

## Magnesium Bromide-Promoted *E/Z*-Isomerization of Carbonyl-Conjugated Nitrones and Highly Stereo- and Regioselective Cycloadditions to Allylic Alcohol Dipolarophiles

Shuji Kanemasa\* and Takashi Tsuruoka†

Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816

†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816

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A Lewis acid promotes the *E*- to *Z*-isomerization of carbonyl-conjugated nitrones. The  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ -catalyzed cycloadditions to allylic alcohols lead to the exclusive formation of the *exo*-stereoisomers of isoxazolidine-5-methanols. Participation of the *Z*-nitronone/ $\text{MgBr}_2$  complexes is suggested.

Two ever known examples of Lewis acid-catalyzed nitronone dipolar cycloadditions include (1) the *endo*- and regioselective nitronone cycloadditions to bidentate and tridentate  $\alpha,\beta$ -unsaturated ketones catalyzed by  $\text{Ti}(\text{OPr-}i)_n\text{Cl}_{4-n}$  ( $n = 2, 3$ )<sup>1</sup> and (2) the *exo*-selective cycloadditions of a benzoylnitronone to allylic alcohols catalyzed by  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  or  $\text{ZnBr}_2$ .<sup>2</sup> In the latter case, high rate acceleration and the dramatic reversal of regioselectivity resulted depending upon the nature and amount of the Lewis acid used.

Tamura has recently reported the effective  $\text{Ti}(\text{OPr-}i)_4$  catalysis in cycloadditions of ester-conjugated nitrones to allylic alcohols.<sup>3</sup> The titanium alkoxide catalyzes the step of ester exchange reaction and the resulting allylic esters of nitrones undergo *exo*-selective reactions to give isoxazolidine-fused lactones, which correspond to the 3,4-*cis*-isomers of isoxazolidine-4-methanol cycloadducts. This offers a convenient method of the in situ preparation of substrates for intramolecular nitronone cycloaddition.

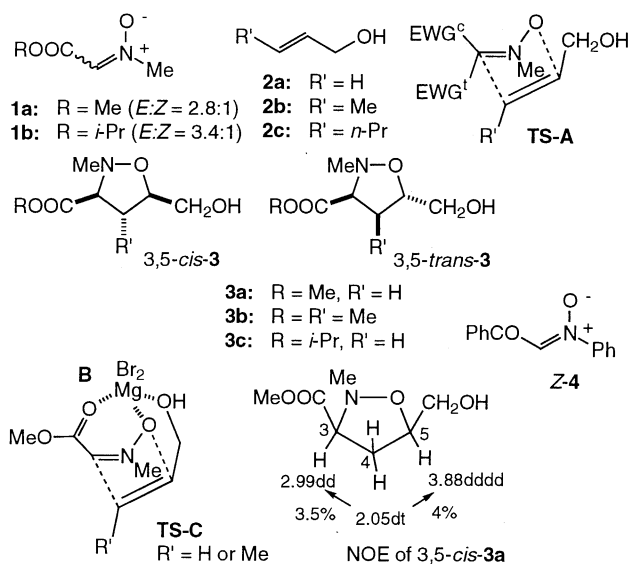
No ester exchange occurs in the  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ -catalyzed cycloadditions of ester-conjugated nitrones to allylic alcohols, the 3,5-*cis*-isomers of isoxazolidine-5-methanol derivatives being obtained as single isomers.<sup>4</sup> In this communication, it is reported that  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  is effective for the *E*- to *Z*-isomerization of carbonyl-conjugated nitrones and that nitronone cycloadditions are highly stereo- and regioselective under these catalyzed conditions.

Methyl (methylimino)acetate *N*-oxide (**1a**) as ester-conjugated nitronone exists as *E/Z* mixtures at room temperature, the isomer ratio depending upon the polarity of solvent employed: *E/Z* = 6 in benzene, 3.8 in chloroform, and 0.67 in dimethyl sulfoxide.<sup>5</sup> This nitronone **1a** (*E/Z* = 2.8) reacted regioselectively with 2-propen-1-ol (**2a**) at room temperature to give a stereoisomeric mixture of 5-hydroxymethylisoxazolidine-3-carboxylate **3a** and the isomer ratio was again dependent upon the reaction solvent used: 3,5-*trans*-**3a** : 3,5-*cis*-**3a** = 63:37 (48 h, 89%) in benzene, 56:44 (24 h, 41%) in dichloromethane, and 22:78 (20 h, 4%) in dimethyl sulfoxide. Thus, the stereoselectivity observed in these nitronone cycloadditions reflected on the *E/Z* isomer ratio of **1a**, as expected from the assumed transition state **TS-A** (Scheme 1,  $\text{R}' = \text{H}$ )<sup>6</sup> in which the hydroxymethyl moiety is located *anti* to the *N*-methyl substituent.<sup>7</sup> However, selectivities are not so exclusive.

A high rate acceleration was observed in the presence of an equimolar amount of  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  to give the 3,5-*cis*-isomer of **3a** as single stereoisomer in 71% yield (Scheme 1 and Table 1, entry 2). With less reactive (*E*)-2-buten-1-ol (**2b**), the excellent improvement of both stereo- and regioselectivities was observed to give 3,5-*cis*-**3b** (entries 3, 4). Structural assignment of **3a,b**

was based on their NOE spectra, one of which is shown in Scheme 1. Possibly  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  promoted the *E*- to *Z*-isomerization of nitronone **1a** (*E/Z* = 2.8), and the resulting *Z*-isomer complex **B** would be the actual reacting species involved. The proposed transition state **TS-C** can explain the observed stereo- and regioselectivities.

$\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  and  $\text{ZnBr}_2$  previously showed the opposite regioselectivities in the cycloadditions of *Z*-**4** to allylic alcohols.<sup>2</sup> However, use of  $\text{ZnBr}_2$  (1 equiv., rt, 24 h) in the reaction of **1a** was not effective at all, formation of a 1:1 mixture of 3,5-*cis*-**3a** and 3,5-*trans*-**3a** (44%) having resulted. Little rate acceleration was observed. When catalyzed by  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv., rt, 6 h),



Scheme 1.

Table 1. Reactions of Nitrones **1**, **4**, **7** with Allylic Alcohols **2a**

Run	Substrate	Temp	Time	Product	Yield <sup>b</sup>	Ratio <sup>c</sup>
1	<b>1a</b> <sup>d</sup> + <b>2a</b> (5) <sup>e</sup>	rt	24 h	<b>3a</b>	41%	<i>cis</i> : <i>trans</i> = 44:56
2	<b>1a</b> <sup>d</sup> + <b>2a</b> (5)	rt	24	<b>3a</b>	71	3,5- <i>cis</i> - <b>3a</b> only
3	<b>1a</b> <sup>d</sup> + <b>2b</b> (5) <sup>e</sup>	83	48	<b>3b</b>	97	four isomers
4	<b>1a</b> <sup>d</sup> + <b>2b</b> (5)	40	48	<b>3b</b>	48	3,5- <i>cis</i> - <b>3b</b> only
5	<i>E</i> - <b>5</b> + <b>2a</b> (5) <sup>e</sup>	110	12	<b>6a</b> + <b>6a'</b>	65	<b>6a</b> : <b>6a'</b> = 69:31
6	<i>E</i> - <b>5</b> + <b>2a</b> (5)	61	2.5	<b>6a</b>	82	single
7	<i>E</i> - <b>5</b> + <b>2b</b> (5)	61	8	<b>6b</b>	50	single
8	<i>E</i> - <b>7</b> + <b>2a</b> (5)	83	2	<b>8a</b>	79	single
9	<i>E</i> - <b>7</b> + <b>2c</b> (5)	83	5	<b>8b</b>	89	single

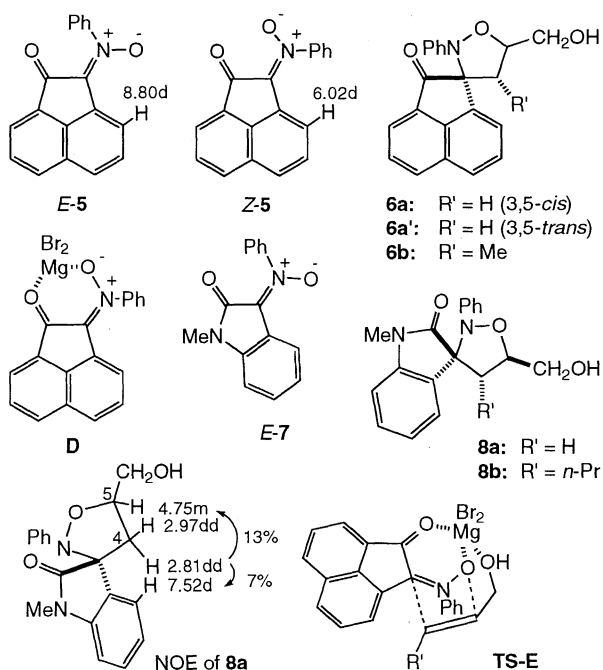
<sup>a</sup>Unless otherwise referred, all reactions were performed in the presence of one equivalent of  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ . <sup>b</sup>Yield of isolated products. <sup>c</sup>Based on <sup>1</sup>H or <sup>13</sup>C NMR spectrum. <sup>d</sup>A 2.8:1 mixture of *E*- and *Z*-**1a** (by <sup>1</sup>H NMR in  $\text{CDCl}_3$ ). <sup>e</sup>In the absence of  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ .

nitronone **1a** was recovered unreacted in 85% yield.

Since nitronone/Ti(OPr-*i*)<sub>4</sub> complexes are soluble in organic solvents, unlike nitronone/MgBr<sub>2</sub> (or ZnBr<sub>2</sub>) complexes, Ti(OPr-*i*)<sub>4</sub> would be a promising Lewis acid in nitronone cycloadditions to allylic alcohols, except for its ready catalysis on ester exchange reaction.<sup>3</sup> This undesired reaction path would be inhibited when the nitronone **1b** bearing a bulky isopropyl ester moiety is used. However, a mixture of 3,5-*cis*-**3c** and 3,5-*trans*-**3c** (30%, 1:1) was produced along with a trace of the isoxazolidine-fused lactone,<sup>8</sup> indicating no effective catalysis;<sup>9</sup> this catalyst could not promote the *E*- to *Z*-isomerization of nitronone **1a** (*E/Z* = 2.8).<sup>10</sup> Stronger titanium catalysts, TiCl<sub>4</sub> and TiCl<sub>2</sub>(OPr-*i*)<sub>2</sub>, were not effective either. As a result, MgBr<sub>2</sub>•Et<sub>2</sub>O was specifically a promising Lewis acid catalyst.

2-(Phenylimino)acenaphthenone *N*-oxide (**5**), as keto nitronone which exists exclusively in an *E*-form in a chloroform solution, underwent isomerization in the presence of MgBr<sub>2</sub>•Et<sub>2</sub>O under reflux in 1,2-dichloroethane to give a 91:9 mixture of *Z/E*-isomers (Scheme 2). The *Z*-enriched mixture isomerized back to pure *E*-**5** in a few hours at room temperature. Under reflux in toluene, keto nitronone **5** showed only a limited reactivity to **2a** to give a stereoisomeric mixture of spiro isoxazolidine **6a** and **6a'** (69:31, entry 5). Under the MgBr<sub>2</sub>•Et<sub>2</sub>O-catalyzed conditions, however, cycloadduct **6a** was produced as single isomer in an excellent yield (entry 6); the exclusively stereo- and regioselective isomer **6b** was obtained from the less reactive dipolarophile **2b** (entry 7). Presumably the *Z*-nitronone/MgBr<sub>2</sub> complex **D** would be involved in the transition state **TS-E** where the magnesium ion coordinates all to the alcohol oxygen, the nitronone oxygen, and the carbonyl oxygen atoms.

An amide type nitronone existing in an *E*-form, 1-methyl-3-



Scheme 2.

phenylimino-2,3-dihydroindol-2-one *N*-oxide (**7**), also showed a poor reactivity to allylic alcohols. However, it reacted with **2a,c** under the MgBr<sub>2</sub>•Et<sub>2</sub>O-catalyzed conditions to give **8a,b** as single stereoisomers (entries 8, 9). Their stereostructures, as well as those of **6a,b**, were determined on the basis of NOE spectrum of **8a** shown in Scheme 2. When the 4-position of **8a** was replaced with a propyl substituent as shown in the case of **8b**, one of H-1 hydrogens of the propyl substituent was strongly shielded ( $\delta$  0.99) by the facing benzo plane, supporting the proposed stereochemistry.

In conclusion, the first examples of Lewis acid-promoted *E*- to *Z*-isomerization of carbonyl-conjugated nitronones have been reported.<sup>11</sup> The *Z*-nitronone/MgBr<sub>2</sub> complexes show an enhanced reactivity to allylic alcohols due to the metal coordination leading to excellent stereo- (*exo*-) and regioselectivities. Although no clear interpretation is in hand for the high magnesium ion specificity, these findings contribute to the stereo- and regiocontrolled ring formation methodology through 1,3-dipolar cycloadditions.

## References and Notes

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- Transition structures of nitronone cycloadditions: see A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez, and G. S. K. Wong, *J. Org. Chem. Soc.*, **49**, 276 (1984); L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc. (B)*, **1971**, 1728.
- Stereoselectivity of nitronone dipolar cycloadditions is mainly determined by the geometry of nitronones as shown in the non-catalyzed cycloaddition of benzoynitronone **Z-4** to **2a**.<sup>2</sup>
- The low yield formation of the isoxazolidine-fused lactone indicates the effective suppression of ester exchange reaction.
- Neither noticeable rate acceleration nor improvement of stereoselectivity was observed in the reaction of **1a** with styrene or ethoxyethene catalyzed by Ti(OPr-*i*)<sub>4</sub>.
- Observed by <sup>1</sup>H NMR in CDCl<sub>3</sub> at room temperature. The Ti(OPr-*i*)<sub>4</sub>-promoted isomerization of allylic nitronone esters, suggested by Tamura,<sup>3</sup> would not be the case.
- E/Z*-Isomerization of nitronones was previously discussed in the acid-catalyzed ring openings of oxaziridines: W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).