Tetrahedron Letters, Vol. 34, No. 1, pp. 87-90, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

Metallic Base-Induced and Lewis Acid-Catalyzed Nitrone Cycloadditions to Allyl Alcohol Dipolarophiles. Highly Effective Regio- and Stereocontrol

Shuji Kanemasa,* Takashi Tsuruoka,† and Eiji Wada

Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816, Japan
†Department of Molecular Scienece and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816, Japan

Keywords: Nitrone, Dipolar cycloaddition, Allyl alcohols, Allyl alkoxides, Lewis acid catalysis, Stereocontrol, Regiocontrol

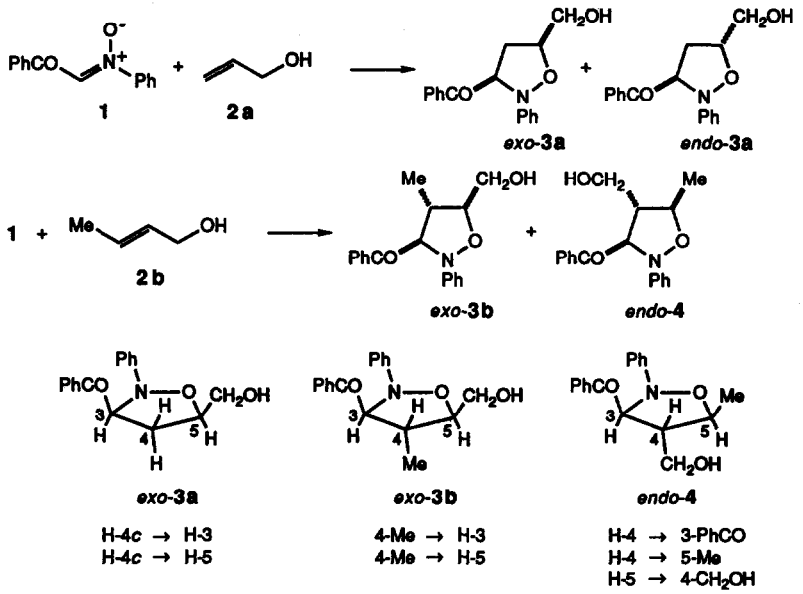
Abstract: *Cycloadditions of N-(benzoylmethylene)aniline N-oxide as a reactive nitrone to allyl alcohol dipolarophiles are accelerated either 1) by pretreatment of the dipolarophiles with an organometallic compound such as ethylmagnesium bromide or diethylzinc, or 2) in the presence of a Lewis acid such as magnesium bromide or zinc bromide. These cycloadditions are highly regio- and stereoselective, both selectivities depending upon the kind of metals included in the organometallics or Lewis acids employed. These reactions offer the first example of regio- and stereocontrol of nitrone cycloadditions to nonactivated olefins.*

In the preceding communication, we have reported the first practical example for Lewis acid catalysis in nitrone cycloadditions to electron-deficient dipolarophiles.[1] Use of bidentate and tridentate enones is responsible for the established rate acceleration as well as high regio- and stereocontrol. These enone dipolarophiles are activated by the incorporation of a Lewis acid. On the other hand, highly selective regio- and stereocontrol have recently been attained in nitrile oxide cycloadditions to allyl alcohols.[2] Magnesium alkoxides of allyl alcohols are specifically useful to lead to the exclusive formation of 2-isoxazoline-5-methanol derivatives through a chelated transition state.

We report here the metallic base-induced and Lewis acid-catalyzed nitrone cycloadditions to allyl alcohol dipolarophiles. The regio- and stereoselectivity depend upon the kind of metals included in the organometallics or Lewis acids employed. These reactions offer the first example of effective regio- and stereocontrol of nitrone cycloadditions to nonactivated olefins.

One of the most reactive nitrones, *N*-(benzoylmethylene)aniline *N*-oxide (**1**), reacted smoothly with 2-propen-1-ol (**2a**, allyl alcohol) at room temperature to give, after 24 h, a 97:3 mixture of isoxazolidine-5-methanol **3a** in 78% yield (Scheme 1, Table 1, entry 1). The major product was assigned as 3,5-*cis* configuration *exo*-**3a** on the basis of ^{1}H NMR spectrum as well as NOE analysis.[3,4] When irradiated at one of H-4 (δ = 2.53), notable NOE enhancement was observed at H-3 (5.22) and H-5 (4.40). On the other hand, reaction of **1** with (*E*)-2-buten-1-ol (**2b**, crotyl alcohol) needed a higher reaction temperature.[5] Under reflux in tetrahydrofuran (THF) for 24 h, an 18:82 mixture of regioisomeric isoxazolidines *exo*-**3b** and *endo*-**4** was produced (94%, entry 6).[6] Stereostructures of isoxazolidine-5-methanol **3b** and -4-methanol **4** were also based on ^{1}H NMR and NOE spectra: *exo*-**3b**: Signal enhancement of H-3 (4.62) and H-5 (3.97) was observed on irradiation at 4-Me (1.17); *endo*-**4**: Signal enhancement of 3-PhCO (δ = 8.18) and 5-Me (1.45) was observed on irradiation at H-4 (2.90).

Pretreatment of allyl alcohol (**2a**) with ethylmagnesium bromide prior to cycloaddition is very effective for rate acceleration (Scheme 2). The reaction of **1** with ally alkoxide **2'a** (X = MgBr) in dichloromethane was rapidly completed within 1 h at room temperature to give **3a** in 93% yield (entry 2, *exo:endo* = 98:2). More effective rate acceleration was achieved in the reaction with crotyl alkoxide **2'b** (X = MgBr), where the regioselectivity observed in the thermal reaction using **2b** was completely reversed (entries 6, 7). Isoxazolidine-5-methanol *exo*-**3b** became the far major regioisomer rather than isoxazolidine-4-methanol *endo*-**4** (*exo*-**3b**:*endo*-**4** = 98:2, entries 6, 7).



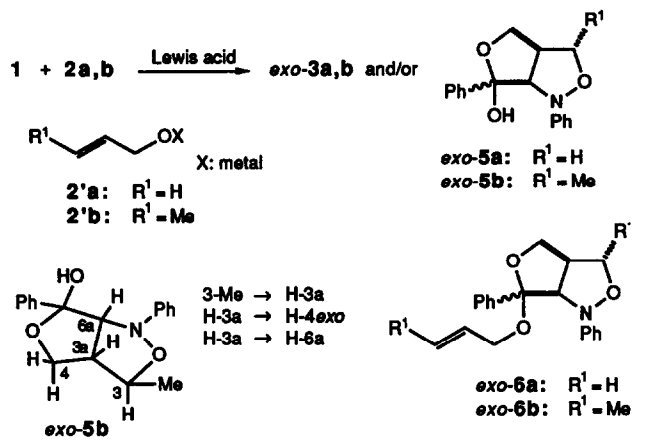
Scheme 1.

Table 1. Lewis Acid-Catalyzed Cycloadditions of **1** to Allyl Alcohol Derivatives **2**

Entry	2	Additive[a]	Equiv	Solvent[b]	Temp	Time/h	Product	Yield/%[c]	Ratio[d]
1	**2a**	-	-	DCM	rt	24	*exo*-**3a** + *endo*-**3a**	78	97:3
2	**2a**	EtMgBr	1	DCM	rt	1	*exo*-**3a** + *endo*-**3a**	93	98:2
3	**2a**	Et_2Zn	1	DCM	rt	3	*exo*-**5a**	57	single
4	**2a**[e]	$MgBr_2{\cdot}Et_2O$	1	DCM	rt	5	*exo*-**3a**	81	single
5	**2a**[e]	$ZnBr_2$	1	DCM	rt	5	*exo*-**6a**	65	single
6	**2b**	-	-	THF	reflux	24	*exo*-**3b** + *endo*-**4**	94	18:82
7	**2b**	EtMgBr	1	DCM	rt	3	*exo*-**3b** + *endo*-**4**	97	98:2
8	**2b**	Et_2Zn	1	DCM	rt	5	*exo*-**5b**	57	single
9	**2b**[e]	$MgBr_2{\cdot}Et_2O$	1	DCM	rt	5	*exo*-**3b**	77	single
10	**2b**	$MgBr_2{\cdot}Et_2O$	0.1	DCM	rt	6	*exo*-**5b**	59	single
11	**2b**[e]	$ZnBr_2$	1	DCM	rt	5	*exo*-**6b**	65	single
12	**2b**	$TiCl_2(i\text{-}PrO)_2$	0.1	DCM	rt	5	*exo*-**6b**	82[f]	single
13	**2b**	$TiCl(i\text{-}PrO)_3$	0.1	DCM	rt	12	*exo*-**6b**	58[f]	single
14	**2b**	$BF_3{\cdot}Et_2O$	0.1	DCM	rt	10	*exo*-**6b**	73[f]	single

[a]Organometallics were treated with allyl alcohols for 30 min prior to cycloaddition. [b]DCM: dichloromethane; THF: tetrahydrofuran. [c]Combined yield of isolated isomers. [d]Determined by ^1H NMR. [e]Five equivalents of **2** were used. [f]Based on **2b**.

To our great surprise, reactions of **1** with zinc alkoxides **2'a,b** (X = ZnEt), prepared in situ from **2a,b** and diethylzinc in dichloromethane, provided the hemiacetal derivatives of isoxazolidine-4-methanols *exo*-**5a,b** as single diastereomers (entries 3, 8).[7,8] Thus, the regioselectivity of nitrone cycloadditions to allyl alkoxides **2'** (X = metal) depends upon the kind of alkoxide metal. Magnesium and zinc alkoxides favor 5-methanol **3a,b** and 4-methanol regioisomers **5a,b**, respectively.



Scheme 2.

Rate acceleration as well as effective regiocontrol are observed also when the reactions of **1** with **2a,b** are performed in the presence of a Lewis acid catalyst (Scheme 2, entries 4, 5, 9, 11). The regioselectivity again depends upon the kinds of metals included in the Lewis acid catalyst. From magnesium bromide- and zinc(II) bromide-catalyzed reactions, *exo*-**3a,b** and *exo*-**6a,b** were produced as single diastereomers, respectively. The latter products **6** which correspond to the *O*-alkylated derivatives of hemiacetals *exo*-**5a,b** are formed because a large excess of alcohols **2** was used under acidic conditions.

A catalytic amount of magnesium bromide works well (entry 10). However, the product (*exo*-**5b**) obtained in this case was regioisomeric to the one yielded in the reaction using an equimolar catalyst (entry 9, *exo*-**3b**). Use of dichlorodiisopropoxytitanium, chlorotriisopropoxytitanium, or boron trifluoride etherate, all in catalytic amounts, gave the equivalent product *exo*-**6b** (entries 12-14).[9,10]

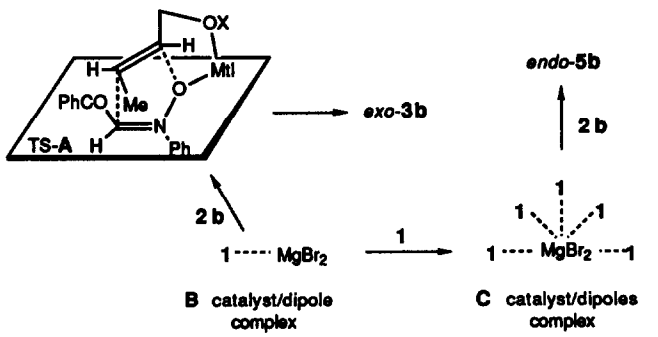


Figure 1. Lewis Acid Catalysis of Nitrone Cycloaddition to Crotyl Alcohol

The molar ratio between nitrone **1** and magnesium bromide is an important factor that determines the regiochemistry of cycloadducts. When each equimolar amount is used, a 1:1 catalyst/dipole complex **B** is formed since nitrone **1** is a strong Lewis base (Fig. 1).[11] The hydroxyl oxygen of crotyl alcohol (**2b**) can coordinate to the metal of **B** to give a dipole/catalyst/dipolarophile(s) complex **A**. Thus, dipole **1** and dipolarophile **2b** react through a chelated transition state TS-**A** to give *exo*-**3b** (Fig. 1). When magnesium bromide is in a catalytic amount, several molecules of nitrone **1** combine with the metal of catalyst to form a catalyst/dipoles complex **C**. Accordingly, further coordination of crotyl alcohol dipolarophile is limited. The exclusive production of *exo*-**3b** in the reaction with crotyl alkoxide **2'b** (X = MgBr) may be on the same basis.

Although the isolated 1:1 catalyst/dipole complex **B** reacted with crotyl alcohol (**2b**) to give *exo*-**3b**,[11] the reaction between equimolar amounts of **1** and **2b** in the presence of a catalytic amount (10 mol%) of **B** gave *exo*-**5b**. Presumably, complex **B** was rapidly transformed to complex **C** when treated with excess of dipole **1**. The reason why the catalytic reaction via complex **C** is so accelerated, so regioselective, and stereoselective remains unsolved.

Partial finantial support to this work by Grant-in-Aid for Scientific Research (No. 03453095) from the Ministry of Education, Science and Culture is acknowledged.

References and Note

1. Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* in press.
2. Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E. *Tetrahedron Lett.* **1991**, *32*, 6367-6370; Kanemasa, S.; Nishiuchi, M.; Wada, E. *ibid.* **1992**, *33*, 1357-1360; Kanemasa, S.; Nishiuchi, M. Submitted for publication.
3. The same reaction was previously performed by Huisgen and coworkers, but stereochemistry of the products remains ambiguous (Huisgen, R.; Hauck, H.; Seidl, H.; Burger, M. *Chem. Ber.* **1969**, *102*, 1117-1128).
4. All new compounds shown in this report were characterized on the basis of analytical and spectral data.
5. This reaction is so slow at room temperature to give a 73:27 mixture of *exo*-**3b** and *endo*-**4** only in 33% yield after 6d.
6. As a typical example, spectral data of *exo*-**3b** are given: Pale yellow liquid; IR (neat) 3400, 1690, 1275, 1050, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.17 (3H, d, $J_{Me\text{-}4}$ = 8.0 Hz, 4-Me), 2.45 (1H, br, OH), 3.03 (1H, ddq, $J_{4\text{-}Me}$ = 8.0, $J_{4\text{-}3}$ = 6.6 Hz, and $J_{4\text{-}5}$ = 7.0 Hz, H-4), 3.80 (1H, dd, J_{gem} = 12.3 and $J_{CH2\text{-}5}$ = 4.6 Hz, one of 5-CH_2), 3.94 - 4.40 (2H, m, H-5 and the other of 5-CH_2), 4.62 (1H, d, $J_{3\text{-}4}$ = 6.6 Hz, H-3), and 6.90 - 8.20 (10H, m, Ph). All the signals were assigned on the basis of an HH-COSY spectrum; ^{13}C NMR ($CDCl_3$) δ = 1630 (4-Me), 44.02 (C-4), 61.06 (5-CH_2), 79.34 (C-5), 85.54 (C-3), 114.06, 122.04, 128.71, 129.17, 129.24, 133.60, 151.18 (each Ph), and 197.89 (PhCO); MS (rel intensity, %) *m/z* 298 (M^+, 2), 193 (base peak), 133 (10), 105 (15), 104 (11), and 77 (21).
7. Hemiacetals **5a,b** are always mixtures of diastereomers due to the mixed stereochemistry at 6-position. The same to their *O*-alkylated derivatives **6a,b**.
8. Stereochemistry of *exo*-**5b** was assigned on the basis of ^1H NMR and NOE spectra (Scheme 2).
9. Type of isomers formd in the reaction of **1** with **2b** in the presence of $MgBr_2 \cdot Et_2O$ also depends upon the polarity of solvent: *exo*-**3b**:*exo*-**5b** = >99:1 (CH_2Cl_2), 77:23 ($MeNO_2$), 35:65 (THF), <1:99 (DMF).
10. One equivalent of **2b** was used therein. Formation of acetal *exo*-**6b** indicates that the rapid *O*-alkylation took place in the presence of a strong Lewis acid.
11. The 1:1 catalyst/dipole complex **B** partly precipitates out of the dichloromethane solution (70%) due to poor solubility. Evaporation of the filtrate affords a further fraction (30%) of the same complex. The complex **B** reacted with free alcohol **2b** to give *exo*-**3b**, while **B** catalyzed the reaction of **1** with **2b** to give *exo*-**5b**, both as single isomers.

(Received in Japan 7 August 1992)