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Rhodium(III)-Catalyzed Dearomatizing (3 + 2) Annulation of 2-Alkenylphenols and Alkynes

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Supporting Information

ABSTRACT: Appropriately substituted 2-alkenylphenols undergo a mild formal [3C+2C] cycloaddition with alkynes when treated with a Rh(III) catalyst and an oxidant. The reaction, which involves the cleavage of the terminal C−H bond of the alkenyl moiety and the dearomatization of the phenol ring, provides a versatile and efficient approach to highly appealing spirocyclic skeletons and occurs with high selectivity.

Metal-catalyzed cycloadditions are among the most efficient tools to construct target-relevant cyclic products from simpler starting materials.[1] While most of these reactions require the activation of π-electrons of unsaturated precursors, the advent of the C−H activation chemistry[2] has brought new ways of achieving related annulations through a dehydrogenative cleavage of X−H and/or C−H bonds.[3] Given that the C−H activation step usually requires a heteroatom-directed group, most of these annulations have been used for the synthesis of heterocycles.[4] In clear contrast, cycloadditions that lead to carbocycles are much scarcer and essentially restricted to processes involving the activation of aromatic C−H bonds.[5] The discovery of new cycloadditions based on the activation of olefinic or aliphatic C−H bonds, which would allow the formation of carbocyclic products other than fused aromatic systems, is of foremost interest.[6]

Herein we describe a formal [3C+2C] cycloaddition between 2-alkenylphenols and alkynes that is catalyzed by Rh(III) under oxidative conditions. The reaction generates spirocyclic products in high yields and excellent regioselectivity and entails a dearomatization of the phenol ring (Figure 1, bottom). Preliminary experiments demonstrate that the spiro-cyclo-adducts can rearrange to interesting azulenones upon heating.

This work stems from our previous observation that *ortho*-vinylphenols react with alkynes in the presence of Rh(III) catalysts to give benzoxepine products (Figure 1, top).[7] In contrast to commonly proposed concerted metalation−deprotonation (CMD) mechanisms for the C−H activation step, some of our data suggested that in these reactions the formation of the key rhodacycle intermediate **B** might involve an alternative pathway involving the attack of the terminal position of the conjugated alkene to the electrophilic Rh complex, followed by rearomatization. To further study the scope of the process and gain more mechanistic insights, we explored the performance of alkenylphenol derivatives equipped with a substituent at the internal position of the alkene.

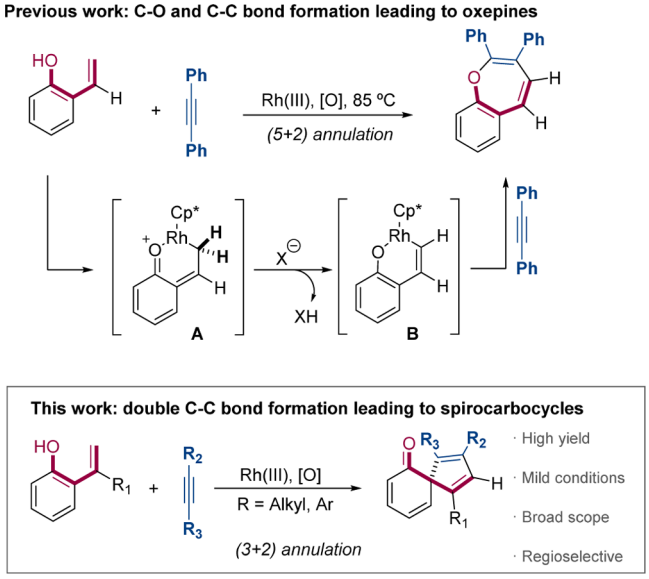

Figure 1. Rhodium(III)-catalyzed annulations of phenols with alkynes.

To our surprise, treatment of 2-(prop-1-en-2-yl)phenol (**1a**) with 1,2-diphenylethyne (**2a**), under the standard conditions developed for the synthesis of benzoxepines ($[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) and 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$, CH_3CN at 85 °C, 4 h, under air), gave a very low yield of the expected benzoxepine **3aa** (15% yield, entry 1, Table 1). The main products of the reaction were the spirocycle **4aa**, formally resulting from a [3C+2C] cycloaddition, and the azulenone **5aa**. Other solvents such as *t*-AmOH (entry 2) or toluene (entry 3) led to lower conversions. Performing the reaction in CH_3CN at room temperature led to moderate conversions, even after 24 h; however, the chemoselectivity was enhanced (entry 4). Slightly heating the reaction mixture at 40 °C allowed the formation of product **4aa** in an excellent 97% yield after less than 2 h of reaction (entry 5). The amount of $Cu(OAc)_2$ can be decreased up to 10% without significantly compromising the efficiency of the reaction (entry 6). We also tested the reaction in the presence of other metal complexes, such as $[Ru(p\text{-cymene})Cl_2]_2$ or $Pd(OAc)_2$, but the conversions were extremely poor (entries 7 and 8). As expected, the reaction does not take place in the absence of the Rh(III) complex (entry 9).

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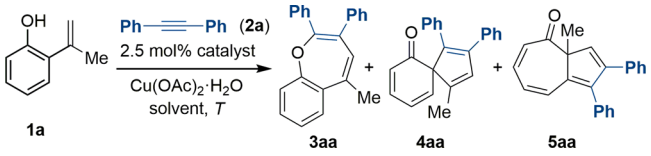
Table 1. Optimization of the Reaction[a]

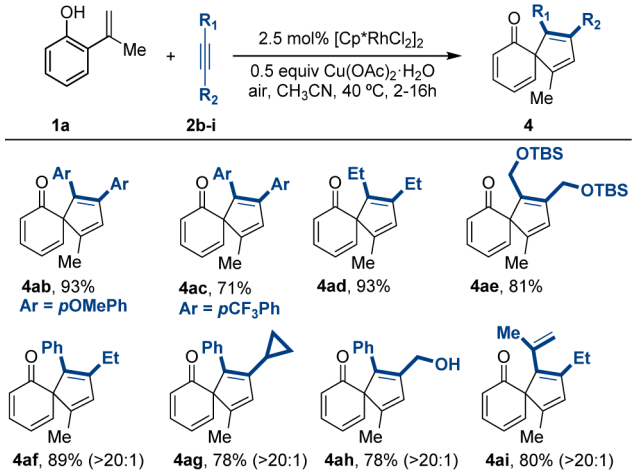


entry	catalyst	solvent	T (°C)	yield (%)[b] 3aa	4aa	5aa
1	$[Cp^*RhCl_2]_2$	CH_3CN	85	15	51	25
2	$[Cp^*RhCl_2]_2$	*t*-amylOH	100	12	18	15
3	$[Cp^*RhCl_2]_2$	toluene	100	8	19	17
4	$[Cp^*RhCl_2]_2$	CH_3CN	rt		44	4
5	$[Cp^*RhCl_2]_2$	CH_3CN	40		97[c]	trace
6	$[Cp^*RhCl_2]_2$	CH_3CN	40		91[d]	8
7	$[Ru(p\text{-cymene})Cl_2]_2$	CH_3CN	40		15	5
8	$Pd(OAc)_2$	CH_3CN	40		<10%	
9	none	CH_3CN	85			

[a]With 0.33 mmol of **2a**, 0.50 mmol of **1a**, 2 mL of solvent, 0.5 equiv of $Cu(OAc)_2{\cdot}H_2O$/air balloon. [b]Isolated yield of based on **2a**. [c]In 2 h. [d]With 0.1 equiv of $Cu(OAc)_2{\cdot}H_2O$, 16 h.

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

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 of $Cu(OAc)_2{\cdot}H_2O$, 2 mL of CH_3CN at 40 °C, air balloon. [b]Isolated yield based on **2**.

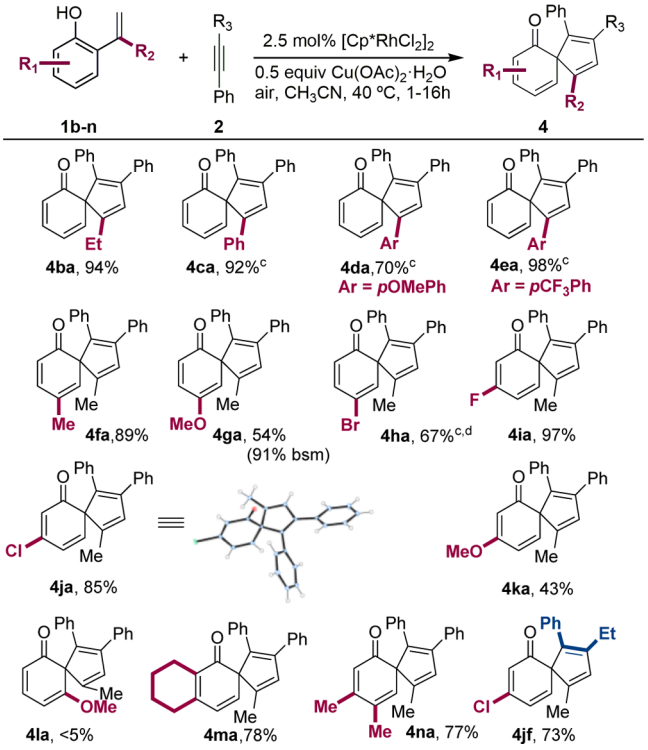
Symmetrical alkynes bearing electron-rich or electron-deficient aryl substituents (**2b** and **2c**) led to the expected products **4ab** and **4ac** in good yields (93 and 71%). Similar results were obtained with symmetrical dialkyl-substituted alkynes like **2d** and **2e** (93 and 81% isolated yields, respectively).

With nonsymmetrical alkynes, the reaction takes place with regioselectivity >20:1, as only one regioisomer was detected in the crude NMR mixture. Thus, alkyne **2f** afforded the product **4af** in an excellent 89% yield, and the cyclopropyl derivative **2g** gave **4ag** in 78% yield. The reaction tolerates free hydroxy groups in the alkyne substituents, therefore **4ah** could be isolated in 78% yield. The reaction also works with enynes like **2i**, which led to the expected cycloadducts with excellent chemo- and regioselectivity (**4ai**, 80% yield).

Next, we also analyzed the scope with respect to the alkenylphenol component by testing substrates **1b–n**, which were easily assembled from the corresponding salicylketones using a Wittig reaction with a methylenephosphorous ylide.[8]

As shown in Scheme 2, the success of the reaction is not restricted to the methylalkene derivative **1a** but also works with

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 of $Cu(OAc)_2{\cdot}H_2O$, 2 mL of CH_3CN at 40 °C, air balloon. [b]Isolated yield based on **2**. [c]At 60 °C. [d]With 18% of the azulenone also isolated in this reaction.

2-alkenylphenols bearing other substituents at the internal position of the alkene, such as ethyl, phenyl, or other aromatic groups. In all cases, the expected spirocyclic products were obtained in excellent yields (**4ba–4ea**, 70–98% yields), although in the substrates with aromatic substituents (**1c–e**), the reaction is slower and required heating at higher temperatures (60 °C) to obtain full conversions in 2 h. We also analyzed the reactivity of precursors with different substituents in the phenyl moiety of the alkenylphenol. Substituents *para* to the hydroxyl group are well-tolerated. While the methyl derivative **4fa** was isolated in an excellent 89% yield, the reaction of methoxy-substituted **1g** is slower and the expected product was isolated in 54% after 8 h (91% based on recovered starting material). The reaction of the bromo derivative **1h** was better carried out at 60 °C (67% of **4ha**), although at the cost of formation of 18% of the azulenone (**5ha**). Substrates **1i** and **1j**, equipped with a fluoro and a chloro group *para* to the alkenyl moiety, are excellent cycloaddition partners (85 and 97% yield, respectively).[9] The reaction is also compatible with the presence of a methoxy substituent at that position, although **4ka** was isolated in low yield due to the stability problems. In the case of substrates with substituents *ortho* to the alkenyl unit, the reaction does not proceed under standard conditions, perhaps because of a steric clash with the

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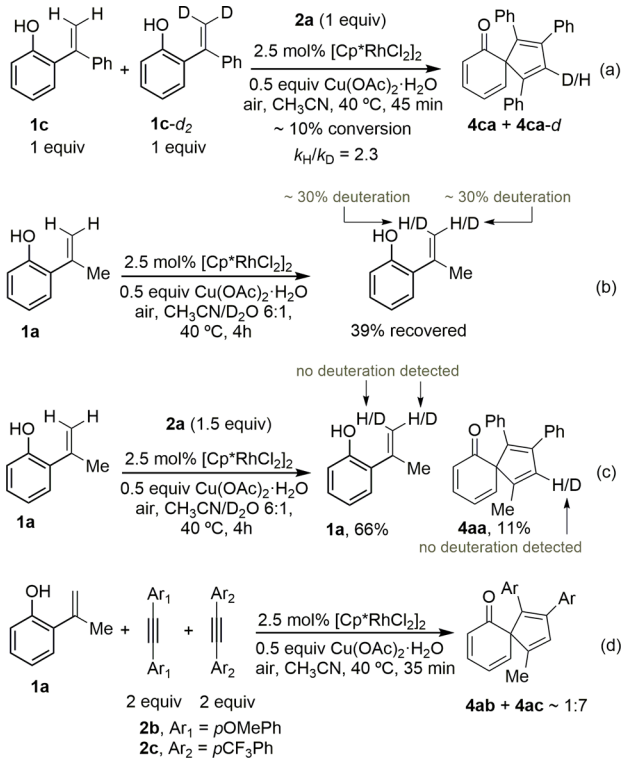
alkene substituent. Meanwhile, the phenyl-disubstituted substrates **1m**−**1n** gave the corresponding spirocycles **4ma** and **4na** in very good yields (78 and 77%). As expected, substrates with substituents at the phenyl ring also react with nonsymmetrical alkynes with total regioselectivity, as exemplified for the synthesis of **4jf**.

To obtain mechanistic information, we carried out several competition and deuteration experiments. An intermolecular competition between **1c** and the dideuterated analogue **1c**-d_2 allowed calculating a kinetic isotope effect k_H/k_D ~2.3, which suggests that the C−H bond cleavage is involved in a rate-determining step (Scheme 3, eq a). Interestingly, treatment of

Scheme 3. Competition Experiments

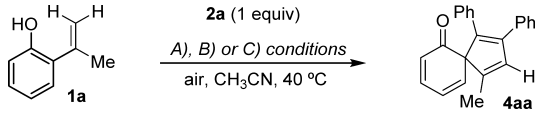


substrate **1a** with the standard reagents, in the absence of **2a**, and in the presence of D_2O, led to recovery of starting material with a significant incorporation of deuterium in both positions of the alkene (eq b). Carrying out the same reaction in the presence of diphenylacetylene **2a** at partial conversions led to the isolation of the nondeuterated products and starting materials (eq c). This lack of deuterium incorporation in this experiment suggests that the alkyne carbometalation is irreversible under the reaction conditions.[10]

Treatment of **1a** with a mixture of electron-rich and electron-poor alkynes **2b** and **2c** under standard conditions led to a preferential formation of product **4ac**, which would be explained in terms of an easier coordination and carbometalation of the electron-poor alkyne (eq d).

Control experiments using stoichiometric amounts of $[Cp^*RhCl_2]_2$ showed that, while this complex by itself is not able to produce cycloadducts, addition of CsOAc triggers a clean formation of the products (Scheme 4). Interestingly, the reaction can also be induced using other bases instead of acetate (Et_3N, TMP, or $KHPO_4^{2-}$). Therefore, the acetate ligand, which is

Scheme 4. Stoichiometric Experiments with Base

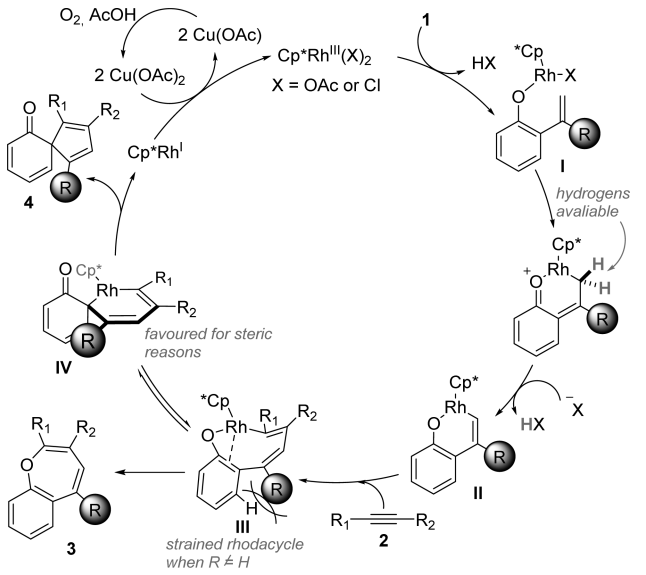


conditions A: $[Cp^*RhCl_2]_2$, 1 equiv, 1h, no reaction
conditions B: $[Cp^*RhCl_2]_2$, 1 equiv, CsOAc 2 equiv, 1h, 86% yield.
conditions C: $[Cp^*RhCl_2]_2$, 1 equiv, Et_3N 2 equiv, 4h, 64% yield.

normally associated with a CMD mechanism,[11] is not essential for the reaction (Scheme 4).

Based on the above information, a putative mechanism for the reaction is shown in Scheme 5. The catalytic cycle is likely

Scheme 5. Proposed Mechanistic Cycle



initiated by the phenolic substrate **1** replacing one of the ligands of the catalyst to give intermediate **I**. The subsequent C−H activation leading to the rhodacycle **II** would involve an intramolecular attack of the conjugated alkene to the electrophilic rhodium followed by rearomatization. Alkyne coordination followed by migratory insertion gives the eight-membered rhodacycle **III** that is in equilibrium with the keto form **IV**. While in the case of alkenylphenol substrates equipped with a nonsubstituted vinyl group the reductive elimination yields oxepine products, the presence of substituents in the alkenyl moiety generates a steric clash that favors a reductive elimination from the less strained rhodacyclohexane **IV**.[12] After the reductive elimination, the Rh(I) species is reoxidized by $Cu(OAc)_2$ to enter a new catalytic cycle.

As shown in Table 1, the annulation reaction, when carried out at higher temperatures (entry 1), in addition to the spirocyclic products generates significant amounts of an azulenone derivative (**5aa**). This product comes from the spirocycle because heating **4aa** in CH_3CN at 85 °C for 12 h produces a ~1:1 mixture of **4aa** and **5aa**. Interestingly, independent heating of an isolated sample of **5aa** for several hours leads to a mixture of both products, a result that confirms the reversibility of the process. This equilibrium may be explained in terms of a rearrangement involving the formation of a zwitterionic cyclopropyl alkoxide species **V** (Scheme 6, eq a).[13] Therefore, extremely simple substrates (**1a** and 1,2-diphenylethyne) can be converted into much more relevant, and structurally unrelated,

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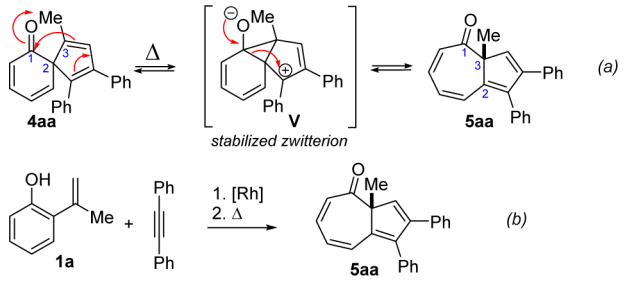
Scheme 6. Rationale for the Formation of 5aa



products (**5aa**) in a extremely straightforward manner (eq b). Further work to shift the equilibrium toward the azulenone and study the scope of this synthetic process is underway.

In summary, we have developed a new type of metal-catalyzed [3C+2C] cycloaddition that can be considered "anomalous" in terms of classical reactivity, as it involves the dehydrogenative cleavage of an O−H and a C−H bond, as well as a dearomatization of a phenyl ring. The reaction allows transforming extremely simple substrates into attractive, chiral spirocyclic products featuring an interesting array of substituents on olefinic positions. The reaction proceeds in an atom-economical manner and takes place with excellent chemo- and regioselectivity. Our results point out the potential of using substituents in key strategic positions of substrates to change reaction outcomes (oxepine vs spirocycle) because of the generation of steric interferences that affect key steps of the mechanism. Finally, preliminary results suggest that the spirocyclic products can be thermolyzed to interesting azulenone products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data 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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(8) See Supporting Information for more details.

(9) CCDC 995496 contains the crystallographic data of **4aj**, which can be obtained via www.ccdc.cam.ac.uk/data_request/cif. See Supporting Information for more information.

(10) Control experiments indicate that in the presence of $Cu(OAc)_2$ alone or CsOAc no deuterium incorporation was observed.

(11) For discussion on concerted metallation−deprotonation mechanisms, see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118−1126 and references therein.

(12) At higher temperatures, we observe formation of some benzoxepine product, which suggests that intermediates **III** and **IV** are in equilibrium.

(13) (a) A [1,5] sigmatropic rearrangement or radical-mediated mechanism may also be possible: Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187−217. (b) For a recent, related rearrangement, see: Li, X.-Y.; Yang, Y.-F.; Peng, X.-R.; Li, M.-M.; Li, L.-Q.; Deng, X.; Qin, H.-B.; Liu, J.-Q.; Qiu, M.-H. *Org. Lett.* **2014**, *16*, 2196−2199.