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Indium Triflate-Assisted Nucleophilic Aromatic Substitution Reactions of Nitrosobenzene-Derived Cycloadducts with Alcohols

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Abstract

Exclusive nucleophilic aromatic substitution of hydrogen in conjunction with cleavage of the N–O bond were observed, when nitrosobenzene-derived nitroso cycloadducts were treated with indium triflate in the presence of alcohols. Aromatic alkoxy-substituted *syn*-1,4 aminocycloalkenol products with good to excellent regioselectivity (16:84 to 0:100, ortho-:para-) were obtained.

Nitroso cycloadducts **1** (Scheme 1), derived from nitroso Diels–Alder reactions (NDA),¹ are valuable synthetic intermediates as they serve as a general scaffold to create unique structural and functional diversity. Several modes of ring-opening reactions of bicyclic oxazines **1** have been established to introduce different functionalities with defined stereo- and regiochemistries.² For example, the C–O bond cleavage of **1a** and **1b** may be induced by Lewis acids to selectively give hydroxamate or hydroxyamino containing *anti*-1,2, *anti*-1,4 and *syn*-1,4-alkoxy-substituted cycloalkenes (Scheme 1, routes A and B).^{2d,2e} The reactivity and stereoselectivity have been demonstrated to depend on the binding ability of Lewis acids with oxazines. Nitrosobenzene-derived cycloadducts (**1c–d**) are unique substrates for this chemistry, since in contrast to **1a** and **1b**, they do not contain additional coordination center(s) attached to the oxazine core. In fact, this apparently simple difference has significant chemical consequences. Here we report the first example of indium triflate-assisted nucleophilic aromatic substitution (S_NAr) of **1c–d** in the presence of alcohols. Nucleophilic aromatic substitution reaction³ occurs at electron deficient aromatic rings and typically involves displacement of halogens or other nucleofugal groups. The reactions described here are unusual in that they involve a S_NAr reaction with net replacement of hydrogen⁴ via a concomitant N–O bond cleavage to afford aromatic alkoxy-substituted *syn*-1,4 amino cycloalkenol products **4** and/or **5** in one step (Scheme 1, route C).

Our studies began with an initial experiment with nitroso cycloadduct **1c** derived from NDA reaction of nitrosobenzene with cyclopentadiene. While the cycloadduct could be formed, the thermal instability of **1c** required that it be treated directly, without isolation, with In(OTf)₃ and MeOH. The reaction produced a complex mixture; however, to our surprise, a para-methoxy-substituted benzene-substituted *syn*-1,4 aminocyclopentenol product, **4a**, as a net result of

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Supporting Information Available: General method, experimental details, ¹H NMR and ¹³C NMR spectra for **1d**, **4a**, **4b–c**, **4f**, **5b–j**, **6**, **10**, **12** and **13**, and COSY and HSQC spectra for **4b** and **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

nucleophilic aromatic substitution and N–O bond cleavage, was isolated in 31% yield after 12 h (Scheme 2).

This finding encouraged us to examine the reaction with more stable, isolable [2.2.2] bicyclic nitroso adduct **1d**. (Table 1). Reaction of **1d** in MeOH with 0.5 equiv of In(OTf)₃ at room temperature occurred, generating a 24% yield of a 15:85 ratio of ortho- and para-methoxylated products, **4b** and **5b**, after prolonged reaction (48 h, entry 1). Again, in contrast to reactions with acyl- and imino-nitroso adducts (**1a** and **1b**), no C–O bond cleaved product was detected by LC/MS and ¹H NMR. Compounds **4b** and **5b** were readily separable by column chromatography, and their structures were further confirmed by 1D and 2D NMR experiments (COSY, HSQC). Variation of the amount of In(OTf)₃ used in the reaction at different temperature was then explored (entries 2–7). Optimized reaction conditions were found when 0.5 equiv of In(OTf)₃ was added to **1d** at 70 °C. This gave **4b** and **5b** in a 16:84 ratio and 71% isolated yield within 2 h (entry 6).

Other Lewis acids [InI₃, La(OTf)₃ and FeCl₃] were also briefly surveyed to determine the generality of nucleophilic aromatic substitution of **1d**. However, none were as effective as In(OTf)₃. Treatment of a methanolic solution of cycloadduct **1d** with InI₃ or La(OTf)₃ at 70 °C only afforded a mixture of **4b** and **5b** in 35% and 28% yields, respectively, even after 24 h. Use of FeCl₃ gave only a trace amount of product. When CuCl was employed, instead of nucleophilic aromatic substitution, a simple N–O bond cleavage occurred, generating *syn*-1,4 aminocyclopentenol **6** in 70% yield (Scheme 3). These experiments indicated that the S_NAr reaction here may depend on the coordinating ability of the Lewis acid, with indium triflate being optimal.

Under the optimized reaction conditions, we expanded the studies to include reactions of **1d** with several representative alcohols. The results are summarized in Table 2. Reactions of **1d** with ⁱPrOH, 1-hexanol and ^tBuOH afforded the corresponding aromatic alkoxyated products in moderate yields (entries 1–3). In order to give compounds more compatible for eventual further elaboration, reactions of **1d** with allyl alcohol, propargyl alcohol and benzyl alcohols were performed. Reaction with allyl alcohol gave a 68% yield of a 13:87 ratio of ortho- and para-allyloxyated compounds **4f** and **5f** (entry 4). Only para-substituted 1,4 aminocyclohexenol **5g** was isolated in 58% yield when propargyl alcohol was used (entry 5). Reactions of **1d** with 5.0 equiv of benzyl alcohol, 4-methoxybenzyl alcohol and 4-nitrobenzyl alcohol in THF generated exclusive para-benzyloxyated products **5h**, **5i** and **5j** in 55%, 49% and 39% yields, respectively (entries 6–8). The regioselectivity for para-alkoxyated product **5** over ortho-alkoxyated product **4** might result from the steric repulsion generated from the attack of alcohol at the ortho-position. Treatment of **1d** with In(OTf)₃ in aqueous THF generated a mixture of aromatic hydroxylated *syn*-1,4 amino cycloalkenol products based on LC/MS analysis.

A control reaction was also run in which **1d** was treated with methanol in the absence of In(OTf)₃ at 70 °C for 12 h. Oxazine **1d** was recovered unchanged, thus indicating that chelation with indium triflate is indeed important for the reaction. A plausible mechanism for the formation of **4b** and **5b** through net nucleophilic aromatic substitution of hydrogen is proposed (Scheme 4).⁵ The reaction might be initiated by coordination between the oxygen atom in oxazine **1d** and indium to generate electron-deficient intermediate **7**, which is susceptible to the addition of methanol to the aromatic ring at either the ortho- or para-positions. Tautomerization of the resulting imines **8** and **9** would generate products **4b** and **5b** with concomitant rearomatization. Alternately, a S_N1 like mechanism involves initial N–O bond cleavage to generate a nitrene cannot be ruled out.

For comparison, iminonitroso cycloadduct **10** was synthesized and subjected to the same reaction conditions (Scheme 5). Consistent with our previous report,^{2e} only C–O bond cleaved products, *anti*-1,2-**12** and *anti*-1,4-**13**, were obtained in 90% yield and in a 1:1 ratio. The likely mechanism involves a formation of coordinated intermediate **11** as a result of a five-membered ring chelation with the In, as well as a subsequent direct (S_N2-like) or indirect (S_N2'-like) nucleophilic displacement of the oxygen during the attack of methanol. These results clearly indicated that the additional chelation between indium and the imino nitrogen of oxazine finely tuned the electronic property of **10** to the favor of C–O bond cleavage.

In summary, we have demonstrated an unprecedented nucleophilic aromatic substitution reaction of nitrosobenzene-derived cycloadducts with alcohols catalyzed by indium triflate. In most cases, regioselective para-aromatic alkoxyated *syn*-1,4 aminocycloalkenol products were obtained. We anticipate that this new aromatic substitution/coupling protocol will be of considerable utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Lewis acid-mediated ring-opening reactions of nitroso cycloadduct **1**

Scheme 2.

$\text{In}(\text{OTf})_3$ -assisted nucleophilic aromatic substitution of **1c** in the presence of MeOH

Scheme 3.
Cu-mediated N–O bond reductive cleavage of **1d**

Scheme 4.
Proposed mechanism for formation of **4b** and **5b** through $\text{In}(\text{OTf})_3$ -assisted $\text{S}_{\text{N}}\text{Ar}$ reaction of **1d**

Scheme 5.

Proposed mechanism for formation of **12** and **13** through $\text{In}(\text{OTf})_3$ -mediated C–O bond cleavage of **10**

Table 1

Optimization of $\text{In}(\text{OTf})_3$ -assisted nucleophilic aromatic substitution of **1d** in the presence of MeOH

Entry	$\text{In}(\text{OTf})_3$ loading ^d	temp (°C)	time (h)	yield ^b (%)	ratio ^c 4b:5b
1	0.5 equiv	25	48	24	15:85
2	1.0 equiv	25	24	69	18:82
3	1.5 equiv	25	12	65	18:82
4	0.5 equiv	40	24	62	12:87
5	0.2 equiv	70	24	57	16:84
6	0.5 equiv	70	2	71	16:84
7	1.0 equiv	70	2	58	17:83

^aRelative to cycloadduct **1d**.

^bIsolated yields.

^cDetermined by ^1H NMR of crude mixture.

Table 2In(OTf)₃-assisted nucleophilic aromatic substitution of **1d** with different alcohols

entry	ROH	product	yield ^b (%)	ratio ^c 4:5
1	(CH ₃) ₂ CHOH	4c + 5c	58	13:87
2	C ₆ H ₁₃ OH	5d	56	0:100
3	(CH ₃) ₃ COH	5e	37	0:100
4	CH ₂ =CHCH ₂ OH	4f + 5f	68	13:87
5	CH=CCH ₂ OH	5g	58	~0:100
6 ^a	C ₆ H ₅ CH ₂ OH	5h	55	0:100
7 ^a	4-CH ₃ OC ₆ H ₅ CH ₂ OH	5i	49	0:100
8 ^a	4-O ₂ NC ₆ H ₅ CH ₂ OH	5j	39	0:100

^a 5.0 equiv of ROH in THF used.^b Isolated yields.^c Determined by ¹H NMR of crude mixutre.