First Successful Metal Coordination Control in 1,3-Dipolar Cycloadditions. High-Rate Acceleration and Regio- and Stereocontrol of Nitrile Oxide Cycloadditions to the Magnesium Alkoxides of Allylic and Homoallylic Alcohols

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Abstract: The first successful control of stereo- and regioselectivity in 1,3-dipolar cycloadditions by metal coordination is described. The presence of magnesium ions dramatically accelerates nitrile oxide dipolar cycloadditions to allylic alcohols, improving both the regio- and stereoselectivity of the reaction. For example, cycloadditions to terminal allylic alcohols bearing α-chirality produce *syn*-stereoisomers of 2-isoxazolines selectively, and reactions involving the magnesium alkoxides of internal allylic alcohols are exclusively regioselective in favor of 5-hydroxymethyl-2-isoxazolines. Metal alkoxides other than magnesium, such as lithium, zinc, and aluminum alkoxides, are less effective. These reactions involve the formation of activated intermediates in which a nitrile oxide and an allylic alkoxide coordinate to the magnesium ion. Theoretical calculations indicate that the formation of the coordinated intermediates enhances the rate of cycloaddition and also improves the *syn*-selectivity.

1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of a variety of complex five-membered heterocycles. Cycloadditions are especially versatile for the preparation of heterocycles with stereogenic centers because the reactions usually proceed in a concerted process.[1] Although many examples of regio- and/or stereoselective 1,3-dipolar cycloadditions have been reported, their selectivity usually depends upon the nature of the dipoles and dipolarophiles used.[1,2] In other words, substrate control is so far the only useful way to control dipolar cycloadditions. It is usually very difficult to achieve high stereo- and/or regiocontrol of dipolar cycloadditions by the use of a metallic additive. A Lewis acid catalyst in the reaction system reacts with 1,3-dipoles to give highly stabilized and/or deactivated dipole/Lewis acid complexes, which usually no longer show dipolar nature. Although some synthetic equivalents of metalated dipoles are known,[3] there are few successful examples available for the Lewis acid catalyzed stereo- and/or regiocontrol of dipolar cycloadditions.[4]

Nitrile oxide cycloadditions offer high synthetic potential because the product 2-isoxazolines can be reductively cleaved to produce β-hydroxy ketones or γ-amino alcohols. Accordingly, development of a regio- and stereoselective nitrile oxide cycloaddition would provide an important synthetic alternative to the stereoselective aldol and related reactions.[5]

Nitrile oxide cycloadditions to terminal alkenes proceed regioselectively to give 5-substituted 2-isoxazolines as single products. On the other hand, reactions with 1,2-disubstituted internal alkenes are sluggish and mixtures of regioisomeric 2-isoxazolines are formed.[6] In the absence of reactive dipolarophiles, nitrile oxides undergo undesired dimerization to provide 2,1,3-oxadiazole 1-oxides.

A problem of diastereoselectivity arises as well in dipolar cycloadditions to alkenes with a chiral center. Allylic alcohols and their ether derivatives bearing an α-chiral center have frequently been employed in nitrone[7] and nitrile oxide cycloadditions,[8] but the diastereoselectivities are not always high. For example, reactions of nitrile oxides with allylic alcohols show modest *syn*-selectivities.[8e,f,i] Only one example of an *anti*-selective nitrile oxide cycloaddition has been known, and that is limited to the reaction of *p*-nitrobenzonitrile oxide with 4,4-dimethyl-1-penten-3-ol having a *tert*-butyldimethylsilyl protecting group

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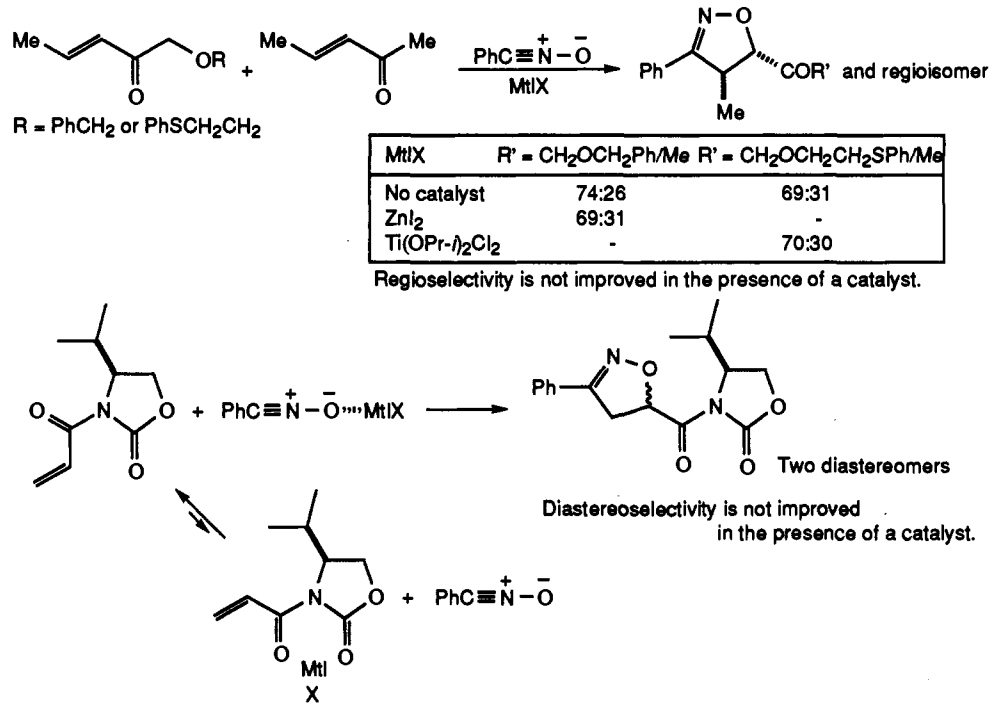
Chart 1



MtlX	R' = CH_2OCH_2Ph/Me	R' = $CH_2OCH_2CH_2SPh$/Me
No catalyst	74:26	69:31
ZnI_2	69:31	-
$Ti(OPr\text{-}i)_2Cl_2$	-	70:30

Regioselectivity is not improved in the presence of a catalyst.

(*syn:anti* = 5:95).[8e,i] A new general method to control the stereoselectivity of nitrile oxide cycloadditions is needed.

In the course of our study on regio- and stereocontrol of dipolar cycloadditions, we initially examined the effect of Lewis acid catalysis in nitrile oxide cycloadditions. At first, we used specifically designed bidentate (or tridentate) α,β-unsaturated ketones and a chiral α,β-unsaturated amide as dipolarophiles (Chart 1) in order to minimize the undesired coordination of nitrile oxides to the Lewis acid.[9] However, all of these attempts failed to improve the selectivity and the reactivity of cycloaddition reactions. Probably the Lewis acids were coordinating predominantly to the nitrile oxide to form stabilized and unreactive dipole/Lewis acid complexes, and such complex formation deactivated cycloaddition to electron-deficient olefins. If this were true, use of electron-rich alkenes would solve the problem.

Interaction of hydroximinoyl chlorides **1** with organometallic compounds offers a new method to generate nitrile oxides (Scheme 1).[10a] The *O*-metalation is followed by 1,3-elimination of a metal chloride, MtlCl, to liberate nitrile oxides **2**. They combine immediately to form nitrile oxide/Lewis acid complexes **B** which still show some reactivity toward electron-deficient alkenes. Cycloadditions using these complexes **B** to 2-(1-hydroxyalkyl)-acrylates are highly *syn*-selective.[10a] Accordingly, cycloadditions of **B** with heterosubstituted electron-rich alkenes, such as allylic alcohols, would be promising since some activation is expected by the formation of dipolarophile/Lewis acid complexes.

In the present paper, we describe the first successful example of stereo- and regiocontrol of dipolar cycloadditions by metal coordination.[10] In nitrile oxide dipolar cycloadditions to allylic alcohols, use of the magnesium alkoxides leads to a large acceleration of the reaction rate. Cycloadditions to the allylic magnesium alkoxides also proceed exclusively in a *syn*-selective manner. The magnesium ion-mediated cycloadditions to internal alkenes provide a useful method for the regioselective preparation of 5-hydroxymethyl-2-isoxazolines. Kinetic and theoretical studies indicate that the high stereo- and regiocontrol are due to the rate enhancement of the cycloadditions proceeding through a chelated transition state.

Results and Discussion

***syn*-Selectivity.** Treatment of benzohydroximinoyl chloride (**1a**) with EtMgBr in CH_2Cl_2 at −78 °C (method B) formed the nitrile oxide/MgBrCl complex **Ba** (Mtl = MgBr). The reaction of **Ba** with 1-pentene-3-ol (**3a**, X = H) gave a 95:5 mixture of *syn*- and *anti*-isomers of 5-(1-hydroxypropyl)-3-phenyl-2-isoxazoline (**4a**) (Scheme 1 and entries 4, 5 of Table 1). The free nitrile oxide **2a**, generated from **1a** and triethylamine (method A), showed only a poor *syn*-selectivity (*syn:anti* = 67:33, entry 1). When THF was the reaction solvent, *syn*-selectivity disappeared completely (entry 6). This result suggests that the reaction proceeds via an intermediate in which one of the two reactants, nitrile oxide **2a** or allylic alcohol **3a**, or both of them coordinate to the magnesium ion. However, this high *syn*-selectivity was not observed when other metal ions were used in the reaction. For example, although nitrile oxide complexes **Ba** (Mtl = Li, EtZn, Et_2Al) could be generated from **1a** by deprotonation with *n*-BuLi, Et_2Zn, Et_3Al (method B), respectively, these complexes showed low *syn*-selectivities (entries 7–9). The complexes **Ba** generated from Et_2AlCl and $EtAlCl_2$ failed to react with **3a** (entry 10).[11]

Allylic alkoxides **3** (X = Mtl) were used to generate complexes **B** from **1**. Treatment of **1a** with **3a** (X = Mtl) at −30 °C in CH_2Cl_2 generated complex **Ba**, which then reacted with allylic alcohol **3a** (X = H) to give cycloadduct **4a** (method C, Table 2). Under these conditions, the *syn*-selectivity depended upon the

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(11) Benzonitrile oxide/aluminum halide complexes **B** (MtlCl = $EtAlCl_2$ or $AlCl_3$) were generated by treatment of **1a** with diethylaluminum chloride or ethylaluminum dichloride. Trapping the resulting dipole with either methyl acrylate or 2-propenol failed.

Scheme 1

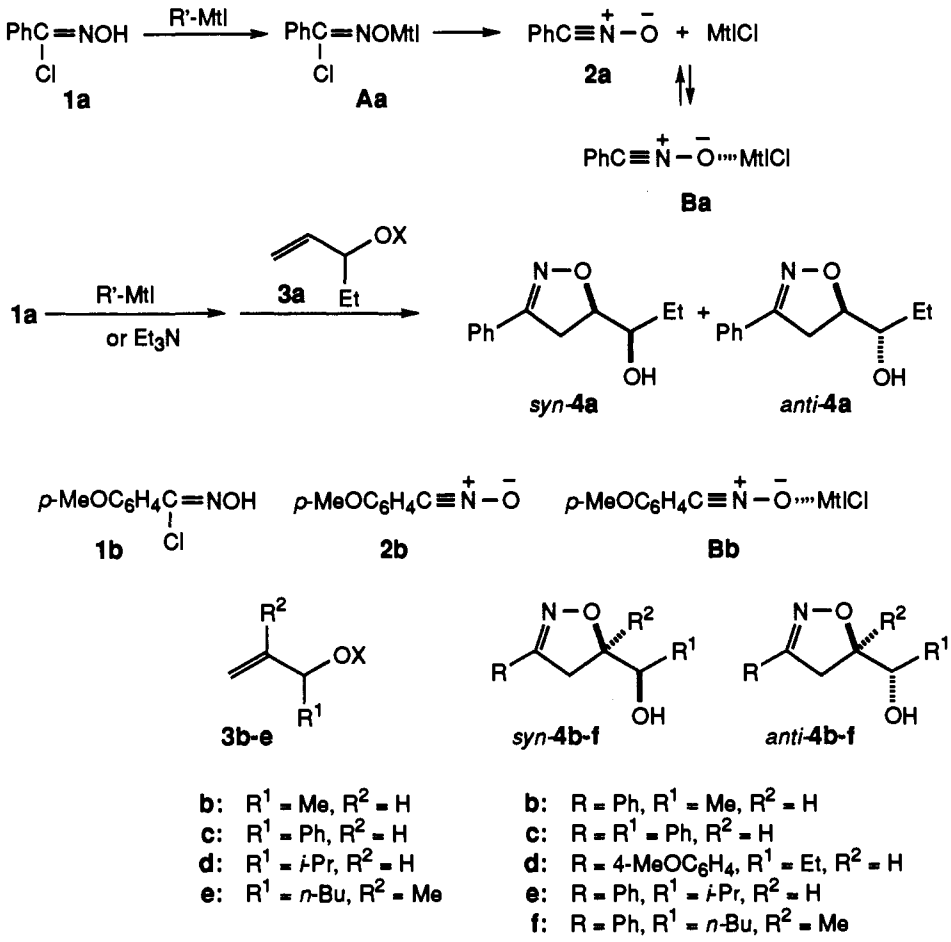


Table 1. Cycloadditions of Benzonitrile Oxides **2** or Benzonitrile Oxide/Lewis Acid Complexes **B** with 1-Substituted Allylic Alcohols **3** (X = H)

entry	3	R^1	R^2	X	1	R'Mtl	method[a]	solvent	temp/°C	time/h	product	yield/%[b]	*syn*:*anti*[c]
1	**3a**	Et	H	H	**1a**	Et_3N	A	CH_2Cl_2	−30	19	**4a**	40	67:33
2	**3b**	Me	H	H	**1a**	Et_3N	A	CH_2Cl_2	−30	9	**4b**	60	61:39
3	**3c**	Ph	H	H	**1a**	Et_3N	A	CH_2Cl_2	−30	24	**4c**	84	56:44
4	**3a**	Et	H	H	**1a**	EtMgBr[d]	B	CH_2Cl_2	−30	41	**4a**	75	95:5
5	**3a**	Et	H	H	**1a**	EtMgBr[d]	B	CH_2Cl_2	rt	1	**4a**	63	95:5
6	**3a**	Et	H	H	**1a**	EtMgBr[d]	B	THF	−30	41	**4a**	66	60:40
7	**3a**	Et	H	H	**1a**	*n*-BuLi[e]	B	CH_2Cl_2	−30	96	**4a**	54	75:25
8	**3a**	Et	H	H	**1a**	Et_2Zn[f]	B	CH_2Cl_2	−30	71	**4a**	79	77:23
9	**3a**	Et	H	H	**1a**	Et_3Al[g]	B	CH_2Cl_2	−40	17	**4a**	32	71:29
10	**3a**	Et	H	H	**1a**	$EtAlCl_2$[h]	B	CH_2Cl_2	rt	16.5		0	
11	**3b**	Me	H	H	**1a**	EtMgBr[d]	B	CH_2Cl_2	−30	12	**4b**	42	87:13
12	**3c**	Ph	H	H	**1a**	EtMgBr[d]	B	CH_2Cl_2	−30	50	**4c**	63	64:36
13	**3a**	Et	H	H	**1b**	EtMgBr[d]	B	CH_2Cl_2	−30	5.5	**4d**	65	95:5

[a] Method A: A mixture of hydroximinoyl chloride **1** and allylic alcohol **3** (X = H) was treated with Et_3N (an equimolar amount). Method B: Hydroximinoyl chloride **1** was treated with an organometallic compound, and the reaction with allylic alcohol **3** (X = H) was followed. [b] Isolated yield. [c] Based on ^1H NMR. [d–h] The following solution was used: *d*, 1 M in THF; *e*, 1.6 M in hexane; *f*,*h*, 1 M in hexane; *g*, 1.8 M in hexane.

molar equivalents of alkoxide **3a** (X = MgBr) used. For example, the *syn*:*anti* ratio gradually rose as the molar amounts of alkoxide **3a** (X = MgBr) increased, and the highest *syn*-selectivity was observed when 2 molar equiv of magnesium alkoxide **3a** (X = MgBr) were employed (Table 2, entries 1–4). The selectivity was not seriously affected by the reaction temperature (entry 5), but vanished when THF was used as reaction solvent (entry 6).

On the basis of these results, the characteristics of the reaction can be summarized: (1) Nitrile oxide cycloadditions to allylic alcohols can be controlled in a *syn*-selective manner in the presence of magnesium ions. The selectivity is improved by using 2 molar equiv of allylic magnesium alkoxide (method C). (2) Allylic magnesium alkoxide **3a** (X = MgBr) is much more reactive than the free alcohol **3a** (X = H). (3) Existence of a small excess of the free alcohol **3a** (X = H) does not affect the *syn*-selectivity.

The presence of 2 molar equiv of isopropyl alcohol made the reaction cleaner and improved the yield of **4a** (almost quantitative), but did not improve the *syn*-selectivity (Table 2, entries 4, 7). However, the use of a large excess of coordinating additive certainly reduced the *syn*-selectivity. For example, the reaction performed in THF gave **4a** as a roughly 2:1 mixture of *syn*- and *anti*-isomers (entry 6).

Since a 1 M THF solution of EtMgBr was used to prepare the allylic magnesium alkoxide **3a** (X = MgBr) in CH_2Cl_2, a small amount of THF always existed in the reaction system. The nitrile oxide cycloadditions were usually performed in a 0.05 M solution of the dipole. When 2 molar equiv of EtMgBr was used in method C, 10 volume percent of THF, or about 15 molar equiv based on complex **Ba** (Mtl = MgBr), was present in the reaction mixture. Nevertheless, the very high selectivity (>99:1) under these

Table 2. Cycloadditions of Benzonitrile Oxide/Lewis Acid Complex **Ba** with Alkoxides of 1-Penten-3-ol **3a** (X = Mtl)

entry	R'Mtl (equiv)[a]	X in **3a**	method[b]	solvent	temp/°C	time/h	product	yield/%[c]	*syn:anti*[d]
1	EtMgBr (1.0)	MgBr/H	C	CH_2Cl_2	−30	12	**4a**	82	93:7
2	EtMgBr (1.2)	MgBr/H	C	CH_2Cl_2	−30	12	**4a**	82	95:5
3	EtMgBr (1.5)	MgBr/H	C	CH_2Cl_2	−30	12	**4a**	92	97:3
4	EtMgBr (2.0)	MgBr/H	C	CH_2Cl_2	−30	12	**4a**	92	>99:1
5	EtMgBr (2.0)	MgBr/H	C	CH_2Cl_2	rt	20 min	**4a**	95	98:2
6	EtMgBr (2.0)	MgBr/H	C	THF	−30	12	**4a**	85	69:31
7	EtMgBr (2.0)	MgBr/H	C[e]	CH_2Cl_2	−30	12	**4a**	97	>99:1
8	*n*-BuLi (2.0)	Li/H	C	CH_2Cl_2	−30	12	**4a**	46	74:26
9	Et_2Zn (2.0)	EtZn/H	C	CH_2Cl_2	−30	12	**4a**	71	77:23
10	Et_3Al (2.0)	Et_2Al/H	C	CH_2Cl_2	−30	215	**4a**	39	68:32
11	EtMgBr	Li	D	CH_2Cl_2	−30	17	**4a**	74	94:6
12	EtMgBr	MgBr	D	CH_2Cl_2	−30	13	**4a**	71	97:3

[a] Unless otherwise indicated in parentheses, an equimolar amount of organometallic compound was used. [b] Method C: hydroximinoyl chloride **1** was treated with allylic alkoxide **3a** (X = Mtl). Method D: hydroximinoyl chloride **1** was treated with an organometallic compound, and the reaction with allylic alkoxide **3a** (X = Mtl) was followed. [c] Isolated yield. [d] Based on ^{1}H NMR. [e] In the presence of isopropyl alcohol (2 molar amounts) as an additive.

Table 3. *syn*-Selective Cycloadditions of Nitrile Oxide/MgBrCl **B** with Alkoxides of Allylic Alcohols **3a–e** (X = Mtl)[a]

entry	**3**	R^1	R^2	**1**	RCNO	time/h	product	yield/%[b]	*syn:anti*[c]
1	**3a**	Et	H	**1a**	PhCNO	12	**4a**	92	>99:1 (67:33)
2	**3b**	Me	H	**1a**	PhCNO	12	**4b**	95	96:4 (61:39)
3	**3c**	Ph	H	**1a**	PhCNO	12	**4c**	94	89:11 (56:44)
4	**3a**	Et	H	**1b**	*p*-$MeOC_6H_4CNO$	12	**4d**	92	>99:1 *e*
5	**3d**	*i*-Pr	H	**1a**	PhCNO	20 min	**4e**	95	97:3 (65:35)
6	**3e**	*n*-Bu	Me	**1a**	PhCNO	12	**4f**	85	96:4 (60:40)

[a] All reactions were performed with 2 molar amounts of magnesium alkoxides **3** (X = MgBr) and **1** in dichloromethane at −30 °C according to method C (refer to the footnote of Table 2). [b] Isolated yield. [c] Based on ^{1}H NMR. The ratio in parentheses is the *syn:anti* selectivity observed in reactions by method A. [d] Reaction in the absence of THF. [e] No isomer ratio is given since the 1:1 adduct **4d** is contaminated by the 1:2 adduct.

Table 4. Regioselective Cycloadditions of Benzonitrile Oxide **2a** or Benzonitrile Oxide/Lewis Acid Complex **Ba** with 2-Buten-1-ol **5a**[a]

entry	X in **5a**	base (equiv)[b]	additive (equiv)	method[c]	temp/°C	time/h	product	yield/%[d]	**6a**:**6'a**[e]
1	H	Et_3N		A	rt	1.5	**6a** + **6'a**	46	46:54
2	H	EtMgBr		B	−30	17	**6a** + **6'a**	20	55:45
3	MgBr/H	**5a** (X = MgBr, 1.0)		C	rt	0.5	**6a** + **6'a**	9	65:35
4	MgBr/H	**5a** (X = MgBr, 2.0)		C	rt	0.5	**6a**	82	>99:1
5	MgBr/H	**5a** (X = MgBr, 2.0)	*i*-PrOH (2.0)[f]	C	rt	0.5	**6a** + **6'a**	92	97:3
6	MgBr	*i*-PrOLi		D	rt	0.5	**6a** + **6'a**	76	96:4
7	Li	EtMgBr		D	rt	2.5	**6a**	66	>99:1
8	Li	EtMgBr		D[g]	rt	5	**6a** + **6'a**	41	93:7
9	Li	*n*-BuLi		D	rt	0.5	**6a** + **6'a**	13	60:40

[a] All reactions were performed in dichloromethane. [b] Unless otherwise indicated in parentheses, an equimolar amount of base was used to generate nitrile oxide **2a**. [c] Methods A–D: refer to the footnote in Tables 1 and 2. [d] Isolated yield. [e] Based on ^{1}H NMR. [f] To a mixture of *i*-PrOH and **1a** was added **5a** (X = MgBr, 2 equiv). [g] In THF.

conditions indicated that the existence of a small excess of THF does not affect the *syn*-selectivity at all.

The high *syn*-selectivity for the reaction is presumed to come from a chelation-controlled transition state involving the magnesium ion. In contrast, the reactions of nitrile oxide complex **B**, generated by the use of *n*-BuLi, Et_2Zn, or Et_3Al in method B or C, showed only poor *syn*-selectivities (entries 8–10), very similar to that for the reaction of free nitrile oxide **2a** with allylic alcohol **3a** (X = H). The high *syn*-selectivity, observed in the reaction of **B** (Mtl = MgBr) with lithium alkoxide **3a** (X = Li) as shown in entry 11, is presumably due to a rapid metal exchange.[12]

Other chiral allylic alcohols **3b–e** showed similar *syn*-selectivities under conditions where 2 molar equiv of alkoxide **3** (X = MgBr) were used (method C, Table 3). The *syn*-selectivity for **3c** was somewhat lower (*syn:anti* = 75:25) than for the other cases. This reaction in the absence of THF exhibited a slightly better *syn*-selectivity (entry 3, *syn:anti* = 89:11).

Regioselectivity. Nitrile oxide cycloadditions to internal alkenes give rise to two serious synthetic problems. Firstly, internal alkenes are much less reactive than terminal alkenes.[13] The cycloadducts are usually obtained in moderate to low yields since the nitrile oxides prefer to form their dimers, the furoxanes. Secondly, regiochemical control of the cycloaddition is poor.[14,15] For example, a mixture of regioisomeric cycloadducts **6a** and **6'a** was formed in a poor ratio and in a low yield in the reaction of free benzonitrile oxide (**2a**) with (*E*)-2-buten-1-ol (**5a**, X = H, Table 4, entry 1). There have been a number of unsuccessful attempts to improve these results. We therefore have attempted to solve these problems by the application of metal coordination control.

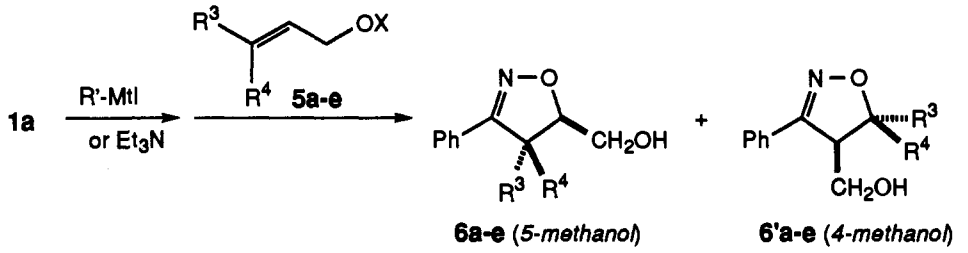
Initially, metal coordination control was applied to the reaction of (*E*)-2-buten-1-ol (**5a**) (Table 4). The use of 1 molar equiv of a Grignard reagent gave poor results (entries 2, 3). However, when an excess amount of magnesium alkoxide **5a** (X = MgBr) was employed in the reaction with **1a**, not only the regioselectivity but also the reactivity was dramatically improved. For example, the cycloaddition promoted by the presence of 2 molar equiv of **5a** (X = MgBr) gave (*E*)-4-methyl-3-phenyl-2-isoxazolidine-5-methanol (**6a**) as a single product in 82% yield (method B, entry

(12) Alkoxide **3a** (X = Li) as stronger base reacts with complex **B** (MtlCl = MgBrCl) as stronger acid to form **3a** (X = MgBr) and **B** (MtlCl = LiCl), both weaker base and acid.

(13) Bast, K.; Christl, M.; Huisgen, R.; Mack, W. *Chem. Ber.* **1973**, *106*, 3312–3344.

(14) Reviews: (a) Paquette, L. A. Asymmetric Cycloaddition Reactions. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 7, pp 455–501. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (c) Taschner, M. J. Asymmetric Diels-Alder Reactions. *Organic Synthesis-Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1989; Vol. 1, pp 1–101. (d) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127–4133.

Scheme 2



5, 6, and 6':

a: R^3 = Me, R^4 = H
b: R^3 = *n*-Pr, R^4 = H
c: R^3 = H, R^4 = *n*-Pr
d: R^3 = Ph, R^4 = H
e: R^3 = R^4 = Me

Table 5. Regioselective Cycloadditions of Benzonitrile Oxide/Lewis Acid Complex **Ba** with Alkoxides of Allylic Alcohols **5a–e** (X = Mtl)[a]

entry	5	R^3	R^4	X	base (equiv)	method[b]	time/h	product	yield/%[c]	6:6' [d,e]
1	**5a**	Me	H	H	**5a** (X = MgBr, 2.0)	C	0.5	**6a**	82	>99:1 (46:54, 46%)
2	**5a**			Li	EtMgBr (1.0)	D	2.5	**6a**	66	>99:1
3	**5b**	*n*-Pr	H	H	**5b** (X = MgBr, 2.0)	C	2.5	**6b** + **6'b**	73	98:2 (55:45, 44%)
4	**5b**			Li	EtMgBr (1.0)	D	2.5	**6b**	68	>99:1
5	**5c**	H	*n*-Pr	H	**5c** (X = MgBr, 2.0)	C	2.5	**6c** + **6'c**	63	94:6 *e*
6	**5c**			Li	EtMgBr (1.0)	D	1.5	**6c** + **6'c**	67	96:4
7	**5d**	Ph	H	H	**5d** (X = MgBr, 2.0)	C	1.5	**6d**	68	>99:1 (20:80, 46%)
8	**5d**			Li	EtMgBr (1.0)	D	3	**6d**	43	>99:1
9	**5e**	Me	Me	H	**5e** (X = MgBr, 2.0)	C	15	**6e** + **6'e**	14	95:5 (1:99, 19%)
10	**5e**			Li	EtMgBr (1.0)	D	17	**6e** + **6'e**	20	97:3

[a] All reactions were performed in dichloromethane. [b] Methods C, D: refer to the footnote in Table 2. [c] Isolated yield. [d] Based on ^{1}H NMR. [e] Results by use of **1a** generated by method A are shown in parentheses. [f] No reaction took place at room temperature for 24 h.

4). The presence of isopropyl alcohol (2 molar equiv)[16] increased the yield of **6a** and **6'a** to 92% combined yield, and the regioselectivity was 97:3 (entry 5).

We tested three combinations of reagents for accelerating the cycloaddition: (1) the nitrile oxide/magnesium halide complex **Ba** (Mtl = MgBr) with lithium alkoxide **5a** (X = Li), (2) the nitrile oxide/lithium chloride complex **Ba** (Mtl = Li) with magnesium alkoxide **5a** (X = MgBr), and (3) the nitrile oxide/lithium chloride complex **Ba** (Mtl = Li) with lithium alkoxide **5a** (X = Li). The first two conditions gave the cycloadducts regioselectively (entries 6, 7). The third cycloaddition, however, occurred with poor regioselectivity (entry 9). Accordingly, the use of magnesium is essential to achieve a high regioselectivity and rate enhancement. Alkoxides **5a** (X = Li, ZnEt, $AlEt_2$) other than magnesium were totally ineffective, resulting in poor regioselectivities and poor yields (10%, 49:51 for X = Li; 9%, 46:54 for X = ZnEt; 14%, 48:52 for X = $AlEt_2$). The regioselectivity was not lowered as drastically when using THF as a highly coordinating solvent (entries 7, 8).

The present method was applied to a variety of 3-substituted and 3,3-disubstituted allylic alcohols **5a–e** (Scheme 2). The results are summarized in Table 5. Generation of the nitrile oxide/magnesium complex **Ba** (Mtl = MgBr) was performed by the application of methods C and D. The regioselectivity of cycloaddition did not depend upon the method of the generation (entries 1, 3, 5, 7, 9 vs 2, 4, 6, 8, 10, respectively). It is interesting that a complete reversal of regioselectivity was observed for certain allylic alcohols. For example, in the reactions of free nitrile oxide **2a** with (*E*)-3-phenyl-2-propenol (**5d**, X = H) and 3-methyl-2-butenol (**5e**, X = H), the 2-isoxazoline-4-methanol regioisomers **6'd,e** were produced in poor yields (**6**:**6'** = 20:80 for **6d** and 1:99 for **6e**). Presumably, the phenyl group (**5d**) and two methyl groups (**5e**) play an important role in regiocontrol for 2-isoxazoline-4-methanols. On the other hand, magnesium alkoxides **5d,e** (X = MgBr) showed reversed regioselectivities to provide 2-isoxazoline-5-methanol derivatives **6d,e** as major products (entries 7–10).

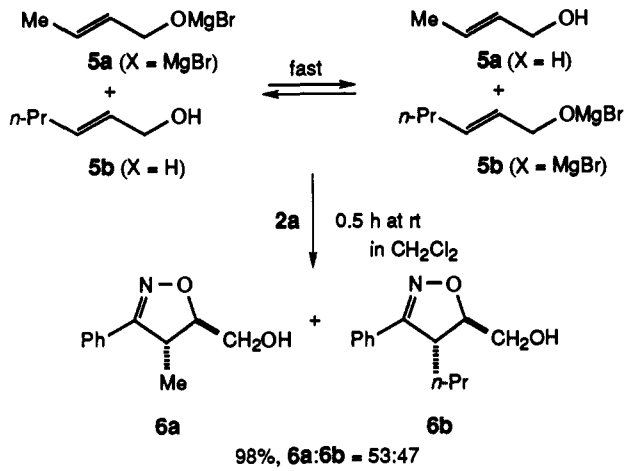
In order to get more information about metal alkoxide exchange, we examined the competitive cycloaddition of **2a** to two different allylic dipolarophiles (Scheme 3). Exposure of free nitrile oxide **2a** to a 1:1 mixture of the magnesium alkoxide of (*E*)-2-butenol **5a** (X = MgBr) and free (*E*)-2-hexenol **5b** (X = H) gave two 2-isoxazoline-5-methanol derivatives **6a,b** in the ratio 53:47. No regioisomers **6'a** and **6'b** were detected. A rapid metal exchange presumably occurred between **5a** (X = MgBr) and **5b** (X = H) to form a 1:1 mixture of two allylic magnesium alkoxides **5a,b** (X = MgBr) along with a 1:1 mixture of free alcohols **5a,b** (X = H). The nitrile oxide reacted with the magnesium complexes to give cycloadducts **6a** and **6b**, regioselectively.

On the basis of this rapid alkoxide exchange, we propose the following simple procedure for the effective regiocontrol of nitrile

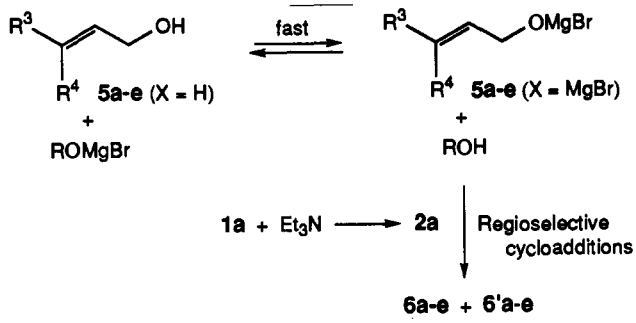
(15) For recent reports on diastereoselective Diels–Alder reactions, see: (a) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 7060–7067. (b) Kahn, S. D.; Hehre, W. J. *Ibid.* **1987**, *109*, 663–666. (c) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256. (e) Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885–5888. (f) Sugahara, T.; Iwata, T.; Yamaoka, M.; Takano, S. *Tetrahedron Lett.* **1989**, *30*, 1821–1824. (g) Waldmann, H. *Liebigs Ann. Chem.* **1990**, 671–680. For enantioselective Diels–Alder reactions, see: (h) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312. (i) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *Ibid.* **1988**, *110*, 6254–6255. (j) Maruoka, K.; Yamamoto, H. *Ibid.* **1989**, *111*, 789–790. (k) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481–1483. (l) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947–1950. (m) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345. (n) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *Ibid.* **1989**, *111*, 5493–5495. (o) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231–7232. (p) Corey, E. J.; Jardine, P. D.-S.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243–9244. (q) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209–1216. (r) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729. (s) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935–938.

(16) Propyl alcohol (2.2 molar amounts) was also utilized as well (75%, 98:2).

Scheme 3



Scheme 4



oxide cycloadditions to allylic alcohols: Free nitrile oxide **2a**, which is generated from **1a** and triethylamine (method A), is treated with free allylic alcohols **5a–e** (X = H) in the presence of the appropriate magnesium alkoxide ROMgBr (method E). A rapid equilibration supposedly takes place between **5a–e** (X = H) and ROMgBr to generate the reactive magnesium alkoxide dipolarophiles **5a–e** (X = MgBr), which then undergo regioselective cycloadditions (Scheme 4). As Table 6 shows, regioselectivity increases with the incremental addition of magnesium bromide butoxide (Table 6, entries 1–6). An alternative procedure to the one above is accomplished by the successive addition of the following materials to butyl alcohol: EtMgBr in CH_2Cl_2, an allylic alcohol **5** (X = H), triethylamine, and finally hydroximinoyl chloride **1** as precursor of nitrile oxide **2** (method E′). We achieved highly regioselective nitrile oxide cycloadditions to allylic alcohols **5** (X = H) by this simple method (entries 7–11).

Homoallylic Alcohols. We investigated an extension of the present methodology to homoallylic alcohol dipolarophiles. Although reaction of free nitrile oxide **2a** with the terminal alkene 4-penten-2-ol (**7a**, X = H) was completely regioselective, the diastereoselectivity was very poor (Scheme 5), giving a 1:1 mixture of stereoisomeric cycloadducts of **8a** (Table 7, entry 1–3). Introduction of a bulkier substituent at the α-chiral center of the homoallylic dipolarophile, such as the *tert*-butyl substituent, did not improve the selectivity, either (entries 4–6).

Improvement of regioselectivity in the presence of magnesium ions was observed in cycloadditions to the internal homoallylic alcohol **9**. The reaction of free nitrile oxide **2a** to a 4-substituted homoallylic alcohol, (*E*)-3-penten-1-ol (**9**, X = H), proceeded nonregioselectively (Scheme 5, Table 7, entry 7). The use of magnesium alkoxide **9** (X = MgBr) generated by either method C or D dramatically improved their regioselectivities to the level of 96:4 (entries 8, 9), though the yields of **10** and **10′** remained very low.

Chemoselectivity and Combination of Regio- and Stereoselectivity. Diene **11**, which has a hydroxyl group in both an allylic and homoallylic position, seemed an attractive probe for the relative effectiveness of magnesium ion catalysis on these two homologous moieties. Treatment of 1,5-hexadien-3-ol (**11**, X = H) with free benzonitrile oxide (**2a**) gave a 67:33 mixture of cycloadducts **12** (67:33) and **13** (59:41) (Scheme 6). This indicated that the allylic alcohol moiety was only slightly more reactive than the homoallylic one. On the other hand, the reaction using magnesium alkoxide **11** (X = MgBr) by method C showed an absolute chemoselectivity for cycloaddition at the allylic moiety (**12** was the only cycloadduct) and good diastereoselectivity (*syn*:*anti* = 99:1 for **12**). Thus, the magnesium alkoxide methodology is much more effective for allylic alcohols than homoallylic alcohols.

A problem of both stereo- and regioselectivity arises in the cycloaddition to the internal allylic alcohol **14** bearing α-chirality. A mixture of four possible isomers of cycloadducts—*anti*- and *syn*-diastereomers for regioisomeric cycloadducts **15** and **16**—in poor combined yield was predicted from the reaction between the free dipole **2a** and **14** (X = H) (Scheme 7). Indeed, the cycloaddition of free nitrile oxide **2a** gave a mixture of the four possible diastereomers. In contrast, the application of method C, employing 2 molar equiv of magnesium alkoxide **14** (X = MgBr), gratifyingly produced a complete regioselective cycloaddition in favor of **15**, in which the *syn*-selectivity was as high as 94:6. Surprisingly, a similar reaction with the magnesium alkoxide of 3-cyclohexenol **17** led to the formation of a complex mixture of many products.

Questions of both chemo- and regioselectivity arise for the two unsymmetrically trisubstituted alkene moieties of the diene alcohol **18**. As expected, free benzonitrile oxide (**2a**) showed a low reactivity to **18**. The cycloaddition gave a mixture of three isomeric cycloadducts in a comparable ratio only when a large excess of free **2a** was used (Scheme 8). However, in the presence of *n*-BuOMgBr (1.3 molar equiv) the reaction proceeded with absolute chemo- and regioselectivity to lead to exclusive formation of **19**, a product not seen in the uncatalyzed reaction.

The cycloaddition to conjugated diene alcohol, (*E*,*E*)-2,4-hexadien-1-ol (**20**), was moderately regioselective for each double bond, with 5-alkenyl-substituted 2-isoxazoline regioisomers having been obtained as major isomers (Scheme 8). Reactivities of the two double bonds of **20** were comparable. The regiochemical preference favoring introduction of the unsaturated substituent at the 5-position is similar to the reaction of the phenyl-substituted allylic alcohol **5d** (Table 5, entry 7). When the same reaction was performed in the presence of *n*-BuOMgBr (1.3 molar equiv), however, this substrate-based regiocontrol was completely overcome and gave 2-isoxazoline-5-methanol **21** as the single isomer.

Kinetic Studies. For our kinetic studies, three types of nitrile oxide cycloadditions were examined (Figure 1): (1) the reaction of free benzonitrile oxide with free dipolarophile alcohols (reaction L), (2) that of a benzonitrile oxide/Lewis acid complex with free dipolarophile alcohols (reaction M), and (3) that of free benzonitrile oxide with the magnesium alkoxides of dipolarophile alcohols (reaction N). As mentioned above, reaction N gave the best stereo- and regiocontrol.

The stabilized benzonitrile oxide/MgBrCl complex must be formed initially in reaction M. The cycloaddition reaction proceeds when the oxygen atom of the dipolarophile coordinates to the magnesium ion. In reaction N, ionic bonding between the magnesium ion and the alkoxide oxygen is formed first, and then nitrile oxide coordinates to this complex. As the negatively charged alkoxide ion coordinates to magnesium, its Lewis acidity becomes weaker. Accordingly, higher acceleration of cycloaddition is expected for reaction N.

Since the rates of reactions M and N are very fast, relative rate accelerations in reactions M and N were estimated by competitive nitrile oxide cycloadditions using two dipolarophiles. Norbornene was selected as the reference dipolarophile. This strained and

Table 6. Highly Regioselective Cycloadditions of Benzonitrile Oxide **2a** with Free Allylic Alcohols **5a–e** (X = H) in the Presence of Butoxymagnesium Bromide[a]

entry	5	R^3	R^4	*n*-BuOMgBr (equiv)	method[b]	time/h	product	yield/%[c]	6:6′ [d,e]
1	**5a**	Me	H	0.1	E	24	**6a** + **6′a**	37	57:43
2				0.3	E	24	**6a** + **6′a**	24	68:32
3				0.5	E	24	**6a** + **6′a**	59	82:18
4				0.8	E	12	**6a** + **6′a**	53	97:3
5				1.05	E	2.5	**6a**	83	>99:1
6				1.3	E	1	**6a**	87	>99:1
7				1.3	E′	1	**6a**	90	>99:1
8	**5b**	*n*-Pr	H	1.3	E′	1	**6b**	90	>99:1
9	**5c**	H	*n*-Pr	1.3	E′	1.5	**6c** + **6′c**	100	98:2
10	**5d**	Ph	H	1.3	E′	1.5	**6d**	92	>99:1
11	**5e**	Me	Me	1.3	E′	13	**6e**	47	>99:1

[a] All reactions were performed in dichloromethane. [b] Method E: free nitrile oxide **2a** was allowed to react with a free allylic alcohol **5** (X = MgBr) in the presence of *n*-BuOMgBr. Method E′: to a solution of butanol are added EtMgBr, an alcohol **5**, Et_3N, and imidoyl chloride **1a** in this order. [c] Isolated yield. [d] Based on ^1H NMR. [e] Results in the presence of *n*-BuOMgBr are shown in parentheses. [f] No reaction took place at room temperature for 24 h.

Scheme 5

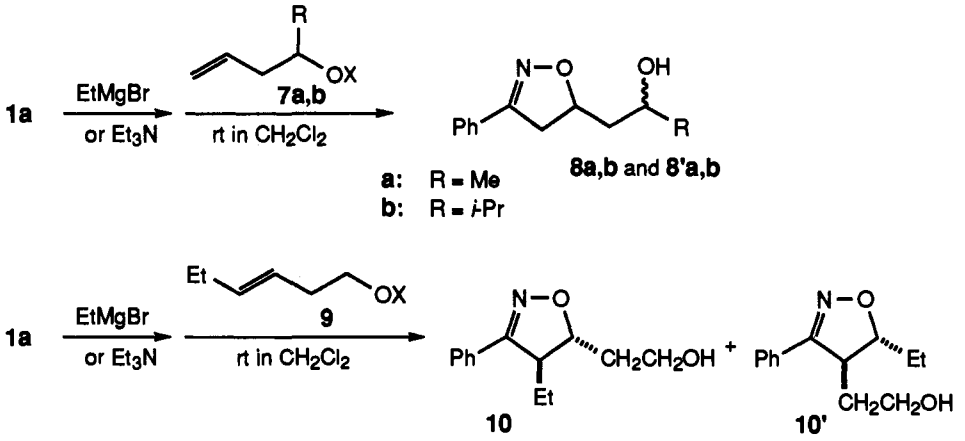
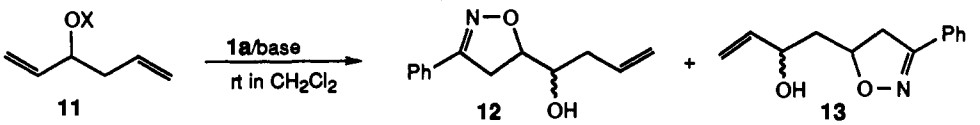


Table 7. Cycloadditions of Benzonitrile Oxide **2a** or Benzonitrile Oxide/Lewis Acid Complex **Ba** with Homoallylic Alcohols **7a,b** and **9**[a]

entry	5	R	X	base (equiv)	method[b]	temp/°C	time/h	product	yield/%[c]	6:6′ [d,e]
1	**7a**	Me	H	Et_3N	A	−30	11	**8a** + **8′a**	47	50:50
2	**7a**		MgBr	**7a** (X = MgBr, 2.0)	C	−30	12	**8a** + **8′a**	64	51:49
3	**7a**		Li	EtMgBr	D	−30	12	**8a** + **8′a**	48	52:48
4	**7b**	*t*-Bu	H	Et_3N	A	−78	36	**8b** + **8′b**	88	51:49
5	**7b**		MgBr	**7b** (X = MgBr, 2.0)	C	−30	20	**8b** + **8′b**	81	55:45
6	**7b**		Li	EtMgBr	D	−30	23	**8b** + **8′b**	52	53:47
7	**9**		H	Et_3N	A	rt	2.5	**10** + **10′**	47	54:46
8	**9**		MgBr	**9** (X = MgBr, 2.0)	C	rt	43	**10** + **10′**	15	82:18
9	**9**		Li	EtMgBr	D	rt	2.5	**10** + **10′**	5	96:4

[a] All reactions were performed in dichloromethane. [b] Methods A, C, D: refer to the footnote in Tables 1 and 2. [c] Isolated yield. [d] Based on ^1H NMR.

Scheme 6



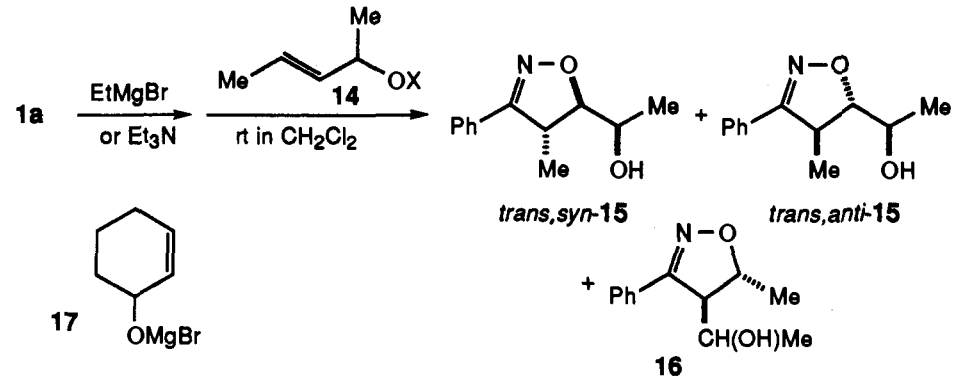
Base	X	Time/h	Yield/%	12 : 13
11 [X = MgBr (2 equiv)]	MgBr	0.15	94	**12** only[1]
Et_3N	H	3	100	67 : 33[2]

[1] **12** consists of two stereoisomers (*syn*:*anti* = 99:1).
[2] **12** (67:33) and **13** (53:47) consist of two stereoisomers each.

reactive olefin bears no additional functional group, so little influence by the presence of a Lewis acid is expected in nitrile oxide cycloadditions. Competitive cycloadditions were performed using 5 molar equiv each of norbornene and of a dipolarophile alcohol at room temperature in CH_2Cl_2. The relative rate was estimated on the basis of product ratios.

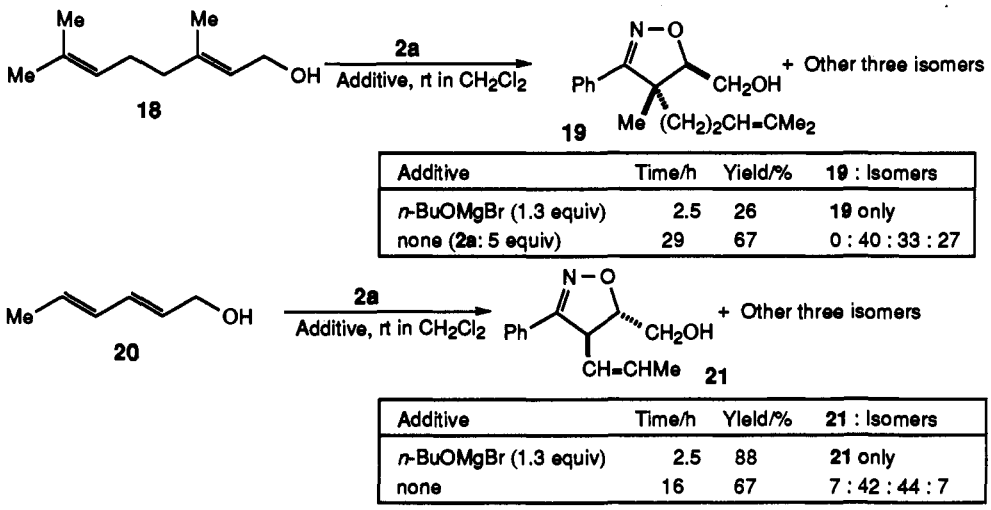
For reaction L, in which a free nitrile oxide **2a** was reacted with free dipolarophile alcohols, reaction rates depended upon the substitution pattern of the dipolarophiles (Table 8). Terminal olefins showed reaction rates about equal to that of the nonfunctionalized terminal alkene 3-phenylpropene (3/100 to 6/100 the rate of norbornene, entries 2–5, 11, 12, 17), indicating that hydrogen-bonding interactions, if any, hardly enhanced the reaction rates. *vic*-Disubstituted internal olefins and a trisubstituted olefin were much less reactive than terminal alkenes (2/10000 to 1/1000 the rate of norbornene, entries 6–10, 13, 14).

Scheme 7



Base	X	Time/h	Yield/%	15 (*syn*:*anti*) : 16
14 [X = MgBr (2 equiv)]	MgBr	1	53	100 (94:6) : 0
Et_3N	H	2	28	82 (55:27) : 18 (12:6)

Scheme 8



Additive	Time/h	Yield/%	19 : Isomers
n-BuOMgBr (1.3 equiv)	2.5	26	19 only
none (2a: 5 equiv)	29	67	0 : 40 : 33 : 27

Additive	Time/h	Yield/%	21 : Isomers
n-BuOMgBr (1.3 equiv)	2.5	88	21 only
none	16	67	7 : 42 : 44 : 7

Reaction M pits an alkene alcohol and norbornene (5 molar equiv each in CH_2Cl_2, Table 8) in competition for the nitrile oxide/MgBrCl complex **Ba** (Mtl = MgBr). These reactions showed low acceleration factors of 3–14 (ratios M/L in Table 8). The acceleration ratios M/L were even lower when substituents were introduced at the α-position of the dipolarophiles (entries 4, 5, 12).

A much greater rate enhancement was observed for reaction N, in which the magnesium alkoxides of dipolarophiles and free nitrile oxide **2a** were used in CH_2Cl_2 (Table 8). A rate acceleration by a factor of more than 2000 was recorded in the reaction of the magnesium alkoxide of 2-propen-1-ol, the parent allylic alcohol (ratio N/L in entry 2). Existence of a substituent at the α-position caused a significant decrease in the rate enhancement (entries 4, 5).

Cycloadditions to internal allylic magnesium alkoxides were interesting (entries 6–10). Reactions of these *vic*-disubstituted olefins are very sluggish under noncatalyzed conditions (6/10000 to 1/1000 the rate of norbornene in reaction L), but rate enhancements of more than 3000 times resulted from the use of magnesium alkoxides (ratios N/L in Table 8). Reactivities of the magnesium alkoxides of allylic alcohols are even greater than that of norbornene in reaction N. With the 1,1,2-trisubstituted olefin **5e**, a rate acceleration of as much as 16 000 times was recorded (entry 10), this providing the maximum accelerating factor in the series.

A homoallylic alcohol was also activated by its conversion to the magnesium alkoxide (490 times, entry 11, a little smaller than the acceleration factor for 2-propen-1-ol), and α-substitution reduced the enhancement ratio to 1/20 (entry 12). The rate acceleration of the internal homoallylic alkoxide was quite small (100 times, entry 13).

Surprisingly, free nitrile oxide **2a** and its complex with MgBrCl **Ba** (Mtl = MgBr) showed similar reactivities to nonactivated olefins (norbornene and 3-phenylpropene) and electron-deficient olefins (3-buten-2-one and methyl acrylate) (entries 1, 15–17). In reactions of **Ba** (Mtl = MgBr) with 3-buten-2-one and methyl acrylate, we assume that the metal-promoted rate acceleration with respect to the dipolarophile effectively competes with the rate deceleration by the complex formation with the dipole.[17]

Solvent Effect on Selectivity and Reaction Rate. The high rate enhancement observed in the kinetic studies above is no doubt the major reason for the excellent stereo- and regiocontrol. However, use of a noncoordinating solvent such as CH_2Cl_2 was necessary to achieve excellent selectivities. *syn*-Selectivities were especially sensitive to the nature of the solvent. Accordingly, the effect of a coordinating additive, THF, on both reaction rate and selectivity was examined.

The relative rate of reaction of the free nitrile oxide **2a** in a competitive experiment between 3-buten-2-ol (**3b**, X = H) and norbornene was 0.059 (Table 8, entry 4), while the stereoselectivity

(17) Rate acceleration has been recently found in nitrone cycloadditions using electron-deficient dipolarophiles in the presence of a Lewis acid (see ref 18).

(18) Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 7889–7892.

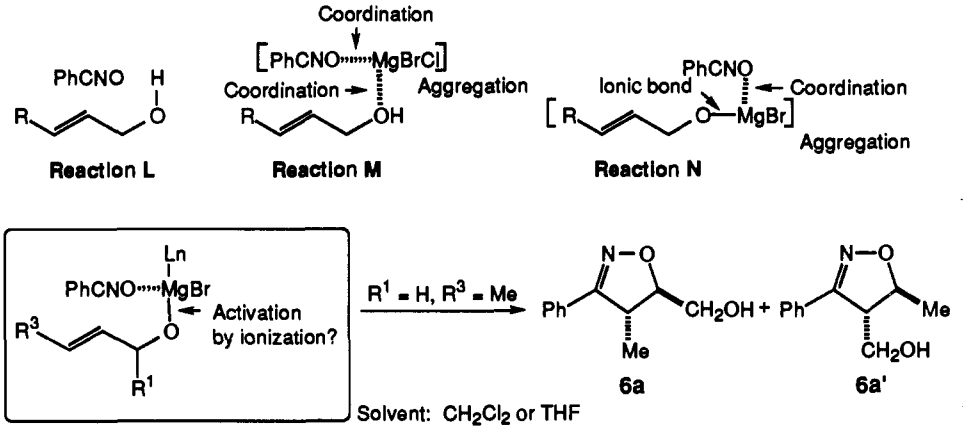


Figure 1. Possible interactions working among dipoles, dipolarophiles, and metals in nitrile oxide cycloadditions to allylic alcohols.

was *syn*-**4b**:*anti*-**4b** = 61:39. On the other hand, a similar reaction of **2a** with the magnesium alkoxide **3b** (X = MgBr) in CH_2Cl_2 was highly accelerated (relative rate = 14) and gave a 96:4 ratio of *syn*-**4b**:*anti*-**4b** (Scheme 9). In THF both the selectivity and the reaction rate were lowered to the level of the uncatalyzed reaction (relative rate = 0.09, *syn*-**4b**:*anti*-**4b** = 68:32). This indicates that in the cases of nitrile oxide cycloadditions using magnesium alkoxides of terminal allylic alcohols, the rate enhancement, and therefore the high *syn*-selectivity, mainly comes from the effective coordination of nitrile oxide dipoles to the magnesium ion rather than the ionization of dipolarophile alcohols.

Reaction of free nitrile oxide **2a** with 2-buten-1-ol (**5a**, X = H), as an internal allylic alcohol substrate, showed a relative rate of 0.0013 and a regioselectivity **6a**:**6'a** of 46:54 (Table 9, entry 7). When the magnesium alkoxide **2a** (X = MgBr) was employed in CH_2Cl_2, the reaction was accelerated by a factor of 6900 (relative rate = 9) to give **6a** as a single isomer (entry 1). The same reaction performed either in the presence of THF (CH_2Cl_2:THF = 10:1 v/v) or in THF itself again sharply decreased the relative rate (entries 5, 6). In both reactions, however, rates were still much greater than that of the uncatalyzed reaction and **6a** was the only regioisomer produced. This striking contrast with the reactions of terminal allylic alcohols will be discussed below.

The presence of an alcoholic additive, if not much more than 1 molar equiv, did not affect the reaction with respect to both rate enhancement and regioselectivity (entries 2–4). Interestingly, the reaction in the presence of 1 molar equiv of *i*-PrOH or *t*-BuOH was even faster than the reaction without additive. This is why the procedure using the magnesium alkoxides of dipolarophile alcohols (2 molar equiv) works so well (method C).

Transition State and MO Calculations. The presence of magnesium ions dramatically improves the reaction rate, regioselectivity, and *syn*-selectivity of nitrile oxide cycloadditions to allylic alcohols. We believe that a chelated transition model **TS-A** or **TS-A'**, where a nitrile oxide and an allylic alcohol coordinate to the magnesium ion, is responsible for the observed high *syn*-selectivities and regioselectivities (Scheme 10). The transition state that contains less steric hindrance from allylic strain between the terminal substituent R^4 and the α-substituent R^1 should be more favored. Thus, the stereoselective formation of *syn*-stereoisomers would arise via the transition state **TS-A**. This chelated transition state explains the observed high regioselectivities as well.

In order to investigate the nature of the magnesium complex in detail, we executed *ab initio* molecular orbital (MO) calculations. Initially, a mono cation complex **C** composed of a formonitrile oxide ligand (HCNO) and an allyl alcohol ligand (CH_2=$CHCH_2OH$) (Scheme 10) was adopted as a simplified model. After optimization, the O–Mg–O angle was estimated to be 180°, indicating that two reacting units, HCNO and CH_2=$CHCH_2OH$ ligands, are located too far to interact with each other. However, complex **C** with only two ligands is not an appropriate candidate for a reactive intermediate in the cycloaddition process. In fact, a tetrahedral or octahedral environment is more plausible for the magnesium complex. We then modified our initial model by adding chloride ion (Cl^-) and THF as presumed ligands (complex **D**, Scheme 10). A Cl^- is likely to coordinate to the magnesium ion of the complex and would arise from the Grignard reagent or magnesium alkoxide chloride employed to generate the nitrile oxides. THF might also serve as a ligand because a THF solution of the Grignard reagent was used. For simplicity of calculation, the THF was replaced with an H_2O molecule, and we optimized the tetrahedral complex **D** (Figure 2). Although this structure may not be the global minimum of the complex, it is good enough for the analysis of the cycloaddition as discussed below.

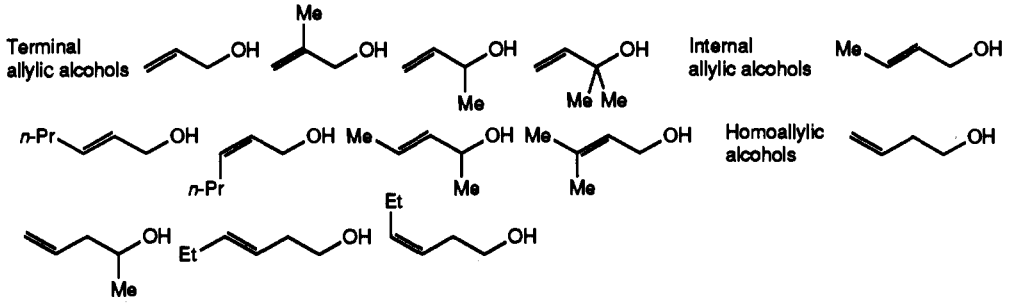
As shown in Figure 2, C(3)–N(2) and N(2)–O(1) lengths of HCNO were estimated to be 1.12 and 1.33 Å, respectively. The Mg(5)–O(6) length was estimated to be 1.84 Å, which was shorter by 0.18 Å than the O(1)–Mg(5) length (2.02 Å). The nitrile oxide unit has a linear structure since the C(3)–N(2)–O(1) angle was 179.4°. The magnesium atom is not located just behind HCNO but at the side of HCNO, since the Mg(5)–O(1)–N(2) angle was estimated to be 118.1°. The dihedral angle of τ-C(11)–C(10)–C(9)–O(6) was estimated to be 122.2°. A view from the top of HCNO shows that all atoms consisting of the reaction centers, C(3) and O(1) in the dipole unit and C(10) and C(11) in the dipolarophile unit, are located almost in the same plane. The C(10)–O(1) and C(11)–C(3) distances in the structure are 3.88 and 6.04 Å, respectively. Thus, the optimized conformation for complex **D** should be advantageous for accelerating cycloaddition between the two reacting ligands, dipole and dipolarophile.

It is interesting to consider the orbital interactions between the two reactive ligands in complex **D**. We call the frontier molecular orbitals (FMOs) in the HCNO unit π_{dipole} and π^*_{dipole} and those in the allyl alcohol unit $\pi_{dipolarophile}$ and $\pi^*_{dipolarophile}$. According to Sustmann's classification,[19] the following two interactions should govern nitrile oxide cycloadditions: one working between π_{dipole} and $\pi^*_{dipolarophile}$ (HO control) and the other between π^*_{dipole} and $\pi_{dipolarophile}$ (LU control). As discussed below, the LU-controlled interaction is calculated to be more important in the nitrile oxide cycloadditions to the magnesium alkoxide of allylic alcohols. The contour maps of $\pi_{dipolarophile}$ and π^*_{dipole} orbitals in complex **D** show that these molecular orbitals of the two reacting units, HCNO and allyl alcohol, involved in complex **D** can interact well with each other to promote the cycloaddition.

Figure 3 summarizes the orbital energy diagram of the related MOs. In order to compare orbital energies in complex **D** with those in the free substrates, energy levels of free HCNO and allyl alcohol are also depicted in the same figure.

(19) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717–2720.

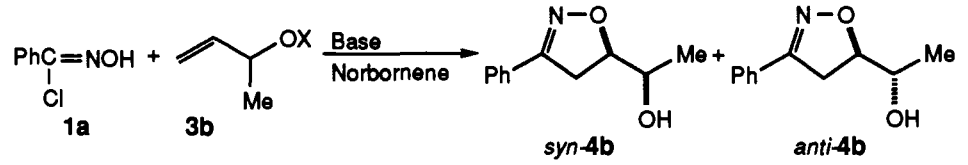
Table 8. Relative Rates in Nitrile Oxide Cycloadditions to Allylic and Homoallylic Alcohol Dipolarophiles TA, IA, and HA[a]



entry	dipolarophile[b]	reaction L[c,d]	reaction M[d,e]	reaction N[d,f]	M/L	N/L
1	norbornene	1	1	1		
			Terminal Allylic Alcohols			
2	2-propen-1-ol	0.064 (1)	0.79	130 (1)	12	2030
3	2-methyl-2-propen-1-ol	0.031 (0.5)	0.42	19 (0.1)	14	610
4	3-buten-2-ol	0.059 (0.9)	0.46	14 (0.1)	8	240
5	2-methyl-3-buten-2-ol	0.048 (0.8)	0.14	3.6 (0.03)	3	75
			Internal Allylic Alcohols			
6	(*E*)-2-buten-1-ol	0.0013 (0.02)	0.014	9 (0.07)	11	6900
7	(*E*)-2-hexen-1-ol	0.0012 (0.02)	0.012	3.8 (0.03)	10	3170
8	(*Z*)-2-hexen-1-ol	0.000 56 (0.009)	0.0063	3 (0.02)	11	5360
9	(*E*)-3-penten-2-ol	0.0009 (0.01)	0.0079	0.76 (0.006)	9	840
10	3-methyl-2-buten-1-ol	0.000 22 (0.003)	0.0013	3.6 (0.03)	6	16 000
			Homoallylic Alcohols			
11	3-buten-1-ol	0.041 (0.6)	0.34	20 (0.2)	8	490
12	4-penten-2-ol	0.034 (0.5)	0.18	1.3 (0.01)	5	40
13	(*E*)-3-hexen-1-ol	0.000 98 (0.02)	0.0072	0.1 (0.0008)	7	100
14	(*Z*)-3-hexen-1-ol	0.000 32 (0.005)	0.0024	0.2 (0.002)	8	625*
			Other Olefins			
15	3-buten-2-one	0.82	0.82		1	
16	methyl acrylate	0.39	0.44		1	
17	3-phenylpropene	0.012	0.018		2	

[a] All reactions were performed in dichloromethane at room temperature using a mixture of two dipolarophiles (each 5 molar amounts). [b] Dipolarophiles were used either in free alcoholic forms (in reactions L and M) or in the forms of magnesium alkoxides (in reaction N). [c] Reaction L: between free nitrile oxide **2a** and free allylic alcohols. [d] The relative rates based on 2-propen-1-ol are shown in parentheses. The relative rates are determined by ^{1}H and/or ^{13}C NMR spectra of the crude reaction mixture. [e] Reaction M: between nitrile oxide complex **Ba** (Mtl = MgBr) and free allylic alcohols. Complex **Ba** was in situ generated from **1a** and EtMgBr so that the solvent system contains some THF (CH_2Cl_2:THF = 40:1 v/v). [f] Reaction N: between free nitrile oxide **2a** and the magnesium alkoxides of allylic alcohols.

Scheme 9



Solvent	X	Base	Relative rate[1]	*syn*-**4b** : *anti*-**4b**
CH_2Cl_2	MgBr	**3b**	14	96 : 4
THF	MgBr	**3b**	0.09	68 : 32
CH_2Cl_2	H	Et_3N	0.059	61 : 39

[1] Relative rate to that of norbornene. Each five equimolar amounts of norbornene and **3b** were used.

The orbital energies of $\pi_{dipolarophile}$ and $\pi^*_{dipolarophile}$ in the free allyl alcohol are calculated to be –0.396 and 0.176 hartree, respectively, and the complex formation raises these energies to –0.349 and 0.188 hartree. In the absence of magnesium ion, the energy gap between π_{dipole} and $\pi^*_{dipolarophile}$ for the HO-controlled interaction is estimated to be 0.552 hartree, while that between π^*_{dipole} and $\pi_{dipolarophile}$ for the LU-controlled interaction is 0.572 hartree. Formation of complex **D** has frontier orbital energies for HCNO lowered by 0.107 and 0.048 hartree for π_{dipole} and π^*_{dipole}, respectively. Change of orbital energies by complex formation causes a great decrease in the energy gap of the LU-controlled interaction from 0.572 to 0.477 hartree. This energy gap is much smaller than that of the HO-controlled interaction (0.671 hartree). As a result, the cycloaddition via complex **D** will be accelerated by the LU-controlled interaction. Formation of the magnesium complex **D** reduces the orbital energy gap and increases the overlap between FMOs, and hence the cycloaddition via the magnesium complex is accelerated compared to the reaction without magnesium. In the LU-controlled cycloadditions (reaction N), more substituted alkene dipolarophiles should show higher acceleration factors. This is the case observed in the reactions of 1,2-disubstituted and 1,1,2-trisubstituted alkenes.

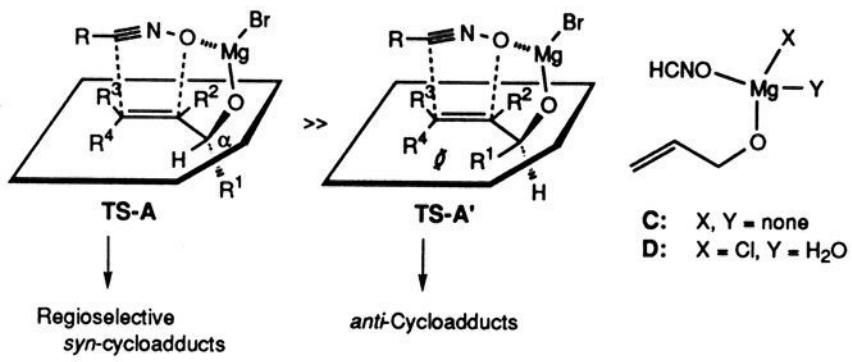
The excellent *syn*-selectivity observed in the cycloadditions of magnesium alkoxides **3** (X = MgBr) prompted us to perform other MO calculations for the two complexes, **E** and **F**, which can be regarded as transition-state models for the formation of *syn*-

Table 9. Effect of Polar Additives on the Relative Rates and Regioselectivities of Nitrile Oxide Cycloadditions to **5a** (X = MgBr)[a]

entry	dipolarophile	additive (equiv to the alkoxide)	relative rate[b]	regioselectivity
1	**5a** (X = MgBr)	none	9	**6a** only
2	**5a** (X = MgBr)	*n*-BuOH (1)	13	**6a** only
3	**5a** (X = MgBr)	*i*-PrOH (1)	19	**6a** only
4	**5a** (X = MgBr)	*t*-BuOH (1)	19	**6a** only
5	**5a** (X = MgBr)	THF (CH_2Cl_2:THF = 10:1 v/v)[c]	1	**6a** only
6	**5a** (X = MgBr)	THF (as solvent)	0.1	**6a** only
7	**5a** (X = H)	none	0.0013	**6a**:**6'a** = 46:54

[a] Benzonitrile oxide (**2a**), generated from **1a** and triethylamine, was allowed to react with a mixture of **5a** (X = MgBr) and norbornene (each 5 molar amounts) in dichloromethane at room temperature. [b] Relative rate to that of norbornene. [c] THF corresponds to about 15 molar amounts to the alkoxide.

Scheme 10



and *anti*-cycloadducts. The optimized geometries and total energies are shown in Figure 4.

The dihedral angle τ-C(11)–C(10)–C(9)–C(12) in **E** was calculated to be 117.6°. Its methyl group C(12) exists out of the plane of the C(10)=C(11) double bond, and the methyl group and vinylic hydrogen at C(10) are far apart, minimizing the steric repulsion between them. On the other hand, in complex **F**, the dihedral angle is estimated at 1.2°. The methyl carbon C(12) is placed almost in the plane of the C(10)=C(11) double bond. This complex **F** contains serious repulsive steric interactions between the methyl group and the vinylic hydrogen because a hydrogen of the methyl group and the vinylic hydrogen are located as close as 2.436 Å. The total energy of **E** and **F** are calculated to be –1127.5520 and –1127.5502 hartrees, respectively. Thus, the complex **E** is more stable by 1.1 kcal/mol than complex **F**. Cycloadditions proceeding through **E** are therefore more favored to give *syn*-adducts stereoselectively than those via **F**.

Levels of stereoselectivity observed in the nitrile oxide cycloadditions to magnesium allylic alkoxides depend upon the nature of the solvent employed. For example, the cycloaddition of the magnesium alkoxide of an α-chiral terminal allylic alcohol **3a** (X = MgBr) in CH_2Cl_2 occurs stereoselectively to give the *syn*-isomer of 5-(1-hydroxypropyl)-2-isoxazoline (Table 2, entry 4, *syn* only). However, the same reaction in THF affords a mixture of *syn*- and *anti*-cycloadducts (Table 1, entry 6, *syn:anti* = 60:40). This diastereomeric ratio is close to that observed in the reaction without magnesium ion (Table 1, entry 1, *syn:anti* = 67:33). Such a dramatic change of stereoselectivity suggests that the effective formation of magnesium complex **D** is quite difficult in THF solution. The magnesium ion would favor coordination to the oxygen atom of THF rather than the oxygen atom of the nitrile oxide.

In order to quantify this solvent effect on the stereoselectivity, we optimized complex **G** (Figure 5) by using *ab initio* MO calculations with the 3-21G* basis sets. This is a model for the magnesium complex, in which HCNO of **D** is replaced with THF. We sought to determine which ligand, THF or HCNO, would coordinate more strongly to magnesium ion by calculating the stabilization energies due to Mg–O bond formation, $\Delta E(X)_{Mg-O}$. This energy can be estimated by the following equation:

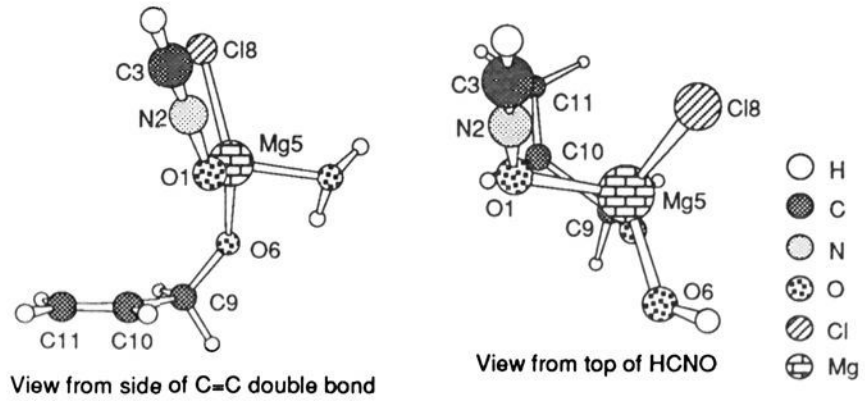


Figure 2. Tetrahedral structure optimized for complex **D**.

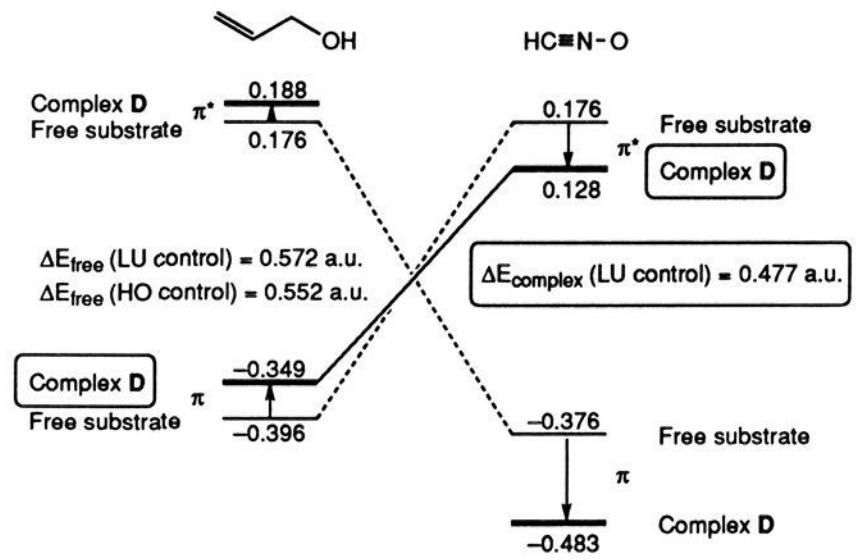


Figure 3. Orbital energies of HCNO and allyl alcohol either in free forms or in magnesium complex **D**.

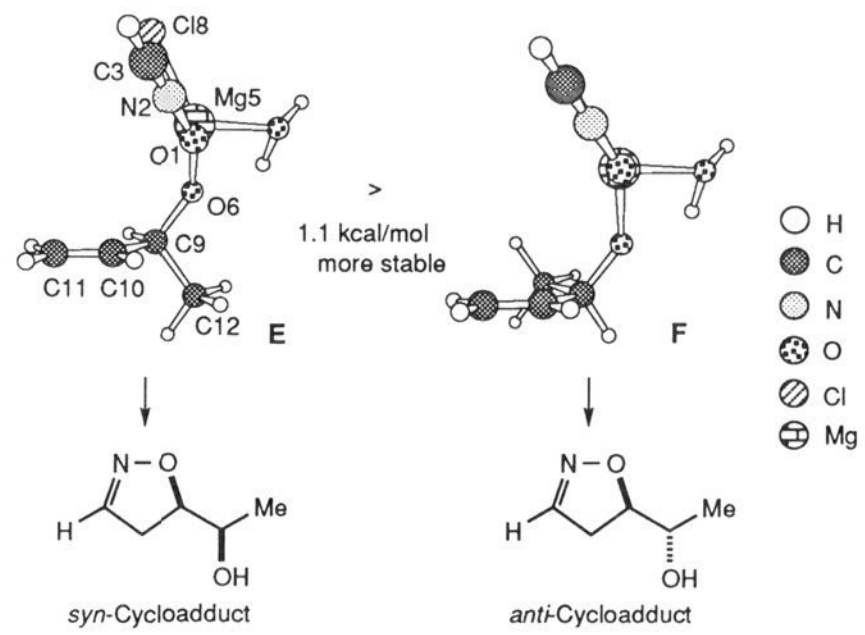


Figure 4. Optimized conformers of methallyl alkoxide complexes **E** and **F**.

$$\Delta E(X)_{Mg-O} = E_Y + E_H - E_X \text{ (X = D or G)}$$

where E_Y is the total energies of H_2O for **G** or HCNO for **D**, and E_H is that of **H**. $\Delta E(D)_{Mg-O}$ and $\Delta E(G)_{Mg-O}$ were calculated to be 44.9 and 48.7 kcal/mol, respectively. This indicates that H_2O coordinates to magnesium ion stronger than HCNO by 3.8 kcal/mol. The magnesium ion forms mostly complex **G**, while very little complex **D** exists in the reaction mixture. Intermolecular cycloaddition of free nitrile oxide to a terminal alkene, such as that of complex **G**, takes place at a high rate. But since **G** imparts no diastereofacial selectivity to the nitrile oxide attack on the C=C double bond, both possible diastereomers for the cycloadduct are formed. Since THF coordinates to magnesium more strongly than H_2O,[20] the above arguments are equally applicable to the reactions when performed in THF.

(20) The stabilization energies of the coordination of H_2O or THF to naked Mg^{2+} were estimated to be 104.9 and 131.5 kcal/mol at the RHF/3-21G level, respectively.

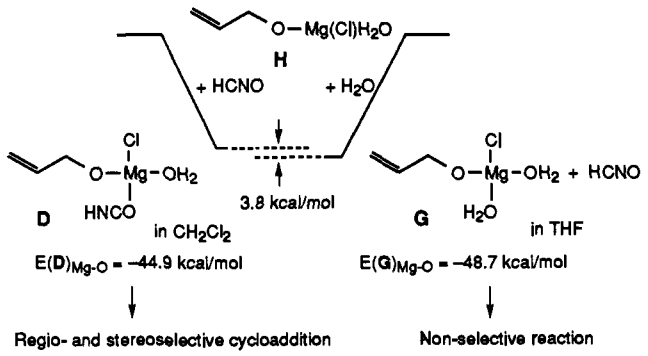


Figure 5. Calculated stabilization energy (3-21G*) by complexation.

While this explains the lack of stereoselectivity toward terminal allyloxymagnesium species in THF, it does not explain why THF has no effect on the regioselectivity of addition to internal allylic alkoxides (Table 4, entries 7, 8). Regioselectivity in THF-free CH_2Cl_2 is governed by geometrical constraints in the nitrile oxide/allyloxymagnesium complex **J** (Figure 6). Even though THF disrupts this complex to form **I**, a small equilibrium concentration of **J** still exists. As the reaction of uncomplexed nitrile oxide with internal alkenes is slow (and coincidentally nonregioselective), the rapid formation of product via **J** is dominant. Thus, regardless of the presence of THF, reaction occurs regioselectively from a nitrile oxide complex.

In conclusion, metal coordination methodology in nitrile oxide cycloadditions to the magnesium alkoxides of allylic and homoallylic dipolarophiles is extremely useful for the stereoselective synthesis of 2-isoxazoline derivatives. Although the question of high magnesium specificity has not been solved so far, the great rate acceleration of dipolar cycloadditions and highly effective stereo- and regiocontrol show synthetic promise. In addition, this novel methodology should be generally applicable to 1,3-dipolar cycloadditions using dipoles other than nitrile oxides, providing a versatile regio- and stereoselective synthetic route to five-membered heterocyclic compounds.[10a,21] Regio- and stereocontrol of nitrone cycloadditions are now under investigation in our laboratory.[19,21]

Experimental Section

General Procedure for the Cycloaddition of Benzonitrile Oxides 2 to Allylic 3, 5 (X = H) or Homoallylic Alcohols 7 (X = H) (Method A). As a typical example, the reaction of **2a** with **5b** (X = H) is described: To a solution of benzohydroximinoyl chloride (**1a**, 0.078 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C under nitrogen triethylamine (70 μL, 0.05 g, 0.5 mmol). After stirring for a few minutes, *trans*-2-hexen-1-ol (**5b**, 59 μL, 0.05 g, 0.5 mmol) was added. The resulting solution was stirred at room tempature for 24 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow residue (0.105 g), which was chromatographed on silica gel with hexane–diethyl ether (1:1 v/v) as an eluent to give a mixture of cycloadducts **6b** and **6'b** (0.048 g, 44%, **6b**:**6'b** = 55:45) as a pale yellow liquid.

General Procedure for the Cycloaddition of Benzonitrile Oxide/Lewis Acid Complexes B to Allylic Alcohols 3, 5 (X = H) (Method B). As a typical example, the reaction of benzonitrile oxide/MgBrCl complex (**Ba**, MtlCl = MgBrCl) with **3a** (X = H) is described: To a solution of benzohydroximinoyl chloride (**1a**, 0.155 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was added at –78 °C under nitrogen EtMgBr (1 M solution in THF, 1 mL, 1 mmol). After stirring at –78 °C for 10 min, 1-penten-3-ol (**3a**, 104 μL, 0.088 g, 1 mmol) was added. The resulting solution was stirred at –78 °C for 10 min and then at –30 °C for 41 h. A similar workup gave a mixture of cycloadducts *syn*-**4a** and *anti*-**4a** (0.12 g, 59%, *syn*-**4a**:*anti*-**4a** = 95:5) as colorless needles.

General Procedure for the Cycloaddition of Benzonitrile Oxides 2 to the Magnesium Alkoxides (X = MgBr) of Allylic 3, 5 or Homoallylic Alcohols 7 (Method C). As a typical example, the reaction of benzohydroximinoyl chloride (**1a**) with the magnesium alkoxide of 1-penten-3-ol (**3a**, X = MgBr, 2 molar amounts) is described: To a solution of 1-penten-3-ol (**3a**, 104 μL, 0.088 g, 1 mmol) in dry CH_2Cl_2 (5 mL) was added at –78 °C under nitrogen EtMgBr (1 M solution in THF, 1 mL, 1 mmol). After stirring for 10 min at –78 °C, a solution of benzohydroximinoyl chloride (**1a**, 0.078 g, 0.5 mmol) in CH_2Cl_2 (5 mL) was added. The resulting solution was stirred at –78 °C for 10 min and at –30 °C for 12 h. A similar workup gave a mixture of cycloadducts *syn*-**4a** and *anti*-**4a** (0.094 g, 92%, *syn*-**4a**:*anti*-**4a** = >99:1) as colorless needles.

General Procedure for the Cycloaddition of Benzonitrile Oxides 2 to Allylic 5 (X = H) or Homoallylic Alcohols 7 (X = H) in the Presence of Butoxymagnesium Bromide (Method E). As a typical example, the reaction of **2a** with **5a** (X = H) in the presence of *n*-BuOMgBr is described: To a solution of butanol (59 μL, 0.048 g, 0.65 mmol) in dry CH_2Cl_2 (5 mL) was added at –78 °C under nitrogen EtMgBr (1 M solution in THF, 0.65 mL, 0.65 mmol). After stirring for 10 min, *trans*-2-buten-3-ol (**5a**, 45 μL, 0.047 g, 0.5 mmol) was added. Benzonitrile oxide (**2a**) in CH_2Cl_2 (5 mL) freshly prepared from benzohydroximinoyl chloride (**1a**, 0.078 g, 0.5 mmol) and triethylamine (70 μL, 0.05 g, 0.5 mmol) followed. The mixture was stirred at room temperature for 1 h. A similar workup gave **6a** (0.083 g, 90%) as a pale yellow liquid.

(5*RS*)-5-[(1*RS*)-1-Hydroxypropyl]-3-phenyl-2-isoxazoline (*syn*-4a): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 81.5 °C; IR (KBr) 3200, 2900, 1440, 1350, and 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.3 Hz, Me of Et), 1.60 (2H, dq, J = 7.3 and 7.1 Hz, CH_2 of Et), 2.55 (1H, br s, OH), 3.24 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 8.4 Hz, one of H-4), 3.36 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 10.6 Hz, the other of H-4), 3.51 (1H, dt, J_{CHCH_2} = 7.1 and J_{CH-5} = 4.4 Hz, 5-CH), 4.66 (1H, ddd, J_{5-4} = 10.6, 8.4, and J_{5-CH} = 4.4 Hz, H-5), and 7.35–7.66 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 10.15 (Me of Et), 26.52 (CH_2 of Et), 37.08 (C-4), 74.34 (5-CH), 83.32 (C-5), 126.69, 128.68, 129.34, 130.13 (each Ph), and 157.12 (C-3). Anal. Found: C, 70.28; H, 7.45; N, 6.55. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82.

(5*RS*)-5-[(1*SR*)-1-Hydroxypropyl]-3-phenyl-2-isoxazoline (*anti*-4a): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 41.5–42.5 °C; IR (KBr) 3350, 2900, 1440, 1350, 900, 750, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.7 Hz, Me of Et), 1.53 (2H, dq, J = 7.7 and 5.1 Hz, CH_2 of Et), 2.37 (1H, br s, OH), 3.20 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 11.0 Hz, one of H-4), 3.41 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 8.8 Hz, the other of H-4), 3.85 (1H, dt, J_{CHCH_2} = 5.1 and J_{CH-5} = 3.3 Hz, 5-CH), 4.67 (1H, ddd, J_{5-4} = 11.0, 8.8, and J_{5-CH} = 3.3 Hz, H-5), 7.35–7.40 (3H, m, Ph), and 7.63–7.67 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 10.15 (Me of Et), 25.70 (CH_2 of Et), 34.41 (C-4), 72.44 (5-CH), 84.23 (C-5), 126.69, 128.68, 129.34, 130.13 (each Ph), and 157.12 (C-3). Anal. Found: C, 70.26; H, 7.26; N, 6.56. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82.

(5*RS*)-5-[(1*RS*)-1-Hydroxyethyl]-3-phenyl-2-isoxazoline (*syn*-4b): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 72–72.5 °C; IR (KBr) 3350, 2850, 1430, 1400, 1350, 1260, 1130, 1060, 1030, 900, 860, 760, 680, 660, 570, and 480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (3H, d, J = 6.6 Hz, Me), 2.49 (1H, br s, OH), 3.17 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 7.7 Hz, one of H-4), 3.34 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 11.0 Hz, the other of H-4), 3.80 (1H, quint, J_{CHMe} = J_{CH-5} = 6.6 Hz, 5-CH), 4.57 (1H, ddd, J_{5-4} = 11.0, 7.7, and J_{5-CH} = 6.6 Hz, H-5), and 7.27–7.65 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.86 (Me), 36.90 (C-4), 69.08 (5-CH), 84.72 (C-5), 126.69, 128.68, 129.27, 130.13 (each Ph), and 157.00 (C-3). Anal. Found: C, 69.35; H, 6.93; N, 7.42. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.

(5*RS*)-5-[(1*SR*)-1-Hydroxyethyl]-3-phenyl-2-isoxazoline (*anti*-4b): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 77–78 °C; IR (KBr) 3300, 2900, 1440, 1360, 1130, 900, 760, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, J = 6.6 Hz, Me), 2.42 (1H, br s, OH), 3.23 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 11.0 Hz, one of H-4), 3.41 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 7.7 Hz, the other of H-4), 4.11 (1H, dq, J_{CHMe} = 6.6 and J_{CH-5} = 3.3 Hz, 5-CH), 4.63 (1H, ddd, J_{5-4} = 11.0, 7.7, and J_{5-CH} = 3.3 Hz, H-5), 7.36–7.41 (3H, m, Ph), and 7.63–7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.30 (Me), 34.44 (C-4), 67.17 (5-CH), 85.20 (C-5), 126.71, 128.71, 129.42, 130.12 (each Ph), and 157.01. Anal. Found: C, 69.18; H, 6.77; N, 7.39. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.

(5*RS*)-5-[(1*RS*)-1-Hydroxybenzyl]-3-phenyl-2-isoxazoline (*syn*-4c): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 153–154 °C; IR (KBr) 3500, 1440, 1360,

(21) Our preliminary work: Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87–90.

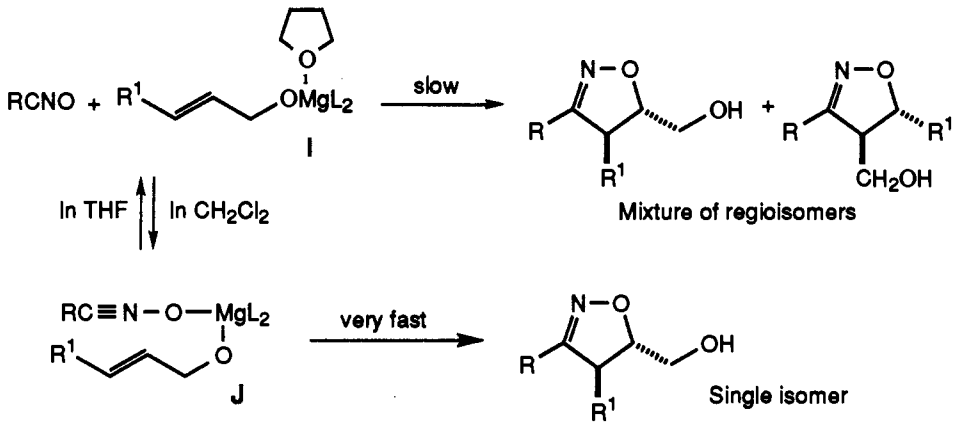


Figure 6. Solvent effect on nitrile oxide cycloaddition to allylic alcohols.

890, 840, 750, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (1H, br s, OH), 3.07 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 7.0 Hz, one of H-4), 3.23 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 10.3 Hz, the other of H-4), 4.63 (1H, d, J_{CH-5} = 7.0 Hz, 5-CH), 4.90 (1H, dt, J_{5-4} = 10.3, 7.0, and J_{5-CH} = 7.0 Hz, H-5), 7.32–7.42 (6H, m, Ph), and 7.59–7.64 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 37.21 (C-4), 75.88 (5-CH), 84.62 (C-5), 126.75, 127.24, 128.53, 128.66, 128.74, 129.10, 130.32, 139.12 (each Ph), and 157.01 (C-3). Anal. Found: C, 75.70; H, 5.99; N, 5.77. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53.

(5*RS*)-5-[(1*SR*)-1-Hydroxybenzyl]-3-phenyl-2-isoxazoline (*anti*-4c): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 155–156 °C; IR (KBr) 3400, 3050, 2900, 1430, 1350, 1060, 940, 880, 840, 740, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.66 (1H, br s, OH), 3.07 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 7.0 Hz, one of H-4), 3.23 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 10.6 Hz, the other of H-4), 4.63 (1H, d, J_{CH-5} = 7.3 Hz, 5-CH), 4.90 (1H, ddd, J_{5-4} = 10.6, 7.0, and J_{5-CH} = 7.3 Hz, H-5), 7.32–7.42 (6H, m, Ph), and 7.59–7.64 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 34.18 (C-4), 72.61 (5-CH), 85.30 (C-5), 125.83, 127.87, 128.64, 128.95, 129.24, 129.30, 130.16, 138.94 (each Ph), and 157.37 (C-3). Anal. Found: C, 75.42; H, 5.97; N, 5.54. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53.

(5*RS*)-5-[(1*RS*)-1-Hydroxyethyl]-3-(*p*-methoxyphenyl)-2-isoxazoline (*syn*-4d): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 116 °C; IR (KBr) 3250, 2880, 1600, 1500, 1450, 1410, 1340, 1290, 1230, 1170, 1110, 890, and 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, d, J = 7.3 Hz, Me of Et), 1.60 (2H, quint, J = 7.3 Hz, CH_2 of Et), 2.70 (1H, br s, OH), 3.21 (1H, dd, J_{gem} = 17.0 and J_{4-5} = 4.0 Hz, one of H-4), 3.32 (1H, dd, J_{gem} = 17.0 and J_{4-5} = 10.6 Hz, the other of H-4), 3.50 (1H, dt, J_{CHCH_2} = 7.3 and J_{CH-5} = 5.1 Hz, 5-CH), 3.80 (3H, s, MeO), 4.61 (1H, ddd, J_{5-4} = 10.6, 4.0, and J_{5-CH} = 5.1 Hz, H-5), and 6.90–7.60 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 10.18 (Me of Et), 26.48 (CH_2 of Et), 37.28 (MeO), 55.30 (C-4), 74.28 (5-CH), 83.06 (C-5), 114.06, 128.22, 156.64 (each Ar), and 161.03 (C-3). Anal. Found: C, 66.43; H, 7.31; N, 5.74. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95.

(5*RS*)-5-[(1*RS*)-1-Hydroxy-2-methylpropyl]-3-phenyl-2-isoxazoline (*syn*-4e): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 111.5–112.5 °C; IR (KBr) 3300, 2900, 1490, 1360, 1060, 920, 750, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, d, J = 7.0 Hz, one Me of *i*-Pr), 1.03 (3H, d, J = 6.6 Hz, the other Me of *i*-Pr), 1.88 (1H, dqq, J = 7.0, 6.6, and 6.6 Hz, CH of *i*-Pr), 2.24 (1H, br s, OH), 3.27 (1H, dd, J = 6.6 and J_{CH-5} = 3.7 Hz, 5-CH), 3.29 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 9.5 Hz, one of H-4), 3.31 (1H, dd, J_{gem} = 16.9 and J_{4-5} = 10.3 Hz, the other of H-4), 4.82 (1H, ddd, J_{5-4} = 10.3, 9.5, and J_{5-CH} = 3.7 Hz, H-5), and 7.34–7.65 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.10, 19.45 (each Me of *i*-Pr), 31.45 (CH of *i*-Pr), 37.57 (C-4), 77.88 (5-CH), 81.58 (C-5), 126.68, 128.68, 129.37, 130.09 (each Ph), and 157.26 (C-3). Anal. Found: C, 71.18; H, 7.84; N, 6.30. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

(5*RS*)-5-[(1*SR*)-1-Hydroxy-2-methylpropyl]-3-phenyl-2-isoxazoline (*anti*-4e): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 64–66 °C; IR (KBr) 3300, 2900, 1440, 1360, 1070, 910, 750, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, d, J = 7.0 Hz, one Me of *i*-Pr), 1.05 (3H, d, J = 7.0 Hz, the other Me of *i*-Pr), 1.77 (1H, dq, J = 7.0 and 6.9 Hz, CH of *i*-Pr), 2.16 (1H, br s, OH), 3.21 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 10.6 Hz, one of H-4), 3.43 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 9.2 Hz, the other of H-4), 3.65 (1H, dd, J = 6.9 and J_{CH-5} = 3.7 Hz, 5-CH), 4.80 (1H, ddd, J_{5-4} = 10.6, 9.2, and J_{5-CH} = 3.7 Hz, H-5), and 7.35–7.67 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.49, 18.86 (each Me of *i*-Pr), 30.52 (CH of *i*-Pr), 34.37 (C-4), 75.79 (5-CH), 82.86 (C-5), 126.68, 128.65, 129.51, 130.06 (each Ph), and 157.39 (C-3). Anal. Found: C, 71.08; H, 7.75; N, 6.19. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

(5*RS*)-5-[(1*RS*)-1-Hydroxypentyl]-5-methyl-3-phenyl-2-isoxazoline (*syn*-4f): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 46 °C; IR (KBr) 3500, 3350, 2950, 2850, 1450, 1360, 920, and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 6.8 Hz, Me of *n*-Bu), 1.20–1.69 (6H, m, CH_2 of *n*-Bu), 1.42 (3H, s, 5-Me), 2.45 (1H, br s, OH), 2.98, 3.36 (each 1H, d, J_{gem} = 16.5 Hz, H-4), 3.59 (1H, dd, J_{CHCH_2} = 8.8 and 2.6 Hz, 5-CH), 7.35–7.40 (3H, m, Ph), and 7.62–7.66 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 14.05, 21.22, 22.66, 28.64, 31.13 (Me and *n*-Bu), 43.24 (C-4), 75.74 (5-CH), 89.60 (C-5), 126.55, 128.64, 129.77, 129.99 (each Ph), and 156.64 (C-3). Anal. Found: C, 72.75; H, 8.71; N, 5.40. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66.

(5*RS*)-5-[(1*SR*)-1-Hydroxypentyl]-5-methyl-3-phenyl-2-isoxazoline (*anti*-4f): colorless liquid from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (KBr) 3400, 2950, 2850, 1450, 1350, 1060, 920, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.1 Hz, Me of *n*-Bu), 1.32–1.59 (6H, m, CH_2 of *n*-Bu), 1.37 (3H, s, 5-Me), 2.34 (1H, br s, OH), 2.84, 3.55 (each 1H, d, J_{gem} = 16.5 Hz, H-4), 3.76 (1H, dd, J_{CHCH_2} = 9.5 and 2.0 Hz, 5-CH), 7.36–7.41 (3H, m, Ph), and 7.63–7.67 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 14.05, 21.22, 22.66, 28.45, 29.69 (Me and *n*-Bu), 40.39 (C-4), 74.57 (5-CH), 90.64 (C-5), 126.55, 128.65, 129.77, 129.99 (each Ph), and 156.91 (C-3). Anal. Found: C, 72.53; H, 8.61; N, 5.51. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66.

***trans*-4-Methyl-3-phenyl-2-isoxazoline-5-methanol (6a):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 1450, 1350, 1080, 890, and 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J_{Me-4} = 7.3 Hz, Me), 2.81 (1H, br s, OH), 3.63 (1H, dq, J_{4-Me} = 7.3 and J_{4-5} = 5.1 Hz, H-4), 3.73 (2H, d, J_{CH_2-5} = 4.0 Hz, CH_2OH), 4.42 (1H, dt, J_{5-4} = 5.1 and J_{5-CH_2} = 4.0 Hz, H-5), 7.37–7.42 (3H, m, Ph), and 7.62–7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.62 (Me), 43.63 (C-4), 63.25 (CH_2OH), 88.69 (C-5), 127.07, 128.43, 128.85, 130.02 (each Ph), and 161.35 (C-3). Anal. Found: C, 69.09; H, 6.90; N, 7.13. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.

***trans*-5-Methyl-3-phenyl-2-isoxazoline-4-methanol (6'a):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 1450, 1350, 1080, 900, and 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J_{Me-5} = 6.4 Hz, 5-Me), 2.48 (1H, br s, OH), 3.47 (1H, ddd, J_{4-CH_2} = 7.3, 4.2, and J_{4-5} = 4.2 Hz, H-4), 3.71 (1H, dd, J_{gem} = 10.6 and J_{CH_2-4} = 7.3 Hz, one of CH_2OH), 3.86 (1H, dd, J_{gem} = 10.6 and J_{CH_2-4} = 4.2 Hz, the other of CH_2OH), 4.85 (1H, dq, J_{5-Me} = 6.4 and J_{5-4} = 4.2 Hz, H-5), 7.27–7.41 (3H, m, Ph), and 7.63–7.71 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 20.94 (Me), 56.95 (C-4), 61.71 (CH_2OH), 81.45 (C-5), 126.89, 128.85, 129.12, 130.10 (each Ph), and 156.51 (C-3). Anal. Found: C, 69.24; H, 7.00; N, 7.16. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.

***trans*-3-Phenyl-4-propyl-2-isoxazoline-5-methanol (6b):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2900, 1440, 1350, 1070, 1040, 890, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.1 Hz, Me of *n*-Pr), 1.37 (2H, quint, CH_2 of *n*-Pr) 1.48–1.75 (2H, m, CH_2 of *n*-Pr), 2.97 (1H, br s, OH), 3.53 (1H, ddd, J_{4-CH_2} = 9.2, 3.3, and J_{4-5} = 4.4 Hz, H-4), 3.62 (1H, dd, J_{gem}

= 12.1 and J_{CH_2-4} = 5.5 Hz, one of CH_2OH), 3.71 (1H, dd, J_{gem} = 12.1 and J_{CH_2-4} = 4.0 Hz, the other of CH_2OH), 4.54 (1H, ddd, J_{5-CH_2} = 5.5, 4.0, and J_{5-4} = 4.4 Hz, H-5), 7.36–7.67 (3H, m, Ph), and 7.56–7.67 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 13.85, 19.94, 33.25 (each *n*-Pr), 48.97 (C-4), 64.10 (*C*H_2OH), 86.53 (C-5), 127.04, 128.81, 128.82, 130.00 (each Ph), and 160.15 (C-3). Anal. Found: C, 71.21; H, 7.86; N, 6.19. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

***trans*-3-Phenyl-5-propyl-2-isoxazoline-4-methanol (6′b):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2900, 1440, 1350, 1040, 890, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz, Me of *n*-Bu), 1.33–1.78 (6H, m, CH_2 of *n*-Bu), 2.22 (1H, br s, OH), 3.50 (1H, dd, J_{gem} = 10.6 and J_{CH_2-4} = 7.3 Hz, one of CH_2OH), 3.73 (1H, ddd, J_{4-CH_2} = 7.3, 4.4, and J_{4-5} = 4.4 Hz, H-4), 3.85 (1H, dd, J_{gem} = 10.6 and J_{CH_2-4} = 4.4 Hz, the other of CH_2OH), 4.72 (1H, ddd, J_{5-CH_2} = 7.3, 5.1, and J_{5-4} = 4.4 Hz, H-5), 7.38–7.41 (3H, m, Ph), and 7.63–7.72 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 13.92, 18.34, 37.25 (each *n*-Pr), 55.33 (C-4), 61.96 (*C*H_2OH), 84.85 (C-5), 126.88, 128.68, 128.85, 129.99 (each Ph), and 156.52 (C-3). Anal. Found: C, 70.92; H, 7.86; N, 6.17. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

***cis*-3-Phenyl-4-propyl-2-isoxazoline-5-methanol (6c):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 2850, 1450, 1350, 1040, 900, 770, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz, Me of *n*-Pr), 1.33 (2H, m, CH_2 of *n*-Pr), 1.46–1.66 (2H, m, CH_2 of *n*-Pr), 2.55 (1H, br s, OH), 3.65 (1H, dt, J_{4-5} = 9.0 and J_{4-CH_2} = 4.0 Hz, H-4), 3.96 (1H, dd, J_{gem} = 12.1 and J_{CH_2-4} = 4.5 Hz, one of CH_2OH), 4.02 (1H, dd, J_{gem} = 12.1 and J_{CH_2-4} = 6.2 Hz, the other of CH_2OH), 4.71 (1H, ddd, J_{5-4} = 9.0 and J_{5-CH_2} = 6.2 and 4.5 Hz, H-5), 7.38–7.45 (3H, m, Ph), and 7.57–7.65 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 14.17, 21.47, 28.47 (each *n*-Pr), 48.09 (C-4), 60.46 (*C*H_2OH), 84.55 (C-5), 127.12, 128.79, 129.20, 130.09 (each Ph), and 161.94 (C-3). Anal. Found: C, 71.17; H, 7.84; N, 6.25. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

***cis*-3-Phenyl-5-propyl-2-isoxazoline-4-methanol (6′c):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3300, 2900, 1440, 1340, 1050, 890, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 7.3 Hz, Me of *n*-Pr), 1.25 (1H, br s, OH), 1.40–2.10 (4H, m, CH_2 of *n*-Pr), 3.61 (1H, ddd, J_{4-5} = 8.8 and J_{4-CH_2} = 5.5 and 3.3 Hz, H-4), 3.81 (1H, dd, J_{gem} = 11.4 and J_{CH_2-4} = 3.3 Hz, one of CH_2OH), 3.89 (1H, dd, J_{gem} = 11.4 and J_{CH_2-4} = 5.5 Hz, the other of CH_2OH), 4.61 (1H, dt, J_{5-4} = 8.8 and J_{5-CH_2} = 5.5 Hz, H-5), 7.38–7.44 (3H, m, Ph), and 7.67–7.76 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 14.12, 20.31, 30.22 (each *n*-Pr), 51.17 (C-4), 58.73 (*C*H_2OH), 84.36 (C-5), 126.96, 128.85, 129.19, 130.13 (each Ph), and 159.04 (C-3). Anal. Found: C, 71.03; H, 7.84; N, 6.32. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

***trans*-3,4-Diphenyl-2-isoxazoline-5-methanol (6d):** colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 93.5–95.5 °C; IR (KBr) 3350, 2900, 1440, 880, 760, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.31 (1H, br s, OH), 3.71 (1H, dd, J_{gem} = 12.5 and J_{CH_2-5} = 4.8 Hz, one of CH_2OH), 3.81 (1H, dd, J_{gem} = 12.5 and J_{CH_2-5} = 3.8 Hz, the other of CH_2OH), 4.55 (1H, ddd, J_{5-4} = 5.9 and J_{5-CH_2} = 4.8 and 3.8 Hz, H-5), 4.70 (1H, d, J_{4-5} = 5.9 Hz, H-4), and 7.16–7.34 (8H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 55.62 (C-4), 62.88 (*C*H_2-OH), 90.58 (C-5), 127.31, 127.54, 127.58, 128.46, 128.52, 129.25, 129.89, 138.97 (each Ph), and 158.74 (C-3). Anal. Found: C, 75.90; H, 6.26; N, 5.28. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53.

***trans*-3,5-Diphenyl-2-isoxazoline-4-methanol (6′d):** colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 122–122.5 °C; IR (KBr) 3500, 3300, 3000, 2850, 1350, 1080, 1060, 1020, 910, 880, 760, 740, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (1H, br s, OH), 3.84 (1H, ddd, J_{5-CH_2} = 6.6, 4.0, and J_{5-4} = 4.4 Hz, H-5), 3.91 (1H, dd, J_{gem} = 10.6 and J_{CH_2-5} = 6.6 Hz, one of CH_2OH), 4.01 (1H, dd, J_{gem} = 10.6 and J_{CH_2-5} = 4.0 Hz, the other of CH_2OH), 5.75 (1H, d, J_{4-5} = 4.4 Hz, H-4), 7.30–7.43 (8H, m, Ph), and 7.67–7.71 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 59.26 (C-4), 61.58 (*C*H_2OH), 85.76 (C-5), 126.99, 127.60, 127.68, 127.99, 128.55, 128.88, 130.19, 141.15 (each Ph), and 156.38 (C-3); Anal. Found: C, 75.53; H, 6.15; N, 5.48. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53.

4,4-Dimethyl-3-phenyl-2-isoxazoline-5-methanol (6e): pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 1460, 1430, 1040, 1000, 900, 770, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31, 1.46 (each 3H, s, Me), 2.20 (1H, br s, OH), 3.80 (1H, dd, J_{gem} = 12.1 and J_{CH_2-5} = 4.0 Hz, one of CH_2OH), 3.87 (1H, dd, J_{gem} = 12.1 and J_{CH_2-5} = 6.6 Hz, the other of CH_2OH), 4.31 (1H, dd, J_{5-CH_2} = 6.6 and 4.0 Hz, H-5), 7.40–7.43 (3H, m, Ph), and 7.59–7.63 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.96, 25.99 (each Me), 50.77 (C-4), 60.99 (*C*H_2OH), 90.55 (C-5), 127.53, 128.64, 128.91, 129.82 (each Ph), and 164.96 (C-3). Anal. Found: C, 70.27; H, 7.51; N, 6.52. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82.

5,5-Dimethyl-3-phenyl-2-isoxazoline-5-methanol (6′e): colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 117–117.5 °C; IR (KBr) 3300, 2950, 1430, 1340, 1270, 1070, 910, 810, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39, 1.60 (each 3H, s, Me), 1.60 (1H, br s, OH), 3.35 (1H, dd, J_{4-CH_2} = 6.2 and 4.0 Hz, H-4), 3.82 (1H, dd, J_{gem} = 11.4 and J_{CH_2-4} = 4.0 Hz, one of CH_2OH), 3.88 (1H, dd, J_{gem} = 11.4 and J_{CH_2-4} = 6.2 Hz, the other of CH_2OH), 7.26–7.43 (3H, m, Ph), and 7.69–7.74 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 20.63, 28.49 (each Me), 56.95 (C-4), 59.57 (*C*H_2OH), 86.64 (C-5), 126.86, 128.85, 129.61, 130.00 (each Ph), and 157.84 (C-3). Anal. Found: C, 70.48; H, 7.34; N, 6.84. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82.

5-(2-Hydroxypropyl)-3-phenyl-2-isoxazoline (8a + 8′a): obtained as an inseparable 1:1 mixture of stereoisomers; colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 76–76.5 °C; IR (KBr) 3350, 2900, 1440, 1360, 1130, 1050, 1020, 910, 890, 870, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3H × 2, d, J = 6.2 Hz, Me), 1.68–1.85 (2H × 2, m, 5-CH_2), 3.03 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 7.0 Hz, one of H-4), 3.05 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 6.6 Hz, the other of H-4), 3.45, 3.49 (each 1H, dd, J_{gem} = 16.5 and J_{4-5} = 3.3 Hz, H-4), 4.04–4.19 (1H × 2, m, C*H*OH), 4.86 (1H × 2, m, H-5), 7.26–7.43 (3H × 2, m, Ph), 7.64–7.69 (2H × 2, m, Ph); ^{13}C NMR ($CDCl_3$) one isomer, δ 23.60 (Me), 40.79 (C-4), 44.05 (5-CH_2), 66.36 (*C*HOH), 78.66 (C-5), 126.69, 128.74, 129.46, 130.18 (each Ph), and 157.01; the other isomer, δ 24.12 (Me), 40.60 (C-4), 44.22 (5-CH_2), 64.94 (*C*HOH), 80.37 (C-5), 126.65, 128.71, 129.63, 130.08 (each Ph), and 156.91 (C-3). Anal. Found: C, 70.11; H, 7.31; N, 6.89. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82.

5-(2-Hydroxy-3-methylbutyl)-3-phenyl-2-isoxazoline (8b + 8′b). 8b: colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 58–58.5 °C; IR (KBr) 3500, 2850, 1430, 1350, 1280, 1010, 890, 840, 780, 750, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, one Me of *i*-Pr), 0.94 (3H, d, J = 6.6 Hz, the other Me of *i*-Pr), 1.58–1.95 (3H, m, 5-CH_2 and CH of *i*-Pr), 2.47 (1H, br s, OH), 3.06 (1H, dd, J_{gem} = 16.7 and J_{4-5} = 8.2 Hz, one of H-4), 3.48 (1H, dd, J_{gem} = 16.7 and J_{4-5} = 10.4 Hz, the other of H-4), 3.74 (1H, m, C*H*OH), 5.01 (1H, ddt, J_{5-4} = 10.4, 8.2 Hz, and J_{5-CH_2} = 4.0 Hz, H-5), 7.38–7.42 (3H, m, Ph), 7.66–7.69 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.23, 18.43 (each Me of *i*-Pr), 34.01 (CH of *i*-Pr), 39.46, 40.57 (C-4 and CH_2), 73.18 (*C*HOH), 78.92 (C-5), 126.57, 128.60, 128.76, 129.94 (each Ph), and 156.97 (C-3). Anal. Found: C, 71.95; H, 8.21; N, 5.90. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. **8′b:** colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 60.5–61.5 °C; IR (KBr) 3400, 2900, 2300, 1440, 1410, 1380, 1350, 900, 750, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (6H, d, J = 7.0 Hz, Me of *i*-Pr), 1.60 (1H, br s, OH), 1.69–1.94 (3H, m, 5-CH_2 and CH of *i*-Pr), 3.08 (1H, dd, J_{gem} = 16.5 and J_{4-5} = 8.1 Hz, one of H-4), 3.48 (1H, dd, J_{gem} = 16.7 and J_{4-5} = 10.3 Hz, the other of H-4), 3.62–3.67 (1H, m, C*H*OH), 4.96 (1H, ddt, J_{5-4} = 10.3, 8.1, and J_{5-CH_2} = 5.9 Hz, H-5), 7.39–7.41 (3H, m, Ph), 7.65–7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.31, 18.28 (each Me of *i*-Pr), 33.75 (CH of *i*-Pr), 38.89, 40.57 (C-4 and CH_2), 74.83 (*C*HOH), 80.84 (C-5), 126.62, 128.63, 129.64, 130.06 (each Ph), and 156.85 (C-3). Anal. Found: C, 72.18; H, 8.31; N, 5.68. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00.

***trans*-4-Ethyl-5-(2-hydroxyethyl)-3-phenyl-2-isoxazoline (10):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 1450, 1350, 1060, 1040, 900, 770, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz, Me of Et), 1.52–2.04 (4H, m, CH_2), 3.32 (1H, dt, J_{4-5} = 8.4 and J_{4-CH_2} = 3.6 Hz, H-4), 3.86 (2H, m, CH_2OH), 4.68 (1H, dt, J_{5-4} = 8.4 and J_{5-CH_2} = 4.2 Hz, H-5), 7.26–7.43 (3H, m, Ph), and 7.67–7.73 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 10.81, 24.16 (each Et), 37.85 (5-CH_2), 54.38 (C-4), 59.70 (*C*H_2OH), 83.90 (C-5), 126.95, 128.81, 129.02, 129.60 (each Ph), and 159.46 (C-3). Anal. Found: C, 70.97; H, 7.90; N, 6.31. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

***trans*-5-Ethyl-4-(2-hydroxyethyl)-3-phenyl-2-isoxazoline (10′):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2920, 1440, 1360, 1040, 890, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, t, J = 7.3 Hz, Me of Et), 1.48–1.84 (4H, m, CH_2), 3.54 (1H, dt, J_{4-5} = 9.5 and J_{4-CH_2} = 3.3 Hz, H-4), 3.69 (2H, m, CH_2OH), 4.47 (1H, dt, J_{5-4} = 9.5 and J_{5-CH_2} = 3.3 Hz, H-5), 7.39–

7.42 (3H, m, Ph), and 7.70–7.73 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 9.42, 27.95 (each Et), 33.99 (4-CH_2), 48.80 (C-4), 60.08 (CH_2OH), 87.92 (C-5), 126.97, 128.84, 129.04, 129.92 (each Ph), and 159.32 (C-3). Anal. Found: C, 70.96; H, 7.91; N, 6.34. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39.

Cycloaddition of 11 Leading to 12 and 13. Method A. To a solution of **1a** (0.078 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C under nitrogen triethylamine (70 μL, 0.05 g, 0.5 mmol). After stirring for a few minutes, 1,5-hexadien-3-ol (**11**, X = H, 236 μL, 2 mmol) was added. The resulting solution was stirred at 0 °C for 3 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow residue (0.139 g), which was then chromatographed through a short column on silica gel with hexane–diethyl ether (1:1 v/v) to give a 67:33 mixture (0.11 g, 100%) of cycloadducts **12** (67:33) and **13** (53:47). **Method C.** To a solution of **11** (118 μL, 1 mmol) in CH_2Cl_2 (5 mL) was added at −78 °C under nitrogen EtMgBr (1 M solution in THF, 1 mL, 1 mmol), and the mixture was stirred at room temperature for 10 min. The THF was removed by evaporation in vacuo and the residual solid was dissolved in dry CH_2Cl_2 (5 mL). A solution of **1a** (0.078 g, 0.5 mmol) in dry CH_2Cl_2 (5 mL) was added, and stirring was continued at 0 °C for 10 min. A similar workup gave **12** (0.1 g, 94%).

5-(1-Hydroxy-3-butenyl)-3-phenyl-2-isoxazoline (12). ***syn*-12:** colorless needles from hexane–Et_2O (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 73.5–74 °C; IR (KBr) 3300, 2900, 1350, 1330, 1060, 940, 900, 750, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90 (1H, br s, OH), 2.34–2.42 (2H, m, $CH_2CH{=}CH_2$), 3.28 (1H, dd, J_{gem} = 16.9 and $J_{4\text{-}5}$ = 8.4 Hz, one of H-4), 3.38 (1H, dd, J_{gem} = 16.9 and $J_{4\text{-}5}$ = 10.6 Hz, the other of H-4), 3.68 (1H, ddd, J_{CHCH_2} = 7.3, 5.9, and $J_{CH\text{-}5}$ = 4.4 Hz, CHOH), 4.70 (1H, ddd, $J_{5\text{-}4}$ = 10.6, 8.4, and $J_{5\text{-}CH}$ = 4.4 Hz, H-5), 5.12–5.22 (2H, m, $=CH_2$), 5.89 (1H, ddt, J_{trans} = 17.2, J_{cis} = 10.3, and J_{CHCH_2} = 3.3 Hz, =CH), 7.36–7.41 (3H, m, Ph), and 7.63–7.66 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 37.05, 38.13 (C-4 and CH_2), 72.25 (5-CH), 82.79 (C-5), 118.20, 126.71, 128.70, 129.24, 130.18, 133.93 (Ph and olefinic C), and 157.12 (C-3). Anal. Found: C, 72.01; H, 7.13; N, 6.21. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. ***anti*-12:** colorless liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); ^{1}H NMR ($CDCl_3$) δ 2.27 (1H, br s, OH), 2.34–2.42 (2H, m, $CH_2CH{=}CH_2$), 3.26 (1H, dd, J_{gem} = 16.5 and $J_{4\text{-}5}$ = 11.0 Hz, one of H-4), 3.44 (1H, dd, J_{gem} = 16.5 and $J_{4\text{-}5}$ = 8.4 Hz, the other of H-4), 3.96 (1H, ddd, J_{CHCH_2} = 7.7, 5.5, and $J_{CH\text{-}5}$ = 4.0 Hz, CHOH), 4.67 (1H, ddd, $J_{5\text{-}4}$ = 11.0, 8.4, and $J_{5\text{-}CH}$ = 4.0 Hz, H-5), 5.12–5.22 (2H, m, $=CH_2$), 5.89 (1H, ddt, J_{trans} = 17.2, J_{cis} = 10.3, and J_{CHCH_2} = 3.3 Hz, =CH), 7.36–7.41 (3H, m, Ph), and 7.63–7.66 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 34.89, 37.55 (C-4 and CH_2), 70.45 (5-CH), 83.68 (C-5), 118.31, 126.71, 128.69, 129.38, 130.12, 133.76 (Ph and olefinic C), and 156.93 (C-3). Anal. Found: C, 71.80; H, 6.89; N, 6.33. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45.

5-(2-Hydroxy-3-butenyl)-3-phenyl-2-isoxazoline (13): obtained as a 51:49 inseparable mixture (by ^{13}C NMR) of two stereoisomers; colorless solid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); mp 98–100 °C; IR (neat) 3300, 1400, 1350, 1120, 980, 920, 880, 810, 750, 680, 660, and 620 cm^{-1}; ^{1}H NMR ($CDCl_3$) is not given because all signals are overlapping to each other; ^{13}C NMR ($CDCl_3$) one isomer, δ 40.65, 42.26 (C-4 and 5-CH_2), 69.85 (CHOH), 78.27 (C-5), 114.74, 126.69, 128.71, 129.50, 130.15, 140.59 (Ph and olefinic C), and 156.94 (C-3); the other isomer, δ 40.68, 42.10 (C-4 and 5-CH_2), 71.03 (CHOH), 79.46 (C-5), 115.40, 126.69, 128.71, 129.57, 130.10, 140.07 (Ph and olefinic C), and 156.88 (C-3). Anal. Found: C, 71.91; H, 7.02; N, 6.40. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45.

Cycloaddition of 14 Leading to 15 and 16. Method A. To a solution of **1a** (0.078 g, 0.5 mmol) in dry CH_2Cl_2 (5 mL) was added at 0 °C under nitrogen triethylamine (70 μL, 0.05 g, 0.5 mmol). After stirring for a few minutes, (*E*)-3-penten-2-ol (**14**, X = H, 51 μL, 0.5 mmol) was added. The resulting solution was stirred at room temperature for 14 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow residue (0.091 g), which was then chromatographed through a short column on silica gel with hexane–diethyl ether (1:1 v/v) to give an 82:18 mixture of regioisomeric cycloadducts **15** and **16** (0.029 g, 28%; **15**, 55:27; **16**, 12:6). **Method C.** To a solution of **14** (102 μL, 1 mmol) in dry CH_2Cl_2 (5 mL) was added at −78 °C under nitrogen EtMgBr (1 M solution in THF, 1 mL, 1 mmol). After stirring for 10 min, **1a** (0.078 g, 0.5 mmol) in dry CH_2Cl_2 (5 mL) was added. Stirring was continued at −78 °C for 10 min and at room temperature for 1 h. A similar workup gave cycloadduct **15** (94:6, 0.054 g, 53%).

(4*RS*,5*RS*)-5-[(1*RS*)-1-Hydroxyethyl]-4-methyl-3-phenyl-2-isoxazoline (*trans,syn*-15): pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2900, 1450, 1380, 1350, 1080, 900, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, d, J_{MeCH} = 6.2 Hz, CH*Me*), 1.34 (3H, d, $J_{Me\text{-}4}$ = 7.3 Hz, 4-Me), 2.53 (1H, br s, OH), 3.54 (1H, dq, $J_{4\text{-}Me}$ = 7.3 and $J_{4\text{-}5}$ = 4.8 Hz, H-4), 3.76 (1H, quint, J_{CHMe} = $J_{CH\text{-}5}$ = 6.2 Hz, CHOH), 4.14 (1H, dd, $J_{5\text{-}CH}$ = 6.2 and $J_{5\text{-}4}$ = 4.8 Hz, H-5), 7.38–7.42 (3H, m, Ph), and 7.64–7.69 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 18.01, 18.37 (each Me), 44.09 (C-4), 68.38 (5-CH), 92.32 (C-5), 127.05, 128.39, 128.82, 130.08 (each Ph), and 161.18 (C-3). Anal. Found: C, 70.18; H, 7.39; N, 6.72. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82.

(4*RS*,5*RS*)-5-[(1*SR*)-1-Hydroxyethyl]-4-methyl-3-phenyl-2-isoxazoline (*trans,anti*-15): pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2900, 1450, 1380, 1350, 1080, 900, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, J_{MeCH} = 6.6 Hz, CH*Me*), 1.34 (3H, d, $J_{Me\text{-}4}$ = 7.3 Hz, 4-Me), 1.98 (1H, br s, OH), 3.81 (1H, dq, $J_{4\text{-}Me}$ = 7.3 and $J_{4\text{-}5}$ = 5.9 Hz, H-4), 4.03 (1H, dq, J_{CHMe} = 6.6 and $J_{CH\text{-}5}$ = 4.0 Hz, CHOH), 4.22 (1H, dd, $J_{5\text{-}4}$ = 5.9 and $J_{5\text{-}CH}$ = 4.0 Hz, H-5), 7.39–7.43 (3H, m, Ph), and 7.65–7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.74, 18.72 (each Me), 41.94 (C-4), 67.60 (5-CH), 92.45 (C-5), 126.99, 127.63, 128.78, 129.96 (each Ph), and 161.15 (C-3). Anal. Found: C, 69.92; H, 7.50; N, 6.61. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Formation of **16** was confirmed on the basis of the ^{13}C NMR spectrum for the mixture with **15**: ^{13}C NMR ($CDCl_3$) major isomer, δ 19.90, 21.87 (each Me), 60.82 (C-4), 65.99 (4-CH), 78.47 (C-5), 127.37, 128.69, 129.21, 130.94 (each Ph), and 156.60 (C-3); minor isomer, δ 19.76, 20.91 (each Me), 61.42 (C-4), 65.86 (4-CH), 78.69 (C-5), 126.88, 128.56, 129.45, 130.94 (each Ph), and 156.60 (C-3).

Cycloaddition of 18 Leading to 19 and Isomers. Method A. To a solution of **1a** (0.156 g, 1 mmol) in dry CH_2Cl_2 (15 mL) was added at 0 °C under nitrogen triethylamine (140 μL, 1 mmol). After stirring for a few minutes, (*E*)-3,7-dimethyl-2,6-octadien-1-ol (**18**, 868 μL, 5 mmol) was added. The resulting solution was stirred at room temperature for 29 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow residue (0.969 g), which was then chromatographed through a short column on silica gel with hexane–diethyl ether (2:1 v/v) to give a 40:33:27 mixture of three isomers of **19** (0.183 g, 67%). **Method E.** To a solution of **1a** (0.078 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) were added at −78 °C under nitrogen butanol (59 μL, 0.65 mmol) and EtMgBr (1 M solution in THF, 0.65 mL, 0.65 mmol). After stirring for 10 min, triethylamine (70 μL, 0.5 mmol) was added. (*E*)-3,7-Dimethyl-2,6-octadien-1-ol (**18**, 87 μL, 0.5 mmol) was added at −78 °C, and stirring was continued at room temperature for 2.5 h. A similar workup gave **19** (0.036 g, 26%).

4-Methyl-4-(4-methyl-3-pentenyl)-3-phenyl-2-isoxazoline-5-methanol (19): pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2900, 1460, 1370, 1030, 900, 770, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, s, 4-Me), 1.52, 1.65 (each 3H, s, $=CMe_2$), 1.68–1.78 (2H, m, one CH_2 of 4-CH_2), 2.01–2.20 (2H, m, the other CH_2 of 4-CH_2), 3.76 (1H, dd, J_{gem} = 12.1 and $J_{CH_2\text{-}5}$ = 4.0 Hz, one of CH_2OH), 3.82 (1H, dd, J_{gem} = 12.1 and $J_{CH_2\text{-}5}$ = 6.2 Hz, the other of CH_2OH), 4.51 (1H, dd, $J_{5\text{-}CH_2}$ = 6.2 and 4.0 Hz, H-5), 5.04 (1H, t, J = 1.5 Hz, =CH), 7.37–7.42 (3H, m, Ph), and 7.58–7.62 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.64, 17.91, 23.05 (each Me), 27.64, 39.50 (each CH_2), 54.54 (C-4), 61.74 (CH_2OH), 88.08 (C-5), 122.99, 127.47, 128.66, 129.34, 129.76, 132.59 (Ph and olefinic C), and 163.19 (C-3). Anal. Found: C, 74.21; H, 8.48; N, 4.93. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12.

5-Methyl-5-(4-methyl-3-pentenyl)-3-phenyl-2-isoxazoline-4-methanol (Regioisomer of **19**): pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3300, 2900, 1440, 1340, 1070, 920, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (6H, s, 5-Me and one of Me_2C=), 1.64 (3H, d, J_{MeCH} = 1.5 Hz, the other of Me_2C=), 2.02 (1H, br s, OH), 2.02–2.13 (4H, m, CH_2), 3.44 (1H, dd, $J_{4\text{-}CH_2}$ = 6.4 and 3.9 Hz, H-4), 3.80 (1H, dd, J_{gem} = 11.5 and $J_{CH_2\text{-}4}$ = 3.9 Hz, one of CH_2OH), 3.86 (1H, dd, J_{gem} = 11.5 and $J_{CH_2\text{-}4}$ = 6.4 Hz, the other of CH_2OH), 7.37–7.40 (3H, m, Ph), and 7.69–7.71 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.65, 18.65, 22.45 (each Me), 25.63, 41.37 (each CH_2), 55.77 (C-4), 59.41 (CH_2OH), 88.94 (C-5), 123.71, 126.86, 128.82, 129.60, 129.92, 132.05 (Ph and olefinic C), and 157.78 (C-3). Anal. Found: C, 74.18; H, 8.44; N, 5.12. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. The other two isomers of **19** were obtained as a 55:45 inseparable mixture: pale yellow liquid (silica gel column chromatography,

hexane–Et_2O, 1:1 v/v); ^{13}C NMR ($CDCl_3$) one isomer, δ 16.26, 20.69, 25.92 (each Me), 28.54, 39.74 (each CH_2), 53.59 (C-4), 59.11 (CH_2-OH), 86.84 (C-5), 124.37, 126.86, 128.76, 129.78, 130.05, 138.09 (Ph and olefinic C), and 161.02 (C-3); the other isomer, δ 16.11, 22.26, 25.77 (each Me), 36.83, 39.54 (each CH_2), 45.08 (C-4), 59.21 (CH_2OH), 87.25 (C-5), 126.43, 126.86, 128.65, 128.76, 130.18, 138.84 (Ph and olefinic C), and 156.08 (C-3). Anal. Found: C, 74.24; H, 8.45; N, 4.99. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12.

Cycloaddition of 20 Leading to 21 and Isomers. Method A. To a solution of **1a** (0.156 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C under nitrogen triethylamine (140 μL, 1 mmol). After stirring for a few minutes, (*E,E*)-2,4-hexadien-1-ol (**20**, 115 μL, 1 mmol) was added. The resulting solution was stirred at room temperature for 16 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a pale yellow residue (0.257 g), which was then chromatographed through a short column on silica gel with hexane–diethyl ether (1:1 v/v) to give a 7:42:44:7 mixture of **21** and its three isomers (0.257 g, 67%). **Method E.** To a solution of **1a** (0.078 g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) were added at −78 °C under nitrogen butanol (59 μL, 0.65 mmol) and EtMgBr (1 M solution in THF, 0.65 mL, 0.65 mmol). After stirring for 10 min, triethylamine (70 μL, 0.5 mmol) was added. (*E,E*)-2,4-Hexadien-1-ol (**20**, 58 μL, 0.5 mmol) was added at −78 °C, and stirring was continued at room temperature for 2.5 h. A similar workup gave **21** (0.092 g, 88%).

***trans*-3-Phenyl-4-[1-(*E*)-propenyl]-2-isoxazoline-5-methanol (21):** pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 1450, 1350, 1080, 1040, 970, 910, 890, 770, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (3H, dd, J_{MeCH} = 6.2 and J_{MeCH} = 1.5 Hz, Me), 2.73 (1H, br s, OH), 3.66 (1H, dd, J_{gem} = 12.2 and $J_{CH_2\text{-}5}$ = 4.8 Hz, one of CH_2OH), 3.81 (1H, dd, J_{gem} = 12.2 and $J_{CH_2\text{-}5}$ = 3.7 Hz, the other of CH_2OH), 4.17 (1H, dd, $J_{4\text{-}CH}$ = 8.8 and $J_{4\text{-}5}$ = 6.6 Hz, H-4), 4.46 (1H, ddd, $J_{5\text{-}4}$ = 6.6, $J_{5\text{-}CH_2}$ = 4.8, and 3.7 Hz, H-5), 5.49 (1H, ddq, J_{trans} = 15.4, $J_{CH\text{-}4}$ = 8.8, and J_{CHMe} = 1.5 Hz, 4-CH=), and 5.71 (1H, dq, J_{trans} = 15.4 and J_{CHMe} = 6.2 Hz, =CHMe); ^{13}C NMR ($CDCl_3$) δ 17.90 (Me), 52.58 (C-4), 62.56 (CH_2OH), 87.86 (C-5), 127.28, 127.73, 128.53, 129.02, 129.90, 130.10 (Ph and olefinic C), and 158.54 (C-3). Anal. Found: C, 71.98; H, 7.01; N, 6.43. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45.

***trans*-3-Phenyl-5-[1-(*E*)-propenyl]-2-isoxazoline-4-methanol** (Regioisomer of **21**): pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2900, 1450, 1360, 1060, 970, 890, 850, 770, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (3H, dd, J_{MeCH} = 6.6 and J_{MeCH} = 1.4 Hz, Me), 1.90 (1H, br s, OH), 3.60 (1H, dt, $J_{4\text{-}CH_2}$ = 6.2, 5.0, and $J_{4\text{-}5}$ = 5.0 Hz, H-4), 3.80 (1H, dd, J_{gem} = 11.0 and $J_{CH_2\text{-}4}$ = 6.2 Hz, one of CH_2OH), 3.86 (1H, dd, J_{gem} = 11.0 and $J_{CH_2\text{-}4}$ = 5.0 Hz, the other of CH_2OH), 5.09 (1H, dd, $J_{5\text{-}CH}$ = 7.5 and $J_{5\text{-}4}$ = 5.0 Hz, H-5), 5.59 (1H, ddq, J_{trans} = 15.2, $J_{CH\text{-}5}$ = 7.5, and J_{CHMe} = 1.4 Hz, 5-CH=), and 5.85 (1H, dq, J_{trans} = 15.2 and J_{CHMe} = 6.6 Hz, =CHMe), 7.39–7.41 (3H, m, Ph), and 7.67–7.70 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.70 (Me), 56.01 (C-4), 61.51 (CH_2OH), 85.35 (C-5), 126.92, 128.88, 129.05, 129.70, 129.99, 130.06 (Ph and olefinic C), and 156.55 (C-3). Anal. Found: C, 71.45; H, 6.91; N, 6.38. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. The other two isomers of **21** were obtained as an 86:14 inseparable mixture: pale yellow liquid (silica gel column chromatography, hexane–Et_2O, 1:1 v/v); IR (neat) 3400, 2950, 2900, 2850, 1440, 1380, 1350, 1080, 1100, 970, 880, 760, and 690 cm^{-1}; ^{13}C NMR ($CDCl_3$) one isomer, δ 17.21 (Me), 47.96 (C-4), 62.45 (CH_2OH), 88.59 (C-5), 127.01, 127.41, 128.15, 128.81, 129.97, 132.74 (Ph and olefinic C), and 160.61 (C-3); the other isomer, δ 19.71 (Me), 52.04 (C-4), 62.68 (CH_2OH), 83.83 (C-5), 127.09, 127.83, 128.26, 128.64, 129.87, 133.30 (Ph and olefinic C), and 160.61 (C-3). Anal. Found: C, 71.28; H, 6.96; N, 6.34. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45.

Method of Calculations. The *ab initio* MO calculations were performed using the GAUSSIAN 86 program[22] at the Institute for Molecular Science and the GAUSSIAN 90 program for the Fujitsu S4/1 (SUN/SPARCstation) computer.[23] Molecular geometries of reactive intermediates were optimized by use of the energy gradient method. We used the 3-21G* basis set,[24] which includes the d-orbital on Mg.

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