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Regio- and Stereoselective Indium Triflate-Mediated Nucleophilic Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene and -[2.2.2]oct-5-ene Systems

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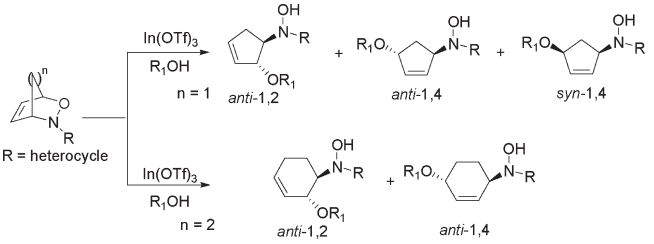

Indium triflate-mediated nucleophilic ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene and -[2.2.2]-oct-5-ene systems with alcohols and water were investigated. Reactions of [2.2.1] bicyclic systems gave *anti*-1,2-, *anti*-1,4- and *syn*-1,4-ring-opened products with moderate to excellent regio- and stereoselectivity. When [2.2.2] bicyclic systems were subjected to similar reaction conditions, only *anti*-1,2 and *anti*-1,4-ring-opened products were obtained.

Nitroso cycloadducts obtained from hetero Diels−Alder (HDA) reactions, such as 3-aza-2-oxabicyclo[2.2.1]hept-5-enes and [2.2.2]oct-5-enes (**1**−**4**), are valuable synthetic intermediates for the construction of a variety of biologically interesting molecules (Scheme 1).[1] The chemistry of acylnitroso cycloadduct **1** has revealed several modes of ring-opening reactions to introduce different functionalities with defined stereo- and regiochemistries.[2−6] Commonly employed strategies involve N−O bond reductive cleavage to form *syn*-1,4-aminocyclopentenols[2] and C−O bond cleavage through metal-mediated reactions in the presence of nucleophiles or electrophiles.[3−5] Recently, stereoselective nitroso HDA reactions using iminonitroso agents have attracted more attention because they facilitate generation of enantiopure 3-aza-2-oxa-bicyclic compounds such as **3** and **4** in a single step.[1b,7] We also successfully utilized iminonitroso Diles−Alder reactions for the derivatization and functionalization of diene-containing natural products for *m*odular *e*nhancement of *N*ature's *d*iversity (MEND).[8] While extensive chemistry has been developed from reactions of acylnitroso agents, elaborations of heteroaryl nitroso adducts such as **3** and **4** have been less explored and are mainly limited to reductive cleavage of the N−O bond.[7] To the best of our knowledge, Lewis acid mediated ring-opening reactions of iminonitroso cycloadducts have not been disclosed in the literature despite their potential synthetic value. Herein, we report recent advances in this area that expand the versatility of Lewis acid mediated nucleophilic ring-opening reactions to a range of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes **3** and -[2.2.2]oct-5-enes **4**.

To begin our investigation, [2.2.1], [2.2.2], and [4.2.2] bicyclic systems **3a**−**d**, **4a**−**c**, and **5a** were prepared by HDA reactions between the corresponding nitroso agents[9] and dienes (Scheme 1). Cycloadduct **3a**, as a model substrate, was then reacted with various Lewis acids in the presence of MeOH at room temperature (Table 1). While a variety of Lewis acids (0.5 equiv), including $FeCl_3$, $CuCl_2$, and $CuSO_4$, induced the ring-opening reactions of **3a** to form *anti*-1,2-, *anti*-1,4-, and *syn*-1,4-disubstituted products **6a**, **7a**, and **8a**, respectively, only low to moderate yields were obtained

(1) For selected reviews, see: (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348. (b) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031–2043. (c) Samarakoon, T; Hanson, R. R. *Chemtracts* **2007**, *20*, 220–229.

(2) For selected examples of reductive N−O bond cleavage of cycloadduct **1**, see: (a) Cesario, C.; Tardibono, L. P.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 448–451. (b) Li, F. Z.; Miller, M. *J. Org. Chem.* **2006**, *71*, 5221–5227. (c) Kim, K.-H.; Miller, M. J. *Tetrahedron Lett.* **2003**, *44*, 4571–4573. (d) Cowart, M.; Bennett, M. J.; Kerwin, J. F. *J. Org. Chem.* **1999**, *64*, 2240–2249. (e) Mulvihill, M. J.; Gage, J. L.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 3357–3363.

(3) For palladium, palladium/indium, or Lewis acid catalyzed ring-opening reactions of cycloadduct **1**, see: (a) Cesario, C.; Miller, M. J. *Org. Lett.* **2009**, *11*, 1293–1295. (b) Tardibono, L. P.; Miller, M. J. *Org. Lett.* **2009**, *11*, 1575–1578. (c) Lee, W.; Kim, K.-H; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 139–149. (d) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139–141. (e) Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 2466–2469. (f) Surman, M. D.; Miller, M. J. *Org. Lett.* **2001**, *3*, 519–521. (g) Mulvihill, M. J.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4874–4875.

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(5) For copper-catalyzed Grignard or organozinc nucleophilic ring-opening reactions of cycloadduct **1**, 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.

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(8) (a) Yang, B. Y.; Miller, P.; Mollmann, U.; Miller, M. J. *Org. Lett.* **2009**, *11*, 2828–2931. (b) Li, F. Z.; Yang, B. Y.; Miller, M. J.; Zajicek, J.; Noll, B. C.; Mollmann, U.; Dahse, H.-M.; Miller, P. *Org. Lett.* **2007**, *9*, 2923–2926. (c) Krchnak, V.; Waring, K. R.; Noll, B. C.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Org. Chem.* **2008**, *73*, 4559–4567.

(9) Syntheses of iminonitroso agents, see: Taylor, E. C.; Tseng, C. P.; Rampal, J. B. *J. Org. Chem.* **1982**, *47*, 552–555.

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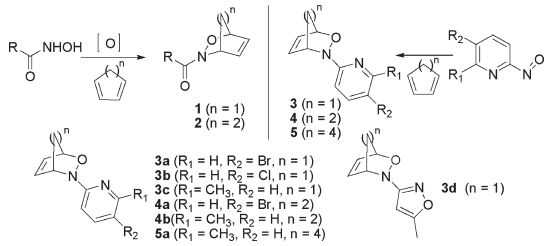
SCHEME 1. Syntheses of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene and -[2.2.2]oct-5-ene and 8-Aza-7-oxabicyclo[4.2.2]dec-9-ene Systems



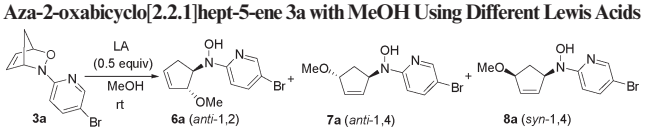
(entries 1−10). Subsequent screening revealed that reaction with 0.5 equiv of indium triflate ($In(OTf)_3$) provided the best yield (92%) of a 2.4:3.7:1 ratio of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products (**6a**/**7a**/**8a**) within 1 h (entry 11). The *anti*-1,2-product **6a** was isolated cleanly after silica gel chromatography, and its structure was determined by 1D and 2D NMR studies (COSY, HETCOR). The regio- and stereochemistry of the generally inseparable *anti*-1,4- and *syn*-1,4-products (**7a** and **8a**) were assigned using comparison of the coupling pattern of the C(5) methylene protons.[10] A plausible mechanism indicated that two major products, **6a** and **7a**, were results of indirect and direct nucleophilic displacement of the oxygen, respectively (Scheme 2, path A and B), though a competitive open cation process might also account for the mixed stereoselectivity and formation of the minor *syn*-1,4 product (**8a**). Variation of the amount of $In(OTf)_3$ used in the reaction was then explored. Increasing the amount of $In(OTf)_3$ to 1.0 equiv gave the products in a similar yield but with slightly compromised stereoselectivity (entry 12). Low conversions were observed when 0.2 and 0.1 equiv of $In(OTf)_3$ were employed even when the reaction time was prolonged (entries 13 and 14). Thus, we selected 0.5 equiv of $In(OTf)_3$ for further studies of the Lewis acid-mediated ring-openings of additional substrates.

The ability to control the stereochemical outcome of the $In(OTf)_3$-mediated ring-opening reactions was further investigated by adding cosolvents to MeOH (Table 2). Use of DCM or toluene as cosolvents in a 1:1 ratio with MeOH gave the products in yields similar to those obtained when MeOH was used alone, but the stereoselectivity decreased slightly (entries 1−3). The use of 1,4-dioxane or THF as cosolvents increased the relative amounts of *anti*-1,4- and *syn*-1,4-products (entries 4−5). This preference was enhanced by increasing the amount of THF in the reactions (entries 5−9). Reduction of the amount of MeOH to only 2 equiv in THF led to a 0.3:1.9:1 ratio of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products (**6a**/**7a**/**8a**) in moderate yield (45%, entry 9).

In an effort to determine the scope of this ring-opening chemistry, we expanded the studies to include reactions of variously substituted 3-aza-2-oxabicyclo[2.2.1]hept-5-ene systems **3a**−**d** with a series of alcohols (Table 3). When **3a** was used, separate reactions with each of the aliphatic alcohols gave the ring-opened products in good to excellent yields (entries 1−3). The preference for the formation of *anti*-1,4-products was enhanced by increasing the size of nucleophile. For example, use of *tert*-butyl alcohol gave a 90% yield

(10) For an explanation of how regio- and stereochemistry of 1,4-aminocyclopentenol systems are determined from the coupling pattern of the C(5) protons, see ref 3g and references therein.

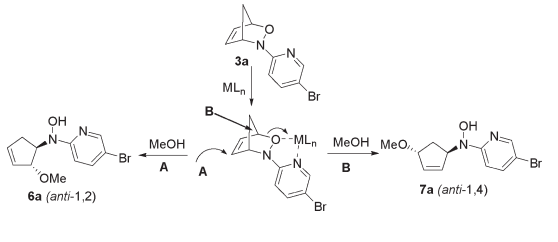
TABLE 1. Lewis Acid-Mediated Nucleophilic Ring-Opening Reaction of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene 3a with MeOH Using Different Lewis Acids



entry	Lewis acid (0.5 equiv)	time (h)	yield[a] (%)	product ratios[b] 6a/7a/8a
1	$FeCl_3$	1	13	2.4:2.1:1
2	$CuCl_2$	1	53	1:3.3:1
3	$CuSO_4$	1	69	2.7:3.3:1
4	$Cu(I)PF_6(MeCN)_4$	1	71	2.5:2.7:1
5	$SnCl_2$	24	32	1.6:2.5:1
6	$ZnBr_2$	24	0	nd
7	$AlCl_3$	8.5	58	1.7:2.7:1
8	$CeCl_3$	24	< 5	nd
9	$La(OTf)_3$	24	66	4.7:4.4:1
10	InI_3	3.5	23	1.9:4.8:1
11	$In(OTf)_3$	1	92	2.4:3.7:1
12[c]	$In(OTf)_3$	1	93	2.2:3.3:1
13[d]	$In(OTf)_3$	5	74	2.6:3.6:1
14[e]	$In(OTf)_3$	24	64	2.5:3.1:1

[a]Isolated yield. [b]Determined by ^1H NMR of the crude mixture. [c]1.0 equiv of $In(OTf)_3$. [d]0.2 equiv of $In(OTf)_3$. [e]0.1 equiv of $In(OTf)_3$.

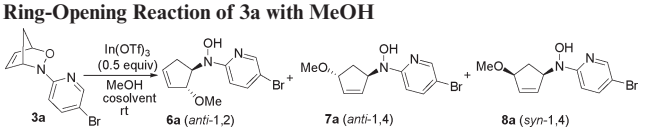
SCHEME 2. Proposed Mechanism for Formation of 6a and 7a in the Lewis Acid Mediated Nucleophilic Ring-Opening Reaction of 3a



of a 1.7:5:1 ratio of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products (**6c**/**7c**/**8c**) (entry 3). Addition of THF to *tert*-butyl alcohol slightly increased the ratio of 1,4-products (entry 4). Similar reactivity and stereoselectivity were noted when **3b** was treated with different alcohols under conditions used in the studies of **3a** (entries 5−7). While only moderate conversions for the ring-opening reactions of **3c** were obtained, improved stereoselectivity favoring the formation of *anti*-1,2- and *anti*-1,4-products was observed (entries 8−10). The reaction of cycloadduct **3d** with MeOH gave a 93% yield of a 1.4:4:1 ratio of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products (**6j**/**7j**/**8j**); however, the yields dropped when bulkier alcohols such as 2-propanol and *tert*-butyl alcohol were used (entries 11−13). In all ring-opening reactions of **3d**, the preference for *anti*-1,4-products (**7j**−**l**) was much more noticeable than with substrates **3a**−**c** (entries 11−13). In order to give compounds more compatible for eventual further elaboration, reactions of **3a** with benzyl alcohol and allyl alcohol were perfomed, generating a mixture of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products in 73% and 57% yields, respectively, with *anti*-1,4-compounds (**7m** and **7n**) as the major products (entries 14 and 15).

The $In(OTf)_3$-mediated ring-opening reactions with 3-aza-2-oxabicyclo[2.2.2]oct-5-ene systems **4a**,**b** were also investigated. The results are summarized in Table 4. Because of the

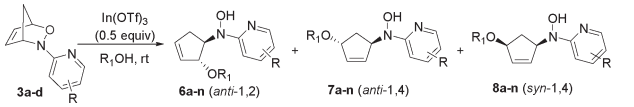
TABLE 2. Effects of Cosolvent on In(OTf)$_3$-Mediated Nucleophilic Ring-Opening Reaction of 3a with MeOH



entry	MeOH/cosolvent	time (h)	yield[a] (%)	product ratios[b] **6a**/**7a**/**8a**
1	MeOH	1	92	2.4:3.7:1
2	MeOH/DCM (1/1)	1	92	2:3.2:1
3	MeOH/toluene (1/1)	1	89	1.9:3:1
4	MeOH/1,4-dioxane (1/1)	1	92	1.4:2.6:1
5	MeOH/THF (1/1)	1	92	1.2:2.4:1
6	MeOH/THF (1/7)	4	94	0.7:1.8:1
7	MeOH (10 equiv) /THF	5	92	0.5:1.9:1
8	MeOH (5 equiv)/THF	12	93	0.4:1.9:1
9	MeOH (2 equiv)/THF	24	45	0.3:1.9:1

[a]Isolated yield. [b]Determined by ^{1}H NMR of crude mixture.

TABLE 3. In(OTf)$_3$-Mediated Nucleophilic Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene 3a−d with Different Alcohols

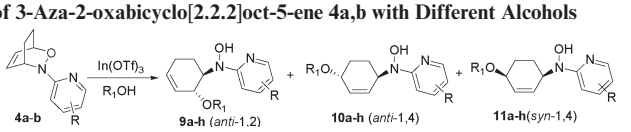


entry	**3**	R_1OH	time (h)	products	yield[a] (%)	ratios[b] **6**/**7**/**8**
1	**3a**	MeOH	1	**6a−8a**	92	2.4:3.7:1
2	**3a**	^{i}PrOH	2	**6b−8b**	97	2.1:4.2:1
3	**3a**	^{t}BuOH[c]	2	**6c−8c**	90	1.7:5:1
4	**3a**	^{t}BuOH[d]	7	**6c−8c**	89	0.6:2.9:1
5	**3b**	MeOH	1.5	**6d−8d**	88	2.3:3.6:1
6	**3b**	^{i}PrOH	2	**6e−8e**	96	2.4:4.6:1
7	**3b**	^{t}BuOH[c]	2.5	**6f−8f**	87	1:3.3:1
8	**3c**	MeOH	6.5	**6g−8g**	63	5.7:4.2:1
9	**3c**	^{i}PrOH	6	**6h−8h**	61	2.8:5:1
10	**3c**	^{t}BuOH[c]	6	**6i−8i**	64	3:6:1
11	**3d**	MeOH	2	**6j−8j**	93	1.4:4:1
12	**3d**	^{i}PrOH	2	**6k−8k**	73	1.6:5:1
13	**3d**	^{t}BuOH[c]	3.5	**6l−8l**	57	1.1:5:1
14	**3a**	BnOH[e]	2	**6m−8m**	73	1:2.6:1
15	**3a**	2-Propen-1-ol[e]	2	**6n−8n**	57	1.2:3.3:1

[a]Isolated yield. [b]Determined by ^{1}H NMR of crude mixture. [c]Reaction temperature, 30 °C. [d]^{t}BuOH (5 equiv)/THF. [e]Alcohol/THF (1/1).

decreased ring strain of the [2.2.2] substrates relative to the [2.2.1] substrates, we anticipated that the ring-opening reactions would be slower. However, reaction with [2.2.2] bicyclic compound **4a** in MeOH with 0.5 equiv of In(OTf)$_3$ at room temperature still occurred, generating a 35% yield of a 1:1 ratio of *anti*-1,2-/*anti*-1,4-products (**9a**/**10a**) after prolonged reaction (24 h, entry 1). Interestingly, no *syn*-1,4-product **11a** was detected, which further supported the proposed reaction mechanism as shown in Scheme 2. Compounds **9a** and **10a** were readily separable by column chromatography, and their regio- and stereochemistries were determined by 1D and 2D NMR experiments.[11] Use of excess In(OTf)$_3$ (1.5 equiv) increased the yield significantly, as expected; however, the reaction still required 24 h (entry 2). Meanwhile, we were pleased to find that at elevated temperature (70 °C) the

TABLE 4. In(OTf)$_3$-Mediated Nucleophilic Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.2]oct-5-ene 4a,b with Different Alcohols



entry	**4**	R_1OH/Time (h)	T (°C)	products	yield[c] (%)	ratios[d] **9**/**10**/**11**
1[a]	**4a**	MeOH/24	25	**9a−11a**	35	1.1:1:0
2[b]	**4a**	MeOH/24	25	**9a−11a**	96	1:1:0
3[a]	**4a**	MeOH/2	70	**9a−11a**	92	1:1:0
4[a]	**4a**	^{i}PrOH/1	70	**9b−11b**	95	1:1:0
5[a]	**4a**	^{t}BuOH/2	80	**9c−11c**	71	0.8:1:0
6[a]	**4b**	MeOH/6	70	**9d−11d**	59	1:1.1:0
7[a]	**4b**	^{i}PrOH/2	70	**9e−11e**	59	1:1:0
8[a]	**4b**	^{t}BuOH/4	80	**9f−11f**	55	1:1:0
9[a]	**4a**	BnOH[e]/3	70	**9g−11g**	67	1:1.3:0
10[a]	**4a**	2-propen- 1-ol[e]/3	70	**9h−11h**	85	1:1.5:0
11[b]	**5a**	MeOH/24	70		0	

[a]0.5 equiv of In(OTf)$_3$. [b]1.5 equiv of In(OTf)$_3$. [c]Isolated yield. [d]Determined by ^{1}H NMR of crude mixture. [e]Alcohol/THF (1/1).

nucleophilic ring-opening reaction of **4a** with 0.5 equiv of In(OTf)$_3$ was complete within 2 h, forming products in 92% yield without loss of stereoselectivity (entry 3). Similar results were obtained when 2-propanol and *tert*-butyl alcohol were used (entries 4 and 5). Although only moderate yields were observed when **4b** was treated with various alcohols, the exclusive selectivity for *anti*-1,2- and *anti*-1,4-products remained (entries 6−8). Again, when benzyl alcohol and allyl alcohol were used, ring-opening reactions of **4a** afforded *anti*-1,2- and *anti*-1,4-products in moderate to good yields (entries 9−10). In contrast, the ring-opening reaction with [4.2.2] bicyclic cycloadduct **5a** derived from cyclooctadiene failed, even with the use of excess In(OTf)$_3$ and at 70 °C (entry 11). Clearly, ring strain of substrates is important for the Lewis acid-mediated ring-opening reactions to occur.

Ring-opening reactions with other non-alcohol nucleophiles were also briefly studied. Attempted Lewis acid-mediated reactions with amines generated complex mixtures. However, use of water in mixed solvent systems was effective in the In(OTf)$_3$-mediated ring-opening reactions (Table 5). Reaction of **3a** with 0.5 equiv of In(OTf)$_3$ in 1:1 water:THF at room temperature gave a 45% yield of a 1:6.7:1 ratio of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products (**12a**/**13a**/**14a**) with *anti*-1,4-product **13a** as the major product (entry 1). [2.2.2] Bicyclic system **4a** again required elevated temperature (70 °C) to induce reaction but generated only *anti*-1,2- and *anti*-1,4-products (**12b** and **13b**) in moderate yield (51%, entry 2). Compared to the typical N−O bond cleavage reactions of nitroso cycloadducts which can only form single *syn*-1,4 amino alcohol products, the methodology presented here allows generation of 1,2- or 1,4-hydroxyamino cyclopentenols and cyclohexenols with some control of regio- and stereochemistry. Moreover, subsequent N−O bond reduction can provide the corresponding amino alcohol compounds.[12]

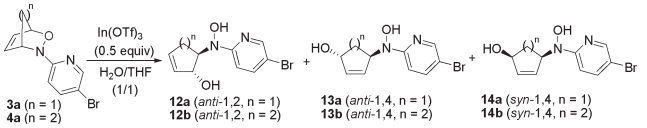
We also conducted an emperiment with cycloadduct **3a** under Brønsted acid conditions.[13] Thus, treatment of **3a** with

(11) The regio- (1,2-cyclohexene vs 1,4-cyclohexene ring-opened products) and stereochemistry (*anti* vs *syn*) of products were confirmed by various 1D and 2D NMR experiments (COSY, HSQC, HMBC, ROESY, and homonuclear decoupling).

(12) For N−O bond reduction of hydroxyamine, see ref 2a and: Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410–415.

(13) For Brönsted acid-mediated ring-opening reaction of cycloadduct **1**, see: (a) Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7535–7538. (b) Brian, S. B.; Miller, M. J. *Tetrahedron Lett.* **2009**, *50*, 796–798.

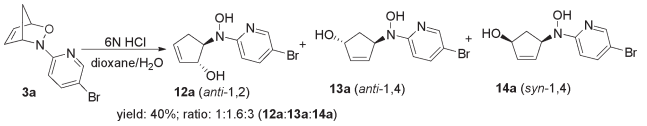
TABLE 5. In(OTf)3-Mediated Nucleophilic Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene 3a and -[2.2.2]oct-5-ene 4a with Water



entry	substrate	T (°C)	time (h)	products	yield[a] (%)	ratios[b] **12**/**13**/**14**
1	**3a**	25	12	**12a**−**14a**	45	1:6.7:1
2	**4a**	70	12	**12b**−**14b**	51	2.3:1:0

[a]Isolated yield. [b]Determined by ^{1}H NMR of the crude mixture.

SCHEME 3. Brønsted Acid-Mediated Ring-Opening Reaction of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene 3a under Aqueous Conditions



3 equiv of 6 N HCl in dioxane for 2 h at 0 °C afforded a 40% yield of a 1:1.6:3 ratio of *anti*-1,2-/*anti*-1,4-/*syn*-1,4-products (**12a**/**13a**/**14a**) (Scheme 3). This result indicated that Brönsted acid (HCl in this case) is sufficient enough to induce the ring-opening reaction without need for metal chelation.

In summary, we have demonstrated that a variety of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene and -[2.2.2]oct-5-ene systems can be solvolytically ring-opened under $In(OTf)_3$ catalyzed conditions. The regio- and stereoselectivity of the products obtained depends on the cosolvents and/or the size of the nucleophiles. Only *anti*-1,2- and *anti*-1,4-alkoxy hydroxyamino-disubstituted cyclohexene products were obtained from [2.2.2] bicyclic systems. Extensions to addtional studies related to natural product functionalization and derivatization are in progress and will be reported in due course.

Experimental Section

General Procedure A for In(OTf)$_3$-Mediated Nucleophilic Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.1]hept-5-ene with Alcohols. A solution of cycloadduct **3** (0.39 mmol) in alcohol (3 mL) was treated at rt with anhydrous $In(OTf)_3$ (0.19 mmol) and stirred under Ar for 1 to 7 h until **3** was consumed. (The reaction was warmed to 30 °C when *tert*-butyl alcohol was used). The mixture was concentrated in vacuo to a slurry, water (3 mL) and EtOAc (5 mL) were added, and the mixture was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography.

General Procedure B for In(OTf)$_3$-Mediated Nucleophilic Ring-Opening Reactions of 3-Aza-2-oxabicyclo[2.2.2]oct-5-ene with Alcohols. A solution of cycloadduct **4** (0.39 mmol) in alcohol (3 mL) was treated at rt with anhydrous $In(OTf)_3$ (0.19 mmol) and quickly heated to 70 or 80 °C. The reaction mixture was stirred under Ar for 1 to 6 h until **4** was consumed. The mixture was cooled to rt and concentrated in vacuo to a slurry, water (3 mL) and EtOAc (5 mL) were added, and the mixture was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography.

All product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures.

***anti*-1-(*N*-(5-Bromo)-2-pyridinyl-*N*-hydroxyamino)-2-methoxycyclopent-3-ene (6a):** clear oil; IR (neat, cm^{-1}) 3427, 3020, 1521, 1424, 1216, 1045; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (s, 1 H), 8.25 (m, 1 H), 7.80 (dd, J = 8.9, 2.4 Hz, 1 H), 7.05 (dd, J = 8.9, 0.6 Hz, 1 H), 5.91 (m, 1 H), 5.84 (m, 1 H), 5.03−4.99 (m, 1 H), 4.65 (br m, 1 H), 3.22 (s, 3 H), 2.48−2.42 (m, 1 H), 2.34−2.28 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 147.5, 140.0, 133.3, 130.2, 111.1, 108.9, 87.0, 65.3, 55.7, 31.9; HRMS (ESI) $[M + H]^+$ calcd for $C_{11}H_{14}BrN_2O_2$ 285.0233, found 285.0231.

***anti*-1-(*N*-(5-Bromo)-2-pyridinyl-*N*-hydroxyamino)-4-methoxycyclopent-2-ene (7a):** clear oil; IR (neat, cm^{-1}) 3407, 3019, 1579, 1458, 1364, 1216, 1091; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 1 H), 8.25 (dd, J = 2.6, 0.6 Hz, 1 H), 7.79 (dd, J = 9.0, 2.6 Hz, 1 H), 7.01 (dd, J = 9.0, 0.6 Hz, 1 H), 6.10 (m, 1 H), 5.87 (m, 1 H), 5.69 (br m, 1 H), 4.52 (br m, 1 H), 3.21 (s, 3 H), 2.05 (ddd, J = 13.8, 7.2, 3.8 Hz, 1 H), 1.80 (ddd, J = 13.8, 8.2, 3.4 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 147.4, 140.0, 134.8, 134.3, 111.4, 109.0, 84.7, 65.2, 55.5, 32.1; HRMS (ESI) $[M + H]^+$ calcd for $C_{11}H_{14}BrN_2O_2$ 285.0233, found 285.0205.

***syn*-1-(*N*-(5-Bromo)-2-pyridinyl-*N*-hydroxyamino)-4-methoxycyclopent-2-ene (8a):** clear oil; IR (neat, cm^{-1}) 3407, 3019, 1579, 1458, 1364, 1216, 1091; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (s, 1 H), 8.23 (dd, J = 2.6, 0.6 Hz, 1 H), 7.79 (m, 1 H), 7.02 (dd, J = 9.0, 0.6 Hz, 1 H), 6.01 (m, 1 H), 5.84 (m, 1 H), 5.45 (m, 1 H), 4.33−4.30 (m, 1 H), 3.23 (s, 3 H), 2.40 (ddd, J = 12.8, 7.6, 7.6 Hz, 1 H), 1.68 (ddd, J = 12.8, 6.6, 6.6 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 147.4, 140.1, 133.9, 133.4, 111.1, 108.8, 83.2, 63.6, 55.3, 31.6; HRMS (ESI) $[M + H]^+$ calcd for $C_{11}H_{14}BrN_2O_2$ 285.0233, found 285.0205.

***anti*-1-(*N*-(5-Bromo)-2-pyridinyl-*N*-hydroxyamino)-2-methoxycyclohex-3-ene (9a):** yellowish oil; IR (neat, cm^{-1}) 3416, 3020, 1520, 1421, 1363, 1216, 1090; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.22 (s, 1 H), 8.19 (dd, J = 2.5, 0.4 Hz, 1 H), 7.75 (dd, J = 9.0, 2.5 Hz, 1 H), 7.01 (dd, J = 9.0, 0.4 Hz, 1 H), 5.76 (m, 1 H), 5.70 (m, 1 H), 4.53 (ddd, J = 12.3, 9.0, 3.2 Hz, 1 H), 4.24−4.21 (m, 1 H), 3.18 (s, 3 H), 2.09 (br m, 2 H), 1.84−1.77 (m, 1 H), 1.57−1.55 (m, 1 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.7, 147.2, 139.7, 128.8, 127.6, 110.3, 107.8, 74.6, 58.9, 54.7, 24.8, 23.6; HRMS (ESI) $[M + Na]^+$ calcd for $C_{12}H_{15}BrN_2NaO_2$ 321.0208, found 321.0209.

***anti*-1-(*N*-(5-Bromo)-2-pyridinyl-*N*-hydroxyamino)-4-methoxycyclohex-2-ene (10a):** white glass; IR (neat, cm^{-1}) 3406, 3020, 1521, 1424, 1216, 1046; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.19 (s, 1 H), 8.23 (dd, J = 2.6, 0.6 Hz, 1 H), 7.79 (dd, J = 8.8, 2.6 Hz, 1 H), 7.02 (dd, J = 8.8, 0.6 Hz, 1 H), 5.87−5.84 (m, 1 H), 5.61−5.59 (m, 1 H), 5.06 (m, 1 H), 3.84 (m, 1 H), 3.25 (s, 3 H), 2.14 (br m, 1 H), 1.78−1.74 (m, 2 H), 1.44−1.37 (m, 1 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.2, 147.4, 140.0, 131.6, 130.4, 111.1, 108.7, 74.7, 56.3, 54.8, 27.8, 22.5; HRMS (ESI) $[M + H]^+$ calcd for $C_{12}H_{16}BrN_2O_2$ 299.0388, found 299.0390.

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Supporting Information Available: General methods, experimental details, characterization data, and copies of ^{1}H, ^{13}C, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.