

# Simple Synthesis of $\alpha$ -Hydroxyamino Carbonyl Compounds: New Scope of the Nitroso Aldol Reaction

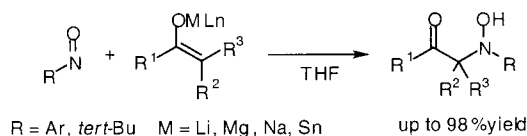
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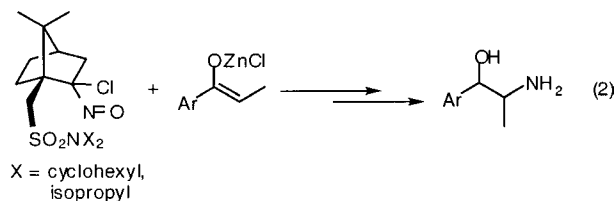
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## ABSTRACT



The reaction of nitroso compounds with enolates, “the nitroso aldol reaction”, occurs in high yield to generate  $\alpha$ -hydroxyamino carbonyl compounds. Yields range from 42% to 98% with N-selectivity >99:1 from commercially available aromatic or aliphatic nitroso compounds and a variety of alkali metal or tin enolates.

Development of new methods for the introduction of a nitrogen atom to a carbonyl group is still a most important synthetic target.<sup>1</sup> Although the addition reaction of nitroso compounds<sup>2</sup> with enolates, “the nitroso aldol reaction”, should be one obvious answer, not many papers have appeared on this simple but important technique. Sasaki and co-workers reported a smooth reaction of a silyl enol ether and nitrosobenzene at room temperature (eq 1).<sup>3</sup> Unfortunately, however, the scope of this reaction was very limited and few aromatic ketone enolates gave the desired product. Oppolzer reported the facile reaction of an enolate anion with very reactive  $\alpha$ -chloronitroso compounds (eq 2).<sup>4</sup> Herein we report a general method for the condensation of carbonyl compounds and nitroso derivatives to generate  $\alpha$ -hydroxyamino carbonyl compounds in high yield (eq 3).

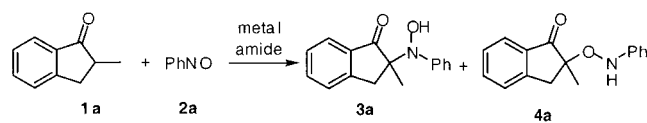


Surprisingly, simple treatment of the enolate of 2-methyl-1-indanone **1a** with readily available nitrosobenzene **2a** proceeded smoothly to generate the desired N-adduct **3a** in high yield. Lithium enolate displayed particularly remarkable reactivity as shown in Table 1.

The reaction was found to be quite general with respect to lithium enolate structures (Table 2). Reactions of disubstituted cyclic ketone enolates in the  $\alpha$ -position of the

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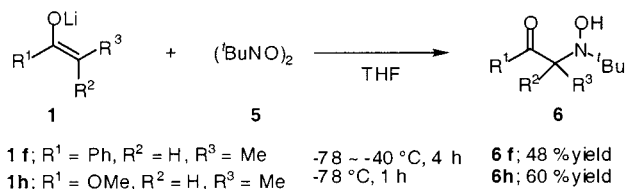
(1) (a) Genet, J.-P.; Greck, C.; Laverne, D. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 65. (b) Greck, C.; Genet, J. P. *Synlett* **1997**, 741. (c) Boche, G. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1995; Vol. E21, p 5133.

**Table 1.** Addition of Alkali Metal Enolate to Nitrosobenzene<sup>a</sup>

entry	metal amide	3a:4a <sup>b</sup>	yield, % <sup>c</sup>	solvent	T (°C)	time
1	LDA	>99:1	93	THF	-78	<5 min
2	<i>i</i> -Pr <sub>2</sub> NMgBr	>99:1	86	Et <sub>2</sub> O	0	2 h
3	NaHMDS	>99:1	90	Et <sub>2</sub> O	0	4 h

<sup>a</sup> The metal enolate **1a** was generated from 2-methyl-1-indanone (1 equiv) and corresponding metalamide (1.1 equiv). The following addition was carried out with nitrosobenzene **2a** (1 equiv) in THF or Et<sub>2</sub>O at the desired temperature. The reaction was quenched by cooled brine solution at this temperature. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis. <sup>c</sup> Isolated yield.

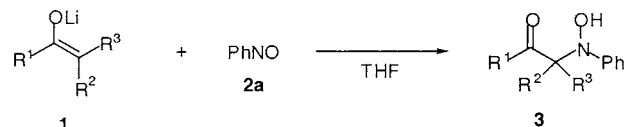
carbonyl (entries 1, 2, 4, and 5) with nitrosobenzene were completed in less than 5 min at -78 °C. Acyclic ketone or ester enolates also afforded moderate to high yields of requisite adducts **3**. Reaction with 2-methyl-2-nitroso-propane dimer **5** afforded the desired adducts **6** (Scheme 1). While alkyl ketone enolates were not sufficiently

**Scheme 1**

reactive to engage in nucleophilic addition to **5**, aromatic ketones such as propiophenone or ester enolates react at low temperature, providing addition products with good yields.

It is noteworthy that the product is exclusively the hydroxyamino ketone and none of the aminoxy compounds

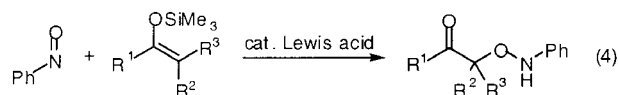
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**Table 2.** Addition of Various Lithium Enolates to Nitrosobenzene<sup>a</sup>

entry	lithium enolate	method <sup>b</sup>	yield, % <sup>c</sup>	T (°C)	time
1		A	93	-78	< 5 min
2		A	87	-78	< 5 min
3		A	47	-78	30 min
		B	45	-78	30 min
4		B	93	-78	< 5 min
5		A	69	-78	< 5 min
6		A	70	-78	30 min
7		B	93	-78	< 5 min
8		A	80	-40	1 h
		A	42	-40	1 h

<sup>a</sup> The reaction was carried out with lithium enolate **1** (1 equiv) and nitrosobenzene **2a** (1 equiv) in THF at the desired temperature for 5 min to 1 h. <sup>b</sup> Method A: lithium enolate was generated from the corresponding ketone and LDA in THF at -78 to 0 °C. Method B: lithium enolate was generated from the corresponding silyl enol ether and *n*-BuLi in THF at 0 °C to rt. <sup>c</sup> Isolated yield.

are produced under the above reaction conditions. In sharp contrast, we recently demonstrated that this reaction in the presence of Lewis acid catalysts is capable of synthesizing α-aminoxy ketones with high O-selectivities (eq 4).<sup>5</sup> It is



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**Table 3.** Addition of Various Tin Enolates to Nitrosobenzene<sup>a</sup>

entry	tin enolate	8 : 9 <sup>b</sup>	yield, % <sup>c</sup>	
1 <sup>d</sup>		7a	>99 : 1	91
2 <sup>e</sup>		7b	>99 : 1	95 <sup>l</sup>
3 <sup>f</sup>		7c	>99 : 1	97
4 <sup>g</sup>		7d	>99 : 1	92
5 <sup>h</sup>		7e	>99 : 1	88
6 <sup>i</sup>		7f	>99 : 1	98
7 <sup>j</sup>		7g	>99 : 1	96
8 <sup>k</sup>		7h	>99 : 1	97 <sup>l</sup>

<sup>a</sup> The reaction was carried out with tin enolate **7** (1 equiv) and nitrosobenzene **2a** (1 equiv) in THF at  $-20\text{ }^{\circ}\text{C}$  for 2 h. <sup>b</sup> Determined by  $^1\text{H}$  NMR analysis. <sup>c</sup> Isolated yield. <sup>d</sup> O-Sn = >99/1. <sup>e</sup> O-Sn/C-Sn = 53/47. <sup>f</sup> O-Sn/C-Sn = >99/1. <sup>g</sup> O-Sn/C-Sn = >99/1. <sup>h</sup> O-Sn/C-Sn = >99/1. <sup>i</sup> O-Sn/C-Sn = >9/1. <sup>j</sup> O-Sn/C-Sn = >99/1. <sup>k</sup> O-Sn/C-Sn = 53/47, E/Z = 7/93. <sup>l</sup> 2 equiv of tin enolate was used.

well-known that aromatic or aliphatic nitroso compounds exist as a mixture of monomer and dimers.<sup>6</sup> Thus, in the Lewis acid promoted nitroso aldol reaction, the aminoxy compounds probably came from a nitrosobenzene dimer that was in situ generated in the presence of Lewis acids (Scheme 2 A). The simple lithium enolates afforded hydroxyamino ketones, probably through the nitrosobenzene monomer (Scheme 2B).

We next turned our attention to use of a more reactive tin enolate **7**<sup>7</sup> in the absence of Lewis acid catalysts. The reactivity of tin enolates toward nitroso derivatives was found to be much higher than that of silyl enol ethers. Thus, each tin enolate reacted very smoothly with nitrosobenzene in high yield with exclusive N-selectivity (Table 3). There were some

**Table 4.** Addition to Various Nitroso Compounds<sup>a</sup>

entry	RNO	yield, % <sup>b</sup>	T (°C)	time	
1	PhNO <b>2a</b>	92	-20	2 h	
2		54	-20	10 h	
3		91	-20	2 h	
4		62	-20	10 h	

<sup>a</sup> The reaction was carried out with tin enolate **7a** (1 equiv) and aromatic nitroso compound **2** (1 equiv) in THF at  $-20\text{ }^{\circ}\text{C}$  for 2 or 10 h. <sup>b</sup> Isolated yield.

cases with tin enolate in both O-Sn and C-Sn forms which required excess enolate loading to effect full conversion (entries 2 and 7). Thus, C-Sn compounds did not react with nitrosobenzene.

Addition of **7a** to several aromatic nitroso compounds was accomplished under optimized reaction conditions (Table 4). The electron-withdrawing group (EWG) substituted aromatic nitroso compound (entry 3) afforded regioselectivity as high as >99:1 in excellent yield. Other aromatic nitroso compounds also serve as viable substrates, although with diminished yield when the electron-donating group was substituted (entries 2 and 4).

In conclusion, the nitroso aldol reaction is a powerful strategy for the introduction of a nitrogen atom into molecules. This method appears to have general application and has been used for the synthesis of  $\alpha$ -hydroxyamino carbonyl systems relevant to the new  $\alpha$ -amino acid derivatives. Investigations continue into the mechanism, regioselectivity, and potential enantioselectivity of the reaction with nitroso compounds as electrophiles.

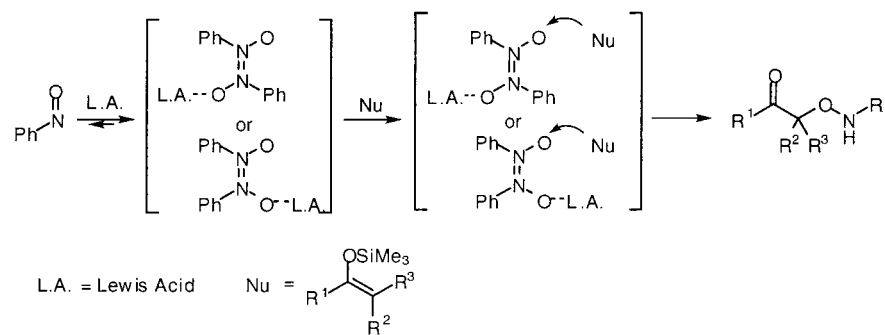
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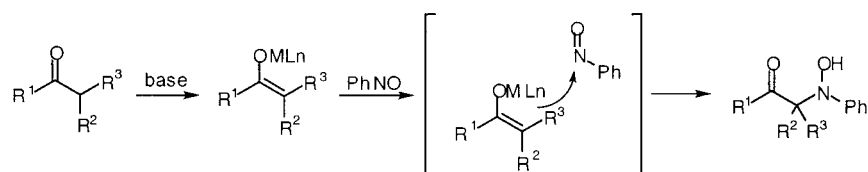
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## Scheme 2

### A. pathway with dimer



### B. pathway with monomer



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