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

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Straightforward assembly of Benzoxepines and Coumarins by means of a Rhodium (III)-Catalyzed C-H Functionalization of *ortho*-vinylphenols

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Supporting Information Placeholder

ABSTRACT: Readily available *ortho*-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 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 to make 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, Bulbophyol B or Janoxepin (see Figure 1),[7] and therefore methods that allow their assembly from readily available precursors are of major interest.[8]
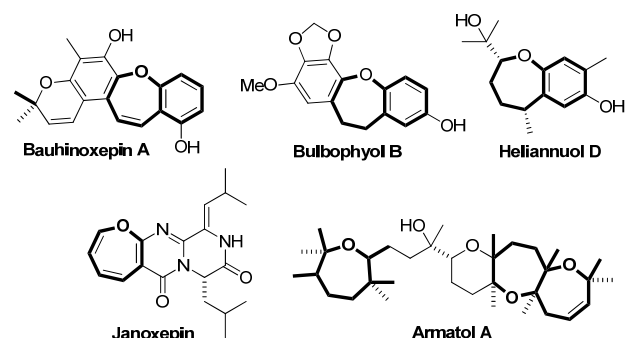
Our work started by identifying 2-hydroxystyrenes as readily available substrates that might engage in rhodium-catalyzed

Figure 1. Representative compounds containing the oxepine core.

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 of 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.[10]
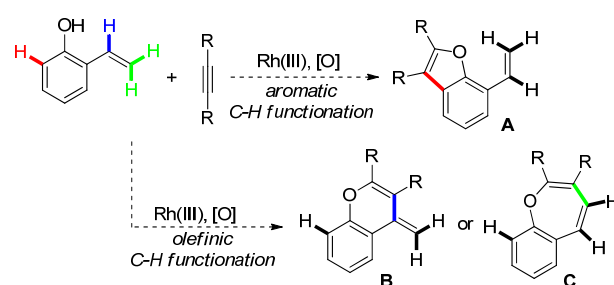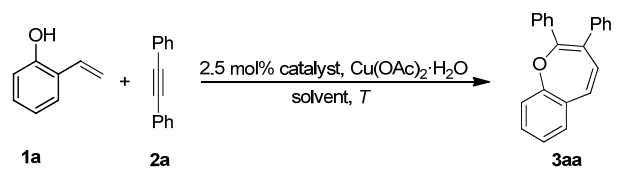

Figure 2. Different annulation options for *ortho*-vinylphenols using a Rh(III) catalyst.

Remarkably, reaction of alkyne **2a** with 2 equiv of 2-vinylphenol (**1a**) in presence of catalytic amounts of [Cp*RhCl$_2$]$_2$ (Cp* = pentamethylcyclopentadienyl) and 2.1 equivalents of Cu(OAc)$_2$·H$_2$O, in toluene at 100 ºC, did not give the benzofurane or chromene type of products, but the oxepine **3aa** in a 52% yield (Table 1, entry 1). Using [Cp*IrCl$_2$]$_2$ instead of the rhodium complex led to the majority recovery of the starting material, while RuCl$_2$(*p*-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 85ºC, entry 7).

With the optimized conditions in hand we investigated the scope with regard to the alkyne component (Scheme 1). Symmetrical alkynes bearing electron-rich or electron-deficient aryl substituents (**2b** and **2c**) led to the expected products **3ab** y **3ac** in good yields (85% and 71%). Dialkyl substituted alkynes like **2d**, **2e** and **2f**, also participate in the process, although the yields are slightly lower (52-65%).

Table 1. Optimization of the reaction[a]

entry	catalyst	1a (equiv)	solvent	T (°C)	yield (%)[b]
1	[Cp*RhCl₂]₂	2	Toluene	100	52
2	[Cp*IrCl₂]₂	2	Toluene	100	0
3	[RuCl₂(p-cymene)]₂	2	Toluene	100	traces
4	[Cp*RhCl₂]₂	2	DMF	100	72
5	[Cp*RhCl₂]₂	2	tAmylOH	100	83
6	[Cp*RhCl₂]₂	2	CH₃CN	85	91
7	[Cp*RhCl₂]₂	1.5	CH₃CN	85	97[c]
8	None	1.5	CH₃CN	85	0

[a] 0.33 mmol of **2a**, 2 mL of solvent, 2.1 equiv of Cu(OAc)₂·H₂O. [b] Isolated yield of **3aa** (based on **2a**). [c] 0.5 equiv. Cu(OAc)₂·H₂O/air balloon.

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 (**2h**, 99% yield, 8:1 regioselectivity) or with an alkyne bearing a hydroxy group like **2i** (65% yield, 11:1).
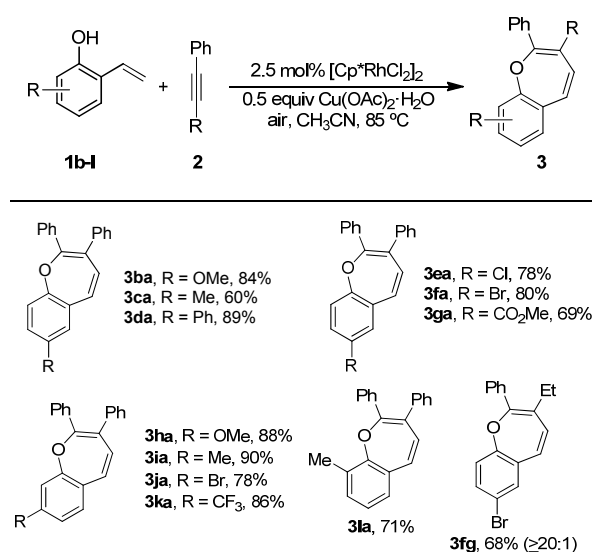
Scheme 1. Scope with respect to the alkyne component.[a,b]
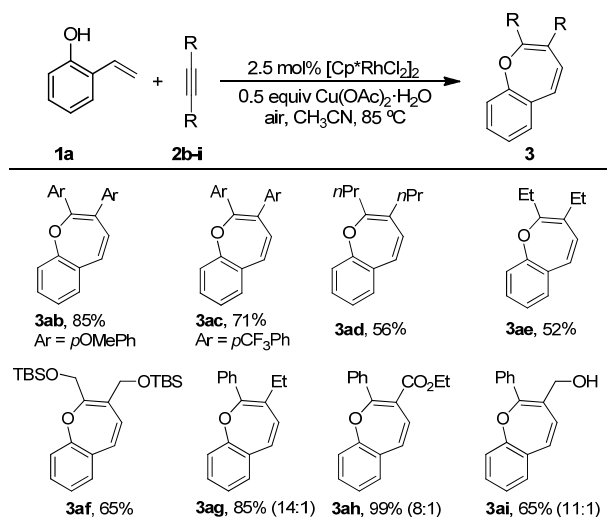
[a] Reaction conditions: 0.33 mmol of **2**, 0.5 mmol of **1a**, [Cp*RhCl₂]₂ (2.5 mol%), 0.5 equiv. Cu(OAc)₂·H₂O, 2 mL of CH₃CN at 85 °C, air balloon, overnight. [b] Isolated yield based on **2.**

The reaction is compatible with a wide variety of substituents in the aryl group of the vinylphenol (Scheme 2). The required phenolic substrates (**1b-l**), when no commercial, are easily assembled from the corresponding salicylaldehydes through a Wittig reaction with a methylenephosphorous ylide.

We first investigated the influence of the substituent in the *para* position to the hydroxyl group. As shown in the 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 *meta* position 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 and only one 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.

Scheme 2. Reaction with phenols equipped with different substituents.

[a] Reaction conditions: 0.33 mmol of **2**, 0.5 mmol of **1**, [Cp*RhCl₂]₂ (2.5 mol%), 0.5 equiv. Cu(OAc)₂·H₂O, 2 mL of CH₃CN at 85 °C, air balloon, overnight. [b] Isolated yield (based on **2**).

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). Curiously, in separate experiments we found that **1a** reacts slightly faster than **1g**.[11] These results are consistent with a an initial and irreversible formation of a phenoxide-Rh complex, as this might be easier for the more acidic substrate **1g**, and with subsequent steps less favourable for substrates with electron deficient phenyl rings.

Scheme 3. Competition experiments

3aa/3ga = 1:8
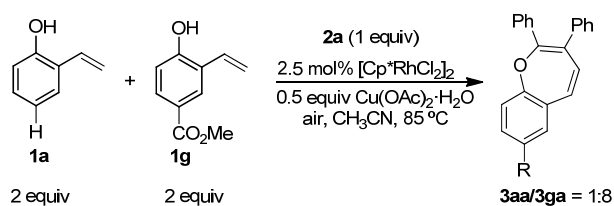
Of mechanistic relevance, treatment of allylphenol **4** with di-phenylacetylene under the standard conditions led to majoritary recovery of the starting materials (Scheme 4), which suggests that the conjugation of the vinyl moiety to the aryl group is critical for a successful outcome.

Scheme 4. Reaction of allyl phenol substrate
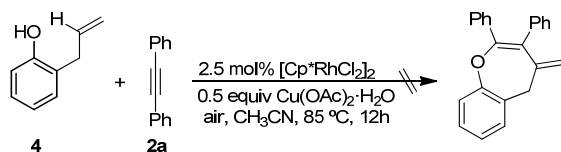
Although a precise reaction mechanism cannot be definitively established, a proposal consistent with the current data is outlined in Scheme 5. The process most probably starts with the phenolic substrate **1** replacing one of the acetates of the catalyst to give intermediate **I**. This complex might evolve to the rhodacycle **II** either through a typical concerted metallation-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 the rearomatized 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 re-oxidized to enter a new catalytic cycle.

Scheme 5. Proposed mechanistic cycle.

Consistent with the formation of rhodacycle **II**, we found that treatment of the *orto*-alkenyl phenols with carbon monoxide

(balloon pressure) under the reaction conditions produces highly appealing coumarin products (**6**) in very good yields.[12]

Scheme 6. Coumarins synthesis.

[a] Reaction conditions: 0.5 mmol of **1a**, [Cp*RhCl$_2$]$_2$ (2.5 mol%), 1.2 equiv. Cu(OAc)$_2$·H$_2$O, 2 mL of CH$_3$CN at 85 ºC, carbon monoxide balloon, overnight.
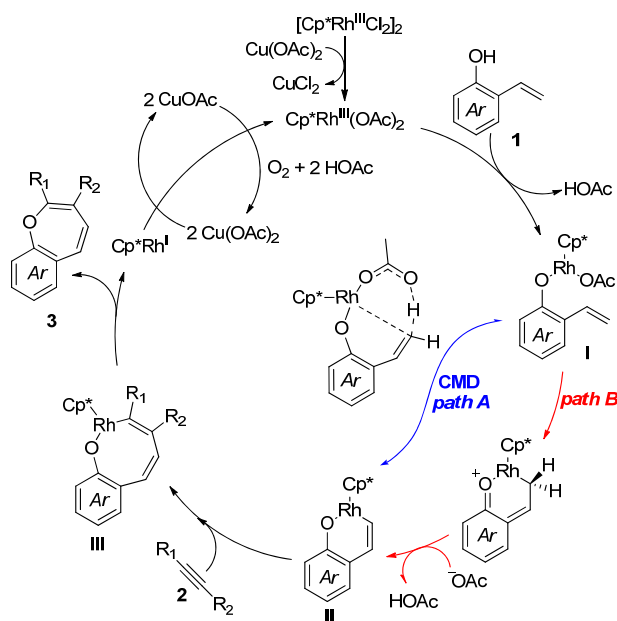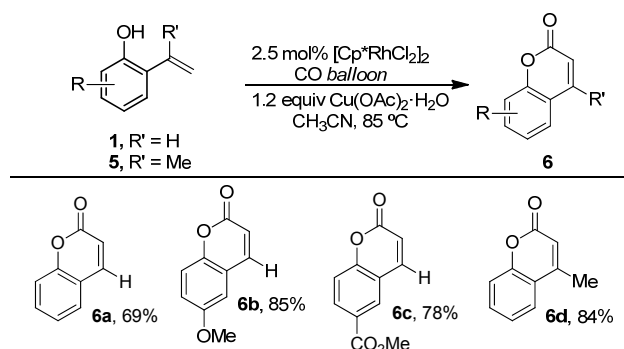
In summary, we have developed the first example of a metal-catalyzed (5+2) cycloaddition formally involving a C-H activation process. The method provides a fast, efficient and practical route to benzoxepines using commercial or readily available *orto*-vinylphenols and alkynes as starting materials. Replacement of the alkyne component by carbon monoxide allows to assemble coumarin derivatives in a straightforward manner. Initial studies suggest a potential new pathway for the C-H activation process involving a dearomatization/aromatization sequence.

ASSOCIATED CONTENT

Supporting Information

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 interests.

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