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## **RESEARCH ARTICLE**



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# Synthesis of 2,3-dihydrobenzofurans *via* the palladium catalyzed carboalkoxylation of 2-allylphenols<sup>†</sup>

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A new Pd-catalyzed alkene carboalkoxylation strategy for the preparation of 2,3-dihydrobenzofurans is described. This method effects the coupling of readily available 2-allylphenol derivatives with aryl triflates to generate a wide range of functionalized 2,3-dihydrobenzofurans in good yields and diastereo-selectivities (up to >20 : 1). Use of newly developed reaction conditions that promote *anti*-heteropallada-tion of the alkene is essential in order to generate products in high yield.

2,3-Dihydrobenzofurans are a valuable structural motif present in numerous naturally occurring and biologically active molecules<sup>1</sup> with notable examples such as the flavaglines,<sup>2</sup> morphine alkaloids,<sup>3</sup> and lignans and neolignanans.<sup>4</sup> The biological importance of this motif has served as inspiration for numerous synthetic approaches to functionalized derivatives.<sup>5</sup> Some examples of these efforts include palladium-catalyzed Wacker-type oxidative cyclizations,<sup>6</sup> intramolecular palladium-catalyzed allylic alkylations,<sup>7</sup> copper or nickel catalyzed alkene diarylation or alkylarylation of allylphenyl ethers,<sup>8</sup> and palladium catalyzed C–H activation/C–O cyclizations.<sup>9</sup> Despite the attention these compounds have received in the synthetic community, a general cross-coupling approach employing aryl electrophiles and simple 2-allylphenol derivatives has yet to be reported.<sup>10</sup>

Over the past decade our group has developed a series of Pd-catalyzed alkene carboalkoxylation and carboamination reactions as a means of accessing functionalized, stereodefined heterocycles.<sup>11</sup> Despite the broad substrate scope of these transformations, previous attempts to access the 2,3dihydrobenzofuran core *via* Pd-catalyzed alkene carboalkoxylation with aryl or alkenyl halide electrophiles were met with limited success. For example, we have previously reported conditions for the construction of chroman derivatives (*e.g.*, **3a**) *via* Pd-catalyzed carboalkoxylation of 2-(but-2-enyl)phenols (*e.g.*, **1**), but the analogous generation of **4a** from 2-allylphenol **2a** proceeded in low yield (37%) (Scheme 1).<sup>12,13</sup> The main side product observed in these reactions resulted from base-



Scheme 1 Pd-catalyzed synthesis of chromans vs. dihydrobenzofurans.

mediated isomerization of the substrate alkene, which appeared to be relatively fast compared to the rate of catalysis.

Our prior studies on the mechanism of related Pd-catalyzed alkene carboamination reactions illustrated the rate of the key

#### Table 1 Ligand and solvent optimization<sup>a</sup>

+ PhOTf OH 2a		Pd(OAc) <sub>2</sub> (2 Ligand (5 m	mol%) nol%) Ph
		LiO <sup>/</sup> Bu, Sol Temperatur	vent e 4a
Entry	Solvent	Ligand	NMR yield <sup>b</sup> (isolated yield)
1	PhCF <sub>3</sub>	SPhos	50
2	PhCF <sub>3</sub>	XPhos	41
3	PhCF <sub>3</sub>	RuPhos	73
4	PhCF <sub>3</sub>	BrettPhos	73
5	PhCF <sub>3</sub>	CPhos	84 (85)
6	<sup>t</sup> BuOH	CPhos	46 <sup>c</sup>
7	PhCF <sub>3</sub>	None <sup>d</sup>	0

<sup>&</sup>lt;sup>*a*</sup> Reaction conditions: 1.0 equiv. 2a, 1.2 equiv. PhOTf, 1.4 equiv. LiO'Bu, 2 mol% Pd(OAc)<sub>2</sub>, 5 mol% ligand, solvent (0.125 M), 98 °C, 16 h. <sup>*b*</sup> NMR yields were determined using phenanthrene as an internal standard. <sup>*c*</sup> The reaction was conducted at 82 °C. <sup>*d*</sup> This control reaction was conducted in the absence of Pd(OAc)<sub>2</sub> and ligand.



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carbon-heteroatom bond-forming step, *syn*-aminopalladation of the alkene, was highly dependent on the electronic properties of the nucleophile, with electron-rich amines undergoing relatively fast reactions.<sup>14</sup> As such, we reasoned that the challenges associated with Pd-catalyzed alkene carboalkoxylations of 2-allylphenols were due at least in part to the relatively poor nucleophilicity of the aromatic alcohol substrate. We have recently demonstrated that Pd-catalyzed alkene carboamination reactions of electron-poor nucleophiles that fail under typical conditions can be conducted in high yield when reaction conditions that favor an anti-aminopalladation mechanistic pathway are employed.<sup>15–17</sup> In this communication we describe the application of these conditions to the Pd-catalyzed synthesis of dihydrobenzofurans from 2-allylphenols, which proceeds through a key anti-oxypalladation of the substrate's pendant alkene.<sup>18</sup>

We began our studies by exploring the coupling of 2-allylphenol 2a and phenyl triflate using conditions analogous to those previously employed in Pd-catalyzed alkene carboamination reactions that proceed *via anti*-aminopalladation of the alkene.<sup>15–17</sup> We were pleased to observe that a number of biaryl phosphine ligands provided the desired product 4a, with CPhos proving optimal to afford 85% yield of 4a (Table 1).



<sup>*a*</sup> Reaction conditions: 1.0 equiv. 2, 1.2 equiv. R-OTf, 1.4 equiv.  $\text{LiO}^{t}$ Bu, 2 mol% Pd(OAc)<sub>2</sub>, 5 mol% CPhos, PhCF<sub>3</sub> (0.125 M), 98 °C, 16 h. <sup>*b*</sup> Yields are isolated yields (average of two or more experiments) of material with >95% purity unless otherwise noted. Diastereomeric ratios were determined by <sup>1</sup>H NMR analysis, and diastereomeric ratios of isolated materials were identical to those of the crude products unless otherwise noted in the ESI. <sup>*c*</sup> The isolated product contained *ca*. 10% of unidentified impurities. <sup>*d*</sup> The reaction was conducted using BrettPhos as ligand. <sup>*e*</sup> The reaction was conducted using a 7.5 mol% loading of CPhos. <sup>*f*</sup> The reaction was conducted using 2.4 equiv. PhOTf and 2.4 equiv. LiOtBu in PhCF<sub>3</sub> (0.008 M). Diastereomeric ratio determined by GC.

With optimized reaction conditions in hand we explored the scope of this transformation (Table 2). We found that the reaction was fairly general with respect to the aryl triflate component, as electron-rich, electron-poor and ortho-substituted electrophiles all provided the desired dihydrobenzofuran products 4a-4d in good vield. However, alkenvl triflates were found to have limited efficacy in this transformation; product 4e was generated in only 25% yield. Substitution on the aromatic ring of the substrate was generally well-tolerated as substrates bearing halogens, methoxy groups, or fused aromatic rings were all converted to the desired products 4f-4l in good vield. The reactions were also effective with substrates bearing allylic substituents to afford trans-2,3-disubstituted products 4m-4p. The diastereoselectivity of these transformations was dependent on the size of the allylic group. Substrates bearing a methyl group were transformed with moderate stereocontrol (5-8:1 dr), whereas substrates that contain an allylic phenyl group were converted with high selectivity (15-29:1 dr). Finally, substitution at the internal alkene carbon atom was also tolerated to generate products 4q-4r. However, larger loadings of CPhos (7.5 mol%) were necessary to obtain reproducible yields. The synthesis of tricyclic rings from exomethylenecycloalkane derivatives proceeded with excellent stereocontrol to afford 4s-4v. The consecutive double carboalkoxylation of 2,3-diallylbenzene-1,4-diol proceeded to afford 4w in modest yield, but with low diastereoselectivity.

To probe the mechanism of this transformation by examining the stereochemistry of the alkene addition we carried out the Pd-catalyzed carboalkoxylation reaction of deuterated substrate d-2a with phenyl triflate (Scheme 2). This reaction afforded d-4a, which results from anti-addition of the oxygen atom and the aryl group to the alkene, in 81% yield and 20:1 dr. Interestingly, when d-2a was coupled with bromobenzene using the conditions previously employed for the synthesis of chromans the stereoisomeric product d-4a, generated via synaddition to the alkene, was formed (albeit in low yield with modest 2:1 dr).<sup>19</sup> This further illustrates the impact of reaction conditions on the stereochemistry of the heteropallada-Pd-catalyzed alkene difunctionalization tion step in reactions.<sup>15–17,20</sup>

Based on the results of the deuterium labelling experiments, the Pd-catalyzed alkene carboalkoxylation reactions of 2-allylphenols likely proceed through the catalytic cycle illus-



Scheme 2 Deuterium labeling experiments.





trated in Scheme 3. Oxidative addition of the aryl triflate to the Pd(0)/CPhos complex (generated in situ) affords intermediate palladium(aryl)triflate complex 5. The cationic Pd-complex then binds to the alkene of substrate 2 to yield 6. Deprotonation of the phenol followed by anti-oxypalladation of the alkene provides intermediate 7, which undergoes reductive elimination to give the product 4 with concomitant regeneration of the Pd(0) catalyst.

Given the utility of these new conditions for Pd-catalyzed alkene-carboalkoxylation reactions of 2-allylphenols, we elected to briefly survey the utility of these conditions in chroman-forming reactions. As shown in Table 3, our newly developed conditions successfully promoted the coupling of 1 with three different aryl triflates to afford chromans 3a-c. The yields obtained using the anti-oxypalladation conditions with phenyl triflate or p-methoxyphenyl triflate as the electrophile

Table 3 Comparison of conditions for chroman synthesis<sup>a</sup>



<sup>a</sup> Reaction conditions for X = OTf: 1.0 equiv. 1, 1.2 equiv. R-OTf, 1.4 equiv. LiO<sup>t</sup>Bu, 2 mol% Pd(OAc)<sub>2</sub>, 5 mol% ligand, solvent (0.125 M), 98 °C, 16 h. Reaction conditions for X = Br: 1.0 equiv. 1, 2.0 equiv. R-Br, 2.0 equiv. NaO<sup>t</sup>Bu, 2 mol% Pd<sub>2</sub>(dba)<sub>3</sub>, 4 mol% S-Phos, toluene (0.25 M), 110 °C. <sup>b</sup> Yields are isolated yields (average of two or more experiments) of material with >95% purity. <sup>c</sup> Yields as reported in ref. 12.

were lower than the analogous reactions we have previously reported with aryl bromide electrophiles and *syn*oxypalladation conditions (entries 1 and 2). However, the *anti*oxypalladation conditions provided results superior to those obtained using the *syn*-oxypalladation conditions with an electron-poor aryl electrophile (entry 3).

## Conclusions

In conclusion, we have developed a new method for the synthesis of 2,3-dihydrobenzofurans *via* the Pd-catalyzed alkene carboalkoxylation of 2-allylphenols. The reactions proceed in good yields with diastereoselectivities of 5:1 to >20:1 dr, and are effective with a broad range of aryl triflate electrophiles. This provides a new means of rapidly generating many different substituted 2,3-dihydrofurans from the corresponding phenol in a short synthetic sequence. Moreover, this further illustrates the utility of conditions that favor *anti*heteropalladation pathways in Pd-catalyzed alkene diffunctionalization reactions of relatively weak nucleophiles.

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