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Rhodium-Catalyzed Spiro Indenyl Benzoxazine Synthesis *via* C-H activation/ Annulation of 3-Aryl-2H-Benzo[*b*][1,4]oxazines and Alkynes

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Abstract: The rhodium (III)-catalyzed annulation of 3-Aryl-2H-Benzo[b][1,4]oxazines with alkynes *via* C-H activation has been developed. This reaction afforded a series of spiro indenyl benzoxazine in high yields under mild reaction condition with good functional group tolerance.

Transition metal-catalyzed annulation reaction *via* C–H bond activation has attracted much attention among the synthetic chemist as a prevailing method because it obviates the prior activation step with excellent atom economy.[1] In particular, transition metal-catalyzed directing group assisted C-H functionalization and annulation with various unsaturated systems such as alkenes, alkynes, and allenes in the construction of carbocycles have become an attractive approach for the synthesis of a wide range of complex compounds.[2-9] Since the pioneering work of Takai's group,[10] many researchers have explored imine-directed intermolecular annulations *via* C-H bond activation in developing the indene ring by imine directed annulation reaction *via* the C-H activation.[11] Cramer,[11f-h] Zhao,[11i,j] Cheng,[11k] Miura[11l] and Wang[11m] groups independently demonstrated the transition metal-catalyzed annulation of aromatic ketimines/ aldimines with alkynes *via* the C-H activation for the generation of indene derivatives. Li,[11n] Deng[11o] and Wang[11p] groups also independently disclosed the metal catalyzed annulation with cyclic *N*-sulfonyl ketimines and alkynes *via* C-H activation to afford spiro indenyl benzosultam. Dong's group developed a novel spirocyclic indenyl phosphoramides from *N*-phosphoryl ketimines and alkynes.[11q] Li's group again disclosed the generation of indene using Rh (III)-catalyst *via* the C-H activation/ annulation of azomethane ylides[11r], *N*-sulfonyl imines[11s] and arylnitrones[11t] with alkynes. However, there is still a need for exploring the scope of imine in designing indene motifs.

Indene motifs are considered as an important building block for the construction of many functional materials,[12] medicines,[13] and biologically active compounds (Figure 1).[14] They can also be used as ligands for transition metals by deprotonation.[15] It is expected that the biologically important indene motifs when combined with other biologically active systems like benzoxazine[16] could result in enhancing the pharmacological activity while retaining high diversity and biological relevance.

Recently, our group has successfully reported the Rh (III) catalyzed ring-opening addition of azabenzonorbornadienes with cyclic *N*-sulfonyl ketimines *via* C-H activation.[17] Thus, we envisaged the synthesis of the spiroindenyl compounds containing the aforementioned important bioactive fragments using Rh (III) catalyst *via* C-H activation with benzoxazine and

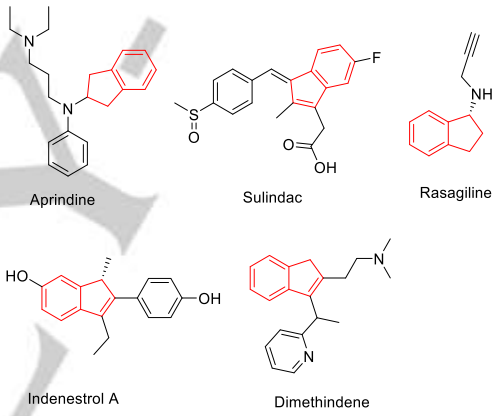


Figure 1. Representives of bioactive indene.

alkynes as coupling partners.

We initiated our investigation by annulative coupling of benzooxazine **1a** with diphenyl acetylene **2a** as the model substrates (Table 1). The coupling of **1a** with **2a** under the catalytic condition of $[RhCp^*Cl_2]_2$ (5 mol%) and $Cu(OAc)_2$ (10 mol%) in DCE at 100 °C for 8 h afforded exclusively the spirooxazine-indene **3a** in moderate yield (Table 1, entry 1). Screening of solvents showed that MeCN was found to be an optimal solvent forming the desired product **3aa** in 99 % yield (entries 1-6). Next, we screened additives; exclusion of additive gave no product (entry 7). Other additives like NaOAc, AgOAc, and $Fe(OAc)_2$ were also checked but were not effective as $Cu(OAc)_2$ (entries 8-10). Other catalysts were also investigated but found to be less effective in this transformation, $[IrCp^*Cl_2]_2$ gave the product in 61 % yield while $RhCl_3{\cdot}3H_2O$ did not give isolable product (entries 11, 12). The absence of catalyst also gave no isolable product (entry 13). Next, we investigated the effect of other reaction parameters like temperature and the catalytic loading on the yield of the reaction. Lowering the temperature lowered the yield of the reaction (entries 14-16). However, to our delight, decrease in the loading of catalyst to 2.5 mol% gave the desired product in excellent yield (entry 17).

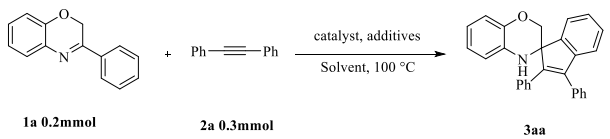
Thus, we have chosen these reaction conditions of entry **17** as the optimal condition.

With the optimal reaction conditions in hand, we explored the scope and generality of this annulation reaction. Various electronically and sterically diverse benzooxazine **1** were examined using internal alkyne **2a** as a coupling partner (Table 2). Both electron-donating, as well as electron-withdrawing groups on the *para*-position of the C3-phenyl ring of **1**, smoothly underwent the annulation reactions providing the corresponding compounds **3ba-3ia** in excellent yields, albeit electron-withdrawing groups required longer reaction time under the same reaction condition. CH_3O-substituent at the *meta*-position gave regioisomers (**3ka** and **3ka'**) in 88% yields. Notably, the annulation of sterically crowded *ortho*-substituted substrate also underwent the reaction to afford the desired spiro compound **3ja** in moderate yield 58%. Disubstituted at the phenyl ring, napthyl and biphenyl at the C3 position also gave the corresponding spirocyclic products **3la**, **3ma** and **3na** respectively in good to excellent yields. However, no **3oa** was detected by using benzoxazine with an ortho-substituted phenyl ring.

We further evaluated the scope of various internal alkynes (**2**) under the optimal reaction conditions by coupling with benzooxirane (**1a**) (Table 3). Pleasingly, all the alkynes regardless of activated or unactivated gave the corresponding annulated products in good to excellent yields. Symmetrically substituted diarylalkynes carrying electron-donating or electron-withdrawing at the *ortho*, *meta*, and *para*-positions were good coupling partners, giving the corresponding annulated products in excellent yields (**3ab**-**3ah**). Aliphatic groups symmetrically substituted in the alkynes were also compatible with the reaction giving the desired products in good yields (**3al**-**3an**). The unsymmetrical alkynes like 2-butynyl alcohol were also well-tolerated, furnishing the corresponding spirocyclic product in regioisomers (**3ao** and **3ao'**) in 99% yield. Aryl-alkyl mixed unsymmetrical alkynes also successfully afforded the desired products (**3ap**, **3ap'** and **3ap**, **3ap'**) as the mixture of two regioisomers in good yields.

Hydrogen-deuterium exchange and KIE experiments were carried out to probe the mechanism of this catalytic reaction (Scheme 1). First, we treated **1a** with 10 equiv. of CH_3COOD under the standard reaction conditions; 49% hydrogen-deuterium-exchange at *ortho*-position of **1a** was observed

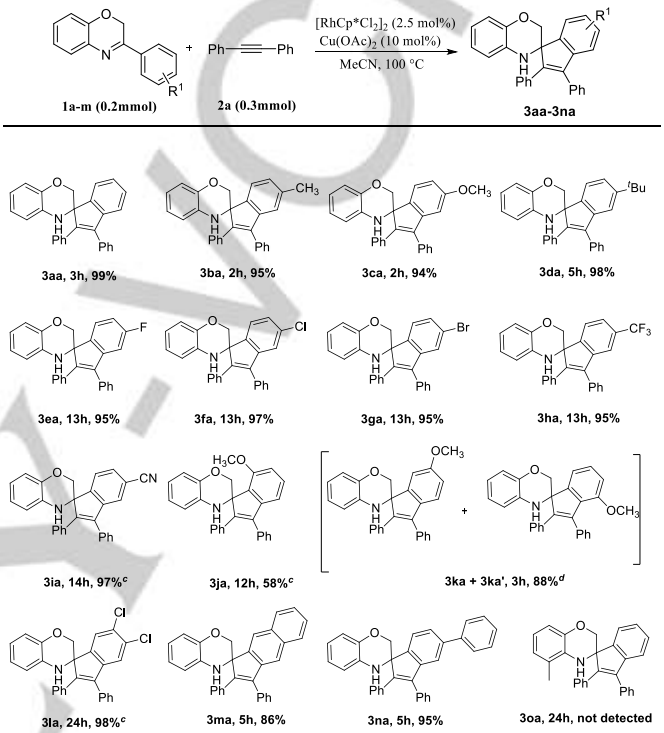
Table 1. Optimizations of reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Time (h)	Yield (%)[b]
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DCE	8	54
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	THF	48	66
3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	Toulene	72	76
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	dioxane	9	67
5	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeCN	3	99
6	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	TFE	72	Trace
7	$[RhCp^*Cl_2]_2$	-	MeCN	72	N.R.
8	$[RhCp^*Cl_2]_2$	NaOAc	MeCN	8	89
9	$[RhCp^*Cl_2]_2$	AgOAc	MeCN	8	95
10	$[RhCp^*Cl_2]_2$	$Fe(OAc)_2$	MeCN	8	95
11	$[IrCp^*Cl_2]_2$	$Cu(OAc)_2$	MeCN	72	61
12	$RhCl_3{\cdot}3H_2O$	$Cu(OAc)_2$	MeCN	72	N.D.
13	-	$Cu(OAc)_2$	MeCN	72	N.D.
14[c]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeCN	8	89
15[d]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeCN	4	96
16[e]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeCN	6	83
17[f]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeCN	3	99

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.01 mmol), additive (0.02 mmol), solvent (2 ml), 100 °C, 1-24h. [b] Yield of isolated product. [c] The reaction was performed at 60 °C. [d] The reaction was performed at 80 °C. [e] 1 mol% $[RhCp^*Cl_2]_2$. [f] 2.5 mol% $[RhCp^*Cl_2]_2$.

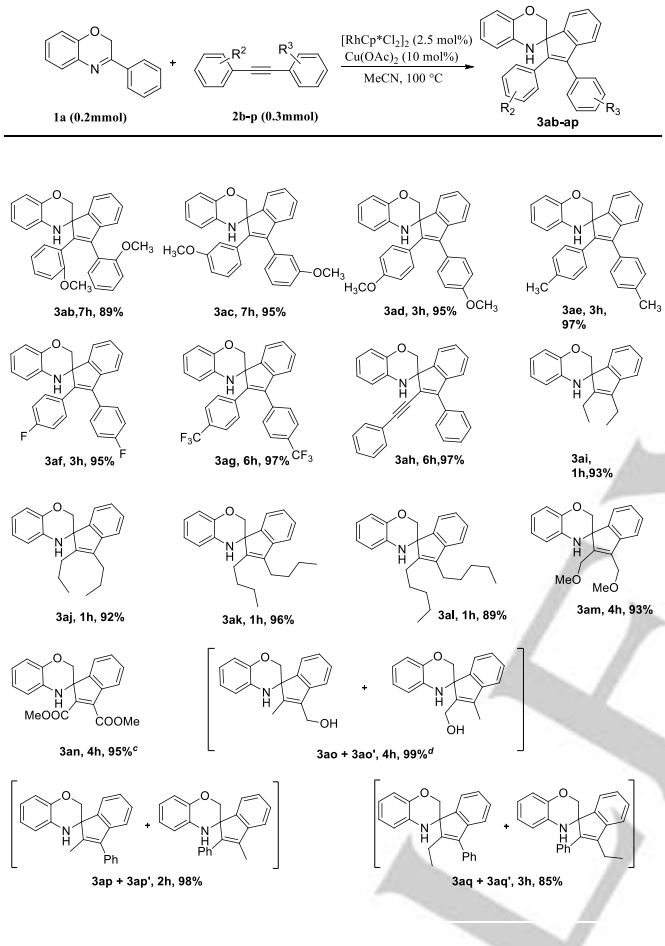
Table 2. Substrate Scope of the Benzoozxazine.[a],[b]



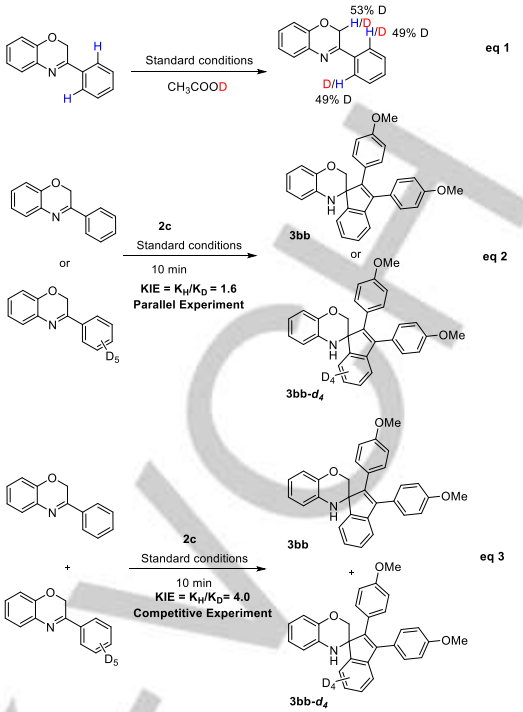
[a] Under Ar atmosphere, $[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol, 2.5 mol%), $Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 10 mol%), Imines (**1a-m**) (0.2 mmol), alkyne (**2a**) (0.3 mmol), and MeCN (2 mL) were added sequentially to a 25 mL Schlenk tube equipped with a magnetic stir bar. [b] All the yields are isolated yields. [c] $[RhCp^*Cl_2]_2$ (6.1 mg, 0.01 mmol, 5 mol%). [d] Regioisomer was determined by NOESY.

indicated by its ^{1}H NMR. This result indicates significant reversible C-H activation of **1a** (eq 1). To further understand the underlying nature of the mechanism of the present reaction, we performed the parallel and competitive reaction of **1a** and deuterium labelled [D5]-**1a** with **2c** under standard reaction conditions and measured the kinetic isotopic effect (KIE) values. An intermolecular parallel experiment of [D5]-**1a** with **2c** showed kH/kD = 1.6 (eq 2). While a KIE value of kH/kD = 4.0 was observed for the intermolecular competition reaction of **1a** and deuterium-labelled [D5]-**1a** with **2c** (eq 3). These suggested that

Table 3. Substrate Scope of the Alkynes.[a],[b]



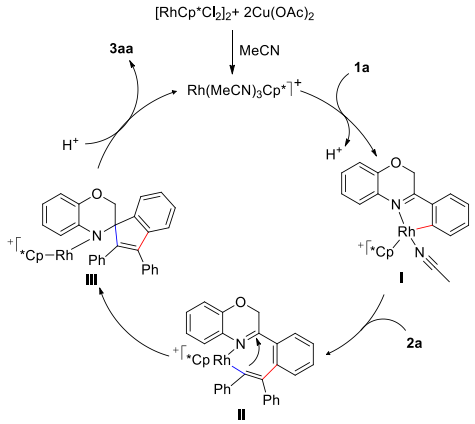
[a] Under Ar atmosphere, [RhCp*Cl$_2$]$_2$ (3.1 mg, 0.005 mmol, 2.5 mol%), Cu(OAc)2 (3.6 mg, 0.02 mmol, 10 mol%), Imine (**1a**) (0.2 mmol), alkynes (**2b-o**) (0.3 mmol), and MeCN (2 mL) were added sequentially to a 25 mL Schlenk tube equipped with a magnetic stir bar. [b] All the yields are isolated yields. [c] [RhCp*Cl$_2$]$_2$ (6.1 mg, 0.01 mmol, 5 mol%). [d] Regioisomer was determined by HMBC.



Scheme 1. H/D Exchange and KIE Experiments

the C-H bond cleavage is involved in the rate-limiting step.

A plausible catalytic cycle is proposed on the basis literature[9e,11i,o] (Scheme 2). The imine nitrogen atom of the benzooxazne directs the *ortho* C-H activation to form a five-membered rhodacycle intermediate **I** which was followed by subsequent insertion of alkyne to form seven-membered ring intermediate **II**. The intermediate **II** then undergo Grignard-like migration to the imine group to generate a rhodium intermediate **III**. The proton generated from C-H activation was consumed by intermediate **III** to generate the final product **3aa** with the regeneration of the rhodium catalyst.



Scheme 2. Plausible mechanism for the annulation reaction of **1a** with internal alkyne **2a**.

In summary, we have successfully developed a highly efficient $[RhCp^*Cl_2]_2$ catalyzed synthesis of novel spirocyclic benzoxazine-indenes from benzoxazine and alkynes *via* imine directed C−H alkenylation/annulation reactions. The methodology could be applied to various benzoxazine and alkynes giving the corresponding products in good yields.

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Keywords: Spirocycles • C-H activation • Annulation • Rhodium catalyst

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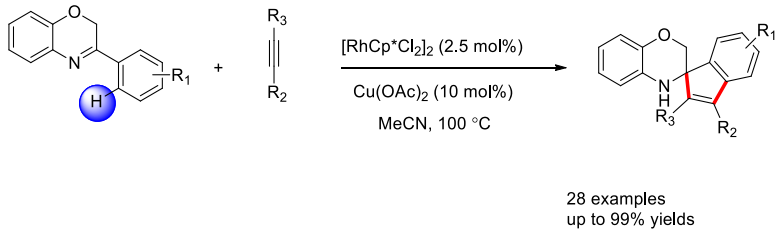

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up to 99% yields

A highly efficient synthesis of novel spirocyclic benzoxazine-indenes from benzoxazine and alkynes *via* imine directed C−H activation/annulation using rhodium catalyst was reported. The methodology could be applied to various benzoxazine and alkynes giving the corresponding spiro indenyl benzoxazine as spirocycles products in good yields.

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