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Palladium(0)-Catalyzed Arylative Dearomatization of Phenols

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Supporting Information

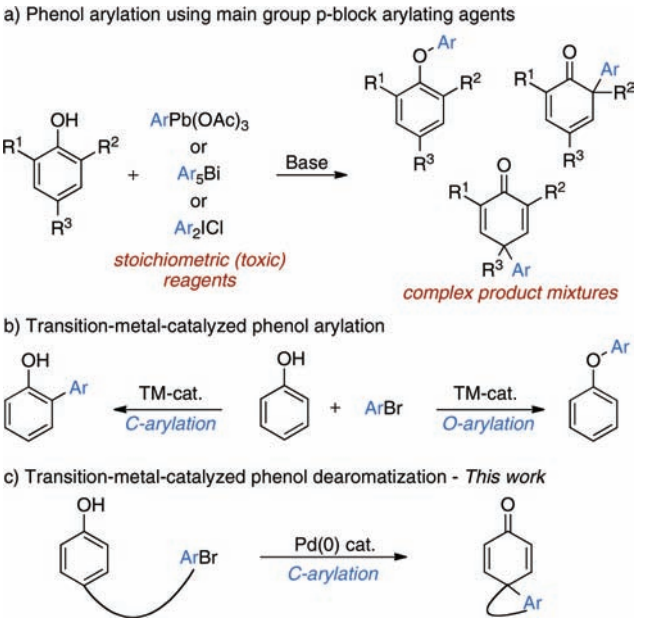
ABSTRACT: The palladium-catalyzed arylative dearomatization of phenols to yield spirocyclohexadienone products in good to excellent yields has been developed. Preliminary results demonstrate that the formation of the spirocyclic all-carbon quaternary center can be accomplished with high levels of enantiocontrol (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 phenols[10] 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).[1e,f,3] Therefore, this system offers new opportunities for enantioinduction using asymmetric catalysis.[12,13]

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

Scheme 1. Methods for Arylation and/or Dearomatization of Phenols



effective for C−C bond-forming processes. With $Pd(dba)_2$ (3 mol %), XPhos (4.5 mol %), and KO*t*-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 K_3PO_4 was employed (entry 2). A further improvement to 34% was obtained with K_2CO_3 (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 K_2CO_3 (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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Scheme 2. Strategy for Pd(0)-Catalyzed Dearomatization of Phenols and Potential Challenges

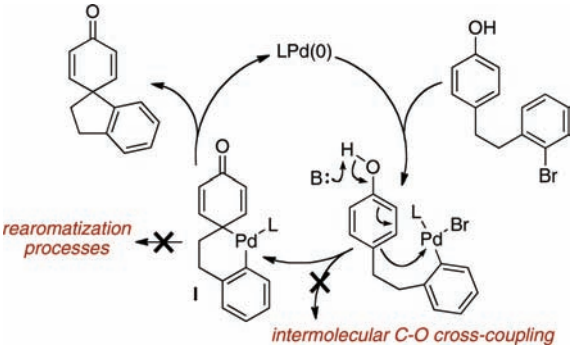
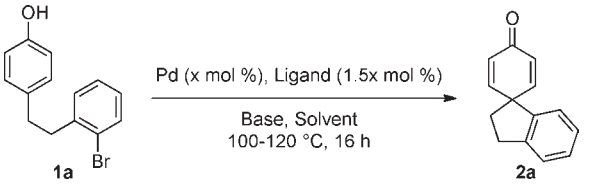
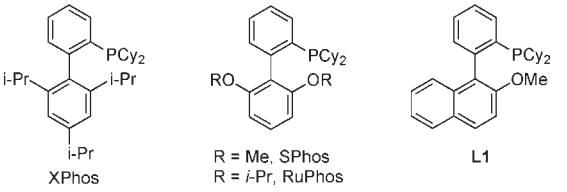


Table 1. Optimization of the Reaction Conditions[a]



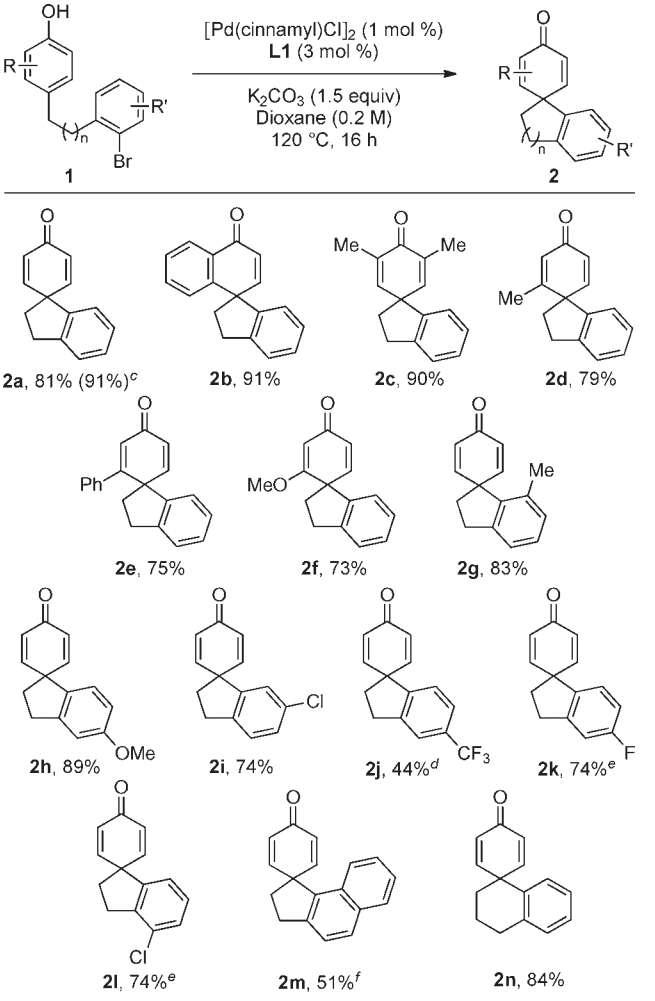
entry	Pd (mol %)	ligand	base	solvent	T (°C)	yield (%)[b]
1	$Pd(dba)_2$ (3)	XPhos	KOt-Bu	THF	100	6
2	$Pd(dba)_2$ (3)	XPhos	K_3PO_4	THF	100	23
3	$Pd(dba)_2$ (3)	XPhos	K_2CO_3	THF	100	34
4	$[Pd(cinnamyl)Cl]_2$ (1.5)	XPhos	K_2CO_3	THF	100	48
5	$[Pd(cinnamyl)Cl]_2$ (1)	XPhos	K_2CO_3	dioxane	120	77
6	$[Pd(cinnamyl)Cl]_2$ (1)	SPhos	K_2CO_3	dioxane	120	43
7	$[Pd(cinnamyl)Cl]_2$ (1)	RuPhos	K_2CO_3	dioxane	120	50
8	$[Pd(cinnamyl)Cl]_2$ (1)	**L1**	K_2CO_3	dioxane	120	93



[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 the indicated temperature for 16 h. [b] GC yield using dodecane as an internal standard.

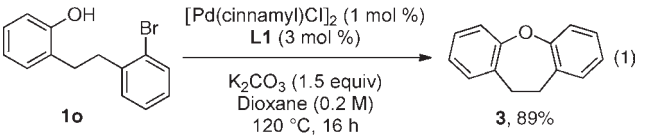
cyclohexadienones **2d**−**f** in good yields. It should be noted that because of the importance of its nucleophilic character in the reaction, substitution on the phenol ring is at present limited to electron-neutral or -donating groups. With respect to the aryl bromide reaction component, electron-neutral (**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

Table 2. Scope of the Pd-Catalyzed Dearomatization of Phenols[a,b]



[a] Reaction conditions: $[Pd(cinnamyl)Cl]_2$ (1 mol %), **L1** (3 mol %), K_2CO_3 (1.5 equiv), and phenol (1.0 mmol) in 1,4-dioxane (5 mL) at 120 °C for 16 h. [b] Isolated yields (averages of two runs). [c] Reaction was 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 %).

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). Diaryl ether **3** resulting from 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.[15] Despite the importance of this motif in natural product synthesis, few asymmetric methods for its

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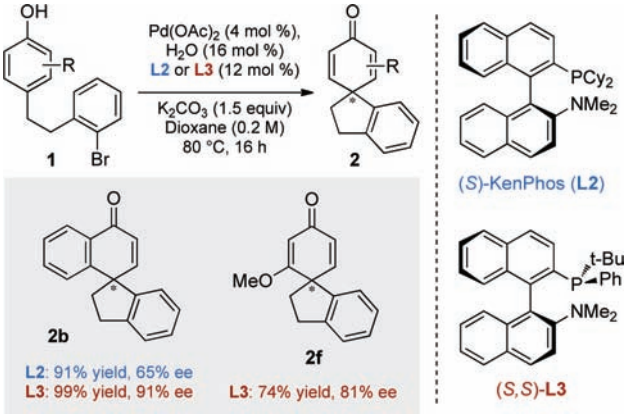
Scheme 3. Asymmetric Dearomatization of Phenols[a,b,c]



[a] Reaction conditions: $Pd(OAc)_2$ (4 mol %), H_2O (16 mol %), **L2** or **L3** (12 mol %), K_2CO_3 (1.5 equiv), and phenol (0.10 mmol) in 1,4-dioxane (0.5 mL) at 80 °C for 16 h. [b] GC yields using dodecane as an internal standard. [c] ee values were determined by HPLC.

preparation exist.[16] An evaluation of chiral ligands revealed that a catalyst based on KenPhos (**L2**)[17] enabled the formation of **2b** in 91% GC yield with a moderate but promising enantiomeric excess of 65% (Scheme 3).[18] Both the yield and ee were further improved to 99 and 91%, respectively, when **L3** was employed; this ligand, which bears an additional element of chirality on the phosphorus atom, had been reported previously by our group in the enantioselective α-arylation and α-vinylation of oxindoles.[19,20] The use of a catalyst based on **L3** was extended to the asymmetric synthesis of **2f**, which was 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.[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(II) 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 **L3**. 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.

■ ASSOCIATED CONTENT

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

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