JOC*Note*

pubs.acs.org/joc

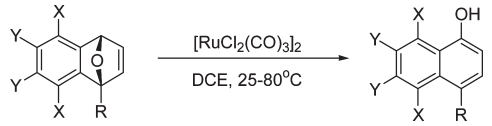
Isomerization of 7-Oxabenzonorbornadienes into Naphthols Catalyzed by $[RuCl_2(CO)_3]_2$

Melissa Ballantine, Michelle L. Menard, and William Tam*

Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, Department of Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1

wtam@uoguelph.ca

Received July 13, 2009

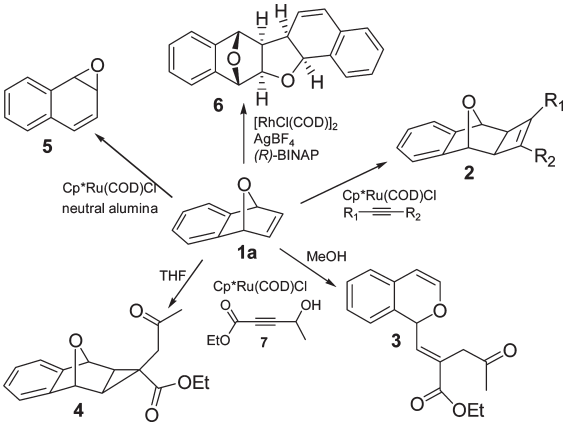


Ruthenium-catalyzed isomerization of 7-oxanorbornadienes into naphthols was investigated. Among the various ruthenium catalysts tested, $[RuCl_2(CO)_3]_2$ gave the highest yields in the isomerization, and various substituted naphthols were synthesized in moderate to excellent yields. Both symmetrical and unsymmetrical 7-oxanorbornadienes were employed in the study, and moderate to excellent regioselectivities were observed.

Oxabicyclic alkenes are valuable synthetic intermediates as they can serve as a general template to create highly substituted ring systems.[1] For instance, asymmetric 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** is 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 is observed and cyclobutene cycloadduct **2** is formed.[4] When oxabenzonorbornadiene **1a** is 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** is formed.[5] On the other hand, if the same reaction between oxabenzonorbornadiene **1a** and the secondary propargylic alcohol **7** is carried out with Cp*Ru(COD)Cl in THF, cyclopropane **4** is produced.[6] More recently, we have observed that in the absence of an alkyne, Cp*Ru(COD)Cl catalyzes the isomerization of oxabenzonorbornadiene **1a** to the corresponding naphthalene oxide **5** when neutral alumina was used in the workup and to 1-naphthol **8a** when silica was used in the workup.[7] We have also reported that asymmetric cationic rhodium(I)-catalyzed cyclodimerization of oxabenzonorbornadiene **1a** produced dimers **6** in excellent enantioselectivity (up to 99% ee).[8]

Brønsted acid catalyzed isomerization of 7-oxabenzonorbornadienes into 1-naphthols is a well-known procedure and a valuable method for incorporating a naphthol fragment in more complex molecules.[9] Similar isomerization has been

SCHEME 1. Previous Studies on Ru- and Rh-Catalyzed Reactions of Oxabenzonorbornadiene 1a



(1) For reviews, see: (a) Rayabarapu, D. K.; Cheng, C. −H. *Acc. Chem. Res.* **2007**, *40*, 971–983. (b) Lautens, M.; Fagnou, K.; Heibert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58.

(2) For selected examples of ring-opening reactions of 7-oxabicyclo-[2.2.1]heptenes, see: (a) Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391–7402. (b) Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837–6846. (c) Chen, C. L.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 4810–4818. (d) Wu, M. −S.; Jeganmohan, M.; Cheng, C. −H. *J. Org. Chem.* **2005**, *70*, 9545–9550. (e) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437–1447. (f) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194–2196. (g) Zhang, T. −K.; Yuan, K.; Hou, X. −L. *J. Organomet. Chem.* **2007**, *692*, 1912–1919.

(3) For selected examples of ring-opening reactions of 7-oxabicyclo-[3.2.1]octenes, see: (a) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879–1882. (b) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090–11091. (c) Lautens, M.; Ma, S.; Chiu, P. *J. Am. Chem. Soc.* **1997**, *119*, 6478–6487. (d) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532–533. (e) Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305–5306.

(4) For selected examples of our recent studies of Ru-catalyzed [2 + 2] cycloadditions of bicyclic alkenes and alkynes, see: (a) Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610–613. (b) Burton, R. R.; Tam, W. *Tetrahedron Lett.* **2006**, *47*, 7185–7189. (c) Burton, R. R.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7333–7336. (d) Allen, A.; Villeneuve, K.; Cockburn, N.; Fatila, E.; Riddell, N.; Tam, W. *Eur. J. Org. Chem.* **2008**, 4178–4192.

(5) (a) Villeneuve, K.; Tam, W. *Eur. J. Org. Chem.* **2006**, 5499–5435. (b) Villeneuve, K.; Tam, W. *Organometallics* **2007**, *26*, 6082–6090.

(6) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843–848.

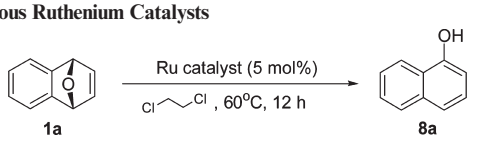
(7) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514–3515. Note that in our previous work using Cp*Ru(COD)Cl that we synthesized, **8a** was obtained in 91%. However, in our present study when we use commercially available Cp*Ru(COD)Cl (from Strem), the highest yield we could obtain was 67%.

(8) Allen, A.; Le Marquand, P.; Burton, R.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7849–7857.

(9) (a) Kaelin, D. E.; Lopez, O.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937–6938. (b) Apsel, B.; Bender, J. A.; Escobar, M.; Kaelin, D. E.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075–1077. (c) Kaelin, D. E.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 12994–12995. (d) Biland-Thommen, A. S.; Raju, G. S; Blagg, J.; White, A. J. F.; Barrett, A. G. M. *Tetrahedron Lett.* **2004**, *45*, 3181–3184.

Published on Web 09/02/2009 DOI: 10.1021/jo901504n

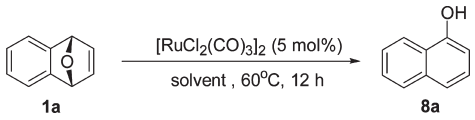
TABLE 1. Isomerization of 7-Oxabenzonorbornadiene 1a into 1-Naphthol with Various Ruthenium Catalysts



		yield (%)[b]	
entry	Ru catalyst[a]	1-naphthnol **8a**	recovered **1a**
1	$Ru(PPh_3)_3Cl_2$	0	50
2	$[Ru(COD)Cl_2]_x$	2	53
3	$CpRu(PPh_3)_2Cl$	0	45
4	CpRu(COD)Cl	0	33
5	CpRu(COD)Br	33	5
6	CpRu(COD)I	4	30
7	Cp*Ru(COD)Cl	67 (65)	0
8	Cp*Ru(COD)Br	57	0
9	Cp*Ru(COD)I	63	22
10	$[CpRu(CH_3CN)]PF_6$	1	3
11	$[Cp^*Ru(CH_3CN)]PF_6$	5	10
12	$[RuCl_2(CO)_3]_2$	100 (100)	0

[a]5 mol % of Ru catalyst was used in all cases. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl; COD = cyclooctadienyl. [b]Yields were based on GC using naphthalene as internal standard. Yields in brackets are isolated yields.

TABLE 2. Effect of Solvents



		yield (%)[b]	
entry	solvent[a]	1-naphthnol **8a**	recovered **1a**
1	DCE	100 (100)	0
2	THF	100	0
3	dioxane	100	0
4	acetone	100	0
5	hexanes	99	0
6	toluene	100	0
7	DMF	0	66
8	DMSO	0	67
9	TEA	0	50

[a]DCE = 1,2-dichloroethane; DMF = *N*,*N*-dimethylformamide; DMSO = dimethyl sulfoxide; TEA = triethylamine. [b]Yields were based on GC using naphthalene as internal standard. Yields in brackets are isolated yields.

previously observed as an unwanted side pathway in the rhodium- or nickel-catalyzed nucleophilic ring opening of oxabenzonorbornadienes.[10,11] In this note, we report our investigation on the isomerization of 7-oxabenzonorbornadienes to naphthols catalyzed by ruthenium catalysts.

To begin our investigations, we screened a variety of ruthenium catalysts; the results are shown in Table 1. Among various ruthenium catalysts tested, Cp*Ru(COD)X (where X = Cl, Br and I, entries 7−9), which were found to be useful catalysts in many of our previous studies of metal-catalyzed reactions of 7-oxabenzonorbornadienes (Scheme 1), gave 1-naphthol **8a** in 57−67%. The best yield (quantitative) was obtained when dichlorotricarbonylruthenium(II) dimer, $[RuCl_2(CO)_3]_2$, was used (entry 12).

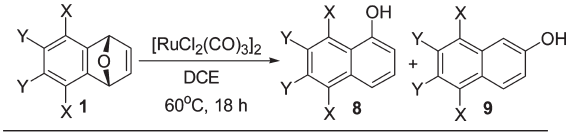
The effect of various solvents on the Ru-catalyzed isomerization of 7-oxabenzonorbornadiene **1a** into 1-naphthol **8a**, using $[RuCl_2(CO)_3]_2$ as the catalyst, is shown in Table 2. Whereas solvents such as DCE, THF, dioxane, acetone, hexanes, and toluene all provided 1-naphthol **8a** in quantitative yields (entries 1−6), the reaction did not occur in DMF, DMSO, and TEA (entries 7−9). The effect of reaction temperature on the $[RuCl_2(CO)_3]_2$-catalyzed isomerization of 7-oxabenzonorbornadiene **1a** into 1-naphthol **8a** in DCE has also been studied. When the reaction was carried out at 80 °C, the starting 7-oxabenzonorbornadiene **1a** was completely consumed and converted into 1-naphthol **8a** in 1 h. At 60 °C it took 2 h for the complete consumption of the starting 7-oxabenzonorbornadiene **1a**, at 40 °C it took 16 h, and at 25 °C it took 168 h.

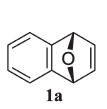
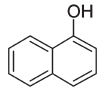
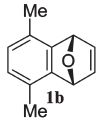
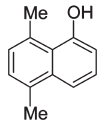
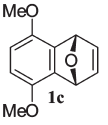
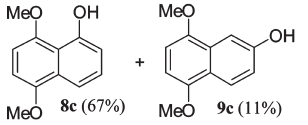
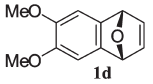
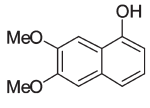
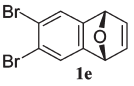
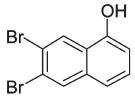
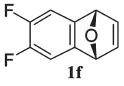
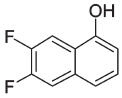
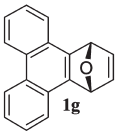
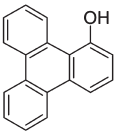
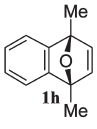
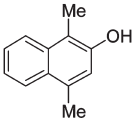
With the optimized conditions for the Ru-catalyzed isomerization of 7-oxabenzonorbornadiene **1a** into 1-naphthol **8a** in hand, the scope of the reaction was then investigated using various 7-oxabenzonorbornadiene substrates; the results are shown in Tables 3 and 4. In the presence of 5 mol % $[RuCl_2(CO)_3]_2$ in DCE, all of the symmetrical 7-oxabenzonorbornadienes **1a**−**h** undergo isomerization to 1-naphthols in good to excellent yields (Table 3). 7-Oxabenzonorbornadienes with electron-withdrawing groups attached to the aryl ring required a much longer reaction time (entries 5 and 6). For example, when dibromo-7-oxabenzonorbornadiene **1e** was treated with 5 mol % of $[RuCl_2(CO)_3]_2$ in DCE for 12 h, only 29% of the corresponding 1-naphthol product **8e** was isolated. It took 144 h to completely consume the dibromo-7-oxabenzonorbornadiene **1e**. Interestingly, whereas both dimethyl-7-oxabenzonorbornadiene **1b** and dimethoxy-7-oxabenzonorbornadiene **1d** gave the 1-naphthol products (**8b** and **8d**) as the only products in good yields (entries 2 and 4), the dimethoxy-7-oxabenzonorbornadiene **1c**, with the methoxy groups at different positions on the aryl ring compared to **1d**, gave both the 1- and 2-naphthol products (**8c** and **9c**) in 68% and 11% isolated yields, respectively (entry 3). Although we do not have a good explanation for this observation, in our previous studies on rhodium(I)-catalyzed cyclodimerization of oxabenzonorbornadienes, we also observed that dimethoxy-7-oxabenzonorbornadiene **1c** and dimethoxy-7-oxabenzonorbornadiene **1d** behaved differently (Scheme 2).[8] While dimethoxy-7-oxabenzonorbornadiene **1c** gave the cyclodimerization product **10** in excellent yield, dimethoxy-7-oxabenzonorbornadiene **1d** did not undergo cyclodimerization. Instead, isomerization of **1d** to 1-naphthol **8d** was observed. Dimethyl-7-oxabenzonorbornadiene **1h**, with the Me groups attached to the bridge junction instead of in the aryl ring, afforded 2-naphthol **8h** in 85% yield (Table 3, entry 8). Note that the classical acid-catalyzed isomerization of some of these 7-oxabenzonorbornadienes (e.g., **1e** and **1f**) led to a complicated mixture of products.[9]

Ru-catalyzed isomerization of unsymmetrical 7-oxabenzonorbornadienes **1i**−**n** into naphthols was also investigated; the results are shown in Table 4. Both unsymmetrical 7-oxabenzonorbornadienes **1i** and **1j** gave a 1:1 inseparable mixture of two 1-naphthol products in excellent yield (entries 1 and 2). On the other hand, for unsymmetrical 7-oxabenzonorbornadiene with an electron-donating OMe group (**1l**, entry 4), 1-naphthol product **8l** was formed preferentially (67%) and 1-naphthol product **9l** was the minor product (5%). With the OMe group at a different position on the aryl ring, unsymmetrical

(10) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259–270. See also ref 8.
(11) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538–3543.

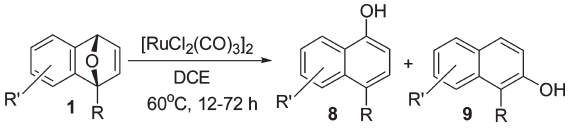
TABLE 3. Ru-Catalyzed Isomerization of Symmetrical 7-Oxabenzonorbornadienes into Naphthols

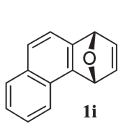
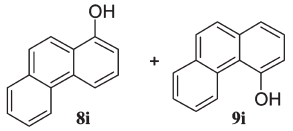
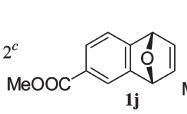
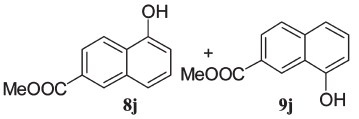
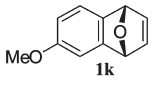
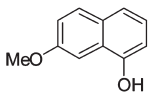
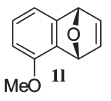
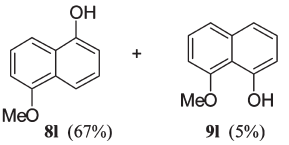
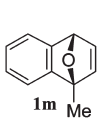
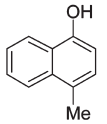
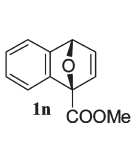
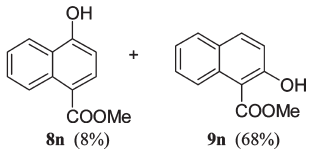


entry[a]	Oxanorbornadiene	Product (yield)[b]
1		 **8a** (100%)
2		 **8b** (83%)
3		 **8c** (67%) + **9c** (11%)
4		 **8d** (82%)
5[c]		 **8e** (90%)
6[d]		 **8f** (87%)
7		 **8g** (95%)
8		 **8h** (85%)

[a]5 mol % of the Ru catalyst was used in all cases. [b]Isolated yields after column chromatography. [c]The reaction was stirred for 144 h. [d]The reaction was stirred for 192 h.

TABLE 4. Ru-Catalyzed Isomerization of Unsymmetrical 7-Oxabenzonorbornadienes into Naphthols



entry[a]	Oxanorbornadiene	Product (yield)[b]
1[c]		 (98%, 1:1 inseparable mixture)
2[c]		 (100%, 1:1 inseparable mixture)
3		 **9k** (83%)
4		 **8l** (67%) **9l** (5%)
5		 **8m** (95%)
6[d]		 **8n** (8%) **9n** (68%)

[a]5 mol % of the Ru catalyst was used in all cases. [b]Isolated yields after column chromatography. [c]The reaction was stirred for 48 h. [d]The reaction was stirred at 80 °C for 72 h.

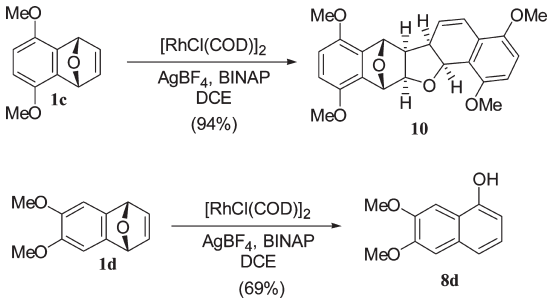
7-oxabenzonorbornadiene **1k** gave a single regioisomer in 83% yield (entry 3). C1-substituted 7-oxabenzonorbornadiene with an alkyl substituent (Me) also gave a single regioisomer of the 1-naphthol product **8m** in excellent yield (entry 5). With an electron-withdrawing C1-substituent (COOMe, entry 6), the 2-naphthol product **9n** was formed as the major regioisomer (68%) and the 1-naphthol product **8n** was the minor isomer (8%).

An explanation for the formation of different regioisomers when the OMe group is located at a different position of the aryl ring (compare Table 3, entries 3 and 4) is proposed in Scheme 3. As a result of the position of the OMe group in **1k**, bond "a" of the C−O bond in the oxabicyclic alkene is more electron-rich. Therefore the Ru will insert in this more electron-rich C−O bond, producing regioisomer **9k** through the formation of intermediates **11** and **12**. On the other hand, the position of the OMe group in **1l** will make bond "b" of the C−O bond in the oxabicyclic alkene more electron-rich. Therefore the Ru will insert in this more electron-rich bond "b", which will result in the formation of intermediates **13** and **14** and lead to the formation of the regioisomer **8l**. Note that isomerizations of **1k** and **1l** with H^+ under protic conditions gave the same major regioisomers as observed in the Ru-catalyzed isomerizations.[12]

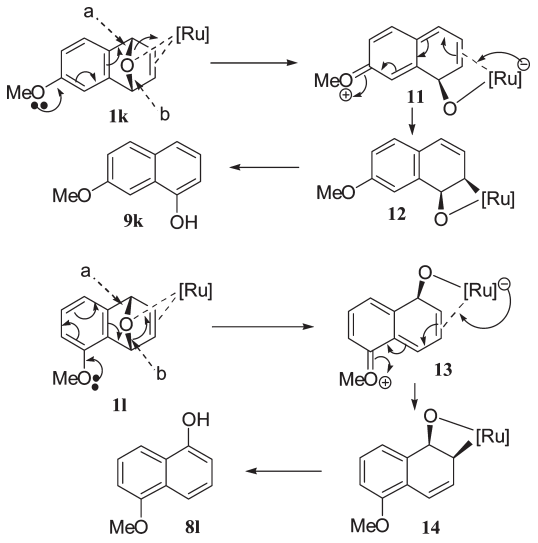
Similar explanations can be used to account for the formation of different regioisomers with C_1-substituted 7-oxabenzonorbornadienes **1m/n** (compare Table 4, entries 5 and 6). With an electron-donating C_1 substitutent (Me), bond "b" of the C−O bond in the oxabicyclic alkene is more electron-rich. The Ru inserting into the more electron-rich C−O bond will result in the formation of intermediates **15** and **16** and lead to the formation of the regioisomer **8m**

(12) (a) Gaviña, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Gil, P. *Tetrahedron* **1986**, *42*, 5641–5648. (b) Batt, D. G.; Jones, D. G.; La Greca, S. *J. Org. Chem.* **1991**, *56*, 6704−6708. See also: (c) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043–8053.

SCHEME 2. Rh-Catalyzed Cyclodimerization and Isomerization of Dimethoxy-7-Oxabenzonorbornadienes 1c and 1d



SCHEME 3. Proposed Explanation for the Formation of Different Regioisomers for 7-Oxabenzonorbornadienes 1k and 1l



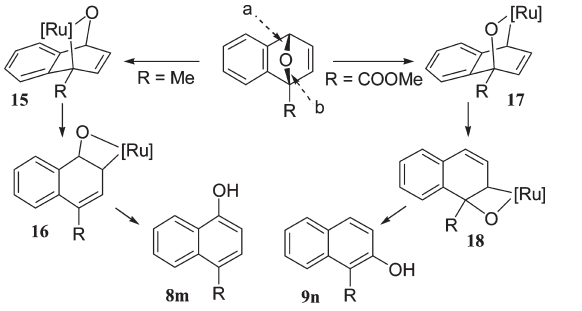
(Scheme 4). With an electron-withdrawing C_1 substitutent (COOMe), bond "a" of the C−O bond in the oxabicyclic alkene is more electron-rich. The Ru inserting in bond "a" will result in the formation of intermediates **17** and **18** and lead to the formation of the 2-naphthol product **9n**.

The possibility of isomerization of nonbenzo 7-oxanorbornadienes and 7-oxanorbornenes was investigated. When 7-oxanorbornadiene **19** and 7-oxanorbornenes **20** and **21** were treated with $[RuCl_2(CO)_3]_2$ in DCE at 60 °C, no reaction was observed and only the starting alkenes were recovered (Scheme 5). However, using Cp*Ru(COD)Cl as the catalyst, 7-oxanorbornadiene **19** gave a homodimerization product **22** in 50% yield. This type of homodimerization product has been observed in the Ni-catalyzed reactions of norbornadienes.[13] 7-Oxanorbornenes **20** and **21** showed no reaction with Cp*Ru(COD)Cl.

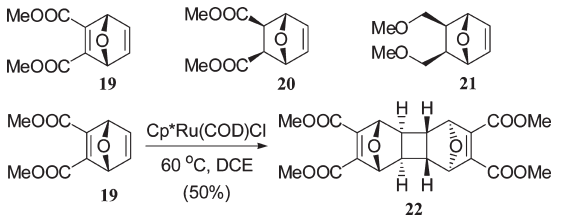
In conclusion, we have investigated the ruthenium-catalyzed isomerization of 7-oxanorbornadienes into naphthols. Among the various ruthenium catalysts tested, $[RuCl_2(CO)_3]_2$ gave the highest yields in the isomerization, and a variety substituted naphthols were synthesized in moderate to excellent yields. Moderate to excellent regioselectivities

(13) (a) Huang, D.-J.; Cheng, C.-H. *J. Organomet. Chem.* **1995**, *490*, C1–C7. (b) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem.—Eur. J.* **2000**, *6*, 3706–3713.

SCHEME 4. Proposed Explanation for the Formation of Different Regioisomers for 7-Oxabenzonorbornadienes 1m and 1n



SCHEME 5. Attempted Isomerization of 7-Oxanorbornadiene 19 and 7-Oxanorbornenes 20 and 21



were observed for the isomerization of unsymmetrical 7-oxanorbornadienes.

Experimental Section

General Procedure for the Ru-Catalyzed Isomerization of 7-Oxanorbornadienes into Naphthols. Inside an inert atmosphere glovebox, a solution of a 7-oxanorbornadiene (0.2 mmol) and 1,2-dichloroethane (0.3 mL) in an oven-dried vial was added to an oven-dried vial containing $[RuCl_2(CO)_3]_2$ (5 mol %). The reaction mixture was taken outside the glovebox and was heated at 60 °C for 12−72 h. The crude product was purified by column chromatography (EtOAc/hexanes mixtures) to give the naphthol products.

4-Methyl-1-naphthol (8m, Table 4, entry 5). Following the above general procedure, using 7-oxabenzonorbornadiene **1m** (28.8 mg, 0.182 mmol), 1,2-dichloroethane (0.3 mL), and $[RuCl_2(CO)_3]_2$ (5.6 mg, 0.011 mmol). The reaction was stirred at 60 °C for 20 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:4) to give 4-methyl-1-naphthol **8m** (27.2 mg, 0.172 mmol, 95%). R_f 0.40 (EtOAc/hexanes = 1:9). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (m, 1H), 7.99 (m, 1H), 7.58 (m, 2H), 7.16 (dd, 1H, J = 7.6, 0.7 Hz), 6.72 (d, 1H, J = 7.6 Hz), 5.37 (br. s, 1H), 2.65 (d, 3H, J = 0.7 Hz). ^{13}C NMR (APT, $CDCl_3$, 100 MHz): δ 149.7, 133.4, 126.7, 126.2, 126.1, 124.9, 124.5, 124.1, 122.0, 108.2, 18.8. HRMS (CI) calcd for $C_{11}H_{10}O$ $[M + H]^+$ 159.0810, found 159.0817.

Acknowledgment. This work was supported by Merck Frosst Centre for Therapeutic Research, Natural Sciences and Engineering Research Council of Canada (NSERC), and Boehringer Ingelheim (Canada) Ltd. M.B. thanks NSERC for providing a postgraduate (CGS D3) scholarship.

Supporting Information Available: Detailed experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.