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RHODIUM-CATALYZED OXIDATIVE OLEFINATION OF N-(2-(4,5-DIHYDROOXAZOL-2-YL)PHENYL)AMIDES WITH ARYLETHENES VIA EXTRAORDINARY N-ARYL C-H BOND FUNCTIONALIZATION

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Abstract – Amide-tethered aryloxazoline motifs are important structural moiety because of ubiquity in medicinal chemistry, functional materials and pincer ligands. In recent years, much attention about N-(2-(4,5-dihydrooxazol-2-yl)phenyl)amides has been focused on *ortho* C−H functionalization of amides. Herein a highly efficient rhodium(III) catalyzed oxidative olefination of N-(2-(4,5-dihydrooxazol-2-yl)phenyl)amides with arylethenes via extraordinary N-aryl C-H bond functionalization was developed.

Alkenes are important structural units because they are ubiquitous in natural products[1] and show significant biological activity.[2] Therefore, the development of effective synthetic methods to construct alkene scaffolds is of intensive interest. The pioneering oxidative Heck reaction works reported by Fujiwara and Moritani,[3] have gradually become important transformation in organic synthesis to construct C-C bond. While with the rapid development of C-H functionalization[4] catalyzed by transition-metal, direct oxidative olefination through important motif as a directing group is still highly desirable.[5-7]

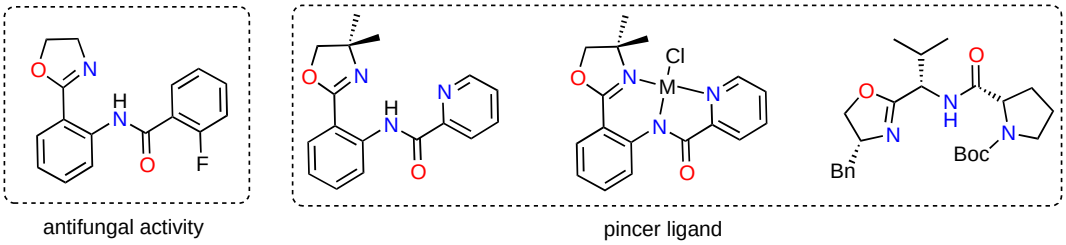
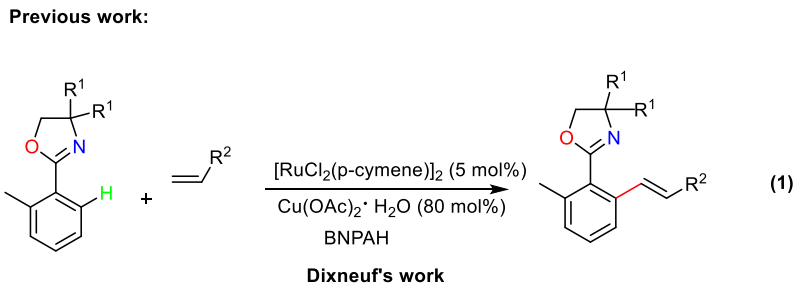
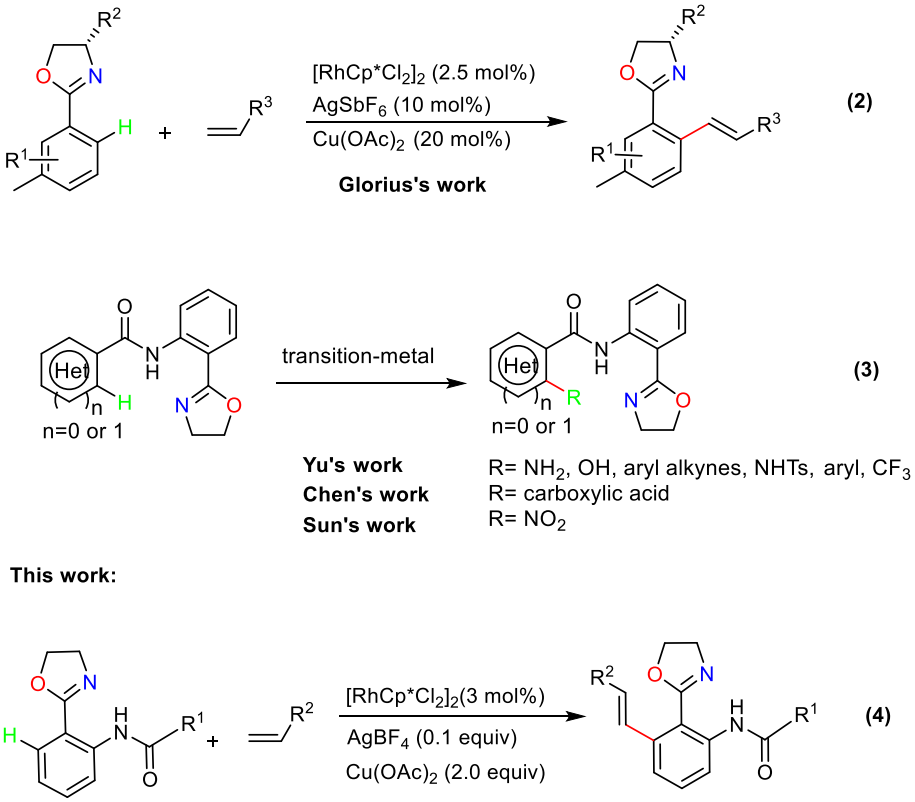


Figure 1. Representative application of compounds containing amide-tethered aryloxazoline scaffolds

Oxazolines play a very important role in organic synthesis, which can be converted to versatile structures[8] and used as intermediates to prepare natural products such as Nataxazole and AJI9561.[9] Moreover, aryl-oxazoline can act as a directing group in C-H functionalization. Dixneuf group reported that functional oxazolines as directing group using ruthenium catalysts by assistance of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (BNPAH) active C-H bond to achieve olefination[10] (**Scheme 1, eq 1**). Highly modular synthesis of readily available 2-aryloxazolines via oxidative olefination was realized by Glorius group[11] (**Scheme 1, eq 2**). Furthermore, amide-tethered aryloxazoline motifs are not only found in medicinal chemistry, functional materials and pincer ligands,[12] but also can be used in many synthesis reactions through the formation of six-membered bidentate metallocycle complex (**Figure 1**). Therefore, their research has attracted the attentions of chemists.[13] In 2014, Yu's group reported a series of amide-tethered aryloxazoline *ortho* C-H functionalization including amidation,[13a,13e] alkynylation,[13b] arylation,[13c] hydroxylation,[13d] arylation,[13e] trifluoromethylation[13f] (**Scheme 1, eq 3**). Subsequently, Chen group and Sun group further expand the diversification of hydrocarbon functionalization and successfully achieved *ortho* C−H acyloxylation,[13g] nitration[13h] (**Scheme 1, eq 3**). Inspired by above research, we envisioned that amide-tethered aryloxazoline moiety could deliver selective oxidative olefination on N-aryl. Herein, we report a rhodium-catalyzed oxidative olefination of N-(2-(4,5-dihydrooxazol-2-yl)phenyl)amides with arylethenes through extraordinary N-aryl C-H bond functionalization (**Scheme 1, eq 4**).



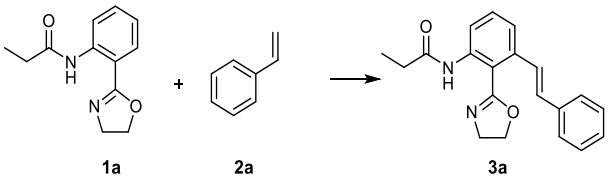


Scheme 1. Aryloxazoline and amide-tethered aryloxazoline C-H functionalization synthetic strategies

Firstly, the reaction of N-(2-(4,5-dihydrooxazol-2-yl)phenyl)amides (**1a**) with styrene (**2a**) as the model substrates has been performed in the presence of $[RhCp^*Cl_2]_2$ (3 mol%) as the catalyst, with an additive $AgSbF_6$ (0.1 equiv) in toluene at 70 °C under air. Encouragingly, the expected product (**3a**) was obtained in yield 15% (Table 1, entry 1). Through further evaluation of other solvents such as DMF, DMSO, MeCN, and DCE (Table 1, entries 2-5), DCE gave the better result (Table 1, entry 5). Then different silver salts $AgNO_3$, AgF_2, $AgBF_4$ were screened (Table 1, entries 7-9), we discovered that $AgBF_4$ can improve the yield increasing to 25% (Table 1, entry 9). In addition, the experiment was conducted in the absence of silver salt, it was found that none of the target product was formed (Table 1, entry 6). Subsequently, in a set of addition of different oxidants was taken into consideration (Table 1, entries 10-13). Surprisingly, $Cu(OAc)_2 \cdot H_2O$ gave the best yield in 70% (Table 1, entry 10). Beyond that, a small improvement was observed in yield to 78% when $Cu(OAc)_2$ was used instead of $Cu(OAc)_2 \cdot H_2O$ under the same conditions (Table 1, entry 14). Different rhodium catalysts have also been screened, to our disappointment, almost no product was afforded (Table 1, entries 15 and 16). Notably, higher or lower reaction temperature substantially led to unsatisfactory results. Even though prolonging the reaction to 24 hours at 60 °C, the desired product was only obtained in 70% yield (Table 1, entries 17-20). Finally, the reaction time was also optimized. When the reaction time was reduced to 8 hours or extended to 10 hours, no benefit to increase yield (Table 1, entries 21 and 22). In the end, the optimum reaction condition was

identified as follow: catalyzed by $[RhCp^*Cl_2]_2$ (3 mol%), $AgBF_4$ (0.1 equiv) as additive, $Cu(OAc)_2$ as oxidant and DCE as the solvent at 70 °C under air.

Table 1. Optimization of the reaction conditions[a]



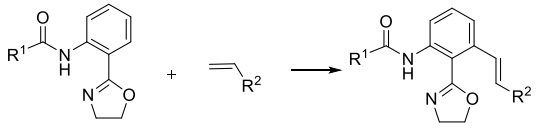
1a 2a 3a

Entry	Catalyst	Additive	Oxidant	Solvent	T/°C	Time/h	Yield[b]/%
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	---	toluene	70	10	15
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$	---	DMF	70	10	trace
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	---	DMSO	70	10	trace
4	$[Cp^*RhCl_2]_2$	$AgSbF_6$	---	MeCN	70	10	0
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	---	DCE	70	10	20
6	$[Cp^*RhCl_2]_2$	---	---	DCE	70	10	0
7	$[Cp^*RhCl_2]_2$	$AgNO_3$	---	DCE	70	10	10
8	$[Cp^*RhCl_2]_2$	AgF_2	---	DCE	70	10	17
9	$[Cp^*RhCl_2]_2$	$AgBF_4$	---	DCE	70	10	25
10	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2 \cdot H_2O$	DCE	70	10	70
11	$[Cp^*RhCl_2]_2$	$AgBF_4$	$K_2S_2O_8$	DCE	70	10	51
12	$[Cp^*RhCl_2]_2$	$AgBF_4$	BQ	DCE	70	10	43
13	$[Cp^*RhCl_2]_2$	$AgBF_4$	Ag_2CO_3	DCE	70	10	54
14	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	70	10	78
15	$Rh(OAc)_4$	$AgBF_4$	$Cu(OAc)_2$	DCE	70	10	0
16	$[Rh(COD)Cl]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	70	10	trace
17	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	40	10	32
18	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	60	10	60
19	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	60	24	70
20	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	90	10	61
21	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	70	8	70
22	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2$	DCE	70	12	72

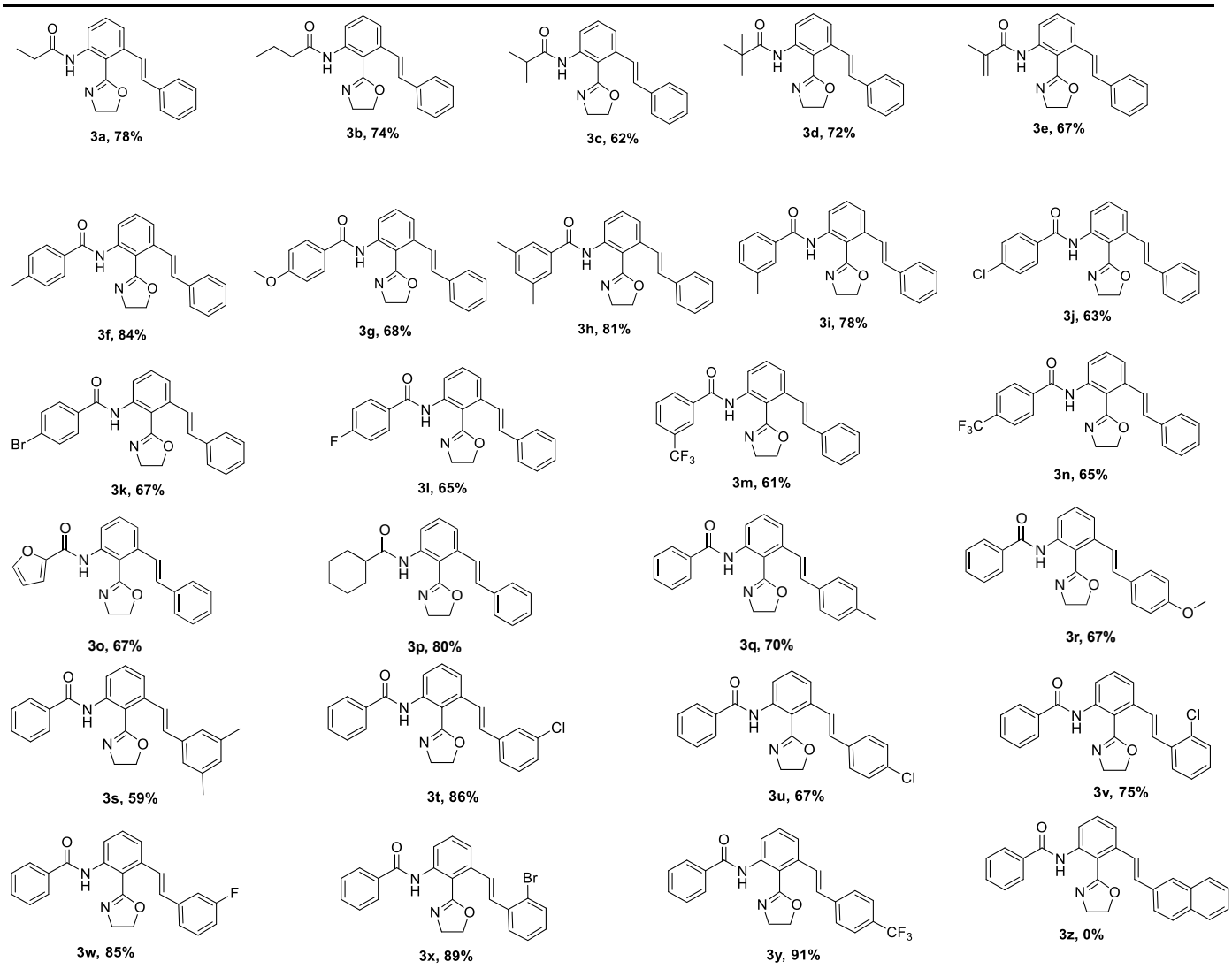
[a] (Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), catalyst (3 mol%), oxidant (2.0 equiv), additive (0.1 equiv), solvent (1 mL), under air for 10 h). [b] (Isolated yield)

With the optimized conditions in hand, substituents scope on the amide backbone was explored, as shown in **Table 2**. A wide variety of substituted amides are compatible with the transformation. Aliphatic groups including ethyl, propyl, *iso*-propyl, *tert*-butyl, *iso*-propenyl, cyclohexyl were tolerated to afford the corresponding products in good yields (**3a-3e, 3p**). Aromatic amides bearing various substitutes such as electron-donating methyl and methoxy (**3f-3i**) and electron-withdraw group including chloro, bromo, fluoro, trifluoromethyl (**3j-3n**) on the phenyl ring were also alkenylated, which exhibited high reactivity and offered desired products in moderate to good yields. In addition, the positions of the substituents on the phenyl ring had little effect on the product yields. To our delighted, the scope of amide backbone could be expanded to heterocyclic furanyl amide system (**1o**). It was also amenable to furnish the desired product (**3o**) in 67% yield.

Table 2. Substrate scope[a,b]



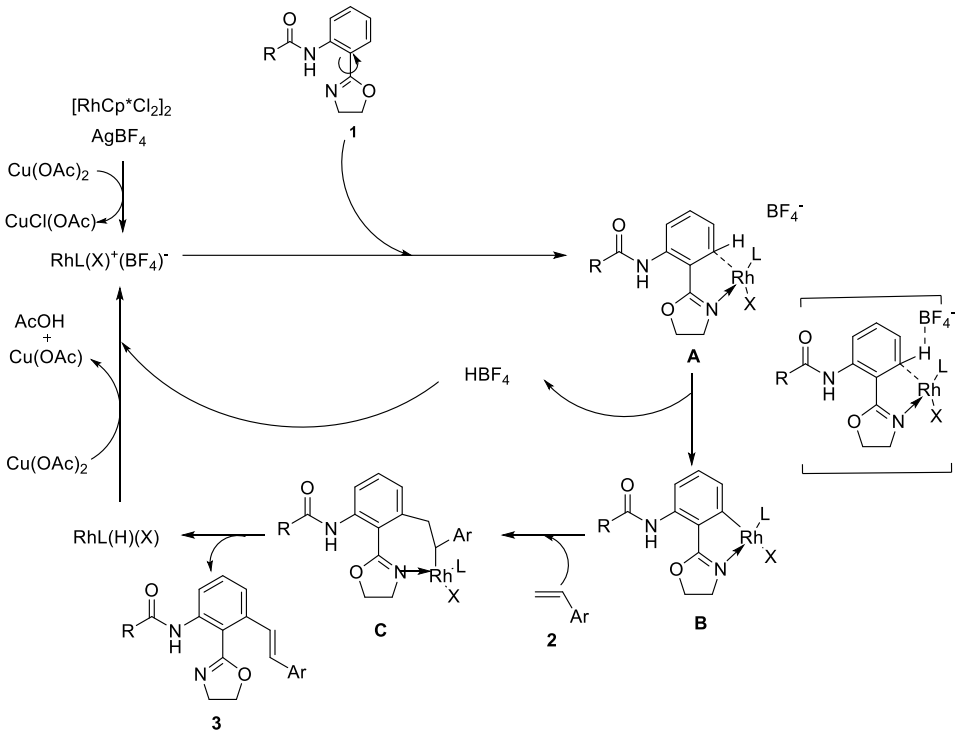
1 2 3



[a] (Reaction conditions: **1** (0.1 mmol), **2** (2.0 equiv), $[Cp^*RhCl_2]_2$ (3 mol%), $Cu(OAc)_2$ (2.0 equiv), $AgBF_4$ (0.1 equiv), DCE(1 mL) ,70 °C under air for 10 h).[b] (Isolated yield)

Subsequently, the substrate scope of substituted styrene was investigated and the results were illustrated in **Table 2**. It was shown that phenyl ring substituted with electron-donating methyl, methoxy (**3q-3s**) and electron-withdrawing (**3t-3y**) chloro, bromo, fluoro, trifluoromethyl could undergo the expected olefinization products in good to excellent yields. Wherein styrene substituted with electron-withdrawing groups gave higher yields of olefinization products than those with electron-donating groups and the effect of substituents positions were not obvious. Moreover, it is noteworthy that styrene containing

trifluoromethyl gave the best yield in 91% (**3y**). In order to further expand the substituents, naphthalene was used as the olefination coupling partner. Unfortunately, the expected coupling product was not detected (**3z**).



Scheme 2. Probable mechanistic pathway for C-H functionalization

On the basis of previous literatures[10,14,15] and present results, a possible mechanism can be depicted in **Scheme 2**. Firstly, the catalytic system $[RhCp^*Cl_2]_2/Cu(OAc)_2/AgBF_4$ generates a cationic rhodium species $RhL(X)^+(BF_4)^-$, in which X is Cl, BF_4 or OAc. Then coordination of the oxazoline N atom and *ortho* phenyl group C atom in **1** gives **A**, and this is followed by concerted metalation-deprotonation at phenyl group assisted by BF_4^- to form five-membered rhodocyclic complex **B**. Subsequently, the arylethenes **2** insertion into C-Rh bond yields intermediate **C**. β-Elimination obtains the arylethenes coupling product **3** and RhL(H)(X), RuL(H)(X) is transformed back into $RhL(X)^+(OAc)^-$ under the action of $Cu(OAc)_2$.

In conclusion, we have successfully developed a rhodium-catalyzed oxidative olefination of N-(2-(4,5-dihydrooxazol-2-yl)phenyl)amides with arylethenes. In the process, extraordinary N-aryl 3-position C-H bond were activated and successfully olefinized. Furthermore, the process conducted under air is attractive and convenient. In general, most functional groups are tolerated and the reaction proceed smoothly in the presence of these groups, which afford moderate to good yields.

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SUPPORTING INFORMATION

Supplementary data (synthesis of the starting materials, experimental procedures, characterization date and ^{1}H, ^{13}C NMR spectra) associated with this article can be found, in the online version, at URL: https:// www.heterocycles.jp/newlibrary/downloads/PDFsi/27007/100/12.

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