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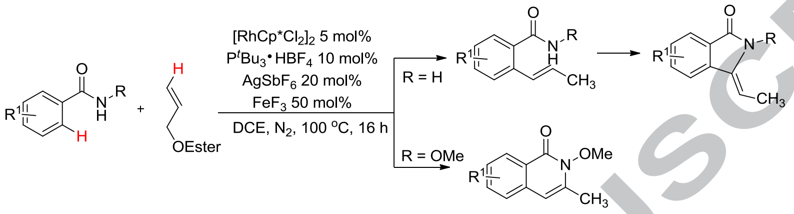

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ABSTRACT

The Rh-catalyzed direct selective oxidation Heck reaction of benzamides with allylic esters has been developed for the synthesis of amides and isoquinolin-1-ones. According to the functional groups on N-atom, benzamides or isoquinolin-1-ones were synthesized under optimal reaction conditions. The ambient catalytic system has good functional group tolerance, afforded corresponding products in moderate to good yields.

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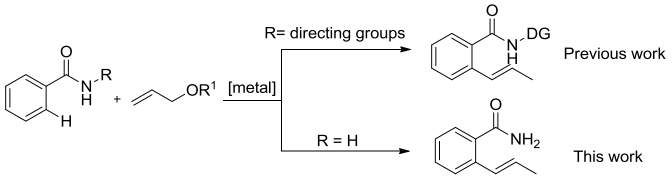
Introduction

The transition metal-catalyzed Mizoroki-Heck reaction is the most useful cross-coupling reaction in carbon-carbon bonds-formation reaction [1]. The oxidative Heck reaction, which applied in C-H bonds instead of C-X bonds in traditional Heck reaction, has attracted much attention. After first reported and further development by Fujiwara [2] and Moritani [3], the oxidative Heck reaction have emerged as powerful strategy for the coupling of arenes and olefins for their atom- and step-economical organic syntheses.

Recently, many reports are well-demonstrated Rh-catalyzed oxidative Heck reaction of electron-rich or electron-poor benzamides with versatile olefins, including Glorius [4], Lam [5], Loh [6], Kim [7], Lu [8] etc [9]. These methods have many advantages, such as reliable yields, good functional group tolerance, ambient reaction conditions, however, among these procedures, the prefunctionalization of *ortho*-directing groups (DG) were absolutely essential, which are limited the scope and the yield of the reaction. On the other hands, applied in the primary benzamides as directing groups in olefination is less exploited [10]. Based on its poor reactivity, the olefination of primary benzamide usually requires harsh reaction conditions, and always afforded diolefination byproducts. Therefore, the development of a simple and convenient Rh-catalyzed oxidative Heck of primary benzamides with commercial available allylic esters remains highly desirable. Herein, we present the primary outcomes of rhodium -catalyzed oxidative Heck reaction of primary benzamides with allylic esters can be used to synthesize benzamides or isoquinolin-1-ones. Importantly, the catalytic system facilitates the coupling partner of benzamide with styrene.



Scheme 1. Transiton metal-catalyzed Heck reaction of benzamides

Results and discussions

The reaction between benzamide (**1a**) and allyl benzoate (**2a**) were chosen as a model reaction to optimize the reaction conditions, and the results were shown in Table 1. Initially, in the presence of $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), FeF_3 (50 mol%) and DCE (2 mL), the reaction performed well to afford target product (*E*)-2-(prop-1-en-1-yl)benzamide (**3a**) in 66% yield, along with byproduct benzoic acid (Table 1, entry 1). Without of the assistance of $AgSbF_6$ and FeF_3, only trace amount of target product was detected by GC-MS analysis, which indicated that $AgSbF_6$ and FeF_3 played critical role in the coupling (Table 1, entry 2). Encouraged by these results, a serials of Rh catalysts including $Rh_2(OAc)_4$, $RhCl_3{\cdot}3H_2O$, $[Rh(cod)Cl_2]_2$ and $[RhCpCl_2]_2$ were examined, they all were inferior to $[RhCp^*Cl_2]_2$ as catalyst in terms of yield (Table 1, entries 3-6). Subsequently, serials of solvent such as THF, DMSO, dioxane, toluene, MeCN and PhCl were also surveyed, and DCE gave the best results (Table 1, entries 7-12). Surprisingly, the addition of $P(t\text{-}Bu)_3{\cdot}HBF_4$ (**L1**, 10 mol%) to the reaction as ligand can be enhanced the yield of the **3a** (Table 1, entry 13). And then, three other ligands including PPh_3 (**L2**), PCy_3 (**L3**) and X-Phos (**L4**) were investigated, they all were found sluggish to the reaction, and $P(t\text{-}Bu)_3{\cdot}HBF_4$ provided the best results (Table 1, entries 14-

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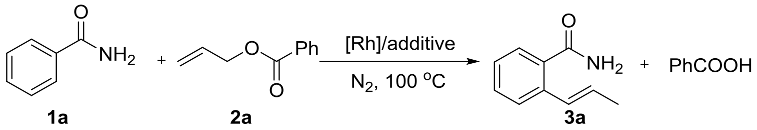
16). Finally, the reaction conducted in 120 °C or 80 °C will diminish the yield of product **3a** (Table 1, entries 17-18).

Table 1. Screening the Reaction Conditions [a]



Entry	[Rh]	Additive	Ligand	Solvent	Yield (%) [b]
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	DCE	66
2	$[RhCp^*Cl_2]_2$	—	—	DCE	trace
3	$Rh_2(OAc)_4$	$AgSbF_6$ FeF_3	—	DCE	trace
4[b]	$RhCl_3\cdot3H_2O$	$AgSbF_6$ FeF_3	—	DCE	trace
5[c]	$[Rh(cod)Cl_2]_2$	$AgSbF_6$ FeF_3	—	DCE	trace
6	$[RhCpCl_2]_2$	$AgSbF_6$ FeF_3	—	DCE	trace
7	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	THF	28
8	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	DMSO	NR
9	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	dioxane	34
10	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	toluene	30
11[d]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	MeCN	NR
12	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	—	PhCl	60
13	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	**L1**	DCE	80
14	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	**L2**	DCE	24
15[e]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	**L3**	DCE	51
16	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	**L4**	DCE	47
17 [c]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	**L1**	DCE	62
18 [d]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ FeF_3	**L1**	DCE	76

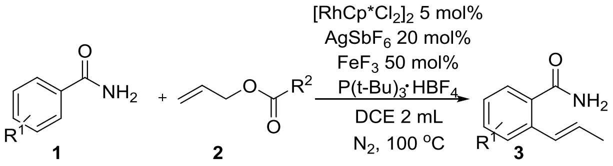
[a] Reaction conditions:**1a** (0.4 mmol), **2a** (0.2 mmol), [Rh] (5 mol %), $AgSbF_6$ (20 mol%), FeF_3 (50 mol%), ligand (10 mol%) in solvent (2.0 mL) at 100 °C for 16 h under nitrogen atmosphere.

[b] isolated yield.

[c] at 120 °C.

[d] at 80 °C.

Table 2. Rh-catalyzed oxidative Heck reaction of benzamides with allylic esters [ab]



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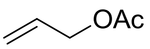
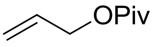
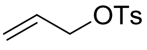


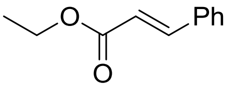
2b, 48%



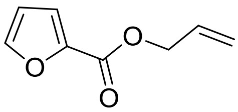
2c, 55%



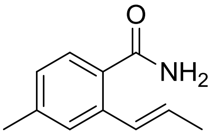
2d, 10%



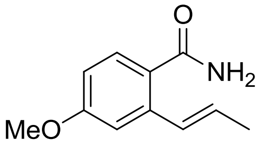
2e, 78%



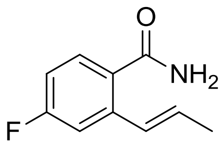
2f, 52%



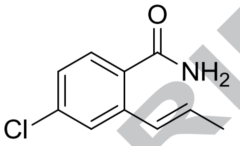
3b, 75%



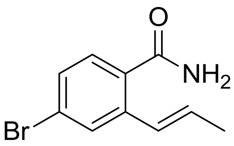
3c, 45%



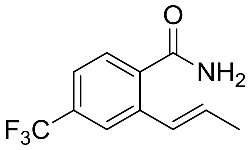
3d, 64%



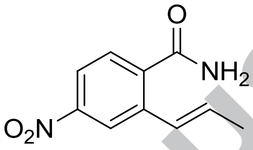
3e, 72%



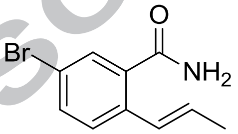
3f, 68%



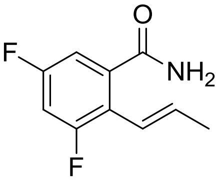
3g, 69%



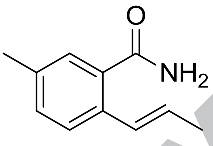
3h, 49%



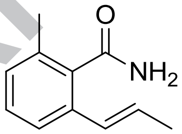
3i, 58%



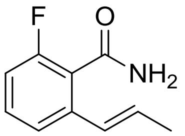
3j,78%



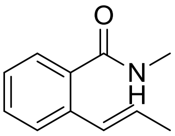
3k, 67%



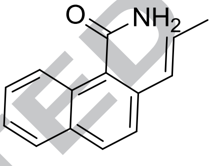
3l, 44%



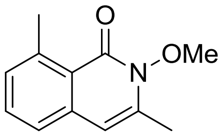
3m, 70%



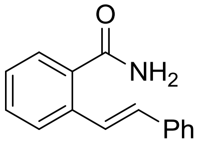
3n, 76%



3o, 68%



3p, 30%[c], 31%[d]



3q, 43%

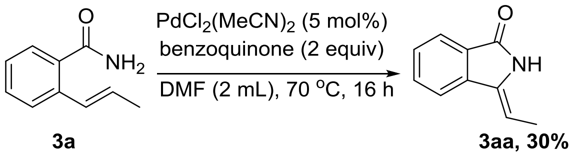
[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol%), FeF_3 (50 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (10 mol%) in DCE (2.0 mL) at 100 °C for 16 h under nitrogen atmosphere.

[b] Isolated yield.

[c] Reacted with **2a**.

[d] Reacted with **2d**.

With the optimized reaction conditions in hands, we next want to expand the scope of substrates **1** and **2**, and the results are indicated in Table 2. Initially, a variety of allylic esters were tested, they all were suitable substrates for the transformation. For example, treatment of benzamide **1a** with allylic acetate **2b** in the reaction, 48% yield of **3a** was isolated. The reaction of **2c** or **2d** reacted with ester **1a** proceeded smoothly, to obtain corresponding products in 55% and 10% yields, respectively. The esters of **2e** and **2f** are facilitates the reaction, to produce target products in moderate yields. Subsequently, the electronic effects of benzamides were also tested, the results disclosed that both electron-withdrawing and electron-donating groups bearing in the aryl ring were tolerated well. For example, electron-donating groups 4-Me or 4-OMe substituted benzamides **1b-1c** performed well in the reaction, to give corresponding products in 75% and 45% yield, respectively. The electron-withdrawing groups, including 4-F, 4-Cl, and 4-Br on the aromatic ring were proceeded quickly in the coupling, resulted in products **3d-3f** in moderate yields. The similar results also achieved when strong electron-withdrawing groups 4-CF_3 and 4-NO_2 were applied. Halo-substituted **1i-1j** also facilitates the transformation, to give target products in 58% and 78% yields, respectively. Under standard reaction condition, the *meta*-Me benzamide reacted **2a** quickly, to afford **3k** in 67% yield. 2-Me and 2-F substituted substrates were well-conducted to form target products **3l-3m** in moderate yield. The N-Me benzamide **1n** served as efficient substrate for the olefination, furnished product **3n** in 76% yields. The 1-naphthamide also underwent the coupling efficiently, to obtain target product **3o** in 68% yield. It is noteworthy that N-OMe-benzamide **1p** was a suitable substrate, subjected in the reaction to produce cyclic product 2-methoxy-3,8-dimethylisoquinolin-1(2H)-one (**3p**) under standard conditions, albeit in a lower yields. Gratifyingly, the styrene also turned out to be good substrate for the olefination, led to (*E*)-2-styrylbenzamide **3q** in 43% yield.



Scheme 2. The application of product **3a**

The application of the products also performed successfully [11]. In the presence of $PdCl_2(MeCN)_2$ (5 mol%), benzoquinone (2 equiv) and DMF (2 mL), the substrate **3a** carried out quickly to give cyclic product (*Z*)-3-ethylideneisoindolin-1-one (**3aa**) in 30% yield (scheme 2).

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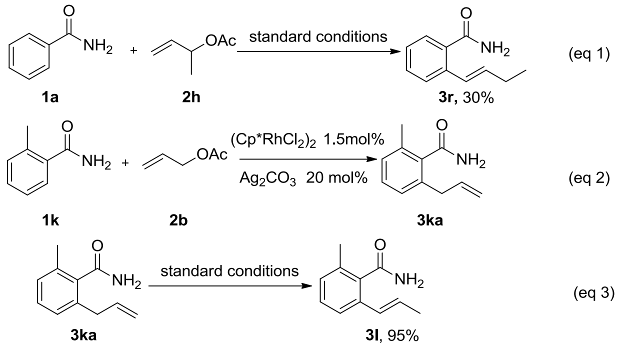
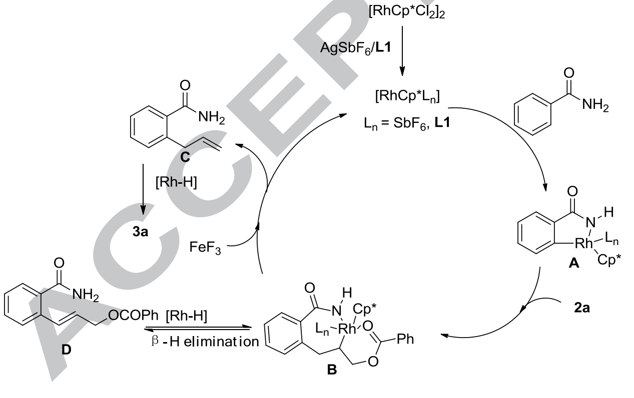


Scheme 3. Control experiments

To explore the mechanism of the oxidative Heck reaction, we carried out several control experiments (scheme 3). Firstly, the reaction of benzamide (**1a**) with branched allylic ester (**2h**) conducted smoothly to give olefination product (**3r**) in 30% yield, which implied that the reaction through a β-OAc elimination pathway. Secondly, we synthesized terminal alkenyl product **3ka** from literature [12], then treatment of it to the reaction under standard conditions, 95% yield of product **3l** was isolated. The result indicated that the oxidative Heck reaction might be involved a proton shift process.

Based on aforementioned results [12], as well as our primary outcomes, a possible mechanism for the oxidative Heck reaction was proposed as outlined in scheme 4. Initially, $[RhCp^*Cl_2]_2$ combine with $AgSbF_6$ and **L1** to form active Rh species, which reacted with **1a** to produce intermediate **A** [9, 13]. After coordination and migratory insertion of allylic ester **2a** to form a seven-membered allylrhodium (III) intermediate **B**, which coordinating with carbonate oxygen and metal [8a, 9]. With the assistance of FeF_3, intermediate **B** through a β-oxygen elimination process led to alkenyl product **C** and regenerate active Rh species [5, 8a, 14]. Finally, product **3a** might be generated via the migratory isomerization of the double bond by the [Rh-H] species. The [Rh-H] species should be afforded by intermediate **B** [8a].



Scheme 4. Possible Mechanism

Conclusions

In summary, we have been developed a Rh-catalyzed selective oxidative Heck reaction of primary benzamides with allylic esters. Under standard reaction conditions, a variety of substrates underwent the reaction successfully to give corresponding products in moderate to good yields. Further work to extend the scope and application of this reaction is currently underway.

Acknowledgments

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(16) **Typical Procedure:** Under nitrogen atmosphere, an oven-dried reaction vessel was charged with benzamide (**1a**, 0.4 mmol), allyl benzoate (**2a**, 0.2 mmol), bis[(pentamethylcyclopentadienyl) dichlororhodium] (5 mol%), silver hexafluoroantimonate (20 mol%), iron (III) fluoride (50 mol%), tri-tert-butylphosphine tetrafluoroborate(10 mol%) and DCE (2 mL). The vessel was sealed and heated at 100 °C (oil bath temperature) for 16 h and then cooled to room temperature. The reaction mixture was filtered and washed

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with ethyl acetate, and then evaporated under vacuum. The residue was purified by silica-gel column chromatography (hexane / ethyl acetate = 2:1) to afford the desired products (**3a**).

(E)-2-(prop-1-en-1-yl)benzamide (3a)**[14]:** White solid (25.8 mg, 80% yield); mp 165-167 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm) 7.75 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.34 (dd, *J* = 7.5 Hz, 15.5 Hz, 2H), 7.23 (t, *J* = 15.0 Hz, 1H), 6.72 (d, *J* = 15.5 Hz, 1H), 6.29-6.22 (m, 1H), 1.84 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ(ppm) 170.9, 135.8, 134.8, 129.2, 128.3, 127.1, 126.9, 126.3, 125.1, 18.5; IR (cm^{-1}): 3378, 3179, 1636, 1563, 1390, 1375, 1123, 966, 768, 708; LRMS (EI, 70 eV) m/z (%): 161 (M$^+$, 19), 146 (100), 128 (12), 115 (59), 91 (25); HRMS (ESI) Calcd for $C_{10}H_{11}NONa^+$ ([M + Na]$^+$) 184.0733, Found: 184.0735.

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