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Ruthenium-Catalyzed Isomerization of Oxa/Azabicyclic Alkenes: an Expedient Route for the Synthesis of 1,2-Naphthalene Oxides and Imines

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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.[1] Similar isomerization has been previously observed as an unwanted side pathway in the rhodium[2]- or nickel[3]-catalyzed nucleophilic ring opening of oxabenzonorbornadienes. However, metal-catalyzed isomerization of 7-oxabicyclic alkenes to naphthalene oxides has not been explored thus far. 1,2-Naphthalene oxides are known to be important intermediates in the metabolism of aromatic hydrocarbons[4] and can be useful synthetic intermediates.[5] The synthesis of these epoxides usually requires several steps.[6] Herein we report an expedient method to form 1,2-naphthalene oxides **3** in mild conditions from readily available 7-oxabenzonorbornadienes **1**, utilizing Cp*Ru(cod)Cl (Cp* = pentamethylcyclopentadienyl; cod = 1,5-cyclooctadiene). This unprecedented example of a nonmetathesis ruthenium-catalyzed ring opening of oxabicyclic alkenes was also extended to the isomerization of 7-azabenzonorbornadienes to the corresponding 1,2-naphthalene imines.

Since 1,2-naphthalene oxides are known to easily isomerize to the related naphthols in the presence of weak acid or mild heat,[7] our initial efforts were concentrated on the elaboration of optimal conditions for the isomerization of **1a** into 1-naphthol **2a** using the ruthenium catalyst Cp*Ru(cod)Cl. We observed that performing the reaction at 60 °C in either THF, nitromethane, or acetone resulted in slow and incomplete reaction. Using toluene, the reaction was found to be complete in 1 h, giving **2a** in 83% yield. To our delight, employing DMF or 1,2-DCE improved the yield to respectively 90% and 91%. In both cases, a complete conversion of **1a** to **2a** was obtained in 15 min.

Using 1,2-DCE as the solvent,[8] we explored the effect of the temperature. Lowering the temperature from 60 to 45 °C did not affect the yield (90%), although 1 h was required for complete conversion. Further decrease of the temperature to 25 °C resulted in no reaction. Other catalysts were also investigated but Cp*Ru(cod)Cl was the most effective one. No reaction occurred when CpRu(cod)Cl, $[Cp^*Ru(CH_3CN)_3]PF_6$, $[CpRu(CH_3CN)_3]PF_6$, or $CpRu(PPh_3)_2Cl$ were used, and longer reaction time was required with Cp*Ru(cod)Br and Cp*Ru(cod)I.[9]

Most importantly, the conversion of **1a** to 1-naphthol could also be "interrupted" at the 1,2-naphthalene oxide intermediate when the manipulations were carefully operated (Scheme 1). We found that performing the isomerization at 60 °C for 15 min followed by cooling the reaction mixture to 0 °C, filtering over neutral alumina, and evaporating the solvent under reduced pressure at low temperature yielded **3a** (containing less than 5% of **2a**) in 86% isolated yield.

To study the generality of this isomerization reaction, several 7-oxabenzonorbornadienes were synthesized, as depicted in Table 1. As previously observed in our ruthenium-catalyzed [2 + 2] cycloaddition reactions,[10] different functional groups are tolerated in the presence of the catalyst. These groups also play a major role

Scheme 1

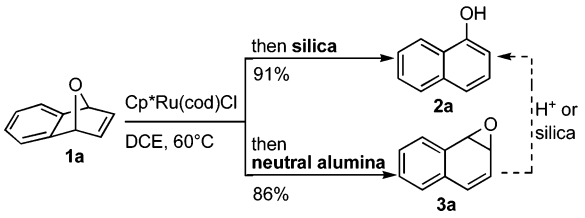
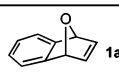
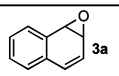
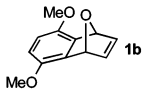
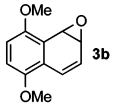
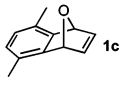
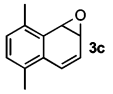
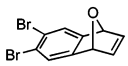
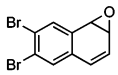
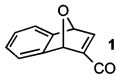
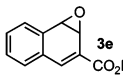
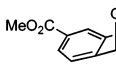
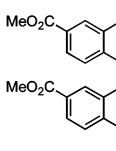
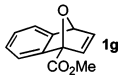
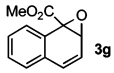
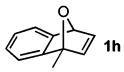
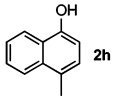


Table 1. Isomerization of Different 7-Oxabenzonorbornadienes

entry	alkene	time[a] (h)	product	yield[c] (%)
1	 **1a**	0.25	 **3a**	86
2	 **1b**	0.25	 **3b**	93
3	 **1c**	0.25	 **3c**	89
4	 **1d**	0.25	 **3d**	88
5	 **1e**	2	 **3e**	82
6	 **1f**	0.25	 **3f** / **3f′**	45 / 35
7	 **1g**	2[b]	 **3g**	81
8	 **1h**	2[b]	 **2h**	85

[a] Cp*Ru(cod)Cl (5 mol %), 1,2-DCE (0.7M), 60 °C. [b] A second portion of Cp*Ru(cod)Cl (5 mol %) was added after 1 h. [c] Isolated yield.

in the stability of the epoxide toward further aromatization to the corresponding naphthol. The presence of an electron-withdrawing group such as an ester (entries 5−7) stabilizes the naphthalene oxide product. The stability of these epoxides (**3e**, **3f**, **3f′**, and **3g**) is indeed reflected in the fact that they can tolerate "for a short period of time" the presence of a weak acid such as silica gel during the purification step. In contrast, electron-donating groups favor the formation of the naphthol product, which occurs in situ in the case of **2h**. When unsymmetrical alkenes were subjected to the reaction conditions, the regioselectivity was significantly affected by the

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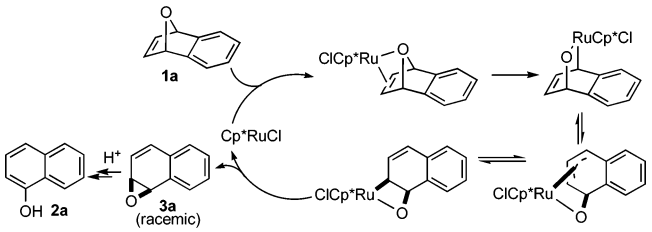
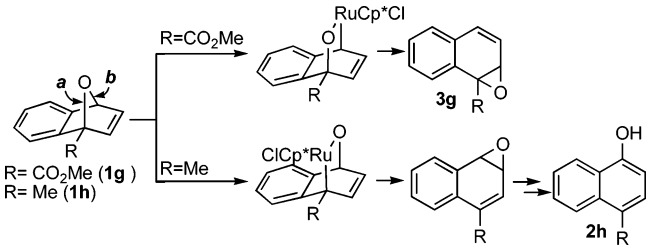
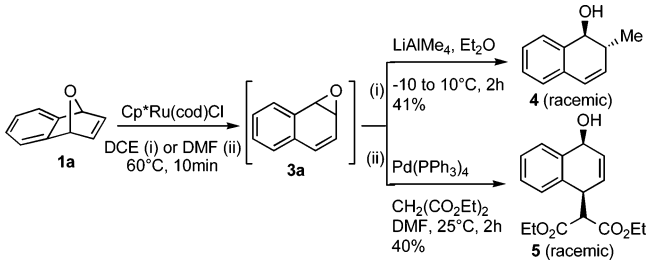
Scheme 2



Scheme 3



Scheme 4



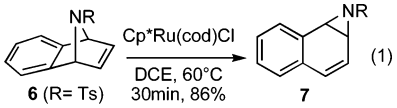
position and the nature of the functional group. In the presence of groups located at the oxabicyclic ring junction (entries 5, 7, and 8), single regioisomers were formed, whereas a poor regioisomeric ratio was observed in the case of a remote ester substituent (entry 6). It is also noteworthy that alkenes **1g** and **1h**, bearing respectively an electron-withdrawing and an electron-donating group at the ring junction, give opposite regioselectivity.

On the basis of the results presented above, a mechanistic pathway divided in two segments accounting for the formation of 1,2-naphthalene oxide and 1-naphthol is proposed in Scheme 2. After dissociation of the cod ligand, the ruthenium catalyst can be chelated by **1a**, which would allow strain release through an oxidative insertion of ruthenium into the C−O bond.[11] Since no nucleophile is present, which precludes nucleophilic ring-opening processes,[2] a reductive elimination closes the epoxide ring and regenerates the catalyst. Finally, the corresponding naphthol **2a** would arise from **3a** as previously described.[7]

One piece of evidence for the insertion into the C−O bond pathway is the fact that opposite regioisomers are formed in the case of **1g** and **1h**. The exclusive formation of 4-methyl-1-naphthol **2h** when **1h** was treated with Cp*Ru(cod)Cl, suggests that oxidative insertion occurs in the most electron-rich C−O bond *a* (Scheme 3).[12] On the other hand, opposite selectivity was observed with alkene **1g**. In this case, oxidative insertion occurs in C−O bond *b*, away from electron-withdrawing methyl ester group.

The instability of arene oxide **3a** could be circumvented by transforming them in situ into more stable products (Scheme 4). On the basis of previous work,[5] we performed a nucleophilic 1,2-addition of $LiAlMe_4$[13] on **3a**, yielding **4** in 41% (unoptimized). Additionally, *cis*-1,4-disubstituted dihydronaphthalenol **5** was synthesized (40% unoptimized yield) by taking advantage of the vinyl epoxide to achieve a palladium-catalyzed allylic substitution with diethylmalonate.[14]

7-Azabenzonorbornadienes could also be subjected to the same conditions. In this case, the choice of the functional group attached on the nitrogen is rather important. No reaction was found to occur when R = CO_2Me or $CO_2{}^tBu$. Alternatively, when utilizing the azabicyclic alkene **6** (R = Ts), the reaction occurred smoothly, and 86% of the aziridine **7**[15] was isolated.



In conclusion, we have demonstrated the first examples of ruthenium-catalyzed isomerization of 7-oxa/azabenzonorbornadienes to their corresponding vinyl epoxides or aziridines. This method presents a mild, simple, and efficient experimental procedure for the preparation of 1,2-naphthalene oxides and imines. Further investigations of the scope of the reaction and the development of a chiral catalyst are currently in progress in our laboratory.

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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.

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(11) C−O insertion has been previously reported with the exact same catalyst, see: Yamamoto, Y.; Nakagai, Y.; Itoh, K. *Chem. Eur. J.* **2004**, *10*, 231 and references therein.
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