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Tunable Arylative Cyclization of 1,6-Enynes Triggered by Rhodium(III)-Catalyzed C−H Activation

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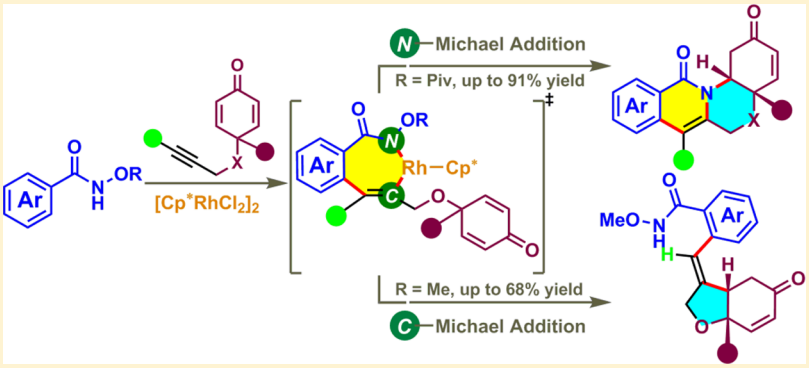
Supporting Information



ABSTRACT: Two tunable arylative cyclizations of cyclohexadienone-containing 1,6-enynes are reported via rhodium(III)-catalyzed C−H activation of O-substituted *N*-hydroxybenzamides. The use of different O substituents, i.e. *O*-Piv and *O*-Me, on the directing group allows the formation of either tetracyclic isoquinolones through an Ⓝ-Michael addition process or hydrobenzofurans through a Ⓒ-Michael addition process. Mechanistic investigations of these two cascade reactions clearly indicated that the C−H bond cleavage process was involved in the turnover-limiting step. Furthermore, the cyclization products could be subjected to various transformations for elaborating the pharmaceutically and synthetically valuable potential. This is the first example of a rhodium(III)-catalyzed arylative cyclization reaction of 1,6-enynes, and the results extend the application realm of Cp*Rh^{III}-catalyzed C−H activation cascade reactions.

INTRODUCTION

Transition-metal-catalyzed direct C−H bond functionalizations have recently emerged as a powerful, atom-economical, and ideal method for the formation of carbon−carbon and carbon−heteroatom bonds.[1] Among such transformations, Cp*Rh^{III}-catalyzed C−H activation, in combination with its subsequent cross-coupling with alkynes, alkenes, allenes, arenes, and heteroatoms, is becoming a rapidly evolving research field.[2] Various neutral and anionic functionalities, such as heterocycles,[3] ketones,[4] and carboxylic acid derivatives,[5−7] have been continually developed as efficient directing groups. As an elegant and green strategy, the use of an oxidizing directing group (an internal oxidant) has drawn much attention due to its dual roles in directing C−H activation and regenerating the catalyst.

In 2010 and 2011, Fagnou and co-workers successively described Cp*Rh^{III}-catalyzed redox-neutral coupling of *N*-methoxy-/*N*-(pivaloyloxy)benzamides with alkynes to afford a wide variety of isoquinolones, which sheds light on the stepwise C−N bond reductive elimination and N−O bond oxidative addition mechanism (Scheme 1a).[8] Roughly at the same time, Rovis and co-workers established an oxidative cyclization between benzamides and alkynes.[7a] These key seminal findings set the stage for intense research activity in the area of Cp*Rh^{III}-catalyzed C−H activation of O-substituted *N*-hydroxybenzamides and related processes.[9,10]

In 2012, using alkyne-tethered hydroxamic esters as an alternative substitution pattern, Park and co-workers subsequently offered a novel approach to isoquinolones, but with reversed regioselectivity (Scheme 1b).[11] In the same year, Glorius and co-workers identified a new method for the coupling of *N*-(pivaloyloxy)benzamides and ethynylboronates for straightforward access to 2-isoquinolinylboronates.[12]

Just recently, Glorius and co-workers also successfully developed the Cp*Rh^{III}-catalyzed C−H activation and 1,3-diyne strategy for the efficient formation of bis-isoquinolones,[13] while Antonchick and co-workers described another elegant alternative organocatalytic gateway from the coupling of *N*-methoxybenzamides and diaryl-alkynes to isoquinolones through a nitrenium ion process.[14]

Despite such exciting advances, Cp*Rh^{III}-catalyzed coupling of O-substituted *N*-hydroxybenzamides and functionalized alkynes mainly focused on the C−N bond reductive elimination

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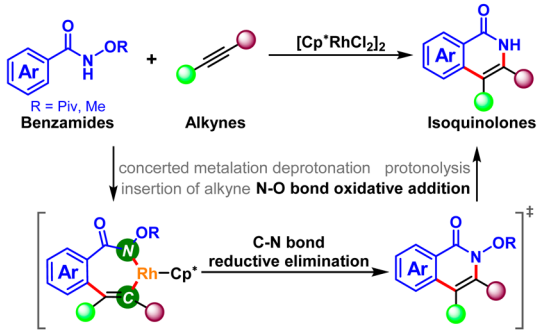
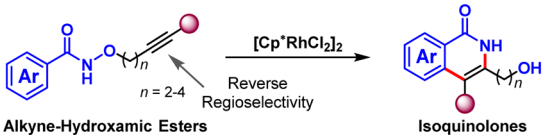
Scheme 1. Cp*Rh^{III}-Catalyzed Cyclization of *N*-Methoxy-/*N*-(Pivaloyloxy)benzamides and Alkynes

(a) Fagnou: Cp*Rh(III)-Catalyzed Cyclization of *N*-Methoxy-/*N*-(Pivaloyloxy)benzamides and Alkynes[8]

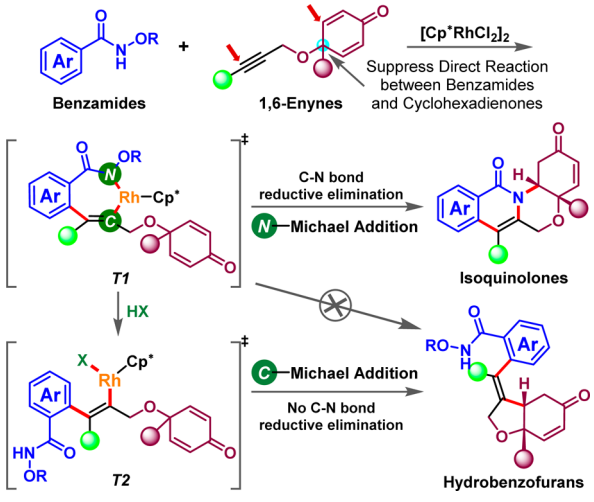


(b) Park: Cp*Rh(III)-Catalyzed Intramolecular Cyclization of Alkyne Tethered Hydroxamic Esters[11]



pathway, and the process without C−N bond reductive elimination has never been uncovered.[10] Considering this concern, we reasoned that Cp*Rh^{III}-catalyzed cyclization of O-substituted *N*-hydroxybenzamides and alkyne-tethered cyclohexadienone[15] could provide another reaction pattern, possibly in a different cascade process. In this case, regioselective insertion of the carbon−carbon triple bond of cyclohexadienone-containing 1,6-enynes into the Rh−Ar bond, derived from Rh(III)-catalyzed C−H activation of O-substituted *N*-hydroxybenzamides, could give the seven-membered rhodacycle intermediate **T1** (Scheme 2). The subsequent C−N bond reductive elimination, N−O bond oxidative addition, and protonolysis of the Rh−N bond could afford the neutral NH functional group, which then undergoes an Ⓝ-Michael addition reaction, leading to the formation of N-substituted isoquinolones.

Scheme 2. Strategic Design for Rh(III)-Catalyzed Cyclization of Benzamides and 1,6-Enynes

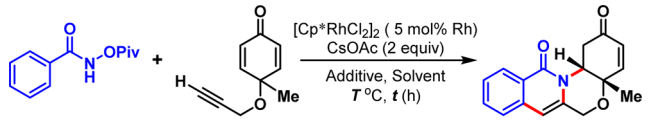


On the other hand, we envisioned that the intermediate **T1** could undergo Ⓒ-Michael addition to furnish the fused bicyclic product hydrobenzofurans due to the presence of the highly reactive Michael acceptor: i.e., cyclohexadienone (Scheme 2). However, to the best of our knowledge, the straightforward Ⓒ-Michael addition has difficulty taking place, due to the steric congestion imposed by the cyclic vinyl Cp*Rh^{III} intermediate **T1**. We supposed that the opened vinyl-Rh(III) intermediate **T2** could be generated in protic media and the subsequent Ⓒ-Michael addition could occur with ease.[10] Thus, no C−N bond reductive elimination process is involved in this sequence, which provides a new catalytic pattern.

RESULTS AND DISCUSSION

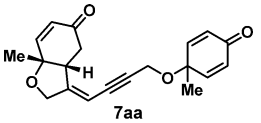
The findings by Fagnou and co-workers[8] showed that *the O*-pivaloyl group in *N*-hydroxybenzamides can potentially chelate Rh(III) and promote C−N bond reductive elimination. Thus, we commenced to examine the Cp*Rh^{III}-catalyzed cyclization of *N*-(pivaloyloxy)benzamide (**1a**) and 1,6-enyne **2a** (Table 1).

Table 1. Reaction Optimization toward Cp*Rh^{III}-Catalyzed Cyclization of *N*-(Pivaloyloxy)benzamide (1a) and 1,6-Enyne 2a[a]



entry	solvent	additive	T (°C)	t (h)	yield (%)[b]
1	MeOH		25	12	5
2	MeOH		60	16	30[e,g]
3	*i*-PrOH		40	30	42[e]
4	*i*-PrOH		60	10	54[e]
5	*t*-BuOH		60	10	35[e]
6	THF		40	10	0
7	MeCN		60	10	17[e]
8	DMF		25	40	55[e]
9[c]	acetone	MS (4 Å, 100 mg)	50	12	85[f]
10[d]	DMF	$Cu(OAc)_2$ (0.4 equiv)	25	16	91[f]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.1 equiv), $[Cp^*RhCl_2]_2$ (0.005 mmol, 5 mol % Rh), CsOAc (2.0 equiv), solvent (1 mL), under N_2. Piv = pivaolyl. [b]Isolated yield. [c]**1a** (1.5 equiv) and **2a** (0.2 mmol). [d]**1a** (2.0 equiv) and **2a** (0.2 mmol). [e]Based on **1a**. [f]Based on **2a**. [g]**3aa** (30% yield) and **7aa** (10% yield).



The reaction was first performed in MeOH at room temperature; most of the starting materials were recovered, and only trace cyclization product was observed (Table 1, entry 1). To our delight, the desired tetracyclic product **3aa** was obtained in 30% yield, accompanied by a 10% yield of dimerization side product **7aa**,[17] when the reaction temperature was raised to 60 °C (Table 1, entry 2). Next, a set of representative protic solvents (*i*-PrOH, *t*-BuOH) and polar solvents (THF, MeCN, DMF) were screened; the reactions still afforded low to moderate yields, and their main side products were the removal of the pivaloyl group in **1a** to the formation of *N*-hydroxybenzamide (Table 1, entries 3−8). Therefore, an

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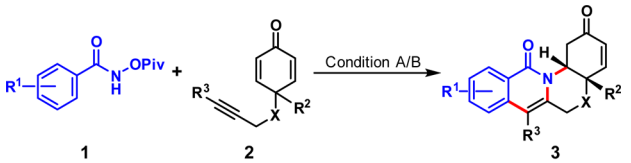
excess amount of benzamide **1a** was used in the next reaction testing. As a result, the yield was greatly increased to 85% when the reaction was conducted in acetone at 50 °C with molecular sieves as an additive (Table 1, entry 9). According to a recent report by Glorius and co-workers, the addition of a substoichiometric amount of $Cu(OAc)_2$ facilitated the C−H bond functionalizations of *N*-(pivaloyloxy)benzamides and significantly improved the reaction yields.[12] In our case, the yield dramatically rose to 91% in the presence of $Cu(OAc)_2$ (40 mol %) (Table 1, entry 10). We therefore proposed that copper could promote the regeneration of the active Rh(III) catalyst from deactivated Rh(I) species.

With the optimal reaction conditions identified, the scope of various 1,6-enynes **2** was investigated. With the R^2 substituent as alkyl, benzyl, and phenyl groups in the terminal alkyne substrates, the reactions proceeded smoothly with moderate to excellent yields (Table 2, entries 1−5). With a heteroatom (N and O) as part of R^2 in substrates **2**, the cyclization reaction performed equally well, albeit in around 40% yields (Table 2, entries 6−9). For the internal alkyne substrates **2j**,**k** regioselective insertion of the internal alkyne bond into the Rh−Ar bond readily occurred, leading to the formation of isoquinolone products (Table 2, entries 10 and 11). However, for the internal alkyne substrate **2l**, due to a lack of obvious steric or electronic differences at both ends of alkyne, the cyclization product **3al** was obtained in 52% yield, accompanied by the regioisomer **3al′** (38% yield; see the Supporting Information), which cannot undergo a further Ⓝ-Michael reaction (Table 2, entry 12). For the C- and N-linked 1,6-enyne substrates **2m**,**n**, the desired cyclization products were also obtained in slightly lower yields (Table 2, entries 13 and 14).

Various *N*-(pivaloyloxy)benzamides **1** were also examined. All 4-substituted *N*-(pivaloyloxy)benzamides, regardless of the electron-donating or electron-withdrawing properties of the substitutent at the phenyl ring, afforded the cyclization products (Table 2, entries 15−19). For 3-methyl-*N*-(pivaloyloxy)benzamide (**1g**), the C−H activation could take place at either the 6- or 2-position, giving the two inseparable cyclization products **3ga** (43% yield) and **3ga′** (8% yield; Table 2, entry 20). Interestingly, 2-methyl-*N*-(pivaloyloxy)benzamide (**1h**) failed to give the cyclization product, probably due to the large steric hindrance of the neighboring substituent.[16a] In most cases in Table 2, the low yields were mainly attributed to the decomposition of **1a** to form *N*-hydroxybenzamide.

The recent findings revealed that selecting *N*-methoxybenzamide as a coupling partner with the reaction of terminal alkene gave the olefinated benzamide, the noncyclized product without the formation of a C−N bond.[10] Thus, we chose *N*-methoxybenzamide (**4a**) as a coupling partner to explore the Ⓒ-Michael addition cyclization potential with 1,6-enyne **2a**. Unfortunately, only the dimerization products of **2a** were observed under the aforementioned conditions (Table 3,

Table 2. Cp*Rh^{III}-Catalyzed Cyclization of *N*-(Pivaloyloxy)benzamides 1 and 1,6-Enynes 2



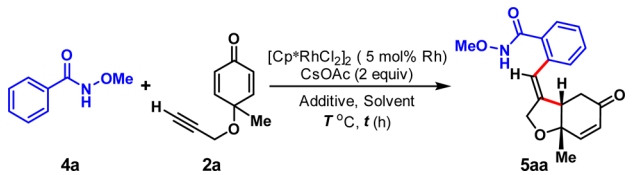
1 2 3

For **2a** to **2i**: X = O, R^3 = H-; For **2j** to **2l**: X = O, R^2 = Me-;
For **2m**: X = -CH_2-, R^3 = H-; For **2n**: X = -NBoc-, R^3 = H-.

entry	1 (R^1)	2 (R^2 or R^3)	*t* (h)	3 (yield (%))[c]
1[b]	**1a** (H)	**2a** (R^2 = Me)	15	**3aa** (91)
2[a]	**1a** (H)	**2b** (R^2 = Et)	12	**3ab** (75)
3[a]	**1a** (H)	**2c** (R^2 = *i*-Pr)	36	**3ac** (65)
4[a]	**1a** (H)	**2d** (R^2 = $PhCH_2$)	24	**3ad** (85)
5[a]	**1a** (H)	**2e** (R^2 = Ph)	36	**3ae** (66)
6[a]	**1a** (H)	**2f** (R^2 = $BocNH(CH_2)_2$)[e]	48	**3af** (40)
7[a]	**1a** (H)	**2g** (R^2 = $AcO(CH_2)_2$)	24	**3ag** (40)
8[a]	**1a** (H)	**2h** (R^2 = $TBSO(CH_2)_3$)[f]	24	**3ah** (40)
9[a]	**1a** (H)	**2i** (R^2 = MeO)	20	**3ai** (47)
10[b]	**1a** (H)	**2j** (R^3 = Me)	12	**3aj** (62)
11[a]	**1a** (H)	**2k** (R^3 = $HOCH_2$)	12	**3ak** (46)
12[a]	**1a** (H)	**2l** (R^3 = $BnOCH_2$)	12	**3al** (52)
13[a]	**1a** (H)	**2m** (R^2 = MeO)	12	**3am** (72)
14[a]	**1a** (H)	**2n** (R^2 = Me)	8	**3an** (44)
15[a]	**1b** (4-MeO)	**2a** (R^2 = Me)	20	**3ba** (49)
16[a]	**1c** (4-F)	**2a** (R^2 = Me)	12	**3ca** (78)
17[b]	**1d** (4-Br)	**2a** (R^2 = Me)	24	**3da** (52)
18[a]	**1e** (4-CF_3)	**2a** (R^2 = Me)	12	**3ea** (68)
19[a]	**1f** (4-Me)	**2a** (R^2 = Me)	36	**3fa** (50)
20[a]	**1g** (3-Me)	**2a** (R^2 = Me)	40	**3ga** (43)[d]

[a]Conditions A: **1** (1.5 equiv), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 5 mol % Rh), CsOAc (2.0 equiv), acetone (1 mL), 50 °C, under N_2. [b]Conditions B: **1** (2.0 equiv), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 5 mol % Rh), CsOAc (2.0 equiv), DMF (1 mL), room temperature, under N_2. [c]Isolated yield, based on **2**. [d]An inseparable regioisomer, **3ga′** (8% yield), was obtained. [e]Boc = *tert*-butoxycarbonyl. [f]TBS = *tert*-butyldimethylsilyl.

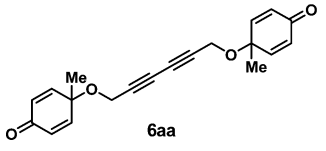
Table 3. Reaction Optimization toward Cp*Rh^{III}-Catalyzed Cyclization of *N*-Methoxybenzamide (4a) and 1,6-Enyne 2a[a]



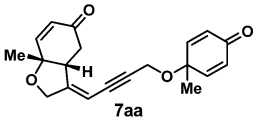
4a 2a 5aa

entry	solvent	additive	*T* (°C)	*t* (h)	yield (%)[b]
1	MeOH	$Cu(OAc)_2$ (0.4 equiv)	50	3	0[c]
2	DMF		60	12	0[d]
3	*n*-BuOH		25	48	9
4	CF_3CH_2OH		25	48	19
5	THF	CF_3CH_2OH (2.0 equiv)	60	24	24
6	1,4-dioxane	PivOH (2.0 equiv)	80	24	39
7[e]	1,4-dioxane	PivOH (2.0 equiv)	80	24	0
8[f]	$ClCH_2CH_2Cl$	PivOH (2.0 equiv)	60	12	62
9[fg]	$ClCH_2CH_2Cl$	PivOH (2.0 equiv)	60	12	63
10[f,h]	$ClCH_2CH_2Cl$	PivOH (2.0 equiv)	60	12	31[i]

[a]Reaction conditions: **4a** (0.4 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 5 mol % Rh), CsOAc (2.0 equiv), solvent (2 mL), under N_2. [b]Isolated yield. [c]**6aa** (66% yield). [d]**7aa** (79% yield). [e]With no CsOAc. [f]Using CsOPiv instead of CsOAc. [g]**4a** (0.3 mmol) was used. [h]**4a** (0.2 mmol) and **2a** (0.6 mmol) were used. [i]Based on **4a**.



6aa



7aa

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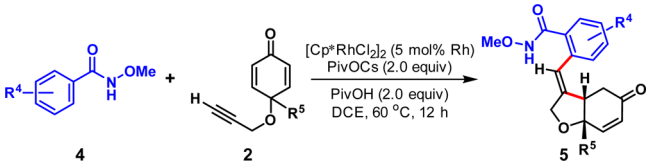
entries 1 and 2).[17] When *n*-BuOH was used as solvent and the reaction temperature was lowered, we were delighted to get the desired bicyclic product **5aa** in 9% yield (Table 3, entry 3). Slightly higher yields were obtained with trifluoroethanol as solvent or additive (Table 3, entries 4 and 5). The yield was further increased to 39% with pivalic acid as additive (Table 3, entry 6).[10] However, no cyclization product was observed in the absence of base (Table 3, entry 7). Fortunately, when the solvent was changed to 1,2-dichloroethane, the yield was greatly raised to 62%. Lowering the loading of *N*-methoxybenzamide (**4a**) had no impact on the yield (Table 3, entries 8 and 9). However, an attempt to increase 1,6-enyne **2a** loading also resulted in a decreased yield (Table 3, entry 10).

With the satisfactory conditions in hand, various 1,6-enynes **2** were then examined. With the R^5 substituent as alkyl, benzyl, and phenyl groups in the terminal alkyne substrates, the ©-Michael addition cyclization occurred readily with good yields (Table 4, entries 1−5). With a heteroatom (N, O, and

Table 4. Cp*Rh^{III}-Catalyzed Cyclization of *N*-Methoxybenzamides 4 and 1,6-Enynes 2[a]



Entry	4 (R_4)	2 (R_5)	5 (yield (%))[b]
1	**4a** (H)	**2a** (Me)	**5aa** (63)
2	**4a** (H)	**2b** (Et)	**5ab** (68)
3	**4a** (H)	**2c** (i-Pr)	**5ac** (61)
4	**4a** (H)	**2d** ($PhCH_2$)	**5ad** (61)
5	**4a** (H)	**2e** (Ph)	**5ae** (67)
6	**4a** (H)	**2o** (4-Br-C_6H_4)	**5ao** (63)
7	**4a** (H)	**2f** ($BocNH(CH_2)_2$)	**5af** (43)
8	**4a** (H)	**2g** ($AcO(CH_2)_2$)	**5ag** (51)
9	**4a** (H)	**2p** (n-PrO)	**5ap** (61)
10	**4a** (H)	**2q** ($Br(CH_2)_3$)	**5aq** (62)
11	**4b** (4-MeO)	**2a** (Me)	**5ba** (55)
12	**4c** (4-F)	**2a** (Me)	**5ca** (57)
13	**4d** (4-Br)	**2a** (Me)	**5da** (66)
14	**4d** (4-Br)	**2o** (4-BrC_6H_4)	**5do** (54)
15	**4e** (4-CF_3)	**2a** (Me)	**5ea** (63)
16	**4f** (4-NO_2)	**2a** (Me)	**5fa** (60)
17	**4g** (4-$MeCO_2$)	**2a** (Me)	**5ga** (63)
18	**4h** (4-Me)	**2a** (Me)	**5ha** (59)
19	**4i** (3-Me)	**2a** (Me)	**5ia** (62)
20	**4j** (2-Me)	**2a** (Me)	**5ja** (61)

[a]Reaction conditions: **4** (0.3 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 5 mol % Rh), CsOPiv (2.0 equiv), PivOH (2.0 equiv), 1,2-dichloroethane (2 mL), under N_2, at 60 °C for 12 h. [b]Isolated yield, based on **2**.

Br) as part of R^5 in substrates **2**, the cyclization reaction proceeded equally well (Table 4, entries 6−10). For the internal alkyne **2j** and the C- and N-linked 1,6-enynes **2m,n** (for the structures of substrates **2j,m,n**, see Table 2), no desired cyclization products were observed under the standard reaction conditions.[16a]

Next, various *N*-methoxybenzamides **4** were also investigated. All 4-substituted substrates, regardless of the electron-donating or electron-withdrawing properties of the substituent at the phenyl ring, delivered the cyclization products (Table 4, entries 11−18). For 3-methyl-*N*-methoxybenzamide (**4i**), the C−H activation selectively occurred at the 6-position, only giving cyclization product **5ia** (Table 4, entry 19). Intriguingly, 2-methyl-*N*-methoxybenzamide (**4j**) also gave the cyclization product (Table 4, entry 20).

The structure and relative configuration of product **5do** were determined by an X-ray diffraction analysis (Figure 1).[18]

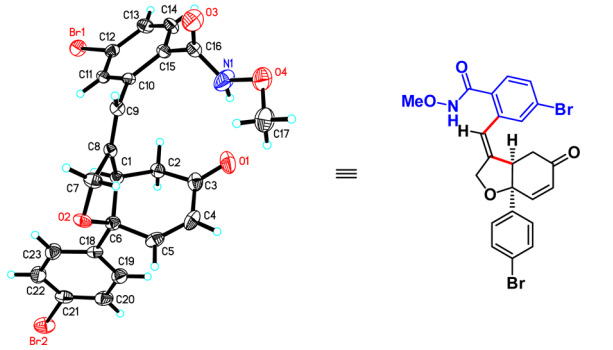


Figure 1. X-ray structure of **5do**.

To get further insight into the mechanism of these cascade reactions, deuterium-labeling experiments were designed to determine the values of the kinetic isotope effects (KIEs).[16] For the Ⓝ-Michael addition process, two parallel reactions, one with the hydrogenated substrate **1a** (1.5 equiv) and the other with the deuterated substrate ***d*$_5$-1a** (1.5 equiv), were conducted separately within 5 min under standard conditions A, which only afforded the intermediates **3aa′** and ***d*$_4$-3aa′**,[19] respectively (Exp. I, Scheme 3). Their relative ratio gave a sketchy KIE value of k_H/k_D = 6.1, indicating that the C−H bond cleavage process should be the turnover-limiting step.[20] The intermolecular KIE experiment was then performed by treating 1.5 equiv of **1a**, 1.5 equiv of ***d*$_5$-1a**, and 1.0 equiv of **2a** within 5 min to give a KIE value of k_H/k_D = 6.7 (Exp. II, Scheme 3). The intramolecular KIE was also determined to be k_H/k_D = 5.7 by treatment of ***d*-1a** with **2a** (Exp. III, Scheme 3). Thus, the intermolecular and intramolecular KIEs provided additional evidence regarding the turnover-limiting step. The KIEs of experiments IV (H/D-alkynes) and V (H/D-cyclohexadienones) were also determined to be 1.2 and 1.0, respectively, demonstrating that the insertion of the carbon−carbon triple bond and Ⓝ-Michael addition steps are not involved in the turnover-limiting step.[16a] For the ©-Michael addition process, similar outcomes were observed. The KIEs of experiments VI−VIII were determined to be 2.0, 6.1, and 4.3, respectively.[16a] These results clearly suggest that the C−H bond cleavage process is equally involved in the turnover-limiting step.

Piecing together these above details, we proposed that their mechanisms differ regarding such O substitution in *N*-hydroxybenzamides (Figure 2). Initially, a highly reactive rhodium(III) species **A**/**F** is generated from the Rh precatalyst $[Cp^*RhCl_2]_2$ in the presence of CsOAc/CsOPiv. Subsequently the chelation-assisted C−H activation occurs at the ortho position via a base-assisted concerted metalation/deprotonation (CMD) pathway,[21] which is the turnover-limiting step in the entire tandem reaction. The five-membered rhodacycle **B**/**G** undergoes regioselective syn addition to the carbon−carbon triple bond in **2** to afford the seven-membered rhodium intermediate **C**/**H**. For *N*-(pivaloyloxy)benzamides, the *O*-

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Scheme 3. Deuterium-Labeling Experiments and Study of the Kinetic Isotope Effects

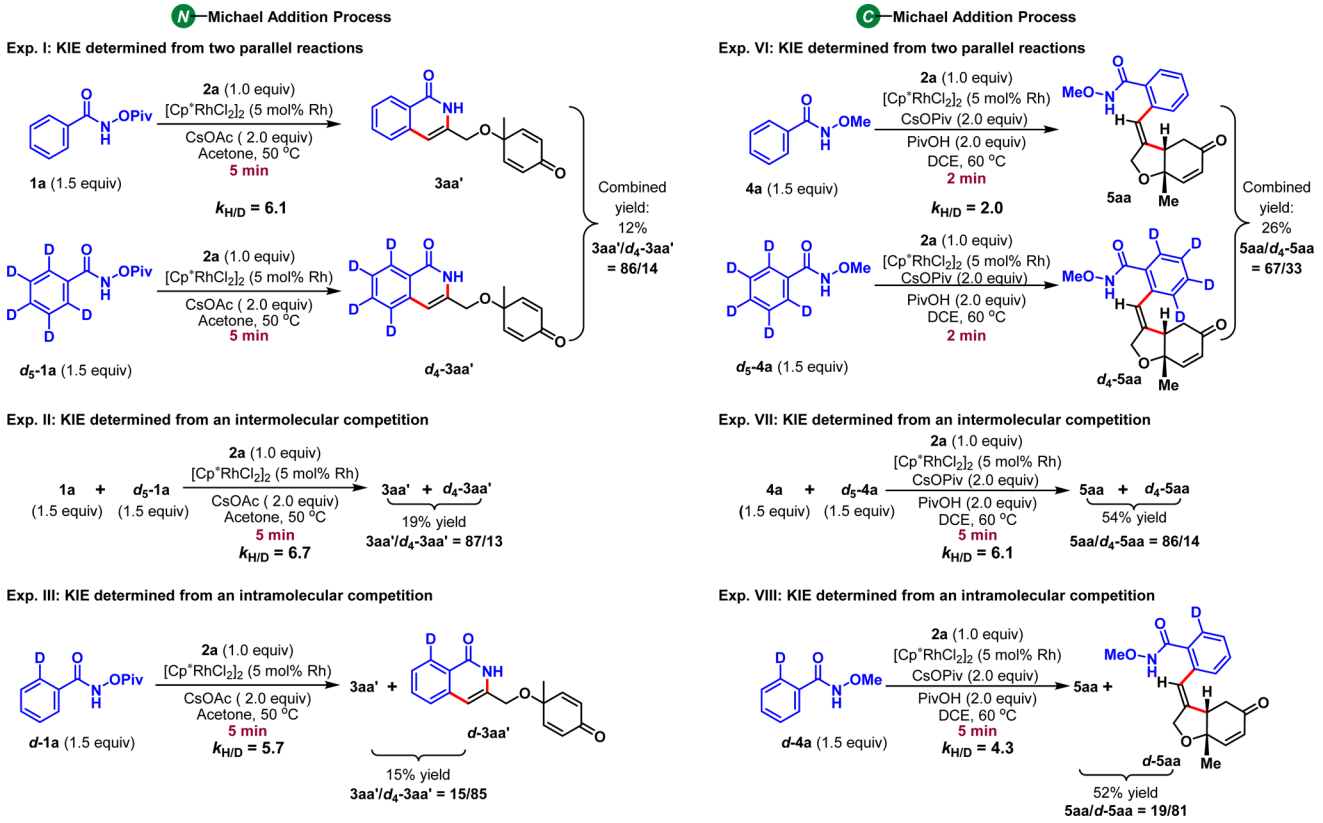

Figure 2. Postulated mechanisms for the two different arylative cyclization reactions.

pivaloyl group can potentially chelate Rh(III) and promote C–N bond reductive elimination, thus allowing the facile formation of intermediate **D** and the Rh(I) species (Cp*Rh). Then, a fast oxidative addition occurs to provide the intermediate **E**, which is readily protonated by acetic/pivalic acid to regenerate the reactive species **A** and liberate the cyclohexadienone-containing isoquinolone intermediate **3′**. Finally, an intramolecular Ⓝ-Michael addition reaction under CsOAc/CsOPiv[19] leads to the formation of the tetracyclic product **3**. On the other hand, for *N*-methoxybenzamides, there is no additional chelating functionality that promotes C–N bond reductive elimination; thus, the seven-membered rhodacycle **H** is rapidly protonated by pivalic acid to give the opened vinyl–Rh(III) intermediate **J**. Next, the favorable six-membered chairlike form of **J** enables syn-migratory insertion in the Ⓒ-Michael addition, providing the oxa-π-allylrhodium intermediate **K**, which is readily protonated by pivalic acid to regenerate **F** and release the product **5**. It should be noted that

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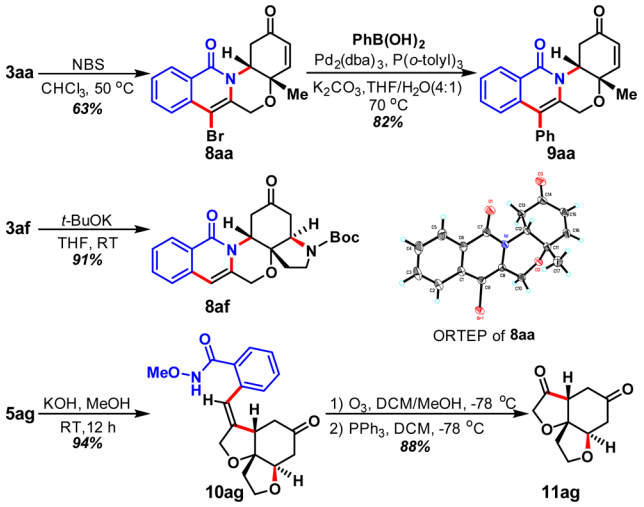
rhodium stayed in a constant oxidation state of +3 throughout this catalytic cycle.

To further demonstrate the synthetic utility of this methodology, the cyclization products were converted into pharmaceutically interesting isoquinolone derivatives and the useful core structures were related to natural products (Scheme 4). When compound **3aa** was treated with NBS, selective

Scheme 4. Transformations of the Cyclization Products



bromination occurred to afford bromide **8aa** in high yield, which could undergo further transformations to furnish diversely useful molecules. For example, the pentacyclic structure **9aa** was accomplished through Suzuki−Miyaura coupling with phenylboronic acid. The relative configuration of **8aa** was unequivocally determined as the cis form on the basis of an X-ray diffraction analysis.[18] Additionally, the existing nitrogen atom in **3af** provided another handle to construct the consecutively pentacyclic skeleton **8af** through aza-Michael addition with excellent yield. Very similarly, removal of the acetyl group in **5ag** and simultaneous in situ oxa-Michael addition under basic conditions led to the formation of product **10ag**. A subsequent ozonolysis produced the tricyclic skeleton **11ag**, serving as the architecture unit of incarviditone.[22]

CONCLUSIONS

In summary, the Cp*Rh^{III}-catalyzed C−H activation of *N*-hydroxybenzamides could undergo tunable arylative cyclization with cyclohexadienone-containing 1,6-enynes on the basis of the selection of different O substitutions. For *N*-(pivaloyloxy)-benzamides, tetracyclic products bearing isoquinolone and cyclohexenone substructures are offered in moderate to excellent yields via an Ⓝ-Michael addition process. However, for *N*-methoxybenzamides, *cis*-hydrobenzofuran frameworks are achieved in moderate yields via a Ⓒ-Michael addition process with a perfect atom economy. We believe that this research could allow researchers to fine tune the reaction selectivity by simply changing substituents on the directing group. Mechanistic investigations of these two cascade reactions clearly indicated that the C−H bond cleavage process was involved in the turnover-limiting step. Furthermore, the cyclization products could be subjected to various transformations for elaborating the pharmaceutical potential. The present results extend the application realm of Cp*Rh^{III}-catalyzed C−H activation cascade reactions. Further studies on asymmetric versions are in progress in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All solvents were dried before use following the standard procedures. Unless otherwise indicated, all starting materials purchased from commercial suppliers were used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 MHz instrument in the indicated solvents. Chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (δ 77.10 ppm) for ^{13}C NMR. Coupling constants (J) are quoted in Hz. IR spectra were recorded on a Nicolet iN 10 MX instrument. ESI mass spectra were recorded on an Agilent1200/G6100A instrument.

General Method A for Cp*Rh^{III}-Catalyzed Cyclization of *N*-(Pivaloyloxy)benzamides 1 and 1,6-Enynes 2. A dried Schlenk flask was charged with cyclohexadienone-containing 1,6-enyne substrate **2** (0.2 mmol), *N*-(pivaloyloxy)benzamide **1** (0.3 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol, 5 mol % as Rh), MS 4 Å (100 mg), CsOAc (76.8 mg, 0.4 mmol, 2.0 equiv), and acetone (dry, 1 mL) under a nitrogen atmosphere. Then the reaction mixture was stirred at 50 °C until the substrate was completely consumed. The resulting mixture was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with DCM (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel (300−400 mesh) column chromatography to afford the desired product **3**.

*cis-4a-Ethyl-1,13a-dihydrobenzo[5,6][1,4]oxazino[4,3-b]-isoquinoline-2,12(4aH,6H)-dione (**3ab**, Table 2, entry 2):* colorless oil, 44.2 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.51−7.44 (m, 2H), 6.80 (d, J = 10.4 Hz, 1H) 6.38 (s, 1H), 6.23 (d, J = 10.4 Hz, 1H), 5.28 (dd, J = 11.6, 5.2 Hz, 1H), 4.92, 4.81 (AB, J_{AB} = 16.0 Hz, 2H), 3.02 (dd, J = 16.4, 5.2 Hz, 1H), 2.66 (dd, J = 16.4, 11.6 Hz, 1H), 1.90−1.70 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.39, 161.78, 146.85, 136.11, 134.31, 132.91, 131.35, 128.04, 126.72, 125.65, 124.64, 72.68, 61.67, 48.57, 39.57, 27.91, 7.56; ESI-MS $[M + H]^+$ 296.2; HRMS (FTMS-ESI) $[M + H]^+$ calcd for $C_{18}H_{18}NO_3^+$ 296.1287, found 296.1281; IR (KBr) ν (cm^{-1}) 2970, 2937, 1690, 1655, 1622, 1598, 1429, 1338, 1294, 1169, 1064, 924, 824, 759, 734, 697.

General Method B for Cp*Rh^{III}-Catalyzed Cyclization of *N*-(Pivaloyloxy)benzamides 1 and 1,6-Enynes 2. A dried Schlenk flask was charged with cyclohexadienone-containing 1,6-enyne substrate **2** (0.2 mmol), *N*-(pivaloyloxy)benzamide **1** (0.4 mmol, 2.0 equiv), $Cu(OAc)_2$ (14.5 mg, 0.08 mmol, 0.4 equiv), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol, 5 mol % as Rh), CsOAc (76.8 mg, 0.4 mmol, 2.0 equiv), and DMF (dry, 1 mL) under a nitrogen atmosphere. Then the mixture was stirred at room temperature until the substrate was completely consumed. The resulting mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with DCM (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel (300−400 mesh) column chromatography to afford the desired product **3**.

*cis-4a-Methyl-1,13a-dihydrobenzo[5,6][1,4]oxazino[4,3-b]-isoquinoline-2,12(4aH,6H)-dione (**3aa**, Table 2, entry 1):* pale yellow semisolid, 51.0 mg, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (d, J = 8.0 Hz, 1H), 7.68−7.66 (m, 1H), 7.50−7.46 (m, 2H), 6.75 (d, J = 10.0 Hz, 1H), 6.37 (s, 1H), 6.18 (d, J = 10.0 Hz, 1H), 5.09 (dd, J = 11.6, 6.8 Hz, 1H), 4.94, 4.89 (AB, J_{AB} = 16.0 Hz, 2H), 3.02 (dd, J = 16.0, 4.8 Hz, 1H), 2.65 (dd, J = 16.0, 12.0 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.46, 161.96, 148.19, 136.11, 133.89, 132.95, 130.54, 128.04, 126.74, 125.63, 124.70, 102.06, 69.91, 61.48, 51.36, 39.34, 22.46; ESI-MS $[M + Na]^+$ 304.0; HRMS (FTMS-ESI) $[M + H]^+$ calcd for $C_{17}H_{16}NO_3^+$ 282.1130, found 282.1125; IR (KBr) ν (cm^{-1}) 3307, 2977, 2925, 2855, 1689, 1655, 1622, 1429, 1336, 1280, 1183, 1102, 1063, 898, 822, 758, 696.

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General Procedure for Cp*Rh^{III}-Catalyzed Cyclization of *N*-Methoxybenzamides 4 and 1,6-Enynes 2. A dried Schlenk flask was charged with cyclohexadienone-containing 1,6-enyne substrate **2** (0.2 mmol), *N*-methoxybenzamide **4** (0.3 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol, 5 mol % as Rh), PivOCs (93.6 mg, 0.4 mmol, 2.0 equiv), PivOH (40.9 mg, 0.4 mmol, 2.0 equiv), and DCE (dry, 2 mL) under a nitrogen atmosphere. Then the mixture was stirred at 60 °C for 12 h. The resulting mixture was cooled to room temperature, diluted with DCM, and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel (300−400 mesh) column chromatography with hexane/ethyl acetate (2/3) eluent (for **5ae**,**ao**,**do**, with $CHCl_3$/MeOH (100/1) eluent) to afford the desired product **5**.

*N-Methoxy-2-((((3a,7a)-cis,E)-7a-methyl-5-oxo-3a,4,5,7a-tetrahydrobenzofuran-3(2H)-ylidene)methyl)benzamide (**5aa**, Table 4, entry 1):* colorless oil, 39.3 mg, 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.76 (s, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 6.50 (d, J = 10.0 Hz, 1H), 5.94 (d, J = 10.0 Hz, 1H), 4.53 (d, J = 13.6 Hz, 1H), 4.25 (d, J = 13.6 Hz, 1H), 3.79 (s, 3H), 3.34 (s, 1H), 2.38 (dd, J = 15.6, 4.8 Hz, 1H), 2.18 (d, J = 15.6 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.74, 167.26, 151.53, 144.14, 134.48, 133.13, 130.36, 129.59, 128.87, 128.11, 127.83, 120.12, 81.33, 70.85, 64.40, 47.17, 37.11, 22.75; ESI-MS: $[M + H]^{\oplus}$ 314.2; HRMS (FTMS-ESI) $[M + Na]^+$ calcd for $C_{18}H_{19}NO_4Na^+$ 336.1206, found 336.1206; IR (KBr) ν (cm^{-1}) 3235, 3060, 2973, 2934, 2851, 1675, 1596, 1569, 1497, 1462, 1442, 1422, 1375, 1281, 1230, 1162, 1116, 1099, 1082, 1042, 890.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and CIF files giving experimental procedures, structural proofs, and spectral data for all new compounds. 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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(18) CCDC 1009132 (**5do**) and 1009131 (**8aa**) contain supplementary crystallographic data for this paper.

(19) The control experiments clearly revealed that only the base, i.e. CsOAc, could independently promote the Ⓝ-Michael reaction of **3aa**′ to afford the product **3aa**. For more details, see the Supporting Information.

(20) Two separate experiments using the hydrogenated and deuterated substrates were carried out to independently assess the rate of reaction for ortho C−H versus C−D bond cleavage. See: Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12426−12429.

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