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ARTICLE TYPE

Rhodium(III)-Catalyzed Formal Oxidative [4+1] Cycloaddition of Benzohydroxamic Acids and α-Diazoesters. A Facile Synthesis of Functionalized Benzolactams

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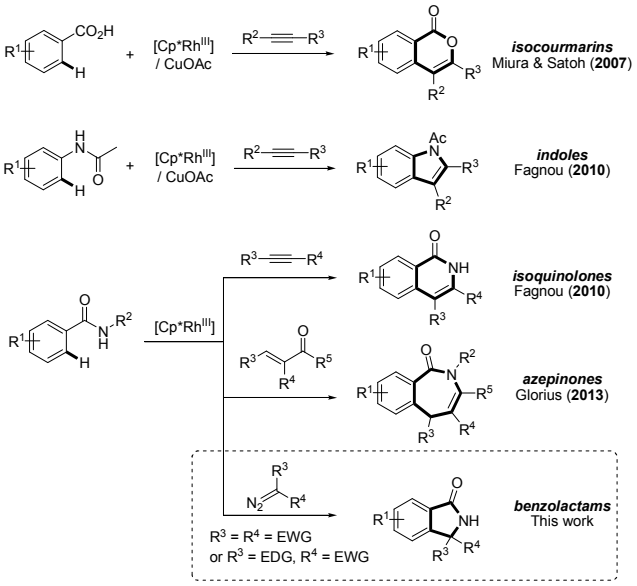
A Rh(III)-catalyzed oxidative [4+1] cycloaddition of benzohydroxamic acids and α-diazoesters is achieved to afford benzolactams in up to 93% yields. With *N*-OAc amido moiety as a directing group, the *ortho*-C-H is selectively functionalized and the catalytic reaction exhibits excellent tolerance to different functional substituents. A notable rhodacyclic complex is isolated and structurally characterized, suggesting C-H/*N*-H cyclometallation is a key step in the catalytic cycle.

Transition metal-catalyzed oxidative coupling of arene C-H bonds is a powerful and atom-economical strategy for construction of carbon-carbon and carbon-heteroatom bonds.[1] Notably, extensive investigations revealed that $[Cp^*RhCl_2]_2$ and derivatives can effect regioselective arene C-H bond activation under mild conditions to form reactive arylrhodium(III) complexes, which would undergo heteroannulation with alkenes and alkynes.[2] Miura and Satoh pioneered in the synthesis of isocoumarin by oxidative dehydrogenative coupling of benzoic acids with alkynes (Scheme 1).[3] Similarly, Fagnou and co-workers also developed the analogous alkyne cycloaddition with benzahydroxamic acids and anilides for the synthesis of isoquinolones and indoles.[4] Recently, Glorius and co-workers achieved the cycloaddition of benzahydroxamic acids with vinyl methyl ketones to afford seven-membered azepinones.[5]

Our approach to develop regioselective oxidative arene C-H coupling reactions is to explore the cross coupling reactions of transition metal aryl complexes with carboradicals[6a–f], nitrenes[6g–h] and carbenes[6i]. Recently, we achieved the *ortho*-selective arene C-H coupling reactions with diazomalonates; acetophenone oximes, arylpyridines, benzoic acids and benzylamines are effective substrates for this transformation.[6i] Pertinent to the coupling reaction of arylrhodium(III) complexes with diazomalonates, an alkylrhodacyclic complex was structurally characterized. It was believed that protonolysis of this alkylrhodacyclic (III) complex should furnish the necessary C-H bond for the product formation. Motivated by the characterization of the alkylrhodacyclic complex, we anticipated that reductive elimination rather than protonolysis should bring about a formal (4+1) cycloaddition.

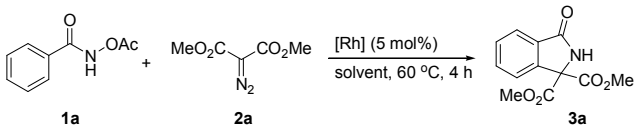


Scheme 1 Rh(III)-catalyzed heteroannulation to build heterocyclic rings.

While the oxidative C-H coupling reactions with alkynes to give six-membered heterocycles have been extensively investigated, the analogous carbenoid cycloadditions to afford five-membered heterocycles are sparse in the literature.[7] Herein we describe the Rh(III)-catalyzed formal (4+1) cycloaddition of diazomalonates with *O*-acetyl benzohydroxamic acids to form oxisoindoles. During our investigation, Rovis and co-workers reported a similar cycloaddition with methyl α-aryldiazoacetates as carbenoid coupling partners.[8]

To begin, *O*-acetyl benzohydroxamic acid **1a** (1 equiv) was treated with diazomalonate **2a** (1.2 equiv) in the presence of $[Cp^*Rh(OAc)_2]$ (5 mol%) in THF (2 mL) at 60 °C for 4 h; the desired lactam **3a** was obtained in 93% yield (Table 1, entry 1). The molecular structure of **3a** was confirmed by single-crystal X-ray diffraction study. Lowering the Rh catalyst loading to 1 mol% also gave 91% product yield, albeit with a longer reaction time (16 h) for complete substrate consumption (entry 2). No product formation was observed in the reaction without the Rh catalyst (entry 3). Employing other solvents such as DMF, DCE, MeCN and toluene, the

Table 1 Reaction optimization[a]



1a 2a 3a

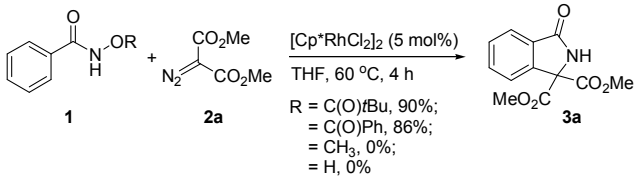
Entry	Rh catalyst	Solvent	Yield[b] (%)
1	Cp*Rh (OAc)$_2$	THF	93
2[c]	Cp*Rh(OAc)$_2$	THF	91
3	-	THF	0
4	Cp*Rh(OAc)$_2$	DMF	95
5	Cp*Rh(OAc)$_2$	DCE	84
6	Cp*Rh(OAc)$_2$	MeCN	82
7	Cp*Rh(OAc)$_2$	Toluene	64
8	Cp*Rh(OAc)$_2$	MeOH	0
9	[(COD)RhCl]$_2$	THF	0
10	(Ph$_3$P)$_3$RhCl	THF	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol) and Rh catalyst (5 mol%) in solvent (2 mL) at 60 °C for 4 h. [b] Yields were determined by ^{1}H NMR analysis using 1,2-dibromoethane as an internal standard. [c] Reaction was run with [Cp*Rh(OAc)$_2$] (1 mol%) for 16 h.

analogous C-H transformations ran smoothly to afford **3a** in 64 – 95% yields (entries 4 – 7). Notably, our previous work on the Rh-catalyzed carbenoid aryl C-H bond functionalizations showed that the MeOH solvent should favor protonolysis of the alkylrhodium(III) intermediate.[6i] However, in this work, no protonolysis product was obtained with MeOH as solvent (entry 8). Other Rh catalysts such as [(COD)RhCl]$_2$ and (Ph$_3$P)$_3$RhCl[1j] exhibited negligible catalytic activity for the carbenoid cycloaddition reaction (entries 9 and 10).

The effect of the *N*-substituent was examined (Scheme 2); benzohydroxamic acids bearing N–OR carboxylate linkage (e.g. R = C(O)*t*Bu or C(O)Ph) were found to be effective substrates for the Rh-catalyzed cycloaddition reaction with **3a** being formed in ca. 90% yields. However, no reactivity was observed with benzohydroxamic acid bearing the hydroxyl or the methoxy groups. This result indicated that carboxylate group is essential to the cycloaddition reaction. Fagnou and co-workers also reported the similar findings in the Rh-catalyzed heteroannulation with alkynes.[2l] Presumably, the *N*–O(carboxylate) linkage should function as internal oxidant that facilitates the reductive elimination step of the rhodacycle intermediates (see later section).

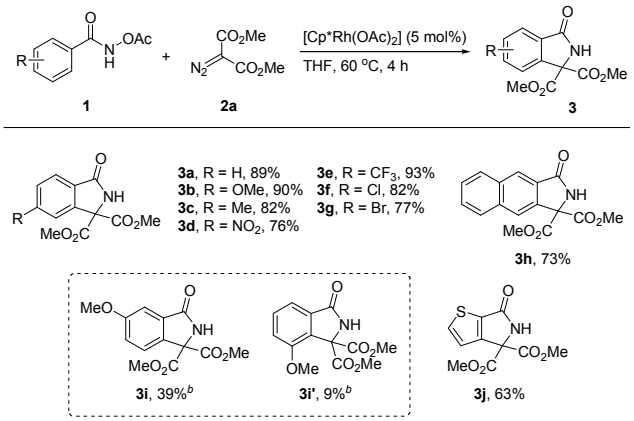
Table 2 depicts the result of the substrate scope study. *O*-Acetyl benzohydroxamic acids bearing electron-releasing and –withdrawing substituents (substituent = OMe, Me, NO_2, CF_3) smoothly reacted with **2a** to give the corresponding lactams (**3b** – **3e**) in 76 – 93% yields. Chloro and bromo substituents were well tolerated, **3f** and **3g** were obtained in



1 2a 3a

Scheme 2 *N*-leaving group effect on Rh(III)-catalyzed cycloaddition of benzohydroxamic acids with **2a**

Table 2 Rh-catalyzed cycloaddition of benzohydroxamic acids 1 with diazomalonate **2a**[a]

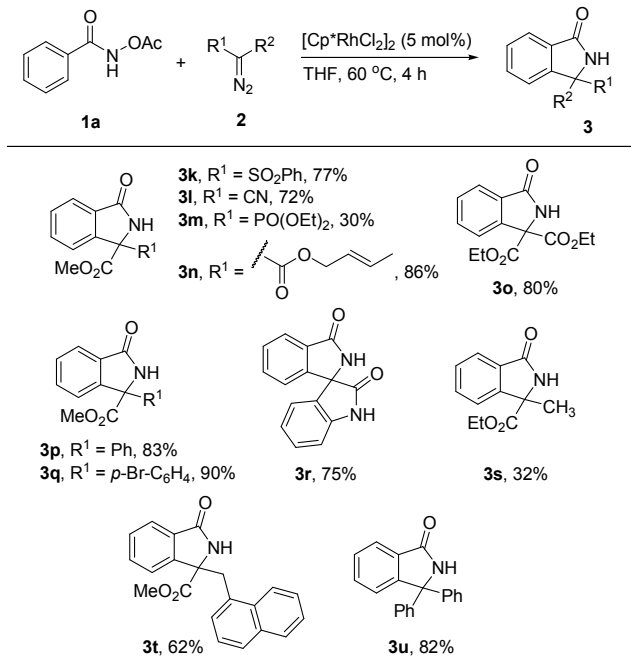


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol) and [Cp*Rh(OAc)$_2$] (5 mol%) in THF (2 mL) at 60 °C for 4 h. Isolated yield. [b] The regioisomeric ratio was determined by ^{1}H NMR analysis.

82 and 77% yields. With the assistance of the amide directing group, the *ortho*-C-H bond was chemoselectively functionalized. When the *di*-substituted benzohydroxamic acid was treated with **2a**, the less hindered *ortho*-C-H bond was functionalized to furnish lactam **3h** exclusively in 73% yield. Nevertheless, the reaction of the *meta*-substituted benzohydroxamic acid afforded a mixture of regioisomeric products in 48% combined yield (**3i**:**3i'** = 4.3:1). It is well established that rhodium-carbenoids would react with oxygen, nitrogen and sulfur atoms to afford reactive ylides. In this work, facile functionalization of the benzohydroxamic acids containing heterocyclic moiety with **2a** was achieved, and **3j** was obtained in 63% yield. No ylide-mediated reactions (e.g. Stevens rearrangement of sulfonium ylides) was observed.

The scope of the diazo reagents was also investigated (Table 3). Apart from diazomalonate **2a**, diazoesters bearing functional groups such as phenylsulfone, cyano and diethyl phosphonate would effectively couple with **1a** under the Rh catalysis to afford the cycloaddition products (**3k** – **3m**) in 30 – 77% yields. It is worth mentioning that the internal C=C bond was also tolerated in the analogous reaction, and **3n** was obtained in 86% yield. Indeed, alkene moieties are known to undergo cyclopropanation with carbenoid species.[9] In addition, donor-acceptor substituted diazo reagents were reactive coupling partners. Treating methyl phenyldiazoacetate and its bromo-substituted derivative with substrate **1a** under standard reaction conditions afforded the corresponding **3p** and **3q** in 83% and 90% yields. Noted that spirocyclic oxindoles are attractive molecules of remarkable biological importance; the Rh-catalyzed reaction with diazooxindole smoothly gave the bicyclic product **3r** in 75% yield. Alkyl diazoacetates are challenging reagents for the carbenoid C-H functionalization; the competitive β-hydride elimination of the putative alkylrhodium complex would terminate the catalytic cycle with inactive Rh-hydride species.[10] Yet in this work, alkyl diazoacetates were found to be effective reagents with **3s** and **3t** being obtained in 32% and 62% yields respectively. Likewise, reaction of diphenyldiazomethane with **1a** gave the

Table 3 Scope of diazo compounds[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol) and [Cp*Rh(OAc)$_2$] (5 mol%) in THF (2 mL) at 60 °C for 4 h. Isolated yield.

desired cycloadduct **3a** in 82% yield.

O-Acetyl benzohydroxamic acids are common substrates for [Cp*Rh]-catalyzed direct arene C-H coupling reactions, including alkyne cycloaddition and aminations. The coupling reactions were believed to occur via some reactive rhodacyclic complexes;[11] however, reports on isolation and structural characterization of the rhodacyclic complexes are sparse. To ascertain the involvement of the rhodacyclic complex in the carbenoid [4+1] cycloaddition, we reacted *O*-acetyl benzohydroxamic acids (0.12 mmol) with [Cp*Rh(OAc)$_2$] (0.1 mmol) in THF at 60 °C for 2 h under a N_2 atmosphere. ^{1}H NMR analysis of the crude mixture revealed a complicated mixture, which was then purified by column chromatography over alumina with diethyl ether as eluent. Removal of the diethyl ether gave a dark orange solid, which was recrystallized from ether to afford **4** as a dark red crystal (5% yield) after 3 days at room temperature. By means of X-ray crystallography, the molecular structure of **4** was established to be a dinuclear arylrhodium(III) complex (Figure 1). The complex exhibits a five-membered cyclic structure with the measured Rh(1)–C(19) distance to be 2.024(3) Å.[12] The four-membered aza-rhodium cycle was characterized by the measured Rh(1)–N(1) and Rh(1)–N(1A) distances being 2.111(3) Å and 2.169(3) Å. As expected, the two Cp rings adopt an anti-conformation. Notably, a methyl group on the Cp rings was acetoxylated with C(10)–O(2) distance being 1.397 Å. In this work, treatment of **4** with diazo **2a** (1.2 equiv) in THF at 60 °C failed to effect any cycloadduct formation, and the complex was fully recovered. This poor reactivity of **4** is attributed to the strong azo-rhodium cycle, which may be

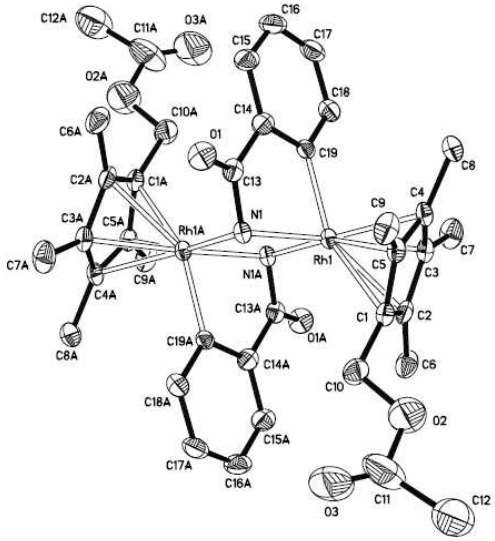
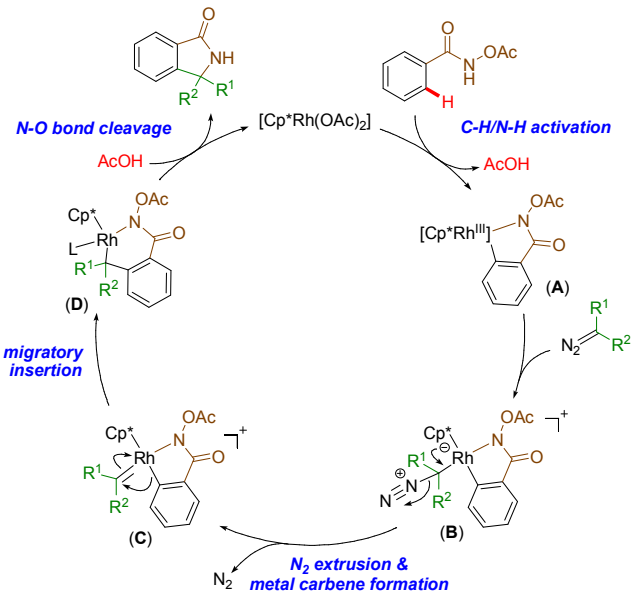


Figure 1. Molecular structure for **4** with 50% displacement ellipsoid. H atoms are omitted for clarity. Selected bond distances [Å] and bond angles [deg]: Rh(1)–N w(1), 2.111(3); Rh(1)–N(1A), 2.169(3); Rh(1)–C(19), 2.024(3) Å; C(10)–O(2), 1.397(8); C(19)–Rh(1)–N(1), 78.11(13); C(19)–Rh(1)–N(1A), 85.48(13); N(1)–Rh(1)–N(1A), 81.24(13); Rh(1)–N(1)–Rh(1A), 98.76(13).



Scheme 3 Proposed mechanism

difficult to dissociate for diazo coordination. Furthermore, we performed a kinetic isotope effect (KIE) study based on two parallel reactions ith d_5-**1a** and **1a** as substrate. While KIE values >2 was seen in many [Cp*Rh^{III}]-catalyzed C-H coupling reactions;[6a,8] however, no KIE was observed for this case with k_H/k_d of 1.03, suggesting that the C-H activation is not involved in the rate-limiting step.

On the basis of our mechanistic studies and literature precedent, a plausible mechanism for this Rh-catalyzed cycloaddition reaction is proposed in Scheme 3. It is postulated that the electrophilic [Cp*Rh(OAc)$_2$] would initially undergo a chelation-assisted C-H/N-H deprotonation

of *O*-acetyl benzohydroxamic acids to form a five-membered rhodacycle (**A**) with elimination of acetic acid. We proposed that coordination of the diazo compound with **A** may form the diazonium intermediate **B**. Extrusion of N_2 from **B** would afford the Rh-carbene **C**, which subsequently undergoes migratory insertion to give **D**. Further C-N bond formation via reductive elimination would furnish the desired product **3** and the *N*-OAc moiety may act as internal oxidant to regenerate the active Rh catalyst.

Conclusion

In conclusion, we have developed a Rh(III)-catalyzed C-H activation/cycloaddition of benzohydroxamic acids with diazo compounds. The functionalized lactam derivatives were obtained in good yields under mild reaction conditions. In this case, external oxidant was not required and diazo bearing different substituents were well-tolerated.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedure, ^1H and ^{13}C NMR data and spectra for all compounds, X-ray crystallographic data. CCDC 987993. See DOI: 10.1039/b000000x/

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