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Ruthenium(II)-Catalyzed Cyclization of Oxabenzonorbornenes with Propargylic Alcohols: Formation of Isochromenes

Karine Villeneuve[a] and William Tam*[a]

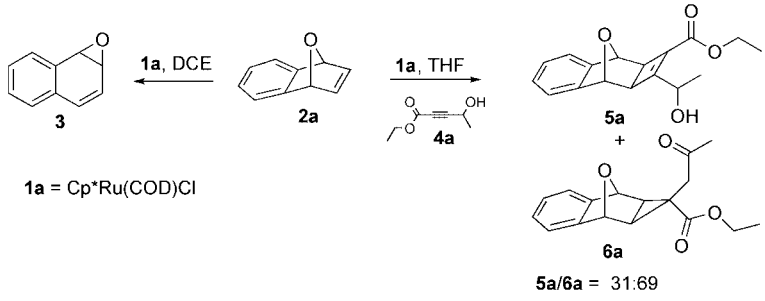
Keywords: Ruthenium / Catalysis / Cyclization / Isochromene / Oxabenzonorbornenes

The ruthenium-catalyzed cyclization of a propargylic alcohol with an oxabenzonorbornene in methanol leads to an unanticipated isochromene framework. The catalytic cycle to form this product is believed to go through an oxidative cyclization of the two unsaturated partners with the ruthenium catalyst, followed by β-hydride elimination, tautomerization and hydroruthenation. The ruthenacyclobutane thus obtained further undergoes [2+2] cycloreversion to form a ruthenium–carbene intermediate that atypically rearranges via a [1,3]-alkoxide shift and finally reductively eliminates to produce the desired compound.

Introduction

The utilization of Cp*Ru(COD)Cl (**1a**) (Cp* = pentamethylcyclopentadienyl; COD = 1,5-cyclooctadiene) in C–C bond formation has considerably increased over the last few years.[1,2] The presence of the labile COD ligand offers a 14-electron complex, which is readily available for oxidative cyclization with two unsaturated moieties. This is the case in several ruthenium-catalyzed reactions such as cyclotrimerization,[3] enyne cyclization,[4] formation of 1,2,3-triazole[5] and [2+2] cycloaddition.[6] On the other hand, **1a** is also known to form ruthenium carbenes with diazoalkanes[7] and to be a useful precatalyst for allylation reactions.[8] We have recently examined different aspects of ruthenium-catalyzed reactions involving oxabenzonorbornenes **2**,[9] and observed that depending on the reaction conditions, several products could be obtained (Scheme 1). When the alkene **2a** is treated with Cp*Ru(COD)Cl, isomerization to the corresponding naphthalene oxide (**3**) is observed.[9b] In the presence of an alkyne, Ru-catalyzed [2+2] cycloaddition usually occurs as the only pathway,[6a–6e] but when the alkyne is a secondary propargylic alcohol such as **4a**, the cyclopropane **6** is often obtained as the major product.[9a]

When performing the reaction in methanol, we found the formation of a new isochromene product **7a** (Scheme 2).[10] Isochromenes are a class of compounds that exhibit diverse biological activities,[11] and the interest for their synthesis has recently exploded.[12,13] In this paper, we wish to reveal how this unprecedented Ru-catalyzed construction of isochromene may occur. Although yields are moderate in some cases, this method allows the use of readily available starting materials for the construction of the synthetically useful



Scheme 1. Different products generated by ruthenium-catalyzed reactions involving oxabenzonorbornenes.

[a] Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, Department of Chemistry, University of Guelph, Guelph, Ontario, N1G 2W1, Canada
Fax: +1-519-766-1499
E-mail: wtam@uoguelph.ca

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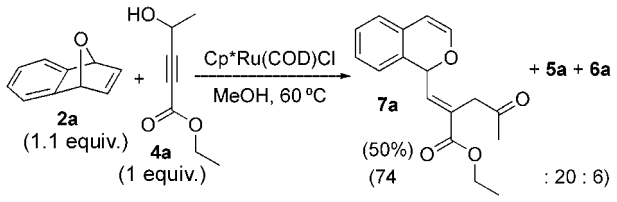
isochromene skeleton. These results also provide new insight about the reactivity of Cp*Ru(COD)Cl and ruthenacyclobutane intermediates.

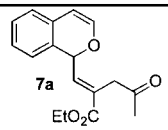
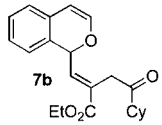
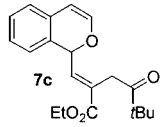
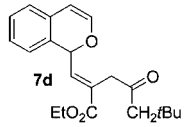
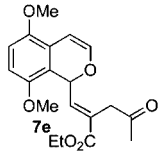
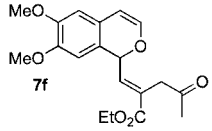
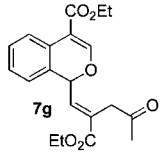
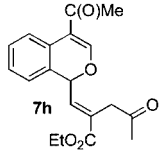
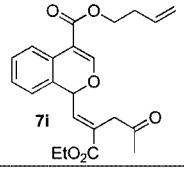


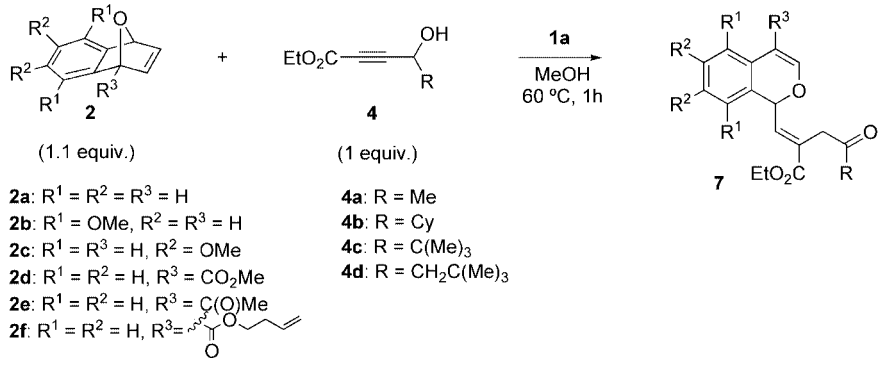
Scheme 2. Preparation of isochromene **7a** from a Ru-catalyzed cyclization of **2a** with **4a**.

Results and Discussion

Table 1 presents several alkyne and alkene partners that were subjected to the optimal reaction conditions with the precatalyst **1a** [Cp*Ru(COD)Cl (5 mol-%)/MeOH/60 °C]. We first turned our attention to different groups at the propargylic position of the acetylene moiety, and found that the steric demand of this group greatly influences the yield of isochromene (Entries 1–4), Scheme 3 and Table 1. When the alcohol side of the alkyne becomes too bulky, such as in the acetylene **4c**, the formation of the [2+2] cycloadduct predominates (Entry 3). However, when the *tert*-butyl group is installed at the homopropagylic position (**4d**, Entry 4), this seems to benefit the formation of the isochromene, and product **7d** was obtained in 70% yield. As for the olefin moiety, other symmetrical oxabenzonorbornenes (**2b** and **2c**) were found to display reactivity comparable to **2a** (Entries 5 and 6). Unsymmetrical alkenes were also tested, and the presence of a polar group at the bridge junction such as methyl ester (**2d**, Entry 7) or methyl ketone (**2e**, Entry 8) appears to favor the sole formation of the isochromenes **7g** and **7h**, respectively. Hence, the presence on the olefin of a group capable of coordinating to the Ru metal seems to dictate the regiochemistry, but also works synergistically with the propargylic alcohol to yield exclusively the isochromene product. The alkene **2f**, bearing two potentially reactive double bonds, also underwent cyclization reaction (Entry 9). Although non-strained alkenes are known to undergo Ru-catalyzed Alder-ene reaction with propargylic alcohols,[14] we were delighted to only isolate the highly

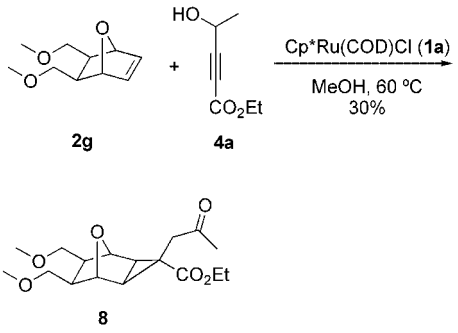
Table 1. Scope of the reaction (see Scheme 3).

Entry	Alkene 2	Alkyne 4	Product 7	Yield[a] [%]
1	**2a**	**4a**		50[b]
2	**2a**	**4b**		50[b]
3	**2a**	**4c**		26[c]
4	**2a**	**4d**		70[b]
5	**2b**	**4a**		60[b]
6	**2c**	**4a**		52[b]
7	**2d**	**4a**		77
8	**2e**	**4a**		63
9	**2f**	**4a**		74



Scheme 3. Synthesis of some isochromenes (see Table 1).

functionalized isochromene **7i** in 74% yield. Conversely, alkene **2g** lacking the aromatic ring, did not provide the rearranged product but rather the cyclopropane **8** (Scheme 4). Thus, the strain in the alkene moiety might play an important role in the formation of the isochromene over the cyclopropane product.



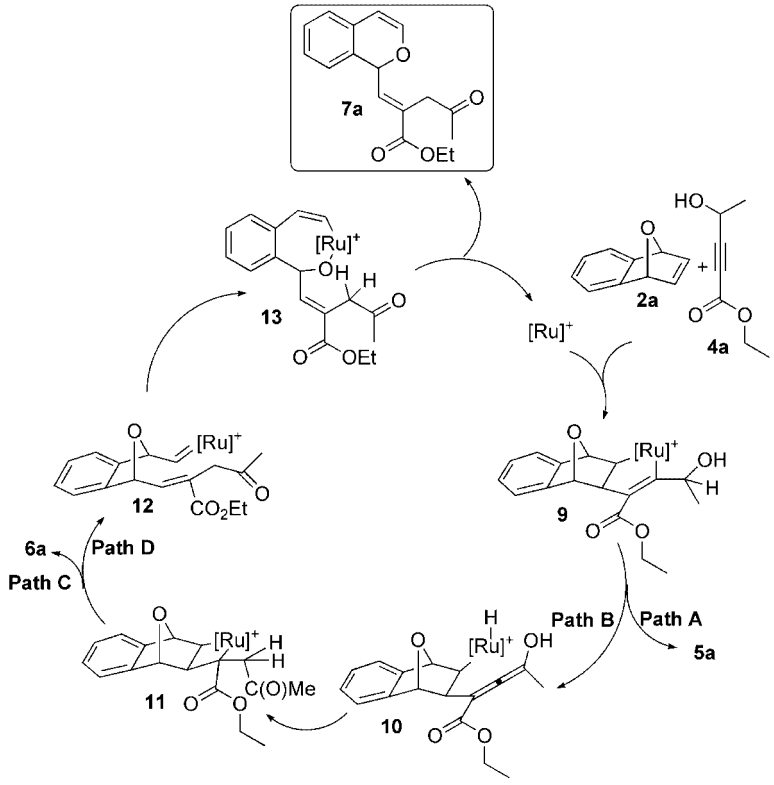
Scheme 4. Ru-catalyzed cyclopropanation of alkene **2g** with **4a**.

Complex **1a** has been postulated by Mitsudo and coworkers to form a neutral [Cp*RuCl] species for ruthenium-catalyzed [2+2] cycloaddition.[6f,6g] On the other hand, it is believed that the cationic ruthenium species is formed in MeOH.[15] When the cationic complex $[Cp^*Ru(CH_3CN)_3]$-PF_6 was utilized in THF with **2a** and **4a**, the isochromene **7a** was obtained as the major product (**5a**/**6a**/**7a**, 20:25:55), suggesting that $[Cp^*Ru]^+$ is the active species.[16]

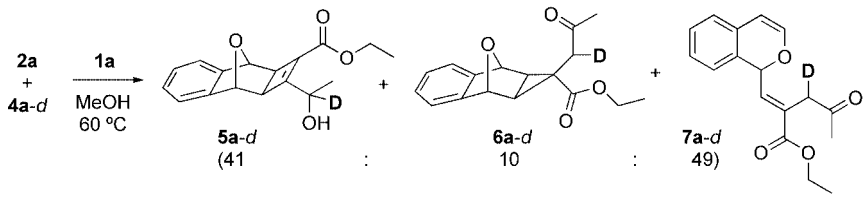
A mechanistic hypothesis accounting for the generation of isochromene is pictured in Scheme 5. After oxidative cyclization, β-hydride elimination of the ruthenacycle **9** would afford the ruthenium hydride **10** (Path B). Alternatively, reductive elimination of **9** would produce the [2+2] cycloadduct **5a** (Path A). Hydroruthenation of the intermediate **10** would generate the ruthenacyclobutane **11**, which is believed to be the second key intermediate in this catalytic pathway, from which the second reaction competition would arise. If **11** reductively eliminates, the cyclopropane **6a** would be obtained (Path C). In contrast, [2+2] cycloreversion of **11**, another important reactivity pattern of ruthenacyclobutanes, would provide the Ru carbene **12** (Path D). The Ru intermediate **12** is then proposed to rearrange to **13** through an atypical 1,3-migration of the alkoxyl group and finally reductively eliminate to produce the isochromene **7a**.[17]

To verify that the formation of the isochromene **7a** is related to the generation of the cyclopropane **6a**, the reaction was performed with the acetylene **4a**-*d* bearing a deuterium at the propargylic position (Scheme 6). The deuterium was found on the carbon atom adjacent to the ketone functionality, as in cyclopropane **6a**-*d*. A significant qualitative isotopic effect was also observed as longer reaction time was required, and the **5a**/**6a**/**7a** ratio changed from 20:6:74 with **4a** to 41:10:49 with **4a**-*d*. This indicates that the ease of breaking the propargylic C–H bond is a determinant factor in the formation of **7a**, which is very comparable to what we found in our previous study of the formation of **6a** (in THF, **5a**/**6a**, 31:69 with **4a** and 54:46 with **4a**-*d*).[9a]

Utilizing the same precatalyst Cp*Ru(COD)Cl (**1a**), Mori and co-workers recently trapped a similar Ru car-

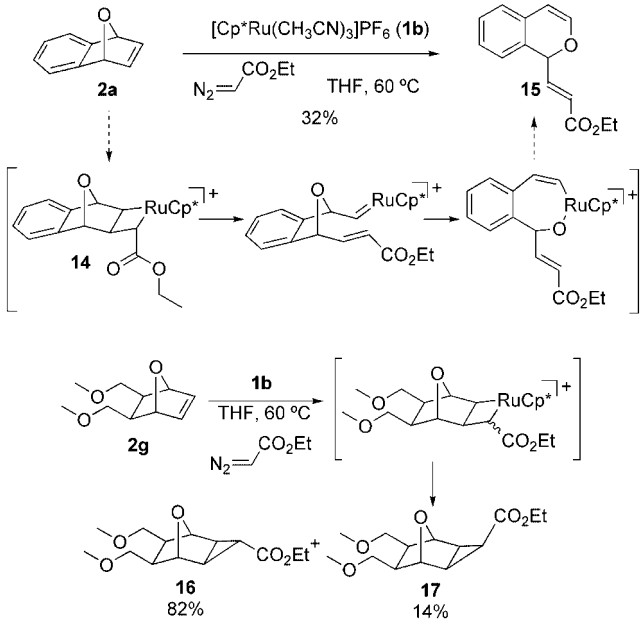


Scheme 5. Proposed mechanism for the formation of **7a**.



Scheme 6. Deuterium labeling.

bene.[4b] So far, all our attempts to trap the intermediate **12** have failed. However, Dixneuf and co-workers have reported the generation of the ruthenium carbene complex by reacting **1a** with ethyl diazoacetate.[7] On the basis of this work, if one could react **2a** with a similar Ru carbene obtained from $[Cp^*Ru(CH_3CN)_3]PF_6$ (**1b**) and ethyl diazoacetate, the related ruthenacycle **14** would be formed (Scheme 7) and the proposed formation of isochromene **7a** from the ruthenacyclobutane intermediate **11** (Scheme 5) could be tested. Indeed, we were pleased to observe that treating **2a** with ethyl diazoacetate in the presence of **1b** produced the isochromene **15**. Such Ru carbene reactivity is very different from what is usually observed.[18] In addition, only the cyclopropane products **16** and **17** were formed when subjecting **2g** to the same reaction conditions (Scheme 7). These results strongly support our mechanistic hypothesis and are also in agreement with the trend of reactivity of these two alkenes (entry 1, Table 1 and Scheme 4).



Scheme 7. Reaction of ruthenium carbenes generated from **1b** and ethyl diazoacetate with alkenes **2a** and **2g**.

Conclusions

To conclude, we have disclosed an unprecedented cationic Ru-catalyzed construction of isochromene from a propargylic alcohol and an oxabenzonorbornene. This strategy involves the employment of readily available starting materials in mild reaction conditions. The catalytic cycle that leads to this product is believed to implicate an oxidative cyclization of the two unsaturated partners with the ruthenium catalyst, followed by a β-hydride elimination, tautomerization and hydroruthenation. The ruthenacyclobutane obtained further undergoes [2+2] cycloreversion to form a Ru-carbene intermediate that uncommonly rearranges through a [1,3]-alkoxide shift and finally reductively eliminates to produce the desired compound. Further investigation of the reaction mechanism and the factors influencing the product distribution are currently in progress.

Experimental Section

Representative Procedure (Isochromene 7a): A mixture of alkene **2a** (204.9 mg, 1.421 mmol), propargylic alcohol **4a** (180.0 mg, 1.266 mmol) and MeOH (1.6 mL) in an oven-dried vial was added by a cannula to an oven-dried screw-cap vial containing Cp*Ru(COD)Cl (weighed out from a dry box, 17.2 mg, 0.0453 mmol) under nitrogen. The reaction mixture was stirred at 60 °C for 1 h. The solvent was evaporated and the crude product was purified by column chromatography (gradient EtOAc/hexanes, 1:19 to 1:4) to provide **7a** (181.2 mg, 0.6330 mmol, 50%).

Supporting Information (see also the footnote on the first page of this article): Experimental and spectroscopic details.

Acknowledgments

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