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Metal Ion-Mediated Diastereoface-Selective Nitrone Cycloadditions. Reaction Mechanism for the Reversal of Regioselectivity Observed in the Magnesium and Zinc Ion-Mediated Nitrone Cycloadditions of Allylic Alcohols

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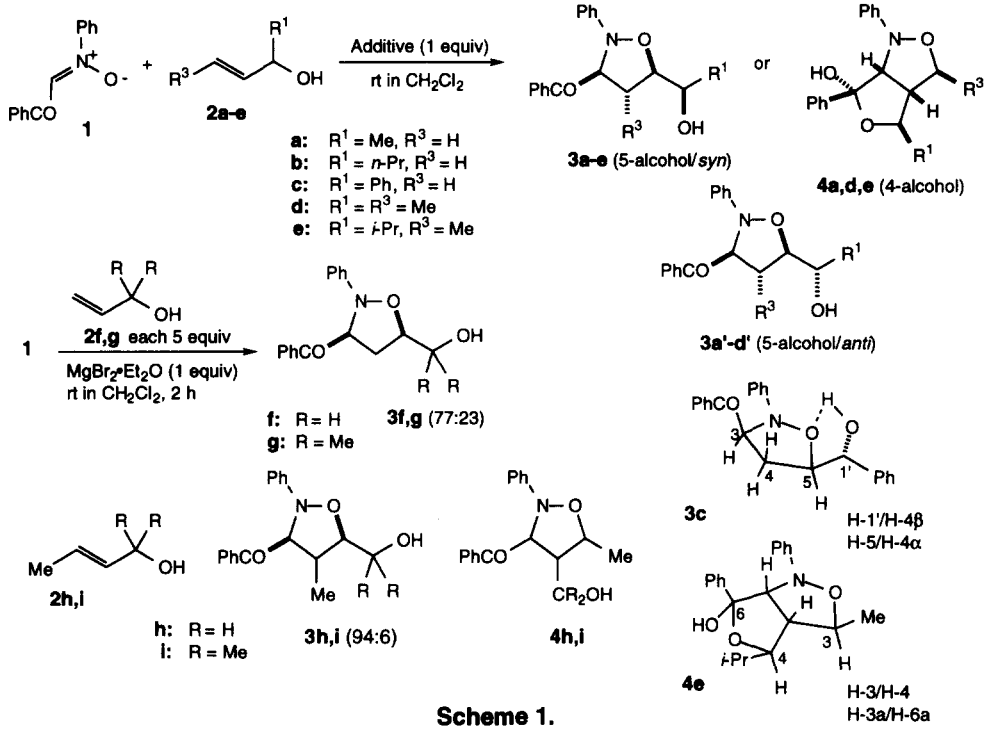
Abstract: Magnesium and zinc ion-mediated cycloaddition reactions of a carbonyl-conjugated nitrone, (*Z*)-*N*-(benzoylmethylene)aniline *N*-oxide to the allylic alcohols bearing a chirality at α-position give isoxazolidine-5-alcohol and isoxazolidine-4-alcohol derivatives, respectively, both in highly *lk*-1,2-inductive manners. α,α-Disubstitution of allylic alcohol dipolarophiles virtually inhibits the zinc ion-catalyzed reaction paths, and use of a coordinating solvent in the magnesium ion-catalyzed reactions leads to the reversal of regioselectivity. Reaction mechanism for the metal ion-catalyzed competitive cycloadditions is proposed.

We have recently developed a new methodology of metal ion-mediated regio- and stereocontrol in nitrile oxide[1] and nitrone[2,3] dipolar cycloadditions to allylic alcohol dipolarophiles. Carbonyl-conjugated nitrones and allylic alcohols undergo absolutely regio- and stereoselective cycloaddition reactions in the presence of a Lewis acid such as $MgBr_2 \cdot Et_2O$ or $ZnBr_2$, while only slow reactions take place under non-catalyzed conditions to produce mixtures of isomeric cycloadducts.[3] Although $MgBr_2 \cdot Et_2O$ (1 equiv) induces the selective formation of the 3,5-*cis* isomers of isoxazolidine-5-methanol regioisomers, $ZnBr_2$ (1 equiv) leads to the hemiacetals derived from the 3,4-*cis* isomers of isoxazolidine-4-methanol regioisomers. Use of a catalytic amount of $MgBr_2 \cdot Et_2O$ shows the latter regioselectivity.[3] However, the reason why such a dramatic change of selectivity has resulted depending upon the nature and the catalytic amount of metal ions has remained unsolved.

When allylic alcohols bearing a chirality at α-position are employed in the metal-mediated nitrone cycloadditions, a question of diastereofacial selectivity arises. Analysis of the stereochemical pathways of this reaction should provide us some important informations to solve the reaction mechanisms for the metal ion-dependent change of regioselectivity. Accordingly, the metal ion-catalyzed nitrone cycloadditions to the allylic alcohols bearing a chirality at α-positon were examined in this communication. Based on the high *lk*-1,2-inductive selectivity and rate enhancement observed in the reactions, a mechanism for the dramatic change of regioselectivity is proposed. Magnesium ion accelerates the intermolecular nitrone/allylic alcohol cycloaddition while zinc ion catalyzes the carbonyl addition of allylic alcohols forming hemiacetal intermediates which then undergoes intramolecular nitrone cycloadditions.

Reaction of (*Z*)-*N*-(benzoylmethylene)aniline *N*-oxide (**1**) with 3-buten-2-ol (**2a**), as a terminal allylic alcohol bearing a small methyl substituent at the chiral center, proceeded smoothly at room temperature without metal ion to give quantitatively a 53:47 mixture of the 3,5-*cis* isomers of isoxazolidine-5-methanol cycloadduct **3a** and **3a'** (Scheme 1 and entry 1 of Table 1). Although the regio- and diastereoselectivities of

this reaction were thus perfect even in the absence of metal ion,[4] the diastereofacial selectivity with respect to the α-chirality of **2a** was very poor (the stereochemical relationship between C-5 and C-1'). This is not surprising. When an equimolar amount of $MgBr_2$•Et_2O was present, the reaction was highly accelerated to be completed in 1 h under equivalent conditions, the stereoselectivity being significantly improved (entry 2, *syn:anti* = 84:16).



Scheme 1.

Not so great improvement of selectivity was recorded when the substituent R^1 at the chiral center was replaced with a propyl or a phenyl substituent as shown in **2b,c** (entries 4-6). Allylic alcohols **2a-c** are all terminal alkenes so that they show some enough reactivity to nitrone **1** even under non-catalyzed conditions. Accordingly, the unsatisfactory diastereofacial selectivities observed would be due to the competitive non-catalyzed cycloadditions which are virtually stereorandom. Thus, the rate acceleration through a chelated transition state is somehow *saturated* in the reaction with terminally unsubstituted allylic alcohols,

To our delight, however, (*E*)-3-penten-2-ol (**2d**) as a disubstituted inner allylic alcohol reacted with **1** in the presence of $MgBr_2$•Et_2O to give a 96:4 stereoisomeric mixture of the 3,5-*cis*-isoxazolidine-5-alcohol derivative **3d** and **3d'** (entry 7). When the α-substituent is bulky isopropyl group, a single stereoisomer of cycloadduct **3e** was only produced (entry 9). Stereostructure of the major diastereomer **3d** was determined to be the *syn*-isomer with respect to the α-chirality (between C-5 and C-1') on the basis of spectral data,[5] especially the NOE spectrum measured in nonpolar deuteriobenzene.[6]

As described above, $ZnBr_2$ and $MgBr_2$•Et_2O show different catalysis in nitrone cycloadditions to allylic alcohols such as 2-propen-1-ol (**2f**) and (*E*)-2-buten-1-ol (**2h**).[3] However, when the α-substituted terminal allylic alcohol **2a** was used in the reaction catalyzed by $ZnBr_2$, the major product obtained was not the expected perhydrofuro[3,4-*c*]isoxazolole **4a** (18%) which corresponds to the cyclized product of an isoxazolidine-4-alcohol regioisomer, but instead a mixture of the isoxazolidine-5-alcohol cycloadducts **3a** and **3a'** was obtained (*syn:anti* = 73:27, 73%, entry 3). This result indicates that the α-substitution of allylic

alcohol dipolarophiles receives little benefit from the $ZnBr_2$-induced transition state so that the noncatalyzed reaction becomes the major reaction path producing **3a** and **3a'**. This was confirmed by the result that the $ZnBr_2$-catalyzed reactions of the inner allylic alcohols **2d,e** were perfectly regio- and *syn*-selective to give **4d,e** as single products (entries 8 and 10).[5]

Table 1. Diastereofacial Selectivities Observed in the Metal Ion-Mediated Cycloaddition Reactions of Benzoylnitrone **1** with α-Chiral Allylic Alcohols

Entry	Allylic alcohols[a]			Additive[b]	Time/h	Products	Yield/%[c]	Isomer ratio[d]
		R^1	R^3					
1	**2a**	Me	H	None	10	**3a + 3a'**	quant	53:47
2				$MgBr_2$•Et_2O	1	**3a + 3a'**	89	84:16
3				$ZnBr_2$	5	**3a + 3a' + 4a**	73 (73:27) + 18[e]	
4	**2b**	*n*-Pr	H	None	10	**3b + 3b'**	95	55:45
5				$MgBr_2$•Et_2O	1	**3b + 3b'**	96	85:15
6	**2c**	Ph	H	$MgBr_2$•Et_2O	1	**3c + 3c'**	91	88:12
7	**2d**	Me	Me	$MgBr_2$•Et_2O	5	**3d + 3d'**	85	96:4
8				$ZnBr_2$	5	**4d**	46	single
9	**2e**	*i*-Pr	Me	$MgBr_2$•Et_2O	5	**3e**	47	single
10				$ZnBr_2$	20	**4e**	33	single
11	**2g**	R = Me		None	24	**3g**	70	single
12				$MgBr_2$•Et_2O	2	**3g**	83	single
13				$ZnBr_2$	5	**3g**	49	single
14	**2i**	R = Me		None	24[f]	**3i + 4i**	15	82:18[g]
15				$MgBr_2$•Et_2O	5	**3i**	6	single

[a]Five equivalents of allylic alcohols were employed in the catalyzed reactions. [b]One equivalent of additive was used. [c]Total yield of isolated isomer mixture. [d]Based on ^1H or ^{13}C NMR spectra. [e]A 73:27 mixture of **3a** and **3a'** was given in 73% yield and **4a** in 18% yield. [f]Reflux in THF. [g]No stereostructure was determined.

When two substituents are introduced at the α-position of 2-propen-1-ol (**2f**) as shown with **2g**, the reactions with nitrone **1** gave the isoxazolidine-5-alcohol derivative **3g** as a single product, regardless of the difference of reaction conditions (entries 11-13). This again indicates a high rate depression of the $ZnBr_2$-catalyzed reaction by steric effects. On the other hand, only a little rate deceleration resulted in the $MgBr_2$•Et_2O-catalyzed reaction where the relative reaction rate of 77:23 (= **3f**:**3g**) was recorded between 2-propen-1-ol (**2f**) and 2-methyl-3-propen-2-ol (**2g**) (Scheme 1). With less reactive (*E*)-2-methyl-3-penten-2-ol (**2i**), however, a decreased reactivity was observed (entries 14, 15). Thus, the competitve reaction of **1** with (*E*)-2-buten-1-ol (**2h**) and **2i** under the $MgBr_2$•Et_2O-catalyzed conditions gave a 94:6 mixture of **3h,i** (Scheme 1).

Based on the metal ion-mediated rate enhancement and diastereofacial selectivities observed above, two reaction modes could be figured out (paths a and b in Figure 1). The carbonyl-conjugated nitrone **1** interacts with a metal ion (Mtl) to form the *Z*-nitrone complex **A**, the metal part of which is further coordinated by an allylic alcohol dipolarophile leading to complex **B**. Although the nitrone cycloaddition via the transition state **TS-C** (path a) can be accelerated to give **3d** when Mtl is Mg^{2+} ion, Zn^{2+} ion would not show such an accelerating effect.[7] Accordingly, the second possible reaction is the Lewis acid-catalyzed carbonyl addition of the alcohol dipolarophile to give the hemiacetal intermediate **D** (path b).[8] Intramolecular dipolar cycloaddition of **D** via the transition state **TS-E** leads to **4d**. These reaction mechanisms are consistent with the Mg^{2+} ion-specific rate acceleration, the diastereofacial selectivities, and the serious rate sensibility to steric effects of the $ZnBr_2$-catalyzed reaction forming the sterically hindered intermediate **D**. Reaction of nitrone **1** with **2h** in dichloromethane in the presence of Mg^{2+} led to the exclusive formation of **3h**, while a 34:66 regioisomeric mixture of **3h** and **4h** in THF. The stability of complex **B** would be reduced in THF

since it is a highly coordinating solvent. When Mg^{2+} ion is catalytic, the reaction via **TS-C** becomes slower to allow the competitive carbonyl addition.

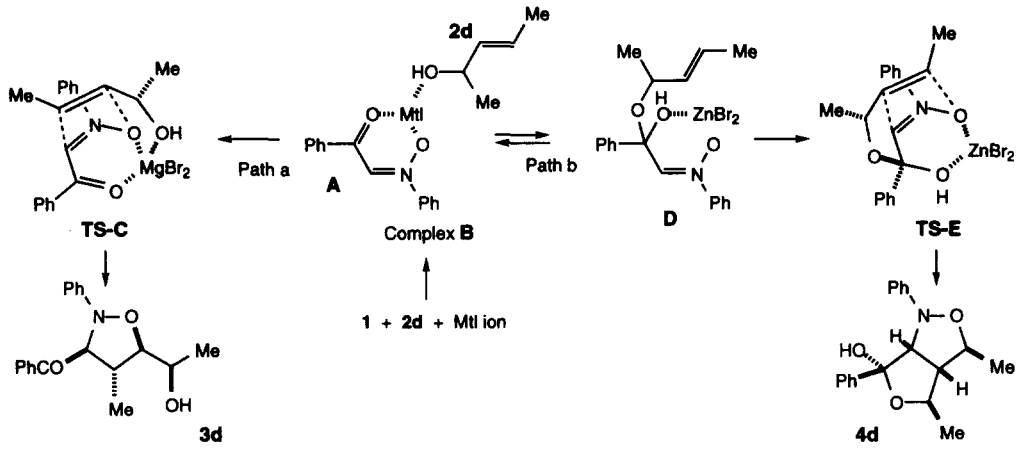


Figure 1. **Two reaction modes of $MgBr_2$•Et_2O-catalyzed (path a) and $ZnBr_2$-catalyzed (path b) cycloadditions of nitrone 1 to the α-chiral inner allylic alcohol 2d.**

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References and Note

1. Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324-2339
2. Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 7889-7892.
3. Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87-90.
4. Reaction of nitrone **1** with 2-propen-1-ol **2f** proceeds in a highly regioselective and stereoselective manner in the absence or presence of $MgBr_2$•Et_2O.[3]
5. Full characterization has been made for the new compounds described here. NMR Spectral data of **3c** and **4e** as typical cycloadducts are given as follows: **3c**: ^{1}H NMR (C_6D_6) δ = 1.75 (1H, br s, OH), 2.29 (1H, ddd, J_{gem} = 10.6, $J_{4\text{-}3}$ = $J_{4\text{-}5}$ = 8.4 Hz, one of H-4), 2.61 (1H, ddd, J_{gem} = 10.6, $J_{4\text{-}5}$ = 7.0, and $J_{4\text{-}3}$ = 3.7 Hz, the other of H-4), 4.46 (1H, ddd, $J_{5\text{-}4}$ = 8.4, 7.0, and $J_{5\text{-}1'}$ = 7.0 Hz, H-5), 4.86 (1H, d, $J_{1'\text{-}5}$ = 7.0 Hz, H-1'), 5.15 (1H, dd, $J_{3\text{-}4}$ = 8.4 and 3.7 Hz, H-3), and 6.9 - 8.1 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 33.99 (C-4), 70.08 (C-3), 75.55 (C-5), 82.40 (C-1'), 114.73, 122.79, 127.04, 128.26, 128.58, 128.72, 129.07, 129.31, 133.59, 135.00, 140.07, 149.99 (each Ph), and 196.54 (CO). **4e**: ^{1}H NMR ($CDCl_3$) δ = 1.05, 1.10, 1.16 (each 3H, each d, J = 7.0 Hz, Me of *i*-Pr and 3-Me), 2.06 (1H, m, CH of *i*-Pr), 2.94 (1H, ddd, $J_{3a\text{-}6a}$ = 9.2, $J_{3a\text{-}4}$ = 8.1, and $J_{3a\text{-}3}$ = 2.6 Hz, H-3a), 4.01 (1H, dd, $J_{4\text{-}3a}$ = 8.1 and $J_{4\text{-}CH}$ = 7.0 Hz, H-4), 4.30 (1H, d, $J_{6a\text{-}3a}$ = 9.2 Hz, H-6a), 4.46 (1H, dq, $J_{3\text{-}Me}$ = 7.0 and $J_{3\text{-}3a}$ = 2.6 Hz, H-3), 5.42 (1H, s, OH), and 6.70-7.66 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 18.39, 19.08, 20.44 (Me), 32.22 (CH of *i*-Pr), 59.56 (C-3a), 80.92, 81.13, 85.68 (C-3, C-4, and C-6a), 102.66 (C-6), 113.63, 121.81, 125.90, 128.24, 128.30, 128.68, 142.84, and 150.98 (each Ph).
6. No NOE signal enhancement was observed between the 1'-phenyl group and H-4α, indicating the lock of conformation due to the hydrogen bond.
7. Magnesium ion-specific rate acceleration has been reported in nitrile oxide cycloadditions to allylic alcohols (See Ref. 1).
8. Titanium ion-catalyzed ester exchange reactions of nitrones with allylic alcohols and subsequent intramolecular cycloadditions are known: (a) Tamura, O.; Yamaguchi, T.; Noe, K.; Sakamoto, M. *Tetrahedron Lett.* **1993**, *34*, 4009-4010. (b) Tamura, O.; Yamaguchi, T.; Okabe, T.; Sakamoto, M. *Synlett* **1994**, 620-622.

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