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Rh(III)-catalyzed [3 + 2] spiroannulation of 2,3-dihydro-1,4-benzoxazines with 4-hydroxy-2-alkynoates through *ortho*-C–H bond functionalization†

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Rhodium(III)-catalyzed [3 + 2]-spiroannulation of 2-aryl-1,4-benzoxazines with 4-hydroxy-2-alkynoates has been developed for the synthesis of highly rigid spirolactones in good yields with high regioselectivity. The reaction proceeds through a cascade of C–H activation followed by C–H annulation and lactonization. In this approach, two C–C and C–O bonds are formed in a single step. This is the first report on the spiroannulation of 2,3-dihydro-1,4-benzoxazines with 4-hydroxy-2-alkynoates.

Introduction

Transition metal catalyzed annulation is a powerful strategy in organic synthesis to construct various polycyclic scaffolds. Recently, numerous transition metal catalytic systems have been developed to facilitate C–H activation without pre-functionalization of the substrates.[1] Among them, rhodium(III) plays a distinctive role in the C–H activation/functionalization of diverse aromatic systems to generate several fused-/spiro-cyclic frameworks, which are frequently found in many biologically active natural products, agrochemicals, and pharmaceutically active ingredients.[2] In particular, Rh-catalyzed intermolecular [3 + 2] annulations are useful to generate diverse scaffolds.[3]

On the other hand, 2,3-dihydro-1,4-benzoxazine motifs are frequently found in natural products and pharmaceuticals, which are known to exhibit potent biological activities such as antihyperlipidemic, anti-arrhythmic and antithrombotic activities, *etc*.[4] As shown in Fig. 1, spiroindanes play a significant role in medicinal chemistry.[5] Consequently, a few [3 + 2] cycloaddition reactions of 2,3-dihydro-1,4-benzoxazines with different unsaturated substrates have been developed to produce spiro-frameworks using transition metal catalysts.[6] For example, the spiroannulation of 2-aryl-1,4-benzoxazines with alkynes has been reported to produce spiroindane derivatives.[7,8] Recently, the C–H functionalization of cyclic ketimines with alkynyl chlorides has also been reported using the Rh(III)Cu(OAc)$_2$ metal complex (Scheme 1).[9]

Results and discussion

Following our interest in transition metal catalyzed C–H functionalization,[10] we herein report a simple and efficient cascade process for the construction of highly rigid spiroindane derivatives through sequential C–H annulation and lactonization. The required precursors, 2-arylbenzoxazines and hydroxy-alkynoates, were prepared according to literature procedures.

Initially, we attempted the C–H annulation of 2-phenylbenzoxazine (**1a**) with ethyl 4-hydroxyl-4-methyl-2-pentynoate (**2a**) using a Rh(III) catalyst in the presence of different bases like NaOAc, KOAc, and K_2CO_3 in various solvents such as THF, TFE, DCE, EtOH, and CH_3CN at different temperatures

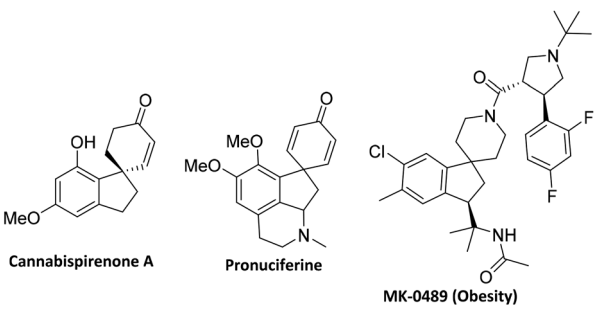

Fig. 1 Examples of spiroindane derivatives.

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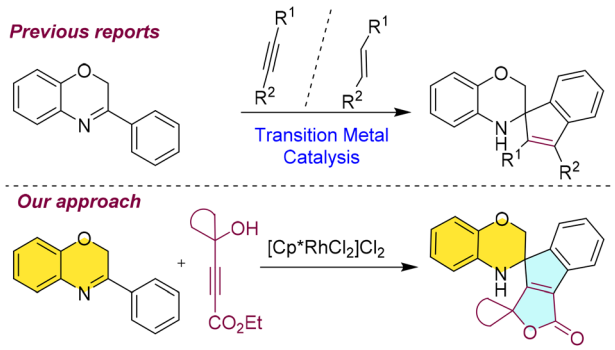
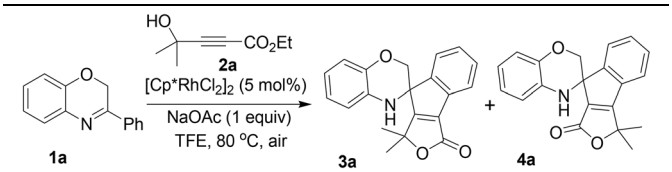


Scheme 1 Examples of metal-catalyzed spiro-annulations.

Table 1 Optimization of the reaction conditions



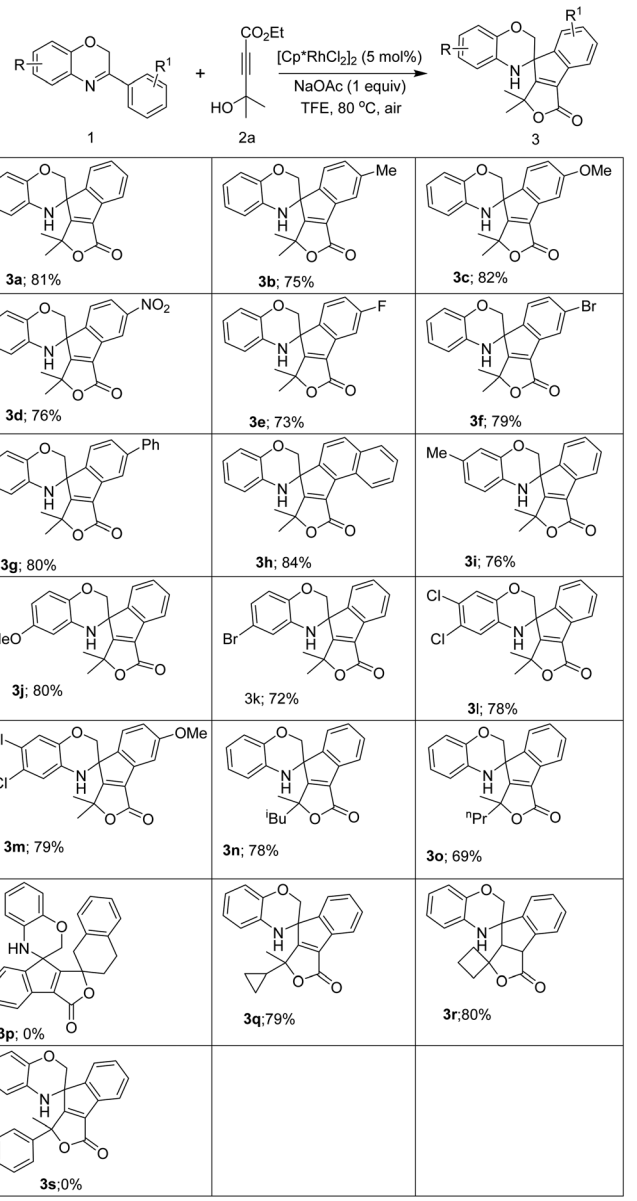
Entry	Catalyst[a]	Base	Solvent	Temp. (°C)	Yield[b] (%) 3a	4a
1	$[Cp^*RhCl_2]_2$	NaOAc	TFE	80	85	0
2	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	TFE	80	—	—
3	$Pd(OAc)_2$	NaOAc	TFE	80	—	—
4	$[Cp^*RhCl_2]_2$	KOAc	TFE	80	72	9
5	$[Cp^*RhCl_2]_2$	K_2CO_3	TFE	80	0	0
6	$[Cp^*RhCl_2]_2$	NaOAc	DCE	80	50	6
7	$[Cp^*RhCl_2]_2$	NaOAc	EtOH	80	10	0
8	$[Cp^*RhCl_2]_2$	NaOAc	CH_3CN	80	17	3
9	$[Cp^*RhCl_2]_2$	NaOAc	TFE	25	—	—
10	$[Cp^*RhCl_2]_2$	NaOAc	TFE	50	23	—

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (5 mol%), base (0.5 mmol), TFE (3 mL), 80 °C for 8 h under an air balloon. [b] Isolated yield.

(Table 1). The reaction proceeds smoothly at 80 °C in the presence of NaOAc in trifluoroethanol (entry 1, Table 1). Other metal catalysts such as Ru(II) and Pd(II) salts failed to give the desired product (entries 2 and 3, Table 1). As with NaOAc, the reaction was quite successful with KOAc (entry 4, Table 1). However, the reaction was unsuccessful in the presence of other bases such as K_2CO_3 (entry 5, Table 1). Other solvents such as DCE, EtOH, and CH_3CN were found to be ineffective (entries 6–8, Table 1). The reaction did not proceed at 25 °C (entry 9, Table 1). The reaction was sluggish even at 50 °C (entry 10, Table 1).

The above results prompted us to examine the scope of this method (entry 1, Table 1); the scope of this method is exemplified with different substrates. Interestingly, various benzoxazines with substituents at the C2 and C3 positions on the phenyl ring participated well in this transformation (**3a–s**). The substituents present on the aromatic ring showed some effect on the conversion. As shown in Table 2, the presence of electron donating groups on both C_2 and C_3 rings (**3b**, **3c**, **3i**, and **3j**) afforded the desired spiro-products in excellent yields. However, the substrates bearing electron-withdrawing substituents on the aryl ring gave the product in a moderate yield (**3d**, Table 2) compared to the halides (**3e**, **3f**, **3g**, **3h**, **3k**, **3l**, and **3m**, Table 2). The alkyl chain did not influence the yield of this reaction. For example, no significant difference in yield was observed either with i-butyl (**2b**) or *n*-propyl (**2c**) substituted alkynoates (**3n** and **3o**, Table 2). However, no reaction was observed with hydroxy alkynoate (**2d**) which is derived from β-tetralone due to its steric hindrance (**3p**, Table 2). This

Table 2 Substrate scope of the formation of spirobenzoxazines[a,b]



[a] All products were well characterized by ^1H & ^{13}C NMR and mass spectrometry. [b] Isolated yields after column chromatography.

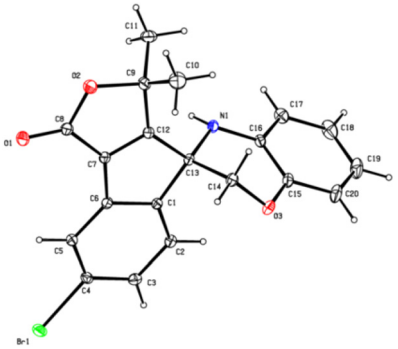


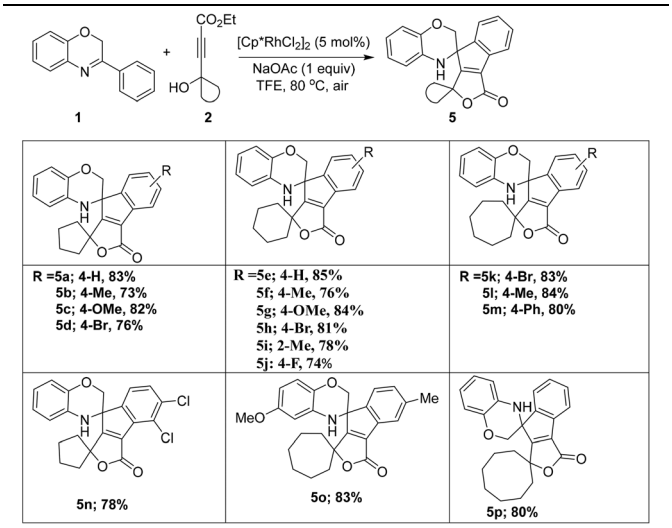
Fig. 2 ORTEP diagram of **3f** (CCDC 2247998†).

method was further extended to other hydroxy alkynoates (**2e** and **2f**) prepared from cyclopropyl ketone and cyclobutanone, respectively. Interestingly, the desired products (**3q** and **3r**) were obtained in 79–80% yields under the present reaction conditions. To our surprise, the hydroxyl propiolate (**2g**) prepared from acetophenone failed to give the desired product.

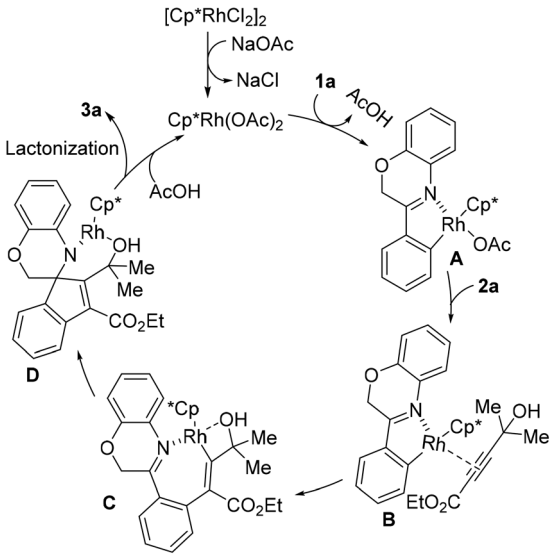
The structure of **3f** was further confirmed by single crystal X-ray crystallographic analysis (Fig. 2).

The scope of this method is further extended to substituted 4-hydroxy-alkynoates (Table 3). It is worth mentioning that both acyclic and cyclic alkynoates actively participated in this transformation. The reactivity of propiolates having a cyclic ring such as cyclopentyl (**2h**), cyclohexyl (**2i**), cycloheptyl (**2j**), and cyclooctyl (**2k**) was examined. The spiroannulation was quite successful with these cycloalkyl propiolates without any significant difference in the activity, affording dispiro-frameworks in good yields (**5a–p**, Table 3). Furthermore, 3,4-dichlorophenyl and *p*-tolylbenzoxazines also gave the spiro-compounds in good yields (entries **5n** and **5o**, Table 3).

Table 3 Substrate scope of benzoxazines[a,b]



[a] All products were well characterized by ^{1}H & ^{13}C NMR and mass spectrometry. [b] Isolated yields after column chromatography.



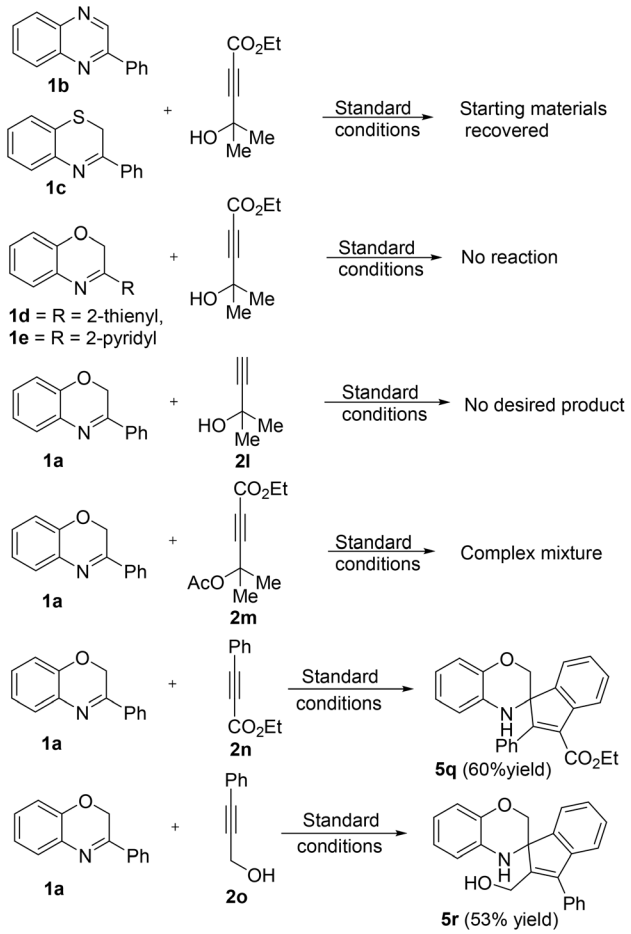
Scheme 2 A plausible reaction mechanism.

Based on the above control experiments and previous reports,[6] we proposed a plausible mechanism, as shown in Scheme 2. Initially, active monomeric rhodium species are generated from $[Cp^*RhCl_2]_2$ and sodium acetate, which activate the C–H bond of 3-phenyl-2*H*-benzo[*b*][1,4]oxazine to give the rhodacycle **A**. Subsequent π-complexation of hydroxy-alkynoate with metallocycle **A** generates the ternary complex **B**. An oxidative insertion of hydroxy-alkynoate into the rhodium–carbon bond of the phenyl ring provides the rhodium complex **C**. An intramolecular addition of alkenyl rhodium to imine generates intermediate **D**. Proto-derhodation and successive lactonization of **D** would give the desired product **3a**.

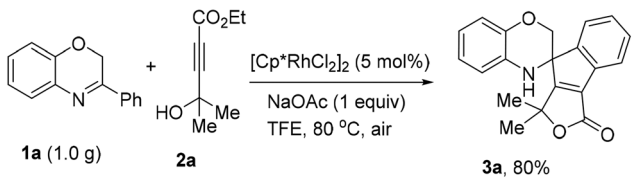
Furthermore, we studied the reactivity of other substrates such as 2-phenylquinoxaline (**1b**) and 3-phenyl-[1,4]thiazine (**1c**) with 4-hydroxy-2-alkynoate (**2a**) under the optimized reaction conditions. Unfortunately, the reaction did not proceed with these substrates and the starting materials were recovered. Similarly, 2-thienyl- and 2-pyridyl substituted benzo[*b*][1,4]oxazines (**1d** and **1e**) also failed to give the desired products. Moreover, the reaction of 2-methylbut-3-yn-2-ol (**2b**) also failed to give the desired product (Scheme 3). Besides, the reaction did not proceed with terminal alkynol (**2l**) and the acetyl derivative of alkynoate (**2m**). Interestingly, other alkyne derivatives such as ethyl 3-phenylpropiolate and 3-phenylprop-2-yn-1-ol (**2n** and **2o**) gave the annulated products (**5q** and **5r**) in good yields.

The feasibility of the current strategy was checked on the gram scale. The reaction was performed on the 1 g scale under the present reaction conditions. The desired product **3a** was obtained in 80% yield, as shown in Scheme 4.

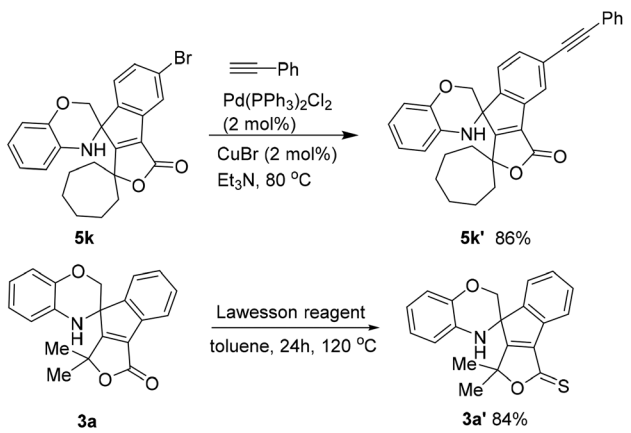
The product was further derivatized by different functional group transformations such as Sonogashira coupling and the lactone was converted into thiolactone using Lawesson's reagent. As shown in Scheme 5, the spiro-compound **5k** was treated with phenylacetylene under Sonogashira conditions to



Scheme 3 Study of the reactivity of different substrates.



Scheme 4 Scale-up synthesis of **3a**.



Scheme 5 Derivatization of **5k** and **3a**.

produce the corresponding product **5k′** in 86% yield. In another experiment, product **3a** was treated with Lawesson's reagent to produce thiolactone **3a′** in 84% yield (Scheme 5).

Conclusions

In summary, we have developed a novel Rh(III)-catalyzed spiroannulation of substituted 1,4-benzoxazines with 4-hydroxy-2-pentynoates to produce the corresponding spirolactones in good yields and high regioselectivity. A large number of diverse spirolactones were prepared by means of a sequential C–H annulation and lactonization reaction. This method provides direct access to pharmaceutically relevant spiroindane scaffolds from readily available 2-aryl benzoxazines and hydroxyalkynoates.

Conflicts of interest

There are no conflicts to declare.

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