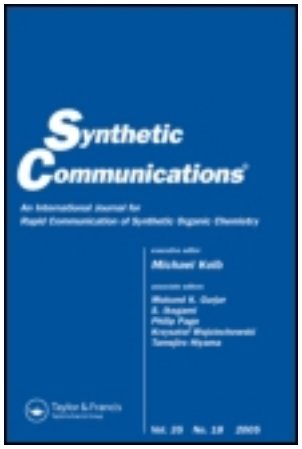

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Ruthenium-Catalyzed Nucleophilic Ring-Opening Reactions of 7-Oxabenzonorbornadienes with Methanol

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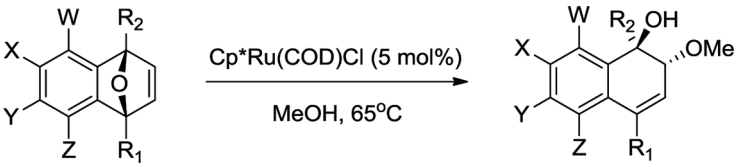
GRAPHICAL ABSTRACT



Abstract *Ruthenium-catalyzed nucleophilic ring-opening reaction of 7-oxabenzonorbornadienes with methanol was investigated. Among various ruthenium catalysts tested, Cp*Ru(COD)Cl gave the greatest yields in the ring-opening reaction. The reactions were found to be highly stereoselective, giving only the anti-ring-opening products in moderate yields. Both symmetrical and unsymmetrical 7-oxabenzonorbornadienes were employed in the study, and moderate to excellent regioselectivities were observed.*

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Keywords Bicyclic alkenes; catalysis; 7-oxanorbornadienes; ring-opening reactions; ruthenium

INTRODUCTION

Oxabicyclic alkenes are valuable synthetic intermediates as they can serve as a general template to create highly substituted ring systems.[1] For instance, metal-catalyzed ring opening of these alkenes allows for the formation of several stereocenters in a single step.[2,3] We have recently investigated different modes of transition metal–catalyzed reactions of oxabenzonorbornadiene **1a** and found that depending on the reaction conditions, several products (**2–6**) could be obtained (Scheme 1). For example, when oxabenzonorbornadiene **1a** was treated with an alkyne in the presence of the ruthenium catalyst, $Cp^*Ru(COD)Cl$ ($Cp^* = 1,2,3,4,5$-pentamethylcyclopentadienyl, COD = cyclooctadienyl), a [2 + 2] cycloaddition was observed and

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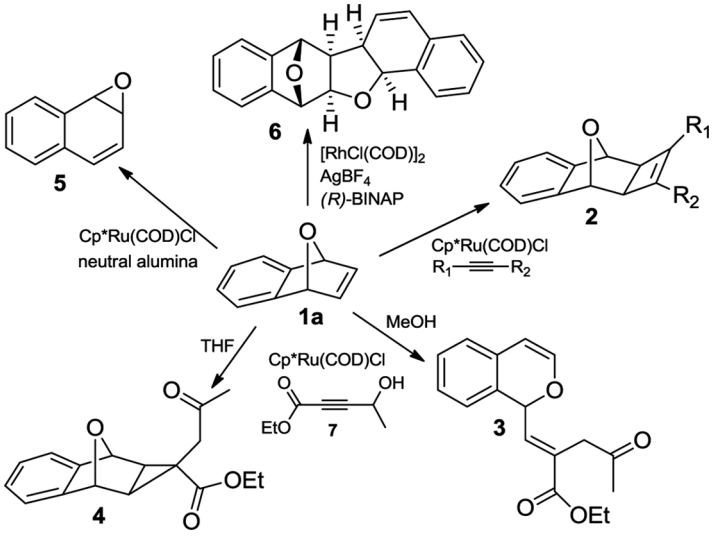


Scheme 1. Our previous studies on transition metal–catalyzed reactions of oxabenzonorbornadiene **1a**.

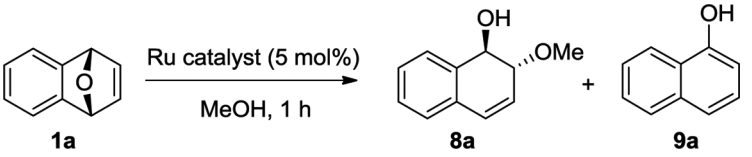
cyclobutene cycloadduct **2** was formed.[4] When oxabenzonorbornadiene **1a** was treated with the secondary propargylic alcohol **7** in the presence of the neutral Ru catalyst, Cp*Ru(COD)Cl, in MeOH, or using a cationic Ru catalyst (e.g., [CpRu $(CH_3CN)_3$]PF_6), isochromene **3** was formed.[5] On the other hand, if the same reaction between oxabenzonorbornadiene **1a** and the secondary propargylic alcohol **7** was carried out with Cp*Ru(COD)Cl in tetrahydrofuran (THF), cyclopropane **4** was produced.[6] We have also observed that in the absence of an alkyne, Cp*Ru (COD)Cl catalyzed the isomerization of oxabenzonorbornadiene **1a** to the corresponding naphthalene oxide **5** when neutral alumina was used in the workup.[7] We have also reported that asymmetric cationic rhodium(I)-catalyzed cyclodimerization of oxabenzonorbornadiene **1a** to produce dimers **6** in excellent enantioselectivity (up to 99% *ee*).[8]

Metal-catalyzed nucleophilic ring-opening reactions of 7-oxabenzonorbornadienes have been studied in the presence of nickel, titanium, zirconium, iron, copper, palladium, and rhodium.[1b] However, to the best of our knowledge, no ruthenium-catalyzed nucleophilic ring-opening reactions of 7-oxabenzonorbornadienes have been reported in the literature. In this article, we report our investigation on the ruthenium-catalyzed nucleophilic ring-opening reactions of 7-oxabenzonorbornadienes with methanol as the nucleophile.

RESULTS AND DISCUSSION

To begin our investigations, we screened a variety of ruthenium catalysts and different reaction conditions, and the results are shown in Table 1. Cationic ruthenium catalysts (entries 1 and 2) showed little reactivity, giving the ring-opening product **8a** in poor yields (7–12%) together with a small amount of 1-naphthol **9a** resulting from the isomerization of **1a**.[7,9] Among various neutral ruthenium catalysts

Table 1. Optimization for Ru-catalyzed ring-opening reactions of 7-oxabenzonorbornadiene **1a** with methanol



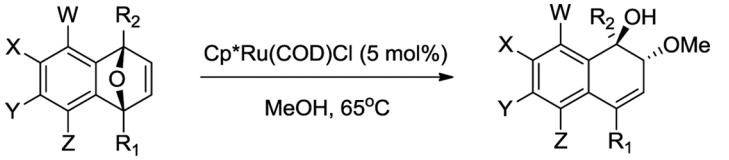
1a **8a** **9a**

Entry	Ru catalyst	T (°C)	Solvent	Yield[a] (%) 8a	9a
1	$[CpRu(CH_3CN)]PF_6$	65	MeOH	7[c]	3
2	$[Cp^*Ru(CH_3CN)]PF_6$	65	MeOH	12[c]	5
3	$Ru(PPh_3)_3Cl_2$	65	MeOH	5[c]	3
4	$[Ru(COD)Cl_2]_x$	65	MeOH	0[c]	0
5	$[RuCl_2(CO)_3]_2$	65	MeOH	0[c]	45
6	$CpRu(PPh_3)_2Cl$	65	MeOH	0[c]	0
7	CpRu(COD)I	65	MeOH	11[c]	5
8	CpRu(COD)Br	65	MeOH	6[c]	6
9	CpRu(COD)Cl	65	MeOH	8[c]	5
10	$Cp^*Ru(COD)I$	65	MeOH	10[c]	11
11	$Cp^*Ru(COD)Br$	65	MeOH	57	17
12	$Cp^*Ru(COD)Cl$	65	MeOH	66	5
13	$Cp^*Ru(COD)Cl$	40	MeOH	62[d]	3
14	$Cp^*Ru(COD)Cl$	25	MeOH	68[e]	2
15	$Cp^*Ru(COD)Cl$	65	THF[b]	8[c]	38
16	$Cp^*Ru(COD)Cl$	65	DCE[b]	5[c]	47
17	$Cp^*Ru(COD)Cl$	65	Toluene[b]	13[c]	36
18	$Cp^*Ru(COD)Cl$	65	Acetone[b]	7	48
19	$Cp^*Ru(COD)Cl$	65	Dioxane[b]	6	42
20	$Cp^*Ru(COD)Cl$	65	Hexanes[b]	0	44

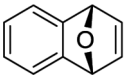
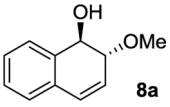
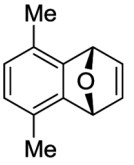
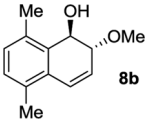
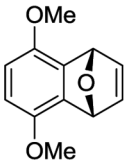
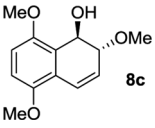
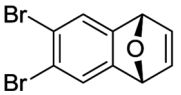
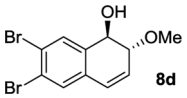
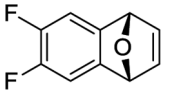
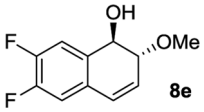
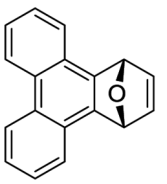
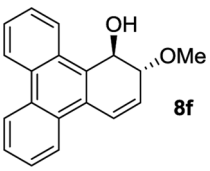
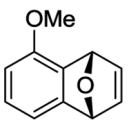
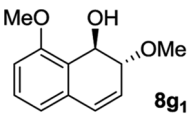
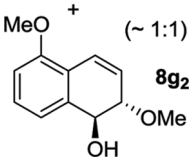
[a]Isolated yield after column chromatography.
[b]20 equivalent of MeOH was used.
[c]7-Oxabenzonorbornadiene **1a** was recovered (22–91%).
[d]The reaction mixture was stirred for 4 h.
[e]The reaction mixture was stirred for 6 h.

tested (entries 3–12), $Cp^*Ru(COD)X$ (where X = Cl and Br, entries 11 and 12), which were found to be useful catalysts in many of our previous studies of metal-catalyzed reactions of 7-oxabenzonorbornadienes (Scheme 1), gave the ring-opening product **8a** in the greatest yields of 57–66%. Decreasing the reaction temperature from 65 °C to 40 °C and 25 °C also afforded **8a** in comparable yields but longer reaction times were required (entries 12–14). However, when MeOH was only used in 20 equivalents and another solvent [such as THF, dichloroethane (DCE), toluene, acetone, dioxane, and hexanes] was used, the yields decreased dramatically (entries 15–20). Similar to rhodium-catalyzed nucleophilic ring-opening reactions of 7-oxabenzonorbornadiene **1a**, these ruthenium-catalyzed nucleophilic ring-opening reactions were found to be highly stereoselective,[10] giving the *anti*-product as the only stereoisomer. The stereochemistry of the product **8a** was confirmed by comparing NMR data with literature values.[10,11]

Table 2. Ru-catalyzed ring-opening reactions of 7-oxabenzonorbornadienes **1a–1k** with methanol

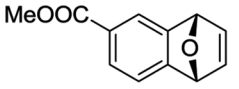
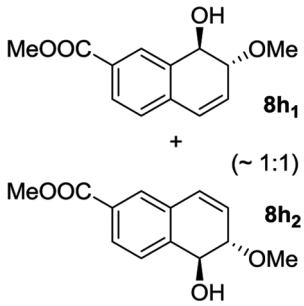
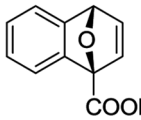
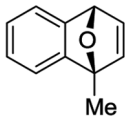
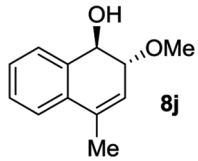
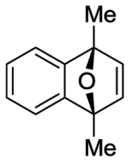


1a-1k **8a-8k**

Entry	7-Oxabenzo-norbornadienes **1**	Nucleophilic ring-opened product **8**	Time (h)	Yield[a] (%) of **8** (**9**)[b]
1	 **1a**	 **8a**	1	66 (5)[b]
2	 **1b**	 **8b**	1	59
3	 **1c**	 **8c**	1	40[c]
4	 **1d**	 **8d**	1	56 (17)[b]
5	 **1e**	 **8e**	2	81 (19)[b]
6	 **1f**	 **8f**	1[d]	26[c]
	 **1g**	 **8g$_1$**		
7		 (~ 1:1) **8g$_2$**	1	30[c]

(*Continued*)

Table 2. Continued

Entry	7-Oxabenzo-norbornadienes **1**	Nucleophilic ring-opened product **8**	Time (h)	Yield[a] (%) of **8** (**9**)[b]
8	 **1h**	 **8h$_1$** + (~ 1:1) **8h$_2$**	2[d]	42
9	 **1i**	—	72	0[e]
10	 **1j**	 **8j**	72	20 (70)[b]
11	 **1k**	—	48	0 (35)[b]

[a]Isolated yield after column chromatography.
[b]Yields in brackets are the amount of the corresponding naphthol isomerization product isolated.
[c]Some 7-oxabenzonorbornadiene was recovered.
[d]The reaction was run at 80 °C.
[e]Decomposition of 7-oxabenzonorbornadiene **1i** was observed.

To investigate the scope of the reactions with different 7-oxabenzonorbornadienes, 7-oxabenzonorbornadienes **1b–1k** were prepared[9] and subjected to the optimized ruthenium-catalyzed nucleophilic ring-opening reaction conditions, and the results are shown in Table 2. Similar to **1a**, substitution on the benzo ring of 7-oxabenzonorbornadiene led to moderate to good yields of the nucleophilic ring-opening products **8b–8e** (Table 2, entries 2–5). With electron-donating groups (Me and OMe, entries 2 and 3), no naphthol isomerization products were detected. However, with electron-withdrawing groups (Br and F, entries 4 and 5), significant amount of the corresponding 1-naphthol isomerization products were isolated.

7-Oxabenzonorbornadiene **1f** required a higher reaction temperature of 80 °C to afford a 26% yield of the nucleophilic ring-opening products **8f** (Table 2, entry 6).

With unsymmetrical 7-oxabenzonorbornadienes **1g** and **1h**, both provided the corresponding nucleophilic ring-opening products in moderate yields as 1:1 mixture of regioisomers (entries 7 and 8). C1-substituted 7-oxabenzonorbornadiene **1i**, with an ester group attached to C1, led only to decomposition of 7-oxabenzonorbornadiene **1i**, and only a trace amount of the nucleophilic ring-opening product was detected by ^{1}H NMR of the crude reaction mixture. With C1-methyl substituted 7-oxabenzonorbornadiene **1j**, a much longer reaction time was required to produce 20% of the nucleophilic ring-opening product **8j**, together with 70% of the corresponding 1-naphthol isomerization product **9j**. 1,4-Dimethyl-7-oxabenzonorbornadiene **1k** failed to product any nucleophilic ring-opening product, and only the corresponding 2-naphthol isomerization product **9k** was isolated in 35% yield.

CONCLUSION

In conclusion we have investigated the ruthenium-catalyzed nucleophilic ring-opening reactions of 7-oxabenzonorbornadienes with methanol as the nucleophile. This represents the first examples of using ruthenium complexes to catalyze this type of nucleophilic ring-opening reactions of 7-oxabenzonorbornadienes. Further investigation to expand the scope of the reactions as well as the study of asymmetric ring-opening reactions will continue in our laboratory.

EXPERIMENTAL

All reactions were carried out in an atmosphere of dry nitrogen or argon. ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz spectrometer. 7-Oxabenzonorbornadienes **1a–1k** were prepared according to literature procedures.[9] ^{1}H NMR and ^{13}C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using internal solvent signals as references and coupling constants are reported in hertz (Hz). A typical procedure for the ruthenium-catalyzed ring-opening reactions of 7-oxabenzonorbornadienes is given. Full experimental detail, with spectroscopic and characterization data and ^{1}H and ^{13}C NMR spectra, are provided in supplementary information.

Typical Procedure for Ruthenium-Catalyzed Ring-Opening Reactions of 7-Oxabenzonorbornadienes: (1R*,2R*)-2-Methoxy-1,2-dihydronaphtalen-1-ol 8a

Inside an inert atmosphere glove box, a solution of 7-oxabenzonorbornadiene **1a** (47.5 mg, 0.329 mmol) and degassed methanol (0.8 mL) in an oven-dried vial was added to an oven-dried screw-cap vial containing Cp*Ru(COD)Cl (7.7 mg, 0.021 mmol). The reaction mixture was stirred outside the glove box at 65 °C for 1 h. The crude product was purified by column chromatography (EtOAc–hexanes = 1:9) to give **8a** (38.1 mg, 0.226 mmol, 66%) as a white solid (mp. 49–51 °C). R_f 0.22 (EtOAc–hexanes = 1:4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 1H, J = 6.8 Hz), 7.24–7.27 (m, 2H), 7.08–7.10 (m, 1H), 6.48 (dd, 1H, J = 9.9, 2.0 Hz), 6.06 (dd, 1H, J = 9.9, 2.3 Hz), 4.91 (d, 1H, J = 10.2 Hz), 4.11 (app dt, 1H, J = 10.3, 2.2 Hz), 3.51 (s, 3H), 2.64 (br s, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 135.8, 131.9, 128.3,

127.9, 127.8, 126.7, 126.3, 125.0, 82.2, 72.4, 56.8. IR (CH_2Cl_2) 3420, 3037, 2979, 2929, 2825, 1455 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{12}O_2$ (M^+) 176.0837; found: 176.0840. Spectral data obtained matched with those reported in the literature.[10a,11]

ACKNOWLEDGMENTS

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