Synthetic Methods

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# Rhodium-Catalyzed (5+1) Annulations Between 2-Alkenylphenols and Allenes: A Practical Entry to 2,2-Disubstituted 2*H*-Chromenes**

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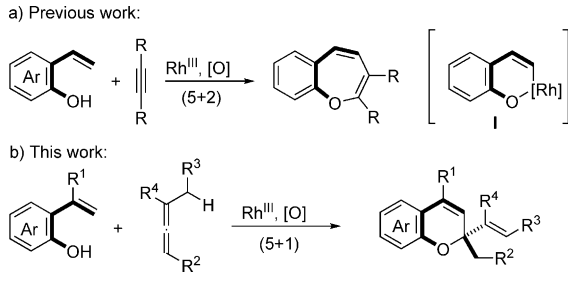
***Abstract:*** *Readily available alkenylphenols react with allenes under rhodium catalysis to provide valuable 2,2-disubstituted 2H-chromenes. The whole process, which involves the cleavage of one C–H bond of the alkenyl moiety and the participation of the allene as a one-carbon cycloaddition partner, can be considered a simple, versatile, and atom-economical (5+1) heteroannulation. 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 rhodium-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 also been 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 rhodium(III) oxidative catalysis (Scheme 1a).[3] These reactions have been proposed to involve the formation of six-membered rhodacycles of type **I**. 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, which are very attractive unsaturated systems and have been scarcely studied in reactions involving the cleavage of C–H bonds.[4,5]

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 (Scheme 1b). Chromane and chromene skeletons, particularly those disubstituted at C2, are found in many biologically active molecules such as those shown in the Figure 1, and the development of practical and versatile routes for their synthesis is of current interest.[6]




***Scheme 1.*** Oxidative annulations of 2-alkenylphenols.

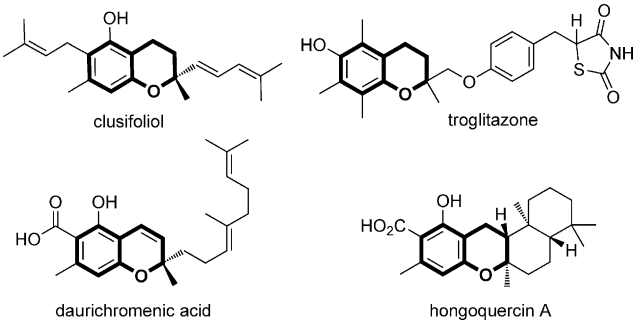



***Figure 1.*** Some examples of pharmacologically relevant chromanes.

Initial reactivity assays were carried out using 2-(prop-1-en-2-yl)phenol (**1a**) and the commercially available vinylidenecyclohexane (**2a**) as an allene partner. The reaction was carried out by heating a mixture of the phenol derivative with 0.7 equivalents of the allene, in toluene at 100 °C, in presence of 2.5 mol% of [{RhCp*$Cl_2$}$_2$] and 2.0 equivalents of Cu(OAc)$_2$·$H_2O$ (Table 1, entry 1). After 1 hour we observed full conversion and the formation of a major product which was identified as the chromene **3aa** (92% yield). Curiously, benzooxepine adducts like **4aa** were not detected under these reaction conditions. We later found that the reaction can be preferably carried out in acetonitrile, because this solvent allowed a decrease in the amount of copper to 0.5 equivalents (under an air atmosphere; entry 2). The reaction also works in other solvents such as 1,4-dioxane, DMF, or MeOH, although the yields are lower (entries 3–5). Other related catalysts such as [{Ru(*p*-cymene)$Cl_2$}$_2$] or [{IrCp*$Cl_2$}$_2$] led to poor conversions (entries 6 and 7). Control experiments confirmed that the reaction does not take place in the absence of the rhodium(III) catalyst or of the copper oxidant (entries 8 and 9).

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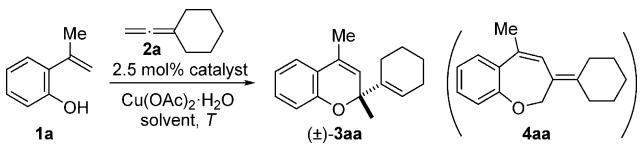
***Table 1:*** Optimization of the annulation of 2-alkenylphenols and allenes.[a]




| Entry | Catalyst | Solvent | $T$ [°C] | **3aa** Yield [%][b] |
|---|---|---|---|---|
| 1 | [{RhCp*Cl$_2$}$_2$] | toluene | 110 | 92[c] |
| 2 | [{RhCp*Cl$_2$}$_2$] | $CH_3CN$ | 85 | 90 |
| 3 | [{RhCp*Cl$_2$}$_2$] | 1,4-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 |

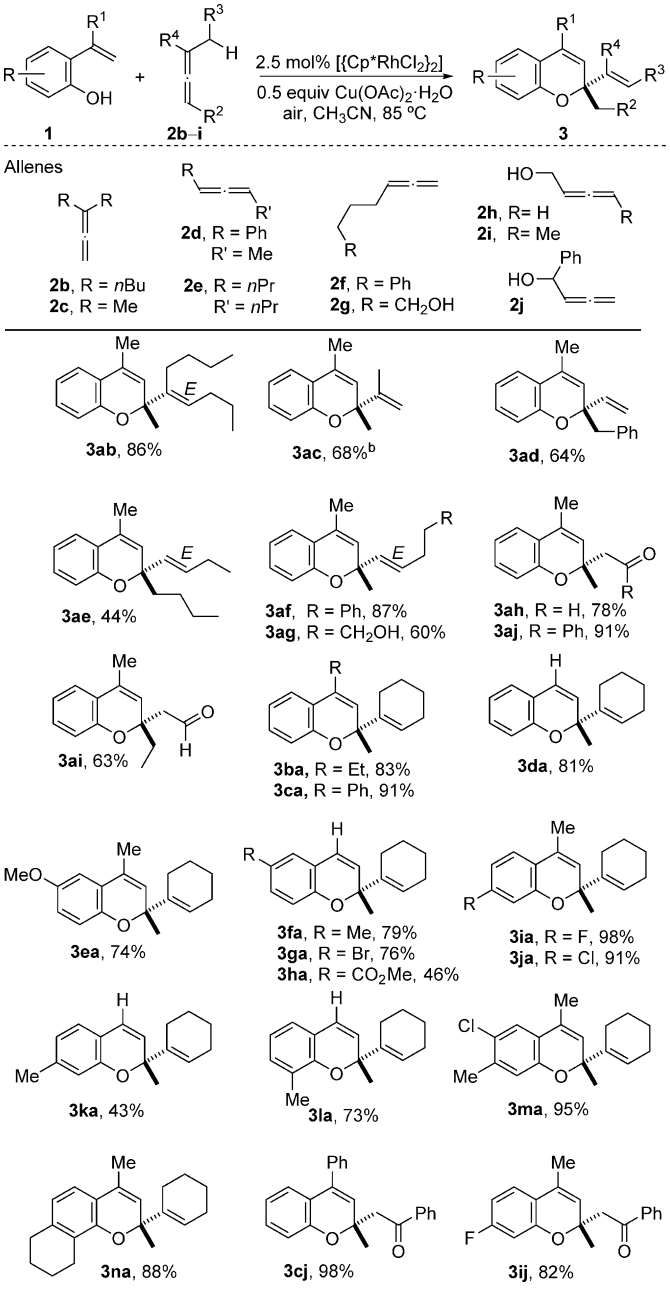
[a] Reaction conditions: **1a** (0.37 mmol), **2a** (0.25 mmol), solvent (2 mL), 0.5 equiv of Cu(OAc)$_2$·H$_2$O/air balloon, 2 h. [b] Yield of isolated product based on **2a**. [c] Used 2.0 equiv Cu(OAc)$_2$·H$_2$O. [d] Without Cu(OAc)$_2$·H$_2$O, 16 h. DMF = *N*,*N*-dimethylformamide, Cp* = $C_5Me_5$.

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** and **2c**, which bear butyl and methyl substituents, respectively. In the 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**, respectively, with the latter being delivered as a single *E* diastereoisomer.

Similar results were obtained with the monosubstituted allenes **2f** and **2g**, which gave the expected products **3af** (87%) and **3ag** (60%), respectively (Table 2). Interestingly, the 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 the 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 electron-acceptor groups in the *para* position to the hydroxy substituent. Therefore the products **3ea**–**ha** were obtained in good yields. 5-Substituted phenol precursors also gave the desired chromenes such as the fluoride derivative **3ia**, chloride **3ja**, and methyl derivative **3ka**. The reaction is also compatible with the presence of groups in the position *ortho* to the hydroxy 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**. As expected, it is possible to combine alkenylphenols other than **1a** with different allenyl derivatives, thus obtaining products such as **3cj** and **3ij** in good yields.

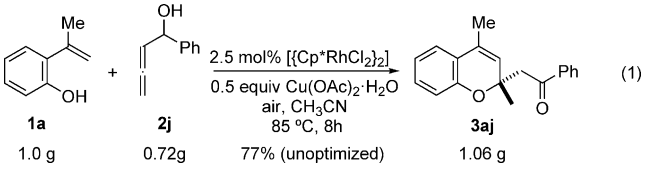
Overall the transformation represents a versatile and atom-economical entry to a great variety of chromenes, and

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



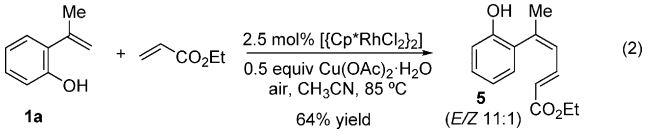

[a] Reaction conditions: **1** (0.37 mmol), **2** (0.25 mmol), $CH_3CN$ (2 mL), 0.5 equiv of Cu(OAc)$_2$·H$_2$O/air balloon, 85 °C, 1–4 h. [b] Yield of isolated product based on **2**. [c] Note that the products **3** are racemic mixtures.

therefore we considered it relevant to check its scalability. As shown in the Equation (1), a preliminary test with the allene **2j**, using 1 gram of the phenol, led to the expected product in good yield.



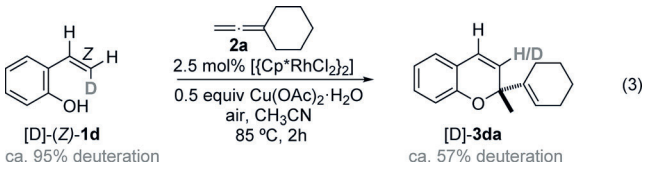

(1)

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 first understand the performance of alkenyl as opposed to allenyl partners, and therefore we treated **1a** with different alkenes under the standard reaction conditions. While non-activated alkenes were unreactive,[7] methylacrylate did react, but gave the conjugated diene **5** instead of a chromene product [Eq. (2)]. These results confirm the uniqueness of allenes to elicit the (5+1) annulation reactivity.



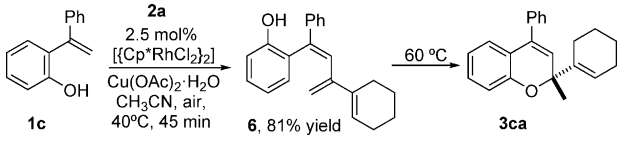
(2)

To gain more mechanistic information we carried out some experiments with deuterium-labeled substrates [Eq. (3)]. Interestingly, treatment of the monodeuterated [D]-(*Z*)-**1d** (95% deuteration) with **2a** under the standard reaction conditions led to the expected product, but only with a 57% deuteration at the labeled carbon (C3). This result is in keeping with our previous hypothesis that the formation of a rhodacycle of type **I** (Scheme 1) might involve a dearomatization/rearomatization process instead of a more standard concerted metalation-deprotonation type of mechanism.[8]



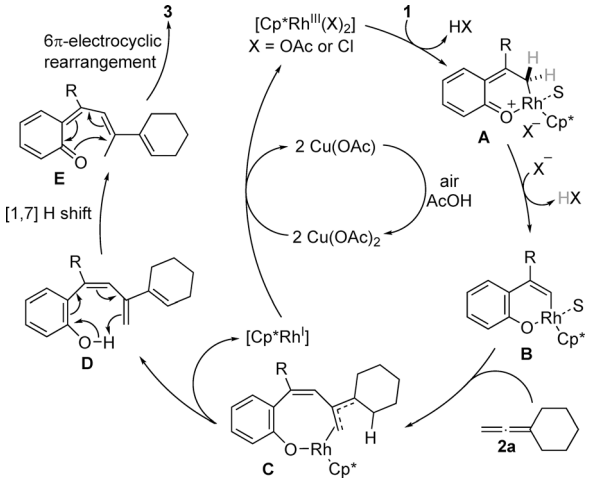
(3)

Particularly enlightening from the mechanistic point of view was the finding that when the reaction between **1c** and **2a** is carried out at 40 °C, the major product of the reaction is the diene **6**, which was isolated and characterized (Scheme 2).[9] Importantly, independent heating of this diene at 60 °C in $CD_3Cl$ produced the chromene **3ca** in quantitative 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,b] 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 rhodium(III) complex generated in situ, with subsequent intramolecular attack of the conjugated alkene on the rhodium to give the intermediate **A**,[11] which rapidly evolves by rearomatization to form a six-membered rhodacycle (**B**). In the next step, allene coordination is followed by migratory insertion to give the π-allylic rhodacycle **C**. This intermediate, instead of undergoing a reductive elimination, evolves through β-hydride elimination[12] to give the conjugated system **D**, an intermediate poised to undergo a [1,7]-proton transfer to generate the dearomatized enone **E**, which evolves by means of a 6π-electrocyclic reaction to the observed chromene.[13] The rhodium(I) species generated in the catalytic cycle is re-oxidized by $Cu(OAc)_2$ to the give active rhodium(III) species.




***Scheme 3.*** Mechanistic proposal.

In summary we have described a new rhodium-catalyzed oxidative annulation formally involving the cleavage of the C–H and 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, permits use of non-dried solvents and air, and requires trivial starting materials. The reaction proceeds through an intriguing sequential mechanism involving an initial rhodium(III)-catalyzed addition followed by a [1,7] sigmatropic hydrogen shift and a 6π-electron electrocyclic ring closure.

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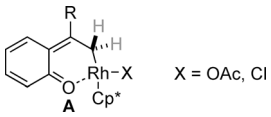
[7] Styrene and cyclohexene were the alkenes tested.

[8] Concerted metalation-deprotonation (CMD) mechanisms, generally proposed for the C–H activation step with palladium(II), ruthenium(II), or rhodium(III), should provide nondeuterated 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 °C, whereas at room temperature they evolve to the chromene products in minutes.

[10] The isolation of the intermediate **6** serves to eliminate the alternative mechanism involving the formation of a rhodacyclobutane by intramolecular nucleophilic attack of the phenoxide to the central carbon of the π-allyl rhodium (**C**), 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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