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Generation of Nitrile Oxides through *O*-Metalation of Hydroximoyl Chlorides. Chelation-Controlled *syn*-Selective Cycloaddition of Nitrile Oxides to α-Substituted Allyl Alcohols

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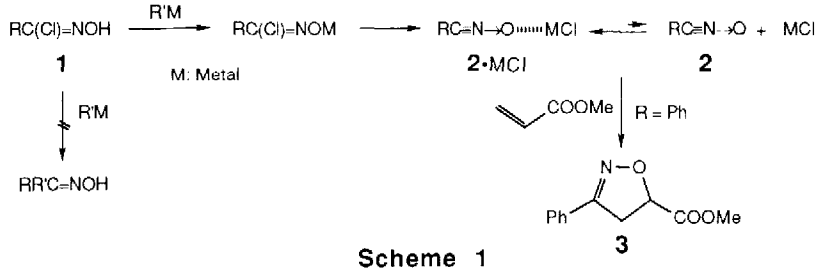
Abstract: New generation of nitrile oxides by treatment of hydroximoyl chlorides with organometallics is reported. Their cycloadditions to the allyl alcohols bearing a chiral center at the 1-position proceed in a syn-selective manner, providing the first example of stereocontrol of 1,3-dipolar cycloaddition by the aid of metal chelation.

Although Lewis acid catalysis is an attracting synthetic tool in the field of cycloaddition as seen in the widespread synthetic applications of Lewis acid-catalyzed diastereoselective and asymmetric Diels-Alder reactions,[1,2] effective use of a Lewis acid in 1,3-dipolar cycloaddition is the subject of few reports.[3,4] Formation of the unreactive complexes between 1,3-dipoles and a Lewis acid is believed to be a major obstacle against the effective catalysis.[5] The present communication describes the first example of chelation-controlled diastereoselective 1,3-dipolar cycloaddition. The nitrile oxide/Lewis acid complexes, generated by a new method consisting of the treatment of hydroximoyl chlorides with organometallics, undergo syn-selective cycloadditions to the allyl alcohols bearing an α-chirality.

Treatment of benzohydroximoyl chloride **1** (R = Ph) with *n*-BuLi, EtMgBr, or Et_2Zn at -30 to -50 °C in THF successfully generated benzonitrile oxide **2** (R = Ph) which was trapped with methyl acrylate to give methyl 3-phenyl-2-isoxazoline-5-carboxylate (**3**) in excellent yield (Scheme 1 and Table 1). No corresponding oximes as alkylation products of **1** were even detected under these conditions. As for the zinc reagent, 0.5 equivalent was enough indicating that the two ethyl moieties were effectively utilized for the generation of **2**. However, alkylaluminum chlorides (Et_nAlCl_{3-n}, n = 1, 2) and **1** failed to produce **3**.



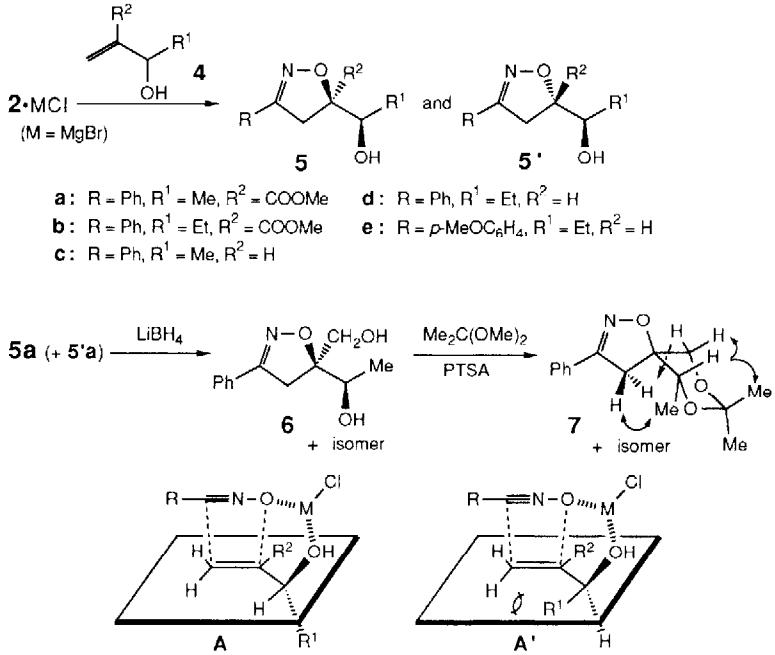
Scheme 1

The first step of *O*-metalation of **1** is followed by the elimination of metal chloride MCl (a Lewis acid) to give nitrile oxide **2** (a Lewis base). Complex formation takes place immediately between **2** and MCl where the equilibrium should lie far to the side of **2**•MCl. As anticipated, complex **2**•MCl was found to be much less reactive to methyl acrylate (an electron-deficient dipolarophile) than the free nitrile oxide **2**;[6] the stronger is Lewis acid MCl, the less reactive is complex **2**•MCl. The above unsuccessful use of alkylaluminum chlorides is one case, and that reaction of **2** with methyl acrylate was totally inhibited by the presence of titanium(IV) triisopropoxide chloride (1 equiv) is another example. A notable advantage is no formation of the dimer of **2**.

Table 1. Generation of Benzonitrile Oxide **2** by Treatment of Benzohydroximoyl Chloride **1** (R = Ph) with Organometallic Compounds Followed by Trapping with Methyl Acrylate[a]

Entry	Organometallic compound (equiv)	Solvent	Temp/°C	Time/h	Yield/%[b]
1	*n*-BuLi (1)	THF	-50	61	89
2	EtMgBr (1)	THF	-30	39	90
3	Et_2Zn (1)	THF	-15	5	67 (16)[c]
4	Et_2Zn (0.5)	THF	-40	48	91

a) Benzohydroximoyl chloride **1** (R = Ph) was treated at -30 to -50 °C with an organometallic compound. After 15 min, methyl acrylate was added and the reaction was continued under the conditions listed above. b) Yield of isolated product **3**. c) The ethyl ester derivative of **3** was accompanied.



Scheme 2

Highly diastereoselective reaction of nitrile oxides has been a central problem in the field of dipolar cycloaddition.[7] If dipolarophile bears a heterosubstituent, the deactivated nitrile oxide/Lewis acid complex **2**•MCl is expected to interact effectively with the heteroatom. Accordingly, synthetic potential of **2**•MCl was examined in the nitrile oxide cycloaddition to allyl alcohols[8] and derivatives.[9,10]

In the reaction of **2** (R = Ph) with methyl 3-hydroxy-2-methylenebutanoate **4** (R^1 = Me, R^2 = COOMe) as an electron-deficient olefin in dichloromethane (Scheme 2), a mixture of *syn*- **5a** and *anti*-cycloadduct **5'a** was produced. The syn selectivity was increased (30:70 to 81:19) when **2** was replaced by **2**•MCl (Table 2, entries 1-3), among which **2**•MgBr gave the best result. Although the ratio was not affected by the reaction temperature (entry 5), use of a polar solvent (THF) decreased the selectivity (entry 4). Structure of **5a** was determined on the basis of: 1) the reduction of the ester group of **5a** with $LiBH_4$, 2) the acetalization of the diol moiety of **6** with $Me_2C(OMe)_2$/PTSA, and 3) the NOE analysis of **7** (Scheme 2).

Table 2. Cycloaddition of **2** Generated by the Metalation Route to Allyl Alcohols and Derivatives **4**

Entry	Precursor[a]	Allyl alcohols and derivatives	Temp ℃	Time h	Product	Yield[b] %	Isomer ratio[c]
1	**1** + *n*-BuLi	**4** (R^1 = Me, R^2 = COOMe)	-30	13	**5a/5'a**	78	47:53 (30:70)
2	**1** + Et_2Zn	**4** (R^1 = Me, R^2 = COOMe)	-30	12	**5a/5'a**	92	74:26
3	**1** + EtMgBr	**4** (R^1 = Me, R^2 = COOMe)	-30	21	**5a/5'a**	86	81:19
4	**1** + EtMgBr[d]	**4** (R^1 = Me, R^2 = COOMe)	-30	24	**5a/5'a**	93	63:37
5	**1** + EtMgBr	**4** (R^1 = Me, R^2 = COOMe)	rt	12	**5a/5'a**	74	83:17
6	**1** + EtMgBr	**4** (R^1 = Et, R^2 = COOMe)	-30	16	**5b/5'b**	81	86:14 (24:76)
7	**1** + EtMgBr	**4** (R^1 = Me, R^2 = H)	-30	12	**5c/5'c**	42	87:13 (61:39)
8	**1** + *n*-BuLi	**4** (R^1 = Et, R^2 = H)	-50	96	**5d/5'd**	54	75:25 (67:33)
9	**1** + Et_2Zn	**4** (R^1 = Et, R^2 = H)	-30	71	**5d/5'd**	79	77:23
10	**1** + Et_3Al	**4** (R^1 = Et, R^2 = H)	-40	17	**5d/5'd**	32	71:29
11	**1** + EtMgBr	**4** (R^1 = Et, R^2 = H)	-30	41	**5d/5'd**	75	95:5
12	**1** + EtMgBr	**4** (R^1 = Et, R^2 = H)	rt	1	**5d/5'd**	63	95:5
13	**1** + EtMgBr[d]	**4** (R^1 = Et, R^2 = H)	-30	41	**5d/5'd**	66	60:40
14	**1** + EtMgBr[e]	**4** (R^1 = Et, R^2 = H)	-30	5.5	**5e/5'e**	65	95:5 (-[f])

a) Unless otherwise referred, **1** (R = Ph) and one equivalent of organometallic compound were used. Solvent: dichloromethane. b) Isolated yield. c) Based on ^1H and/or ^{13}C NMR of the crude products. The isomer ratio in parenthesis was obtained from the reaction of **2** generated from **1** and Et_3N. d) Solvent: THF. e) **1** (R = *p*-$MeOC_6H_4$) was used. f) The 1:2 adduct was only isolated.

More fruitful were the cycloadditions to nonactivated allyl alcohols. Although the use of *n*-BuLi, Et_2Zn, or Et_3Al in the reaction of **1** (R = Ph) with 1-penten-3-ol **4** (R^1 = Et, R^2 = H) could not improve the selectivity (entries 8-10), EtMgBr again showed the best syn selectivity (95:5, entry 11).[11] Proper choice of the solvent was important (entry 13). Some other examples are summarized in Table 2.

In conclusion, the nitrile oxide/Lewis acid complex **2**•MCl undergo syn-selective cycloadditions to the allyl alcohols bearing an α-chiral center. Presumably the metal chelation is responsible for the observed syn selectivity. We believe that the transition state **A** consisting of a 5/5 chelated ring system with less allylic strain would be more favorably involved in the reaction.

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11. Structure of **5c,d** was determined by comparison with the authentic samples reported in Refs. 8e and 9b.

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