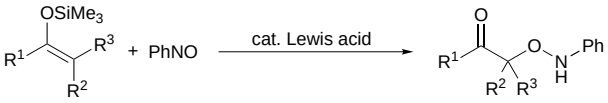
The following article was originally published online as *Angew. Chem.* **2002**, *114*, 3112–3114; *Angew. Chem. Int. Ed.* **2002**, *41*, 2986–2988 (Issue 16). It was corrected on September 16th 2002 because, in the original version, two equations were inadvertently omitted. The scientific content was not changed at all.

Peter Gölitz, Editor

Lewis Acid Promoted, O-Selective, Nucleophilic Addition of Silyl Enol Ethers to N=O bonds**

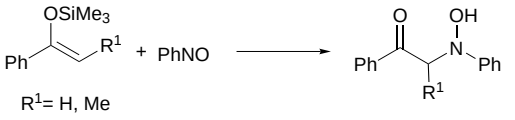
Norie Momiyama and Hisashi Yamamoto*

We report herein the first regioselective synthesis of α-aminooxy ketones from silyl enol ethers and nitrosobenzene [Eq. (1)]. The direct introduction of aminooxy or hydroxyamino groups at the α position of carbonyl compounds has not



(1)

been part of synthetic practice, in sharp contrast to the very widespread addition of formyl electrophiles at the α position of ketone enolates or their equivalents, that is, aldol synthesis.[1] In fact, there are only a few reports on the use of nitrosobenzene[2] for nucleophilic addition with the silyl enol ethers of acetophenone and propiophenone to generate the corresponding α-hydroxyamino derivatives [Eq. (2)].[3] We



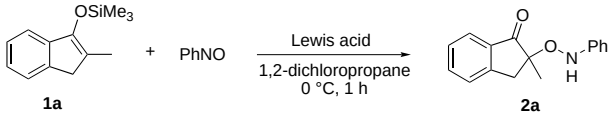
(2)

were surprised to learn that treatment of silyl enol ethers with nitrosobenzene in the presence of various Lewis acid catalysts proceeds smoothly to generate previously unknown α-aminooxy ketones in high yields. The present procedure has important implications in the N–O–C-bond construction from these simple starting compounds and can open a new entry to useful building blocks for potentially important, biologically active compounds.[4]

Our initial design of a nucleophilic addition of silyl enol ethers to nitrosobenzene rested on finding a suitable catalyst that could facilitate N-alkylation with various silyl enol ethers. Trimethylsilyl triflate was chosen as a Lewis acid for this reaction based on its use in Mukaiyama-type aldol reactions.[5] However, nucleophilic addition catalyzed by trimethylsilyl triflate did *not* provide the N-adduct (hydroxyamino ketone). An X-ray crystallographic study or chemical transformation with acetyl chloride demonstrated that the N-adduct was not formed; instead the O-adduct (aminooxy ketone) was the product of the reaction [Eq. (1)].[6] We then focused on Lewis acid catalyzed O-selective nucleophilic addition as a new strategy for constructing N–O–C bonds.

A variety of Lewis acid catalysts were examined and are summarized in Table 1. Alkylsilyl triflates efficiently mediated the O-selective nucleophilic addition of silyl enol ether **1a** to nitrosobenzene (1,2-dichloropropane, 0 °C) to give the O-adduct **2a** in excellent yield (Table 1). The use of triethylsilyl triflate (10 mol %) led to the isolation of **2a** in 94 % yield (Table 1, entry 3); even a lower amount of the catalyst (1 mol %) still provided the product in 74 % yield (Table 1, entry 5). Titanium(IV) chloride, iron(III) chloride, and cop-

Table 1. O-Alkylation of **1a** catalyzed by various Lewis acids.



1a **2a**

Entry	Lewis acid	Equiv [mol %]	Yield [%][a]
1	none		< 1
2	Me_3SiOTf	5	86
3	Et_3SiOTf	10	94
4	Et_3SiOTf	5	88
5	Et_3SiOTf	1	74
6	$tBuMe_2SiOTf$	5	83
7	$TiCl_4$	5	71
8	$FeCl_3$	5	60
9	Me_3SiNTf_2	5	54
10	[AgOTf]	5	52
11	$[Cu(OTf)_2]$	5	58
12	$[Sn(OTf)_2]$	5	50

[a] Yield of isolated product.

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[**] We thank Prof. Akira Yanagisawa (Department of Chemistry, Faculty of Science, Chiba University) for helpful discussion, Dr. Yujiro Hoshino for stimulating discussion and X-ray crystallographic analysis, and Mr. Kin-ichi Oyama (Chemical Instrument Center of Nagoya University) for measurement of ESI mass spectra.

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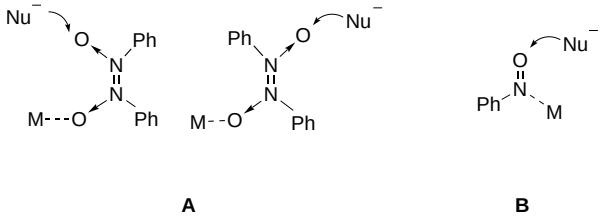
  0044-8249/02/4116-2986 $ 20.00+.50/0

per(II) triflate also led to the formation of **2a** in moderate to good yields (Table 1, entries 7, 8, 11).

Since aromatic C-nitroso compounds are known to exist as blue or green monomers and colorless dimers,[7] chemical models of the catalyst–nitrosobenzene complex predict the two coordination geometries **A** and **B** (Scheme 1). However,



A **B**

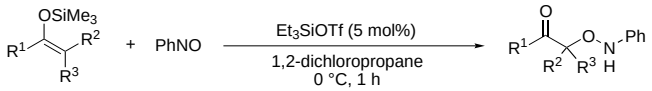
Scheme 1. Proposed active species of nitrosobenzene in the presence of Lewis acid.

as Lewis acids promote the dimerization of the monomer nitrosobenzene,[8,9] O-alkylation may proceed via intermediacy of the Lewis acid coordinated nitroso dimer complex **A**. This process does not proceed through an aldol pathway in which nitrosobenzene behaves like a carbonyl compound **B** (Scheme 1).

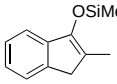
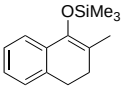
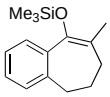
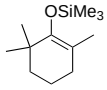
Significant structural variation in the silyl enol ether component is possible without any loss in regioselectivity (Table 2). An aromatic substituent such as phenyl provides good reactivity in this reaction (Table 2, entries 1–3). The reaction of α-disubstituted substrates (Table 2, entries 1–3, 5–6) is more facile than that of monosubstituted (Table 2, entries 4, 8).

In conclusion, we have documented a new strategy for aminooxy ketone synthesis that has enabled the development of the first highly O-selective, Lewis acid catalyzed, nucleophilic addition reaction to N=O bonds. Further studies to address the scope of this reaction and the coordination chemistry of the N=O bond are underway.

Table 2. O-Alkylation of various silyl enol ethers.



1 **2**

Entry	**1**		Yield [%][a]
1		**1a**	94
2		**1b**	51
3		**1c**	62
4		**1d**	44
5		**1e**	54
6		**1f**	62
7		**1g**	46
8		**1h**	37

[a] Yield of isolated product.

Experimental Section

General procedure: an oven-dried Schlenk tube equipped with a magnetic stirrer was charged with nitrosobenzene (1 equiv, 107.1 mg, 1 mmol) under argon. The tube was fitted with a septum cap, 1,2-dichloropropane (3 mL) was added through a syringe, and the solution was then stirred at room temperature for 5 min. After cooling to 0 °C, trimethylsilyl enol ether (1 equiv, 1 mmol) was added to the resulting green solution at this temperature. A solution of the Lewis acid (0.05 equiv, 0.05 mmol) in dry 1,2-dichloropropane (2 mL) was added to the mixture at 0 °C over a period of 10 min with a syringe pump. The mixture was stirred for 1 h at 0 °C to produce a cloudy orange mixture. The reaction mixture was quenched with cooled brine (20 mL), and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure after filtration. The residual crude product in 1,2-dichloropropane was purified by chromatography, with cooling, on a two-layered column filled with Florisil (upper layer) and silica gel (lower layer) with a mixture of ethyl acetate and hexane as the eluent to give the product.

2a: Nitrosobenzene (1 equiv), triethylsilyl triflate (23 μL, 0.1 mol) and **1a** (230 μL, 1 mmol) were treated as described in the General Procedure. Purification by flash column chromatography (eluent by hexane/ethyl acetate 7:1) provided **2a** (238.1 mg, 94 %) as a yellowish oil. TLC $R_f = 0.30$ (hexane/ethyl acetate 3:1); IR (neat): $\tilde{\nu} = 3270, 3050, 2977, 2926, 1715, 1605, 1495, 1470, 1304, 1233, 907\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.78$ (d, 1H, $J = 7.7$ Hz; ArH), 7.78 (t, 1H, $J = 7.4$ Hz; ArH), 7.34–7.40 (m, 2H; ArH), 7.23 (t, 2H, $J = 8.0$ Hz; ArH), 7.13 (s, 1H; NH), 6.91–6.94 (m, 3H; ArH), 3.54 (d, 1H, $J = 16.8$ Hz; CH_aH_b), 3.13 (d, 1H, $J = 16.8$ Hz; CH_aH_b), 1.49 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 205.3, 151.6, 148.3, 135.5, 134.4, 128.8$ (2C), 127.7, 126.7, 124.4, 122.1, 114.3 (2C), 87.1, 38.0, 21.9 ppm; elemental analysis: calcd for $C_{16}H_{15}NO_2$: C 75.87, H 5.97, N 5.53; found: C 75.76, H 6.13, N 5.64.

Received: April 19, 2002 [Z19114]

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[7] D. A. Dieterich, I. C. Paul, D. Y. Curtin, *J. Am. Chem. Soc.* **1974**, *96*, 6372.

[8] To elucidate the mechanism of this reaction, in situ infrared spectroscopy[10] and ESI mass spectra[11] of the trimethylsilyl triflate–nitrosobenzene complex were measured; detailed results will be published in due course.

[9] For examples of C-nitroso–metal complexes, see: a) D. Mansuy, M. Drem, J. C. Chottard, J. P. Girault, J. Guilhem, *J. Am. Chem. Soc.* **1980**, *102*, 844; b) M. A. Andres, C. F. Cheng, *J. Am. Chem. Soc.* **1982**, *104*, 4268; c) E. R. Møller, K. R. Jørgensen, *J. Am. Chem. Soc.* **1993**, *115*, 11 814; d) R. S. Strivastava, K. M. Nicholas, *J. Org. Chem.* **1994**, *59*, 5365; e) M. Johannsen, K. R. Jørgensen, *J. Org. Chem.* **1995**, *60*, 5979; f) R. S. Strivastava, M. A. Khan, K. M. Nicholas, *J. Am. Chem. Soc.* **1996**, *118*, 3311; g) R. S. Strivastava, K. M. Nicholas, *J. Am. Chem. Soc.* **1997**, *119*, 3302; h) J. R. Bleeke, J. M. B. Blanchard, *J. Am. Chem. Soc.* **1997**, *119*, 5443; i) K. R. Flower, A. P. Lightfoot, H. Wan, A. Whiting, *Chem. Commun.* **2001**, 1812.

[10] In situ IR spectra were recorded on a ReactIR 1000 instrument from ASI Applied Systems. Trimethylsilyl triflate (1 equiv) was added to a solution of nitrosobenzene (1 equiv) in 1,2-dichloropropane; as trimethylsilyl triflate was added, the absorption at 1505 cm^{-1} (nitrosobenzene N=O stretch) decreased in intensity while the absorption at 1264 cm^{-1} (*trans* azoxybenzene N–O stretch) simultaneously increased in intensity.

[11] ESI mass spectra of the trimethylsilyl triflate–nitrosobenzene complex showed peaks at m/z 214 ($Ph_2N_2O_2^+$) and m/z 329 [$Et_3Si(PhNO)_2^+$], thus confirming the presence of the dimer.

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