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Ruthenium-Catalyzed Nucleophilic Ring-Opening Reactions of a 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene with Alcohols

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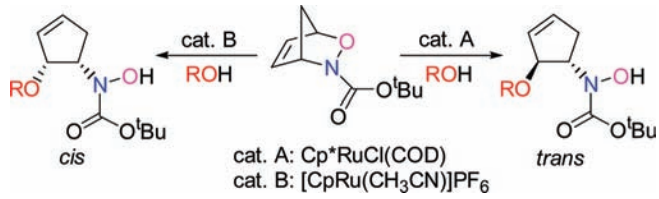
ABSTRACT



Ruthenium-catalyzed nucleophilic ring-opening reactions of a 3-aza-2-oxabicyclo[2.2.1]hept-5-ene with alcohols were investigated. When a neutral ruthenium(II) catalyst, Cp*RuCl(COD), was used in MeOH, the *trans*-1,2-ring opened product was formed as the only regio- and stereoisomer. On the other hand, when a cationic ruthenium(II) catalyst, [CpRu(CH$_3$CN)$_3$]PF$_6$, was used in MeOH, the *cis*-1,2-ring opened product was formed exclusively. Moderate to excellent stereoselectivity (70:30 to 100:0) was observed with various alcohols.

Heterobicyclic alkenes such as **1**−**5** (Figure 1) are valuable synthetic intermediates as they can serve as a general template to create highly substituted ring systems.[1] For example, ring-opening reactions of these alkenes allow for the formation of several stereocenters in a single step.[2−5] We have recently examined different aspects of Ru-catalyzed reactions involving oxa- and azanorbornadienes **1a** and **3** and found that depending on the reaction conditions different products (**6**−**10** and **13**) could be obtained (Scheme 1).[4b,6−10]

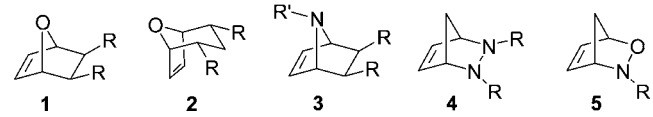


Figure 1. Heterobicyclic alkenes.

3-Aza-2-oxabicyclo[2.2.1]hept-5-enes **5** are readily available by the hetero-Diels−Alder reaction between cyclopentadiene and nitroso dienophiles, and they are useful synthetic intermediates.[11] Several modes of ring-opening reactions of these 3-aza-2-oxabicyclo[2.2.1]hept-5-ene ring systems have been studied in the literature (Scheme 2), including: (i) reductive cleavage of the N−O bond (path a);[12] (ii) oxidative cleavage of the C═C bond (path b);[13] (iii) cleavage of the C═C bond by metathesis reactions (path c);[14] (iv) acid-

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(1) For reviews, see: (a) Bournaud, C.; Chung, F.; Luna, A. P.; Pasco, M.; Errasti, G.; Lecourt, T.; Micouin, L. *Synthesis* **2009**, 869–887. (b) Rayabarapu, D. K.; Cheng, C.-H. *Acc. Chem. Res.* **2007**, *40*, 971–983. (c) Lautens, M.; Fagnou, K.; Heibert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58. (d) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348.

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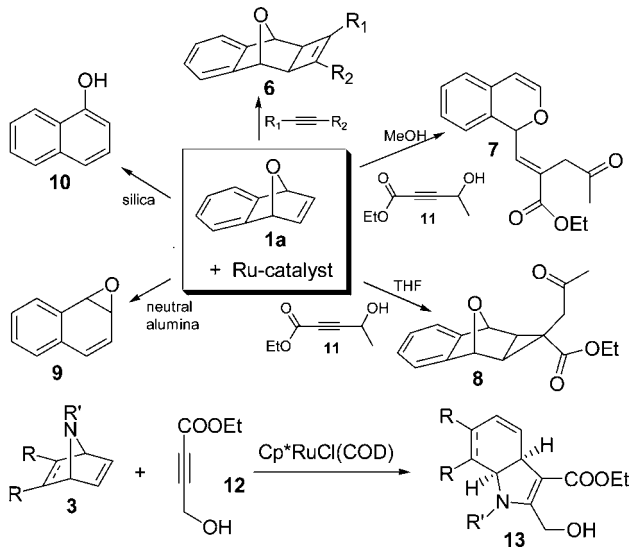
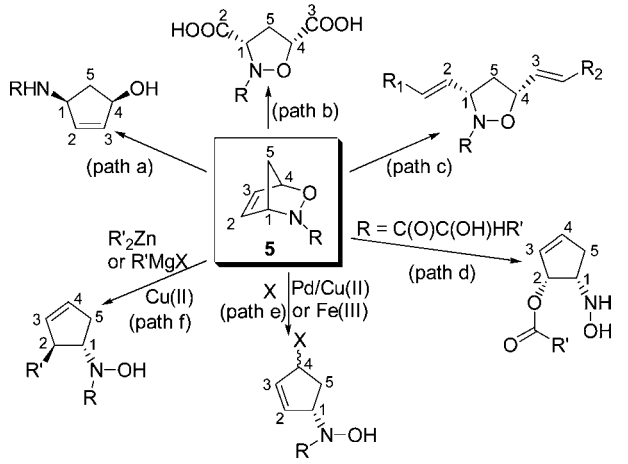
Scheme 1. Ru-Catalyzed Reactions of Oxa- and Azanorbornadienes



Scheme 2. Different Modes of Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.1]hept-5-enes **5**



mediated ring-opening rearrangement (path d);[15] (v) Pd and Lewis acid catalyzed ring-opening reactions (path e);[16] and (vi) Cu-catalyzed Grignard or organozinc or nucleophilic ring-opening reactions (path f).[17] In this paper, we report our initial results on Ru-catalyzed nucleophilic ring-opening reactions of a 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5** with alcohols. To the best of our knowledge, no examples of Ru-catalyzed nucleophilic ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes **5** have been reported in the literature.

To begin our investigation, 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** was prepared[18] and was subjected to various Ru catalysts in the presence of MeOH (Table 1). Unlike using Pd(0),[16d] Pd/Cu(II),[16c] Pd/InI,[16a] or Lewis acids (such as Fe(III) or Cu(II))[16b] which results in the formation of 1,4-cyclopentene ring-opened products (Scheme 2, path e), the use of Ru catalysts lead to the formation of 1,2-cyclopentene ring-opened products instead. Using neutral Ru catalysts (Table 1, entries 1−10), the *trans*-1,2-cyclopentene ***trans*-14** was formed as the only product in low to moderate yields. On the other hand, when a cationic

(2) For selected examples of ring-opening reactions of 7-oxabicyclo-[2.2.1]heptenes **1**, 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.

(3) For selected examples of ring-opening reactions of 7-oxabicyclo-[3.2.1]octenes **2**, 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 ring-opening reactions of 7-azabicyclo-[2.2.1]heptenes **3**, see: (a) Tenaglia, A.; Marc, S. *J. Org. Chem.* **2008**, *73*, 1397–1402. (b) Burton, R. R.; Tam, W. *Org. Lett.* **2007**, *9*, 3287–3290. (c) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465–3468.

(5) For selected examples of ring-opening reactions of 2,3-diazabicyclo[2.2.1]heptenes **4**, see: (a) Bournaud, C.; Lecourt, T.; Micouin, L.; Meliet, C.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2008**, 2298–2302. (b) Menard, F.; Weise, C. F.; Lautens, M. *Org. Lett.* **2007**, *9*, 5365–5367. (c) Bertolini, F.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 9173–9176. (d) John, J.; Sajisha, V. S.; Mohanlal, S.; Radhakrishnan, K. V. *Chem. Commun.* **2006**, 3510–3512. (e) Pineschi, M.; Moro, F. D.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605–3607.

(6) 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.

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

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

(9) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514–3515.

(10) For examples of Rh-catalyzed asymmetric dimerization of oxabenzonorbornadienes, see: (a) Allen, A.; Le Marquand, P.; Burton, R.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7849–7857. (b) Nishimura, T.; Kawamoto, T.; Sasaki, K.; Tsurumaki, E.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 1492–1493.

(11) For reviews, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. See also ref 1d.

(12) For selected examples of reductive N−O bond cleavage of 3-aza-2-oxa bicyclo[2.2.1]heptenes **5**, see: (a) Cesario, C.; Tardibono, L. P.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 448–451. (b) Galvani, G.; Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Biomol. Chem.* **2008**, *6*, 1063–1070. (c) Li, F.; Miller, M. *J. Org. Chem.* **2006**, *71*, 5221–5227. (d) Kim, K.-H.; Miller, M. J. *Tetrahedron Lett.* **2003**, *44*, 4571–4573. (e) Cowart, M.; Bennett, M. J.; Kerwin, J. F. *J. Org. Chem.* **1999**, *64*, 2240–2249. (f) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602–4611.

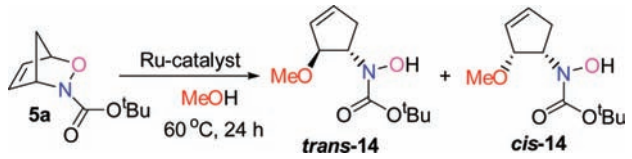
(13) For selected examples of oxidative cleavage of the C═C bond of 3-aza-2-oxa bicyclo[2.2.1]heptenes **5**, see: (a) Nora, G. P.; Miller, M. J.; Möllmann, U. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3966–3970. (b) Pepper, A. G.; Procter, G.; Voyle, M. *Chem. Commun.* **2002**, 1066–1067. (c) Heinz, L. J.; Lunn, W. H. W.; Murff, R. E.; Paschal, J. W.; Spangle, L. A. *J. Org. Chem.* **1996**, *61*, 4838–4841.

(14) For selected examples of clevage of the C═C bond of 3-aza-2-oxa bicyclo[2.2.1]heptenes **5** by metathesis reactions, see: (a) Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 1485–1488. (b) Ellis, J. M.; King, S. B. *Tetrahedron Lett.* **2002**, *43*, 5833–5835.

(15) For acid-mediated ring-opening reaction of 3-aza-2-oxa bicyclo-[2.2.1]heptenes **5**, see: Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7535–7538.

(16) For palladium and Lewis-acid catalyzed ring-opening reactions of 3-aza-2-oxa bicyclo[2.2.1]heptenes **5**, see: (a) Lee, W.; Kim, K.-H; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 139–149. (b) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139–141. (c) Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 2466–2469. (d) Surman, M. D.; Miller, M. J. *Org. Lett.* **2001**, *3*, 519–521. (e) Mulvihill, M. J.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4874–4875.

Table 1. Ru-Catalyzed Nucleophilic Ring-Opening Reaction of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** with MeOH Using Different Ru Catalysts



entry	Ru catalyst[a]	yield (%)[b]	ratio *trans*-14:*cis*-14
1	$RuCl_2(PPh_3)_3$	3	100:0
2	$[RuCl_2(CO)]_2$	23	100:0
3	$[RuCl_2(COD)]_x$	14	100:0
4	$CpRuCl(PPh_3)_2$	39	100:0
5	CpRuCl(COD)	43	100:0
6	CpRuBr(COD)	40	100:0
7	CpRuI(COD)	18	100:0
8	Cp*RuCl(COD)	66 (57)	100:0
9	Cp*RuBr(COD)	46	100:0
10	Cp*RuI(COD)	0	N/A
11	$[CpRu(CH_3CN)_3]PF_6$	48 (44)	0:100
12	$[Cp^*Ru(CH_3CN)_3]PF_6$	14	0:100

[a] 5−10 mol % of Ru catalyst was used. [b] Yields were based on GC using naphthalene as the internal standard. Yields in brackets are isolated yields.

Ru catalyst was used (entries 11−12), the *cis*-1,2-cyclopentene ***cis*-14** was formed instead. While the neutral Cp*RuCl(COD) catalyst gave the highest yield of ***trans*-14** (entry 8), the cationic $[CpRu(CH_3CN)]PF_6$ catalyst provided the best yield for the ***cis*-14** 1,2-cyclopentene ring-opened product (entry 11).[19]

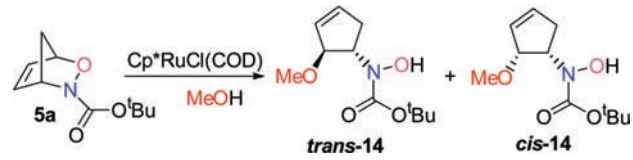
The effects of reaction temperature, time, and the use of cosolvent when Cp*RuCl(COD) is used in the presence of MeOH are shown in Table 2. Very little reaction is observed when the reaction is carried out at 25 °C (Table 2, entry 1). At 40 °C, the reaction was completed in 18 h, giving the optimized yield of ***trans*-14** as the only product. Increasing the temperature to 60 °C led to a slight decrease in yield (compare entries 3 and 6). Note that when 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** was treated with Cp*RuCl(COD) in THF or 1,2-dichloroethane (DCE) at 40 or 60 °C in the absence of MeOH decomposition of **5a** was observed (lots of spots were observed on TLC). When cosolvents such as THF and DCE were used in a 1:1 ratio with MeOH (entries 7 and 10), the reaction also proceeded and gave results similar to using MeOH alone.

(17) For copper-catalyzed Grignard or organozinc nucleophilic ring-opening reactions, see: (a) Pineschi, M.; Moro, F. D.; Crotti, P.; Macchia, F. *Pure Appl. Chem.* **2006**, *78*, 463–467. (b) Pineschi, M.; Moro, F. D.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605–3607. (c) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *J. Org. Chem.* **2001**, *67*, 4115–4121. (d) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Tetrahedron Lett.* **2002**, *43*, 1131–1134.

(18) Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M.-C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. *Tetrahedron* **2004**, *60*, 2559–2567.

(19) The regio- (1,2-cyclopentene vs 1,4-cyclopentene ring-opened products) and stereochemistry (*trans* vs *cis*) of the products were confirmed by various 1D and 2D NMR experiments (HCOSY, HSQC, and NOE).

Table 2. Effects of Reaction Temperature, Time, and Cosolvent

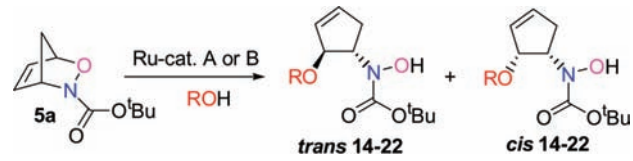


entry[a]	temp (°C)	time (h)	cocolvent[b]	yield (%)[c]	ratio *trans*-14:*cis*-14
1	25	72	–	0	N/A
2	40	2	–	63	100:0
3	40	18	–	74(62)	100:0
4	60	0.5	–	44	100:0
5	60	1	–	54(50)	100:0
6	60	24	–	66(57)	100:0
7	40	18	THF	69	100:0
8	40	18	THF[d]	26	100:0
9	40	18	toluene	0[e]	N/A
10	40	18	DCE	67	100:0
11	40	18	hexanes	50	74:26
12	40	18	1, 4-dioxane	82	90:10

[a] 10 mol % of Cp*RuCl(COD) was used. [b] MeOH/cosolvent (1:1). [c] Yields were based on the GC using naphthalene as internal standard. Yields in brackets are isolated yields. [d] MeOH/THF (1:5). [e] Decomposition of **5a** was observed.

However, an increase in the amount of cosolvent led to a significant decrease in yield (entry 8). The use of toluene as cosolvent shut down the reaction (entry 9), and the use of hexanes or 1,4-dioxane as cosolvents led to the formation of some ***cis*-14** (entries 11 and 12).

Table 3. Ru-Catalyzed Nucleophilic Ring-Opening Reaction of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** with Different Alcohol Nucleophiles



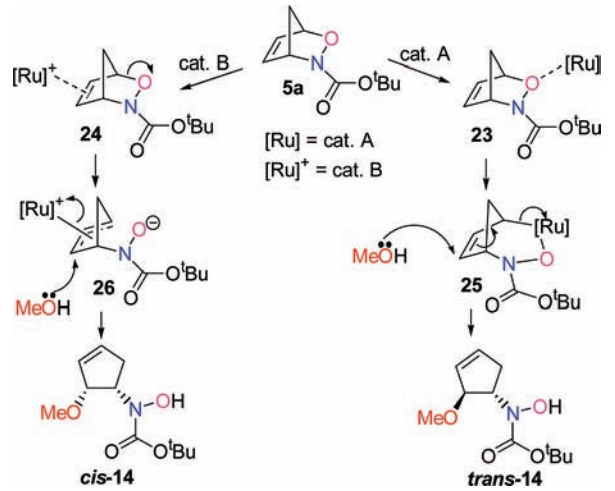
entry	Ru catalyst[a]	ROH	temp (°C)	time (h)	isolated yield (%)[b]	ratio *trans*:*cis*
1	A	MeOH	40	18	62	100:0
2		EtOH	40	18	85	100:0
3		^{i}PrOH	60	72	55	100:0
4		^{n}BuOH	60	60	42	100:0
5		^{i}BuOH	40	60	37	89:11
6		^{s}BuOH	60	72	28	100:0
7		neopentylOH[c]	60	72	26	100:0
8		$HO(CH_2)_2OH$[d]	40	18	63	100:0
9		$MeO(CH_2)_2OH$	40	16	71	100:0
10	B	MeOH	40	18	44	0:100
11		EtOH	40	18	72	21:79
12		^{i}PrOH	60	71	46	30:70
13		^{n}BuOH	60	72	46	22:78
14		^{i}BuOH	60	72	51	26:74
15		^{s}BuOH	60	72	41	29:71
16		neopentylOH[c]	60	72	43	18:82
17		$HO(CH_2)_2OH$[d]	40	19	0	N/A
18		$MeO(CH_2)_2OH$	40	19	41	23:77

[a] Ru catalyst A = Cp*RuCl(COD), Ru catalyst B = $[CpRu(CH_3CN)_3]PF_6$. [b] Isolated yields after column chromatography. When a *trans*/*cis* mixture was obtained, the yields represented the combined isloated yields. In most cases, the *trans* and *cis* isomers were separable by column chromatography. [c] THF was used as a cosolvent. [d] DCE was used as a cosolvent.

The scope of the Ru-catalyzed nucelophilic ring-opening reactions of **5a** using various alcohol nucleophiles is shown in Table 3. When the neutral Cp*RuCl(COD) catalyst (A) was used (entries 1−9), all the alcohol nucleophiles gave the *trans* 1,2-ring-opened products as the only regio- and stereoisomers, except for ^{i}BuOH which gave a 89:11 mixture of *trans*/*cis* isomers. While good yields were obtained with nonbulky 1° alcohols, for bulky 1° alcohols (^{i}BuOH and neopentylOH, entries 5 and 7) and 2° alcohols (^{i}PrOH and ^{s}BuOH, entries 3 and 6) low to moderate yields were observed and required longer reaction time and higher temperature. With 3° alcohols (e.g., ^{t}BuOH), only decomposition was observed. When the cationic Ru catalyst [CpRu(CH_3CN)]PF_6 (B) was used (entries 10−18), the reactions were still highly regioselective, giving only the 1,2-ring-opening products (no 1,4-ring-opening products were observed). When MeOH was used as the nucleophile, the *cis*-1,2-cyclopentene ring-opening product was formed exclusively (entry 10). All other alcohols gave a mixture of the *trans*/*cis* isomers in favor of the *cis* isomers. In all cases, the *trans* and *cis* isomers were readily separable by column chromatography, and their regio- and stereochemistry were identified by various NMR experiments (HCOSY, HSQC, and NOE).

Our rationale for the formation of the different stereosiomers using the two different catalysts is shown in Scheme 3. As we previosuly observed in the reactions of **1a**, the neutral Cp*RuCl(COD) catalyst prefers to coordinate to the oxygen of the bicyclic alkene.[6c,9] Thus, when the neutral Cp*RuCl(COD) (cat. A) was used, the Ru coordinates to the oxygen of the bicyclic alkene **5a**, giving intermediate **23**. Insertion of the Ru to the C−O bond would give **25**.[9] The MeOH nucleophile will add from the less hindered, *exo* face of the bicyclic framework, resulting in the formation of ***trans*-14**. On the other hand, when the cationic [CpRu(CH_3CN)]PF_6 (cat. B) was used, the Ru coordinates with the alkene to give intermediate **24**. Formation of a π-allyl complex followed by addition of the MeOH from the *endo* face gives the *cis*-1,2-ring-opened product ***cis*-14**.

Scheme 3. Proposed Mechanism



In summary, we have demonstrated unprecedented Ru-catalyzed nucleophilic ring-opening reactions of a 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5** with alcohols. The reactions were found to be highly regioselective, giving only the 1,2-cyclopentene ring-opening products. The *trans* and *cis* isomers could be generated selectively by using either a neutral or a cationic Ru catalyst. 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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