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Rhodium-Catalyzed Ring-Opening Reactions of a 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene with Arylboronic Acids

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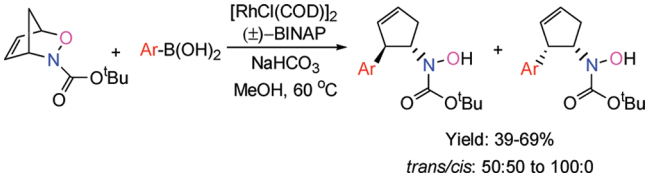

Rhodium-catalyzed ring-opening reactions of a 3-aza-2-oxabicyclo[2.2.1]hept-5-ene with arylboronic acids were investigated. The use of $[RhCl(COD)]_2$, (±)-BINAP, and $NaHCO_3$ in MeOH at 60 °C was found to be the optimized conditions for the ring-opening reactions to give the 1,2-ring-opened products. Various arylboronic acids were examined, and low to moderate yields were obtained and stereoselectivities (*trans*/*cis*) from 50:50 to 100:0 were observed.

Introduction

Transition-metal-catalyzed ring-opening reactions of heterobicyclic alkenes[1] such as 7-oxabicyclo[2.2.1]heptenes **1**,[2] 7-oxabicyclo[3.2.1]octenes **2**,[3] 7-azabicyclo[2.2.1]heptenes **3**,[4] 2,3-diazabicyclo[2.2.1]heptenes **4**,[5] and 3-aza-2-oxabicyclo[2.2.1]heptenes **5** (Figure 1) are very useful methodologies in organic synthesis. These methods allow the formation of several stereocenters in a single step and are useful to create highly substituted ring systems efficiently. The combination of a strained bicyclic structure and a carbon−carbon double bond in the bicyclic framework of these bicyclic alkenes allows them to be easily activated by transition-metal

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(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 Pd-catalyzed ring opening reactions of heterobicyclic alkenes, see: (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3944–3947. (b) Li, L. −P.; Rayabarapu, D. K.; Nandi, M.; Cheng, C. −H. *Org. Lett.* **2003**, *5*, 1621–1624. (c) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695–3698. See also ref 2c and 2e.

(7) For selected examples of Rh-catalyzed ring-opening reactions of heterobicyclic alkenes, see: (a) Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837–6846. (b) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194–2196. (c) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884–14892. (d) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311–1314. (e) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390–391. (f) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259–270. (g) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067–5072. (h) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650–5651.

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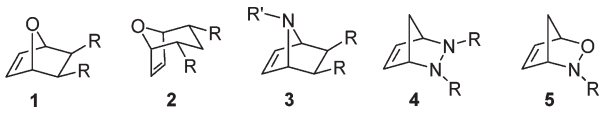
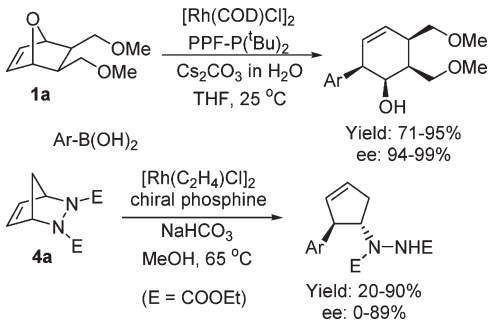


FIGURE 1. Heterobicyclic alkenes.

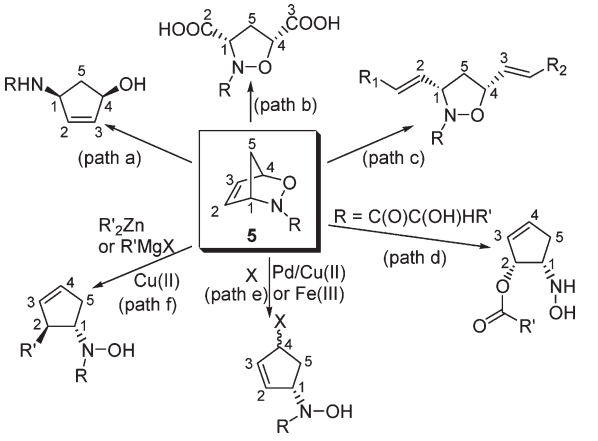
SCHEME 1. Rh-Catalyzed Ring-Opening Reactions of 1a and 4a with Arylboronic Acids



catalysts in a face-selective manner. Various transition metals, such as palladium,[6] rhodium,[7] nickel,[8] copper,[9] iron,[10] titanium,[11] and zirconium,[11] were found to be effective catalysts in the ring-opening reactions of heterobicyclic alkenes. In particular, the use of rhodium catalysts allowed the addition of various nucleophiles such as alcohols,[7f,h] amines,[7a,f] carboxylates,[7g] thiols,[7b] and arylboronic acids[7d,e] to selected heterobicyclic alkenes with good control of regio-, stereo-, and enantioselectivities. For example, asymmetric Rh-catalyzed ring-opening reactions of 7-oxabicyclo[2.2.1]-heptene **1a** and 2,3-diazabicyclo[2.2.1]heptene **4a** with arylboronic acids gave the corresponding ring-opening products in good yields and excellent enantioselectivities (Scheme 1).[7d,e] However, to the best of our knowledge, no example of Rh-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo-[2.2.1]heptenes **5** with arylboronic acids have been reported in the literature. Unlike heterobicyclic alkenes **1** and **4** which are symmetrical, 3-aza-2-oxabicyclo[2.2.1]heptenes **5** are unsymmetrical, and it would be interesting to study the regio- (1,2-vs 1,4-ring-opening) and stereoselectivities (*trans* or *cis*) of the ring-opening reactions of this class of heterobicyclic alkene.

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.[12] Several modes of ring-opening reactions of

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



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);[13] (ii) oxidative cleavage of the C=C bond (path b);[14] (iii) cleavage of the C=C bond by metathesis reactions (path c);[15] (iv) acid-mediated ring-opening rearrangement (path d);[16] (v) palladium- and Lewis acid-catalyzed ring-opening reactions (path e);[17] and (vi) copper-catalyzed Grignard or organozinc nucleophilic ring-opening reactions (path f).[18] We have recently reported the first examples of Ru-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** with alcohols (Scheme 3),[19] and 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 Cp*RuCl-(COD) catalyst or a cationic $[CpRu(CH_3CN)]PF_6$ catalyst.

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(13) For selected examples of reductive N−O bond cleavage of 3-aza-2-oxabicyclo[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.

(14) For selected examples of oxidative cleavage of the C=C bond of 3-aza-2-oxabicyclo[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.

(15) For selected examples of clevage of the C=C bond of 3-aza-2-oxabicyclo[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.

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

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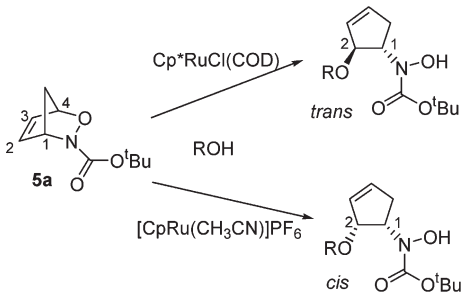
(18) For copper-catalyzed Grignard or organozinc nucleophilic ring-opening reactions, see: (a) Pineschi, M.; Moro, F. D.; Crotti, P.; Macchia, F. *Pure Appl. Chem.* **2006**, *78*, 463–467. (b) Pineschi, M.; Moro, F. D.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605–3607. (c) Surman, M. D.;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

(19) Machin, B. P.; Howell, J.; Mandel, J.; Blanchard, N.; Tam, W. *Org. Lett.* **2009**, *11*, 2077–2080.

SCHEME 3. Ru-Catalyzed Ring-Opening Reactions of 5a with Alcohols



In this paper, we report our investigation of the Rh-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]heptenes **5** with arylboronic acids.

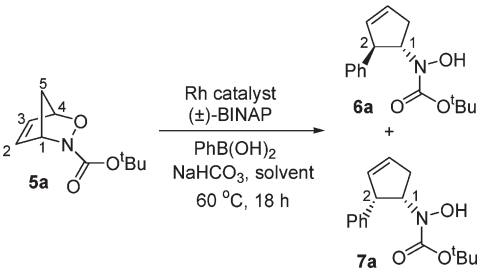
Results and Discussion

To begin our investigation, 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** was prepared and was subjected to various Rh catalysts in the presence of different solvents (Table 1). No reaction was observed in the absence of a Rh catalyst (Table 1, entry 1), and very little reaction was observed when the catalyst loading is less than 3 mol %. Among the nine Rh catalysts examined, four of them (Table 1, entries 2−5) led to decomposition of the starting 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a**. The most effective Rh catalyst was found to be the neutral $[Rh(COD)Cl]_2$ dimer (Table 1, entry 10), giving the 1,2-ring-opened products **6a** and **7a** in 69% combined isolated yield. These diastereoisomers are separable by column chromatography (49% of *trans*-**6a** and 20% of *cis*-**7a**), and their structures were identified by various NMR experiments (HCOSY, HSQC, and NOE). The structure of *trans*-**6a** was also confirmed by comparing the NMR data with the literature data (*trans*-**6a** was previously synthesized in 39% yield by the Cu-catalyzed ring-opening reaction of **5a** using PhMgBr).[18c] Using $[Rh(COD)Cl]_2$ as the catalyst, the effect of different solvents was studied. Surprisingly, the reaction is very sensitive to the solvent used. Other than MeOH, the use of other solvents such as 1,2-dichloroethane, THF, acetone, and toluene simply led to decomposition of the starting 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** (entries 13−16). Even the use of other alcoholic solvents such as EtOH and CF_3CH_2OH led to poor results (entries 11 and 12). It has been observed in the literature that fluorinated solvents enhance the reactivity of some Rh-catalyzed reactions;[20] unfortunately, it is not the case in our study.

The effects of different phosphine ligands and different bases have also been studied. Unlike the solvent which showed a dramatic effect in the Rh-catalyzed ring-opening reaction, the use of different phosphine ligands and different bases showed very little effect. All the bidentate phosphines (dppe, dppp, dppf, and BINAP) as well as monodentate phosphines (Ph_3P, Cy_3P, $^tBu_3P$, $^nBu_3P$) tested gave the 1,2-ring-opened products **6a** and **7a** in similar yields (50−70%) and diastereoselectivities (56:44 to 75:25). Note that even in the absence of any phosphine ligands, a similar result was obtained (52% yield, dr = 71:29). We have also attempted a kinetic resolution using a chiral BINAP ((*R*)-BINAP) instead of the racemic BINAP. The reaction was stopped at ~40% and ~20% completion. Although no kinetic resolution was observed in both cases (both the recovered starting material and the products have 0% ee as indicated by HPLC using chiral columns), the stereoselectivity was changed slightly (at 20% completion, the *trans*/*cis* ratio was 80:20; and at 40% completion, the *trans*/*cis* ratio was 69:31 which was essentially the same as when the reaction was allowed to go to completion). The use of different bases ($NaHCO_3$, Na_2CO_3, K_2CO_3, K_3PO_4, KF, CsF, ^tBuOK) also showed very little effect on the yields and diastereoselectivities in the Rh-catalyzed ring-opening reaction. In the absence of any bases, a similar result was obtained (57% yield, dr = 70:30).

The optimized reaction conditions for the Rh-catalyzed ring-opening reaction were found to be using $[Rh(COD)Cl]_2$ (6 mol %), (±)-BINAP (12 mol %), $NaHCO_3$ (2 equiv), and $PhB(OH)_2$ (2 equiv) in MeOH at 60 °C. Control experiments showed that under the optimized reaction conditions and in the absence of the phenylboronic acid, decomposition of the starting 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** was observed. This could account for the moderate yields in these ring-opening reactions. Note that other than the 1,2-ring-opened products **6a** and **7a**, we were not able to isolate any other products (such as the 1,4-ring-opened products as shown in Scheme 2). Control experiments were also carried out to determine if the ring-opened products **6a** and **7a** are stable under the reaction conditions and whether or not they

TABLE 1. Effect of Different Rh Catalysts and Solvents

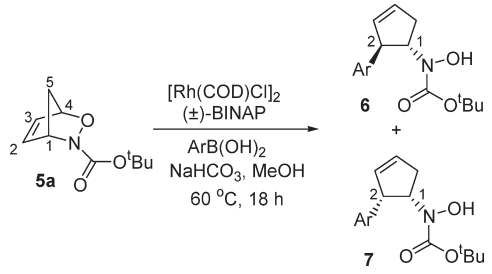


entry	Rh catalyst[a]	solvent	yield[b] (%)	ratio[c] *trans*-**6a**: *cis*-**7a**
1	none	MeOH	0[d]	
2	$Rh_2(OAc)_4$	MeOH	0[e]	
3	$[Rh(C_8H_{14})_2Cl]_2$	MeOH	0[e]	
4	$[Rh(NBD)Cl]_2$	MeOH	0[e]	
5	$Rh(PPh_3)_3Cl$	MeOH	0[e]	
6	$[Rh(CO)_2Cl]_2$	MeOH	32	63:37
7	$[Rh(C_2H_4)_2Cl]_2$	MeOH	42	55:45
8	$[Rh(COD)_2]BF_4$	MeOH	45	69:31
9	$[Rh(COD)_2]OTf$	MeOH	58	71:29
10	$[Rh(COD)Cl]_2$	MeOH	69	71:29
11	$[Rh(COD)Cl]_2$	EtOH	22	64:36
12	$[Rh(COD)Cl]_2$	CF_3CH_2OH	0[f]	
13	$[Rh(COD)Cl]_2$	1,2-dichoroethane	0[e]	
14	$[Rh(COD)Cl]_2$	THF	0[e]	
15	$[Rh(COD)Cl]_2$	acetone	0[e]	
16	$[Rh(COD)Cl]_2$	toluene	0[e]	

[a]Typical conditions: Rh catalyst (6 mol %), (±)-BINAP (12 mol %), $NaHCO_3$ (2 equiv), $PhB(OH)_2$ (2 equiv). [b]The combined yield of *trans*-**6a** and *cis*-**7a** after column chromatography. **6a** and **7a** are separable by column chromatography. [c]The ratio of isolated products. [d]No reaction was observed, and only **5a** was recovered. [e]Decomposition of **5a** was observed as indicated by TLC. [f]30% of **5a** was recovered.

(20) (a) Saito, A.; Ono, T.; Hanzawa *J. Org. Chem.* **2006**, *71*, 6437–6443. (b) Begue, J.; Bonnet-delpon, D.; Crousse, B. *Synlett* **2004**, 18–29.

TABLE 2. Rh-Catalyzed Ring-Opening Reaction of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene 5a with Different Arylboronic Acids



entry[a]	Ar	products **6/7**	yield[b] (%)	ratio[c] *trans*-**6**:*cis*-**7**
1	Ph	**6a/7a**	69	71:29
2	4-Et-C_6H_4	**6b/7b**	60	67:33
3	4-Me-C_6H_4	**6c/7c**	64	61:39
4	3-Me-C_6H_4	**6d/7d**	67	65:35
5	2-Me-C_6H_4	**6e/7e**	55	51:49
6	4-MeO-C_6H_4	**6f/7f**	55	69:31
7	3-MeO-C_6H_4	**6g/7g**	61	53:47
8	2-MeO-C_6H_4	**6h/7h**	52	62:38
9	4-Me_2N-C_6H_4	**6i/7i**	66	67:33
10	4-Cl-C_6H_4	**6j/7j**	44	86:14
11	3-Cl-C_6H_4	**6k/7k**	48	71:29
12	2-Cl-C_6H_4	**6l/7l**	39	100:0
13	4-F-C_6H_4	**6m/7m**	46	83:17
14	3-F-C_6H_4	**6n/7n**	68	68:32
15	2-F-C_6H_4	**6o/7o**	44	90:10
16	4-Ac-C_6H_4	**6p/7p**	54	80:20
17	1-naphthyl	**6q/7q**	53	68:32

[a]Typical conditions: $[Rh(COD)Cl]_2$ (6 mol %), phosphine (12 mol %), base (2 equiv), $ArB(OH)_2$ (1.1−2 equiv). [b]The combined yield of *trans*-**6** and *cis*-**7** after column chromatography. Most **6** and **7** are separable by column chromatography; see the Supporting Information [c]The ratio of isolated products.

interconvert to one another. After separation and isolation of the ring-opened products **6a** and **7a** by column chromatography, they were resubmitted individually to the Rh-catalyzed ring-opening reaction conditions (in the absence of **5a**). Both **6a** and **7a** were recovered, and it was found that they were both stable under the reaction conditions, very little decomposition was observed, and they do not interconvert to one another.

The scope of the Rh-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a** using various boronic acids is shown in Table 2. In general, moderate yields and low to moderate stereoselectivity were observed with various arylboronic acids. Several trends can be observed in these studies. The presence of an *ortho* substituent of the arylboronic acids usually lowers the yield (compare entry 5 with entries 3 and 4; compare entry 8 with entries 6 and 7; compare entry 12 with entries 10 and 11; and compare entry 15 with entries 13 and 14). Electron-donating groups on the aryl ring of the arylboronic acids usually gave higher yields than those with electron-withdrawing groups (compare substrates at the same position on the aryl ring, e.g., at the *para* position, Me and Me_2N groups gave yields of 64% and 66% but Cl, F, and Ac groups gave much lower yields of 44%, 46%, and 54%). Substrates with a halogen substituent (Cl or F) gave a higher stereoselectivity (compare entries 10−15 with entries 3−5 and 6−8). Note that in the case of the 2-chlorophenylboronic acid (entry 12), only one stereoisomer of the 1,2-ring-opened product (*trans*-**6l**) was isolated, although the yield was only 39%. In all cases, other than the 1,2-ring-opened products **6** and **7**, we were not able to isolate any other products (such as the 1,4-ring-opened products as shown in Scheme 2).

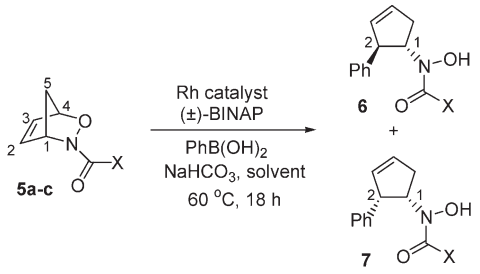
All of these diastereoisomers (*trans*-**6**:*cis*-**7**) are separable by column chromatography and their structures were identified by various NMR experiments (HCOSY, HSQC, and NOE). Upon analysis of the ^1H NMR spectra of each set of stereoisomers some general trends can be observed. One noticeable difference is seen in the splitting pattern in the ^1H NMR spectra of the proton on C-2. In the *cis* isomer (**7**), this proton appears as a singlet, and in the corresponding *trans* isomer (**6**), it typically appears as a complex multiplet. A second difference can be seen at the proton on C-1 in the *trans* isomer (**6**); in the majority of cases, this proton appears as a very well resolved quartet. For the *cis* isomers, the *tert*-butyl peak singlet is slightly more downfield, at approximately 1.45 ppm, whereas for the *trans* isomers, the *tert*-butyl peak is found at approximately 1.20 ppm in all cases. We also observed a difference in the ^{13}C NMR of each isomer. The C-1 carbon on the *cis* isomer appears significantly more downfield (around 90 ppm) than the C-1 carbon of the *trans* isomer (around 70 ppm). The structure of the *trans* isomer **6q** was also confirmed by X-ray crystallography.[21]

The use of alkyl or alkenyl boronic acids such as methylboronic acid, cyclohexylboronic acid, and *trans*-2-phenylvinylboronic acid only led to decomposition of the starting 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a**, and no desired ring-opening products could be isolated. Thus, under these reaction conditions, the reaction only works for aryl boronic acids. Other than 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5a**, Rh-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo-[2.2.1]hept-5-enes **5b** and **5c**, with an amide instead of the Boc group, have also been investigated (Scheme 4). 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene **5b**, with an electron-donating amide group (MeO), gave the ring-opening products in 74% yield with a *trans*/*cis* ratio of 66:34. 3-Aza-2-oxabicyclo-[2.2.1]hept-5-ene **5c**, with an electron-withdrawing amide group (F), gave the ring-opening products in 21% yield with a *trans*/*cis* ratio of 88:12. The very low yield of the 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **5c** in the Rh-catalyzed ring-opening reaction was due to the decomposition of **5c** under the reaction conditions.

It has been proposed that Rh-catalyzed ring-opening reactions of 7-oxabicyclic alkene **1a** with arylboronic acids go through the intermediate **8** in which the active Rh catalytic species coordinates to both the alkene and the oxygen and delivers the Ar group from the *exo* face to provide the observed *cis* product **9** (Schemes 1 and 5).[1c,7d] For the Rh-catalyzed ring-opening reactions of 2,3-diazabicyclo[2.2.1]heptene **4a** with arylboronic acids,[7e] the active Rh catalytic species probably coordinates only to the alkene and delivers the Ar group from the *exo* face to provide the observed *trans* product **11** via the intermediate **10** (Schemes 1 and 5). Unlike the Rh-catalyzed ring-opening reactions of **1a** and **4a** with arylboronic acids in which only one stereoisomers was formed in each case, our Rh-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo-[2.2.1]heptenes **5** with arylboronic acids gave both *trans*

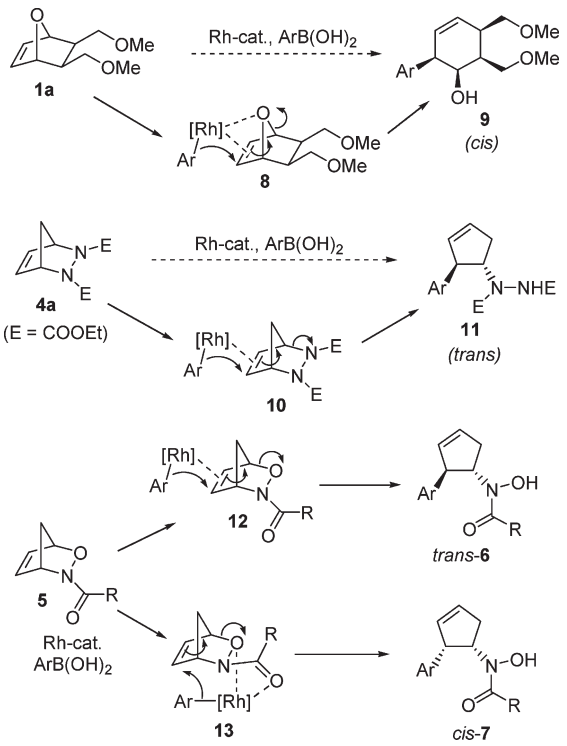
(21) Lough, A. J.; Machin, B. P.; Tam, W. *Acta Crystallogr.* **2009**, *E65*, o1481.

SCHEME 4. Rh-Catalyzed Ring-Opening Reaction of 3-Aza-2-oxabicyclo[2.2.1]hept-5-enes 5a−c with Phenylboronic Acid



X	Yield (%)	*trans*-**6** : *cis*-**7**
O^{t}Bu (**5a**)	69	**6a:7a** = 71:29
4-MeO-C_4H_6 (**5b**)	74	**6r:7r** = 66:34
4-F-C_4H_6 (**5c**)	21	**6s:7s** = 88:12

SCHEME 5. Proposed Mechanism



and *cis* 1,2-ring-opening products (**6** and **7**). Our rational is shown in the bottom of Scheme 5. The active Rh catalytic species could either coordinate to the bicyclic alkene (intermediate **12**) and deliver the Ar group from the *exo* face to provide the *trans*-1,2-ring-opening product **6** or coordinate to both of the oxygen atoms of the heterobicyclic alkene and the carbonyl group of the amide or carbamate (intermediate **13**) and deliver the Ar group from the *endo* face to provide the *cis*-1,2-ring-opening product **7**. This coordination to the oxygen atom of the heterobicyclic alkene of **5a** and to the oxygen atom of the carbonyl group of the amide or carbamate has previously been proposed in other metal-catalyzed and Lewis acid-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]heptenes **5**.[17c,e,19] Alternatively, the Rh catalytic species could also bind on the *endo* face of the bicyclic alkene with the assistance of one of the heteroatoms within the ring and deliver the Ar group from the *endo* face to provide the *cis*-1,2-ring-opening product **7**.

Conclusion

In summary, we have demonstrated the first examples of rhodium-catalyzed ring-opening reactions of a 3-aza-2-oxabicyclo[2.2.1]hept-5-ene with arylboronic acids. The use of $[RhCl(COD)]_2$, (±)-BINAP, and $NaHCO_3$ in MeOH at 60 °C was found to be the optimized conditions for the ring-opening reactions to give the 1,2-ring opened products. Various arylboronic acids were examined, and low to moderate yields were obtained with stereoselectivities (*trans*/*cis*) from 50:50 to 100:0 being observed. Further investigations of the mechanism and applications of this reaction are currently in progress in our laboratory.

Experimental Section[22]

General Procedure for Rhodium-Catalyzed Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.1]hept-5-enes with Arylboronic Acids. A 3-aza-2-oxabicyclo[2.2.1]hept-5-ene (0.1−0.5 mmol, 1 equiv) was added into an oven-dried vial containing an arylboronic acid (1−2 equiv) and $NaHCO_3$ (2 equiv), and the vial was purged with nitrogen and transferred into a drybox. In the drybox, to a second oven-dried vial were added $[Rh(COD)Cl]_2$ (6 mol %), (±)-BINAP (12 mol %), and methanol (1 mL), and the mixture was stirred for 30 min. Methanol (1.3 mL) was added to the vial containing the bicyclic alkene, and arylboronic acid and was transferred to the vial containing the Rh catalyst and phosphine. The vial was sealed with a screw cap, removed from the drybox, heated to 60 °C, and stirred for 18 h. The crude products were purified by column chromatography (EtOAc−hexanes mixture) and concentrated in vacuo to give the corresponding 1,2-cyclopentene ring-opened product.

Ring-Opening Products 6a and 7a (Table 2, Entry 1). Following the general procedure above with 3-aza-2-oxabicyclo-[2.2.1]hept-5-ene **5a** (24.6 mg, 0.125 mmol), phenylboronic acid (18.2 mg, 0.149 mmol), $[Rh(COD)Cl]_2$ (3.3 mg, 0.007 mmol), (±)-BINAP (9.5 mg, 0.015 mmol), $NaHCO_3$ (25.1 mg, 0.303 mmol), and methanol (2.3 mL), the crude product was purified by column chromatography (EtOAc/hexanes = 1:4) to provide a separable mixture of 1,2-cyclopentene ring-opened product **6a** (16.7 mg, 0.061 mmol, 49%) as an orange oil and 1,2-cyclopentene ring-opened product **7a** (6.8 mg, 0.025 mmol, 20%) as a brown oil. Relative regio- and stereochemistry of each isomer was confirmed by various 2-D NMR (COSY, HSQC, HMBC) experiments and 1-D GOESY experiments performed on a 600 MHz NMR spectrophotometer.

***trans*-*N*-*tert*-Butoxycarbonyl-*N*-hydroxyamino-2-phenylcyclopent-3-ene (6a):** R_f 0.42 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2, cm^{-1}) 3204 (br. s), 3055 (s), 2984 (s), 2686 (w), 1686 (s), 1454 (w), 1421 (w), 1395 (m), 1369 (m), 1265 (s), 1159 (s), 1112 (s), 896 (m), 745 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (br. s, 1H), 7.21 (m, 2H), 7.14 (m, 3H), 5.80 (m, 1H), 5.64 (m, 1H), 4.52 (q, 1H, J = 7.8 Hz), 4.10 (m, 1H), 2.72 (m, 1H), 2.53 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 157.0, 143.9, 132.8, 129.8, 128.4, 127.6, 126.4, 81.7, 68.0, 52.2, 34.5, 27.9; HRMS (ESI) calcd for $C_{16}H_{21}NO_3$ (M + Na) 298.1419, found 298.1426.

(22) A representative procedure of the rhodium-catalyzed ring opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes with arylboronic acids and characterization of a cycloadduct is described here. For the procedures and characterization of other ring opening products, see the Supporting Information.

***cis*-*N*-*tert*-Butoxycarbonyl-*N*-hydroxyamino-2-phenylcyclopent-3-ene (7a):** R_f 0.60 (EtOAC/hexanes = 1:4); IR (CH_2Cl_2, cm^{-1}) 3363 (br. m), 3055 (s), 2986 (s), 2932 (s), 1747 (s), 1439 (m), 1422 (m), 1369 (m), 1265 (s), 1158 (m), 1104 (m), 896 (m), 741 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 2H), 7.22−7.14 (m, 4H), 5.89 (m, 1H), 5.77 (m, 1H), 4.45 (dt, 1H, J = 2.7 Hz), 4.07 (s, 1H), 2.73 (m, 1H), 2.55 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 157.0, 142.3, 131.9, 129.5, 128.6, 127.5, 126.5, 92.8, 81.7, 56.3, 37.4, 27.2; HRMS (ESI) calcd for $C_{16}H_{21}NO_3$ (M + NH_4) 293.1865, found 293.1875.

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