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Metal ion-mediated diastereoface-selective 1,3-dipolar cycloaddition of nitrile oxides with dipolarophiles bearing an oxazolidinone chiral auxiliary

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Abstract

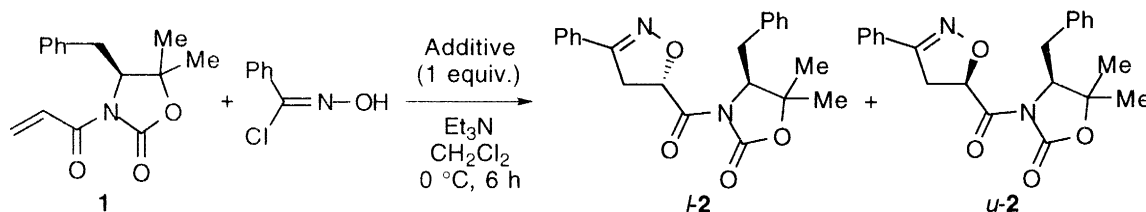
Magnesium ion-mediated cycloaddition reactions of nitrile oxides to chiral 3-acryloyl-2-oxazolidinones lead to highly diastereoselective formation of 2-isoxazolines. The magnesium ion serves to fix the α,β -unsaturated moiety through chelation to effect chiral shielding. These asymmetric reactions provide the first successful examples of Lewis acid-mediated stereocontrol of nitrile oxide cycloaddition reactions to electron-deficient dipolarophiles. © 2000 Elsevier Science Ltd. All rights reserved.

Since Lewis acids are a powerful tool in organic synthesis, one of today's challenges in the field of 1,3-dipolar cycloaddition reactions¹ is the Lewis acid-induced control of regio-, diastereo-, and enantioselectivity in these reactions.² However, only limited examples are known for the successful Lewis acid catalysis in 1,3-dipolar cycloaddition reactions. Nitron cycloadditions have been most widely utilized for enantioselective reactions as one exception.^{3,4} Nitrile oxides are 1,3-dipoles having one oxidation level higher than nitrones; their cycloaddition reactions to alkene dipolarophiles lead to the formation of 2-isoxazolines whose synthetic versatility has been well established.⁵ Therefore, the Lewis acid-catalyzed reaction control of nitrile oxide cycloadditions must be an important research subject, but up to the present only a few reports are known for metal ion-mediated nitrile oxide cycloadditions.^{6,7} In all the previous successful examples, allylic alcohols have been employed as dipolarophiles. It has been proposed that the reaction mechanism involves a metal-coordinated nitrile oxide and dipolarophile interaction. It is believed that nitrile oxides strongly coordinate to a Lewis acid, even if it is a weak Lewis acid, to be deactivated as 1,3-dipoles.⁸ In some cases, nitrile oxide-Lewis acid complexes show high reactivity to nucleophilic reagents as shown in the Friedel–Crafts reactions of nitrile oxides with electron-rich aromatics in the presence of strong Lewis acids such as AlCl_3 ,⁹ gaseous BF_3 ,¹⁰ etc.

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In this communication, we wish to describe the first successful examples of metal ion-mediated asymmetric 1,3-dipolar cycloaddition of nitrile oxides with electron-deficient chiral dipolarophiles. Several chiral dipolarophiles have been designed for diastereoselective nitrile oxide cycloadditions without the assistance of a Lewis acid catalyst.^{11,12} Nevertheless, a new methodology for stereocontrol in nitrile oxide cycloadditions by a Lewis acid is indispensable to achieve enantioselective cycloaddition reaction by a chiral Lewis acid catalyst. Not only the choice of a proper chiral auxiliary,¹³ but also the Lewis acid is important to attain high stereocontrol of nitrile oxide cycloaddition reactions using chiral electron-deficient dipolarophiles.¹⁴ Among a great number of known chiral auxiliaries, we have selected the chiral oxazolidinone auxiliary bearing a benzyl shielding group at the 4-position. Two methyl substituents are introduced at the 5-positions of the oxazolidinone ring to effect chiral shielding by the 4-benzyl moiety.¹⁵

The reaction of enantiopure (*S*)-3-acryloyl-4-benzyl-5,5-dimethyl-2-oxazolidinone (**1**) with benzonitrile oxide at 0°C in dichloromethane, without metal ions, gave a 43:57 mixture of diastereomeric cycloadducts *l*-**2** and *u*-**2** in 95% combined yield (Scheme 1 and Table 1, entry 1). Although the reactions also proceeded smoothly in the presence of a Lewis acid (1 equiv. to **1**), diastereoselectivities of the reactions were not improved. MgBr₂ was the only exception which showed an increased diastereoselectivity of 71:29 in favor of *l*-**2** (entry 3). Decrease of the amount of MgBr₂ to 0.5 equiv. to **1** decreased the selectivity under similar conditions (entry 4). Use of the 5,5-dimethyl-4-phenyl-2-oxazolidinone chiral auxiliary together with MgBr₂ slightly increased the diastereoselectivity (69/31), while both the 4-isopropyl-5,5-dimethyl-2-oxazolidinone and 4-benzyl-2-oxazolidinone auxiliaries were not effective as shown in Scheme 2.



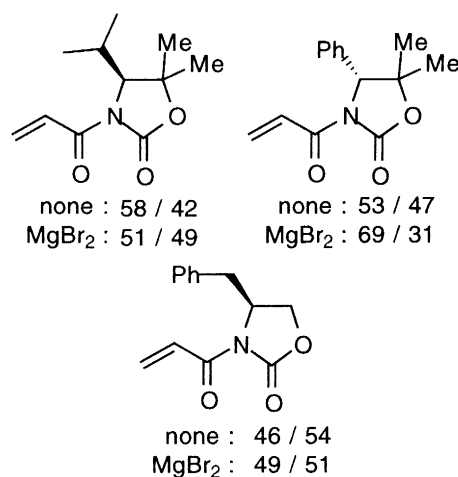
Scheme 1.

Table 1
Effect of metal ion in cycloaddition of benzonitrile oxide with **1**^a

Entry	Additive (equiv.)	Ratio ^c <i>l</i> - 2 / <i>u</i> - 2
1 ^b	none	43 / 57
2 ^b	ZnI ₂ (1.2)	45 / 55
3	MgBr ₂ (1.0)	71 / 29
4	MgBr ₂ (0.5)	48 / 52
5	Cu(OTf) ₂ (1.0)	51 / 49
6	Ni(ClO ₄) ₂ (1.0)	43 / 57
7	Fe(ClO ₄) ₂ (1.0)	45 / 55
8	Ti(OPr- <i>i</i>) ₄ (1.0)	30 / 70

a) Molar concentration of **1** was 0.083 M unless otherwise noted. b) **1**, 0.17 M.

c) Determined by ¹H NMR.



Scheme 2.

Some rate enhancement has been observed in the magnesium ion-mediated cycloaddition reactions of mesityl nitrile oxide to allylic alcohols when the reaction is carried out in a dilute solution.¹⁶ Accordingly, such dilution effect was examined in the present reaction. Dilution from 0.083 M to 0.017 M solution resulted in the disappearance of diastereoselectivity (*l*-2/*u*-2=49/51), but to our delight, the reaction performed in a higher concentration (0.25 M) unexpectedly gave us excellent diastereoselectivity (*l*-2/*u*-2=96/4) (Table 2). However, higher concentration than 0.25 M in dichloromethane failed because of the solubility problem (Fig. 1).

Table 2
Solvent effect in cycloaddition of benzonitrile oxide with **1**

Entry	Solvent	no additive ^a	MgBr ₂ ^b
		<i>l</i> -2 / <i>u</i> -2 ^c	<i>l</i> -2 / <i>u</i> -2 ^c
1	CH ₂ Cl ₂	43 / 57 (95)	96 / 4 (86)
2	CCl ₄	44 / 56 (62)	51 / 49 (88)
3	Et ₂ O	41 / 59 (75)	51 / 49 (94)
4	THF	41 / 59 (50)	49 / 51 (94)
5	CH ₃ CN	41 / 59 (85)	93 / 7 (93)

a) **1**, 0.17 M. b) **1**, 0.25 M.

c) Isolated yield is in parenthesis.

One possible explanation for the magnesium ion-mediated diastereoselective reaction observed above is that, when both nitrile oxide and dipolarophile coordinate to the same magnesium ion, the dipolar cycloaddition reaction between these two substrates is accelerated as a metal ion-tethered intramolecular reaction, similarly to the previous example which was demonstrated in the magnesium ion-mediated nitrile oxide reactions to allylic alcohols.⁶ If this is the case, addition of a coordinating additive should disfavor the chelation transition structure to lower the diastereoselectivity. Actually, the ratio of *l*-2/*u*-2 was decreased to 49/51 in the reaction performed in THF, but, surprisingly, high diastereoselectivity (*l*-2/*u*-2=93/7) was maintained in acetonitrile. Although we are so far unable to explain why magnesium bromide is specifically favored and why high concentration provides high diastereoselectivity, the reaction mechanism involved in the present reaction would be different from that of the magnesium

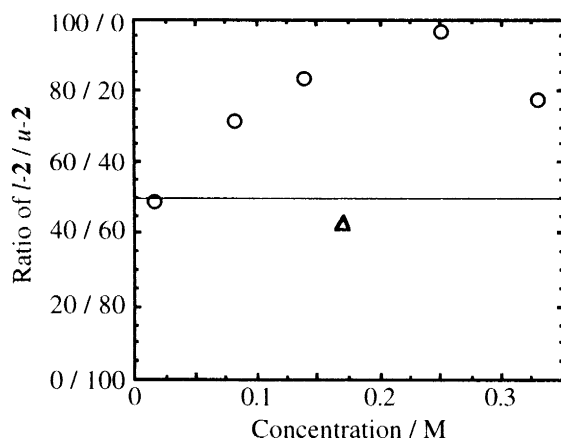
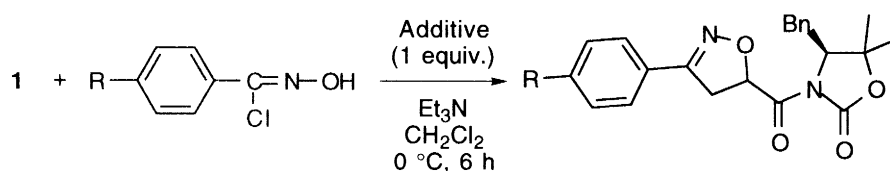


Fig. 1. Effect of concentration in MgBr₂-mediated cycloaddition of benzonitrile oxide with **1**: (○) MgBr₂ (1 equiv.); (△) no additive

ion-tethered intramolecular cycloaddition proposed for the nitrile oxide cycloaddition reactions of the magnesium^{6,16} and zinc alkoxides of allylic alcohols.⁷

Examination of the electronic nature of benzonitrile oxides should be interesting in the magnesium ion-based stereocontrol of nitrile oxide cycloaddition reactions with electron-deficient dipolarophiles. The more electron-donating nitrile oxides are more nucleophilic but, at the same time, more coordinating to the Lewis acid catalyst. Which is more reactive, an electron-donating or -withdrawing nitrile oxide to **1** under the MgBr₂-catalyzed conditions? A variety of *p*-substituted benzonitrile oxides were applied to the cycloaddition reactions to the chiral dipolarophile **1** in dichloromethane at 0°C in the presence of an equimolar amount of magnesium bromide. As shown in Table 3, the nitrile oxides having an electron-donating substituent at the *p*-position showed higher diastereoselectivities (Table 3, entries 1 and 2).¹⁷ These results indicate that the reaction of more nucleophilic nitrile oxides proceeded more effectively through the dipolarophile–MgBr₂ complex leading to higher diastereoselectivities. The anticipated deactivation of the Lewis acid catalyst by coordination of 1,3-dipoles, nitrile oxides in this case, is not so important.

Table 3
Diastereoselectivity (*l*-2/*u*-2) in the reaction of various nitrile oxides with **1**

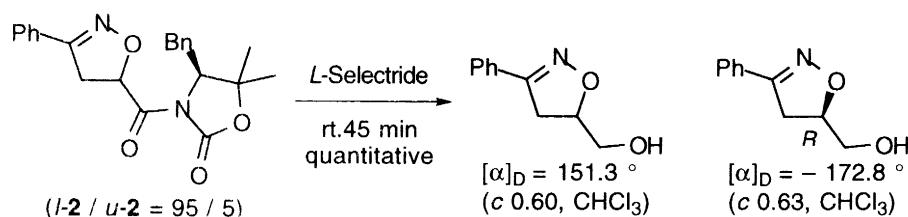


Entry	R	no additive ^a	MgBr ₂ ^{b,c}
1	H	43 / 57	96 / 4 (86)
2	MeO	52 / 48	91 / 9 (85)
3	NO ₂	44 / 56	73 / 27 (92)
4	Cl	43 / 57	64 / 36 (77)
5	F	39 / 61	76 / 24 (92)

a) **1**, 0.17 M. b) **1**, 0.25 M. c) Isolated yield is in parenthesis.

The structure of major diastereomer *l*-2 (90% de) was identified to be 5*S*-stereoisomer on the basis

of the reductive removal¹² of the chiral auxiliary with L-Selectride[®] at room temperature, followed by comparison of the specific optical rotation of the obtained 2-isoxazoline-5-methanol with that of the authentic 5*R*-stereoisomer (Scheme 3).¹³



Scheme 3.

In conclusion, we have developed a novel methodology for the magnesium ion-based stereocontrol of nitrile oxide cycloaddition reactions with electron-deficient dipolarophiles. Studies are in progress to clarify details of the reaction mechanisms.

Acknowledgements

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17. The representative procedure for the diastereoselective cycloaddition of benzonitrile oxide to **1** is as follows: a solution of **1** (64.8 mg, 0.25 mmol) and benzohydroximoyl chloride (42.8 mg, 0.275 mmol) in dry CH₂Cl₂ (1 ml) was added to magnesium bromide (46.0 mg, 0.25 mmol), dried previously at 140°C for 24 h under reduced pressure, and stirred at 0°C for 20 min under N₂ atmosphere. After triethylamine (42 μl, 0.3 mmol) was added, the mixture was stirred at 0°C for 6 h, quenched with saturated NaCl aq. (5 ml), and extracted with EtOAc (10 ml×4). The combined extracts were dried over anhydrous MgSO₄ and evaporated under reduced pressure. The residue obtained was chromatographed on silica gel with hexane–EtOAc (5/1 v/v) as an eluent to give a mixture of cycloadducts *u*-**2** and *l*-**2**.