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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 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 acids⁷ to provide *syn*-1,2, *anti*-1,2, *anti*-1,4, or *syn*-1,4-disubstituted cyclopentenols (**5–9**) in a selective fashion. This route is of particular interest because it allows 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 aminocyclopentenols.^{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 to identify 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

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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 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, ⁱPrOH, and tertiary alcohol, ^tBuOH, respectively, at room temperature. The results are summarized in Table 1. We were pleased to find that 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** 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 was retained even when larger alcohol nucleophiles such as ⁱPrOH or ^tBuOH were used (entries 2–3). The preference for *anti*-1,4-ring-opening products was greatly improved compared to the reactions catalyzed by FeCl₃ or CuCl₂.¹⁹ 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, 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 products (**12a–f**).

We next examined the reactions of 3-aza-2-oxabicyclo[2.2.2]oct-5-ene systems **2c–2d** 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 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 CuSO₄ or CuCl₂ 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 ⁱPrOH and ^tBuOH were used (entries 2–3). Reactions with carbamate-based [2.2.2] cycloadduct **2d** required prolonged reaction time. In this case, exclusive *anti*-1,2-products **10j–10l** and *anti*-1,4-products **11j–11l** were obtained in moderate yields with MeOH, ⁱPrOH, and ^tBuOH, 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.

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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 CuCl₂ or FeCl₃-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 CuCl₂ 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 ^tBuOH 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).

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

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**

Scheme 3.

Proposed mechanism for $\text{In}(\text{OTf})_3$ -mediated nucleophilic ring-opening reaction of acylnitroso adducts **2a-b**

Table 1

In(OTf)₃-mediated nucleophilic ring-opening reactions of cycloadducts **2a–2b** (n = 1) with different alcohols

Entry ^a	Substrate	R ₂ OH	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>i</i> -PrOH	25	2	10b–12b	63	8:76:15	Bn	<i>i</i> -Pr
3	2a	<i>t</i> -BuOH	25	2	10c–12c	61	7:73:20	Bn	<i>t</i> -Bu
4	2b	MeOH	25	2	10d–12d	61	32:52:16	O <i>t</i> -Bu	Me
5	2b	<i>i</i> -PrOH	25	2	10e–12e	64	26:57:17	O <i>t</i> -Bu	<i>i</i> -Pr
6	2b	<i>t</i> -BuOH	25	2	10f–12f	59	23:57:20	O <i>t</i> -Bu	<i>t</i> -Bu

^a 0.5 equiv of In(OTf)₃

^b Isolated yield.

^c Determined by ¹H NMR of crude reaction mixture.

Table 2

In(OTf)₃-mediated nucleophilic ring-opening reactions of cycloadducts **2c–2d** (n = 2) with different alcohols

Entry ^a	Substrate	R ₂ OH	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>i</i> -PrOH	70	6	10h–12h	54	17:83:0	Bn	<i>i</i> -Pr
3	2c	<i>t</i> -BuOH	70	6	10i–12i	51	20:80:0	Bn	<i>t</i> -Bu
4	2d	MeOH	70	24	10j–12j	50	25:75:0	O <i>t</i> -Bu	Me
5	2d	<i>i</i> -PrOH	70	24	10k–12k	45	44:56:0	O <i>t</i> -Bu	<i>i</i> -Pr
6	2d	<i>t</i> -BuOH	70	24	10l–12l	43	37:63:0	O <i>t</i> -Bu	<i>t</i> -Bu

^a 0.5 equiv of In(OTf)₃

^b Isolated yield.

^c Determined by ¹H NMR of crude reaction mixture.