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Ruthenium(II)-Catalyzed Cyclization of Azabenzonorbornadienes with Alkynes

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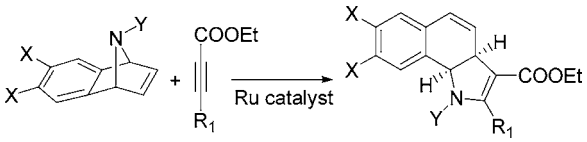
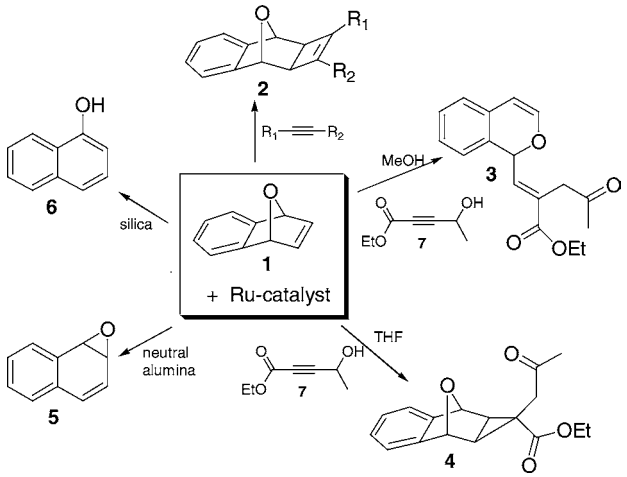
ABSTRACT



The ruthenium-catalyzed cyclization of azabenzonorbornadienes with alkynes leads to an unanticipated dihydrobenzoindole framework. Depending on the structure of the alkyne and the Ru catalyst, either a dihydrobenzoindole and/or a [2+2] cycloaddition product could be formed. Cp*Ru(COD)Cl was found to be an active catalyst for the cyclization of an azabenzonorbornadiene with a propargylic alcohol to produce the dihydrobenz[*g*]indole as a single regio and stereoisomer in good yield. For other alkynes, selective formation of the dihydrobenz[*g*]indole is possible by using a cationic Ru catalyst, [Cp*Ru(CH_3CN)$_3$]PF_6.

Aza- and 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 the formation of several stereocenters in a single step. They are also useful building blocks in molecular architecture.[2] We have recently examined different aspects of ruthenium-catalyzed reactions involving oxabenzonorbornadiene **1** and found that, depending on the reaction conditions, several products (**2**−**6**) could be obtained (Scheme 1). For example, when oxabenzonorbornadiene **1** is treated with an alkyne in the presence of the ruthenium catalyst, Cp*Ru(COD)Cl, a [2+2] cycloaddition is observed, and cyclobutene cycloadduct **2** is formed.[3] When oxabenzonorbornadiene **1** is treated with the secondary propargylic

Scheme 1. Ru-Catalyzed Reactions of Oxabenzonorbornadiene



(1) (a) Lautens, M.; Fagnou, K.; Heibert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (c) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884. (e) Wu, M.-S.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2005**, *70*, 9545. (f) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373. (g) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734. (h) Cabrera, S.; Arrayás, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc. Chem.* **2005**, *127*, 17938. (i) Li, M.; Yan, X.-X.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. *Org. Lett.* **2004**, *6*, 2833 and references therein.

(2) For selected examples of molecular architecture, see (a) Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Philp, D.; Stoddart, J. F. *Pure Appl. Chem.* **1993**, *65*, 119. (b) Warrener, R. N.; Margetic, D.; Sun, G.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1999**, *40*, 4111. (c) Warrener, R. N.; Butler, D. N.; Margetic, D.; Pfeffer, F. M.; Russell, R. A. *Tetrahedron Lett.* **2000**, *41*, 4671. (d) Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363. (e) Warrener, R. N.; Margetic, D.; Foley, P.; Butler, D. N.; Winling, A.; Beales, K. A.; Russell, R. A. *Tetrahedron* **2001**, *57*, 571. (f) Dalphond, J.; Bazzi, H. S.; Kahrim, K.; Sleiman, H. F. *Macromol. Chem. Phys.* **2002**, *203*, 1988. (g) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.

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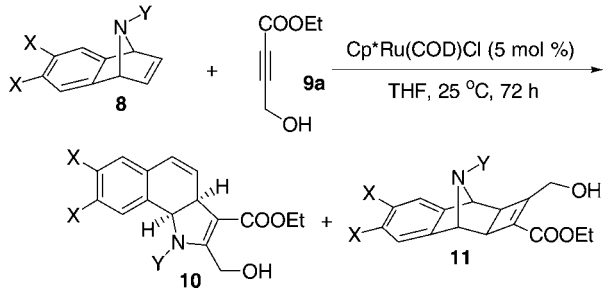
Table 1. Ru-Catalyzed Cyclization of Azabenzonorbornadienes **8a**−**f** with Alkyne **9a**



				yield (%)[a]	
entry	8	Y	X	**10**	**11**
1	**8a**	BOC	H	78 (**10a**)	0
2	**8b**	BOC	Br	59 (**10b**)	0
3	**8c**	COOMe	H	77 (**10c**)	0
4	**8d**	COOBn	H	80 (**10d**)	0
5	**8e**	C(O)^{t}Bu	H	0	82 (**11e**)
6	**8f**	Ts	H	0	trace

[a] Isolated yield after column chromatography.

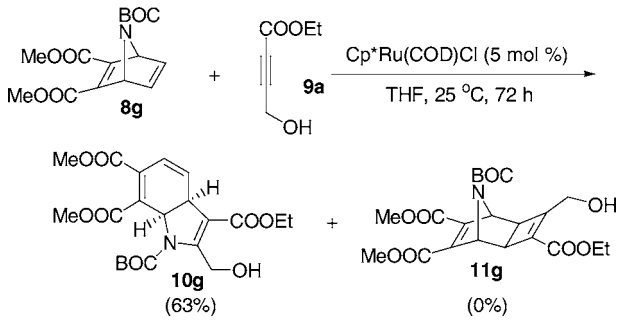
alcohol **7** in the presence of the neutral Ru catalyst, Cp*Ru(COD)Cl, in MeOH or using a cationic Ru catalyst (e.g., $[CpRu(CH_3CN)_3]PF_6$), isochromene **3** is formed.[4] However, if the same reaction between **1** and **7** is carried out with Cp*Ru(COD)Cl in THF, cyclopropane **4** is produced.[5] More recently, we have observed that in the absence of an alkyne, Cp*Ru(COD)Cl catalyzes the isomerization of **1** to the corresponding naphthalene oxide **5** or naphthol **6**.[6]

When we tried to expand the scope of the above reactions using azabenzonorbornadienes, an unexpected result was obtained. When azabenzonorbornadiene **8a** was treated with alkyne **9a** in the presence of Cp*Ru(COD)Cl (5 mol %) in THF at 25 °C, we anticipated [2+2] cycloadduct **11a** would be formed. However, an unanticipated cyclization product **10a**, with a dihydrobenz[*g*]indole framework, was formed as a single regio and stereoisomer (the CH_2OH group of the alkyne ended up adjacent to the nitrogen in the dihydroindole ring, and the two hydrogens in the ring junction are *cis* to each other),[7] and no [2+2] cycloadduct **11a** was detected (Table 1, entry 1). This unexpected result is incredibly interesting and exciting because this reaction provides a novel and very efficient method for the construction of the benzoindole framework,[8] which is present in a number of biologically important compounds, and multiple step syntheses are usually required to generate such a ring system.[9] In this work, we report our initial results on this unprecedented Ru(II)-catalyzed cyclization of azabenzonorbornadienes with alkynes for the formation of the dihydrobenz[*g*]indole framework.

For azabenzonorbornadienes **8a**−**d**, with a carbamate group on the nitrogen (Y = BOC, COOMe or COOBn), good yields of the dihydrobenz[*g*]indoles **10a**−**d** were obtained when treated with alkyne **9a** in the presence of Cp*Ru(COD)Cl (5 mol %) in THF at 25 °C (Table 1, entries 1−4). In all cases, single regio and stereoisomers were obtained, and no [2+2] cycloadduct was detected. However, when the carbamate group was replaced by an amide group (R = CO^{t}Bu, entry 5), only the corresponding [2+2] cycloadduct **11e** was obatined in 82% yield. With a tosyl group on the nitrogen (R = Ts, entry 6), very little reaction was observed.

Azanorbornadiene **8g**, with two methyl ester groups attached to the azabicyclic alkene instead of the benzo group, also undergoes a similar cyclization reaction with alkyne **9a** to provide a single regio and stereoisomer of dihydroindole **10g** as the only product in 63% yield (Scheme 2). Thus, the benzo group of the azabicyclic alkene is not a requirement for this novel type of Ru-catalyzed cyclization.

Scheme 2. Ru-Catalyzed Cyclization of Azanorbornadiene **8g** with Alkyne **9a**



Further investigation of this Ru-catalyzed cyclization of azabenzonorbornadiene **8a** with several different alkynes is shown in Table 2. Literature precedents have shown that varying the halide on certain transition-metal catalysts can

(3) For our recent studies of Ru-catalyzed [2+2] cycloadditions of bicyclic alkenes and alkynes, see (a) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031. (b) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367. (c) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051. (d) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123. (e) Villeneuve, K.; Tam, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 610. (f) Villeneuve, K.; Riddell, N. G.; Jordan, R. W.; Tsui, G.; Tam, W. *Org. Lett.* **2004**, *6*, 4543. (g) Jordan, R. W.; Khoury, P. R.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2004**, *69*, 8467. (h) Riddell, N. G.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (i) Riddell, N. G.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1943. (j) Liu, P.; Jordan, R. W.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2006**, *71*, 3793. (k) Jordan, R. W.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2006**, *71*, 5830.

(4) Villeneuve, K.; Tam, W. *Eur. J. Org. Chem.* **2006**, 5499.

(5) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843.

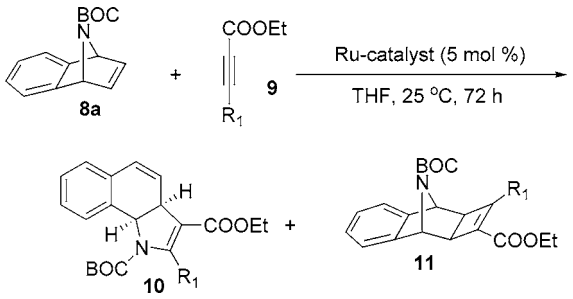
(6) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514.

(7) The regio and stereochemistry of dihydrobenz[*g*]indoles **10** were established by NMR experiments (^{1}H, APT, HCOSY, HSQC, and GOESY).

(8) Dihydrobenzoindoles can be converted to the corresponding benzoindoles by dehydrogenation using Pd/C, see Vernon, J. M.; Ahmed, M.; Kricka, L. J. *J. Chem. Soc. Perkin Trans. I* **1978**, 837.

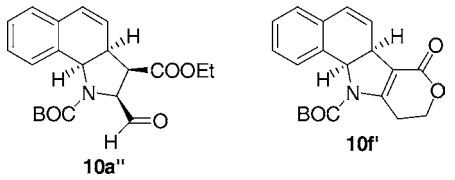
(9) For examples of the structures and synthesis of biologically active compounds containing the benzoindole framework, see (a) Mazza, F. C.; Blake, A. D. *Protein Pept. Lett.* **2004**, *11*, 141. (b) Pinna, G. A.; Pirisi, M. A.; Grella, G. E.; Gherardini, L.; Mussinu, J. M.; Paglietti, G.; Ferrari, A. M.; Rastelli, G. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 337. (c) Kurumi, M.; Sasaki, K.; Takata, H.; Nakayama, T. *J. Heterocycl. Chem.* **2001**, *38*, 6129. (d) Pinna, G. A.; Curzu, M. M.; Sechi, M.; Chelucci, G.; Vianello, P.; Maciocco, E. *IL Farmaco* **1998**, *53*, 684. (e) Ferlin, M. G.; Chiarelotto, G.; Malesani, G. *J. Heterocycl. Chem.* **1989**, *26*, 245. (f) Bhovi, M. G.; SGadaginamath, G. *Indian J. Chem., Sect. B* **2005**, *44B*, 794. (g) Bhovi, M. G.; SGadaginamath, G. *Indian J. Chem., Sect. B* **2005**, *44B*, 1068.

Table 2. Ru-Catalyzed Cyclization of Azabenzonorbornadiene **8a** with Alkynes **9a**−**f**



				yield (%)[a]	
entry	**9**	R_1	Ru-catalyst	**10**	**11**
1	**9a**	CH_2OH	Cp*Ru(COD)Cl	78	0
2			Cp*Ru(COD)Br	77	0
3			Cp*Ru(COD)I	0[c]	0
4[b]			$[Cp^*Ru(CH_3CN)_3]PF_6$	0[d]	0
5	**9b**	Me	Cp*Ru(COD)Cl	35	56
6			Cp*Ru(COD)Br	28	60
7			Cp*Ru(COD)I	0[c]	0
8[b]			$[Cp^*Ru(CH_3CN)_3]PF_6$	82[e]	0
9	**9c**	^{n}Bu	Cp*Ru(COD)Cl	32	62
10[b]			Cp*Ru(COD)Cl	19	75
11[b]			$[Cp^*Ru(CH_3CN)_3]PF_6$	81[f]	0
12	**9d**	CH_2OTBS	Cp*Ru(COD)Cl	10[g]	0
13[b]			$[Cp^*Ru(CH_3CN)_3]PF_6$	35[h,g]	0
14	**9e**	CH_2CH_2OTBS	Cp*Ru(COD)Cl	15[g]	25
15[b]			$[Cp^*Ru(CH_3CN)_3]PF_6$	40[i,g]	0
16	**9f**	CH_2CH_2OH	Cp*Ru(COD)Cl	22	75
17[b]			$[Cp^*Ru(CH_3CN)_3]PF_6$	36[j,k]	29

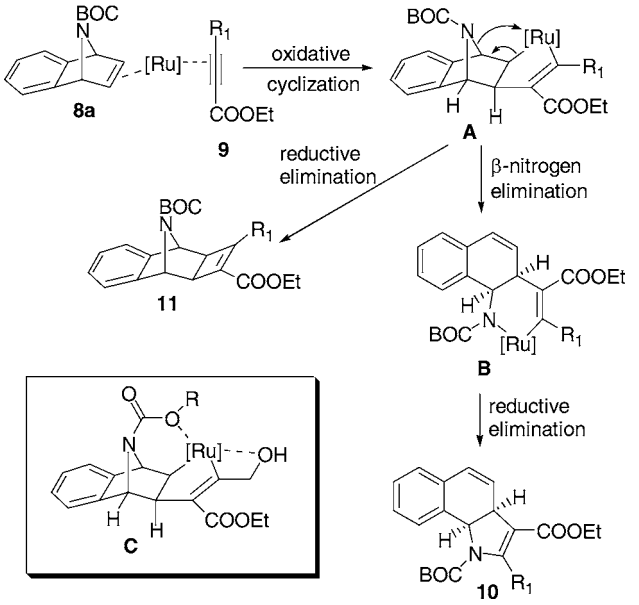
[a] Isolated yield after column chromatography. [b] Reaction was carried out at 65 °C as very little reaction was observed at 25 °C. [c] No reaction was observed, and only starting materials were recovered. [d] 46% of compound **10a″** was formed instead. [e] As an 8:1 mixture of two regioisomers. [f] As a 7:1 mixture of two regioisomers. [g] The reaction did not go to completion, and starting materials were recovered. [h] As a 4:1 mixture of two regioisomers. [i] As a 6:1 mixture of two regioisomers. [j] 36% of the lactonized product **10f′** was isolated as the major product instead of **10f**. [k] As a 5:1 mixture of two regioisomers.



modulate their activity and/or selectivity.[10] For alkyne **9a**, the use of both Cp*Ru(COD)Cl and Cp*Ru(COD)Br afforded the dihydrobenz[*g*]indole **10a** as a single regio and stereoisomer in comparable yields (entries 1 and 2). However, Cp*Ru(COD)I was found to be completely inactive, and only starting materials were recovered (entry 3). Interestingly, the use of a cationic Ru(II) catalyst (entry 4) provided compound **10a″** instead of the dihydrobenz[*g*]indole **10a**. Resubmitting the dihydrobenz[*g*]indole **10a** to the reaction conditions (5 mol % $[Cp^*Ru(CH_3CN)_3]PF_6$ in THF at 65 °C) did not afford compound **10a″**, and only **10a** was recovered. For alkynes **9b** and **9c** (without the propargylic alcohol group), a different trend was observed. When Cp*Ru(COD)Cl and Cp*Ru(COD)Br were used (entries 5, 6, and 9), a mixture of the dihydrobenz[*g*]indole **10** (as a single regio and stereoisomer) and the [2+2] cycloaddition product **11** was formed. However, the use of the cationic Ru catalyst (entries 8 and 11) gave only the dihydrobenz[*g*]indole **10** in good yields, but in these cases, instead of a single regio and stereoisomer as observed previously, two regioisomers were formed in a ratio of 7−8:1. (The major regioisomer was **10**, with the R_1 group adjacent to the nitrogen in the dihydroindole ring, and the minor isomer was **10′** with the COOEt group adjacent to the nitrogen in the dihydroindole ring.) Both alkynes **9d** and **9e** were found to be less reactive than alkynes **9a**−**c**, and the reactions did not go to completion regardless of which catalyst was being used. Reaction of homopropargylic alcohol **9f** using Cp*Ru(COD)Cl provided **10f** and the [2+2] cycloadduct **11f** in 22% and 75%, respectively. Using the cationic Ru catalyst gave 36% of the lactonized product **10f′**, together with 29% of **11f**.

A plausible mechanism has been devised for the formation of the dihydrobenz[*g*]indole **10** (Scheme 3). After coordination of the azabicyclic alkene and the alkyne with the Ru catalyst, oxidative cyclization would provide ruthenacyclopentene intermediate **A**. Reductive elimination of **A** would give the corresponding [2+2] cycloaddition product **11**, as commonly observed with carbo and oxabicyclic alkenes.[3] Alternatively, a β-nitrogen elimination[11] of **A** would produce a six-membered azaruthenium complex **B** (this would explain the *cis* orientation of the two hydrogens in the ring junction) followed by reductive elimination to produce the observed

Scheme 3. Plausible Mechanistic Pathway for the Formation of Dihydrobenz[*g*]indole **10**



(10) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(11) A similar type of β-oxygen elimination has been reported with Ni-catalyzed cyclization reactions with oxabicyclic alkenes, see Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.−H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286.

dihydrobenz[*g*]indole **10**. In our previous studies on Ru-catalyzed [2+2] cycloadditions of norbornadienes with unsymmetric alkynes, we have demonstrated that when one of the substituents on the alkyne is an ester, usually the first carbon−carbon bond being formed in the oxidative cyclization step is between the bicyclic alkene and the alkynyl carbon that is attached to the ester (not to the alkynyl carbon attached to the R_1 group).[3g,j] This would explain the regiochemistry of the dihydrobenz[*g*]indole **10** in which the R_1 group is adjacent to the nitrogen in the dihydroindole ring.

The possibility of the coordination of the carbamate oxygen and the propargylic alcohol group to the [Ru] in the ruthenacyclopentene **C** (Scheme 3) may explain some of the results shown in Tables 1 and 2. The results in Table 1 show that for azabenzonorbornadienes **8a**−**d**, with a carbamate group on the nitrogen (Table 1, entries 1−4), the dihydrobenz[*g*]indoles **10a**−**d** were formed as the only products. However, when the carbamate group was replaced by an amide group (R = CO^{t}Bu, Table 1, entry 5), only the corresponding [2+2] cycloadduct **11e** was obtained. The coordination of the carbamate oxygen to the [Ru] in the ruthenacyclopentene **C** (Scheme 3) may slow down the reductive elimination step (**A** to **11**), and the alternative pathway **A** to **B** dominates, which would lead to the formation of the dihydrobenz[*g*]indole **10**. In Table 2, the propargylic alcohol **9a** exclusively produced the dihydrobenz[*g*]indole **10a**, whereas other alkynes without the propargylic alcohol group gave a mixture of the dihydrobenz[*g*]indole **10** and the [2+2] cycloaddition product **11**. This may due to the fact that the propargylic alcohol group could coordinate to the Ru in the ruthenacyclopentene **C** (Scheme 3) and slow down the reductive elimination step (**A** to **11**); thus, the alternative pathway **A** to **B** becomes the dominate reaction pathway.

In summary, we have demonstrated an unprecedented Ru(II)-catalyzed cyclization of azabenzonorbornadienes with alkynes for the formation of the dihydrobenz[*g*]indole framework. Cp*Ru(COD)Cl was found to be an active catalyst for the cyclization of azabenzonorbornadienes **8a**−**d** with propargylic alcohol **9a** to produce the dihydrobenz[*g*]indole **10a**−**d** as single regio and stereoisomers. For other alkynes **(9b**−**e**), selective formation of the dihydrobenz[*g*]indole **10** is possible by using a cationic Ru catalyst, [Cp*Ru(CH$_3$CN)$_3$]PF$_6$. This novel reaction provides an efficient route to the synthesis of the benz[*g*]indole framework that is present in a number of biologically important compounds. Further investigations of the scope, mechanism, and applications of this reaction are currently in progress in our laboratory.

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

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