Rhodium-catalyzed (5+1) annulations between 2-alkenylphenols and allenes. A practical entry to 2,2-disubstituted *2H*-chromenes

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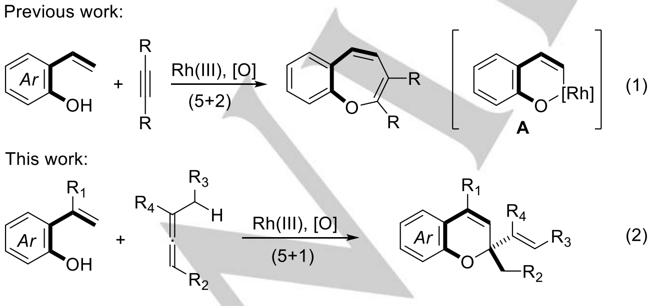
Abstract: Readily available alkenylphenols react with allenes under rhodium catalysis to provide valuable 2,2-disubstituted *2H*-chromenes. The whole process, which involves the cleavage of one C-H bond of the alkenyl moiety and the participation of the allene as 1C cycloaddition partner, can be considered as a simple, versatile and atom economical (5+1) hetero-annulation. The reaction tolerates a broad range of substituents both in the alkenylphenol and in the allene, and most probably proceeds through a mechanism involving a Rh-catalyzed C-C coupling followed by two sequential pericyclic processes.

In recent years there has been a boost in the development of transition-metal catalyzed reactions involving the cleavage of non-activated C-H bonds.[1] While in most of the cases these reactions entail functionalization processes, over the last years there have been also many reports on the development of annulation reactions.[2] In this context, we recently demonstrated that 2-alkenylphenols can be engaged in interesting annulations with alkynes using Rh(III) oxidative catalysis [Eq. (1); Scheme 1].[3] These reactions have been proposed to involve the formation of six-membered rhodacycles of type **A**. The synthetic and mechanistic relevance of the transformation called for exploring the performance of unsaturated partners other than alkynes. In particular, we were interested in checking the reactivity of allenes, very attractive unsaturated systems that have been scarcely studied in reactions involving the cleavage of C-H bonds.[4,5]



Scheme 1. Oxidative annulations of 2-alkenylphenols.

Herein we demonstrate that allenes react selectively with *ortho*-alkenylphenols, but instead of providing oxepine adducts, they work as one-carbon annulation components to give interesting 2,2-disubstituted chromenes [Eq. (2); Scheme 1]. Chromane and chromene skeletons, particularly those disubstituted at the carbon 2, are found in many biologically active molecules like those shown in the Figure 2, and the development of practical and versatile routes for their synthesis is of current interest.[6]

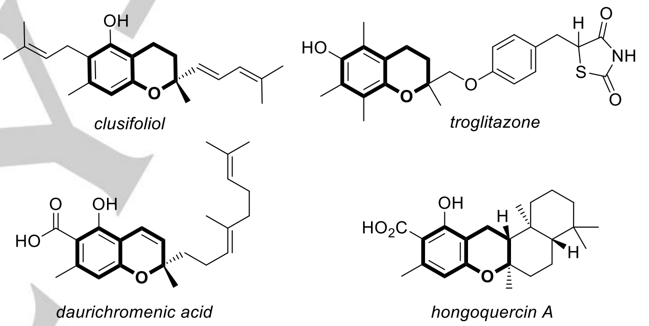


Figure 1. Some examples of pharmacologically relevant chromanes.

Initial reactivity assays were carried out using 2-(prop-1-en-2-yl)phenol (**1a**) and the commercially available vinylidenecyclohexane (**2a**) as allene partner. The reaction was carried out by heating a mixture of the phenol derivative with 0.7 equiv of the allene, in toluene at 100 ºC, in presence of 2.5% of [RhCp*Cl$_2$]$_2$ and 2.1 equivalent of Cu(OAc)$_2$·H$_2$O (Table 1, entry 1). After 1h we observed full conversion and the formation of a highly majoritary product that was identified as the chromene **3aa** (92% yield). Curiously, benzooxepine adducts like **4** were not detected under these conditions. We later found that the reaction can be preferable carried out in acetonitrile, because this solvent allowed decreasing the amount of copper to 0.5 equivalents (under an air atmosphere, entry 2). The reaction also works in other solvents such as dioxane, DMF or MeOH, although the yields were lower (entries 3 to 5). Other related catalysts such as [Ru(*p*-cymene)Cl$_2$]$_2$ or [IrCp*Cl$_2$]$_2$ led to poor conversions (entries 6 and 7). Controls experiments confirmed that the reaction does not take place in the absence of the Rh (III) catalyst or of the copper oxidant (entries 8 and 9).

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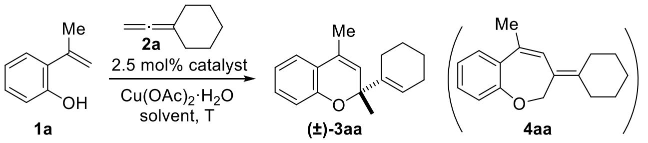
The novelty of the annulation and the relevance of the products led us to study the scope of the process. As shown in the Table 2, the reaction works well with other 1,1-disubstuted allenes such as **2b** or **2c**, which bear butyl or methyl substituents. In this latter case it was necessary to perform the experiment in a sealed tube because of the low boiling point of the allene. 1,3-Disubstituted allenes, such **2d** and **2e**, featuring alkyl or aromatic substituents, also participated in the annulation to give **3ad** and **3ae**, this latter as a single *E* diastereoisomer.

Table 1. Optimization of the annulation of 2-alkenylphenosl and allenes.[a]



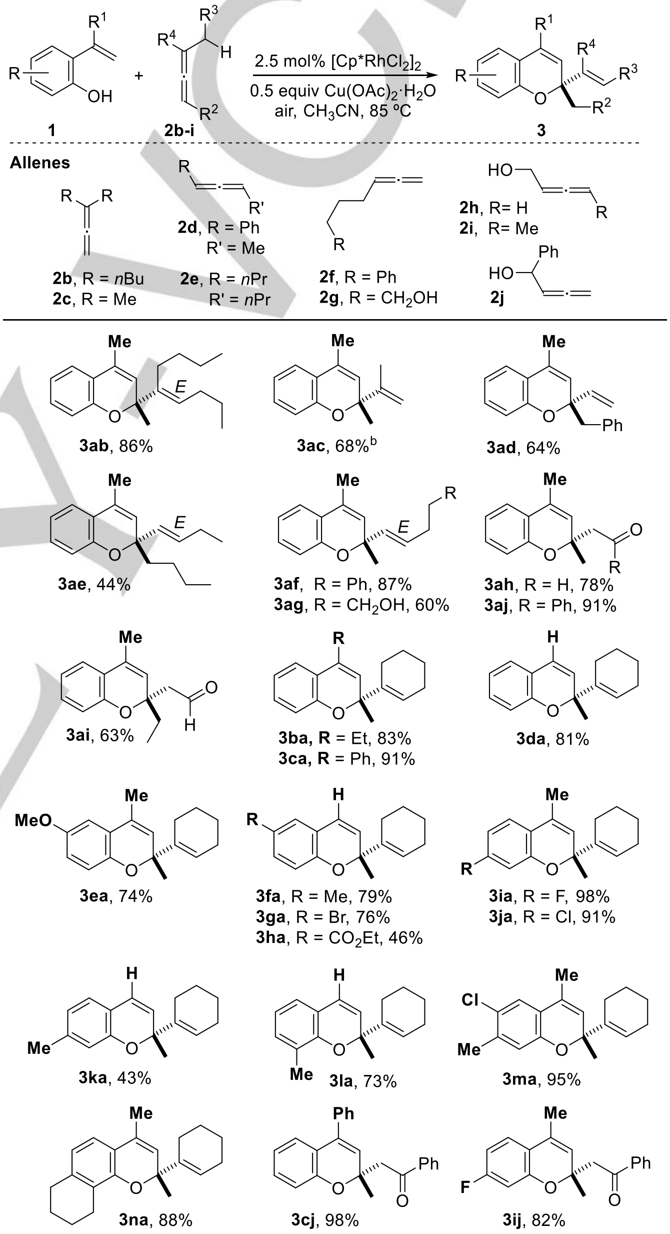
entry	Catalyst	solvent	T ºC	Yield **3aa** (%)[b]
1	$[RhCp^*Cl_2]_2$	toluene	110	92[c]
2	$[RhCp^*Cl_2]_2$	CH_3CN	85	90
3	$[RhCp^*Cl_2]_2$	dioxane	85	82
4	$[RhCp^*Cl_2]_2$	DMF	85	77
5	$[RhCp^*Cl_2]_2$	MeOH	65	54
6	[Ru(*p*-cymene)$Cl_2]_2$	CH_3CN	85	31
7	$[IrCp^*Cl_2]_2$	CH_3CN	85	13
8	-	CH_3CN	85	-
9[d]	$[RhCp^*Cl_2]_2$	CH_3CN	85	<5%

[a] 0.5 mmol of **1a**, 0.33 mmol of **2a**, 2 mL of solvent, 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$/air balloon, 2h. [b] Isolated yield based on **2a**. [c] 2.1 equiv. $Cu(OAc)_2 \cdot H_2O$. [d] Without $Cu(OAc)_2 \cdot H_2O$, 16h.

Similar results were obtained with the mono-substituted allenes **2f** and **2g**, which gave the expected products **3af** and **3ag** in 87 and 60% yield. Interestingly, allenyl alcohols **2h**, **2i** and **2j** led to the expected chromenes featuring a carbonyl group in the tether, with the formation of **3ai** being completely regioselective. Next we investigated the scope of the reaction with regard to the 2-alkenylphenol unit, using vinylidenecyclohexane as allene partner. As shown in the table, the reaction tolerates different substituents in the internal position of the alkene such as ethyl (**1b**) or phenyl (**1c**), but also works with 2-hydroxystyrene (**1d**). The process is also highly tolerant to the presence of substitutions in the aromatic ring, including electron-donor or acceptor groups in *para* to the hydroxyl substituent. Therefore products **3ea**-**3ha** could be obtained in good yields. 5-substituted phenol precursors also gave the desired chromenes like the fluoride **3ia**, chloride **3ja** or methyl derivative **3ka** (98, 91 and 43% yield, respectively).

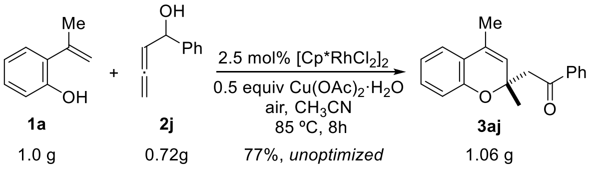
The reaction is also compatible with the presence of groups in *ortho* to the hydroxyl group of the phenol precursor, thus **3la** was obtained in 73%. Substrates with further substituents in the phenyl ring reacted to give the expected chromanes, such as **3ma** or **3na** (95 and 88% yield, respectively). As expected, it is possible to combine alkenylphenols other than **1a** with different allenyl derivatives, and therefore products like **3cj** and **3ij** can be obtained in good yields.

Table 2. Scope of the (5+1) annulation.[a-c]



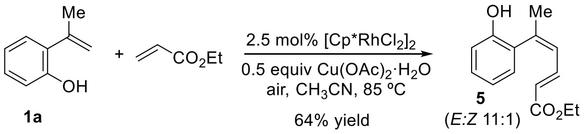
[a] 0.50 mmol of **1**, 0.33 mmol of **2**, 2 mL of CH_3CN, 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$/air balloon, 85 ºC, 1-4h. [b] Isolated yield of based on **2**. [c] Note that products **3** are racemic mixtures.

Overall the transformation represents a versatile and atom economical entry to a great variety of chromenes, and therefore we considered relevant to check its scalability. As shown in the Equation (3), a preliminary test with the allene **2j**, using 1 gram of the phenol, led to the expected product in good yield.



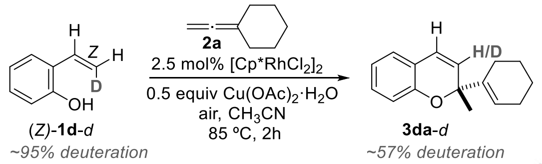
(3)

While the above data indicate that the alkenylphenol-allene annulation has a significant synthetic potential, its mechanism was intriguing. In this context it was important to know first the performance of alkenyl as opposed to allenyl partners, and therefore we treated the alkenylphenol **1a** with different alkenes under the standard reaction conditions. While non-activated alkenes were unreactive,[7] methylacrylate did react, but to give the conjugated diene **5** instead of a chromene product [Eq. (4)]. These results confirm the uniqueness of allenes to elicit the (5+1) annulation reactivity.



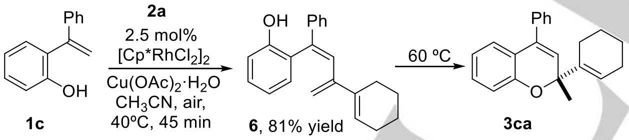
(4)

To gain more mechanistic information we carried out some experiments with deuterium-labeled substrates [Eq. (5)]. Interestingly, treatment of monodeuterated (*Z*)-**1d**-*d* (95% deuteration) with **2a** under the standard reaction conditions led to the expected product, but only with a 57% of deuteration at the labeled carbon (C3). This result is in consonance with our previous hypothesis that the formation of a rhodacycle of type **A** (see Scheme 1) might involve a dearomatization/rearomatization process instead of a more standard CMD type of mechanism.[8]



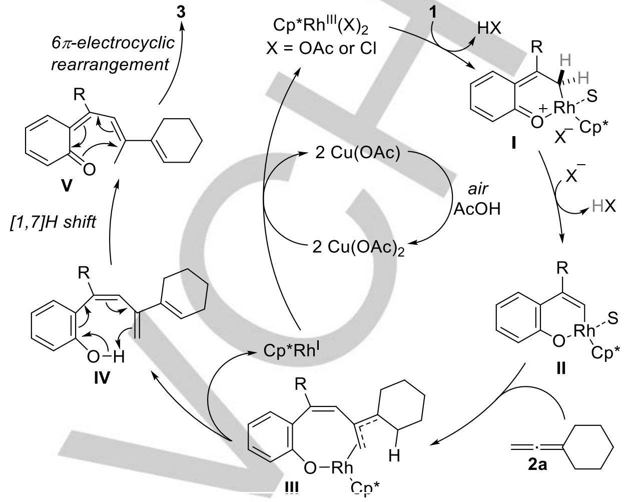
(5)

Particularly enlightening from the mechanistic point of view was the finding that when the reaction between **1c** and the allene **2a** is carried out at 40 ºC, the major product of the reaction is the diene **6**, that could be isolated and characterized.[9] Importantly, independent heating of this diene at 60 ºC in CD$_3$Cl produced the chromene **3ca** in quantitatively yield within minutes.



Scheme 2. Isolation of a key acyclic intermediate.

These results, together with the information acquired in previous studies on the cycloadditions of the alkenylphenols with alkynes,[3a,3b] suggest that the reaction might proceed through the mechanism indicated in the Scheme 3.[10] The catalytic cycle is likely initiated by coordination of the phenolic substrate **1** to a reactive Rh(III) complex generated in situ, followed by intramolecular attack of the conjugated alkene to the rhodium to give intermediate **I**,[11] which rapidly evolves by rearomatization to form a six-membered rhodacycle **II**. In a next step, allene coordination is followed by migratory insertion into the allene to give a π-allylic rhodacycle **III**. This intermediate, instead of undergoing a reductive elimination, evolves by β-hydride elimination,[12] to give the conjugated system **IV**, an intermediate that is poised to undergo a [1,7]-proton transfer to generate a dearomatized enone **V**, which evolves by means of a 6π-electrocyclic reaction to the observed chromene.[13] The Rh(I) species generated in the catalytic cycle is re-oxidized by Cu(OAc)$_2$ to the give active Rh(III) species.



Scheme 3. Mechanistic proposal.

In summary we have described a new rhodium-catalyzed oxidative annulation formally involving the cleavage of a C-H and the O-H bond of 2-alkenylphenols. Key for the success of the reaction is the use of allenyl derivatives as reaction partners. The transformation proposes a straightforward, atom economical access to highly appealing chromene skeletons, is operationally simple, allows "wet" solvents and air atmosphere, and requires trivial starting materials. The reaction proceeds through an intriguing sequential mechanism involving an initial Rh(III)-catalyzed addition followed by a [1,7] sigmatropic hydrogen shift and a 6π-electron electrocyclic ring closure.

Acknowledgements

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Keywords: C-H activation • chromene • rhodium • allene • alkenylphenol

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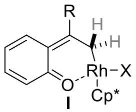
[7] Styrene and cyclohexene were the alkenes tested.

[8] Concerted Metalation-Deprotonation (CMD) mechanisms, generally proposed for the C-H activation step with Pd(II), Ru(II) or Rh(III), should provide non-deuterated products.

[9] The presence of a phenyl substituent in the intermediate **6** increases its thermal stability. In most of the other reactions, the dienic intermediates are not detected at 85 ºC, whereas at room temperature they evolve to the chromene products in minutes.

[10] The isolation of intermediate **6** comes to discard an alternative mechanism involving the formation of a rhodacyclobutane by intramolecular nucleophilic attack of the phenoxide to the central carbon of the π-allyl rhodium (**III**), followed by β-hydride elimination and reductive elimination.

[11] An intermediate with an acetate or chloride still bound to rhodium could be also proposed.



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X = OAc, Cl

[12] This may involve a previous protonolysis step of the Rh-O bond by the AcOH.

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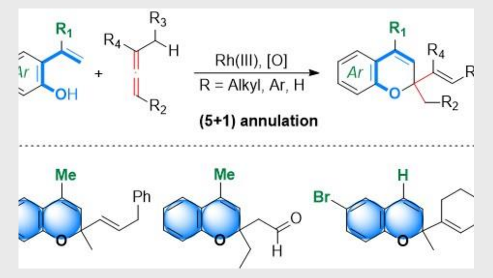
COMMUNICATION

The synthesis of *2H*-chromene skeletons was achieved by means of a Rh(III)-catalyzed oxidative annulation of 2-alkenylphenols and allenes. This unconventional (5+1) process involves the cleavage of the terminal C-H bond of the alkenyl moiety and the participation of the allene as one-carbon cycloaddition component.



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