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

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A Lewis acid promotes the *E*- to *Z*-isomerization of carbonyl-conjugated nitrones. The $MgBr_2 \cdot Et_2O$-catalyzed cycloadditions to allylic alcohols lead to the exclusive formation of the *exo*-stereoisomers of isoxazolidine-5-methanols. Participation of the *Z*-nitrone/$MgBr_2$ complexes is suggested.

Two ever known examples of Lewis acid-catalyzed nitrone dipolar cycloadditions include (1) the *endo*- and regioselective nitrone cycloadditions to bidentate and tridentate α,β-unsaturated ketones catalyzed by $Ti(OPr\text{-}i)_nCl_{4-n}$ (n = 2, 3)[1] and (2) the *exo*-selective cycloadditions of a benzoylnitrone to allylic alcohols catalyzed by $MgBr_2 \cdot Et_2O$ or $ZnBr_2$.[2] 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.

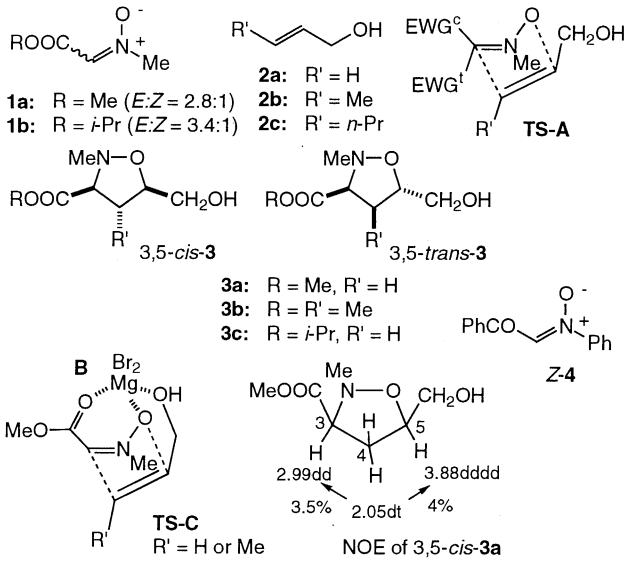
Tamura has recently reported the effective $Ti(OPr\text{-}i)_4$ catalysis in cycloadditions of ester-conjugated nitrones to allylic alcohols.[3] The titanium alkoxide catalyzes the step of ester exchange reaction and the resulting allylic esters of nitrones undergo *exo*-selective reactions to give isoxazolidine-fused 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 nitrone cycloaddition.

No ester exchange occurs in the $MgBr_2 \cdot Et_2O$-catalyzed cycloadditions of ester-conjugated nitrones to allylic alcohols, the 3,5-*cis*-isomers of isoxazolidine-5-methanol derivatives being obtained as single isomers.[4] In this communication, it is reported that $MgBr_2 \cdot Et_2O$ is effective for the *E*- to *Z*-isomerization of carbonyl-conjugated nitrones and that nitrone cycloadditions are highly stereo- and regioselective under these catalyzed conditions.

Methyl (methylimino)acetate *N*-oxide (**1a**) as ester-conjugated nitrone 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.[5] This nitrone **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 nitrone cycloadditions reflected on the *E/Z* isomer ratio of **1a**, as expected from the assumed transition state **TS-A** (Scheme 1, R' = H)[6] in which the hydroxymethyl moiety is located *anti* to the *N*-methyl substituent.[7] However, selectivities are not so exclusive.

A high rate acceleration was observed in the presence of an equimolar amount of $MgBr_2 \cdot Et_2O$ 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 $MgBr_2 \cdot Et_2O$ promoted the *E*- to *Z*-isomerization of nitrone **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.

$MgBr_2 \cdot Et_2O$ and $ZnBr_2$ previously showed the opposite regioselectivities in the cycloadditions of *Z*-**4** to allylic alcohols.[2] However, use of $ZnBr_2$ (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 $BF_3 \cdot Et_2O$ (1 equiv., rt, 6 h),



Scheme 1.

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

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

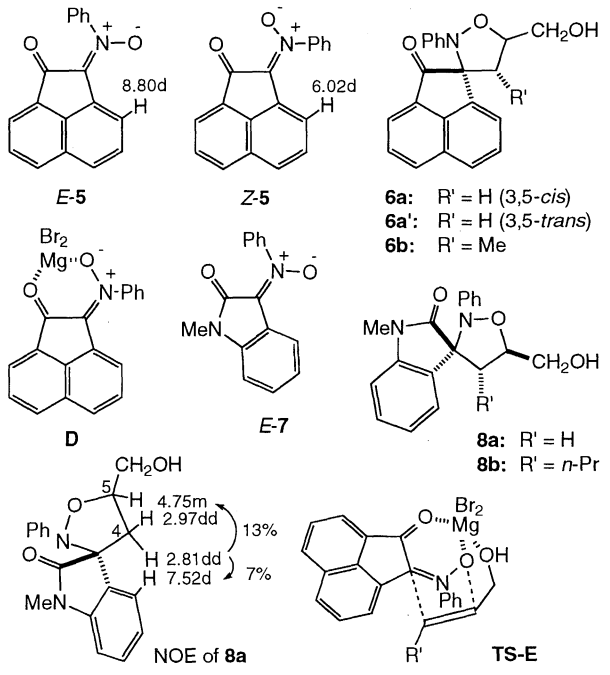
[a]Unless otherwise referred, all reactions were performed in the presence of one equivalent of $MgBr_2 \cdot Et_2O$. [b]Yield of isolated products. [c]Based on ^1H or ^{13}C NMR spectrum. [d]A 2.8:1 mixture of *E*- and *Z*-**1a** (by ^1H NMR in $CDCl_3$). [e]In the absence of $MgBr_2 \cdot Et_2O$.

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

Since nitrone/Ti(OPr-*i*)$_4$ complexes are soluble in organic solvents, unlike nitrone/$MgBr_2$ (or $ZnBr_2$) complexes, Ti(OPr-*i*)$_4$ would be a promising Lewis acid in nitrone cycloadditions to allylic alcohols, except for its ready catalysis on ester exchange reaction.[3] This undesired reaction path would be inhibited when the nitrone **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,[8] indicating no effective catalysis;[9] this catalyst could not promote the *E*- to *Z*-isomerization of nitrone **1a** (*E*/*Z* = 2.8).[10] Stronger titanium catalysts, $TiCl_4$ and $TiCl_2$(OPr-*i*)$_2$, were not effective either. As a result, $MgBr_2$•Et_2O was specifically a promising Lewis acid catalyst.

2-(Phenylimino)acenaphthenone *N*-oxide (**5**), as keto nitrone which exists exclusively in an *E*-form in a chloroform solution, underwent isomerization in the presence of $MgBr_2$•Et_2O 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 nitrone **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 $MgBr_2$•Et_2O-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*-nitrone/$MgBr_2$ complex **D** would be involved in the transition state **TS-E** where the magnesium ion coordinates all to the alcohol oxygen, the nitrone oxygen, and the carbonyl oxygen atoms.

An amide type nitrone existing in an *E*-form, 1-methyl-3-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 $MgBr_2$•Et_2O-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 (δ 0.99) by the facing benzo plane, supporting the proposed stereochemistry.



Scheme 2.

In conclusion, the first examples of Lewis acid-promoted *E*- to *Z*-isomerization of carbonyl-conjugated nitrones have been reported.[11] The *Z*-nitrone/$MgBr_2$ 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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2 S. Kanemasa, T. Tsuruoka, and E. Wada, *Tetrahedron Lett.*, **34**, 87 (1993).

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6 Transition structures of nitrone 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.

7 Stereoselectivity of nitrone dipolar cycloadditions is mainly determined by the geometry of nitrones as shown in the non-catalyzed cycloaddition of benzoylnitrone *Z*-**4** to **2a**.[2]

8 The low yield formation of the isoxazolidine-fused lactone indicates the effective suppression of ester exchange reaction.

9 Neither noticable rate acceleration nor improvement of stereoselectivity was observed in the reaction of **1a** with styrene or ethoxyethene catalyzed by Ti(OPr-*i*)$_4$.

10 Observed by ^{1}H NMR in $CDCl_3$ at room temperature. The Ti(OPr-*i*)$_4$-promoted isomerization of allylic nitrone esters, suggested by Tamura,[3] would not be the case.

11 *E*/*Z*-Isomerization of nitrones was previously discussed in the acid-catalyzed ring openings of oxaziridines: W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).