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Mechanistic Study of the Oxidative Coupling of Styrene with 2-Phenylpyridine Derivatives Catalyzed by Cationic Rhodium(III) via C−H Activation

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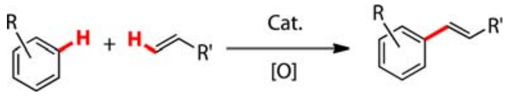
Supporting Information

ABSTRACT: The Rh(III)-catalyzed oxidative coupling of alkenes with arenes provides a greener alternative to the classical Heck reaction for the synthesis of arene-functionalized alkenes. The present mechanistic study gives insights for the rational development of this key transformation. The catalyst resting states and the rate law of the reaction have been identified. The reaction rate is solely dependent on the catalyst and alkene concentrations, and the turnover-limiting step is the migratory insertion of the alkene into a Rh−C(aryl) bond.

Catalytic dehydrogenative cross-coupling reactions offer the desirable possibility of forming a new C−C bond directly from two simple C−H bonds. Alongside the atom economy advantage, this is fundamentally fascinating because a catalytic system allows the coupling of two stable centers.[1] In this regard, the oxidative version of the Heck cross-coupling, also known as the Fujiwara−Moritani reaction,[2] is an interesting approach that provides access to aryl-functionalized alkenes directly from two C−H bonds without the need for prefunctionalized partners (Scheme 1). This method is also of particular interest for the prospective production of styrene directly from benzene and ethylene.[3]

Scheme 1. The Fujiwara−Moritani (Oxidative Heck) Reaction



A number of substrates have been oxidatively coupled to alkenes using Pd(II) as a catalyst and various oxidants [$Cu(OAc)_2$, Ag_2CO_3, benzoquinone, etc.].[1a,4] More recently, Rh(III) complexes have proven to be efficient and versatile catalysts for a variety of oxidative cross-couplings[5] and especially for the Fujiwara−Moritani reaction,[6] even allowing the coupling of simple unactivated alkenes.[6n] However, this methodology could be made even more useful by broadening the types of directing groups and the range of C−H bonds that can be functionalized and identifying more convenient and cost-effective stoichiometric oxidants.[1a] To improve these cross-couplings on a rational basis, it is crucial to understand their mechanism. While arylations of different substrates with cationic Rh(III) catalysts have been investigated,[7] there are few reports on the mechanism of oxidative reactions,[8] none of which include alkenes. Here we report a mechanistic study of the coupling of 2-phenylpyridine with styrene catalyzed by $[Cp^*RhCl_2]_2$ ($Cp^* = C_5Me_5$), activated by $AgSbF_6$, and employing a copper carboxylate as the oxidant. We also report a kinetic study that identifies the resting states and the turnover-limiting step for this transformation.

We chose 2-(4-fluorophenyl)pyridine (**1**) as a substrate because it is known to form stable rhodacycles,[9] and 4-fluorostyrene (**2**) was selected because styrene derivatives are known to be efficiently coupled by Rh(III).[10] Fluorine substitution at the para positions of both reagents provided a convenient ^{19}F NMR handle that allowed careful monitoring of their concentrations during the reaction and the observation of catalyst resting states. We previously reported the coupling of aryl oximes with simple alkenes using a mixture of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ as the catalyst in tetrahydrofuran (THF).[6n] We therefore tested the coupling of **1** with **2** under the same conditions. Although $Cu(OAc)_2$ gave excellent yields as an oxidant, it exhibits low solubility in THF. This would hamper NMR monitoring and make a kinetic study challenging. To ensure the homogeneity of the reaction solutions, we addressed this problem by using as the oxidant copper heptanoate (**4**), which is fully soluble in THF. Employing 2 equiv of pyridine relative to styrene to avoid any overalkylation, we recovered the expected coupling product **3** in 91% yield (Scheme 2). An added benefit was that the solubility of **4** allowed us to reduce the amount of oxidant to 1 equiv, where previously 2.1 equiv of $Cu(OAc)_2$ was needed.

With this model in hand, our first objective was to gain insight into the nature of the catalyst resting state or states and their formation. It has been shown earlier that the C−H activation of phenylpyridine by $[Cp^*RhCl_2]_2$ leads to cyclo-

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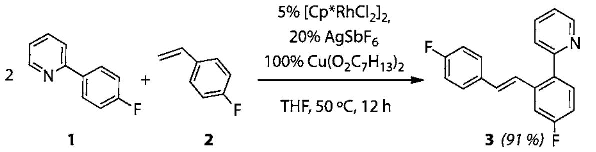
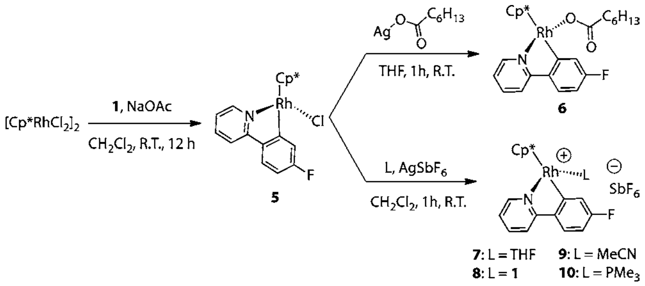
Scheme 2. Rh(III)-Catalyzed Oxidative Coupling of 2-(4-Fluorophenyl)pyridine (1) and 4-Fluorostyrene (2)[a]



[a] Conditions: 0.1 mmol of **1**, 0.05 mmol of **2**, 2.5 μmol of $[Cp^*RhCl_2]_2$, 0.01 mmol of $AgSbF_6$, 0.05 mmol of $Cu(O_2C_7H_{13})_2$ (**4**), 1 mL of THF, T = 50 °C, 12 h.

metalated Rh complexes that are either neutral when an acetate salt is employed[9b] or cationic when $AgSbF_6$ is used.[7] In the present case, the reaction mixture contained both $AgSbF_6$ and copper carboxylate salts. To distinguish cationic from neutral rhodacycles under the operating conditions, we synthesized a series of such complexes with different ligands (Scheme 3) and compared their ^{19}F NMR chemical shifts. We observed that the ^{19}F signals appear between −107 and −109 ppm for cationic complexes **7**−**10** and at ca. −111 ppm for neutral complexes **5** and **6** in THF-d_8.

Scheme 3. Syntheses of Neutral and Cationic Rhodacycles



We were also able to obtain single crystals useful for X-ray diffraction analysis of complexes **5**−**7**, **9**, and **10**. The solid-state structures present the expected piano-stool geometry (Figure 1). The Rh−C distances are slightly longer for the cationic complexes, although the differences are small and within experimental error: **5**, 2.024(2) Å ≤ **6**, 2.030(6) Å < **9**, 2.042(4) Å ≤ **7**, 2.046(7) Å < **10**, 2.065(7) Å.[11]

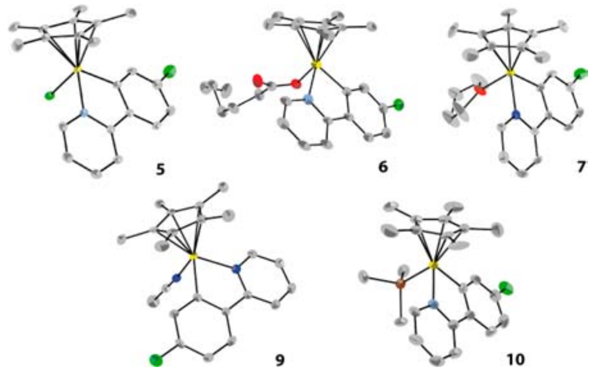
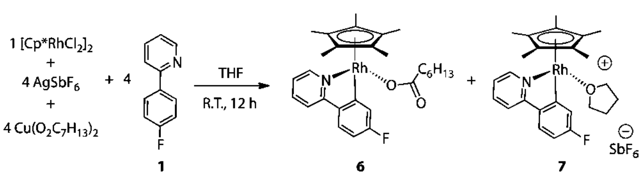


Figure 1. ORTEP views of complexes **5**−**7**, **9**, and **10**. H atoms and SbF_6^- counteranions have been omitted for clarity.

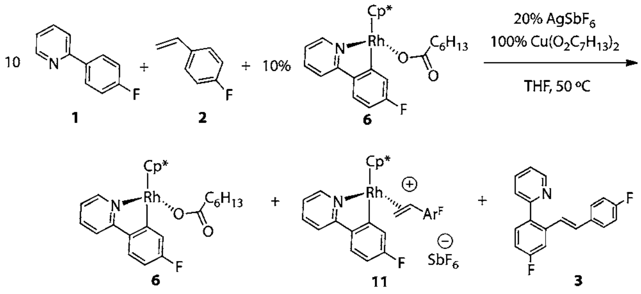
We then carried out the stoichiometric cyclometalation of **1** by $[Cp^*RhCl_2]_2$ and $AgSbF_6$ in the presence of **4** (4:1:4:4 respectively) in THF. By comparing the ^{19}F and ^1H NMR data of the reaction mixture to those of synthesized samples, we confirmed the formation of neutral carboxylate-ligated rhodacycle **6** and cationic rhodacycle **7** (Scheme 4).

Scheme 4. C−H Activation and Cyclometalation of 1



We next utilized ^{19}F NMR spectroscopy to monitor an actual catalytic run with **6** as the precatalyst.[12] Although **6** was the predominant resting state, part of the rhodium was transformed into a new species characterized by a set of two ^{19}F resonances at −108.5 and −110.0 ppm, and we reasoned that this species was rhodacycle styrene adduct **11** (Scheme 5). When the temperature was increased, the signals of **6** and **11** became broader, fading into the baseline at 65 °C. Upon cooling, the signals became sharper again, and two rotamers of **11** could be observed at 25 °C [see below and Figure S-2 in the Supporting Information (SI)]. This fluxional behavior can be attributed to ligand exchange between **6** and **11**.

Scheme 5. Resting States during Oxidative Coupling

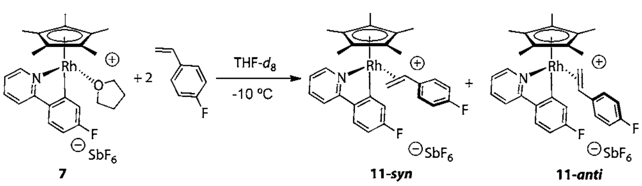


	6	11	3
t = 0 min, 50 °C	6.3 %[a]	2.1 %	0 %
t = 30 min, 50 °C	5 %[a]	1.9 %	23 %
t = 40 min, 25 °C	8 %	2 %[b]	30 %

[a] The integration is not fully accurate because the NMR signals were broad. [b] Two rotamers.

The independent synthesis and isolation of **11** from **2** and $[Cp^*RhCl_2]_2$ by addition of $AgSbF_6$ proved to be difficult. We observed the formation of a dark-violet species whose ^1H and ^{19}F NMR spectra were in agreement with the structure of **11**, but it decomposed rapidly into an undefined mixture of products. However, in situ NMR monitoring of the addition of **2** to rhodacycle **7** in THF-d_8 at −10 °C showed the clean formation of **11** as a mixture of the syn and anti rotamers (Scheme 6).

Scheme 6. Formation of the Rhodacycle Styrene Adduct



By varying the temperature, we observed the reversible interconversion of the rotamers due to free rotation of styrene around the Rh−alkene bond (Figure S-3). This result confirmed that **11** is indeed a π-olefin complex and not a new metallacycle formed by styrene insertion into the Rh−C bond. Although we were not able to observe the insertion process, it is safe to assume that it takes place, leading to the eventual formation of **3**. This would be in agreement with the work of Jones and co-workers, who showed that the reaction of ethylene or propylene with Ir or Rh metallacycles leads to unstable π-alkene complexes similar to **11** with iridium or to insertion products with rhodium.[13]

From the above experiments, we concluded that **6** and **11** are both resting states of the catalyst. These two species interconvert through the exchange of the carboxylate anion for styrene. This process is upstream from the migratory insertion of styrene into the Rh−C bond. Since the ring-expanded metallacycle could not be detected, it is reasonable to assume that the ensuing steps leading to **3** are faster than the alkene insertion, which determines the rate of the catalytic reaction.

This qualitative conclusion was tested by carrying out a kinetic study designed to establish the rate law of the catalytic transformation. We monitored the progress of the reaction by ^{19}F NMR spectroscopy at 65 °C using **6** as the precatalyst and an excess of **1** relative to **2**. With a 10-fold excess of **1**, the reaction followed pseudo-first-order kinetics with $k = 0.0269$ min^{-1} for the consumption of **2** and a slightly lower rate ($k = 0.024$ min^{-1}) for the formation of product **3** (Figure 2). The rate of consumption of **2** was the same (within experimental error) when the original catalyst, 5% [Cp*RhCl$_2$]$_2$, was used instead of **6**, confirming that the same active species are generated in both cases.

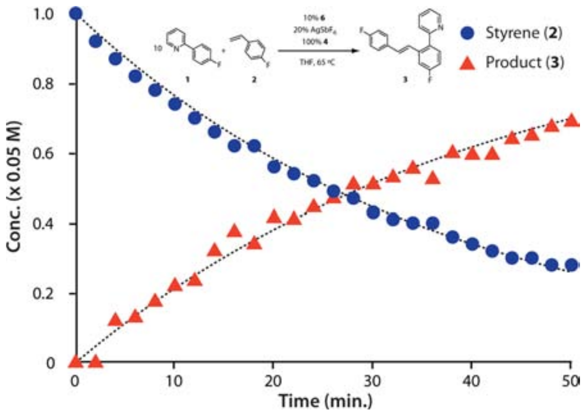


Figure 2. Plots of the concentrations of substrate **2** and product **3** vs time obtained by ^{19}F NMR monitoring. Conditions: 0.5 mmol of **1**, 0.05 mmol of **2**, 5 μmol of **6**, 0.01 mmol of AgSbF$_6$, 0.05 mmol of **4**, 0.7 mL of THF, 0.3 mL of THF-d_8, 1 μL of C$_6$F$_6$ (as an internal standard), T = 65 °C. Black dashed lines are fits using the equations $[\mathbf{2}]_t = [\mathbf{2}]_0 e^{-kt}$ (k = 0.0269 min^{-1}) and $[\mathbf{3}]_t = [\mathbf{2}]_0(1 - e^{-kt})$ (k = 0.024 min^{-1}).

The order of each reactant was then determined by measuring the reaction rates in the presence of variable excess concentrations of **1**, catalyst **6**, AgSbF$_6$, and **4** (Table S-1 in the SI). The kinetic analysis showed a zeroth-order dependence on **4** and **1** and a first-order dependence on catalyst **6** (see the SI). Interestingly, in early experiments the silver salt exhibited apparently bimodal behavior. Initially, the consumption of the starting material followed first-order kinetics with a similar rate for all silver concentrations (7.5−30 mol % relative to **2**), indicating a zeroth-order dependence on [Ag]. However, for AgSbF$_6$ concentrations lower than 20 mol %, the behavior changed, and the styrene consumption deviated from first-order behavior after 12 min (Figure S-8). We believe that this was due to inadvertent catalyst decomposition, so in subsequent reactions the silver concentration was kept at 20 mol %. First-order behavior was reproducibly observed in these runs.

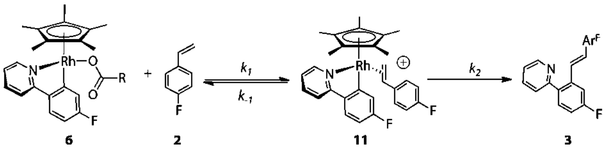
Monitoring the reactions under operating catalytic conditions established that the concentrations of **6** and **11** hardly varied during the course of the reaction. Assuming a steady-state situation for **11** (eq 3) allows its concentration to be expressed according to eq 4. Substitution of eq 4 into the rate law (eq 2) furnishes eq 5, which expresses the rate as a function of the concentrations of reactants **6** and **2**. Using eq 5, we obtained excellent fits with k_{obs} = 2.72 min^{-1} for the consumption of styrene **2** in catalytic runs with different amounts of catalyst **6**, showing that only the catalyst and styrene concentrations are kinetically relevant.

$$\frac{d[\mathbf{3}]}{dt} = k_2[\mathbf{11}] \tag{2}$$

$$\frac{d[\mathbf{11}]}{dt} = k_1[\mathbf{6}][\mathbf{2}] - k_{-1}[\mathbf{11}] - k_2[\mathbf{11}] = 0 \tag{3}$$

$$[\mathbf{11}] = \frac{k_1[\mathbf{6}][\mathbf{2}]}{k_{-1} + k_2} \tag{4}$$

$$\frac{d[\mathbf{3}]}{dt} = \frac{k_1 k_2[\mathbf{6}][\mathbf{2}]}{k_{-1} + k_2} = k_{\mathrm{obs}}[\mathbf{6}][\mathbf{2}] \tag{5}$$

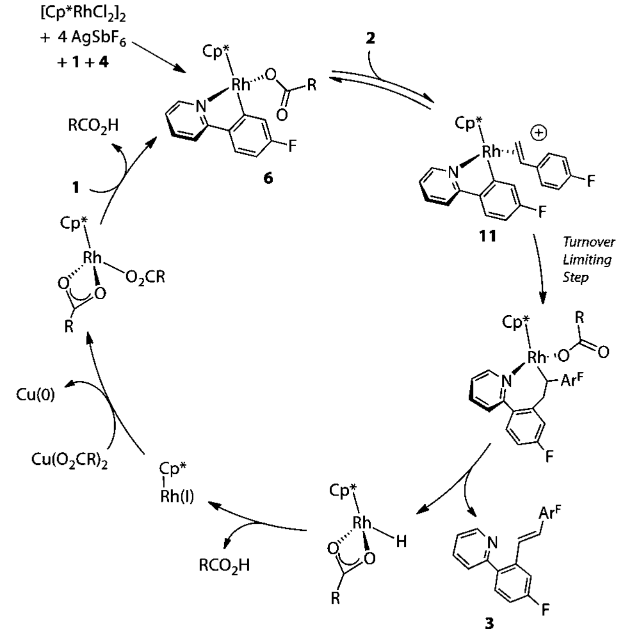


(1)

In Scheme 7 we depict a mechanism for this transformation that is consistent with our qualitative observations and kinetic results. The mixture of [Cp*RhCl$_2$]$_2$, AgSbF$_6$, **1**, and **4** gives rise initially to resting state **6** through a C−H activation mechanism of concerted metalation/deprotonation.[14] Complex **6** is in equilibrium with **11** through exchange of styrene with carboxylate. In the turnover-limiting step, the coordinated styrene undergoes migratory insertion to give a new metallacycle, probably stabilized by a carboxylate ligand similar to that in **6**. This new rhodacycle then undergoes β-elimination to release the organic product **3** and a rhodium hydride complex that upon elimination of carboxylic acid is reduced to Rh(I). The latter is then reoxidized by copper to close the catalytic cycle. This Rh(III/I) catalytic cycle involving the sequence C−H activation, alkene insertion, β-elimination, and oxidation is in agreement with previous reports on Rh(III) catalysis[7,8] and rhodacycle reactivity toward unsaturated molecules[9a,13,15] and is similar to that proposed for Pd(II/0).[5a,16]

In conclusion, by using a soluble copper carboxylate and fluorine-substituted reactants that allowed monitoring by ^{19}F NMR spectroscopy, we were able to carry out a mechanistic study and propose a catalytic cycle for the oxidative coupling of styrene to phenylpyridine catalyzed by Rh(III). We hope that the understanding provided for this transformation will

Scheme 7. Proposed Catalytic Cycle



contribute to the development of other reactions involving the direct coupling of two C−H bonds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details for the synthesis and characterization; kinetic experiments; NMR spectra for all compounds; and crystallographic data for **5**−**7**, **9**, and **10**. 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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(11) Complexes **5**−**9** all served as active precursors for the catalytic reaction. Only **10** was inactive because styrene could not displace the PMe_3 ligand.

(12) The same experiment was conducted using $[Cp^*RhCl_2]_2$ as a precatalyst, but several unidentified species were observed along with **6** and **11**. Starting with **6** resulted in cleaner NMR spectra.

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