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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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Supporting Information

ABSTRACT: Herein we disclose the assembly of benzoxepines and coumarins from 2-alkenylphenol precursors using $[Cp^*RhCl_2]_2$ as the precatalyst 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.

KEYWORDS: *multigram-scale synthesis, benzoxepines, coumarins, cycloadditions, Rh catalysis, C−H activation*

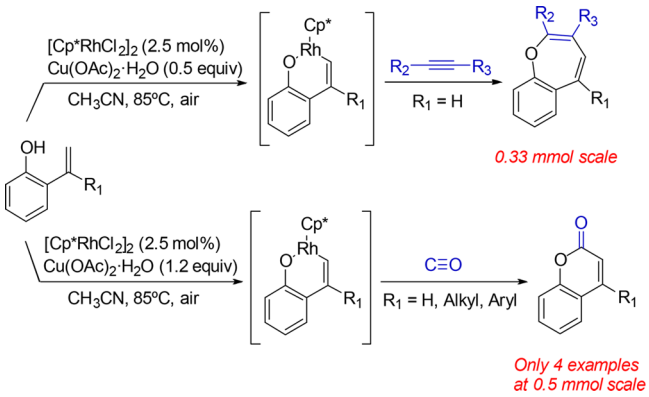
INTRODUCTION

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 prefunctionalized substrates and facilitate the shortening of synthetic routes.[5] However, 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, making scale-up of these processes very difficult. Moreover, the usual need for high catalyst loadings of precious metals is an important limitation. Therefore, most experiments dealing with transition metal-catalyzed reactions based on C−H activation have been carried out on a small scale.

Recently, as part of our research program on the discovery of metal-catalyzed C−H activation/annulation methods,[6] we disclosed rhodium-catalyzed formal (5 + 2) and (5 + 1) cycloadditions of 2-alkenylphenols with alkynes and carbon monoxide, respectively (Scheme 1). These reactions provide a simple route towards benzoxepine and coumarin skeletons,[6g,7] which are frameworks that form the basic structural motifs of many bioactive natural products[8−11] (Figure 1) and/or can be used as fluorescent probes in chemical biology.[12]

Our initial reports presented a limited scope, especially in the case of the coumarins, and dealt with the synthesis of the products on a very small scale.[6g] Considering that the experimental setup is very simple and that the reactions are tolerant to moisture and 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) 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.

Scheme 1. Rh-Catalyzed Synthesis of Benzoxepines and Coumarins: Previous Contributions



RESULTS AND DISCUSSION

In the aforementioned rhodium-catalyzed processes, most of the experiments were carried out using between 2.5 and 5 mol % loadings of the precious metal catalyst, which are 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 a 0.5 mol % loading of the rhodium complex, we were able to obtain benzoxepine **3aa** in a quite good 71% yield (entry 1, Table 1). A slight increase in the amount of catalyst (0.75 mol %) yielded **3aa** in 79% yield (entry 2). The observation that after several hours the reaction mixture turned 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

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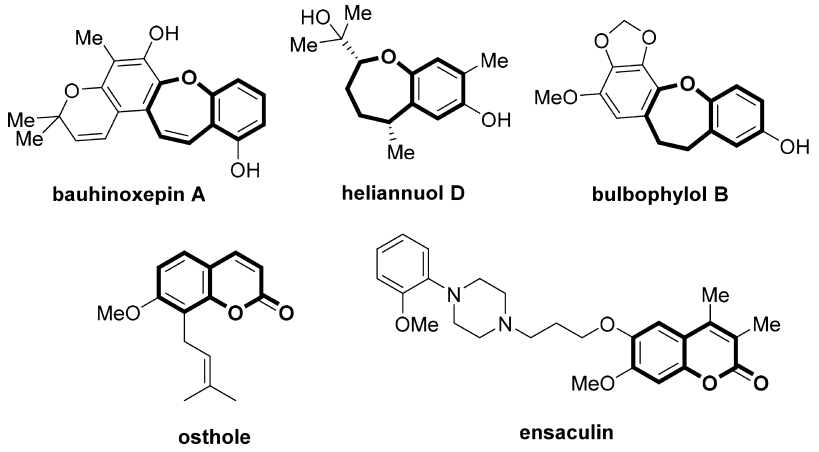
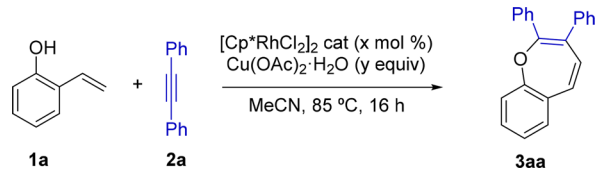


Figure 1. Representative compounds bearing benzoxepine or coumarin cores.

Table 1. Optimization of the Reaction Conditions[a]



entry	[Rh] loading (mol %)	equiv of $Cu(OAc)_2·H_2O$	yield of **3aa** (%)[b]
1	0.5	0.5	71
2	0.75	0.5	79
3	0.75	0.5	70[c]
4	0.75	0.2	68[d]
5	**0.75**	**0.5**	**84**[d,e]

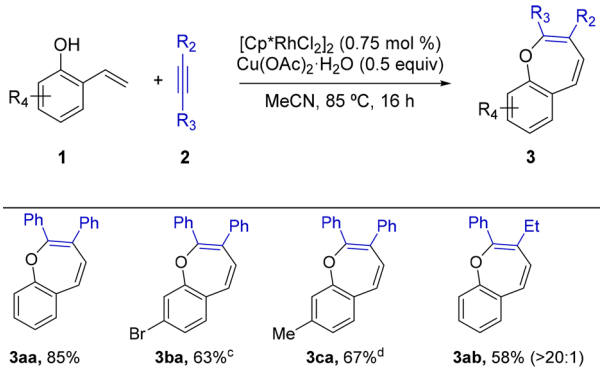
[a]Reaction conditions: 5.6 mmol of **2a**, 8.4 mmol of **1a**, and 35 mL of MeCN. [b]Yields of pure isolated products. [c]Using an O_2 atmosphere. [d]A continuous flow of air was bubbled through the reaction mixture. [e]2-Vinylphenol **1a** was added over 2.5 h with a syringe pump.

because the vinylphenol partially degraded (entry 3). Decreasing the amount of the copper-based oxidant to prevent this degradation resulted in a lower efficiency, even when air was bubbled through the mixture (entry 4). We finally found that slow addition of the 2-vinylphenol into the reaction mixture helped to prevent its degradation and allowed the cycloadduct to be isolated in a satisfactory 84% yield (entry 5).

At this point we explored the feasibility of performing the annulation on a multigram scale (33 mmol of the alkyne) (Scheme 2). We were glad to find that the reaction can be efficiently performed on 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** were obtained in synthetically useful yields. The formation of **3ba** confirmed that the reaction tolerates aryl bromides, which are usually sensitive to transition metals. On the other hand, when diphenylacetylene was replaced by but-1-yn-1-ylbenzene, the corresponding cycloadduct **3ab** was also obtained in nearly 60% yield with complete control of the regioselectivity.

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.[6g] We have now found that the reaction tolerates different substitutions on both

Scheme 2. Large-Scale Preparation of Benzoxepines via Rh-Catalyzed (5 + 2) Cycloaddition of 2-Vinylphenols and Alkynes[a,b]



[a]Reaction conditions: 33 mmol of **2**, 49.5 mmol of **1**, 0.75 mol % $[Cp*RhCl_2]_2$, and 0.5 equiv of $Cu(OAc)_2·H_2O$ in 200 mL of MeCN. [b]Yields of pure isolated products are shown. [c]Using 1 mol % $[Cp*RhCl_2]_2$. [d]The reaction was run for 36 h.

the aromatic moiety 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**; Scheme 3). Substituents at the internal position of the alkene are compatible with the reaction, with **4f** being isolated in 86% yield. 2-Alkenylphenols bearing a methyl group at the internal position of the alkene, and with *m*- and *p*-halogen substitution relative to the hydroxy substituent also participated in the annulation to give the corresponding coumarin products **4g** in 53% yield and **4h** in 69% yield. 2-Alkenylphenols with more than one substituent on 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 on a multigram scale with no erosion of the reaction yield, as exemplified by the 33 mmol scale synthesis of **4f**. This reaction allowed up to 4.7 g of this product to be obtained in a single 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 that

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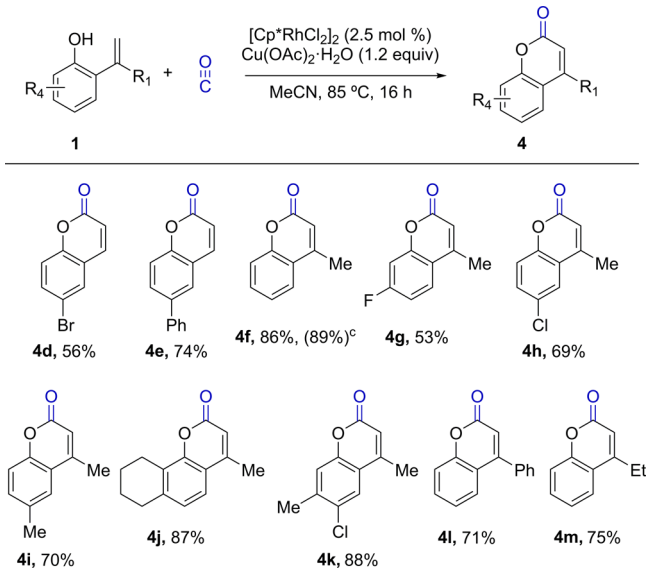
Org. Process Res. Dev. 2019, 23, 1669−1673

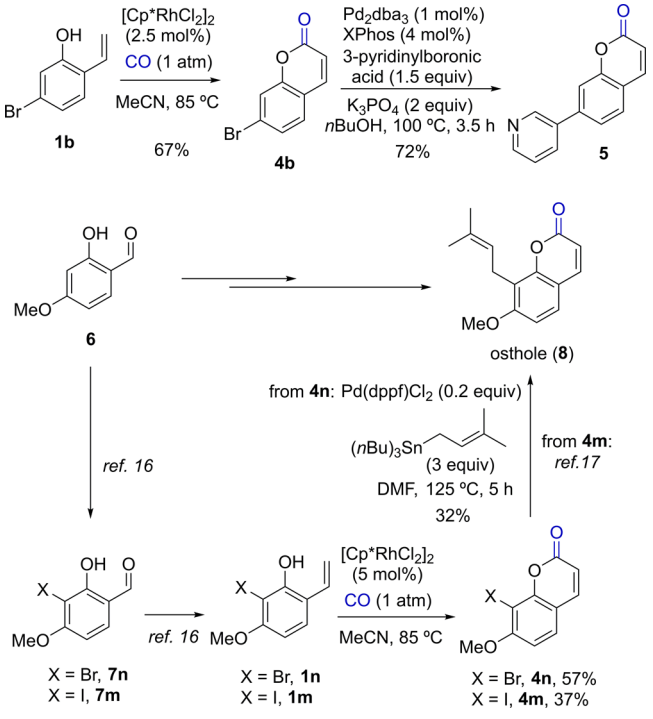
Scheme 3. Assembly of Coumarins via Rh-Catalyzed (5 + 1) Cycloaddition of 2-Alkenylphenols and Carbon Monoxide[a,b]



[a]Reaction conditions: 0.5 mmol of **1**, 2.5 mol % $[Cp^*RhCl_2]_2$, and 1.2 equiv of $Cu(OAc)_2{\cdot}H_2O$ in 2 mL of MeCN. [b]Yields of pure isolated products are shown. [c]33 mmol scale reaction.

is used for postmenopausal breast cancer treatment,[13] and the natural product osthole (**8**), which has been found in several medicinal plants such as *Cnidium monnieri* and presents interesting medicinal properties.[14] Coumarin **5** was obtained in only two steps from 5-bromo-2-vinylphenol (**1b**) using our carbonylation reaction to give **4b** (67% yield) and a subsequent Suzuki–Miyaura coupling[15] (Scheme 4). On the other hand, osthole was prepared from commercially available 2-hydroxy-4-methoxybenzaldehyde (**6**) in a four-step sequence. Aldehyde **6** was transformed into brominated and iodinated vinylphenols **1n** and **1m** by halogenation followed by Wittig reaction with PPh_3MeBr.[16] Coumarins **4n** and **4m** were then assembled using our rhodium-catalyzed carbonylation protocol in 57% and 37% yield, respectively. The synthesis was completed using a Stille coupling with the corresponding allylstannane.[17]

Scheme 4. Synthesis of CYP19 Inhibitor 5 and the Natural Product Osthole (8)



CONCLUSION

A practical, economical, and scalable process for the preparation of benzoxepines from simple 2-alkenylphenol and alkyne precursors has been developed. The reactions can be carried out using only a 0.75 mol % loading of the precious metal catalyst (rhodium complex). Using carbon monoxide instead of an alkyne as the reaction partner affords a variety of coumarins featuring different substitutions. This reaction is also amenable to being carried out on 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-bottom flask equipped with a condenser and sealed with a rubber septum, the corresponding alkyne (33 mmol) was added to a solution of $[Cp^*RhCl_2]_2$ (153 mg, 0.75 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (3.29 g, 0.5 equiv) in MeCN (200 mL) under a continuous air flow. The reaction mixture was then heated to 85 °C, and the corresponding 2-vinylphenol (49.5 mmol, 1.5 equiv) was added dropwise over 2.5 h via a syringe pump. The reaction mixture was stirred for the given time, 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.

Experimental Procedure for the Rh-Catalyzed Preparation of Coumarins. To a solution of $[Cp^*RhCl_2]_2$ (7.7 mg, 2.5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (120 mg, 1.2 equiv) in MeCN (2 mL) purged with CO was added the corresponding 2-alkenylphenol (0.5 mmol). The flask containing the reaction mixture was sealed with a rubber septum, and a CO atmosphere was injected into the flask with a balloon. The reaction mixture was heated to 85 °C, stirred for 16 h, cooled to room temperature, 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.

Experimental Procedure for the Large-Scale Rh-Catalyzed Preparation of Coumarins and Characterization of the Products. In a two-neck round-bottom flask equipped with a condenser and sealed with a rubber septum, the corresponding 2-alkenylphenol (33 mmol) was added to a solution of $[Cp^*RhCl_2]_2$ (510 mg, 2.5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (7.91 g, 1.2 equiv) in MeCN (135 mL). The resulting mixture was purged with CO, and a CO atmosphere was injected into the system with a balloon. The reaction mixture was heated to 85 °C, stirred for 16 h at that temperature, cooled to room temperature, filtered through Celite, and washed with hexanes and diethyl ether. The solvents were

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Org. Process Res. Dev. 2019, 23, 1669–1673

removed in vacuo, and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding coumarin.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00191.

Detailed experimental procedures, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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