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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.^{1,2} 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.³ 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).⁴ 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.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 providing spirocyclic compounds, an important motif in natural products and material science (Scheme 1c).¹¹ Notably, this transformation is mechanistically unique compared to traditional oxidative dearomatization processes involving attack of a nucleophile onto an “activated” electrophilic phenol (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 product reductive elimination from palladacycle **I** over rearomatization processes

sbuchwal@mit.edu.

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

(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 KO^t-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 K₃PO₄ 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%, 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 K₂CO₃ (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.

(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.¹⁵ Despite the importance of this motif in natural product synthesis, few asymmetric methods for their 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, 65% enantiomeric excess (Scheme 3).¹⁸ 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.^{19,20} 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.^{18,21}

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 dearomatization 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 dearomatized 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.

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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, b,c

^a Reaction conditions: $\text{Pd}(\text{OAc})_2$ (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 hours.

^b GC yields using dodecane as an internal standard.

^c ee values were determined by HPLC.

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 ₃ PO ₄	THF	100	23
3	Pd(dba) ₂ (3)	XPhos	K ₂ CO ₃	THF	100	34
4	[Pd(cinnamyl)Cl] ₂ (1.5)	XPhos	K ₂ CO ₃	THF	100	48
5	[Pd(cinnamyl)Cl] ₂ (1)	XPhos	K ₂ CO ₃	Dioxane	120	77
6	[Pd(cinnamyl)Cl] ₂ (1)	SPhos	K ₂ CO ₃	Dioxane	120	43
7	[Pd(cinnamyl)Cl] ₂ (1)	RuPhos	K ₂ CO ₃	Dioxane	120	50
8	[Pd(cinnamyl)Cl] ₂ (1)	L1	K ₂ CO ₃	Dioxane	120	93

XPhos

SPhos

RuPhos

L1

^aReaction 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.^bGC yield using dodecane as an internal standard.

Table 2

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

^a Reaction conditions: [Pd(cinnamyl)Cl]₂ (1 mol %), **L1** (3 mol %), K₂CO₃ (1.5 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).

^cReaction performed on 10 mmol scale.

^dConcentration = 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 %).