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Advanced Synthesis & Catalysis

Reaction of Cycloalkene-1-carboxamides with Aryl Boronates via Rhodium(III)-Catalyzed C–H Activation: A Versatile Route to 3,4-Cycloalkaquinolin-2(1*H*)-ones

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This research work is dedicated to 100th anniversary of Nankai University

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Abstract: Under rhodium(III) catalysis, substituted *N*-methoxycycloalkene-1-carboxamides successfully reacted with aryl boronic acid pinacol esters to provide 3,4-cycloalkaquinolin-2(1*H*)-ones via direct functionalization of the β-alkenyl C–H bond and form C–C/C–N bond in one pot. The gram-scale synthesis of the title compound demonstrated the great synthetic utility of this methodology.

Keywords: 3,4-cycloalkaquinolin-2(1*H*)-ones; Rhodium; C–H activation; aryl boronates; cyclohexene-1-carboxamides

Introduction

Cycloalkaquinolinones are widespread in natural occurring and synthetic bioactive compounds and exhibit biological and pharmacological properties, such as Orixalone D, Meloscine and **FK389** (Figure 1).[1] Hence, much effort has been foused on how to obtain them rapidly under mild reaction conditions with simple and readily available starting materials. For instance, Knochel and Wang developed routes to access unsaturated tricyclic derivatives of quinolin-2(1*H*)-ones through an intermolecular Suzuki cross-coupling reaction (Scheme 1a).[2,3] Wang successfully synthesized the target molecules with 2-vinyl-phenyl oxamic acid *via* a hypervalent iodine(III)-mediated intramolecular decarboxylative Heck-type reaction (Scheme 1b).[4] Hashimoto and Harayama prepared cycloalkaquinolinones through cyclization of 2-bromo-*N*-arylcyclohex-1-enecarboxamide at the presence of $Pb(OAc)_2$ (Scheme 1c).[5,6] Zhang and Xu reported transformed acrylamides with 2-(trimethylsilyl) phenyl trifluoromethanesulfonate to 2-quinolinones through copper-mediated bidentate carboxamide- directed cascade C–H/N–H annulation (Scheme 1d).[7–8] In addition, this kind of compounds can also be obtained with the aid of microwave or strong acid (Scheme 1e).[9–12] Although a variety of methods above have been documented, the very limited availability of prefunctionalized β-substituted cyclohexene-1-carboxamides (or esters) and 2-substituted phenyltrifluoromethane sulfonate calls for a more straightforward alternative method with wide scope under mild conditions for the synthesis of cycloalkaquinolinones. Herein, we wish to report a new rhodium(III)-catalyzed C–H activation reaction for the synthesis of cycloalkaquinolinones through the direct cross-coupling reaction of different readily available *N*-methoxycycloalkene-1-carboxamides with aryl boronic acid pinacol esters (Scheme 1).

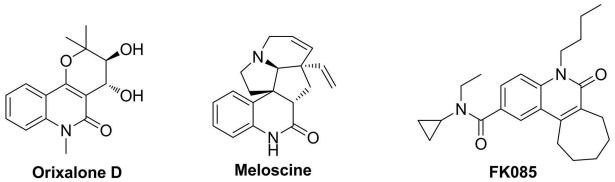
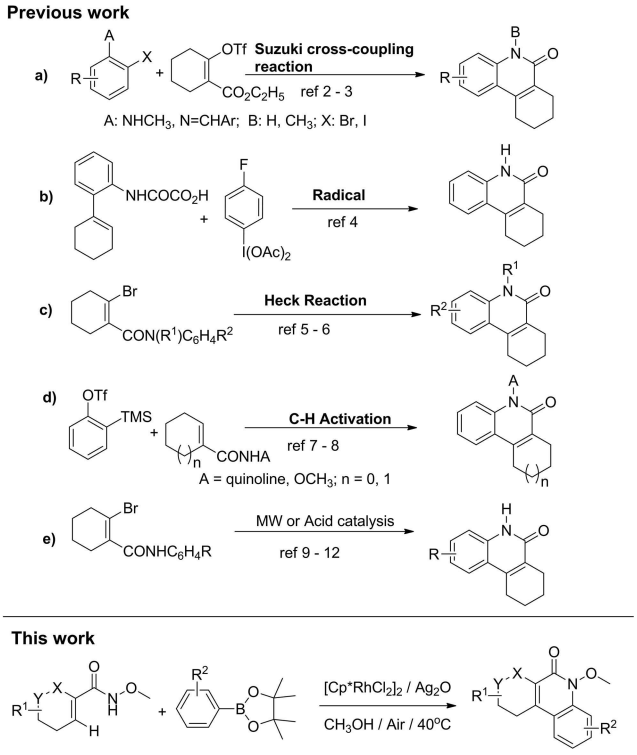


Figure 1. Selected bioactive cycloalkaquinolinones.



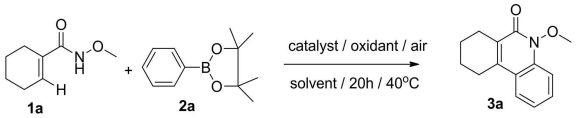
Scheme 1. Strategies for the synthesis of cycloalkaquinolinones.

Results and Discussion

Our study commenced from the model reaction of *N*-methoxycyclohex-1-enecarboxamide (**1a**) and phenyl boronic acid pinacol ester (**2a**) in the presence of Ag_2O as the oxidant (Table 1). Initially, the model reaction was carried out at 40 °C in methanol with different catalysts (Table 1, entries 1–7). To our surprise, when $[RhCp^*Cl_2]_2$ was used as catalyst, **3a** was formed in 40% yield (Table 1, entry 1). When the reaction temperature was raised to 60 °C or lowered to 35 °C, both of **3a**'s yields were decreased, which indicated 40 °C was the optimum temperature (Table 1, entries 8–9). When the reaction was conducted in different solvents, the yields of **3a** fallen in 0–34% (Table 1, entries 10–16). In order to ameliorate the reaction efficiency, various oxidants were used. Unfortunately, no improvement was observed and the best yield was only 17% at the presence of AgOAc (Table 1, entries 17–25). To our delight, when the solvent volume was increased from 0.5 to 2 mL, the yield was significantly improved (55%) (Table 1, entry 26). In further, the reaction time was reduced to 12 h, the yield was increased to 63% (Table 1, entry 27). When the ammount of catalyst was increased to 5 mol% and compound **3a** was afforded in 93% yield and this result was the best (Table 1, entry 28). Finally, when the reaction was performed in nitrogen or oxygen atmosphere respectively, the yield was decreased sharply to 59% and 70% (Table 1, entries 29–30).

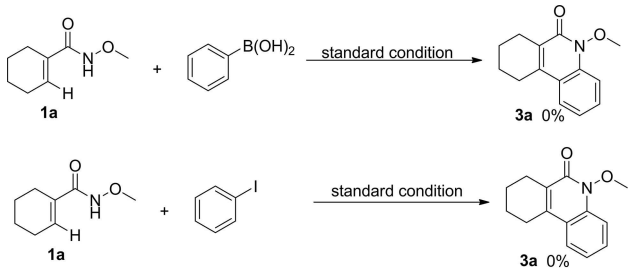
In order to make this reaction more practical, phenyl boronic acid pinacol ester was replaced by

Table 1. Optimization of the Reaction Conditions.[a]



entry	catalyst	oxidant	solvent	Yield (%)[b,c]
1	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	40
2	$[IrCp^*Cl_2]_2$	Ag_2O	MeOH	trace
3	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	Ag_2O	MeOH	19
4	$[CyRuCl_2]_2$	Ag_2O	MeOH	trace
5	$Pd(PPh_3)_4$	Ag_2O	MeOH	trace
6	$Pd(OAc)_2$	Ag_2O	MeOH	trace
7	$Pd_2(dba)_3$	Ag_2O	MeOH	trace
8[d]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	32
9[e]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	21
10	$[RhCp^*Cl_2]_2$	Ag_2O	DCE	trace
11	$[RhCp^*Cl_2]_2$	Ag_2O	THF	23
12	$[RhCp^*Cl_2]_2$	Ag_2O	1,4-dioxane	26
13	$[RhCp^*Cl_2]_2$	Ag_2O	toluene	trace
14	$[RhCp^*Cl_2]_2$	Ag_2O	DMF	27
15	$[RhCp^*Cl_2]_2$	Ag_2O	H_2O	12
16	$[RhCp^*Cl_2]_2$	Ag_2O	HFIP	34
17	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeOH	trace
18	$[RhCp^*Cl_2]_2$	Ag_2CO_3	MeOH	9
19	$[RhCp^*Cl_2]_2$	AgOAc	MeOH	17
20	$[RhCp^*Cl_2]_2$	AgOTf	MeOH	trace
21	$[RhCp^*Cl_2]_2$	CF_3CO_2Ag	MeOH	10
22	$[RhCp^*Cl_2]_2$	$AgSbF_6$	MeOH	trace
23	$[RhCp^*Cl_2]_2$	MnO_2	MeOH	7
24	$[RhCp^*Cl_2]_2$	TBHP	MeOH	9
25	$[RhCp^*Cl_2]_2$	$K_2S_2O_8$	MeOH	trace
26[f]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	55
27[g]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	63
28[h]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	93(89)
29[i]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	59
30[j]	$[RhCp^*Cl_2]_2$	Ag_2O	MeOH	70

[a] **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (2 mol%), oxidant (0.8 mmol), solvent (0.5 mL), 40 °C, 20 h, air;
[b] the yields were determined by the ^1H NMR integration method using trimethoxybenzene as the internal standard;
[c] value in parentheses indicates isolated yield with respect to **1a**;
[d] 60 °C;
[e] 35 °C;
[f] MeOH 2 mL;
[g] MeOH 2 mL, 12 h;
[h] MeOH 2 mL, 12 h, $[RhCp^*Cl_2]_2$(5 mol%);
[i] MeOH 2 mL, 12 h, $[RhCp^*Cl_2]_2$(5 mol%), N_2;
[j] MeOH 2 mL, 12 h, $[RhCp^*Cl_2]_2$(5 mol%), O_2.



Scheme 2. Reactions between **1a** and phenylboronic acid or iodobenzene.

phenylboronic acid and iodobenzene respectively. Unfortunately, no product (**3a**) was detected (Scheme 2).

Under the optimized conditions, the scope of the reaction of **1a**–**1c** with aryl boronic acid pinacol esters **2a**–**2m** was firstly explored (Table 2).

As listed in table 2, the following could be concluded:

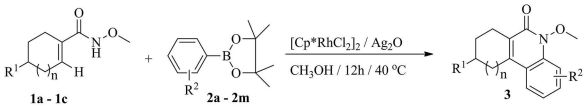
1) When R^2 was an electron-donating group or a halo atom, compound **3** was always afforded with higher yields, such as **3a** (89%), **3b** (84%), **3c** (80%), **3e** (78%), **3t** (92%); when R^2 was an electron-withdrawing group (such as 4-CHO, 3-CF_3), the yields of **3g**, **3j** and **3u** were decreased significantly (**3g** 52%; **3j** 58%; **3u** 45%). In particular, When R^2 was 4-nitro group, no product (**3h**) was detected (Table 2), suggesting that the electron-withdrawing group made the transmetalation of **2a** difficult.

2) When **1a** was reacted with 2-methoxyphenyl boronic acid pinacol ester, the **3n**'s yield was only 47%, which may be resulted from steric effect (Table 2). However, when 2-methoxy group was replaced with 2-nitro group, no product (**3o**) was detected, suggesting that an electron-donating group was preferred.

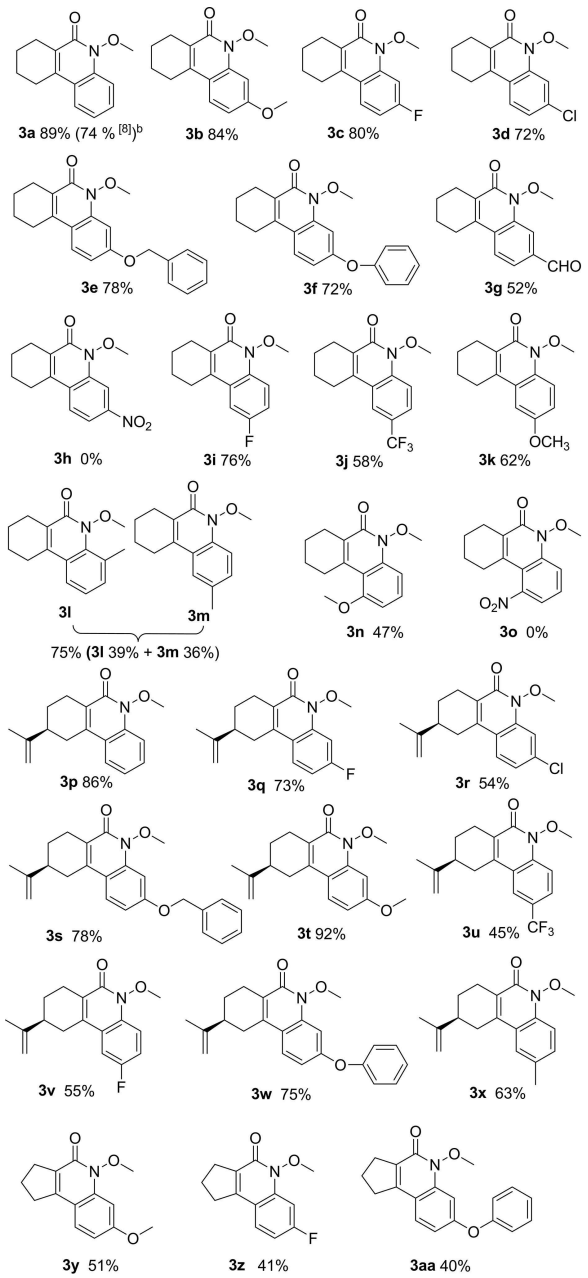
3) Traditionally, when 3-substituted aryl boronic acid pinacol esters **2** reacted with **1**, two products should be produced (Scheme 3). For example, when 3-methlphenyl boronic acid pinacol ester (**2k**) was reacted with **1a** two products were obtained (**3l** 39% and **3m** 36%) (Table 2). 2D NOESY spectra of **3l** and **3m** confirmed the position of methyl group. Some of the major long-range correlations observed in the 2D NOESY contour plots of compounds **3l** and **3m** were outlined in the structure (Figure 2). However, when R^2 was 3-F, 3-CF_3 or 3-OCH_3, only compound **3**–**b** was isolated, such as **3i**, **3j**, **3k**, **3u**, **3v**, and **3x**.

4) When R^1 was a (*S*)-prop-1-en-2-yl group (**1b**) instead of hydrogen, no remarkable effect was observed. However, when 4-methoxyphenyl boronic acid pinacol ester was reacted with **1b**, the yield of product **3t** was upto 92% (Table 2).

Table 2. Scope of the Cyclization Reactiona.[a]

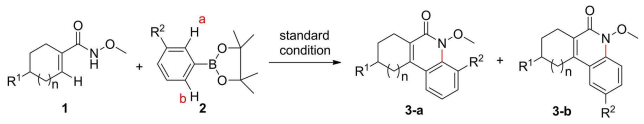


1a: R^1 = H, n = 1; **1b**: R^1 = (*S*)-prop-1-en-2-yl, n = 1; **1c**: R^1 = H, n = 0.
R^2 : H, 4-OCH_3, 4-Cl, 4-F, 4-PhO, 4-PhCH_2O, 4-CHO, 4-NO_2, 3-CF_3, 3-F, 3-CH_3, 2-NO_2, 2-CH_3O.



[a] **1** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), Ag_2O (0.8 mmol), CH_3OH (2 mL). Isolated yields were calculated with respect to **1**.
[b] The value in brackets had been reported in reference 8.

5) When **1a** was replaced by *N*-methoxycyclopentene -1-carboxamide (**1c**), the yields of corresponding



Scheme 3. Reactions between **1** and 3-substituted arylboronic acid pinacol esters **2**.

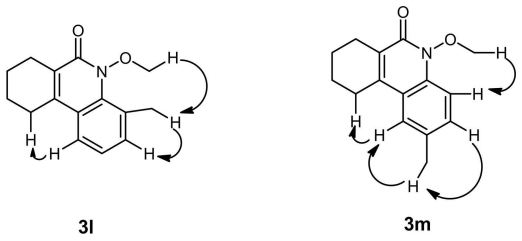


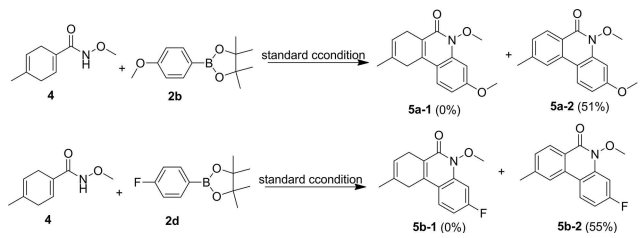
Figure 2. Selected long-range 2D NOESY correlations found in the corresponding contour plots of compounds **3l** and **3m**.

compounds **3** were decreased significantly (**3y** 51% *vs* **3b** 84%; **3z** 41% *vs* **3c** 80%; **3aa** 40% *vs* **3f** 72%), presumably due to the detrimental effect of the tension of cyclopentene (Table 2).

However, when *N*-methoxy-4-methylcyclohexa-1,4-dienecarboxamide **4** was reacted with arylboronic acid pinacol esters (such as **2b** and **2d**), normal product **5a–1** or **5b–1** was not detected. Interestingly, compounds **5a–2** and **5b–2** were isolated with 51% and 55% yield respectively, suggesting that an oxidative dehydrogenation reaction might be involved from **5a–1**/**5b–1** to **5a–2**/**5b–2** (Scheme 4).

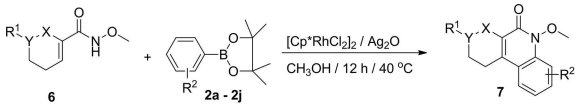
To further explore the scope of the reaction, we investigated the reaction of various arylboronic acid pinacol esters **2** with **6a** and **6b** under the optimized conditions. Thus, the treatment of **6a** with 4-methoxylphenyl-, 4-fluorophenyl-, 3-fluorophenyl-, 4-phenoxyphenyl-, 4-benzyloxyphenyl- and phenylboronic acid pinacol esters **2** provided target products **7a–7g** in 55–86% yield (Table 3). The reactions of **6b** with **2** suggested that, at the presence of transitional metals and methanol, the protecting group (*N*-Boc) was stable (Table 3).

To probe the synthetic utility of this method, a scale-up reaction of 10 mmol was carried out under the

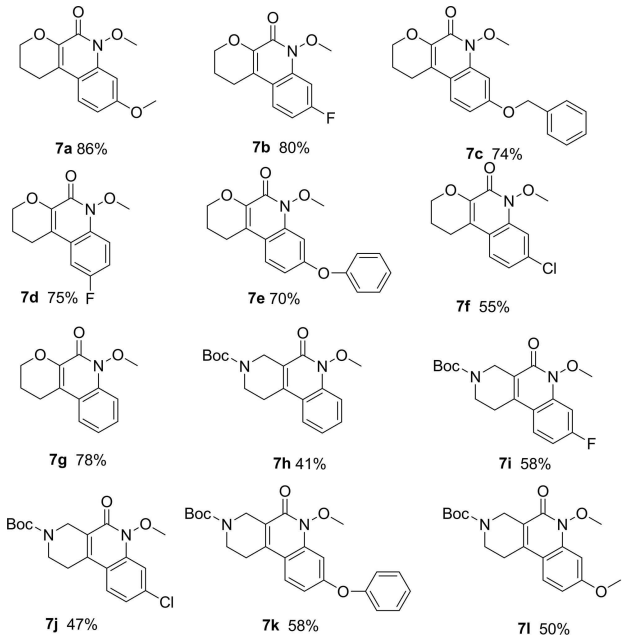


Scheme 4. Reactions between **4** and **2**.

Table 3. Scope of the Cyclization Reactiona.[a]



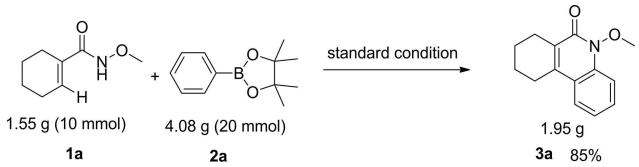
6a: R^1 = H; X = O; Y = CH. **6b:** R^1 = Boc; X = CH_2; Y = N.
R^4 : H, 4-OCH_3, 4-Cl, 4-F, 4-PhO, 4-$PhCH_2O$, 3-F.



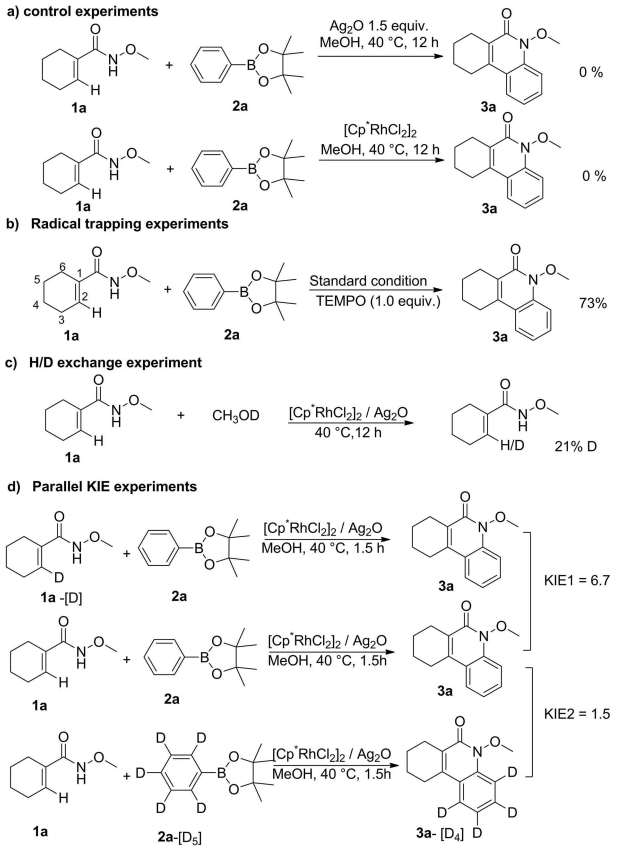
[a] **6** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), Ag_2O (0.8 mmol), CH_3OH (2 mL). Isolated yields were calculated with respect to **6**.

optimized conditions (Scheme 5). Through the reaction of *N*-methoxycyclohexene-1-carboxamide **1a** with phenylboronic acid pinacol ester **2a**, the pure product **3a** was obtained in 85% yield after 12 h.

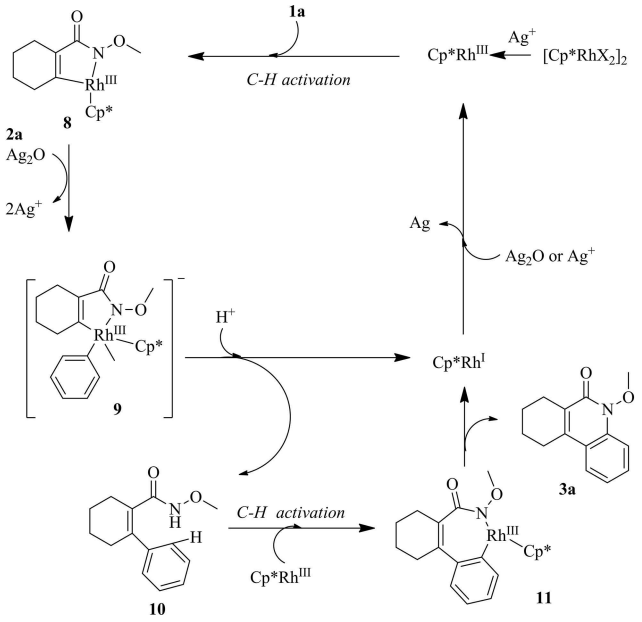
To gain further understanding of the mechanistic details of this catalytic reaction, a series of control experiments were performed (Scheme 6). Firstly, in absence of the catalyst $[Cp^*RhCl_2]_2$ or the oxidant Ag_2O, no product **3a** was detected, suggesting that both of them were crucial to this reaction (Scheme 6a). Secondly, a radical trapping experiment with TEMPO was carried out under the optimized conditions and compound **3a** was obtained in 73% yield, suggesting that a radical reaction was not involved in this transformation (Scheme 6b). Thirdly, H/D exchange of



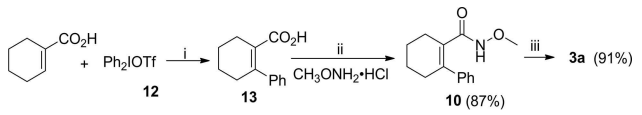
Scheme 5. Gram scale reaction.



Scheme 6. Control Experiments.



Scheme 7. A proposed mechanism for the catalytic reaction.



Scheme 8. Strategies for the synthesis of compound **3a**. (i) 2.5 mol%$[Cp^*IrCl_2]_2$, 15 mol %$AgNTf_2$, 3 equiv. PivOH, 200 mg 4ÅMS, cylcohexane, 100 °C,12 h, Ar;[15] (ii) EDCI (1.2 equiv.), DMAP(1.2 equiv.); (iii) 2 mol% $[Cp^*RhCl_2]_2$, 1.5 equiv. Ag_2O, MeOH, 40 °C, 1 h.

1a at the C2-position (21% D) indicated that a reversible deprotonative C–H bond activation step might be involved in this reaction (Scheme 6c). Finally, the kinetic isotope effect studies (KIE1 and KIE2) were conducted (Scheme 6d). The KIE1 value (6.7) suggested that the cleavage of the C–H bond of **1a** was involved in the rate-determining step. The KIE2 value (1.5) indicated that the C–H bond cleavage of the benzene ring of **2a** is not the product-determining step.

Based on the above experiments and the relevant reports,[13–14] a plausible mechanism is proposed (Scheme 7). With the help of Ag_2O, $[Cp^*RhCl_2]_2$ readily coordinates to the nitrogen atom and subsequent C(sp^2)–H bond activation leads to a five-membered rhodacycle **8**. Transmetalation with **2a** then forms intermediate **9**, which undergoes reductive elimination to give the *N*-methoxy-2-phenylcyclohex-1-enecarboxamide **10** and a Rh^I species. Subsequent deprotonative coordination of the nitrogen atom in **10** to Rh^{III} and C–H activation give rhodacycle **11**. Further reductive elimination of **11** affords **3a** and Rh^I species, which is oxidized by Ag_2O or Ag^+ to regenerate the active Rh^{III} species for the next cycle. Other proof which **3a** could be synthesized by heating compound **10** in 91% yield also support compound **10** as a catalytic intermediate (Scheme 8).

Conclusion

We have developed a direct and efficient Rh(III)-catalyzed amide-directed C–H functionalizations of cycloalkenes with aryl boronates. The present reaction enables the synthesis of cycloalkaquinolinones in high yield through the direct cross-coupling reaction of readily available *N*-methoxycycloalkene carboxamides with aryl boronates, while tolerating many sensitive functional groups. Therefore, this method supplies an efficient and convenient approach for modification of interesting molecules. Mechanistic studies revealed that the present reaction might involve a rhodium-catalyzed dual C–H activation process.

Experimental Section

To an oven-dried 15 mL sealed tube was added substrate **1**, **4** or **6** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%,), Ag_2O (0.8 mmol) and CH_3OH (2.0 mL) were added to the vial. The

mixture was stirred at 40 °C (oil bath temperature) for 12 h. After this time, the resulting mixture was cooled down to room temperature, filtered through a short pad of silica gel. The silica gel was eluted with ethyl acetate (5 mL). After concentrated under vacuum, the residue was purified by preparative TLC, to afford the desired product **3**, **5** and **7** (eluent: PE/EA = 4/1).

Acknowledgements

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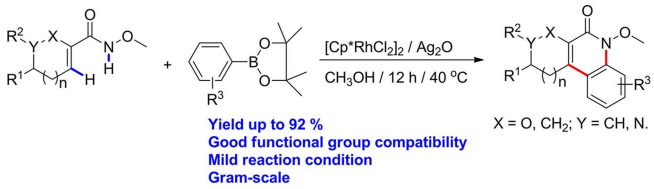
FULL PAPER

Reaction of Cycloalkene-1-carboxamides with Aryl Boronates via Rhodium(III)-Catalyzed C–H Activation: A Versatile Route to 3,4-Cycloalkaquinolin-2(1*H*)-ones



Yield up to 92 %
Good functional group compatibility
Mild reaction condition
Gram-scale

Adv. Synth. Catal. **2019**, *361*, 1 – 7

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