Practical, Large-Scale Preparation of Benzoxepines and Coumarins through Rhodium(III)-Catalyzed C–H Activation/Annulation Reactions

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Practical, Large-Scale Preparation of Benzoxepines and Coumarins through Rhodium(III)-Catalyzed C–H Activation/Annulation Reactions

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ABSTRACT

Herein we disclose the assembly of benzoxepines and coumarins from 2-alkenylphenol precursors using \([\text{Cp}^*\text{RhCl}_2]_2\) as pre-catalyst, and alkynes or carbon monoxide as reacting partners. The preparation of benzoxepines and coumarins can be scaled up to 33 mmol, using low catalyst loadings.

INTRODUCTION

Transition metal-catalyzed cycloadditions provide atom-economical approaches to heterocyclic products from simple and readily available reactants.\(^{1-3}\) Recently, a number of cycloaddition methodologies based on metal-promoted C–H activation have flourished.\(^4\) These strategies are very attractive for the Pharmaceutical Industry, as they avoid the use of functionalized substrates, and facilitate the shortening of synthetic routes.\(^5\) However, and despite the clear advantages of these ring-building methodologies, there are still important challenges to overcome for these technologies to be adopted for large-scale transformations. In many cases, metal-promoted C–H functionalization reactions require relatively complex experimental conditions, stoichiometric oxidants, high temperatures, and water-free atmospheres, which makes very difficult to scale-up the processes. Moreover, the usual need for high catalyst loadings of precious metals is also an important limitation. Therefore, most experiments dealing with transition metal-catalyzed reactions based on C–H activation have been carried out in a small scale.

Recently, as part of our research program on the discovery of metal-catalyzed C–H activation/annulation methods,\(^6\) we have disclosed rhodium-catalyzed formal (5+2) and (5+1)
cycloadditions of 2-alkenylphenols with either alkynes or carbon monoxide, respectively. These reactions provide a simple way to build benzoepine and coumarin skeletons,\textsuperscript{6g,7} a type of frameworks that form the basic structural motif of many bioactive natural products,\textsuperscript{8–11} and/or can be used as fluorescent probes in chemical biology.\textsuperscript{12}

**Scheme 1.** Rh-catalyzed synthesis of benzoepines and coumarins. Previous contributions.

**Figure 1.** Representative compounds bearing benzoepine or coumarin cores.

Our initial reports presented a limited scope, especially in the case of the coumarins and dealt with the synthesis of the products in a very small scale.\textsuperscript{6g} Considering that the experimental set-up is very simple, and that the reactions are tolerant to moisture and are carried out under air, we reasoned that it would be worth expanding the scope, and exploring large-scale applications. Herein we demonstrate that these annulations can be efficiently carried out in a large-scale,
multigram setup (33 mmol scale) and using small amounts of the rhodium catalyst (< 1 mol% catalyst). We also demonstrate that the rhodium-catalyzed (5+1) synthesis of coumarins presents a very good scope and can be used for the straightforward synthesis of relevant products.

RESULTS AND DISCUSSION

In the above rhodium-catalyzed processes, most of the experiments were carried out using between 2.5 and 5 mol% of the precious metal catalyst, which is too high in terms of cost and sustainability (Table 1). Therefore, we first explored the viability of decreasing the loading of the catalyst. Gratifyingly, using only 0.5 mol% of the rhodium complex, we were able to obtain the benzoxepine in a quite good 71% yield (Entry 1, Table 1). A slight increase in the amount of catalyst (0.75 mol%), yielded 3 in 79% yield (Entry 2, Table 1). The observation that after several hours the reaction mixture turns brown, suggested that the copper oxidant was readily consumed, and therefore we tested the reaction using an oxygen atmosphere. However, the yield was lower, likely because the vinylphenol degrades partially (Entry 3). Decreasing the amount of the copper-based oxidant to prevent this degradation resulted in a lower efficiency, even bubbling air through the mixture. We finally found that a slow addition of the 2-vinylphenol into the reaction mixture helped to prevent its degradation and allowed to isolate the cycloadduct in a satisfactory 84% yield (Entry 5).
Table 1. Optimization of the reaction conditions.\textsuperscript{a}

```
\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & [Rh] (mol \%) & Cu(OAc)\textsubscript{2} \cdot H\textsubscript{2}O (equiv) & Yield of 3 (%)\textsuperscript{b} \\
\hline
1 & 0.5 & 0.5 & 71 \\
2 & 0.75 & 0.5 & 79 \\
3 & 0.75 & 0.5 & 70\textsuperscript{c} \\
4 & 0.75 & 0.2 & 68\textsuperscript{d} \\
5 & 0.75 & 0.5 & 84\textsuperscript{d,e} \\
\hline
\end{tabular}
\end{table}
```

\textsuperscript{a} Reaction conditions: 5.6 mmol of 2a, 8.4 mmol of 1a, 35 mL of MeCN. \textsuperscript{b} Yields are of pure isolated product. \textsuperscript{c} Using an O\textsubscript{2} atmosphere. \textsuperscript{d} A continuous flow of air was bubbled through the reaction. \textsuperscript{e} 2-vinylphenol 1 was added over 2.5 h with a syringe pump.

At this point we explored the feasibility of performing the annulation in a multigram scale (33 mmol of the alkyne, Scheme 2). We were glad to find that the reaction can be efficiently performed at this large scale, not only with 2-vinylphenol (1a) but also with other precursors containing substitutions on the aromatic ring. Therefore, products 3ba and 3ca could be obtained in synthetically useful yields. The formation of 3ba confirms that the reaction tolerates aryl bromides, which are usually sensitive to transition metals. On the other hand, when diphenylacetylene is replaced by but-1-yn-1-ylbenzene, the corresponding cycloadduct 3ab was also obtained in near 60\% yield, with complete control of the regioselectivity.
Scheme 2. Large-scale preparation of benzoxepines via Rh-catalyzed (5+2) cycloaddition of 2-vinylphenols and alkynes.\textsuperscript{a,b}

\[ \text{RH} \quad \begin{array}{c}
\text{OH} \\
\text{R}_1\text{-C=C-} \\
\end{array} 
\begin{array}{c}
\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} \quad (0.75 \text{ mol %}) \\
\text{MeCN, 85 }\text{ºC, 16 h} \\
\end{array} 
\begin{array}{c}
\text{R}_2
\end{array} 
\begin{array}{c}
\text{R}_3
\end{array} \rightarrow \begin{array}{c}
\text{R}_4
\end{array} \begin{array}{c}
\text{R}_5
\end{array} \]

\[ 3 \text{aa, 85%} \quad 3 \text{ba, 63%}\text{c} \quad 3 \text{ca, 67%}\text{d} \quad 3 \text{ab, 58% (>20:1)} \]

\text{a} Reaction conditions: 33 mmol of 2, 49.5 mmol of 1, 0.75 mol % \([\text{Cp*RhCl}_2]\)\textsubscript{2} and 0.5 equiv \Cu(OAc)\textsubscript{2}·H\textsubscript{2}O in 200 mL of MeCN.\textsuperscript{b} Yields are of pure isolated products. \textsuperscript{c} 1 mol % of \([\text{Cp*RhCl}_2]\)\textsubscript{2}. \textsuperscript{d} Reaction run for 36 h.

We then devoted our efforts to expanding the scope of the rhodium-catalyzed formal (5+1) cycloaddition between 2-alkenylphenols and carbon monoxide. In 2014, our group reported preliminary examples demonstrating the feasibility of the process, but we did not explore its scope.\textsuperscript{6g,12} We have now found that the reaction tolerates different substitutions in both the aromatic and the alkene moiety of the substrate. Therefore, products 4d and 4e, resulting from the use of aryl substituted vinylphenols, were obtained in good yields (56% for 4d and 74% for 4e, respectively). Substituents in the internal position of the alkene are compatible with the reaction, with 4f being isolated in an 86% yield. 2-Alkenylphenols bearing a methyl group in the internal position of the alkene, and with meta- and para-halogen substitution relative to the hydroxy substituent, also participated in the annulation, to give the corresponding coumarin products with a 53% yield for 4g and 69% yield for 4h. 2-Alkenylphenols with more than one substitution in the aromatic ring also led to very good yields of the expected highly functionalized products (4j and 4k). Finally, the reaction not only works with methyl substituted...
alkenes, but ethyl and aryl substituents are also well tolerated, and products 4l and 4m were efficiently formed and isolated. Importantly, the synthesis of coumarins can also be carried out in a multigram scale with no erosion on the reaction yields, as exemplified by a 33 mmol scale synthesis of 4f. This reaction allowed to produce up to 4.7 g of this product in a single reaction.

**Scheme 3.** Assembly of coumarins via Rh-catalyzed (5+1) cycloaddition of 2-alkenylphenols and carbon monoxide.\textsuperscript{a,b}

\[ \text{Reaction conditions: } 0.5 \text{ mmol of } 1, \ 2.5 \text{ mol } \% \text{ of } [\text{Cp}^*\text{RhCl}_2], \ 1.2 \text{ equiv Cu(OAc)}_2\cdot\text{H}_2\text{O} \text{ in } 2 \text{ mL of MeCN.} \]

\[ \text{Yields are of pure isolated products.} \]

\[ \text{33 mmol scale reaction.} \]

The simplicity of the method prompted us to use it for the synthesis of biorelevant coumarins, such as 7-(pyridin-3-yl)coumarin (5), an inhibitor of the aromatase CYP19, used for post-menopausal breast cancer treatment;\textsuperscript{13} and the natural product osthole (6), which has been found in several medicinal plants such as *Cnidium monnieri* and presenting interesting medicinal properties\textsuperscript{14}. Coumarin 5 was obtained in only two steps from 4-bromo-2-hydroxybenzaldehyde (1b), by using our carbonylation reaction to give 4b (67% yield) and a subsequent Suzuki-
Miyaura coupling\textsuperscript{15} (Scheme 4). On the other hand, osthole (8) was prepared from commercially available 2-hydroxy-4-methoxybenzaldehyde (6) in a four-step sequence. 2-Hydroxy-4-methoxybenzaldehyde (6) was transformed into brominated and iodinated vinylphenols 1\textsubscript{n} and 1\textsubscript{m} by halogenation followed by Wittig reaction with PPh\textsubscript{3}MeBr.\textsuperscript{16} Coumarins 4\textsubscript{n} and 4\textsubscript{m} were then assembled using our rhodium-catalyzed carbonylation, in 57\% and 37\% yield respectively. The synthesis was completed using a Stille coupling with the corresponding allyl stannane.\textsuperscript{17}

**Scheme 4.** Synthesis of the CYP19 inhibitor 5, and the natural product osthole (8).

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**CONCLUSION**

A practical, economical and scalable process has been developed for the preparation of benzoxepines from simple 2-alkenylphenol and alkyne precursors. The reactions can be carried out using only 0.75 mol\% of the precious metal catalysts (rhodium complex). Using carbon monoxide instead of alkynes as reaction partner allow to produce a variety of coumarins
featuring different substitutions. This reaction is also amenable of being carried out in a multigram scale, using a very simple experimental setup. We have applied this last reaction to the synthesis of two biorelevant coumarins.

EXPERIMENTAL SECTION

Experimental procedure for the large-scale Rh-catalyzed preparation of benzoxepines

In a two-neck round bottomed flask equipped with a condenser and sealed with a rubber septum, the corresponding alkyne (33 mmol) was added to a solution of [Cp*RhCl₂]₂ (153 mg, 0.75 mol%) and Cu(OAc)₂·H₂O (3.29 g, 0.5 equiv) in MeCN (200 mL) under continuous air flow. The reaction was then heated up to 85 °C and the corresponding 2-vinylphenol (49.5 mmol, 1.5 equiv) was added dropwise for 2.5 h via syringe pump. The reaction was stirred for the given time. After that time the reaction was filtered through Celite® and washed with hexanes and diethyl ether. The solvents were removed in vacuo and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding benzoxepines 3aa-3ab.

Experimental procedure for the Rh-catalyzed preparation of coumarins

To a solution of [Cp*RhCl₂]₂ (7.7 mg, 2.5 mol%) and Cu(OAc)₂·H₂O (120 mg, 1.2 equiv) in MeCN (2 mL) purged with CO was added the corresponding 2-alkenylphenol (0.5 mmol). The reaction was sealed with a rubber septum and a CO atmosphere was injected in the flask with a balloon. The reaction mixture was heated up to 85 °C and stirred for 16 hours and then cooled to room temperature. The reaction was filtered through Celite and washed with hexanes and diethyl ether. The solvents were removed in vacuo and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding coumarin products 4d-4m.
Experimental procedure for the large-scale Rh-catalyzed preparation of coumarins, and characterization of the products

In a two-neck round bottomed flask equipped with a condenser and sealed with a rubber septum, the corresponding 2-alkenylphenol (33 mmol) was added to a solution of [Cp*RhCl₂]₂ (510 mg, 2.5 mol%) and Cu(OAc)₂ H₂O (7.91 g, 1.2 equiv) in MeCN (135 mL), the resulting mixture was purged with CO and a CO atmosphere was injected in the system with a balloon. The reaction was heated up to 85 °C and stirred for 16 hours at that temperature. After that time the reaction was cooled to room temperature. The reaction was filtered through Celite and washed with hexanes and diethyl ether. The solvents were removed in vacuo and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding coumarin product 4f.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data and spectra and other information included.

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