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Rhodium(III)-Catalyzed C-H Activation: An Oxidative Intramolecular Heck-Type Reaction Directed by a Carboxylic Acid

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Abstract

Carboxylic acids effectively direct C-H activation for Rhodium(III)-catalyzed intramolecular Heck-type reactions. A catalytic amount of $\text{Cu}(\text{OAc})_2$ is used as the external oxidant with oxygen likely acting as the terminal oxidant. Additionally, a novel electron-deficient Rh^{III} catalyst was found to be more effective than $[\text{RhCp}^*\text{Cl}_2]_2$ with some substrates. A wide variety of complex dihydrobenzofurans, dihydrobenzopyrans, and other bicycles that can be easily further functionalized are now accessible through relatively mild reaction conditions.

Graphical Abstract

Keywords

C-H activation; Heck reaction; Rhodium (III) catalysis; cyclization; dihydrobenzofurans

Rh^{III} catalysis has allowed for the development of many new reactions through C-H activation utilizing the direction of a neighboring functional group.¹ A substantial number of reactions have been reported including but not limited to hydroarylations, olefinations, amidoarylations, and halogenations.^{2,3} Many different directing groups have been utilized in these C-H activation reactions. Some are highly specialized moieties needed to bind a reactive metal to direct the activation of a nearby carbon-hydrogen bond.

Although this strategy is quite powerful, the utility of this approach is diminished by the necessity to install and remove exotic directing groups, especially when this group is not a part of the targeted molecule in the context of a synthetic route. This can increase the number of operations needed to access a specific target by two or more synthetic operations as well as significantly worsen the atom economy of the process.

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The burden of needing a directing group is lessened when an easily installed, functionalizable directing group is utilized. Carboxylic acids are a very desirable directing group as they generally are stable, readily available, and accessible starting materials. They have seen sporadic use as directing groups in C-H activation reactions.^{4,5,6} Additionally, they provide straightforward access to esters, amides, alcohols, aldehydes, and amines.

Carboxylic acids can also be used as traceless directing groups through a protodecarboxylation sequence.⁷

This work began as we looked to expand previous work in this group using amides as directing groups. Three different intramolecular cyclization pathways (hydroarylation, Heck-type, and amidoarylation) were accessible from a substrate bearing an amide directing group and a tethered alkene.^{8,9} Control between these pathways could be obtained through the choice of the amide directing group. The oxidative Heck-type and amidoarylation reactions take place under mild conditions due to the intramolecular nature of the reaction and the efficient oxidation provided by the NO directing group.¹⁰ We thus felt that there would be considerable value in identifying conditions whereby carboxylic acid and/or ester substrates could undergo the same cyclizations.

When the carboxylic acid substrate **1a** was reacted with $[\text{RhCp}^*\text{Cl}_2]_2$ in 1,2-dichloroethane, no reaction resulted. Excitingly, the introduction of base (CsOAc) into the reaction led to the formation of a significant amount of oxidative-Heck product (**2a**). This proved that the carboxylate could direct C-H activation and catalyst turnover could occur without the presence of an oxidizing group built into the substrate. Changing the base to K_2CO_3 and using water as a co-solvent led to a further increase in conversion. With a relatively clean reaction mixture containing only starting material and product, it seemed likely that catalyst decomposition was responsible for the arrest in reaction rate. Presumably some reoxidation of the catalyst was occurring with oxygen from the air, but it seemed likely that a better reoxidant was needed to regenerate the active catalyst. The introduction of $\text{Cu}(\text{OAc})_2$ as a co-catalyst was successful in increasing the conversion to practical levels (78% conv., entry 4). Performing the reaction in an atmosphere of oxygen slightly increased the conversion and allowed for a moderate isolated yield (entry 5, 69% yield).¹¹ An attempt to perform this reaction without $\text{Cu}(\text{OAc})_2$ and only with O_2 as the terminal oxidant resulted in a lower conversion. Furthermore, the Rh(III) catalyst was found to be necessary as a reaction with oxidant but without $[\text{RhCp}^*\text{Cl}_2]_2$ yielded no detectable product. A brief survey of Rh(III) catalysts containing different Cp ligands¹² led to the finding of $[\text{RhCp}^{(\text{CF}_3)_2\text{Ar}}\text{Cl}_2]_2$ as the optimal catalyst for this reaction with high conversion and an 83% isolated yield of the desired product **2a**.

With suitable conditions in hand, we sought to define the scope of this reaction. Variation of the aryl group was well tolerated. A sterically demanding ortho methyl benzoic acid (**1b**) was cyclized in 77% yield. Two electron-rich substrates (**1c-d**) reacted to provide **2c** and **2d** in good yield. A fluorine-substituted benzoic acid **1e** was also a suitable substrate giving **2e** in 82% yield. Substrate **1f** containing a tethered cyclohexene formed spirocyclic cyclohexene **2f** in moderate yield. Substrate **1g** containing two tethered alkenes gave product in 49% yield. A new *E*-alkene product **2h** was formed from **1h** with excellent control of

olefin geometry. Two cyclizations occurred with diene substrate **1i** to give the tricycle **2i** as an inseparable 1:1 mixture of diastereomers in 54% yield.

Disubstituted alkenes present an additional challenge of product selectivity in this reaction due to the possibility of β -H elimination from two different carbons and the formation of *E*- and *Z*-olefin isomers. Reaction of disubstituted alkene **4a** somewhat unexpectedly yielded trisubstituted product **5a** in good yield and *E:Z* selectivity.¹³ Upon monitoring of the reaction by HPLC, it was found that the expected terminal alkene product did form. This compound then quickly isomerizes to **5a**. The rate of this isomerization is fast enough to prohibit the isolation of the intermediate product.¹⁴

Interestingly, this isomerization rate is much slower for substrates with a longer carbon chain extending from the alkene. This allowed for the isolation of the disubstituted alkene products **6b** and **6c** with good *E:Z* ratios from substrates **4b** and **4c**. Although full conversion was not achieved, carbon-tethered substrate **4d** successfully cyclized to form **6d** in moderate yield and *E:Z* selectivity.

In summary, a Rhodium(III)-catalyzed intramolecular Heck-type reaction directed by carboxylic acid has been demonstrated. A catalytic amount of Cu(OAc)₂ efficiently reoxidizes Rh(I) to Rh(III). Pivotal to the successful reactions of several substrates was the application of a new, electron-deficient RhCp catalyst ([RhCp^{(CF₃)₂Ar}Cl₂]₂) which can lead to increased selectivities and yields.¹⁵

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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13. Use of Z-disubstituted alkene substrates led to low conversions and poor Z:E ratios of the products.
14. A screen of different Cp catalysts revealed [RhCp(CF₃)₂ArCl₂]₂ to be the most selective in terms of di- vs. tri-substituted alkene selectivity and E/Z selectivity.
15. **General Procedure for the synthesis of 2a:** A 1.5 dram vial was charged with a stirbar, the acid substrate (0.1 mmol, 1 equiv.), [RhCp*Cl₂]₂ (1.5 mg, 2.5 μmol, 0.025 equiv.) or [RhCp(CF₃)₂ArCl₂]₂ (2.5 mg, 2.5 μmol, 0.025 equiv.), Cu(OAc)₂ (8.0 mg, 40 μmol, 0.4 equiv) and K₂CO₃ (38.4 mg, 200 μmol, 2 equiv.), followed by addition of 1,2-DCE:H₂O (1:1, 500 μL, 0.2 M). The vial was flushed with oxygen, sealed, and stirred at 60 °C for the indicated time. The reaction mixture was allowed to cool and was quenched with 1M aqueous HCl until fully precipitated (pH = ~1). The suspension was then extracted twice with EtOAc. The combined organic layers were washed once with water and once with saturated aqueous NaCl before drying over magnesium sulfate. The solution was filtered and concentrated by rotary evaporation. The crude residue was purified by column chromatography (ethyl acetate/hexanes). **2a:** R_f = 0.29 (25% EtOAc/hexanes); IR (film) 3082, 2962, 2925, 2879, 1696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 7.6 Hz, 1H), 7.25 (dd, J = 7.6 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.17 (dd, J = 17.6, 10.8 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 5.09 (d, J = 17.6 Hz, 1H), 4.40 (d, J = 8.4 Hz, 1H), 4.27 (d, J = 8.4 Hz, 1H), 1.64 (s, 3H), (acid proton signal too broadened to assign); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 160.9, 142.0, 135.6, 128.6, 127.0, 123.6, 115.0, 113.6, 84.1, 49.4, 23.3; MS (ESI+APCI): Exact mass calcd for C₁₂H₁₁O₃ [M-H]⁻ 203.1, found 203.1.

• *Previous work: amide directed*

• *Desired:*

Scheme 1.
Previous and Current Work

Scheme 2.

Scope of Intramolecular Heck-type Reactions. ^aReactions conducted on 0.1 mmol scale in 1,2-dichloroethane:water (250 μ L each, 0.2 M) in sealed vials purged under an O₂ atmosphere at 60 °C. ^bIsolated with 20% impurity.

Scheme 3.

^aSee Scheme 2 for reaction conditions. ^b10:1 *E/Z*. ^c7:1 *E/Z*. ^d5 mol% $[\text{RhCp}^*\text{Cl}_2]_2$, 80 mol% $\text{Cu}(\text{OAc})_2$ used. Reaction time = 35h. Isolated as a 3:1 product:substrate mixture (yield based on recovered starting material), product was 5:1 *E/Z*.

Table 1

Optimization of Intramolecular Oxidative Heck Reaction

Entry	Catalyst	Base ^a	Oxidant ^b	Solvent	Conv. (%) ^c
1	[RhCp*Cl ₂] ₂	none	none	1,2-DCE	0
2	[RhCp*Cl ₂] ₂	CsOAc	none	1,2-DCE	26
3	[RhCp*Cl ₂] ₂	K ₂ CO ₃	none	1,2-DCE:H ₂ O	40
4	[RhCp*Cl ₂] ₂	K ₂ CO ₃	Cu(OAc) ₂	1,2-DCE:H ₂ O	78
5	[RhCp*Cl ₂] ₂	K ₂ CO ₃	Cu(OAc) ₂ /O ₂	1,2-DCE:H ₂ O	88 ^d
6	[RhCp*Cl ₂] ₂	K ₂ CO ₃	O ₂	1,2-DCE:H ₂ O	45
7	None	K ₂ CO ₃	Cu(OAc) ₂ /O ₂	1,2-DCE:H ₂ O	0
8	[RhCp bis(CF ₃ Ph)Cl ₂] ₂	K ₂ CO ₃	Cu(OAc) ₂ /O ₂	1,2-DCE:H ₂ O	99 ^e

^a 2 equiv. used^b 40 mol% Cu(OAc)₂ used^c Conversion determined by HPLC^d 69% Isolated yield^e 83% Isolated yield