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

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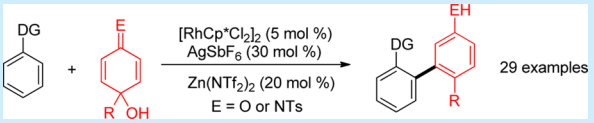
Supporting Information

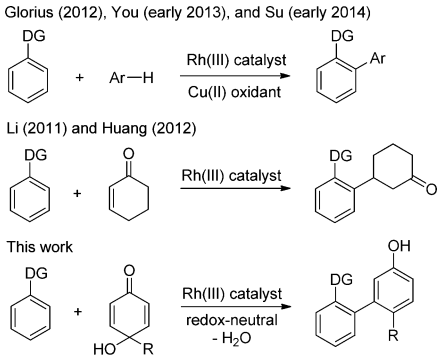
ABSTRACT: Rhodium(III)-catalyzed arylation of arenes bearing a chelating group has been realized via a redox-economy process using 4-hydroxycyclohexa-2,5-dienones as the arylating reagents, leading to the synthesis of 3-arylated phenols. This redox-neutral process proceeds via a C−H activation pathway 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.[1] 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.[2] 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,[3] alkenes,[4] alkynes,[2e,5] and a broad scope of activated π bonds such as aldehydes,[6] ketones,[7] isocyanates,[8] isonitrile,[9] activated carbenes,[10] and azides.[11] 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.[12]

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[14] and Huang[15] have independently applied Rh(III) catalysts to the redox-neutral insertion of arene C−H bonds into α,β-unsaturated ketones,[16] leading to β-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 4-hydroxycyclohexa-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 synthesis of 3-arylated phenols as the coupling products, which are widely present as an important structure motif in natural products and pharmaceuticals.[17] In fact, this rearomatization strategy has been utilized in coupling reactions.[18] However, challenges remain in this process. This dienone is already a disubstitituted cyclic olefin with no ring strain. This is made worse by the γ-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.

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



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 $[Cp^*RhCl_2]_2$(5 mol %)/$AgSbF_6$(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 $AgSbF_6$ 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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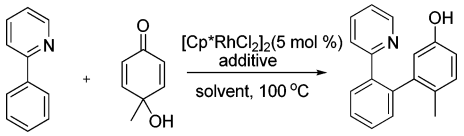
Table 1. Screening of the Reaction Conditions[a,b]



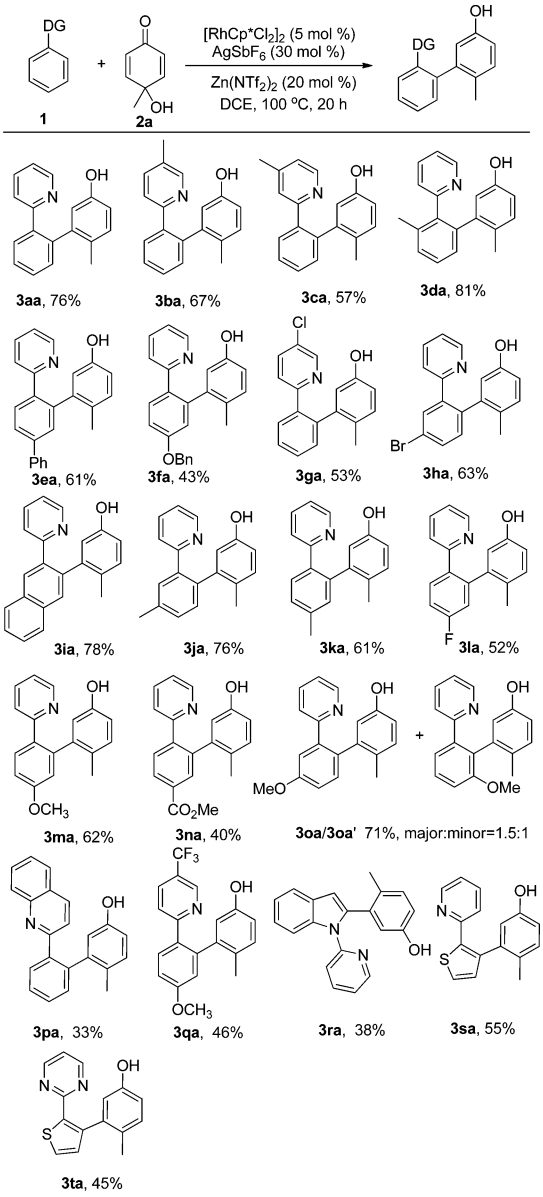
entry	additive (mol %)	solvent	yield
1	$AgSbF_6$ (20)	DCM	45
2	$AgSbF_6$ (30)	DCM	51
3[c]	none	DCM	39
4	$AgSbF_6$ (30)	DCE	68
5	$AgSbF_6$ (30)	1,4-dioxane	trace
6	$AgSbF_6$ (30)	PhCl	37
7	$AgSbF_6$ (30)	THF	trace
8	$AgSbF_6$ (30)	acetone	trace
9	$AgSbF_6$ (30)/HOAc (200)	DCE	46
10	$AgSbF_6$ (30)/PivOH (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

[a]Reactions conditions: 2-phenylpyridine **1a** (0.2 mmol), **2a** (0.24 mmol), 20 h, $[RhCp^*Cl_2]_2$ (5 mol %), solvent (2 mL), sealed tube under argon. [b]Isolated yield after chromatography. [c]$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (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 $Zn(NTf_2)_2$ (20 mol %) was introduced as an additional additive, the yield of **3aa** was increased to 76%, while using a larger amount of $Zn(NTf_2)_2$ also caused inhibition. In all cases, no diarylation was detected. Thus the optimal conditions constitute the combination of $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (30 mol %), and $Zn(NTf_2)_2$ (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 well-tolerated, and the products were isolated in yields ranging from 40% to 81%. Introduction of a relatively bulky substituent (CH_3, 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 (**3oa**, **3oa′**), 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[a,b]



[a]Reactions conditions: arene (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. [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 α 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 β-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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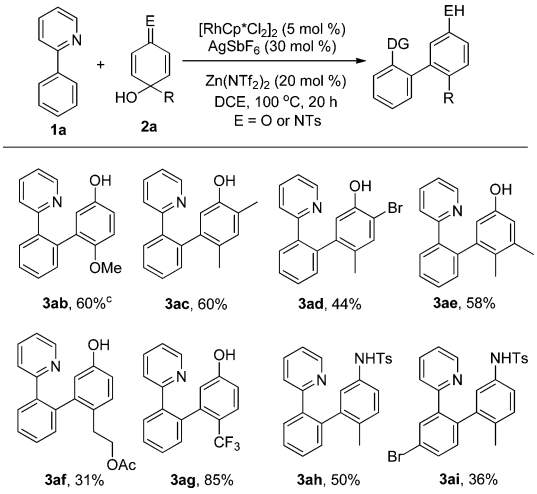
Scheme 3. Arylation of Arenes: Scope of the Dienone[a,b]

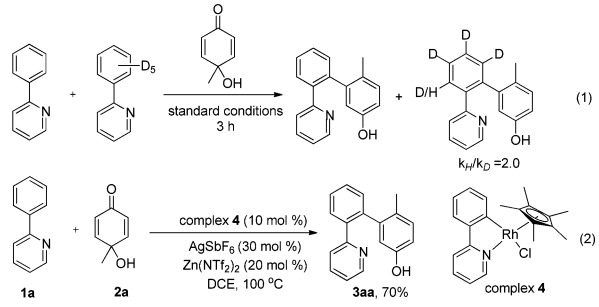


[a]Reactions conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (30 mol %), $Zn(NTf_2)_2$ (20 mol %), DCE (2 mL), 100 °C, 20 h, sealed tube under argon. [b] Isolated yield. [c] T = 40 °C.

methyl group in the dienone substrate with a CF_3 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_3 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

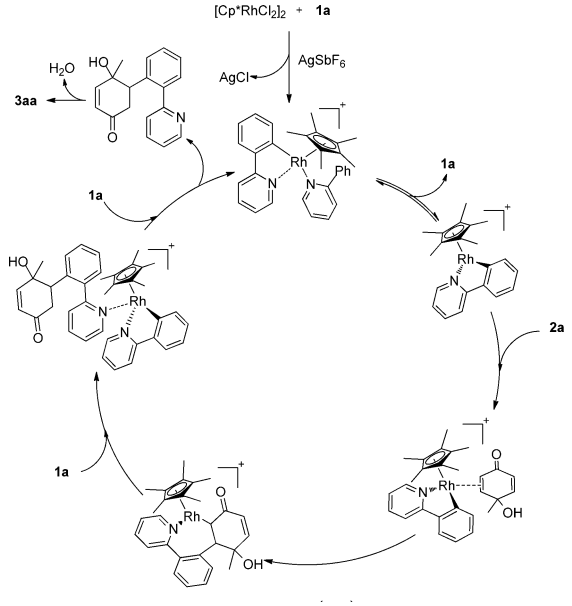
Scheme 4. Mechanistic Studies



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}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 $Zn(NTf_2)_2$ 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 di- and 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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Notes

The authors declare no competing financial interest.

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