Construction of Isochromenes via a Ruthenium-Catalyzed Reaction of Oxabenzonorbornenes with Propargylic Alcohols

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The ruthenium-catalyzed cyclization of a propargylic alcohol with an oxabenzonorbornene in methanol leads to the creation of an isochromene framework. The proposed mechanism herein discussed for the formation of the product involves six major steps, the first four being oxidative cyclization, β-hydride elimination, hydroruthenation, followed by [2+2] cycloreversion. The ruthenium carbene formed at this stage undergoes a [1,3]-alkoxide shift that provides the observed product after reductive elimination. This process, believed to occur via a cationic ruthenium species, is in competition with two other pathways, ruthenium-catalyzed [2+2] cycloaddition and cyclopropanation. Although both $[Cp^*Ru(CH_3CN)_3]PF_6$ and Cp*Ru(COD)Cl are effective catalysts, the latter gives better yield and product ratio. The reaction was also found to proceed with high regioselectivity and product selectivity when unsymmetrical alkenes bearing a coordinating functional group at the bridge junction were used.

Introduction

Oxabicyclic alkenes are valuable synthetic intermediates as they can serve as useful building blocks in molecular architecture[1] or as a general template to create highly substituted rings. For instance, transition metal-catalyzed asymmetric ring opening[2] of these alkenes allows the formation of several stereocenters in a single step. Numerous transition metals have been explored, such as rhodium,[3] palladium,[4] and nickel.[5] In our research program investigating ruthenium-catalyzed reactions, we have recently examined different aspects involving oxabenzonorbornenes **2**.[6] Ruthenium catalysts are known for their chemical transformation versatility,[7,8] but they can be highly substrate-, ligand-, and solvent-dependent.[9] We found that, by varying the reaction conditions, several products could be obtained (Scheme 1). For example, when alkene **2a** is treated with Cp*Ru(COD)Cl (**1a**) (Cp* = pentamethylcyclopentadienyl; COD = 1,5-cyclooctadiene), isomerization to the corresponding naphthalene oxide **3** is observed.[6c] When an alkyne is added to the reaction mixture, Ru-catalyzed [2+2] cycloaddition usually occurs as the only pathway.[6a,b] However, when the alkyne is a secondary propargylic alcohol such as **4a**, cyclopropane **6a** is obtained in a significant amount or as the major product.[6b] Cyclopropane **6a** is postulated to be generated through oxidative cyclization of the two unsaturated partners, followed by β-hydride elimination, hydroruthenation, and reductive elimination. It was shown that this pathway can, on the other hand, be mostly suppressed by utilizing Cp*Ru(COD)I (**1b**) as the precatalyst. More unexpectedly, when performing the same reaction in a protic solvent such as methanol, the formation of the isochromene product **7a** is taking place.[10] In this Article, we wish to provide more insight about the formation of isochromene **7a** and the competition between these ruthenium-catalyzed processes.

Results and Discussion

Ruthenium(II)-Catalyzed Formation of Isochromene. Isochromenes are a class of compounds that exhibit diverse biological activities,[11] and the interest for their synthesis has recently exploded. The most common approach involves different variations of intramolecular cyclization of acetylenic aldehydes or ketones.[12] Other methods also include Pd-catalyzed tandem reaction of pinacolone with aryl bromides,[13] intramolecular carbolithiation of propargylic acetals,[14] intramolecular

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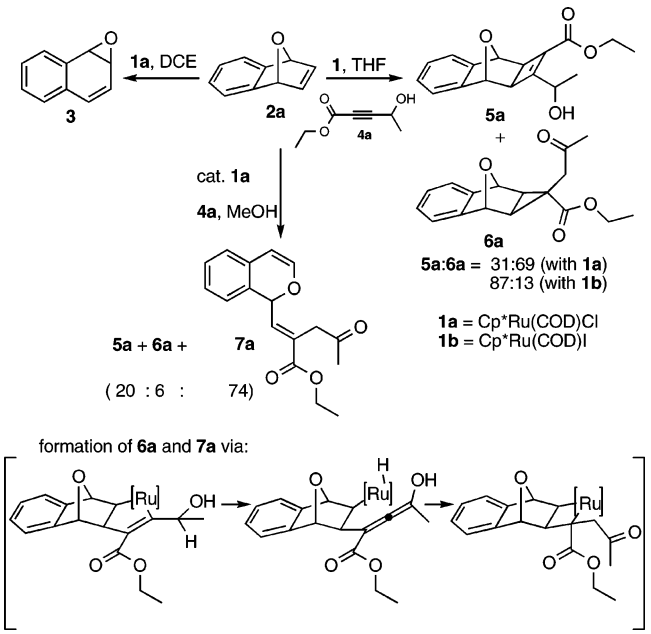
Scheme 1. Different Products Formed via Ruthenium-Catalyzed Reactions Involving Oxabicyclic Alkenes



iridium hydride-catalyzed alkyne hydroalkoxylation,[15] Pd-catalyzed reaction of 2-iodophenyloxyallene with bicyclic alkenes,[16] and 1,6-addition of nucleophiles to benzopyranylidenetungsten(0) complexes.[17]

When alkene **2a** and alkyne **4a** were reacted in MeOH in the presence of Cp*Ru(COD)Cl (**1a**), the new product, significantly less polar than **5a** and **6a**, was easily isolated as a sole isomer by column chromatography on silica. It displayed some spectral patterns similar to those observed for **6a**. The molecular ion peak (M^+, 286) indicated that **7a** is a 1:1 adduct of **2a** and **4a** with no incorporation of methanol. However, in comparison to **6a**, ^{1}H and ^{13}C (JMOD) NMR spectra of **7a** clearly showed the loss of symmetry in the molecule, the disappearance of the bridged structure, and the presence of three vinylic protons. Further NMR experiments (HMBC, HSQC), IR spectroscopy, and mass spectrometry allowed one to elucidate the structure of **7a**, and GOESY NMR experiments assigned the stereochemistry of the trisubstituted double bond (Figure 1). Finally, the structure of **7a** was unequivocally confirmed by X-ray analysis.[18]

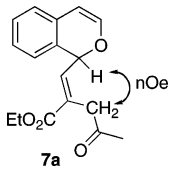
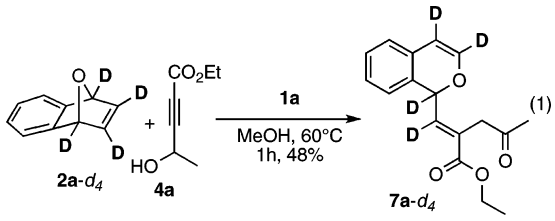


Figure 1. GOESY experiment allowing one to determine the stereochemistry of the trisubstituted double bond in **7a**.

Because the formation of isochromene **7a** from alkene **2a** and alkyne **4a** could not be directly extrapolated, deuteration experiments were designed so that the change in atom connectivity from the starting materials to the product could be explained. Reaction of **2a**-d_4 with **4a** produced the fully tetradeuterated isochromene **7a**-d_4 in a yield of 48% (eq 1).



When the propargylic position was deuterated (**4a**-*d*), the deuterium was found on the carbon adjacent to the ketone, as in cyclopropane **6a**-*d* (Scheme 2). In this case, a significant empirical isotopic effect was observed as longer reaction time was needed and the **5a**:**6a**:**7a** ratio changed from 20:6:74 with **4a** to 41:10:49 with **4a**-*d*. This clearly 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 observed in our previous study of the formation of **6a**.[19] We thus hypothesized that the formation of **7a** may be related to the formation of **6a** (vide infra). On the other hand, when the reaction was performed in MeOD, no substantial difference in the products distribution was found. However, unlike the 100% deuterium incorporation obtained for the reaction with **4a**-*d*, the reaction in MeOD produced **7a**-*d*′ with 86% of D-incorporation. This is presumably due to an incomplete exchange of a labile proton in **4a** or an intermediate with the solvent. It is also noteworthy that these two reactions produce the opposite major diastereomer (Scheme 3).

Factors Influencing the Formation of Isochromene versus [2+2] Cycloadduct and Cyclopropane. To understand the formation of **7a**, several reaction parameters were studied: the catalyst, the presence of additives, the solvent, and the substituents on the two reactive moieties.

Catalyst Effect. While **1a** efficiently catalyzes the formation of **7a**, other Ru-complexes such as CpRu(COD)Cl, [CpRu(CH_3CN)$_3$]PF_6, and CpRu(PPh_3)$_2$Cl were found to be inactive. This agrees with our previous observation for the formation of **5a** and **6a**, where the more electron-rich Cp*Ru(COD)Cl was required for the reaction to occur.[6b] However, when [Cp*Ru(CH_3CN)$_3$]PF_6 (**1c**) was utilized in MeOH, a complex mixture with trace amounts of **5a**, **6a**, and **7a** was obtained (entry 2, Table 1).

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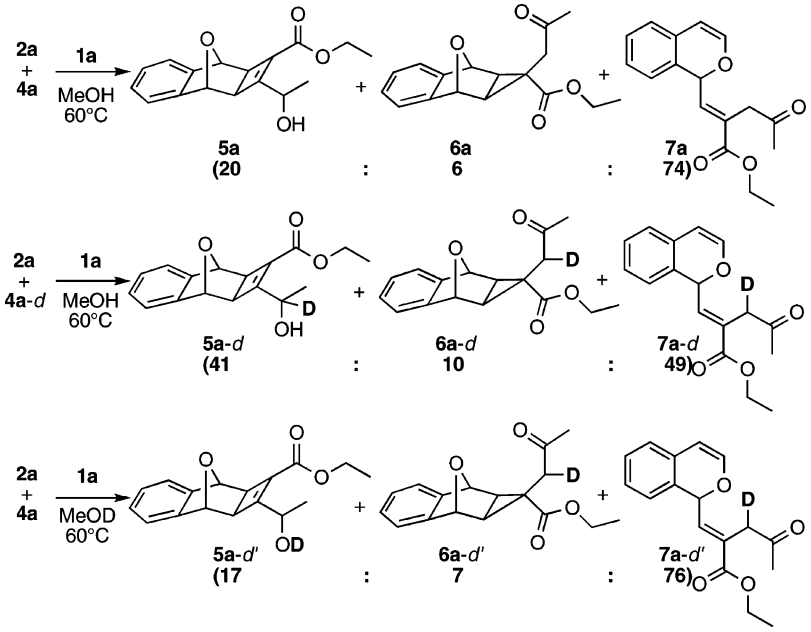
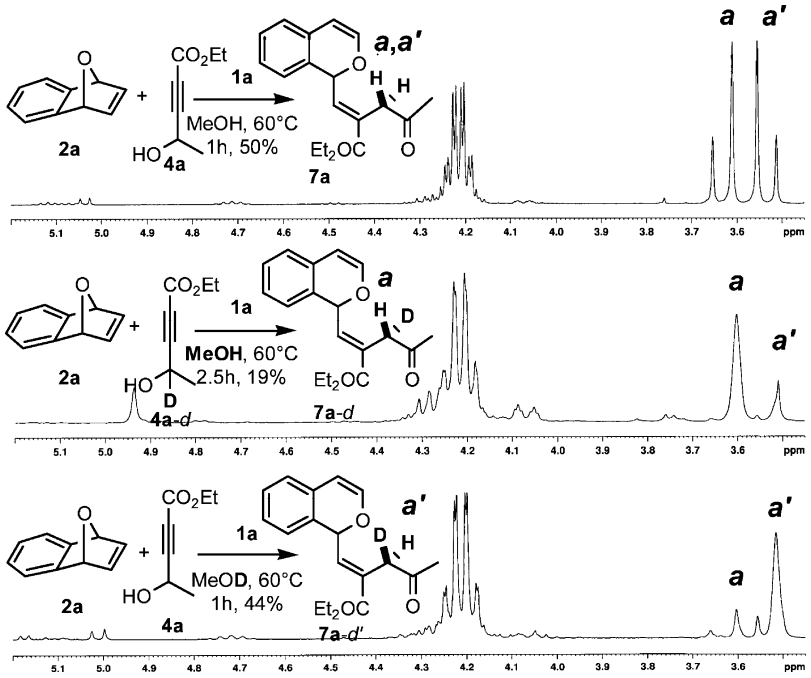
(19) In THF, the **5a**:**6a** ratio for the reaction with **4a** was 31:69, whereas 54:46 was obtained with **4a**-*d*; see ref 6b.

Scheme 2. Deuterium Labeling Experiments



Scheme 3. Partial ^{1}H NMR Spectra of 7a, 7a-*d*, and 7a-*d*′



Intrigued by the fact that isochromene **7a** is formed predominantly in MeOH (entry 1), whereas cyclopropane **6a** is the major product and **7a** is not observed in THF (entry 3), investigation of the nature of the active catalytic species was undertaken. Complex **1a** has been postulated by Mitsudo and co-workers[20] to form a neutral [Cp*RuCl] species for ruthenium-catalyzed [2+2] cycloaddition; on the other hand, it is believed that a cationic ruthenium species is formed in MeOH.[21] To verify this, Cp*Ru(COD)Cl was treated with AgOTf in THF to form $[Cp^*Ru]^+$ prior to adding alkyne **4a** and alkene **2a**, and, indeed, isochromene **7a** was obtained as the major product, although the yield was decreased (entry 4). A similar result was also found when $[Cp^*Ru(CH_3CN)_3]PF_6$ was utilized (entry 5). Thus, the formation of **7** appears to proceed via an active cationic ruthenium species, and a protic solvent is not necessarily required.

Additive Effect. Attention was also drawn to the fact that cationic ruthenium complex $[Cp^*Ru(CH_3CN)_3]PF_6$ (**1c**) was giving a much more complex products mixture in MeOH (entry 2, Table 1) than in THF (entry 5, Table 1), whereas an overall yield for the three products of 69% was obtained with Cp*Ru(COD)Cl in MeOH (entry 1, Table 1). A closer look at the presence of the halide on the Ru-complex was then taken. Varying the concentration of chloride ions through addition of tetrabutylammonium chloride revealed the importance of the

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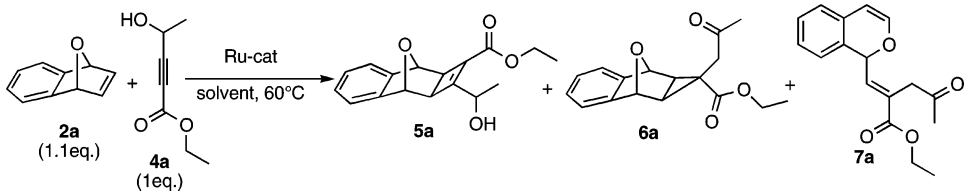
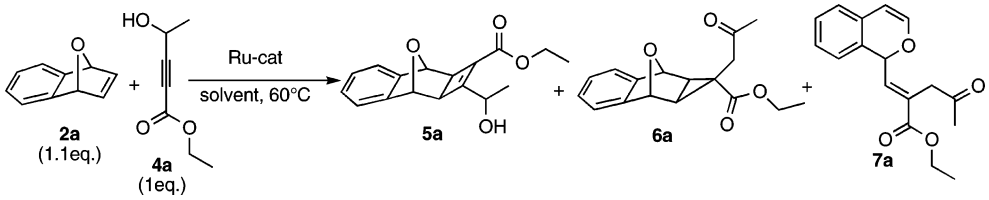
Table 1. Effect of Catalytic Species on the Reaction Outcome



entry	reaction conditions[a]	ratio[b] 5a:6a:7a	yield[c] (%) 5a	6a	7a
1	**1a**/MeOH	20:6:74	14	4	51 (50)
2	**1c**/MeOH	N/A	trace	trace	trace
3	**1a**/THF	31:69:0	25	56	0
4	**1a**/AgOTf[d]/THF	18:11:71	8	5	31
5	**1c**/THF	20:25:55	11	14	31

[a] Ru-complex (5 mol %): **1a** = Cp*Ru(COD)Cl, **1c** = $[Cp^*Ru(CH_3CN)_3]PF_6$. [b] Determined by analysis of the crude ^1H NMR spectrum. [c] Yields were based on the ^1H NMR spectrum of the crude reaction mixture with mesitylene as internal standard. Yields in brackets are isolated yields. [d] 1 equiv with respect to the ruthenium precatalyst.

Table 2. Effect of Halide Additives on the Reaction Outcome



entry	precatalyst[a]	solvent	additive[b]	ratio[c] 5a:(6a+7a)	ratio[c] 5a:6a:7a	yield[d] (%) 5a	6a	7a
1	**1a**	MeOH	none	20:80	20:6:74	14	4	51
2	**1a**	MeOH	Bu_4NCl(9)[e]	20:80	20:7:73	17	6	62
3	**1c**	MeOH	none	N/A	N/A	trace	trace	trace
4	**1c**	MeOH	Bu_4NCl(12)	16:84	16:15:69	14	13	59
5	**1a**	THF	Bu_4NCl(10)	N/A	N/A	trace	13	0
6	**1c**	THF	Bu_4NCl(10)	N/A	N/A	trace	14	0
7	**1a**	MeOH	Bu_4NI(10)	44:56	44:5:51	36	4	41
8	**1b**	MeOH	none	40:60	40:2:58	35	2	51
9	**1a**	THF	none	31:69	31:69:0	25	56	0
10	**1b**	THF	none	87:13	87:13:0	55	8	0

[a] Ru-complex (5 mol %): **1a** = Cp*Ru(COD)Cl, **1b** = Cp*Ru(COD)I, **1c** = $[Cp^*Ru(CH_3CN)_3]PF_6$. [b] Numbers in bracket are the number of equivalents with respect to the ruthenium precatalyst. [c] Determined by analysis of the crude ^1H NMR spectrum. [d] Yields were based on the ^1H NMR spectrum of the crude reaction mixture with mesitylene as internal standard. [e] Similar result was obtained when utilizing Bu_4PCl instead of Bu_4NCl.

halide (TBAC, entries 1−10, Table 2). Although no significant difference was observed with Cp*Ru(COD)Cl (entry 2), adding TBAC significantly improved the overall yield of the reaction (entry 4) when cationic ruthenium complex **1c** was used as precatalyst.[22] In contrast, the presence of a large excess of TBAC in THF completely deactivates both **1a** and **1c** precatalysts (entries 5 and 6). Furthermore, similarly to what was previously shown for the formation of the cyclopropane **6a**,[6b] varying the halide on the catalyst drastically influences the product distribution, as the formation of the [2+2] cycloadduct **5a** over cyclopropane **6a** was following the trend I > Br > Cl. As expected, performing the reaction in the presence of **1a** with tetrabutylammonium iodide or with Cp*Ru(COD)I (**1b**) increased the formation of **5a** versus **6a** and **7a** (compare entries 7 and 8 with 1, Table 2). However, this change in the **5a**:(**6a**+**7a**) ratio is not as important as what we observed in THF (compare entries 8 with 1 and 10 with 9).

Along with halide-based salts, other additives were tested. However, none of these proved effective. The presence of the strongly coordinating ligand triphenylphosphine completely deactivates the catalyst,[23] and no reaction was found to occur. The use of acid such as *p*-toluenesulfonic acid[24] or strong chloride scavenger like silver triflate[25] produces complex products mixture with trace amounts of products. The weaker chloride scavenger NH_4PF_6[9a,22,26] was compatible with the reaction conditions, although no yield or ratio improvement was obtained.

Solvent Effect. It is evident that solvent plays a crucial role in the formation of **7a**. The preceding study[6b] of the formation of **6a** versus **5a** has shown only a minor difference in the product distribution when the polarity of the aprotic solvent was varied. To further confirm that the polarity is not playing a considerable

(22) Such chloride ion effects have been previously reported for CpRu(COD)Cl, see: Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615.

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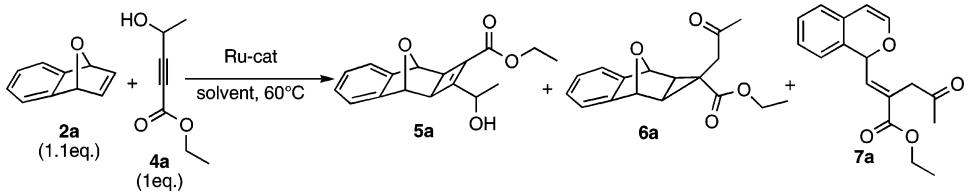
Table 3. Solvent Effect



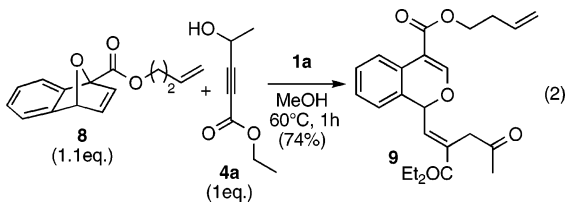
entry	catalytic system[a]	solvent	ratio[b] **5a**:(**6a**+**7a**)	ratio[b] **6a**:**7a**	ratio[b] **5a**:**6a**:**7a**	yield[c] (%) **5a**	**6a**	**7a**
1	**1a**	CH_3CN	29:71	100:0	29:71:0	19	46	0
2	**1a**/AgOTf	CH_3CN	29:71	96:4	29:68:3	25	59	3
3	**1c**	CH_3CN	28:72	92:8	28:66:6	23	53	5
4	**1a**	TFEOH	68:32	6:94	68:2:30	34	1	15
5	**1a**	MeOH	20:80	8:92	20:6:74	14	4	51
6	**1a**	EtOH	21:79	9:90	21:8:71	17	7	58
7	**1a**	*n*-PrOH	22:78	24:76	22:19:59	15	13	41
8	**1a**	*i*-PrOH	28:72	50:50	28:36:36	20	26	26

[a] Ru-complex (5 mol %): **1a** = Cp*Ru(COD)Cl, **1c** = $[Cp^*Ru(CH_3CN)_3]PF_6$. [b] Determined by analysis of the crude ^1H NMR spectrum. [c] Yields were based on the ^1H NMR spectrum of the crude reaction mixture with mesitylene as internal standard.

role in the formation of **7a**, the reaction of **2a** and **4a** in presence of Cp*Ru(COD)Cl was performed in acetonitrile, whose dielectric constant is comparable to methanol (entry 1, Table 3). Not surprisingly, no isochromene was produced, and a **5a**:**6a** ratio of 29:71 was observed. However, when the cationic ruthenium complex **1c** was utilized instead of **1a** (entries 2 and 3), very little **7a** was generated and cyclopropane **6a** was the major product formed. This is especially different from what is observed in THF (entries 4 and 5, Table 1), which suggests that the way the solvent acts as a ligand on the ruthenium may prevent or favor the formation of one product versus another.[27] Consequently, the active intermediate in the formation of **6a** is also probably a cationic ruthenium species. Other protic solvents were then investigated (entries 4−8, Table 3). With the exception of trifluoroethanol, no difference in the **5a**:(**6a**+**7a**) ratio was observed. In contrast, a much broader variation of the **6a**:**7a** ratio was found, especially in the case of *n*-propanol and isopropanol.

Substrate Scope. Table 4 presents several alkyne and alkene partners that were subjected to the reaction conditions with the precatalyst **1a**. Unlike secondary alcohol **4a**, alkynes **4b** (primary alcohol) and **4c** (tertiary alcohol) (entries 2 and 3) only generated the [2+2] cycloadduct. This further suggests that isochromenes are formed through a reaction path similar to the one for cyclopropanes **6**, because the same trend (i.e., only **5** was produced) was observed when the reaction was performed in THF.[6b] Other secondary propargylic alcohols such as those described in entries 4−9 were also tested. Steric hindrance at the propargylic position appears to play a dual role in the product distribution. A small increase of the steric hindrance does not affect the outcome of the reaction (compare entries 1 and 4), but when the alcohol side of the alkyne becomes too bulky, the [2+2] cycloadduct predominates. This is demonstrated with alkyne **4e** (entry 5), bearing a *tert*-butyl group at the propargylic position, from which **5e** was isolated in a yield of 54%. On the other hand, utilizing alkyne such as **4f** (entry 6) seems beneficial for the formation of the isochromene product, and **7g** was isolated in 70% yield. In contrast, the presence of a phenyl group (entries 7 and 8) somewhat appreciably decreases the yield. The other side of the alkyne was also modified, and it was found that substituting the ethyl for the bulkier *tert*-butyl ester greatly enhances the formation of the [2+2] cycloadduct **5i** over the isochromene **7i** (compare entries 1 and 9).

As for the olefin moiety, other symmetrical oxabenzonorbornenes (**2b** and **2c**) were also exposed to the reaction conditions with **4a** and were found to display reactivity comparable to **2a** (entries 10 and 11, Table 4). In opposition, oxanorbornene **2d** and oxanorbornadiene **2e** (entries 12 and 13), lacking the aromatic ring, did not provide the rearranged product but rather the cyclopropane. This establishes the importance of the ring strain in the formation of **7**. The use of **2f**, bearing a carbon-based bridgehead, prevents the pathway leading to the formation of **6** and **7** (entry 14). Unsymmetrical alkenes were also utilized, and it was found that the presence and the nature of a group at the bridge junction critically modify the outcome of the reaction. The methyl group that bears alkene **2g** increases the steric congestion at the reaction center, and cycloadduct **5o** was formed as the major product (entry 15). Alternatively, the presence of a polar group at the bridge junction such as methyl ester (**2h**, entry 16) or methyl ketone (**2i**, entry 17) appears to promote the formation of the isochromene, and **7p** and **7q** were, respectively, generated as sole products. Hence, the presence on the olefin of a group capable of coordinating to the Ru-metal can dictate the regiochemistry, but most importantly works synergistically with the propargylic alcohol to yield exclusively the isochromene product. Finally, alkene **8** (eq 2), bearing two potentially reactive double bonds, was synthesized. Although non-strained alkenes are known to undergo Ru-catalyzed Alderene reaction with propargylic alcohols,[9c,28] we were delighted to only isolate the highly functionalized isochromene **9** in 74% yield.



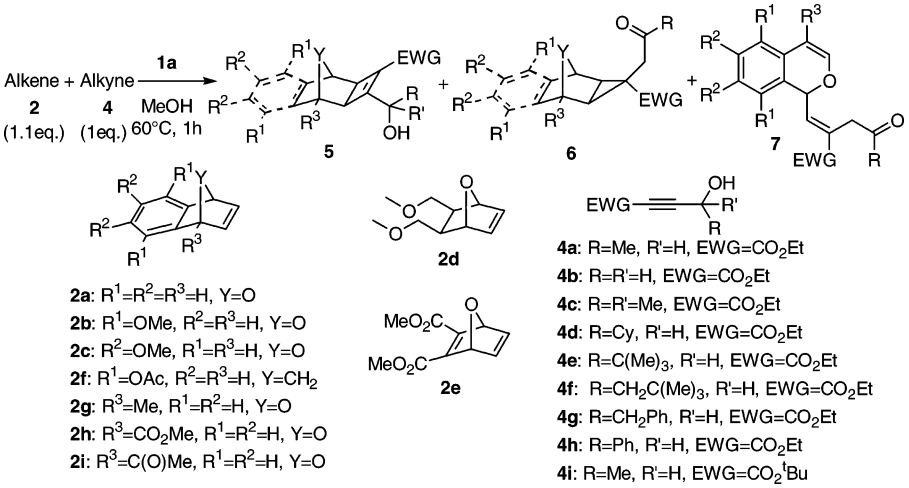
(2)

Reaction Mechanism. From the effects of reaction parameters, the focus was then turned on how the isochromenes **7** are

(27) Similar argument has been presented for the use of acetonitrile in other Ru-catalyzed processes, see: Kondo, T.; Morisaki, Y.; Uenoyama, S.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 8657.

(28) Trost, B. M.; Müller, T. J. J. *J. Am. Chem. Soc.* **1994**, *116*, 4985.

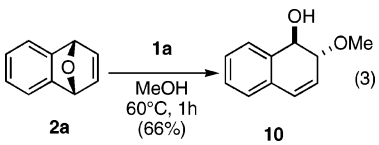
Table 4. Scope of the Reaction



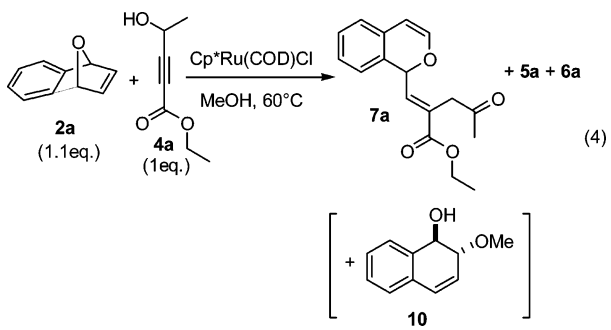
entry	alkyne	alkene	isolated product (yield[b])
1	**4a**	**2a**	**7a** (50%)
2	**4b**	**2a**	**5b** (38%)
3	**4c**	**2a**	**5c** (57%)
4	**4d**	**2a**	**7d** (50%)
5	**4e**	**2a**	**5e** (54%)
			7e (26%)
6	**4f**	**2a**	**7f** (70%)
7	**4g**	**2a**	**7g** (34%)
8	**4h**	**2a**	**7h** (33%)
9	**4i**	**2a**	**5i** (32%)
			7i (37%)
10	**4a**	**2b**	**7j** (60%)
11	**4a**	**2c**	**7k** (52%)
12	**4a**	**2d**	**6l** (30%)
13	**4a**	**2e**	**6m** (77%)
14	**4a**	**2f**	**5n** (50%)
15	**4a**	**2g**	**5o** (53%)
16	**4a**	**2h**	**7p** (77%)
17	**4a**	**2i**	**7q** (63%)

[a] Determined by analysis of the characteristic peaks in the crude ^{1}H NMR spectrum. [b] Isolated yields after column chromatography.

formed. Although oxidative cyclization of the alkene and the alkyne moieties with the ruthenium catalyst would be the first obvious step in the formation of the isochromene, another pathway could not be ruled out yet. As mentioned above (Scheme 1), alkene **2a** exhibits a competitive reactivity in the presence of the precatalyst **1a**, where either opening of the oxygen-bridge or oxidative cyclization with an alkyne can occur. In addition, when **2a** is treated with **1a** in MeOH, racemic 1,2-dihydro-2-methoxy-1-naphthalenol **10** is obtained in a yield of 66% (eq 3). However, the ring-opening pathway could be excluded by rationalizing the regiochemistry obtained in isochromene **7p** (entry 16, Table 4). If the first step involves a pathway similar to that for the formation of **11** through the intermediate **13** (Scheme 4), isochromene **14** would be the expected product. On the other hand, Burton and Tam have recently shown that propargylic alcohol **4c** reacts in a highly regioselective fashion with **2h** to give almost exclusively cycloadduct **12**.[29] Consequently, the fact that **7p** was isolated indicates the formation of intermediate **15** via oxidative cyclization.



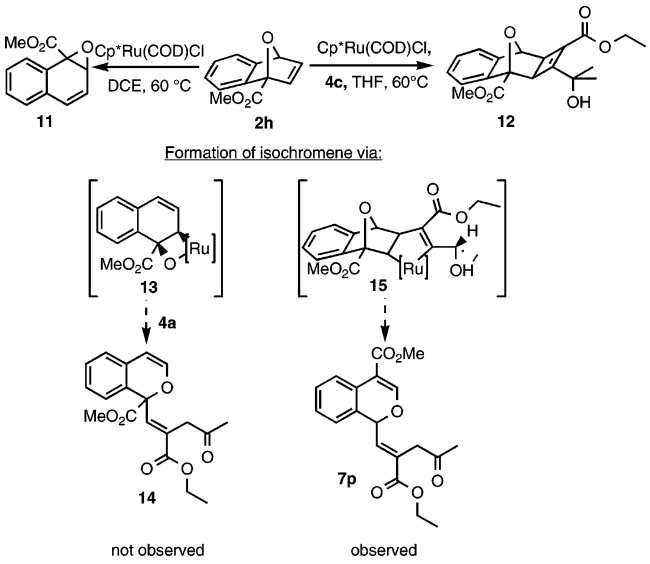
Thus, several reaction pathways are available under the actual reaction conditions (Cp*Ru(COD)Cl, MeOH, 60 °C), and although the formation of **10** is possible, it should be noted that this compound is produced only when an excess of **2a** is used (eq 4). To better understand these competitive processes, the reaction was monitored directly by ^{1}H NMR spectroscopy (Figure 2). We found that the formation of the nucleophilic ring-opening product **10** did not occur until the concentration of the alkyne is low (T = 20 min, Figure 2). This shows that if both the alkyne and the alkene are available to complex to the catalyst, oxidative cyclization occurs more rapidly, and, as a result, only excess oxabicyclic alkene is converted into **10**.



On the basis of all of the information mentioned above, a possible mechanistic path accounting for the formation of the

(29) Burton, R. R.; Tam, W. *Tetrahedron Lett.* **2006**, *47*, 7185.

Scheme 4. Rationalizing the Oxidative Cyclization Step



three products is pictured in Scheme 5. After oxidative cyclization of **2a** and **4a** with **1a**, four possible ruthenacycle intermediates can be formed (Scheme 6). Upon reductive elimination of any of them, cycloadduct **5a** is generated. However, only **16** and **16′** can undergo further β-hydride elimination as the β-hydrogen is not accessible in **21** and **21′**. This could explain why some [2+2] cycloadduct is present in most cases, and would be in coherence with previous work on Ru-catalyzed Alder-ene reaction of propargylic alcohols by Trost and coworkers.[9c,28] They have shown that increasing steric hindrance at the propargylic position improves the ratio favoring **22** (Scheme 7). Also, although their precatalyst of choice was CpRu(COD)Cl, the **5a**:(**6a**+**7a**) ratio of 20:80 (entry 5, Table 3) is very similar to the **22**:**23** ratio they observed with alkyne **4a** (4.5:1). This would also be consistent with the **5a**:(**6a**+**7a**) ratio of 68:32 obtained in trifluoroethanol (entry 4, Table 3), as they also notice a lower **22**:**23** ratio of 2.3:1 in this solvent.

It was previously emphasized (Table 2) that the presence of a halide ion plays a dual role in the reaction process. Although the ionization of the halide is not necessary for the generation of [2+2] cycloadduct, it seems required for the formation of cyclopropane and isochromene products. On the other hand, the presence of the halide counteranion appears to be crucial for the products formation, especially in MeOH where only trace amounts of the products were found when $[Cp^*Ru(CH_3CN)_3]PF_6$ was used. The halide moiety is suspected to stabilize the cationic ruthenium intermediates involved in the catalytic cycle. Thus, we postulate that the observed difference in reactivity is due to this ion-pairing.[30] Once ruthenacycles **16** and **16′** are produced, either reductive or β-hydride elimination can occur, and increasing the steric hindrance should favor the reductive elimination process (Scheme 5).[31] Therefore, decreasing steric bulk of the halide (I > Br > Cl) is in good agreement with the above observation, where more β-hydride elimination was observed with X = Cl than with X = I. This would also explain

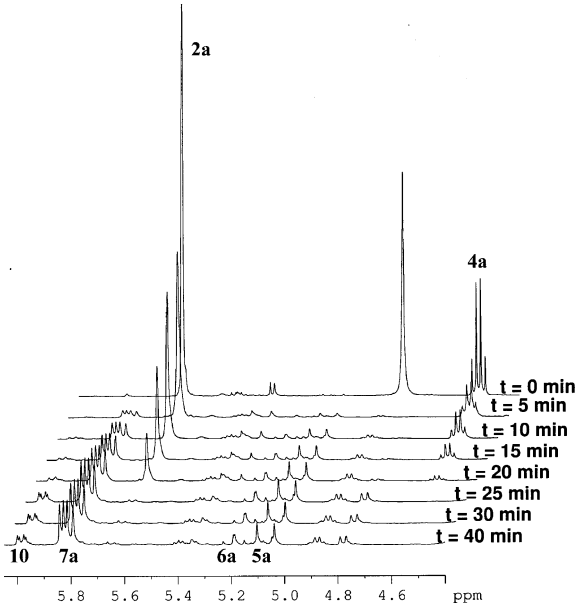


Figure 2. Partial 400 MHz ^{1}H NMR spectrum at 60 °C in MeOD of the crude reaction between **2a** and **4a** in the presence of **1a** over time (**2a**:**4a** = 1.1:1).

the fact that the halide effect is greater in aprotic than protic solvents, because ion-pairing is expected to be tighter in the first case.

Decomplexation of the alcohol is also necessary to generate the proper orbital alignment for β-hydride elimination, and the presence of an oxygen at the bridgehead of the bicyclic framework may assist this departure. The allenol **17** can then tautomerize to the corresponding ketone prior to undergoing hydroruthenation and thus generate the ruthenacyclobutane **18**. If this intermediate reductively eliminates, cyclopropane **6a** is formed (path C). Alternatively, [2+2] cycloreversion of **18** would form the ruthenium carbene **19** (path D), which could rearrange to **20** through a 1,3-migration of the alkoxide group and finally reductively eliminate to produce the isochromene **7a**.[32] In addition to the similar isotopic effects observed in the formation of both products, the fact that the cis relationship of the ketone and the isochromene groups in **7a** matches the stereochemistry in cyclopropane **6a** (with the ketone group syn to the bicyclic structure) suggests that both products originate from the same intermediate **18** (Figure 3). Moreover, the isomer of isochromene **7a** where these two groups are trans, like in the case of **6a**,[6b] was not observed.

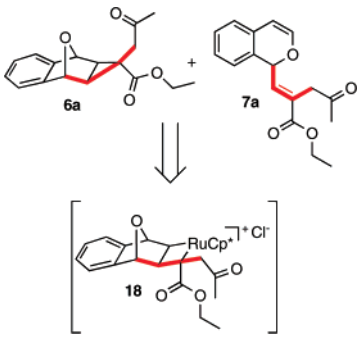


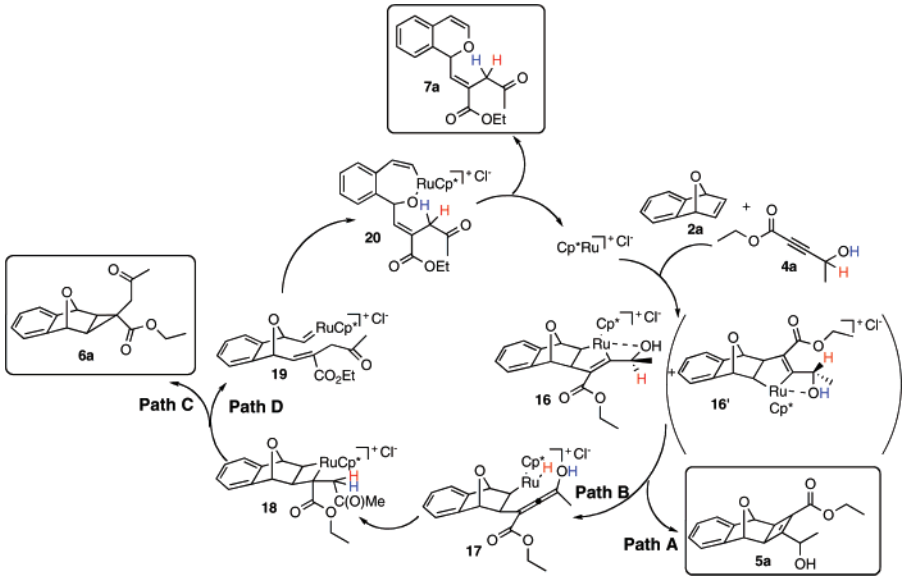
Figure 3. **5a** and **7a** possibly arise from the same intermediate **18**.

(30) Ion-pairing is known to considerably affect chemical reactions, see: Macchioni, A. *Chem. Rev.* **2005**, *105*, 2039.

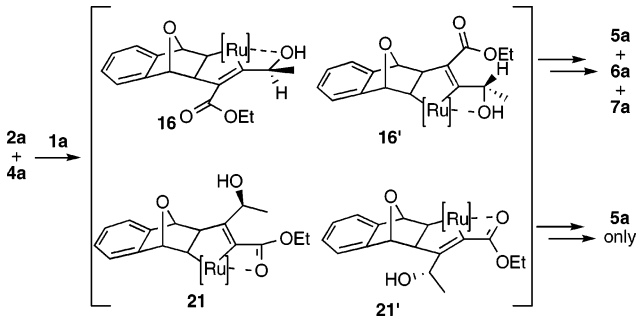
(31) In our previous report on ruthenium-catalyzed cyclopropanation of oxabicyclic alkenes with propargylic alcohols, a 1,2-hydride migration was also postulated as another possible path. This is, however, probably not at play, because the variation of the products distribution with the solvent polarity is of small magnitude. This change is probably due to a better ionization of the chloride in more polar solvents.

(32) Ruthenium carbene rearrangements have been proposed in other ruthenium-catalyzed reactions, see: (a) Reference 24a. (b) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579.

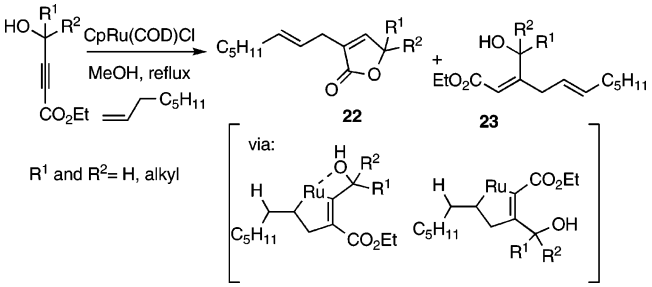
Scheme 5. Plausible Mechanistic Pathway for the Formation of 7a



Scheme 6. Four Possible Ruthenacyclopentene Intermediates

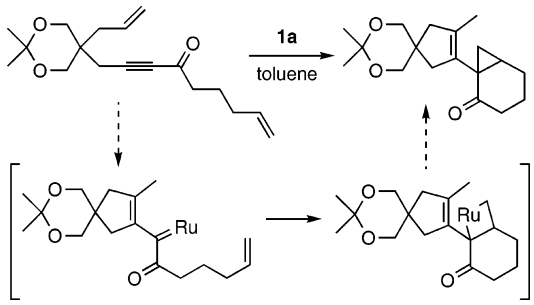


Scheme 7. Alder-ene Reaction Reported by Trost and Co-workers



Utilizing the same precatalyst Cp*Ru(COD)Cl (**1a**), Mori and co-workers recently trapped similar ruthenium carbene (Scheme 8).[9a,33] So far, all of our attempts to trap the intermediate **14** (Scheme 5 and eq 2) have failed.[34] On the other hand, Dixneuf and co-workers have reported the generation of ruthenium carbene by reacting **1a** with ethyl diazoacetate.[35] On the basis of this work, if one could react **2a** with a similar ruthenium carbene obtained from **1c** and ethyl diazoacetate, the related ruthenacycle **24** would be formed, and the proposed formation of isochromene from ruthenacyclobutane intermediate **18** could be tested (Scheme 9). Indeed, when performing this reaction, isochromene **25** was obtained in 32% yield. Such ruthenium carbene reactivity is very different from that usually observed.[36,37] In addition, subjecting **2d** to the same reaction

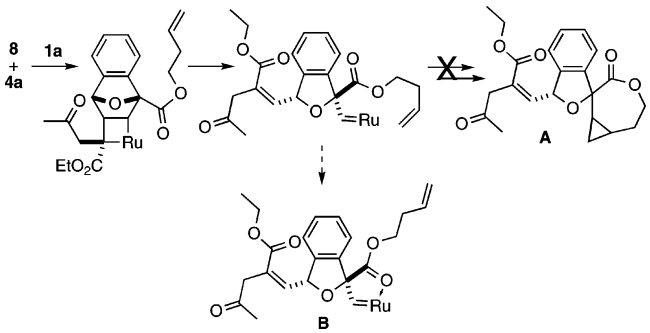
Scheme 8. Ruthenium-Catalyzed Reaction of Enyne Described by Mori and Co-workers



conditions produced only cyclopropane products **26** and **27** (Scheme 9). These results strongly support our mechanistic hypothesis and are also in agreement with the trend of reactivity shown in Table 4 for those two alkenes. Thus, the strain in the alkene moiety plays an important role in the formation of the isochromene over the cyclopropane product. Presumably, an

(33) Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606.

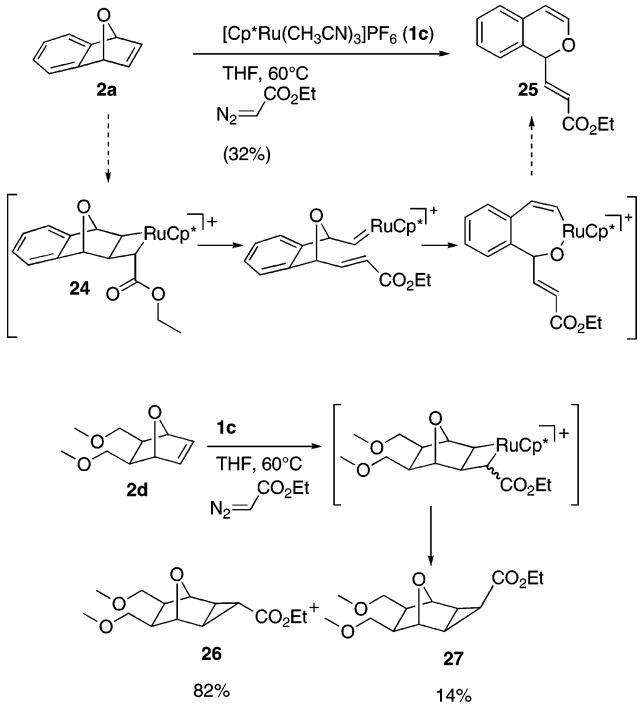
(34) It was hoped that product **A** could be isolated. A possible reason for this unreactivity towards intramolecular cyclopropanation would be the formation of a chelated subtrate-carbene complex such as **B** that would prevent this pathway.



Similar stable complexes have been previously described, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. F. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260.

(35) (a) Monnier, F.; Castillo, D.; Dérien, S.; Toupet, L.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5474. (b) Eckert, M.; Monnier, F.; Shchetnikov, G. T.; Titanyuk, I. D.; Osipov, S. N.; Toupet, L.; Dérien, S.; Dixneuf, P. H. *Org. Lett.* **2005**, *7*, 3741.

Scheme 9. Reaction of a Ruthenium Carbene Generated from 1c and Ethyl Diazoacetate with Alkenes 2a and 2d



increase of the strain in the ruthenacyclobutane **18** could favor the retro [2+2] cycloaddition over the reductive elimination step. As for the influence of the solvent, its mode of action in the [2+2] cycloreversion/reductive elimination dual of the ruthenacyclobutane intermediate still needs to be clarified.

Conclusion

To summarize, we have found a Ru-catalyzed cyclization of oxabenzonorbornenes with propargylic alcohols. Although yields are moderate in some cases, this method allows the use of readily available starting materials for the construction of the synthetically useful isochromene skeleton. The catalytic cycle to form this product is believed to involve an oxidative cyclization of the two unsaturated partners with the ruthenium catalyst, followed by a β-hydride elimination, tautomerization, and hydroruthenation. The ruthenacyclobutane thus obtained further undergoes [2+2] cycloreversion to form a ruthenium carbene intermediate that rearranges via a [1,3]-alkoxide shift group and finally reductively eliminates to produce the desired compound. Cationic ruthenium intermediate is proposed to be the active catalyst species. This process is in competition at different stages of the catalytic cycle with two other reactions, Ru-catalyzed [2+2] cycloaddition and cyclopropanation of the alkyne with the alkene. Therefore, several factors need to be taken into consideration to influence the outcome of the reaction such as the nature (e.g., polarity, acidity, complexing abilities) of the solvent, the steric bulkiness of the propargylic alcohol, as well as the strain and the nature of the bridgehead group of the alkene. Depending on the reaction conditions, each compound can be obtained as the major product: Cp*Ru(COD)I in THF would generate the [2+2] cycloadduct **5**, Cp*Ru(COD)Cl in CH_3CN or THF would mainly give the cyclopropane **6** product, whereas Cp*Ru(COD)Cl in MeOH would produce the isochromene **7**.

Experimental Section

A representative procedure, including characterization of the key product **7a**, is described here. Full details are found in the Supporting Information.

General Procedure for the Preparation of Isochromene Products. Isochromene 7a. A mixture of alkene **2a** (205 mg, 1.42 mmol), acetylene **4a** (180 mg, 1.27 mmol), and MeOH (1.6 mL) in an oven-dried vial was added via a cannula to an oven-dried screw-cap vial containing Cp*Ru(COD)Cl (weighed out from a dry box, 17 mg, 0.045 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 elution, EtOAc:hexanes = 1:19 to 1:4) to provide **7a** (181 mg, 0.633 mmol, 50%). R_f 0.33 (EtOAc/hexanes = 1:4); IR (neat) 3070, 2985, 2955, 2936, 1720, 1713, 1622 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.26 (m, 2H), 7.17 (app t, 1H, J = 7.5 Hz), 6.99 (app t, 2H, J = 7.5 Hz), 6.53 (d, 1H, J = 5.7 Hz), 5.84 (d, 1H, J = 5.7 Hz), 5.73 (d, 1H, J = 8.8 Hz), 4.18−4.24 (m, 2H), 3.63 (d, 1H, J = 17.1 Hz), 3.53 (d, 1H, J = 17.1 Hz), 2.23 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 204.5, 166.5, 144.5, 139.5, 129.6, 129.4, 128.7, 128.0, 127.2, 124.4, 123.5, 105.5, 73.7, 61.4, 41.8, 29.9, 14.1. HRMS (EI) calcd for $C_{17}H_{18}O_4$ (M^+), 286.1205; found, 286.1207.

Acknowledgment. This work was supported by NSERC (Canada). K.V. would like to thank NSERC for providing a CGS-D2 scholarship. The authors would also like to acknowledge Gavin Chit Tsui and Ryan Burton for the synthesis of some starting materials.

Supporting Information Available: Detailed procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OM7004518

(36) In general, ruthenium carbenes undergo metathesis or cyclopropanation reaction. For reviews on ruthenium-catalyzed metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. For reviews covering cyclopropanation involving ruthenium carbenes, see ref 7. For other non-metathesis reactions, see: Alcaide, B.; Almendros, P. *Chem.-Eur. J.* **2003**, *9*, 1259.

(37) It is noteworthy that alkene **2a** is known to undergo ring-opening polymerization metathesis with catalysts such as $[RuCl_2(p\text{-cymene})]_2$ (Delaude, L.; Demonceau, A.; Noels, A. F. *Macromolecules* **1999**, *32*, 2091) and $RuCl_2(CHPh)(PCy_3)_2$ (Amir-Ebrahimi, V.; Corry, D. A.; Hamilton, J. G.; Thompson, J. M.; Rooney, J. J. *Macromolecules* **2000**, *33*, 717. Amir-Ebrahimi, V.; Rooney, J. J. *J. Mol. Catal. A* **2004**, *212*, 107).