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Mechanism of the Rhodium(III)-Catalyzed Arylation of Imines via C−H Bond Functionalization: Inhibition by Substrate

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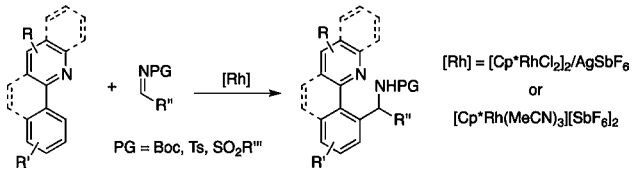
Supporting Information

ABSTRACT: Rh(III)-catalyzed arylation of imines provides a new method for C−C bond formation while simultaneously introducing an α-branched amine as a functional group. This detailed mechanistic study provides insights for the rational future development of this new reaction. Relevant intermediate Rh(III) complexes have been isolated and characterized, and their reactivities in stoichiometric reactions with relevant substrates have been monitored. The reaction was found to be first order in the catalyst resting state and inverse first order in the C−H activation substrate.

Arylations of alkenes and alkynes have been well explored in the area of chelation-controlled Rh-catalyzed C−H bond functionalization.[1] Our groups and the Shi group recently extended the scope of such reactions to Rh(III)-catalyzed arylation of imines (Scheme 1).[2] This transformation provides a convenient synthesis of α-branched amines with simultaneous C−C bond formation. The reaction can be conducted under mild conditions and displays excellent functional group compatibility.[2] Further advances in this field include the arylation of other polarized C−X multiple bonds such as aldehydes,[3] isocyanates,[4] isonitriles,[5] and CO.[6]

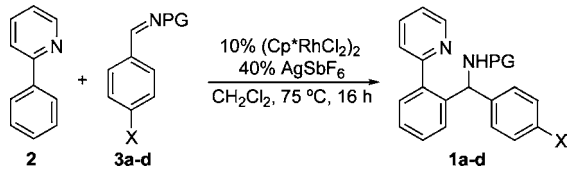
Scheme 1. Rh(III)-Catalyzed Imine Arylation



While the mechanism of chelation-controlled Rh(III) catalysis assisted by acetate has been explored,[7] only limited information is available for the arylation of imines employing either $[Cp^*Rh(MeCN)_3][SbF_6]_2$ or a mixture of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ as a catalyst. Herein we report an investigation of the mechanistic steps of the reaction from catalyst initiation to C−C bond formation and subsequent catalyst propagation (product release). Relevant intermediates were isolated and characterized by X-ray diffraction (XRD). In an unusual finding, the rate law for the reaction revealed substrate inhibition of the catalyst.

For our mechanistic investigations, we first studied the arylation of N-protected aromatic imines bearing *N*-tosyl, *N*-Boc, and *N*-isopropoxycarbonyl protecting groups with 2-phenylpyridine (**2**) (Table 1). A considerably higher yield of

Table 1. Protecting Groups in Imine Arylation[a]



entry	PG	X	product	% yield
1	Ts	H	**1a**	40[2a]
2[b]	Boc	H	**1b**	55[2a]
3	Boc	H	**1b**	82[2a]
4	Boc	CF_3	**1c**	95[2a]
5	C(O)O*i*Pr	H	**1d**	81

[a]0.05 mmol of **3**, 0.10 mmol of **2**, 5.0 μmol of $[Cp^*RhCl_2]_2$, 0.02 mmol of $AgSbF_6$, 0.70 mL of CH_2Cl_2, T = 75 °C, t = 16 h. [b]0.05 mmol of **2**.

Boc-amine **1a** was observed when a 2-fold excess of **2** relative to imine **3a** was employed (entries 2 and 3).[2a]

In addition to previously reported transformations using *N*-Boc- and *N*-tosyl-protected imines,[2a] isopropoxycarbonyl was included as a protecting group to provide a model substrate for our kinetic analysis of the reaction. This was necessary because kinetic study employing *N*-tosylimines would provide only limited information as a result of the reversibility of C−C bond formation and an unfavorable equilibrium between the substrate and product.[2a] On the other hand, while the reaction with *N*-Boc-protected imine **3b** is not reversible,[2a] competitive deprotection of the Boc group under the slightly acidic reaction conditions complicates the kinetic analysis. The *N*-isopropoxycarbonylimine functionality in **3d** is comparably electrophilic to the *N*-Boc imine and gives similar yields (82 vs 81%) but is stable toward acids. Importantly, no back reaction to **2** or **3d** was observed when *N*-isopropoxycarbonylamine **1d** was treated with

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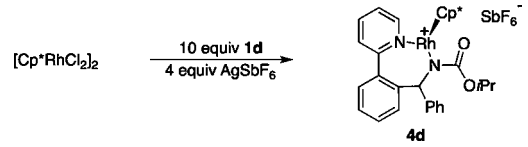
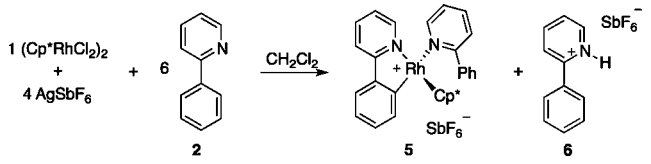
Scheme 2. Irreversibility of C−C Bond Formation



20 mol % of Rh(III) catalyst (Scheme 2). However, quantitative formation (with respect to Rh) of complex **4d** was observed.

Our first objective was to gain insight regarding the nature of the catalytic species and which reagents are involved in its formation. To address this issue, we heated **2**, $[Cp^*RhCl_2]_2$, and $AgSbF_6$ (6:1:4) in CH_2Cl_2 to 75 °C for 16 h (Scheme 3).

Scheme 3. Cyclometalation



We observed the formation of a mixture of cyclometalated Rh complex **5**, pyridinium salt **6**, and AgCl.[8] The mixture exhibited broadened resonances in the ^1H NMR spectra indicative of ligand exchange with **2**. From a concentrated solution of **5** and **6** in $CHCl_3$, single crystals of **5** suitable for XRD analysis were obtained (Figure 1). Cp* complex **5** has a three-legged piano

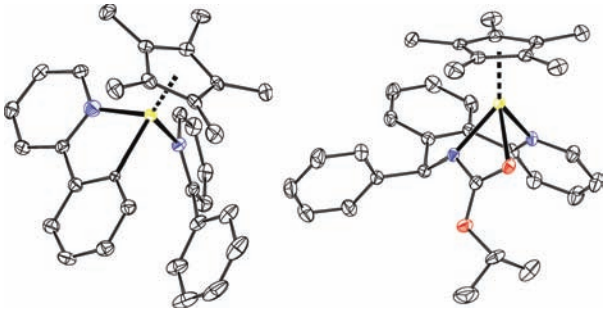


Figure 1. Thermal ellipsoid plots of (left) **5** and (right) **4d** depicted at the 50% probability level. H atoms and SbF_6 anions have been omitted for clarity.[9,10]

stool configuration, with one 2-phenylpyridine acting as a bidentate $\kappa C,\kappa N$ ligand and the other saturating the free valence site of the Rh center as a monodentate κN ligand.

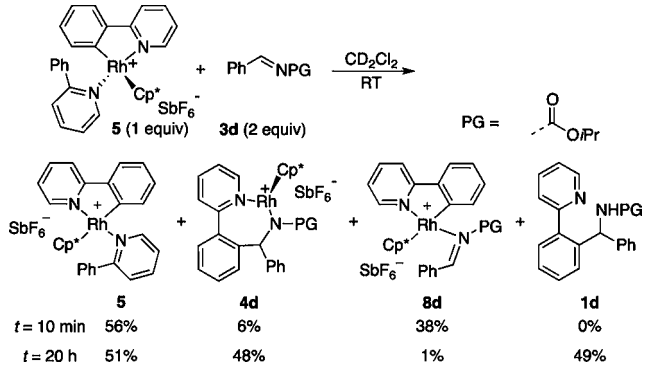
Cyclometalation of **2** could also be performed at room temperature. Presumably, during cyclometalation of $[Cp^*RhCl_2]_2$ with **2**, one molecule of **2** acts as a base in a concerted metalation−deprotonation (CMD)-type mechanism[11] similar to the acetate-assisted mechanism described by Jones et al.[7a]

Quantitative separation of **5** from **6** proved difficult, and only moderate yields of **5** could be obtained. Therefore, we sought an alternative preparative route to **5**. Complex **7**, which is readily available by cyclometalation of $[Cp^*RhCl_2]_2$ with **2** in the presence of NaOAc,[12] served as a convenient precursor and afforded **5** in 99% yield by chloride abstraction with $AgSbF_6$ in the presence of excess **2** (Scheme 4).[13] In CH_2Cl_2 solution, decomposition of **5** began to occur within a few hours at room temperature, whereas no decomposition was observed in a solution containing excess **2**.

Scheme 4. Alternative Access to Resting State 5

To investigate the C−C bond-formation step of imine arylation, we monitored the reaction of a 1:2 mixture of **5** and imine **3d** in CD_2Cl_2 at room temperature (Scheme 5). Initial

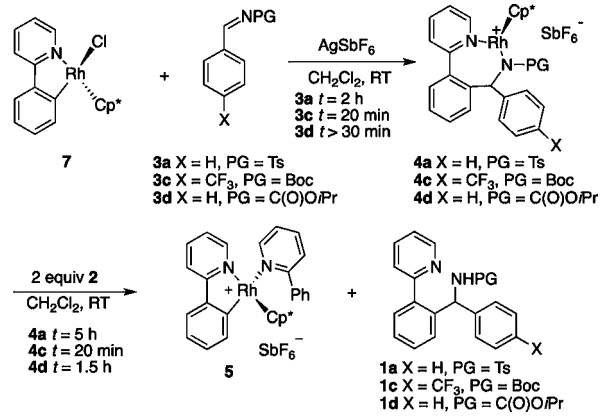
Scheme 5. Resting States during Imine Arylation



formation of imine adduct complex **8d** was observed, and this material was consumed almost completely within 20 h in favor of **4d** with concomitant formation of amine **1d**.[14]

We next developed an independent synthesis of complexes **4a**, **4c**, and **4d** by adding CH_2Cl_2 solutions of the respective imines to a mixture of $AgSbF_6$ and **7** at room temperature (Scheme 6).[15] After crystallization, complexes **4a**, **4c**, and **4d**

Scheme 6. C−C Bond Formation and Propagation



were obtained in 73, 81, and 66% yield, respectively. These materials were stable in CD_2Cl_2 for several days.

We were able to obtain single crystals of **4a**, **4c**, and **4d** suitable for XRD analysis by slow diffusion of *n*-pentane into a saturated solution of the respective compounds in CH_2Cl_2. The solid-state structure of Cp* complex **4d** (Figure 1) exhibits a three-legged piano stool configuration, with the deprotonated amine **1d** acting as a tridentate ligand that coordinates to the Rh center via its two N atoms and the carbonyl oxygen of the protecting group.

To gain further insight into the catalyst propagation step, complexes **4** were next treated with 2 equiv of the unsubstituted

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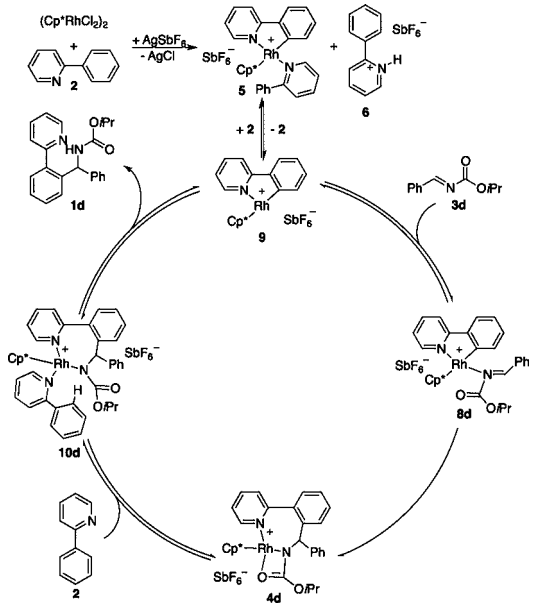
starting material **2**. For **4a**, the C−H activation complex **5** was quantitatively generated within 5 h with concomitant release of the amine product **1a** (Scheme 6). Similarly, **4c** reacted to give complex **5** within 30 min and **4d** within 1.5 h.

From these stoichiometric transformations (Schemes 5 and 6), we conclude that $AgSbF_6$ and pyridinium salt **6** play nonessential roles during imine insertion into the Rh−C bond and during amine release/catalyst propagation, while the 18-valence-electron (VE) complexes **5** and **4a,c,d** represent resting states of the reaction whose relative amounts depend on the respective amounts of substrates **2** and **3** and product **1**.

We propose a catalytic cycle for the Rh(III)-catalyzed arylation of imines (Scheme 7) in which the precatalyst mixture of $AgSbF_6$

Scheme 7. Proposed Mechanistic Cycle



and $[Cp^*RhCl_2]_2$ rapidly forms resting state **5** and pyridinium salt **6**, with **2** acting as a base during CMD. To enter the catalytic cycle, 18-VE complex **5** needs to lose ligand **2**, yielding 16-VE complex **9**. Addition of imine **3d** leads to complex **8d**, which is transformed to **4d** by insertion of the C−N double bond into the Rh−C bond. The catalytic cycle proceeds by coordination of **2** to give intermediate **10d**. Presumably, the amide nitrogen ligand in **10d** acts as a base during CMD, releasing amine **1d** with simultaneous cyclometalation of **2** to regenerate catalyst **9**.

However, alternate mechanisms involving cocatalysts such as pyridinium salt **6** or $AgSbF_6$ are also possible. To determine the effects of such additives, we decided to conduct a kinetic analysis of the reaction (^{1}H NMR monitoring) employing imine **3d** as a model substrate (see above). To simplify the kinetic analysis, a 6-fold excess of **2** relative to **3d** was used to suppress resting state **4d** in favor of **5**.[16] Lastly, we switched from CH_2Cl_2 to 1,2-dichloroethane (DCE) to eliminate complications that might result from monitoring the reaction above the reaction solution's boiling point.

Figure 2 depicts the consumption of **3d** and formation of **1d** over time using 11 mol % **5** as a catalyst. The reaction followed first-order kinetics with $k = 0.24$ h^{-1} for **1d** formation (Table 2, entry 1) and a slightly larger rate constant for **3d** consumption ($k = 0.28$ h^{-1}). In subsequent runs of the reaction, varying amounts of **6** were added. The reaction remained first-order in

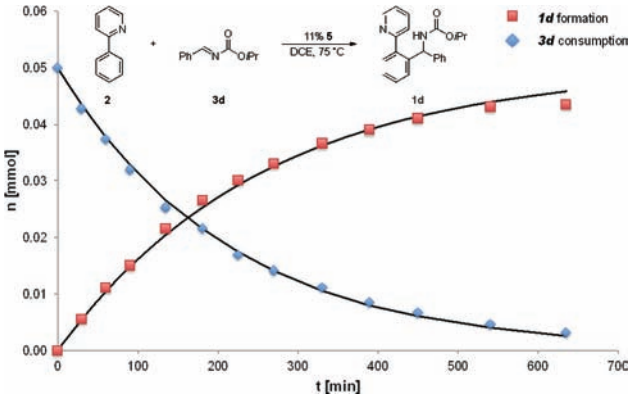


Figure 2. Monitoring (^{1}H NMR) of the arylation of imine **3d** with **2**. Conditions: 0.050 mmol of **3d**, 0.300 mmol of **2**, 0.050 mmol of C_6Me_6 (as internal NMR standard), 5.6 μmol of **5**, 0.70 mL of DCE, $T = 75$ °C. Black lines (simulated): $[\mathbf{3d}]_t = [\mathbf{3d}]_0 e^{-kt}$ ($k = 0.24$ h^{-1}) and $[\mathbf{1d}]_t = [\mathbf{3d}]_0(1 - e^{-kt})$ ($k = 0.28$ h^{-1}).

Table 2. Reaction Rates[a]

entry	[Rh]	additive (mol %)	k[b] (h^{-1})	k_{rel}
1	**5**[c]	none	0.24	1.00
2	**5**[c]	**6** (5)	0.27	1.13
3	**5**[c]	**6** (10)	0.31	1.30
4	**5**[c]	**6** (20)	0.35	1.48
5	**5**[c]	**6** (40)	0.25	1.05
6	**5**[c]	$AgSbF_6$ (12)	0.32	1.36
7	$[Cp^*RhCl_2]_2$[d]	$AgSbF_6$ (23)	0.28	1.20

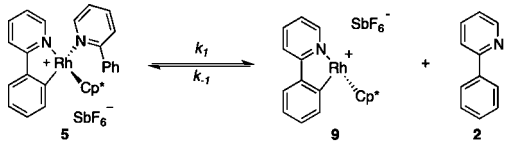
[a]0.05 mmol of **1d**, 3.00 mmol of **2**, 0.05 mmol of C_6Me_6, DCE (total volume 0.70 mL), $T = 75$ °C. [b]Determined from logarithmic plots over the first 5−6 h (75−80% conversion) [c]5.6 μmol. [d]2.8 μmol.

all cases. While 20 mol % **6** increased the reaction rate by a factor of 1.48 (entries 2−4), addition of 40 mol % **6** resulted in in only a very modest effect (entry 5). Similarly, $AgSbF_6$ also resulted in only a small increase in the rate (entry 6). These modest effects on the reaction rate could either result from direct involvement of **6** or $AgSbF_6$ or be promoted by a change in the polarity of the medium.

When we employed a 1:4 mixture of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ as a catalyst, the reaction maintained first-order kinetics with $k = 0.28$ h^{-1} (Table 2, entry 7), which is very similar to the rate constant observed when **5** and **6** were employed in a 1:1 ratio ($k = 0.31$ h^{-1}; entry 3). We consider this observation as evidence that the precatalyst mixture of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ forms **5** and **6** as the catalytically active compounds in the reaction.

To determine the rate law, we monitored the reaction with various amounts of resting state **5** and substrate **2**. The reaction was found to be first order in **5** and inverse first order in **2**.[14]

We propose the mechanism shown in eqs 1 and 2 for this overall transformation. Complex **9** is produced in a fast



(1)

equilibrium from resting state **5** by dissociation of **2** (eq 1). The time dependence of [**9**] is given by the sum of its rates of

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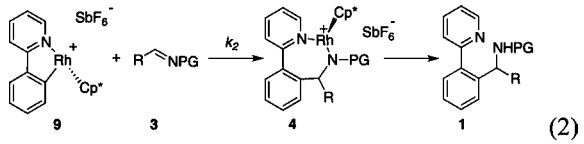

(2)

formation from **5** and consumption by reaction with **3d** and **2** (eq 3).[17] Setting d[**9**]/dt equal to zero and solving for [**9**] gives

$$-\frac{d[9]}{dt} = 0 = k_1[5] - k_{-1}[9][2] - k_2[9][3d] \quad (3)$$

$$[9] = \frac{k_1[5]}{k_{-1}[2] + k_2[3d]} \approx \frac{k_1[5]}{k_{-1}[2]} \quad (4)$$

the steady-state concentration (eq 4). We assume that $k_{-1}[2] \gg k_2[3d]$ because stoichiometric transformations (Scheme 6) indicated that $k_{-1} > k_2$[18] and at least a 4-fold excess of **2** relative to **3d** was used in the kinetics studies. Insertion of eq 4 into eq 5

$$-\frac{d[3d]}{dt} = \frac{d[4d]}{dt} = k_2[3d][9] \quad (5)$$

$$-\frac{d[3d]}{dt} = \frac{k_1k_2[3d][5]}{k_{-1}[2]} = k_{obs}\frac{[3d][5]}{[2]} \quad \left(k_{obs} = \frac{k_1k_2}{k_{-1}}\right) \quad (6)$$

yields eq 6 as our expression for the rate law. With k_{obs} = 0.060 h^{-1}, eq 6 produced excellent fits for the observed amine formation in the catalytic runs with 4−8 equiv of **2**.[14]

In conclusion, we have provided a detailed study of the mechanism of Rh(III)-catalyzed imine arylation with 2-phenylpyridine (**2**). The precatalyst mixture of [Cp*RhCl$_2$]$_2$ and AgSbF$_6$ leads to cyclometalation of **2** to yield resting state **5** and pyridinium salt **6** via a CMD mechanism. After formation of **5**, both AgSbF$_6$ and **6** are not essential for catalysis. While the basicity of **2** plays an important role during catalyst initiation (cyclometalation), it also accounts for substrate inhibition by stabilizing resting state **5**. Insertion of imines into the Rh−C bond affords amide complex **4**. Product release from intermediate **4** occurs simultaneously with cyclometalation with **2**, regenerating **5**, during which the deprotonated amine ligand serves as a base during CMD. Thus, only catalyst initiation benefits from the basicity of **2**, while this basicity inhibits catalyst turnover. In consequence, possible future directions for imine arylation could include an alternate catalyst initiation, potentially permitting a broader scope of the arylating substrate.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for syntheses; kinetic experiments; NMR spectra for all compounds; and crystallographic data (CIF) for **4a**, **4c**, **4d**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) In a control experiment using **6** instead of [Cp*RhCl$_2$]$_2$ as a catalyst for imine arylation, no catalytic activity was observed, excluding the possibility of a Rh-free, acid-catalyzed mechanism (1.0 equiv of **1c**, 1.5 equiv of **2**, 0.4 equiv of **6**, CH_2Cl_2, 16 h at 75 °C).

(9) Crystal data for **5**: $C_{32}H_{32}F_6N_2RhSb$, M_r = 783.26, orthorhombic space group $P2_12_12_1$, T = 100(2) K, a = 13.046(3) Å, b = 13.991(3) Å, c = 16.446(3) Å, $\alpha = \beta = \gamma$ = 90°, V = 3002.0(10) Å^3, μ = 1.512 mm^{-1}, Z = 4, 153584/9171 collected/unique reflns, R_1 = 0.02, wR_2 = 0.05, GOF = 1.080.

(10) Crystal data for **4d**: $C_{33}H_{38}F_6N_2O_2RhSb$, M_r = 904.21, monoclinic space group $P2_1/c$, T = 123(2) K, a = 18.8446(9) Å, b = 9.9469(4) Å, c = 19.9152(9) Å, α = 90°, β = 100.0660(10)°, γ = 90°, V = 3675.5(3) Å^3, Z = 4, μ = 1.391 mm^{-1}, 33709/6747 collected/unique reflns, R_1 = 0.02, wR_2 = 0.06, GOF = 1.059.

(11) This mechanism is frequently also described as electrophilic C−H bond activation. Recently, the term CMD has become more dominant and will be used in this manuscript. For a review, see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

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(13) Both **5** and a 1:1 **7**/AgSbF$_6$ mixture displayed catalytic activity, but no imine (**3c**) arylation was observed when **7** was employed alone.

(14) See the Supporting Information (SI) for detailed information.

(15) In analogy to the transformation in Scheme 6, intermediate formation of **8d** was observed by NMR in the synthesis of **4d**.

(16) Complexes **4d** (minor) and **5** (major) were observed by ^{1}H NMR spectroscopy during a catalytic transformation employing a 1:1 ratio of **2** and **3d**. When the reaction was run with a 4:1 ratio of **2** and **3d** as substrates, only **5** could be detected by ^{1}H NMR. Also see ref 14.

(17) Since the formation of **4d** is irreversible, subsequent steps leading to **1d** can be omitted in the rate law analysis.

(18) A solution of complex **5** in CD_2Cl_2 did not display any traces of **9** detectable by ^{1}H NMR spectroscopy at rt. Reaction of **3d** with **9** at rt yielded **8d**, which was slowly converted into **4d**.