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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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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. A detailed mechanistic study provides insights for the rational future development of this new reaction. Relevant intermediate Rh(III)-complexes have been isolated, characterized, and their reactivity 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.

Arylation of alkenes and alkynes have been well explored in the area of chelation-controlled rhodium-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. Further advancements in this field include the arylation of other polarized C–X multiple bonds such as aldehydes,[3] isocyanates,[4] isonitriles,[5] and carbon monoxide.[6]

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 subsequently, catalyst propagation (product release). Relevant intermediates were isolated and characterized by X-ray diffraction. In an unusual finding, the rate law of the reaction was determined, revealing 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). For Boc-amine **1a** a considerably higher yield was observed when a twofold excess of **2** with regard to imine **3a** was employed (Table 1, entry 2 and 3).[2a]

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ASSOCIATED CONTENT

Supporting Information. Experimental details for syntheses, kinetic experiments and NMR spectra for all compounds described, X-ray crystallographic data for **4a, 4c**, **4d**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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 analysis employing *N*-tosyl-imines would provide only limited information due to the reversibility of C–C bond formation, and an unfavorable equilibrium between 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 kinetic analysis. The *N*-isopropoxycarbonyl-imine functionality in **3d** is comparably electrophlic to the *N*-Boc imine and gives similar yields (82% vs. 81%), but is stable to acids. Importantly, no back reaction to **2** or **3d** was observed when *N*-isopropoxycarbonyl amine **1d** was treated with 20 mol % of Rh(III) catalyst (Scheme 2). However, quantitative formation (with respect to rhodium) 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). We observed formation of a mixture of cyclometallated rhodium- complex **5**, pyridinium salt **6** and AgCl.[8] The mixture exhibited broadened resonances in the ^1H NMR spectra that are indicative of a ligand exchange with **2**. From a concentrated solution of **5** and **6** in $CHCl_3$ single crystals of **5** suitable for X-ray diffraction analysis could be obtained (Figure 1). Cp*-complex **5** has a three legged piano stool configuration with one 2-phenylpyridine acting as a bidentate *κC*-,*κN*-ligand, and one 2-phenylpyridine saturating the free valence site of the rhodium center as a monodentate *κN*-ligand.

Cyclometallation of **2** could also be performed at room temperature. Presumably, during cyclometallation of $[Cp^*RhCl_2]_2$ with **2**, one molecule of **2** acts as a base in a concerted metallation-deprotonation type mechanism (CMD),[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**, readily available by cyclometallation 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 solution (CH_2Cl_2), decomposition of **5** began to occur within a few hours at room temperature, whereas no decomposition was observed in a solution containing excess **2**.

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 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**, **c**, and **d** by adding a solution of the respective imines in CH_2Cl_2 to a mixture of $AgSbF_6$ and **7** at room temperature (Scheme 6).[15] After crystallization complexes **4a, c,** and **d** were obtained in 73%, 81%, and 66% yields, respectively. These materials were stable in CD_2Cl_2 for several days.

We were able to obtain single crystals of **4a**, **c**, and **d** suitable for X-ray diffraction analysis by slow diffusion of *n*-pentane into a saturated solution of the respective compounds in CH_2Cl_2 (Figure 1).[16] The solid-state structure of Cp*-complex **4d** depicted a three-legged piano stool configuration with the deprotonated amine **1d** acting as a tridentate ligand, which coordinates to the rhodium center via its two nitrogen 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 heterocycle 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 (Scheme 5 and 6) we conclude that $AgSbF_6$ and pyridinium salt **6** play a non-essential role 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**, and **d** represent resting states of the reaction whose relative amounts depend on the respective amounts of the substrates **2**, **3**, and product **1**.

We propose a catalytic cycle for the Rh(III)-catalyzed arylation of imines (Scheme 7) in which the pre-catalyst mixture of $AgSbF_6$ 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 rapidly transformed to **4d** by insertion of the C–N double bond into the Rh–C bond. The catalytic cycle proceeds by coordination of **2** yielding intermediate **10d**. Presumably, the amide nitrogen ligand in **10d** acts as a base during CMD, releasing amine **1d** with simultaneous cyclometallation of **2** regenerating catalyst **9**.

However, alternate mechanisms involving co-catalysts 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 (*vide supra*). To simplify the kinetic analysis a six-fold excess of **2** with respect to **3d** was used to suppress resting state **4d** in favor of **5**.[17] 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.

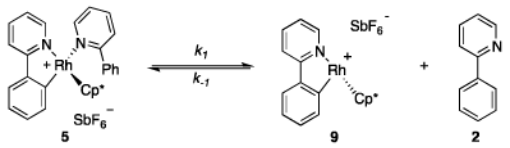
Figure 2 depicts consumption of **3d** with formation of **1d** over time using 11 mol % of **5** as a catalyst. The reaction followed first order kinetics with $k = 0.24\ h^{-1}$ (Table 2, entry 1) for **1d** formation and a slightly higher rate constant for **3d** consumption of $k = 0.28\ h^{-1}$. In subsequent runs of the reaction, variable amounts of **6** were added. The reaction remained first order in all cases. While 20 mol % of **6** increased the reaction rate by a factor of 1.48 (Table 2, entries 2 – 4), addition of 40 mol % of **6** resulted in only in a very modest effect (Table 2, entry 5). Similarly, $AgSbF_6$ also resulted in only a small increase in the rate (Table 2, 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 mixture of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ (1:4) as a catalyst, the reaction maintained first order kinetics. The reaction rate was determined as $k = 0.28\ h^{-1}$ (Table 2, entry 7), which is very similar to the rate constant observed when **5** and **6** were employed in a 1:1 ratio ($k = 0.31\ h^{-1}$, Table 2, entry 3). We consider this observation as evidence that the pre-catalyst mixture of $[Cp^*RhCl_2]_2/AgSbF_6$ forms **5** and **6** as the catalytically active compounds in the reaction.

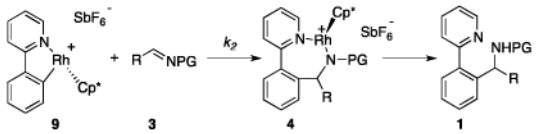
To determine the rate law we monitored the reaction with variable amounts of resting state **5** and 2-phenylpyridine (**2**). The reaction was found to be first order in **5**[18] and inverse first order in **2**.[19]

We propose the mechanism shown in eqs 1 and 2 for this overall transformation. Complex **9** is produced in a fast equilibrium from resting state **5** by dissociation of **2** (eq 1). We formulate the steady state concentration of **9** by the sum of its formation from **5** and consumption by reaction with **3d** and **2** (eq 3).[20] Solving for [**9**] gives eq 5. We assume that

$k_{-1}[\mathbf{2}] \gg k_2[\mathbf{3d}]$, because stoichiometric transformations (Scheme 6) indicated that $k_{-1} > k_2$,[21] and at least a four fold excess of **2** with regard to **3d** was used during kinetics. Insertion of eq 5 into eq 3 yields eq 6 as an expression for our rate law. With $k_{obs} = 0.060$ h^{-1}, eq 6 produces excellent fits for the observed amine formations in the catalytic runs with 4, 5, 6, 7, and 8 equiv of 2-phenylpyridine (**2**).[19]



(1)



(2)

$$-d\frac{[\mathbf{3d}]}{dt}=\frac{d[\mathbf{4d}]}{dt}=k_2[\mathbf{3d}][\mathbf{9}] \tag{3}$$

$$-\frac{d[\mathbf{9}]}{dt}=0=k_1[\mathbf{5}]-k_{-1}[\mathbf{9}][\mathbf{2}]-k_2[\mathbf{9}][\mathbf{3d}] \tag{4}$$

$$[\mathbf{9}]=\frac{k_1[\mathbf{5}]}{k_{-1}[\mathbf{2}]+k_2[\mathbf{3d}]} \approx \frac{k_1[\mathbf{5}]}{k_{-1}[\mathbf{2}]} \tag{5}$$

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

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 cyclometallation 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 non-essential for catalysis. While the basicity of **2** plays an important role during catalyst initiation (cyclometallation), 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 cyclometallation 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 it 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. In a control experiment employing **6** instead of $[Cp^*RhCl_2]_2$ as a catalyst for imine arylation no catalytic activity was observed, excluding the possibility of a rhodium-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**: $C_{32}H_{32}F_6N_2RhSb$, Mr = 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 reflections collected/unique, R1 = 0.02, wR2 = 0.05, GOF = 1.080.
10. Crystal data for **4d**: $C_{33}H_{38}F_6N_2O_2RhSb$, Mr = 904.21, mono-clinic space group $P2_1/c$, T = 123(2) K, a = 18.8446(9) Å, b = 9.9469(4) Å, c = 19.9152(9) Å, $\alpha = 90°$, β = 100.0660(10)°, γ = 90°, V = 3675.5(3) $Å^3$, Z = 4, μ = 1.391 mm^{-1}, 33709/6747 reflections collected/unique, R1 = 0.02, wR2 = 0.06, GOF = 1.059.
11. This mechanism is frequently also described as electrophilic C–H bond activation. However, more recently, the term CMD has become more dominant and will be used in this manuscript. For a recent review see: Lapointe D, Fagnou K. Chem Lett. 2010; 39:1118.
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13. Both **5** and a mixture of **7**/$AgSbF_6$ (1:1) displayed catalytic activity, but no imine (**3c**) arylation was observed when **7** was employed alone as the catalyst.

14. See SI for detailed information about additional experiments employing stoichiometric amounts of imines **3c** and **3d**, mixtures of **3** and **2**, as well as the dependence of the **2** : **4a** ratio on **2**, **1a**, and **3a** concentration.
15. In analogy to the transformation outlined in Scheme 6, in the synthesis of **4d** intermediate formation of **8d** was observed by NMR.
16. Only **4d** is shown. The structures of **4a** and **c** are very similar and may be found in the SI.
17. 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. See also ref. 14.
18. 7.5, 10.0, 15.0, and 20.6 mol% of **5** relative to **3d**, respectively, 0.050 mmol of **3d**, 0.300 mmol of **2**, 0.050 mmol of C_6Me_6 as internal standard, DCE (total volume: 0.70 mL), T = 75.0 °C (see SI).
19. 3.98, 4.94, 6.00, 7.05, 8.06 equiv of **2** relative to **3d**, respectively, 0.050 mmol of **3d**, 0.050 mmol of C_6Me_6 as internal standard, DCE (total volume: 0.70 mL), T = 75.0 °C (see SI).
20. Since the formation of **4d** is irreversible, subsequent steps leading to **1d** can be omitted in the rate law analysis.
21. A solution of complex **5** in CD_2Cl_2 does not display any traces of **9** detectable by ^{1}H NMR spectroscopy at room temperature. Reaction of **3d** with **9** yields **8d** at room temperature, which is slowly converted into **4d**.

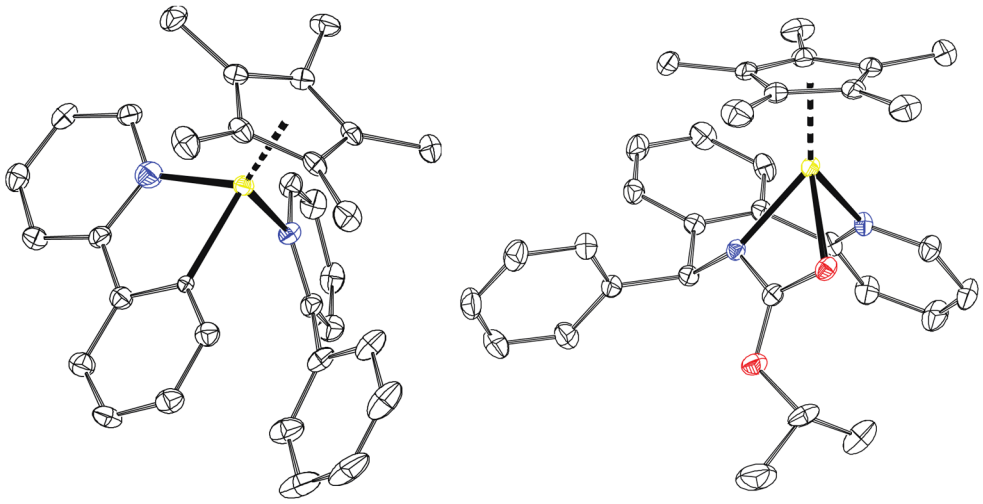


Figure 1.
Thermal ellipsoid plot of **5** (left) and **4d** (right) depicted at the 50% probability level. Hydrogen atoms and SbF_6 anions are omitted for clarity.[9,10]

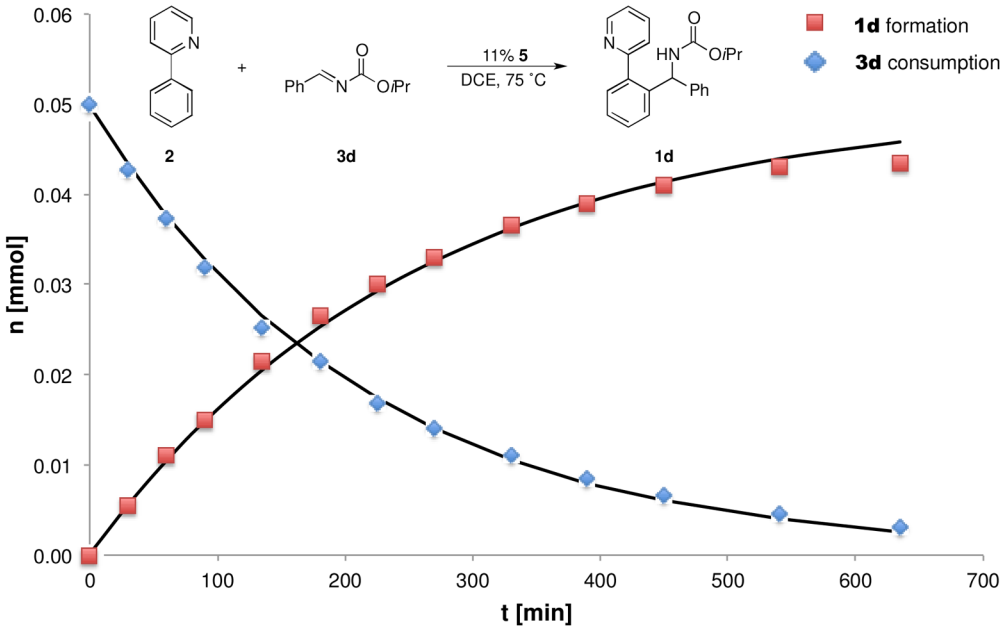
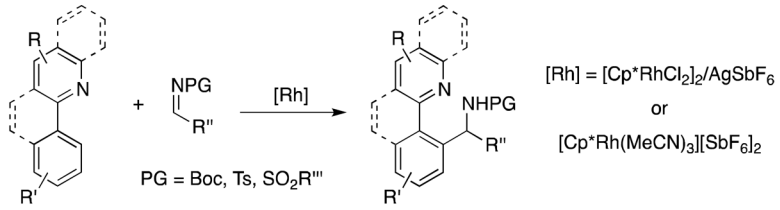
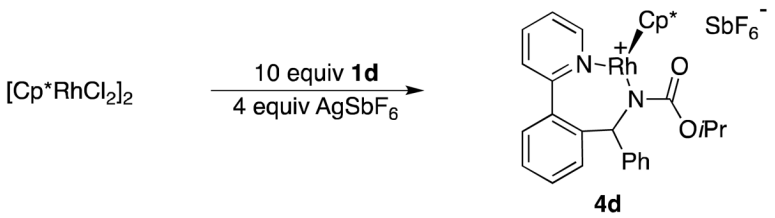


Figure 2.

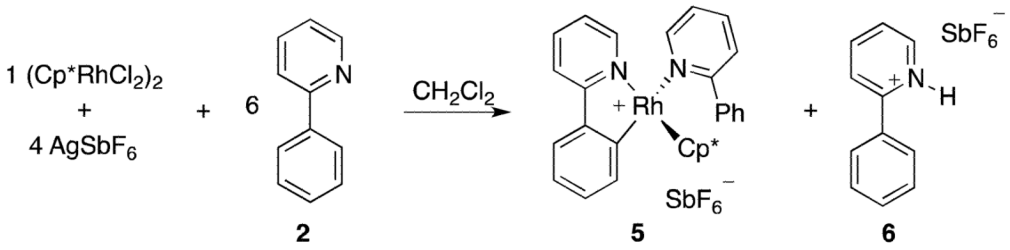
Monitoring (^{1}H NMR) of imine (**3d**) arylation with **2**. Conditions: 0.050 mmol of **3d**, 0.300 mmol of 2, 0.050 mmol of hexamethylbenzene (C_6Me_6), 5.6 μmol of **5**, 0.70 mL of 1,2-dichloroethane (DCE), T = 75 °C. Black line (simulated): $[\mathbf{3d}]_t = [\mathbf{3d}]_{t=0} - e^{-k\cdot t}$ (k = 0.24 h^{-1}) and $[\mathbf{1d}]_t = [\mathbf{3d}]_{t=0} - (1 - e^{-k\cdot t})$ (k = 0.28 h^{-1}).



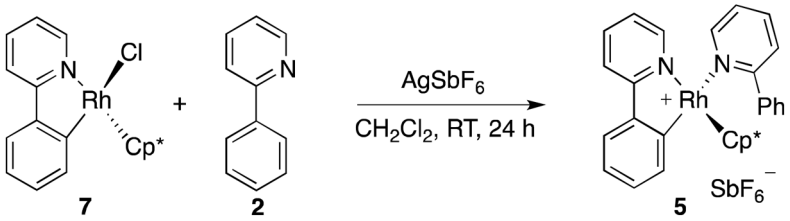
Scheme 1.
Rh(III) Catalyzed Imine Arylation



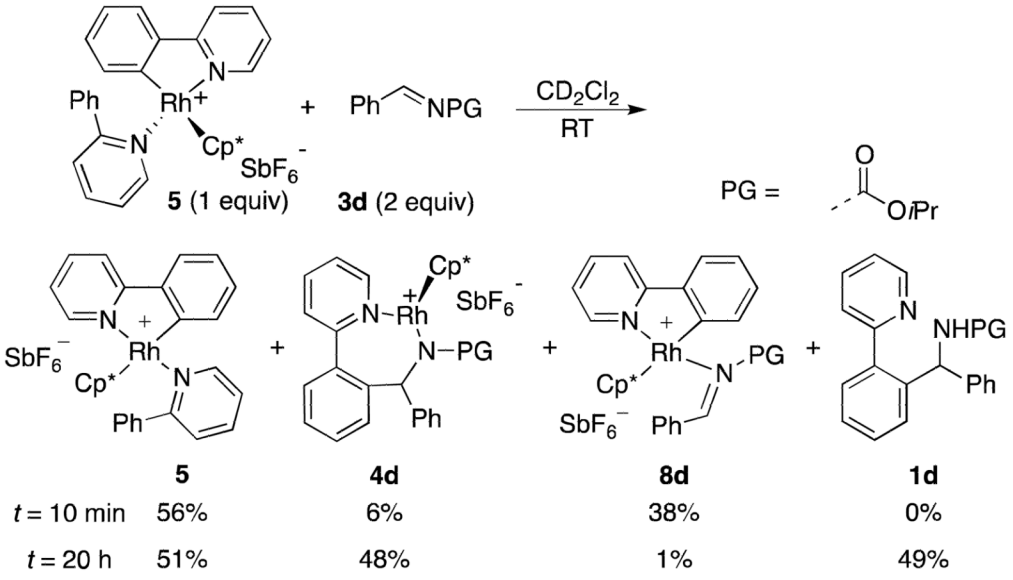
Scheme 2.
Irreversibility of C–C Bond Formation



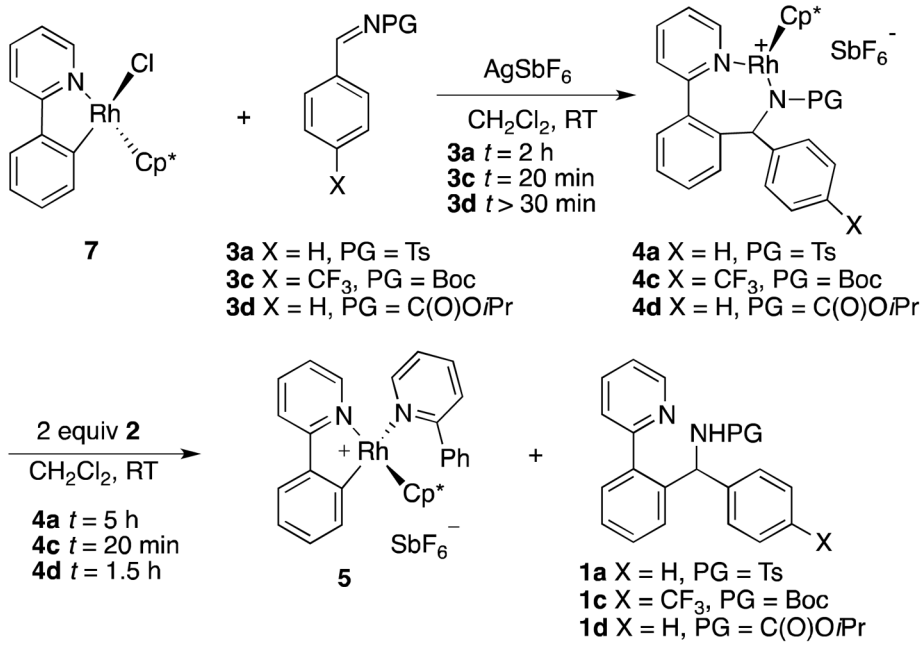
Scheme 3.
Cyclometallation



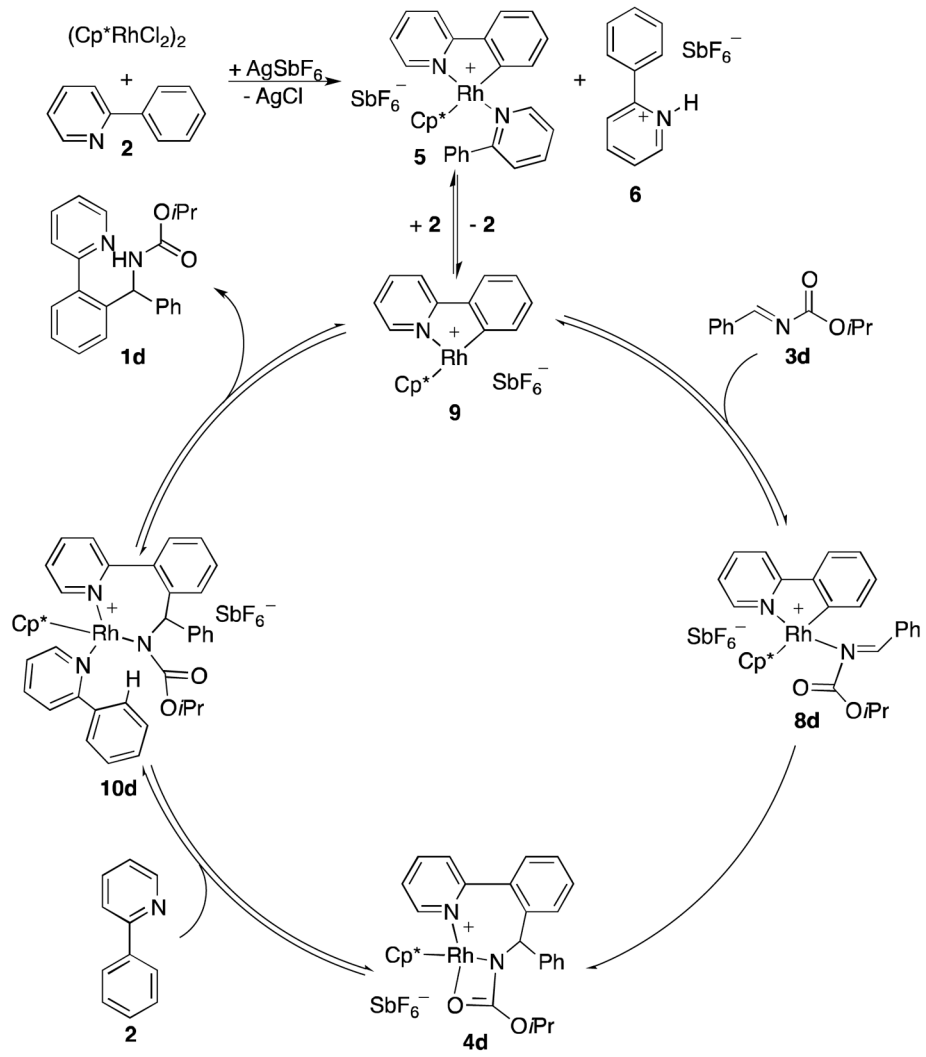
Scheme 4.
Alternative Access to resting state 5



Scheme 5.
Resting states during imine arylation



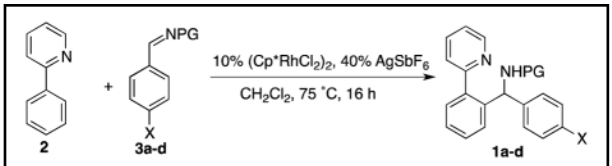
Scheme 6.
C–C Bond Formation and Propagation



Scheme 7.
Proposed Mechanistic Cycle

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**.

Table 2

Reaction rates[a]

entry	[Rh]	6 [mol%]	$AgSbF_6$ [mol%]	k^b [h^{-1}]	k_{rel}
1	5[c]	0	-	0.24	1.00
2	5[c]	5	-	0.27	1.13
3	5[c]	10	-	0.31	1.30
4	5[c]	20	-	0.35	1.48
5	5[c]	40	-	0.25	1.05
6	5[c]	-	12	0.32	1.36
7	$[Cp^*RhCl_2]_2$[d]	-	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 plot over first 6.5 h (75 – 80% conversion).

[c] 5.6 μmol.

[d] 2.8 μmol.