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Straightforward Assembly of Benzoxepines by Means of a Rhodium(III)-Catalyzed C−H Functionalization of *o*-Vinylphenols

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Supporting Information

ABSTRACT: Readily available *o*-vinylphenols undergo a formal (5 + 2) cycloaddition to alkynes when treated with catalytic amounts of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$. The reaction, which involves the cleavage of the terminal C−H bond of the alkenyl moiety, generates highly valuable benzoxepine skeletons in a practical, versatile, and atom-economical manner. Using carbon monoxide instead of an alkyne as reaction partner leads to coumarin products which formally result from a (5 + 1) cycloaddition.

Metal-catalyzed cycloadditions involving the coordination and activation of π-electrons have revolutionized the way of making cyclic compounds.[1] In recent years there have been an increasing number of reports on a new type of metal-catalyzed annulations that involve as a key step the activation of C−H bonds.[2] These reactions have provided for the easy construction of a variety of rings, mainly five- and six-membered heterocycles, through formal (3 + 2)[3] or (4 + 2)[4] cycloadditions. Remarkably, the assembly of larger rings by means of related annulations remains to be developed.[5]

Herein we describe a new type of heteroannulation involving a C−H activation process that allows the synthesis of benzoxepines from extremely simple precursors in a formal (5 + 2) cycloaddition reaction.[6] The benzoxepine skeleton forms the basic core of many molecules with pharmacological importance such bauhinoxepin A, bulbophylol B or janoxepin (see Figure 1),[7] and therefore methods that allow their assembly from readily available precursors are of major interest.[8]

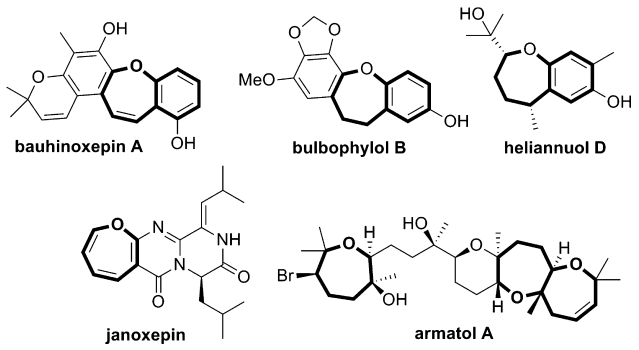

Figure 1. Representative compounds containing the oxepine core.

Our work started by identifying 2-hydroxystyrenes as readily available substrates that might engage in rhodium-catalyzed heteroannulations with alkynes via reactions involving a C−H activation step. At the outset, the regiochemistry of the potential annulation was quite unpredictable, as *a priori* there are three different C−H positions susceptible to activation, and therefore the reaction might lead to five-, six-, or seven-membered rings. While the formation of benzofuranes from phenols using Rh(III) catalysts has not been described,[9] precedents in the annulation of naphthols with alkynes pointed to the formation of chromene-type molecules (**B**) as a viable outcome for the reaction (Figure 2).[10]

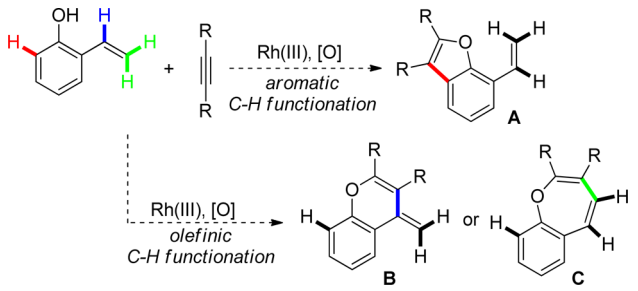

Figure 2. Different annulation options for *o*-vinylphenols using a Rh(III) catalyst.

Remarkably, reaction of alkyne **2a** with 2 equiv of 2-vinylphenol (**1a**) in the presence of catalytic amounts of $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) and 2.1 equiv of $Cu(OAc)_2{\cdot}H_2O$, in toluene at 100 °C, did not give the benzofurane- or chromene-type of products but gave the oxepine **3aa** in 52% yield (Table 1, entry 1). Using $[Cp^*IrCl_2]_2$ instead of the rhodium complex led to the majoritary recovery of the starting material, while $RuCl_2(p\text{-cymene})]_2$ induced the decomposition of **1a**. After screening several solvents, we found that using acetonitrile instead of toluene leads to a considerable increase in the yield up to 91%. Finally, we found that carrying out the reaction under an air atmosphere (balloon) allowed to decrease the amount of **1a** and $Cu(OAc)_2$ to 1.5 equiv and 0.5 equiv, respectively, without compromising the yield (97%, after 1h at 85 °C, entry 7). The loading of $Cu(OAc)_2$ can be decreased to 10%; however, the reaction is slower (entry 8).

With the optimized conditions in hand we investigated the scope with regard to the alkyne component (Scheme 1).

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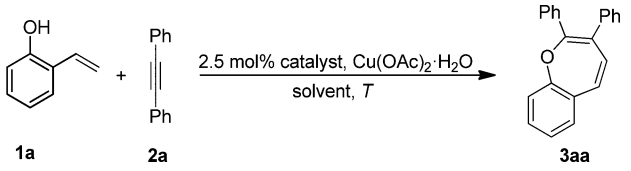
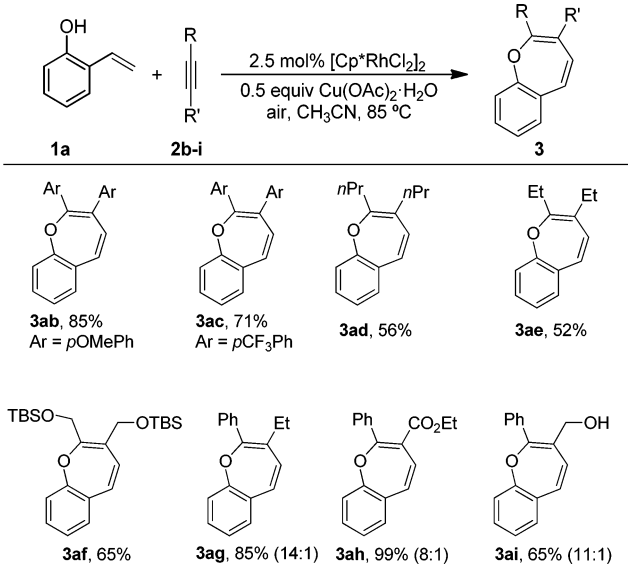
Table 1. Optimization of the Reaction[a]



entry	catalyst	1a (equiv)	solvent	T (°C)	yield (%)[b]
1	$[Cp^*RhCl_2]_2$	2	toluene	100	52
2	$[Cp^*IrCl_2]_2$	2	toluene	100	0
3	$[RuCl_2(p\text{-cymene})]_2$	2	toluene	100	traces
4	$[Cp^*RhCl_2]_2$	2	DMF	100	72
5	$[Cp^*RhCl_2]_2$	2	*t*AmylOH	100	83
6	$[Cp^*RhCl_2]_2$	2	CH_3CN	85	91
7	$[Cp^*RhCl_2]_2$	1.5	CH_3CN	85	97[c]
8	$[Cp^*RhCl_2]_2$	1.5	CH_3CN	85	87[d]
9	none	1.5	CH_3CN	85	0

[a]0.33 mmol of **2a**, 2 mL of solvent, 2.1 equiv of $Cu(OAc)_2{\cdot}H_2O$. [b]Isolated yield of **3aa** (based on **2a**). [c]0.5 equiv $Cu(OAc)_2{\cdot}H_2O$/air balloon. [d]0.1 equiv of $Cu(OAc)_2{\cdot}H_2O$/air balloon, 16 h.

Scheme 1. Scope with Respect to the Alkyne Component[a,b]



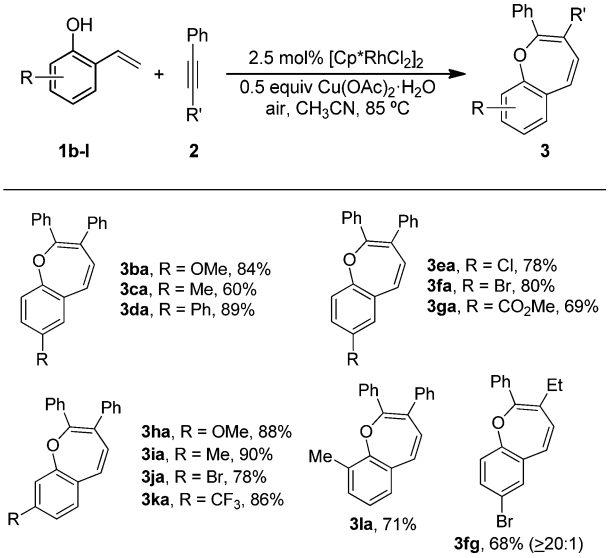
[a]Reaction conditions: 0.33 mmol of **2**, 0.50 mmol of **1a**, $[Cp^*RhCl_2]_2$ (2.5 mol %), 0.5 equiv $Cu(OAc)_2{\cdot}H_2O$, 2 mL of CH_3CN at 85 °C, air balloon, overnight. [b]Isolated yield based on **2**.

Symmetrical alkynes bearing electron-rich or electron-deficient aryl substituents (**2b** and **2c**) led to the expected products **3ab** and **3ac** in good yields (85% and 71%). Dialkyl-substituted alkynes, such as **2d**, **2e**, and **2f**, also participate in the process, although the yields are slightly lower (52–65%).

Interestingly, with unsymmetrical aryl-alkyl alkynes the reaction takes place with high regioselectivity, leading to products in which the phenyl group is in the carbon tethered to the oxygen group of the product. Thus, alkyne **2g** afforded the product **3ag** in excellent yield and regioselectivity (14:1). Similar results were obtained with an alkynylester (**3ah**, 99% yield, 8:1 regioselectivity) or with an alkyne bearing a hydroxy group like **2i** (65% yield, 11:1).

The reaction is compatible with a wide variety of substituents in the aryl group of the vinylphenol (Scheme 2). The required

Scheme 2. Reaction with Phenols Equipped with Different Substituents[a,b]



[a]Reaction conditions: 0.33 mmol of **2**, 0.50 mmol of **1**, $[Cp^*RhCl_2]_2$ (2.5 mol %), 0.5 equiv $Cu(OAc)_2{\cdot}H_2O$, 2 mL of CH_3CN at 85 °C, air balloon, overnight. [b]Isolated yield (based on **2**).

phenolic substrates (**1b–1l**), when there are no commercial sources, are easily assembled from the corresponding salicylaldehydes through a Wittig reaction with a methylene-phosphorous ylide.

We first investigated the influence of the substituent in the position *para* to the hydroxyl group. As shown in Scheme 2, the reaction works in substrates bearing substituents with either electron-donating or electron-withdrawing properties, including methoxy, methyl, phenyl, chloro, bromo, or ester groups, and the oxepine products are obtained in good to excellent yields (**3ba–3ga**, 60–89%) Moreover, substituents in the position *meta* to the hydroxyl group such as methoxy, methyl, bromide, and trifluoromethyl (phenols **1h–1k**) or in *ortho* (**1l**), are also tolerated, and the products **3ha–3la** are isolated with good yields. Finally, reaction of bromo-substituted vinyphenol (**1f**) with the asymmetric alkyne **2g** led to the corresponding product **3fg** in 68% yield as a single regioisomer.

Interestingly, the reaction does not proceed in substrates with alkyl substituents at the terminal position of the alkene such as (*E*)-2-(prop-1-en-1-yl)phenol, which decomposed under the reaction conditions.

Competition experiments revealed that the phenol **1g** reacts preferentially to **1a** when mixed together with the alkyne **2a** under the standard reaction conditions (Scheme 3). However, in separate experiments we found that **1a** reacts faster than electron-deficient substrates **1g** of **1k**.[11] This divergence could be explained in terms of an initial and irreversible formation of a phenoxide–Rh complex, as this might be easier for the more acidic substrate **1g**; however, the subsequent C–H activation step might be more favorable for the more electron-rich substrate **1a**.

Intermolecular competition experiments between **1a** and the deuterated analogue **1a**-d_2, demonstrated a kinetic isotope effect (k_H/k_D = 2.7), which suggests that the C–H bond cleavage is involved in the rate-limiting step.

Of mechanistic relevance, treatment of allylphenol **4** with diphenylacetylene under the standard conditions led to

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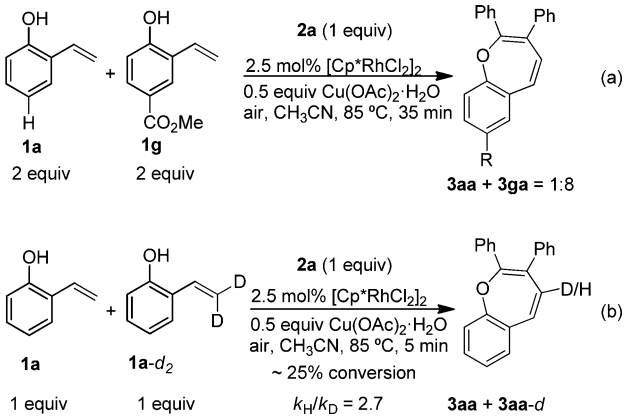
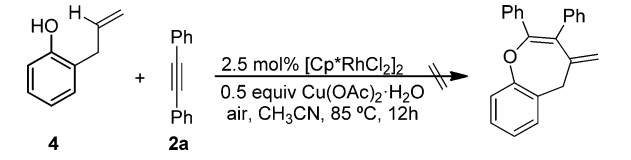
Scheme 3. Competition Experiments



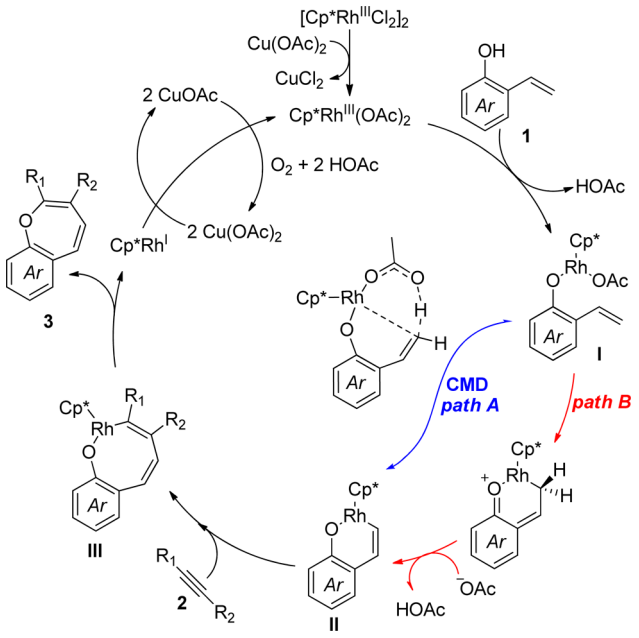
recovery of a majority of the starting materials (Scheme 4), which suggests that the conjugation of the vinyl moiety to the aryl group is critical for a successful outcome.

Scheme 4. Reaction of 2-Allylphenol



Although a precise reaction mechanism cannot be definitively established, a proposal consistent with the current data is outlined in Scheme 5. The process most probably starts with the phenolic substrate **1** replacing one of the acetates of the catalyst to give intermediate **I**.[12] This complex might evolve to the rhodacycle **II** either through a typical concerted metalation−deprotonation step (CMD) or by an intramolecular electrophilic attack of the conjugated alkene to the electrophilic rhodium (**I**) followed by a base-assisted deprotonation to yield

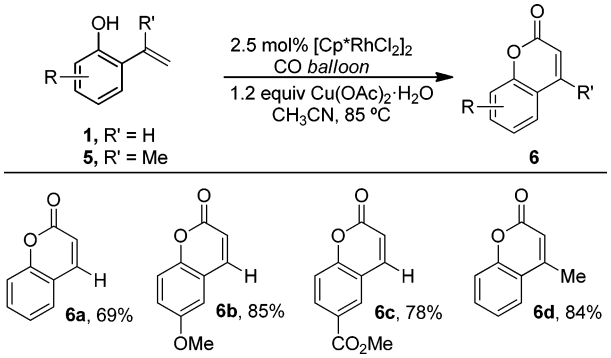
Scheme 5. Proposed Mechanistic Cycle



the re-aromatized intermediate (**II**). From intermediate **II** the process should involve alkyne coordination followed by migratory insertion to give intermediate **III**, which evolves through reductive elimination to the final product and a Rh(I) species which is then reoxidized to enter a new catalytic cycle.

Consistent with the formation of rhodacycle **II**, we found that treatment of the *o*-alkenyl phenols with carbon monoxide (balloon pressure) under the reaction conditions produces highly appealing coumarin products (**6**) in very good yields (Scheme 6).[13]

Scheme 6. Synthesis of Coumarins[a]



[a]Reaction conditions: 0.50 mmol of **1a**, $[Cp^*RhCl_2]_2$ (2.5 mol %), 1.2 equiv $Cu(OAc)_2·H_2O$, 2 mL of CH_3CN at 85 °C, carbon monoxide balloon, overnight.

In summary, we have developed the first example of a metal-catalyzed (5 + 2) cycloaddition formally involving a C−H activation process. The method provides a fast, efficient, and practical route to benzoxepines using commercial or readily available *o*-vinylphenols and alkynes as starting materials. Replacement of the alkyne component by carbon monoxide allows assembly of coumarin derivatives in a straightforward manner. Further mechanistic studies are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) NMR analysis of the reaction using an internal standard indicated that, while **3aa** was formed in 45% yield after 10 min of reaction, **3ga** was formed in 28% yield. The formation of the trifluoromethylaryl derivative **3ka** is also much slower than that of **3aa** (see SI for more details).

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