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Regio- and stereochemically controlled formation of hydroxamic acids from indium triflate-mediated nucleophilic ring-opening reactions with acylnitroso-Diels–Alder adducts

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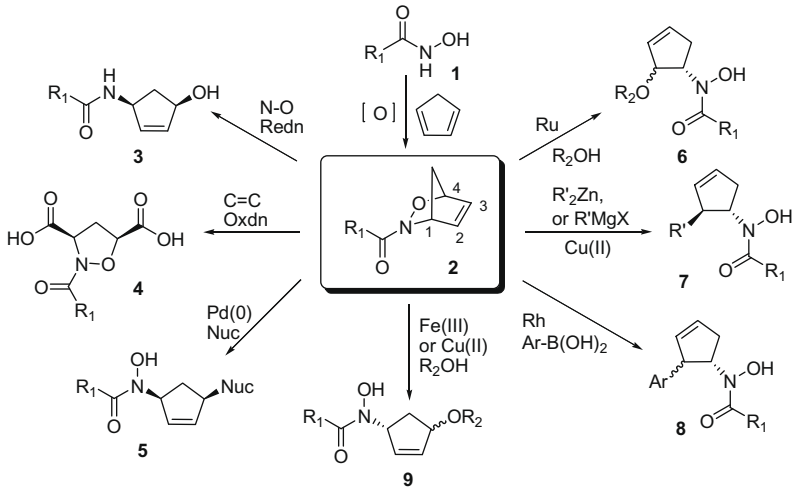
ABSTRACT

Treatment of acylnitroso-Diels–Alder [2.2.1] bicyclic adducts **2a–b** with indium triflate in an alcohol solvent induces ring-opening reactions to afford monocyclic anti-1,2-, anti-1,4-, and syn-1,4-hydroxamic acids with good to excellent regio- and stereoselectivity (up to 7:86:7). Treatment of [2.2.2] bicyclic nitroso adducts **2c–d** under similar reaction conditions generates only anti-1,2- and anti-1,4-hydroxamic acids with anti-1,4-product being predominant (up to 17:83).

3-Aza-2-oxabicyclo[2.2.1]hept-5-ene systems (**2**), derived from the hetero Diels–Alder reactions between transient acylnitroso species and cyclopentadiene, are valuable precursors for a variety of biologically interesting compounds.[1] Acylnitroso adducts **2** are susceptible to several modes of ring-opening reactions to introduce different functionalities with defined stereo- and regiochemistries (Scheme 1). For instance, cycloadducts **2** can be elaborated through reductive cleavage of the N–O bond to form *syn*-1,4 aminocyclopentenols **3**,[2] or by oxidative cleavage of the C=C bond to afford diacids **4**.[3] An alternate strategy to induce the ring-opening of **2** involves the cleavage of the C–O bond through metal-mediated reactions in the presence of nucleophiles. We and others have demonstrated that the C–O bond cleavage can be induced by palladium(0),[4] ruthenium,[5] rhodium,[6] and Lewis acids[7] to provide *syn*-1,2, *anti*-1,2, *anti*-1,4, or *syn*-1,4-disubstituted cyclopentenes (**5–9**) in a selective fashion. This route is of particular interest because



Scheme 1. Ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes **2**.

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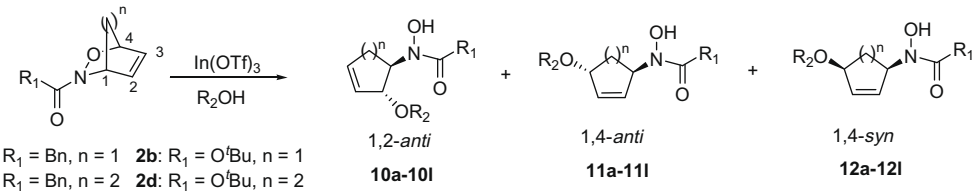


Scheme 2. In(OTf)$_3$-mediated nucleophilic ring-opening reaction of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes **2a**–**b** and [2.2.2]oct-5-enes **2c**–**d**.

Table 1
In(OTf)$_3$-mediated nucleophilic ring-opening reactions of cycloadducts **2a**–**b** (n = 1) with different alcohols

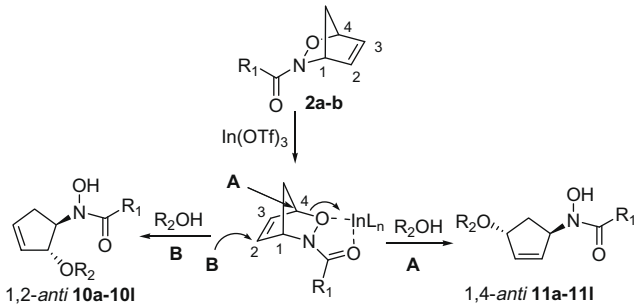
Entry[a]	Substrate	R_2OH	Temp (°C)	Time (h)	Products (n = 1)	Yield[b] (%)	Product ratios,[c] **10**:**11**:**12**	R_1	R_2
1	**2a**	MeOH	25	1.5	**10a**–**12a**	63	7:86:7	Bn	Me
2	**2a**	^{i}PrOH	25	2	**10b**–**12b**	63	8:76:15	Bn	^{i}Pr
3	**2a**	^{t}BuOH	25	2	**10c**–**12c**	61	7:73:20	Bn	^{t}Bu
4	**2b**	MeOH	25	2	**10d**–**12d**	61	32:52:16	O^{t}Bu	Me
5	**2b**	^{i}PrOH	25	2	**10e**–**12e**	64	26:57:17	O^{t}Bu	^{i}Pr
6	**2b**	^{t}BuOH	25	2	**10f**–**12f**	59	23:57:20	O^{t}Bu	^{t}Bu

[a] 0.5 equiv of In(OTf)$_3$.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of crude reaction mixture.

it allows the generation of a hydroxamic acid moiety, a key structural element in a wide range of biologically active compounds.[8] Hydroxamates often act as potent and selective inhibitors of metalloprotease enzymes such as matrix metalloproteinases (MMPS),[9] histone deacetylases (HDACs),[10] and peptidyl deformylase (PDF).[11]

Previously, we reported Cu(II) and Fe(III)-mediated nucleophilic ring-openings of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **2** with alcohols to afford synthetically useful 1,4-disubstituted hydroxamic acid-containing aminocylopentenols.[4c,7a] Our continued interest in hydroxamic acids led us to develop an improved and versatile method for Lewis acid-mediated C–O bond cleavage reactions. In this regard, we thought of identifying more efficient Lewis acids. In recent years, indium(III) compounds have attracted a great deal of interest as mild and water-tolerant Lewis acids inducing high regio-, stereo-, and chemoselectivity in various organic transformations.[12] Among the various In-based reagents, indium triflate (In(OTf)$_3$) is found to be a more effective catalyst than conventional Lewis acids in promoting a number of transformations[13] including, for example, Friedel–Crafts acylation of alcohols and amines,[14] tetrahydropyranylation of alcohols,[15] and ring-opening of aziridines.[16] Our own work also found indium triflate to be a very efficient catalyst for promoting nucleophilic ring-opening reactions of iminonitroso-derived adducts.[17] Herein we wish to report the regio- and stereochemically controlled formation of hydroxamic acids from indium triflate-mediated nucleophilic ring-opening reactions of acylnitroso adducts **2** (Scheme 2).

Our investigation began with the treatment of *N*-phenylacetyl [2.2.1] cycloadduct **2a** with 0.5 equiv of In(OTf)$_3$ in the presence of three representative alcohols including MeOH, secondary alcohol, ^{i}PrOH, and tertiary alcohol, ^{t}BuOH, respectively, at room temperature. The results are summarized in Table 1. We were pleased to find that the reaction with MeOH generated a 7:86:7 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-methoxylated cyclopentene containing hydroxamic acid products (**10a**:**11a**:**12a**)[18] in 63% yield with *anti*-1,4-product **11a** being predominant within 1.5 h. The In(OTf)$_3$ offered a more potent Lewis acid source, as was evident by the shorter reaction times observed with the use of In(OTf)$_3$. High regio- and stereoselectivity were retained even when larger alcohol nucleophiles such as ^{i}PrOH and ^{t}BuOH were used (entries 2–3). The preference for *anti*-1,4-ring-opening products was greatly improved compared to the reactions catalyzed by $FeCl_3$ or $CuCl_2$.[19]



Scheme 3. Proposed mechanism for In(OTf)$_3$-mediated nucleophilic ring-opening reaction of acylnitroso adducts **2a**–**b**.

The indium-catalyzed ring-opening reactions of *N*-alkoxy carbamate [2.2.1] cycloadduct **2b** were also investigated under the same reaction conditions. Separate reactions with each of the above-mentioned alcohols gave the corresponding *N*-hydroxy carbamate products in moderate yields (59–61%) with compromised stereoselectivity (Table 1, entries 4–6). For example, use of methanol gave a 61% yield of a 32:52:16 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-ring-opened products (**10d**:**11d**:**12d**) (entry 4). A plausible mechanism is that *anti*-1,4- and *anti*-1,2-products, **11a**–**f** and **10a**–**f**, might result from direct (S_N2) and indirect (S_N2-like) nucleophilic displacement of the oxygen during the attack of alcohols (Scheme 3, paths A and B), though a competitive open cation process might also account for the mixed stereoselectivity and formation of the minor *syn*-1,4 products (**12a**–**f**).

We next examined the reactions of 3-aza-2-oxabicyclo[2.2.2]oct-5-ene systems **2c**–**d** with In(OTf)$_3$ in the presence of alcohols. Because of the decreased ring strain and consequent reduced reactivity of the [2.2.2] substrates relative to the [2.2.1] substrates, we conducted reactions at elevated temperature (70 °C). The results are summarized in Table 2. Nucleophilic ring-opening reaction of *N*-phenylacetyl [2.2.2] cycloadduct **2c** with 0.5 equiv of In(OTf)$_3$ and MeOH was complete within 6 h, generating a 57% yield of a 18:82 ratio of *anti*-1,2-:*anti*-1,4-products (**10g**:**11g**) with *anti*-1,4-compound **11g** as the major product (entry 1). No *syn*-1,4-product **12g** was detected, which further supported the proposed

Table 2
$In(OTf)_3$-mediated nucleophilic ring-opening reactions of cycloadducts **2c–d** ($n = 2$) with different alcohols

Entry[a]	Substrate	R_2OH	Temp (°C)	Time (h)	Products ($n = 2$)	Yield[b] (%)	Product ratios,[c] **10**:**11**:**12**	R_1	R_2
1	**2c**	MeOH	70	6	**10g–12g**	57	18:82:0	Bn	Me
2	**2c**	^{i}PrOH	70	6	**10h–12h**	54	17:83:0	Bn	^{i}Pr
3	**2c**	^{t}BuOH	70	6	**10i–12i**	51	20:80:0	Bn	^{t}Bu
4	**2d**	MeOH	70	24	**10j–12j**	50	25:75:0	O^{t}Bu	Me
5	**2d**	^{i}PrOH	70	24	**10k–12k**	45	44:56:0	O^{t}Bu	^{i}Pr
6	**2d**	^{t}BuOH	70	24	**10l–12l**	43	37:63:0	O^{t}Bu	^{t}Bu

[a] 0.5 equiv of $In(OTf)_3$.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of crude reaction mixture.

reaction mechanism as shown in Scheme 3. In contrast, previous studies[7a] reported a mixture of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-products (**10g**:**11g**:**12g**) when cycloadduct **2c** was treated with $CuSO_4$ or $CuCl_2$ in the presence of MeOH. Compounds **10g** and **11g** were readily separable by column chromatography, and their regio- and stereochemistries were determined by relevant NMR experiments.[20] Similar results were obtained when ^{i}PrOH and ^{t}BuOH were used (entries 2–3). The reactions with carbamate-based [2.2.2] cycloadduct **2d** required prolonged reaction time. In this case, exclusive *anti*-1,2-products **10j–l** and *anti*-1,4-products **11j–l** were obtained in moderate yields with MeOH, ^{i}PrOH, and ^{t}BuOH, respectively (entries 4–6).

In summary, we found that indium triflate is an effective Lewis acid in promoting the nucleophilic ring-opening of a variety of acylnitroso hetero Diels–Alder cycloadduct systems. Predominant *anti*-1,4-hydroxamic acid containing cycloalkenes were obtained with [2.2.1] systems. Exclusive *anti*-1,2-products and *anti*-1,4-products with a ratio up to 17:83 were generated with [2.2.2] systems.

Acknowledgments

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18. The structure of *anti*-1,2-product **10a** was determined by 1D and 2D NMR studies (COSY, HSQC). The regio- and stereochemistry of *anti*-1,4- and *syn*-1,4-products (**11a** and **12a**) were assigned using comparison of the coupling pattern of the C(5) methylene protons, see Ref. 4c.
19. In the $CuCl_2$ or $FeCl_3$-mediated nucleophilic ring-opening reactions of cycloadduct **2a**, the selectivity for *anti*-1,4-product was decreased when bulky nucleophiles were used. For example, reaction of **2a** with $CuCl_2$ in the presence of MeOH generated a 5:70:25 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-products (**10a**:**11a**:**12a**); however, use of ^{t}BuOH gave a 1:22:77 ratio of *anti*-1,2-:*anti*-1,4-:*syn*-1,4-products (**10c**:**11c**:**12c**); for more examples, see Ref. 7a.
20. 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).