

# Rhodium(III)-Catalyzed Redox-Neutral C—H Arylation via Rearomatization

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Supporting Information

**ABSTRACT:** Rhodium(III)-catalyzed arylation of arenes bearing a chelating group has been realized via a redox-economy process using 4-hydroxycyclohexa-2,5-dienones as the arylating reagents, leading to the synthesis of 3-arylated phenols. This redox-neutral process proceeds via a C—H activation pathway with rearomatization being the driving force.

Recently, rhodium(III) Cp\* complexes have been extensively explored as active catalysts for activation of arene C–H bonds, particularly for C–C and C–N bond formation. A large number of new synthetic methods have been developed by following this Rh(III)-catalyzed C–H activation strategy under both oxidative and redox-neutral conditions. In most cases, the C–H activation of arenes is facilitated by an *ortho* chelating group, and a large variety of coupling partners has been established, including strained rings, alkenes, alkynes, and a broad scope of activated  $\pi$  bonds such as aldehydes, ketones, isocyanates, isonitrile, activated carbenes, and azides. Therefore, rhodium(III) catalyzed C–H activation has been recognized as a powerful strategy for new bond construction with high functional group compatibility, high catalytic efficiency, a broad substrate scope, and operational simplicity. It has been realized as an important complement to C–H activation catalyzed by other metal systems such as palladium, ruthenium, and copper.

Despite the significant progress, it remains necessary to develop new methods of C-C coupling. In particular, although biaryls are known as important building blocks in the pharmaceutical industry and in material studies, only limited examples of C-H arylation of arenes have been realized by Rh(III) catalysis. 13 These oxidative systems utilized a (hetero)arene as the arylating reagent for direct C-H/C-H coupling (Scheme 1). On the other hand, Li<sup>14</sup> and Huang<sup>15</sup> have independently applied Rh(III) catalysts to the redox-neutral insertion of arene C-H bonds into  $\alpha_{\beta}$ -unsaturated ketones, <sup>16</sup> leading to  $\beta$ -aryl ketone products. Clearly, C–H arylation under redox-neutral conditions would be highly desirable. To achieve this redox-economic C-H arylation process, the oxidizing power needs to be restored into the arylating reagent. With this hypothesis in mind, we have designed substituted 4hydroxycyclohexa-2,5-dienones as the arylating reagent, which can be regarded as an internal oxidizing coupling partner because, following insertion of the olefin into the arene C-H bond, eventual rearomatization should be realized upon dehydration and tautomerization. This would lead to the

Scheme 1. Rhodium(III)-Catalyzed C-C Coupling

synthesis of 3-arylated phenols as the coupling products, which are widely present as an important structure motif in natural products and pharmaceuticals. <sup>17</sup> In fact, this rearomatization strategy has been utilized in coupling reactions. <sup>18</sup> However, challenges remain in this process. This dienone is already a disubstitituted cyclic olefin with no ring strain. This is made worse by the  $\gamma$ -branching which further lowers its reactivity toward migratory insertion of an incipient Rh–C bond. In addition, the phenol product and the water coproduct may also exhibit product inhibition.

We initiated our studies with the screening of the conditions for the coupling of 2-PhPy and 4-hydroxy-4-methylcyclohexa-2,5-dienone. It was found that while a clean coupling occurred when [Cp\*RhCl<sub>2</sub>]<sub>2</sub>(5 mol %)/AgSbF<sub>6</sub>(20 mol %) was applied as a catalyst, the desired product 3aa was isolated in only 45% yield due to low conversion (Table 1). Using a slightly higher ratio (6:1) of AgSbF<sub>6</sub> to the rhodium increased the yield of 3aa to 51%. However, using a larger ratio caused inhibition. A screening of solvents revealed that essentially no conversion was observed in oxygen-containing solvents, and DCE was

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Table 1. Screening of the Reaction Conditions a,b

onter	additive (mol %)	solvent	yield
entry	, ,		,
1	$AgSbF_6$ (20)	DCM	45
2	$AgSbF_6$ (30)	DCM	51
$3^c$	none	DCM	39
4	$AgSbF_6$ (30)	DCE	68
5	$AgSbF_6$ (30)	1,4-dioxane	trace
6	$AgSbF_6$ (30)	PhCl	37
7	$AgSbF_6$ (30)	THF	trace
8	$AgSbF_6$ (30)	acetone	trace
9	AgSbF <sub>6</sub> (30)/HOAc (200)	DCE	46
10	AgSbF <sub>6</sub> (30)/PivOH (200)	DCE	41
11	$AgSbF_6 (30)/Zn(NTf_2)_2 (20)$	DCE	76
12	$AgSbF_6 (30)/Zn(NTf_2)_2 (40)$	DCE	42
13	$AgSbF_{6} (30)/Zn(OTf)_{2} (20)$	DCE	44
14	$AgSbF_6$ (30)/ $Al(OTf)_3$ (20)	DCE	nd
15	$AgSbF_6 (30)/In(OTf)_3 (20)$	DCE	trace
16	$AgSbF_6 (30)/Cu(OTf)_2 (20)$	DCE	40
17	$AgSbF_6 (30)/Ca(OTf)_2 (20)$	DCE	65

"Reactions conditions: 2-phenylpyridine 1a (0.2 mmol), 2a (0.24 mmol), 20 h, [RhCp\*Cl<sub>2</sub>]<sub>2</sub> (5 mol %), solvent (2 mL), sealed tube under argon. <sup>b</sup>Isolated yield after chromatography. <sup>c</sup>[Cp\*Rh-(MeCN)<sub>3</sub>](SbF<sub>6</sub>)<sub>2</sub> (10 mol %) was used.

identified as the optimal one. Addition of AcOH or PivOH, which was often used as an additive to facilitate C–H activation, failed to give any positive effect. To our delight, when  $\text{Zn}(\text{NTf}_2)_2$  (20 mol %) was introduced as an additional additive, the yield of **3aa** was increased to 76%, while using a larger amount of  $\text{Zn}(\text{NTf}_2)_2$  also caused inhibition. In all cases, no diarylation was detected. Thus the optimal conditions constitute the combination of  $[\text{Cp*RhCl}_2]_2$  (5 mol %), AgSbF<sub>6</sub> (30 mol %), and  $\text{Zn}(\text{NTf}_2)_2$  (30 mol %) in DCE at 100 °C for 20 h. In contrast to the good yield of **3aa** using 4-hydroxy-4-methylcyclohexa-2,5-dienone as a substrate, switching to 4-methoxy-4-methylcyclohexa-2,5-dienone afforded **3aa** in only 42% yield.

With the establishment of the optimal conditions, the scope and limitation of this coupling system were next explored. The scope of the arene in the coupling with 2a was examined first (Scheme 2). Introduction of a variety of electron-donating and -withdrawing, as well as halogen, substituents into either the pyridine ring or the phenyl ring of 2-phenylpyridines is welltolerated, and the products were isolated in yields ranging from 40% to 81%. Introduction of a relatively bulky substituent (CH<sub>3</sub>, Br) into the meta position caused the C-H arylation to occur at a less hindered ortho position (3ha, 3ja). In line with this observation, the C-H arylation took place at the less hindered ortho position for the 2-(2-naphthyl)pyridine substrate (3ia). In contrast, when a meta OMe group was installed, a mixture of two regioisomeric products was obtained in a 1.5:1 ratio (30a, 30a'), probably due to the reduced steric bulk of this group. Instead, the directing effect of the OMe group might be operational. When the directing group (DG) was changed to a quinolyl group, a lower yield of the coupled product (3pa, 3ra) was isolated, likely due to the increased

Scheme 2. Arylation of Arenes: Scope of the Arene<sup>a,b</sup>

"Reactions conditions: arene (0.2 mmol), **2a** (0.24 mmol), [RhCp\*Cl<sub>2</sub>]<sub>2</sub> (5 mol %), AgSbF<sub>6</sub> (30 mol %), Zn(NTf<sub>2</sub>)<sub>2</sub> (20 mol %), DCE (2 mL), 100 °C, 20 h, sealed tube under argon.  $^b$  Isolated yield.

steric hindrance of the DG. The arene ring is not limited to benzene rings. Indoles and thiophenes also coupled with 2a, but in moderate or low yield (3sa, 3ta).

The scope of the dienone substrate was next explored in the coupling with 2-PhPy (Scheme 3). Introduction of a substituent into the  $\alpha$  position of the carbonyl group is tolerated (3ac, 3ad), and C–H arylation occurred at the less hindered olefin unit. This observation is also in line with a  $\beta$ -methyl substituted dienone, where a 3,4,5-trisubstituted phenol (3ae) was obtained. Variation of the 4- substituent to different alkyls and to methoxy has been performed (3ab, 3af, 3ag). Thus 4,4-dimethoxycyclohexa-2,5-dienone coupled with higher reactivity even at 40 °C, and the product (3ab) was isolated in 60% yield, while the reaction performed under the standard conditions led to decomposition. To our delight, replacing the

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Scheme 3. Arylation of Arenes: Scope of the Dienone a,b

<sup>a</sup>Reactions conditions: **1a** (0.2 mmol), **2a** (0.24 mmol),  $[RhCp*Cl_2]_2$  (5 mol %),  $AgSbF_6$  (30 mol %),  $Zn(NTf_2)_2$  (20 mol %), DCE (2 mL), 100 °C, 20 h, sealed tube under argon. <sup>b</sup> Isolated yield. <sup>c</sup> T=40 °C.

methyl group in the dienone substrate with a CF<sub>3</sub> increased the coupling efficiency and product **3ag** was isolated in high yield, likely ascribable to the enhanced electrophilicity of the dienone substrate induced by the CF<sub>3</sub> group. Importantly, the dienone can be extended to its *N*-Ts imine derivative, where the analogous product **3ah** was obtained in 50% yield, while 2-(3-bromophenyl)pyridine coupled to give **3ai** with lower efficiency, indicating that these conditions are not optimal for the *N*-Ts imine substrate.

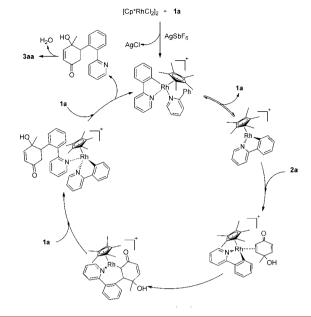
Several experiments have been carried out to probe the reaction mechanism. Cyclometalated Rh(III) complex 4 was prepared and was designated as a catalyst precursor (10 mol %) for the coupling of 2-PhPy and 2a in the presence of  $AgSbF_6$  (30 mol %) and  $Zn(NTf_2)_2$  (20 mol %) (Scheme 4). The fact

#### Scheme 4. Mechanistic Studies

that product 3aa was isolated in comparable yield (70%) suggests the relevancy of C–H activation, and a cationic cyclometalated rhodium(III) species is likely involved. To further probe this C–H activation process, the intermolecular KIE has been measured using an equimolar mixture of 2-PhPy and 2-PhPy- $d_5$  in the competitive coupling with 2a at a low conversion. A KIE value of 2.0 was obtained from  $^1\mathrm{H}$  NMR analysis, and this suggests that the C–H cleavage is probably involved in the rate-limiting step.

A plausible mechanism to account for this catalytic process is given in Scheme 5 on the basis of our observations and literature precedent. Cyclometalation of 2-PhPy affords a

## Scheme 5. Proposed Mechanism



cationic rhodium(III) intermediate. Subsequent olefin insertion into the incipient Rh–C bond generates a Rh(III) alkyl intermediate, where the olefin insertion is proposed to be facilitated by  ${\rm Zn}({\rm NTf_2})_2$  which enhanced the electrophilicity of the dienone substrate. Protonolysis of the Rh–alkyl bond or ligand metathesis/cyclometalation with an incoming 2-PhPy releases the Rh(III) species, and the alcohol intermediate undergoes dehydration and tautomerization to furnish the final product.

In summary, we have realized a Rh(III)-catalyzed C–H arylation of arenes using cyclohexa-2,5-dienones as an arylating substrate by taking advantage of rearomatization. This reaction proceeds via a C–H activation pathway to afford diand trisubstituted phenols. A relatively broad spectrum of both coupling partners has been defined. The current C–H acrylation method expanded the strategy and applications of Rh(III)-catalyzed C–H activation/C–C coupling reactions and may find synthetic utility in the construction of complex molecules.

## ASSOCIATED CONTENT

#### Supporting Information

Experimental details, characterization data, and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Note

The authors declare no competing financial interest.

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