DOI: 10.1002/adsc.201601308

Advanced Synthesis & Catalysis

Rhodium(III)-Catalyzed Controllable C–H Bond Functionalization of Benzamides and Vinylidenecyclopropanes: A Directing Group Determined Reaction Pathway

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Received: November 27, 2016; Revised: January 2, 2017; Published online: ■■ ■■, 0000

Supporting information for this article is available under http://dx.doi.org/10.1002/adsc.201601308.

Abstract: A controllable rhodium(III)-catalyzed C–H bond activation of benzamides and vinylidenecyclopropanes (VDCPs) by changing the directing group from C(O)NH–OPiv to C(O)NH–OBoc has been disclosed, affording two different major products in good yields under mild condition, respectively. The substrate scope has been investigated and a plausible reaction mechanism has been also proposed on the basis of previous literature.

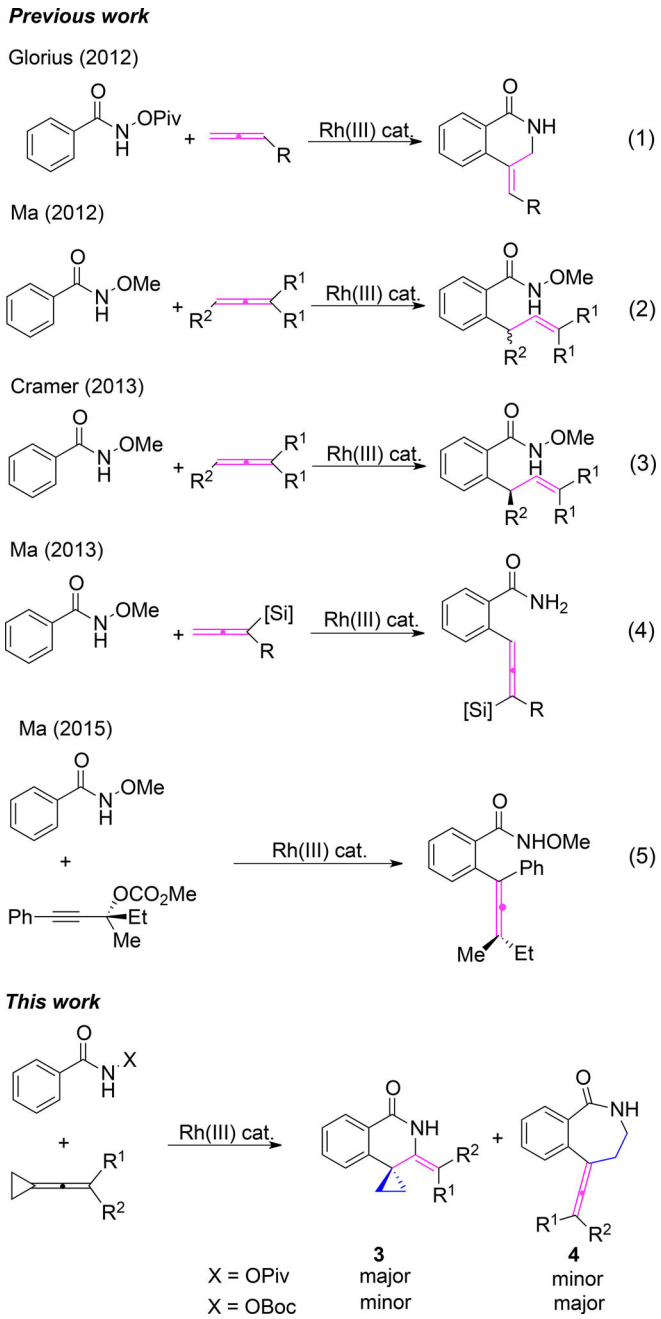
Keywords: allenes; benzamides; C–H bond activation; directing groups; rhodium(III)-catalyzed process; vinylidenecyclopropanes

Introduction

During the past decades, C–H bond functionalizations have emerged as a powerful tool in organic synthesis.[1] Great progress has been made in transition metal-catalyzed C–H bond functionalization for building various C–C and C–X bonds, and has afforded a streamlined and step-economical method for building desired valuable heterocycles without pre-activation of the coupling partner.[2] In addition to the widely explored C–H activation/functionalization reactions catalyzed by transition metals such as Pd, Ru, and Cu, Rh(III) complexes have been well-recognized as catalysts for C–H activation.[3] Rh(III)-catalyzed C–H activation stands out with high activity, broad substrate scope, high functional group tolerance and mild condition. Rh(III)-catalyzed synthesis of nitrogen-containing unsaturated heterocycles can be accessed through coupling of amides, amines, oximes, and anilines with alkynes to access isoquinolones,[4] pyridones,[5] isoquinolines,[6] pydridines,[7] indoles,[8] and pyrroles.[9]

Over the past decades, the synthesis of allenes has made significant progress and a large number of useful and practical methods have been explored. With the aid of allenes, scientists can rapidly generate complex molecular structures from easily accessible starting materials under mild reaction conditions. Despite the significance of allenes in organic chemistry, the role of allenes is limited in transition metal-catalyzed C–H bond functionalization. In 2012, Glorius reported the annulative coupling between benzimides and allenes [Scheme 1, Eq. (1)].[10] After that, Ma reported the *ortho*-allylation of *N*-methoxybenzamides with polysubstituted allenes [Scheme 1, Eq. (2)].[11] In 2013, Cramer reported the first enantioselective allylation of *N*-methoxybenzamides with polysubstituted allenes [Scheme 1, Eq. (3)].[11c] In the same year, Rh(III)-catalyzed C–H activation was applied to the synthesis of functionalized allenes [Scheme 1, Eqs. (4) and (5)] by the group of Ma.[12]

In these reactions, the directing groups played a significant role in C–H bond functionalizations. In general, the functional groups C(O)NH–OMe and C(O)NH–OPiv were used quite often in this aspect. In any sense, the directing groups can determine the reaction pathway to give different products. For example, in 2011, Glorius reported the first example of the reaction of benzamides and olefins, in which C(O)NH–OMe underwent β-hydride elimination to



Scheme 1. Rh(III)-catalyzed C–H functionalization involving allenes and our work.

give acyclic olefins, but C(O)NH–OPiv proceeded through reductive elimination to give cyclic benzamides.[13a] After that, Sun and co-workers reported different outcomes in the reaction of benzamides with methylenecyclopropanes (MCPs), in which the product selectivity depended on the aromatic rings and reaction temperature[13c] (a benzene ring gave [4+2] cycloadducts, but furan and thiophene produced [4+3] cycloadducts). However, the reports with regard to the selective production of C–H bond functionalization products on the basis of different directing groups are rare.[14]

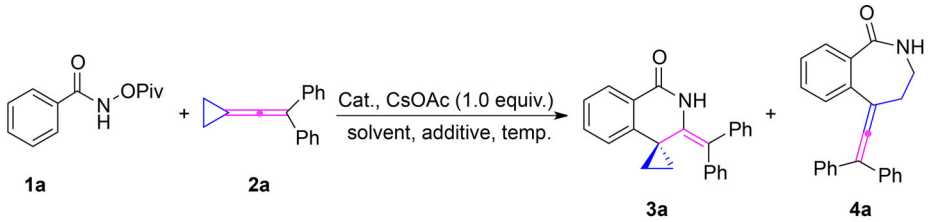
Results and Discussion

In this contribution, we report controllable C–H bond functionalizations of benzamides and vinylidenecyclopropanes (VDCPs) through changing the directing group from C(O)NH–OPiv to C(O)NH–OBoc, affording different major products **3** and **4** under mild conditions, respectively.

We initially started our investigation by examining the reaction outcomes of benzamide **1a** (1.0 equiv.) and VDCP **2a** (1.2 equiv.) in MeOH in the presence of $[Cp^*RhCl_2]_2$ at room temperature and the results are summarized in Table 1. To our delight, the corresponding products **3a** and **4a** were formed in 82% total yield along with the product ratio of 3:1 (Table 1, entry 1). To improve the yield of **a**, we performed this reaction by changing the additive, solvent, ratio of reactants and reaction temperature (Table 1). We found that utilization of CF_3CH_2OH[15] instead of MeOH as the solvent did not improve the yield of **3a** and **4a** as well as their ratio (Table 1, entry 2). On raising the reaction temperature to 30 or 50 °C, no improvements were observed (Table 1, entries 3 and 4). $[CP^*RhCl_2]_2$ is essential for this reaction because when using $[(p\text{-cymene})RuCl_2]_2$, $[Cp^*RuCl_2]_2$ and $[Cp^*IrCl_2]_2$ as catalysts,[16a–i] no reaction occurred or only traces of **3a** and **4a** were afforded upon heating at 50 °C in the presence of $[Cp^*RuCl_2]_2$ (Table 1, entries 5–10). Using $Cp^*Rh(MeCN)_3(SbF_6)_2$ as the catalyst did not bring any beneficial effect to the reaction outcome (Table 1, entry 11). Changing the employed amount of **1a** did not give better results as well (Table 1, entries 12 and 13). Next, CsF (1.0 equiv.) was added to improve the reaction outcome,[16j,k] giving **3a** and **4a** in 94% total yield along with the product ratio of 3:1 at room temperature (Table 1, entry 14). When the reaction was carried out at 0 °C, the products **3a** and **4a** were formed in 92% total yield along with the product ratio of 4:1 (Table 1, entry 15). On adding CsF, the total yield of **3a** and **4a** reached up to 99% along with the product ratio of 5:1 (Table 1, entry 16). The use of PivOH instead of CsF did not further improve the yield of **3a** and **4a** (Table 1, entry 17). We identified that the optimized reaction conditions are use of $[Cp^*RhCl_2]_2$ (3.0 mol%) as the catalyst, CsOAc as base, CsF as additive and carrying out the reaction in MeOH (2.0 mL) at 0 °C for 36 h (Table 1, entry 16) (for more detailed information, see the Supporting Information).

Having the optimized conditions in hand, the scope of benzamides bearing diverse substituents on the aromatic ring was examined and the results are shown

Table 1. Optimization of the reaction conditions of benzamides and VDCPs toward the synthesis of **3a**.



1a **2a** **3a** **4a**

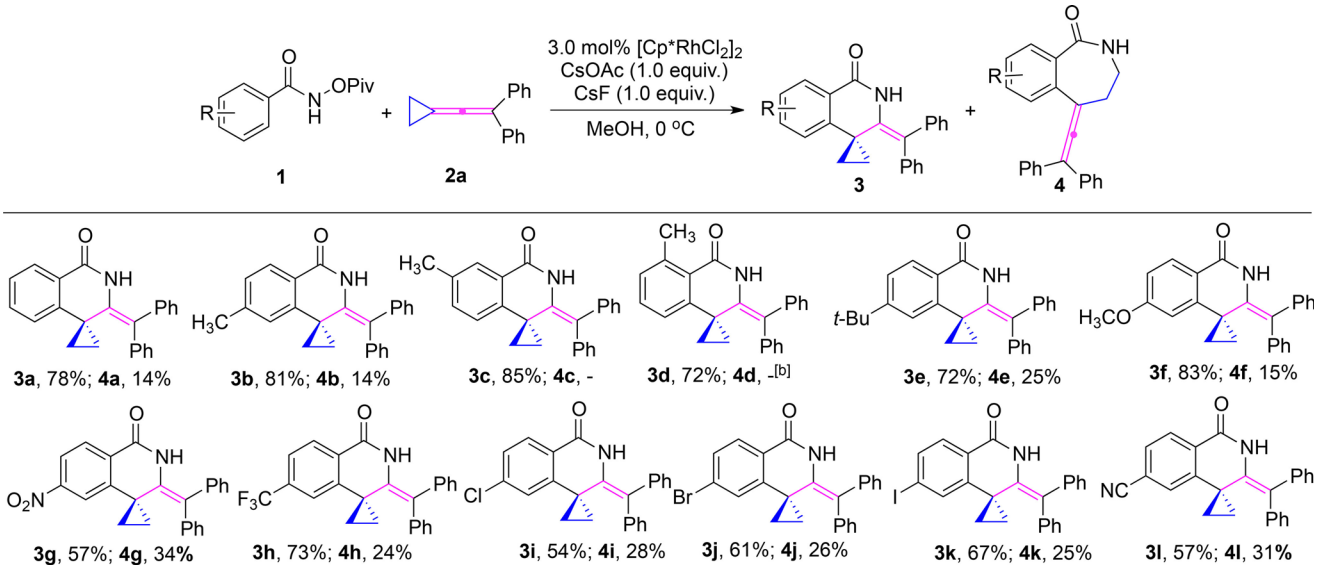
Entry[a]	**2a** (equiv.)	Cat.	Additive (equiv.)	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	
							3a	**4a**
1	1.3	$[Cp^*RhCl_2]_2$	-	MeOH	r.t.	3	63	19
2	1.3	$[Cp^*RhCl_2]_2$	-	CF_3CH_2OH	r.t.	3	46	11
3	2.0	$[Cp^*RhCl_2]_2$	-	MeOH	30	2	66	27
4	2.0	$[Cp^*RhCl_2]_2$	-	MeOH	50	2	62	33
5	1.3	$[Cp^*IrCl_2]_2$	-	MeOH	r.t.	12	-	-
6	1.3	$[Cp^*IrCl_2]_2$	-	MeOH	50	12	-	-
7	1.3	$[Cp^*RuCl_2]_2$	-	MeOH	r.t.	12	-	-
8	1.3	$[Cp^*RuCl_2]_2$	-	MeOH	50	12	3	10
9	1.3	$[(p\text{-cymene})RuCl_2]_2$	-	MeOH	r.t.	12	-	-
10	1.3	$[(p\text{-cymene})RuCl_2]_2$	-	MeOH	50	12	-	-
11	1.3	$Cp^*Rh(MeCN)_3(SbF_6)_2$	-	MeOH	r.t.	3	58	17
12	0.7	$[Cp^*RhCl_2]_2$	-	MeOH	r.t.	3	46	17
13	2.0	$[Cp^*RhCl_2]_2$	-	MeOH	r.t.	3	66	21
14	2.0	$[Cp^*RhCl_2]_2$	CsF (1.0)	MeOH	r.t.	3	71	23
15	2.0	$[Cp^*RhCl_2]_2$	-	MeOH	0	36	74	18
16	**2.0**	**$[Cp^*RhCl_2]_2$**	**CsF (1.0)**	**MeOH**	**0**	**36**	**83 (78)[c]**	**16 (14)[c]**
17	2.0	$[Cp^*RhCl_2]_2$	PivOH (1.0)	MeOH	0	36	80	18

[a] The reactions were carried out using **1a** (0.2 mmol), **2a** (0.7–2.0 equiv.), Cat. (0.006 mmol), in the indicated solvent (2.0 mL) in a Schlenk tube at the indicated temperature.
[b] Determined by ^1H NMR spectroscopic data.
[c] Isolated yields.

in Table 2. As for various benzamides **1a**–**1l** having either electron-donating or electron-withdrawing groups on the aromatic rings, we found that the substituents on the aromatic rings did not have a significant impact on the reaction outcomes, giving the desired products **3a**–**3l** in 57–85% yields. When R = 2-MeC_6H_4 and 3-MeC_6H_4, the corresponding products **4c** and **4d** could not be detected, respectively, perhaps due to the steric effect. As for substrates **1b**, **1e** and **1f**, in which R = 4-MeC_6H_4, 4-$MeOC_6H_4$, or 4-*t*-BuC_6H_4, the reactions took place smoothly to afford the desired products **3b**, **3e** and **3f** in 72–83% yields along with better product ratio of **3** and **4** (≧3:1). In the cases of the substrates **1g** and **1h** bearing strongly electron-withdrawing groups, such as NO_2 or CF_3, the reactions took place efficiently with this catalytic system, giving the desired products **3g** and **3h** in 57% and 73% yields, respectively, also along with the formation of **4g** and **4h**. With substrates **1i–1l**, in which R = 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, and 4-CNC_6H_4, the reactions proceeded also very well to afford the desired products **3i–3l** in 54–67% yields along with 1.9:1 to 2.7:1 product ratios of **3** and **4**. In conclusion, substrates with electron-donating groups on the aromatic rings favored the production of **3**.

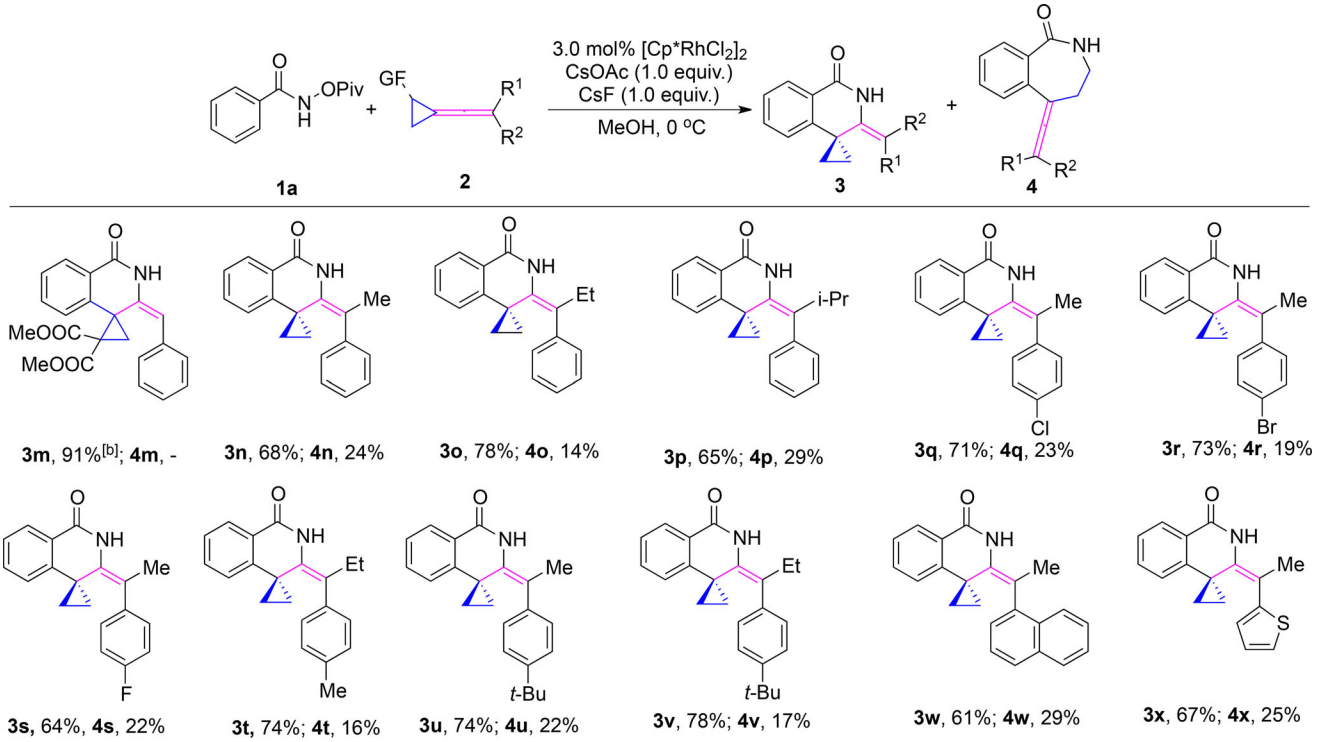
To further evaluate the generality of this reaction, the scope of vinylidenecyclopropanes (VDCPs) was then examined (Table 3). VDCP **2b** having two *gem*-substituted ester groups on the cyclopropyl ring gave the desired product **3m** in high yield (91%) without the formation of **4m**. VDCPs with methyl, ethyl, isopropyl groups at the allenyl moiety were also tolerated, affording the desired products **3n**, **3o** and **3p** in 68–78% yields along with 2.3:1 to 5.6:1 product ratios of **3** and **4**. A wide range of substituents on the aromatic ring of VDCPs was compatible. For example, halogen-substituted VDCPs were applicable in this transformation and the reactions proceeded very well to furnish the corresponding products **3q**, **3r** and **3s** in moderate yields and 3.1:1 to 3.8:1 product ratios. Upon introduction of electron-donating groups such as methyl and tertiary butyl on the phenyl ring, VDCPs **2** gave the desired products **3t**, **3u** and **3v** in high yields along with 3.3:1 to 4.9:1 product ratios.

Table 2. Reaction scope of benzamides for the synthesis of **3**.[a,b]



[a] Isolated yields are given, *reaction conditions:* **1** (0.2 mml), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (3.0 mol%), CsOAc (0.2 mmol), CsF (0.2 mmol), MeOH (2.0 mL), 0 °C, under an argon atmosphere.
[b] Conducted at −10 °C for 16 h.

Table 3. Reaction scope of VDCPs toward the synthesis of **3**.[a,b]



[a] Isolated yields are given, *reaction conditions:* **1a** (0.2 mml), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (0.006 mmol), CsOAc (0.2 mmol), CsF (0.2 mmol), MeOH (2.0 mL), 0 °C, under an argon atmosphere.
[b] Conducted at −5 °C for 16 h.

Non-phenyl group-containing VDCPs, such as those substrates bearing 1-naphthyl and 2-thiopheneyl groups at the allenyl moiety, were also tolerated in this transformation, affording the desired products **3w** and **3x** in 61% and 67% yields, respectively. The structures of **3q** and **4q** have been unambiguously

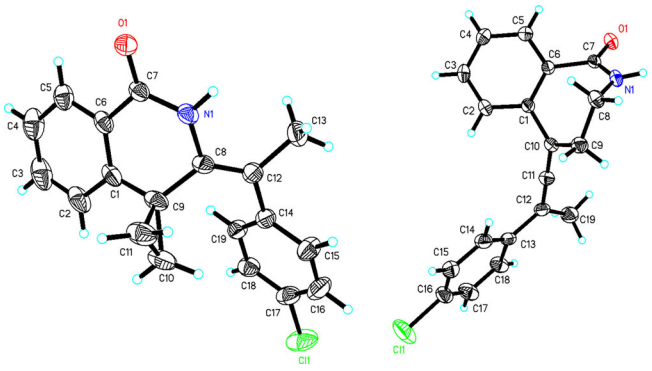


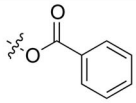
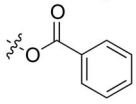
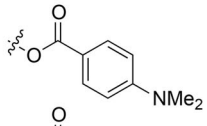
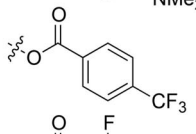
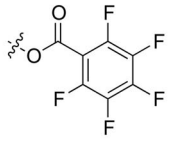
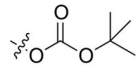
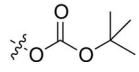
Figure 1. X-ray crystal structures of products **3q** (*left*)and **4q** (*right*).

confirmed by X-ray diffraction. Their ORTEP drawings are shown in Figure 1 and the corresponding CIF data have been included in the Supporting Information.

Interestingly, when the C(O)NH–OPiv directing group was changed to C(O)NH–OBz, the ratio of **3a** and **4a** became to about 1:2 along with 66% total yield (Table 4, entry 1). To further investigate this phenomenon and improve the yield and product ratio of **4a**, several directing groups were tested. The results are demonstrated in Table 4. Substrate **5** reacted with VDCPs in MeOH at room temperature, giving **3a** and **4a** in 77% total yield along with a >1:2 product ratio of **3a** and **4a** (Table 4, entry 2). On introduction of an electron-donating group at the benzoyl moiety (X = 4-dimethylaminobenzoyl) the substrate produced **3a** and **4a** in 77% total yield along with a >1:1.2 product ratio (Table 4, entry 3). However, on introducing a strongly electron-withdrawing group at the benzoyl

Table 4. Optimization of the reaction conditions of benzamides with VDCPs toward the synthesis of **4a**.

5–9 **2a** **3a** **4a**

Entry[a]	X	No.	Temp. [°C]	Base (equiv.)	Yield [%][b]	
					3a	**4a**
1		**5**	0	CsOAc (1.0)	23	43
2		**5**	r.t.	CsOAc (1.0)	25	52
3		**6**	r.t.	CsOAc (1.0)	36	41
4		**7**	r.t.	CsOAc (1.0)	19	54
5		**8**	r.t.	CsOAc (1.0)	21	65
6		**9**	r.t.	CsOAc (1.0)	8	45
7		**9**	r.t.	PhCOONa (0.3)	11	67

[a] The reaction was carried out using **5–9** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.006 mmol), in the indicated solvent (2.0 mL) in a Schlenk tube at the indicated temperature.

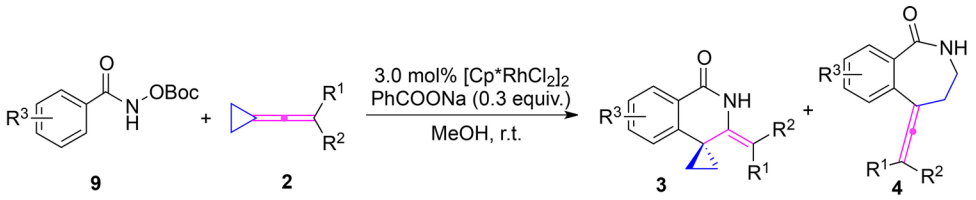
[b] Isolated yields.

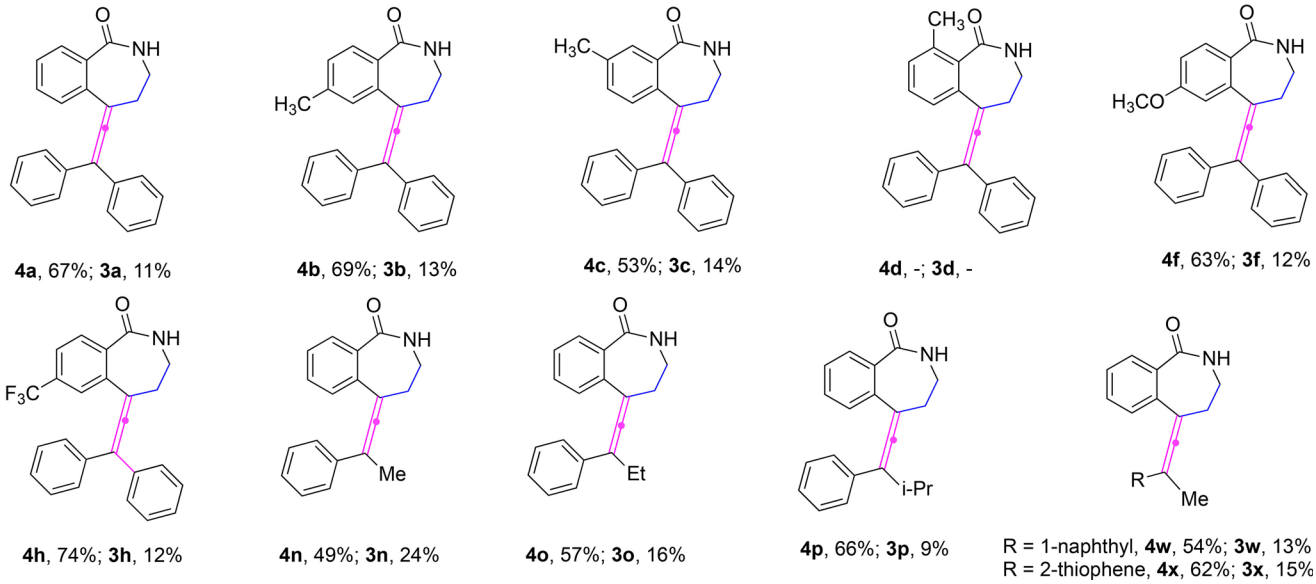
moiety (X = 4-triflourmethylbenzoyl or 2,3,4,5,6-pentaflourobenzoyl), the desired products **3a** and **4a** were obtained in 73% and 86% yields as well as 1:2.8 and 1:3.1 product ratios, respectively (Table 4, entries 4 and 5). Moreover, inspired by Cramer and Fagnou's findings,[17] we also changed the directing group to C(O)NH–OBoc and found that the reaction of substrate **9** with **2a** provided **3a** and **4a** in 53% yield along with a 1:6 product ratio (Table 4, entry 6). The poor total yield of **3a** and **4a** was presumably due to the instability of **9** in the presence of CsOAc. Using PhCOONa as a base, the total yield of **3a** and **4a** increased to 78% along with a 1:6.1 product ratio, which was determined as the optimal conditions for the production of **4a** (Table 4, entry 7).

Thus, by changing the directing group to C(O)NH–OBoc, product **4a** could be mainly obtained. The generality of this transformation was studied as well and the results are shown in Table 5. Electron-rich benzamides were applicable in this transformation to furnish the benzamides **4b** and **4f** in 63–69% yields and 1:5 to 1:6 product ratios of **3** and **4**. Introducing a substituent at the *meta*-position of benzamide gave the desired product **4c** in 53% yield along with a 1:3.8 product ratio. However, none of the desired product **4d** was obtained from the *ortho*-substituted benzamide because of the poor stability of the corresponding benzamide **9** under the standard conditions. Electron-deficient benzamides gave the desired product **4h** in 74% yield and a 1:6.2 product ratio was obtained. VDCPs **2** with a methyl, ethyl or isopropyl group at the allenyl moiety were also tolerated in this transformation, giving the desired products **4n**, **4o** or **4p** in 49–66% yields and 2:1 to 7:1 product ratios. Non-phenyl group-containing VDCPs were also compatible, affording the corresponding products **4w** and **4x** in 54–62% yields.

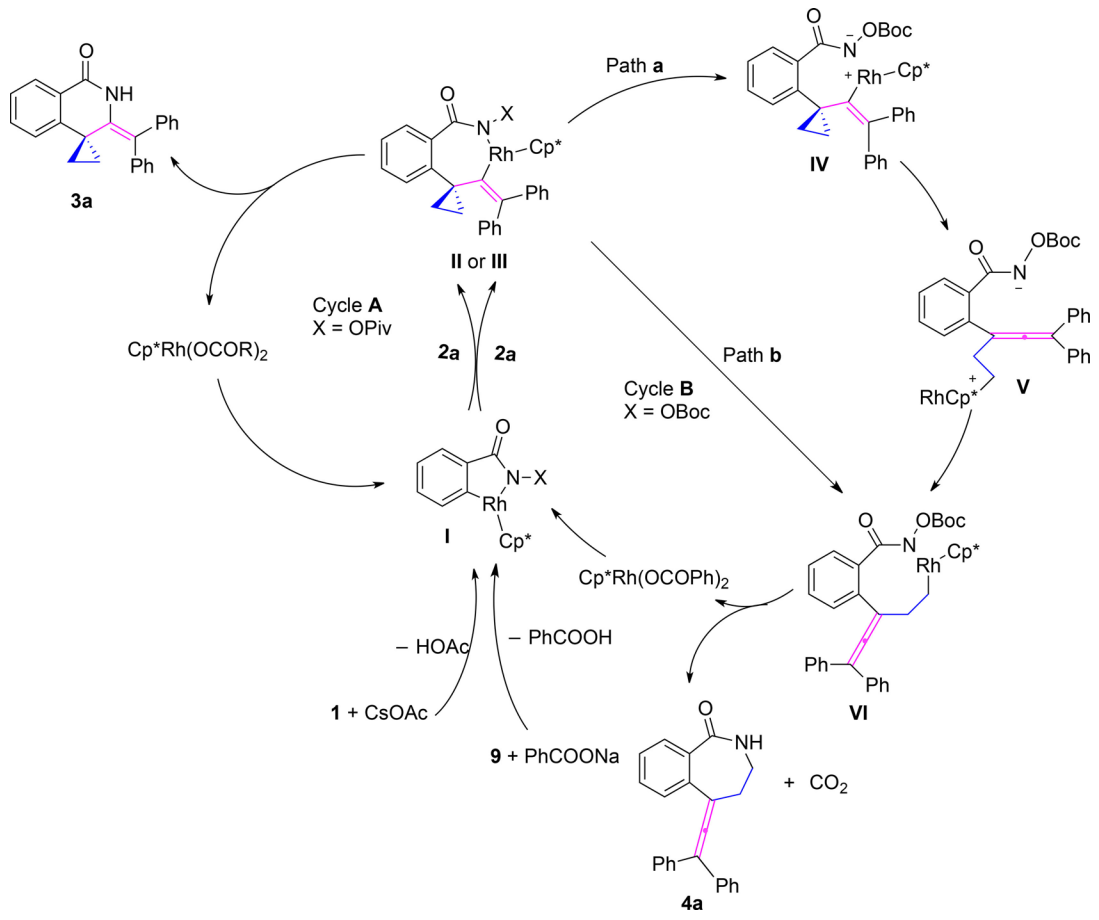
A plausible mechanism has been depicted in Scheme 2 taking substrate **1** or **9** in the reaction with **2a** under Cp*Rh(III) catalysis as an example on the basis of previous literature reports.[18] Substrate **1** or **9** reacts with Cp*Rh(III) through direct C–H activation to form intermediate **I**, which is followed by the insertion of VDCP **2a** to form intermediate **II** when the directing group is C(O)NH–OPiv. Subsequent reductive elimination along with internal oxidation leads to C–N bond formation/N–O bond cleavage to give **3a** along with the regeneration of the Rh(III) catalyst to start a new catalytic cycle (cycle **A**). When the directing group is C(O)NH–OBoc, the insertion of **I** with

Table 5. Reaction scope toward the synthesis of **4**.[a,b]





[a] Isolated yields are given, *reaction conditions:* **9** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (0.006 mmol), CsOAc (0.2 mmol), MeOH (2.0 mL), room temperature, under an argon atmosphere.
[b] Isolated yields.



Scheme 2. Proposed mechanism for the reactions.

2a gives intermediate **III**, which undergoes N–Rh bond cleavage to form intermediate **IV**. Then Cp*Rh(III)-catalyzed β-C elimination of cyclopropane generates intermediate **V**, which undergoes N–Rh bond reformation to afford intermediate **VI**. Similar reductive elimination and internal oxidation lead to C–N bond formation/N–O bond cleavage to produce **4a** and regenerate the Rh(III) catalyst for the next catalytic cycle (cycle **B**, path **a**). Intermediate **III** may also undergo β-C elimination of cyclopropane generating intermediate **VI** directly (cycle **B**, path **b**). Considering the rationale of these different reaction pathways, we believe that the electron-withdrawing property and steric effect of N–OBoc make intermediate **III** more easily undergo a β-C elimination[19] (see the Supporting Information for further information).

Conclusion

In summary, we have developed a useful and controllable C–H functionalization using VDCPs as new substrates with high product selectivity through changing the directing group from C(O)NH–OPiv to C(O)NH–OBoc, affording two different major products in good yields under mild conditions. A plausible mechanism has been also proposed on the basis of previous literature reports and our own examination. Efforts are in progress to apply this new methodology to the synthesis of interesting biologically active compounds.

Experimental Section

General Procedure for Synthesis of 3

Under an argon atmosphere, compound **1** (0.2 mmol), **2** (0.4 mmol) $[Cp^*RhCl_2]_2$ (5.0 mg, 0.06 mmol), CsF (30.4 mg, 0.2 mmol) and CsOAc (38.4 mg, 0.2 mmol) were weighed into a Schlenk tube. MeOH (2.0 mL) was added and the mixture was stirred at 0 °C until compound **1** was consumed completely. The reaction mixture was filtered through Celite. The filtrate was concentrated under the reduced pressure and the residue was purified by a silica gel column flash chromatography (eluent: petroleum ether/ethyl acetate = 4/1) to afford the product **3**.

General Procedure for Synthesis of 4

Under an argon atmosphere, compound **9** (0.2 mmol), **2** (0.4 mmol) $[Cp^*RhCl_2]_2$ (3.7 mg, 0.006 mmol) and PhCOONa (8.6 mg, 0.06 mmol) were weighed into a Schlenk tube. MeOH (2.0 mL) was added and the mixture was stirred at 25 °C until compound **9** was consumed completely. The reaction mixture was filtered through Celite. The filtrate was concentrated under the reduced pressure and the residue was purified by silica gel column flash chromatography (eluent: petroleum ether/ethyl acetate = 2/1) to afford the product **4**.

Supporting Information Available

Detailed descriptions of experimental procedures and the spectroscopic data of the products as well as the crystal structures are presented in the Supporting Information. CCDC 1436566 (**3q**) and CCDC 1440757 (**4q**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We are grateful for the financial support from the National Basic Research Program of China [(973)-2015CB856603], the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), and the National Natural Science Foundation of China (20472096, 21372241, 21572052, 20672127, 21421091, 21372250, 21121062, 21302203, and 20732008).

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