to 48%, which could be further enhanced to 77% by performing the reaction at 120 °C in 1,4-dioxane (entries 4–5). Finally, an evaluation of biarylphosphine ligands revealed L1 to be optimal, providing 2a in 93% GC yield (entries 5–8).

Illustrative examples of the scope of this dearomatization protocol with respect to substitution on the phenol and benzene rings, as well as to the length of the tether are shown in Table 2. Submitting 1a to [Pd(cinnamyl)Cl]$_2$ (1 mol %), L1 (3 mol %) and K$_2$CO$_3$ (1.5 equivalents) in dioxane at 120 °C for 16 hours 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 cyclohexadienones 2d, 2e and 2f in good yields. It should be noted that due to 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, 2m) and -donating (2h) groups are well tolerated. Substrates with electron-withdrawing substituents proved to be more challenging and required either higher dilutions (2j) or increased catalyst loadings (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 both 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). Diaryl ether 3, resulting from an intramolecular C–O cross-coupling, was preferentially formed over the spirocyclohexa-2,4-dienone product.

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 their preparation exist. An evaluation of chiral ligands revealed that a catalyst based on KenPhos (L2) enabled the formation of 2b in 91% GC yield with a moderate, but promising, 65% enantiomeric excess (Scheme 3). Both yield and ee could be further improved to 99% and 91%, respectively, when L3 was employed; this ligand, bearing an additional element of chirality on the phosphorus atom, had been previously reported by our group in the enantioselective α-arylation and α-vinylation of oxindoles. The use of a catalyst based on L3 was extended to the asymmetric synthesis of 2f, obtained in 74% GC yield and 81% ee. Importantly, employing 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.
Finally, studies have 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 to induce nucleophilic attack of the Pd(II) center (Scheme 2).

In conclusion, we have developed the first transition-metal catalyzed arylative de-aromatization of phenols to provide spirocyclohexadienones bearing all-carbon quaternary centers in good to excellent yields. Initial studies have demonstrated that the development of a highly enantioselective variant of this reaction is practical with ee’s up to 91% currently being obtained when a catalyst system based on L3 is employed. The scope of electron-rich arenes that may be de-aromatized using this palladium-catalyzed protocol, with a focus on the development of asymmetric intermolecular processes, is currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health for financial support of this work (Grant GM46059). S.R. thanks NSERC for a CGS-D postgraduate fellowship and a MSFSS award. M.A.A. thanks the Spanish MEC for a doctoral fellowship. The Varian 300 MHz NMR spectrometer used for a portion of this work was purchased with funds from the National Science Foundation (Grants CHE 9808061 and DBI 9729592). We would also like to thank a reviewer for bringing reference 8 to our attention.

References


8. For the use of a Pd(0)-catalyzed arylovial de-aromatization in the synthesis of a salutaridine derivative, see: Wiegand S, Schäfer HJ. Tetrahedron. 1995; 51:5341.


11. For a review on the synthesis of spirocyclics, see: Kotha S, Deb AC, Lahiri K, Manivanna E. Synthesis. 2009:165.


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 supporting information for additional details.


Scheme 1.
Methods for the Arylation and/or Dearomatization of Phenols
Scheme 2.
Strategy for the Pd(0)-Catalyzed Dearomatization of Phenols and Potential Challenges
Scheme 3. Asymmetric Dearomatization of Phenols\textsuperscript{a,b,c}

\textsuperscript{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 hours.

\textsuperscript{b} GC yields using dodecane as an internal standard.

\textsuperscript{c} ee values were determined by HPLC.
### Table 1

Optimization of the Reaction Conditions\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (mol %)</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)(_2) (3)</td>
<td>XPhos</td>
<td>KOt-Bu</td>
<td>THF</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)(_2) (3)</td>
<td>XPhos</td>
<td>K(_3)PO(_4)</td>
<td>THF</td>
<td>100</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)(_2) (3)</td>
<td>XPhos</td>
<td>K(_2)CO(_3)</td>
<td>THF</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>[Pd(cinnamyl)Cl](_2) (1.5)</td>
<td>XPhos</td>
<td>K(_2)CO(_3)</td>
<td>THF</td>
<td>100</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>[Pd(cinnamyl)Cl](_2) (1)</td>
<td>XPhos</td>
<td>K(_2)CO(_3)</td>
<td>Dioxane</td>
<td>120</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>[Pd(cinnamyl)Cl](_2) (1)</td>
<td>SPhos</td>
<td>K(_2)CO(_3)</td>
<td>Dioxane</td>
<td>120</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>[Pd(cinnamyl)Cl](_2) (1)</td>
<td>RuPhos</td>
<td>K(_2)CO(_3)</td>
<td>Dioxane</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>[Pd(cinnamyl)Cl](_2) (1)</td>
<td>(L_1)</td>
<td>K(_2)CO(_3)</td>
<td>Dioxane</td>
<td>120</td>
<td>93</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: Pd source (x mol %), ligand (1.5:1 ligand:Pd ratio), base (1.5 equiv) and 1a (0.1 mmol) in solvent (0.2 M) at indicated temperature for 16 hours.

\(^b\) GC yield using dodecane as an internal standard.
Table 2

Scope of the Pd-Catalyzed Dearomatization of Phenols$^{a,b}$

<table>
<thead>
<tr>
<th>Reaction conditions: $\text{[Pd(cinnamyl)Cl]_2 (1 mol %)}, \text{L1 (3 mol %)}, \text{K}_2\text{CO}_3 (1.5 \text{ equiv})$, Dioxane (0.2 M) 120 °C, 16 h</th>
<th>Isolated yields (average of two runs).</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Reaction Scheme" /></td>
<td><img src="image" alt="Yield Results" /></td>
</tr>
<tr>
<td>2a, 81% (91%)$^c$</td>
<td>2b, 91%</td>
</tr>
<tr>
<td>2c, 90%</td>
<td>2d, 79%</td>
</tr>
<tr>
<td>2e, 75%</td>
<td>2f, 73%</td>
</tr>
<tr>
<td>2g, 83%</td>
<td><img src="image" alt="Other Yields" /></td>
</tr>
<tr>
<td>2h, 89%</td>
<td>2i, 74%</td>
</tr>
<tr>
<td>2j, 44%$^d$</td>
<td>2k, 74%$^e$</td>
</tr>
<tr>
<td>2l, 74%$^e$</td>
<td>2m, 51%$^f$</td>
</tr>
<tr>
<td>2n, 84%</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: $\text{[Pd(cinnamyl)Cl]_2 (1 mol \%)}, \text{L1 (3 mol \%)}, \text{K}_2\text{CO}_3 (1.5 \text{ equiv})$ and phenol (1.0 mmol) in 1,4-dioxane (5 mL) at 120 °C for 16 hours.

$^b$ Isolated yields (average of two runs).
c. Reaction performed on 10 mmol scale.

d. Concentration = 0.05 M.

e. [Pd(cinnamyl)Cl]₂ (2 mol %), L₁ (6 mol %).

f. [Pd(cinnamyl)Cl]₂ (2.5 mol %), L₁ (7.5 mol %).