Lewis Acid Coordinated Nitrile Oxide and Nitrile Imine 1,3-Dipoles. *syn*-Selective Cycloadditions to 2-(1-Hydroxyalkyl)acrylates

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Treatment of carbohydroximoyl chlorides with organometallics or carbohydrazonoyl chlorides with metal alkoxides or amides offers a new generation of Lewis acid-coordinated nitrile oxide and nitrile imine 1,3-dipoles, respectively. These 1,3-dipole/Lewis acid complexes undergo *syn*-selective cycloaddition reactions to 2-(1-hydroxyalkyl)acrylates through a chelated transition state, while free dipoles show *anti*-selectivities.

Nitrile oxides and nitrile imines, especially the formers, are one of the most widely utilized 1,3-dipoles in organic synthesis since the cycloadducts produced through their cycloadditions have high synthetic potentials as functionalized heterocycles.[1,2] The general method of generating such 1,3-dipoles consists of the treatment of precursor chlorides such as carbohydroximoyl and carbohydrazonoyl chlorides with tertiary amine bases such as triethylamine.[3,4] Such in situ generated 1,3-dipoles show high reactivities toward olefinic dipolarophiles having either electron-withdrawing and -donating substituents to offer a convenient route to 2-isoxazoline and pyrazoline heterocycles.

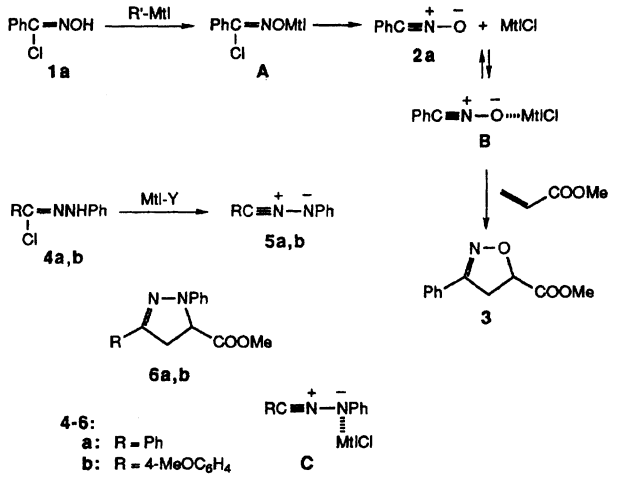
In the course of our study on the chelation-mediated stero- and regiocontrol of 1,3-dipolar cycloadditions we needed an effective entry to the facile generation of 1,3-dipole/Lewis acid complexes. The conventional generation method always provides the 1,3-dipoles accompanied by undesired triethylammonium chloride. Our idea for the new generation of 1,3-dipole/Lewis acid complexes is based on the direct treatment of precursors with organometallics. For example, *O*-metalation of a carbohydroximoyl chloride with an organomagnesium chloride would spontaneously undergo 1,3-elimination of magnesium chloride to generate the corresponding nitrile oxide. Thus formed dipole and Lewis acid should combine each other to give the nitrile oxide/magnesium chloride complex.[5]

The present paper reports a new generation of Lewis acid-coordinated nitrile oxide and nitrile imine 1,3-dipoles by treatment of carbohydroximoyl chlorides with organometallics or carbohydrazonoyl chlorides with metal alkoxides or amides, respectively. These 1,3-dipole/Lewis acid complexes undergo *syn*-selective cycloaddition reactions to 2-(1-hydroxyalkyl)acrylates through a chelated transition state, while free dipoles show *anti*-selectivities.[6]

Results and Discussion

Treatment of benzohydroximoyl chloride (**1a**) with butyllithium, ethylmagnesium bromide, or diethylzinc at −30 to −50 °C in tetrahydrofuran (THF), followed by reaction with methyl acrylate as acceptor molecule, gave methyl 3-phenyl-2-isoxazoline-5-carboxylate (**3**) in good yields, indicating the successful generation of benzonitrile oxide (**2a**) (Scheme 1 and Table 1, Entries 2—4). No formation of ketone oximes as undesired nucleophilic substitution products to **1a** or nucleophilic addition products to **2a** was observed.[7] The first step involved in this new nitrile oxide generation is the *O*-metalation of highly acidic oxime proton to form the metalated carbohydroximoyl chloride intermediate **A** which then undergoes smooth 1,3-elimination of the corresponding metal chloride MtlCl to generate **2a**. Half an equimolar amount of diethylzinc was sufficient (Entry 5). Thus, ethylzinc chloride which is the elimination product in the first generation of **2a** can further react with **1a** to generate the second molecule of **2a**.

Metal chloride MtlCl, produced together with nitrile oxide **2a** in the elimination step, is a Lewis acid. Immediately after the metal chloride is liberated, it should combine with nitrile oxide **2a** which is a strong Lewis base to form the nitrile oxide/Lewis acid complex **B**.[5,7] In the nitrile oxide cycloadditions to electron-deficient dipolarophiles, it is believed that the highest occupied molecular orbital (HOMO) of nitrile oxide interacts with the lowest unoccupied molecular orbital (LUMO) of dipolarophile.[8] Accordingly, deactivation of nitrile



Scheme 1.

Table 1. Generation of Nitrile Oxide **2a** and Nitrile Imines **5a,b** from Carbohydroximoyl Chloride **1a** and Carbohydrazonoyl Chlorides **4a,b** and Subsequent Trapping with Methyl Acrylate[a)]

Entry	Precursor	R	Base[b)]	Equiv	Dipole	Temp/°C	Time/h	Product	Yield/%[c)]
1	**1a**	Ph	Et_3N	1	**2a**	−30	7	**3**	94
2			*n*-BuLi	1		−50	61		89
3			EtMgBr	1		−30	39		90
4			Et_2Zn	1		−30	15		94
5			Et_2Zn	0.5		−30	48		91
6	**4a**	Ph	Et_3N	1	**5a**	R.T.	3	**6a**	97
7			LDA	1		R.T.	2		57
8			$(i\text{-Pr})_2NMgBr$	1		R.T.	2		89
9	**4b**	4-$MeOC_6H_4$	LDA	1	**5b**	−50	3	**6b**	63
10			EtOLi	1		−50	20		83
11			$(i\text{-Pr})_2NMgBr$	1		R.T.	2		98
12			EtOMgBr	1		R.T.	24		29

a) All reactions were performed in THF with methyl acrylate (equimol.). b) A precursor was treated with a base at −78 °C, methyl acrylate was added, and then the reaction was continued under the reaction conditions shown in Table. c) Isolated yield.

oxide **2a** would occur by the formation of Lewis acid complex **B**. The LiCl complex **B** (Mtl=Li) may be scarcely deactivated because LiCl is a weak Lewis acid, while the MgBrCl complex **B** (Mtl=MgBr) should be extremely deactivated. However, this complex **B** (Mtl=MgBr) showed sufficient reactivity toward methyl acrylate to give the corresponding cycloadduct in an excellent yield (Entry 3). Use of alkylaluminum chlorides such as diethylaluminum chloride and ethylaluminum dichloride led to either failure of generating nitrile oxide **2a** or some depressed reactivity of the nitrile oxide/aluminum Lewis acid complexes.

It should be emphasized that the clean and high yield formation of cycloadduct **3** in the reaction of nitrile oxide/Lewis acid complex **B** compensates for the decreased reactivity of dipole, no dimeric product, 3,4-diphenyl-2,1,5-oxadiazol 1-oxide in the case of **2a**, being even detected. This makes a striking contrast to the fact that nitrile oxide **2a** undergoes ready dimerization when it is generated by the usual method using triethylamine and when no acceptor molecule is present or acceptor molecules are poor in reactivity.[9)] However, nitrile oxide/Lewis acid complexes **B** are stable under the reaction conditions and they slowly react with acceptor molecules.

The above *O*-metalation/1,3-elimination procedure as a new nitrile oxide generation method can be applied with a minor revision to generating nitrile imine 1,3-dipoles from carbohydrazonoyl chloride precursors. Treatment of *N*-phenylbenzohydrazonoyl chloride (**4a**) with organometallics such as butyllithium, ethylmagnesium bromide, and diethylzinc failed to generate benzonitrile *N*-phenylimine (**5a**). Formation of complex mixture of many products resulted, in which the alkylation product of **4a** was contained. Presumably, *N*-metalation of carbohydrazonoyl chloride **4a** may be more difficult than the *O*-metalation of carbohydroximoyl chloride **1a**.[10)] The organometallic nucleophile still remains unreacted when some part of nitrile imine **5a** has been generated so that they get a chance to react with each other giving the alkylated products.

Such difficulty was solved by use of metal alkoxides or amides instead of organometallics. For example, lithium diisopropylamide (LDA, Entries 7 and 9), magnesium bromide diisopropylamide (Entries 8 and 11), and magnesium bromide ethoxide (Entry 12) worked well. The nitrile imines **5a,b** generated from **4a,b** were trapped with methyl acrylate to give cycloadducts **6a,b** (Scheme 1).

When a chiral center substituted by a hydroxyl group is introduced to the acrylate skeleton, this hetero substituent will coordinate to the metal atom of complex **B** in the transition state of nitrile oxide cycloaddition. Accordingly, high diastereofacial selection is expected in the reactions of the nitrile oxide/Lewis acid complex **B**. Methyl 2-(1-hydroxyalkyl)acrylates **7** were the electron-deficient olefinic dipolarophiles of our choice.

Reaction of the benzonitrile oxide **2a**, generated from **1a** and triethylamine, with methyl 2-(1-hydroxyethyl)acrylate (**7a**) in dichloromethane at −30 °C gave a 70:30 mixture of diastereomers of cycloadduct **8a** (Scheme 2 and Table 2, Entry 1). The major and minor diastereomers were determined to be *anti*-**8a** and *syn*-**8a**, respectively, on the basis of chemical conversions and ^1H NMR analysis. This will be described below. Such *anti*-selectivity observed in the reaction of **2a** to **7a** is opposite to the *syn*-selectivity usually observed in nitrile oxide cycloadditions to 1-chiral allylic alcohols.[11)]

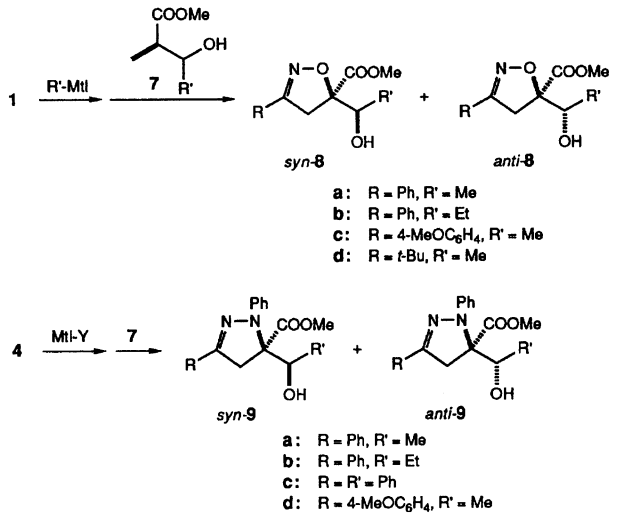
When nitrile oxide/LiCl complex **B** (Mtl=Li) was employed instead of free **2a**, the *anti*-selectivity was lowered (Entry 2). And, the reversal of selectivity took place by use of magnesium and zinc complexes **B** (Mtl=MgBr and Mtl=EtZn and/or ZnCl) to provide *syn*-selective cycloadducts *syn*-**8a** (Entries 3 and 5). It is no doubt that the chelate formation in the transition state is responsible for such *syn*-selectivity.

The best *syn*-selectivity of 92:8 was observed when two molar amounts of the magnesium alkoxide derived

Table 2. Reactions of Nitrile Oxides **2a**—**c** with Methyl 2-(1-Hydroxyalkyl)acrylates **7a**,**b**

Entry	Dipole	R	Base[a]	Dipolarophile	R′	Solvent[b]	Method[c]	Temp/°C	Time/h	Product	Yield/%[d]	*syn*:*anti*[e]
1	**2a**	Ph	Et_3N	**7a**	Me	DCM	A	−30	12	**8a**	90	30:70
2	**2a**		*n*-BuLi	**7a**		DCM	B	−30	13	**8a**	78	47:53
3	**2a**		Et_2Zn	**7a**		DCM	B	−30	12	**8a**	92	74:26
4	**2a**		$EtAlCl_2$	**7a**		DCM	A	R.T.	24	**8a**	Trace	—
5	**2a**		EtMgBr	**7a**		DCM	B	−30	21	**8a**	86	81:19
6	**2a**		EtMgBr	**7a**		DCM	C	−30	21	**8a**	100	92:8
7	**2a**		EtMgBr	**7a**		DCM	C	R.T.	1	**8a**	100	89:11
8	**2a**		EtMgBr	**7a**		THF	B	−30	24	**8a**	93	63:37
9	**2a**		Et_3N	**7b**	Et	DCM	A	−30	18	**8b**	87	24:76
10	**2a**		EtMgBr	**7b**		DCM	B	−30	16	**8b**	81	86:14
11	**2a**		EtMgBr	**7b**		DCM	C	−30	13	**8b**	100	96:4
12	**2b**	4-$MeOC_6H_4$	Et_3N	**7a**		DCM	B	R.T.	4	**8c**	97	46:54
13	**2b**		EtMgBr	**7a**		DCM	B	R.T.	4	**8c**	63	83:17
14	**2c**	*t*-Bu	Et_3N	**7a**		DCM	A	R.T.	3	**8d**	84	34:66
15	**2c**		EtMgBr	**7a**		DCM	B	R.T.	5	**8d**	83	83:17

a) Used for the generation of nitrile oxides **2a**—**c** from precursors **1a**—**c**. b) DCM: dichloromethane; THF: tetrahydrofuran. c) Method A: Nitrile oxides **2** were generated from **1** and Et_3N at the temperature listed in Table and then **7** was added. Method B: Nitrile oxides **2** were generated from **1** and an organometallic compound at −78 °C prior to the addition of **7**. Method C: Each two molar amounts of **7** and EtMgBr were treated at −78 °C, and then **1** was added. d) Isolated yield. e) Determined by ^1H NMR spectrum of the crude product.



Scheme 2.

from dipolarophile **7a** (2 mol amounts) were used as a base for the generation of 1,3-dipole **2a** from **1a** and also as a dipolarophile (Entry 6). This method was useful even in the reaction performed at room temperature (Entry 7). Use of THF instead of dichloromethane lowered selectivity (Entry 8).

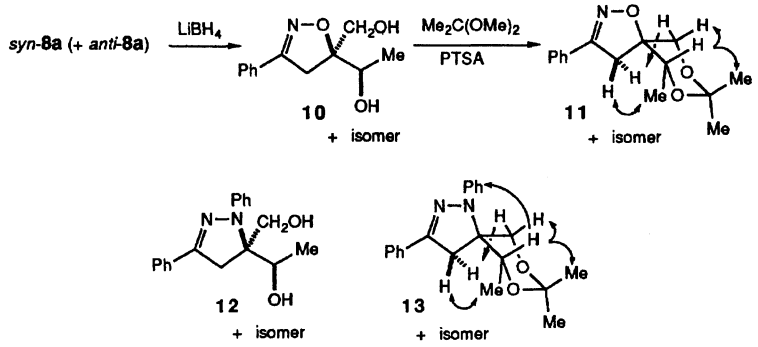
Generation of similar nitrile oxide complexes **1**·MtlCl (R=4-$MeOC_6H_4$ and *t*-Bu) was carried out and used in *syn*-selective reactions with **7a** and methyl 2-(1-hydroxypropyl)acrylate (**7b**) as shown in Scheme 2 and Table 1 (Entries 9—15).

Structures of two diastereomers of cycloadduct **8a**, and those of other derivatives **8b**—**d**, were determined on the basis of their chemical conversions as well as comparison of spectral data (Scheme 3). A 74:26 mixture of *syn*-**8a** and *anti*-**8a** was reduced with lithium borohydride leading to diol **10** and its diastereomer. Acetalization of this mixture with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTSA) gave a 76:24 mixture of spiro compound *syn*-**11** and its diastereomer *anti*-**11** in a total yield of 98%. The major isomer *syn*-**11**, after separation from the minor one *anti*-**11** by column chromatography on silica gel, was determined to be *syn*-product on the basis of NOE spectrum.

Notable NOEs were observed between 6-Me/one of H-4 (isoxazoline) and H-10 (equatorial)/the other of H-4 (isoxazoline), no signal enhancement being observed between H-6 and H-10 (both axial)/H-4s (isoxazoline). Based on the stable conformation of the 1,3-dioxane ring in which the 6-Me moiety must occupy an equatorial position to minimize 1,3-diaxial repulsion, the *syn*-structure of *syn*-**11** was assigned. Accordingly, the minor isomer was identified to be *anti*-**8**. The low field shift of H-4s (δ=3.28 and 3.53) of *syn*-**11**, when compared with those (δ=2.91 and 3.02) of *anti*-**11**, also confirms the assigned stereochemistry.

Reactions of the nitrile imines **5a**,**b**, generated from **4a**,**b** and a variety of metallic bases, with methyl 2-(1-hydroxyalkyl)acrylates **7a**—**c** were examined (Scheme 2 and Table 3). When **5a** was generated from **4a** by the usual triethylamine method, the selectivity of reaction was only moderate in favor of *anti*-cycloadduct *anti*-**9a** (70:30, Entry 1). Structures of *anti*-**9a** and *syn*-**9a** were again confirmed by their conversions to a spiro derivative *syn*-**13** and its diastereomer *anti*-**13** through a sequence of ester reduction and acetalization followed by an NOE analysis (Scheme 3).

The lithium complex of nitrile imine **5a** showed either no selectivity (Entry 2) or *anti*-selectivities (Entries 3 and 4). Especially when two molar amounts of the lithium alkoxide derived from **7a** and lithium diisopro-



Scheme 3.

Table 3. Reactions of Nitrile Imines **5a,b** with Methyl 2-(1-Hydroxyalkyl)acrylates **7a—c**

Entry	Dipole	R	Base[a]	Dipolarophile	R′	Solvent[b]	Method[c]	Temp/°C	Time/h	Product	Yield/%[d]	*syn*:*anti*[e]
1	**5a**	Ph	Et_3N	**7a**	Me	DCM	A	R.T.	18	**9a**	90	30:70
2	**5a**		LDA	**7a**		DCM	B	−50	1	**9a**	53	46:54
3	**5a**		LiOEt	**7a**		DCM	B	−50	25	**9a**	90	63:37
4	**5a**		LDA[f]	**7a**[f]		DCM	D	−50	7	**9a**	100	79:21
5	**5a**		$(i\text{-Pr})_2NMgBr$	**7a**		DCM	B	R.T.	41	**9a**	70	87:13
6	**5a**		EtOMgBr	**7a**		DCM	B	R.T.	87	**9a**	20	96:4
7	**5a**		EtOMgBr	**7a**		DCM	B	Reflux	18	**9a**	60	95:5
8	**5a**		EtMgBr[f]	**7a**[f]		DCM	D	R.T.	48	**9a**	37	96:4
9	**5a**		Et_3N/EtMgBr[g]	**7a**[g]		DCM	C	R.T.	18	**9a**	18	93:7
10	**5a**		Et_3N	**7b**	Et	DCM	A	R.T.	10	**9b**	90	24:76
11	**5a**		Et_3N/EtMgBr[g]	**7b**[g]		DCM	C	R.T.	25	**9b**	66	82:18
12	**5a**		Et_3N	**7c**	Ph	DCM	A	R.T.	21	**9c**	94	27:73
13	**5a**		Et_3N/EtMgBr[g]	**7c**[g]		DCM	C	R.T.	40	**9c**	47	95:5
14	**5b**	4-$MeOC_6H_4$	Et_3N	**7a**		DCM	B	R.T.	20	**9d**	94	26:74
15	**5b**		MeOMgBr	**7a**		DCM	B	Reflux	37	**9d**	50	91:9

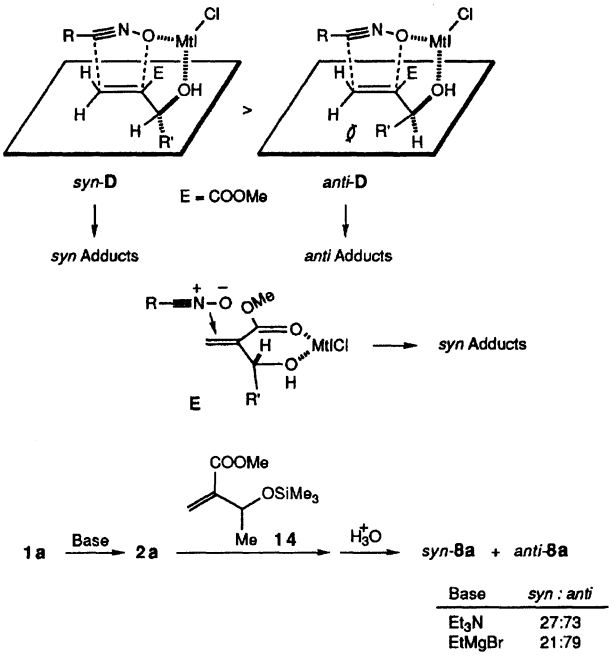
a) Used for the generation of nitrile imines **5a,b** from precursors **4a,b**. b) DCM: dichloromethane; THF: tetrahydrofuran. c) Method A: Nitrile imines **5** were generated from **4** and Et_3N at room temperature and then **7** was added. Method B: Nitrile imines **5** were generated from **4** and a base and the addition of **7** is followed. Method C: Nitrile imines **5**, generated from **4** and Et_3N, were treated with the dipolarophile **7** pretreated with EtMgBr. Method D: Dipolarophile **7** (2 mol amounts) was treated with a base (2 mol amounts) and precursor **4** was added to the resulting solution. d) Isolated yield. e) Determined by ^1H NMR spectrum of the crude product. f) Two molar amounts of base were pretreated with **7** (2 mol amounts), and the metalated dipolarophiles served not only as bases for dipole generation but also as dipolarophiles. g) The dipolarophiles metalated with EtMgBr was reacted with the nitrile imines **5** generated from **4** and Et_3N.

pylamide (LDA) were used as a base for the generation of **5a** and also as a dipolarophile, a moderate *syn*-selectivity (79 : 21) was observed (Entry 4). The magnesium complex **C** (R=Ph, Mtl=MgBr) provided much better *syn*-selectivities (Entries 5—9, 96 : 4 at best), while the yields are usually poor. Use of alkoxide bases gives better *syn*-selectivities than use of amide bases (Entries 2 vs. 3 and 5 vs. 6). Reaction under heating in a low boiling solvent such as dichloromethane results in the increase of reaction yield without decrease of selectivity (Entries 6 and 7). Although two molar amounts of the magnesium alkoxide derived from **7a** and EtMgBr can be employed as well (Entry 8), the reaction of free **5a** with the magnesium alkoxide of **7a** is rather ineffective with respect to the product yield (Entry 9). Other dipoles **5b** and dipolarophiles **7b,c** reacted to show similar selectivites (Entries 10—15).

The transition state leading to *syn*-selectivity is explained in Scheme 4 with the example of nitrile oxide cycloaddition. The metal atom of nitrile oxide/Lewis acid complex can coordinate to the alcoholic oxygen atom of dipolarophile **7**. The transition state takes the fused five–five ring system.

When the subsituent R′ at the chiral center is located inside of the concave of fused ring system (*anti*-**D**), serious allylic strain works. Accordingly, the reaction proceeds through sterically less hindered transition state *syn*-**D**. In such reaction mechanism, coordination ability of the metal atom of the nitrile oxide/Lewis acid complex **B** is important. Lithium and zinc metals do not form stable complexes. When the dipolarophiles are ionized, they become stronger ligands to the metal Mtl so that *syn*-selectivity increases.

Lewis acid MtlCl would be able to interact with olefin alcohol **7** as a chelating ligand to produce a complex **E**, so that nitrile oxide may attack the diastereoface op-



Scheme 4.

posite to substituent R′. This is another possible explanation for the observed *syn*-selectivity. In this case, dipolarophile **7** should be highly activated toward nitrile oxide cycloaddition that must be finished in a few minutes under the reaction conditions applied.[12] However, some decrease of reactivity of nitrile oxide was actually observed, indicating that nitrile oxide **2** was deactivated by the metal coordination. Accordingly, participation of chelate **E** is excluded.

When the hydroxyl group is protected with a bulky trimethylsilyl moiety, the chelated transition state must be destabilized. This anticipation is true (Scheme 4). The reaction of benzonitrile oxide with methyl 2-[1-(trimethylsilyloxy)ethyl]acrylate (**14**) resulted in moderate *anti*-selectivities (diastereoselectivity: 79 to 73%) regardless of the generation method of nitrile oxide.

Experimental

General. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 and A-702 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM EX-90 (^{1}H NMR: 90 MHz) and GSX-270 (270 MHz for ^{1}H NMR and 67.94 MHz for ^{13}C NMR) instruments. Chemical shifts are reported in parts per million downfield (δ) from internal tetramethylsilane at 27 °C unless otherwise stated. Elemental analyses were performed with a Hitachi 026 CHN analyzer. For preparative column chromatography, Wakogel C-200, Wako C-300, and Merck Silica gel 60 were employed.

General Procedure for the New Generation Method of Nitrile Oxides. As a typical procedure, reaction of benzohydroximoyl chloride (**1a**)[13] with EtMgBr is presented: To a solution of **1a** (0.156 g, 1 mmol) in dry THF (5 ml) was added slowly EtMgBr (1.01 M solution in THF (M=mol dm^{-3}), 1 ml, 1 mmol) by use of a syringe at −78 °C under nitrogen. After stirring for 10 min at −78 °C, methyl acrylate (0.103 g, 1.2 mmol) was added. The mixture was stirred at −30 °C for 39 h, poured into aqueous NH_4Cl (6 ml), and then extracted with CH_2Cl_2 (3 ml×3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane–diethyl ether (2 : 1 v/v) to give **3** (0.185 g, 90%) as colorless solid.

Butyllithium and Et_2Zn can be employed instead of EtMgBr in a similar procedure and the results are listed in Table 1.

Methyl 3-Phenyl-2-isoxazoline-5-carboxylate (3). Colorless needles (diethyl ether–hexane); mp 72—73 °C (lit,[14] mp 72—73 °C); IR (Nujol) 2900, 2850, 1750, 1440, 1350, 1210, 1170, 1020, 880 and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.65 (1H, d, $J_{4\text{-}5}$=10.3 Hz, one of H-4), 3.66 (1H, d, $J_{4\text{-}5}$=8.1 Hz, the other H-4), 3.81 (3H, s, COOMe), 5.19 (1H, dd, $J_{5\text{-}4}$=10.3 and 8.1 Hz, H-5), 7.40—7.44 (3H, m, Ph), and 7.66—7.69 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=38.92 (C-4), 52.93 (COOMe), 77.98 (C-5), 126.95, 128.52, 128.81, 130.55 (each Ph), 156.08 (C-3), and 170.72 (COOMe). Found: C, 64.14; H, 5.47; N, 6.65%. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%.

General Procedure for the New Generation Method of Nitrile Imines. As a typical procedure, reaction of *N*-phenyl-4-methoxybenzohydrazonoyl chloride (**4b**)[15] with (*i*-Pr)$_2$NMgBr is presented: To a solution of diisopropylamine (0.05 g, 0.5 mmol) in dry THF (0.5 ml) was added EtMgBr (0.99 M solution in THF, 0.5 ml, 0.5 mmol) at room temperature under nitrogen. The mixture was stirred at this temperature for 3 h, cooled down to −78 °C, and then **4b** (0.13 g, 0.5 mmol) in dry CH_2Cl_2 (5 ml) was added slowly by use of a syringe. After stirring at −78 °C for 10 min, methyl acrylate (0.043 g, 0.5 mmol) was added. The mixture was stirred at room temperature for 2 h, poured into aqueous NH_4Cl (3 ml), and then extracted with CH_2Cl_2 (2 ml×3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane–diethyl ether (3 : 2 v/v) to give **6b** (0.152 g, 98%) as colorless solid.

Lithium diisopropylamide, LiOEt, EtOMgBr can be also employed instead of (*i*-Pr)$_2$NMgBr in a similar procedure and the results are listed in Table 1.

Methyl 1,3-Diphenyl-2-pyrazoline-5-carboxylate (6a). Pale yellow needles (MeOH); mp 106—107 °C; IR (Nujol) 2900, 1730, 1590, 1450, 1380, 1330, 1260, 1130, 1010, and 745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.39 (1H, dd, J_{gem}=17.2 and $J_{4\text{-}5}$=6.6 Hz, one of H-4), 3.64 (1H, dd, J_{gem}=17.2 and $J_{4\text{-}5}$=12.8 Hz, the other of H-4), 3.73 (3H, s, COOMe), 4.80 (1H, dd, $J_{5\text{-}4}$=12.8 and 6.6 Hz, H-5), 6.80—6.90 (1H, m, Ph), 7.09—7.13 (2H, m, Ph), 7.24—7.41 (5H, m, Ph), and 7.68—7.72 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=38.18 (C-4), 52.73 (COOMe), 61.67 (C-5), 112.42, 119.77, 125.84, 128.56, 128.92, 129.18, 131.98, 144.59 (each Ph), 146.94 (C-3), and 171.97 (COOMe). Found: C, 73.06; H, 5.83; N, 10.11%. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99%.

Methyl 3-(4-Methoxyphenyl)-1-phenyl-2-pyrazoline-5-carboxylate (6b). Colorless prisms (CH_2Cl_2–hexane); mp 114—115 °C; IR (Nujol) 2900, 1740, 1600, 1500, 1460, 1380, 1250, 1140, 1040, 880, 840, 750, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.39 (1H, dd, J_{gem}=17.2 and $J_{4\text{-}5}$=7.0

Hz, one of H-4), 3.64 (1H, dd, $J_{gem}=17.2$ and $J_{4\text{-}5}=12.8$ Hz, the other of H-4), 3.74 (3H, s, COOMe), 3.83 (3H, s, *p*-MeO), 4.78 (1H, dd, $J_{5\text{-}4}=12.8$ and 7.0 Hz, H-5), 6.83—6.93 (3H, m, Ph), 7.08—7.12 (2H, m, Ph), 7.25—7.31 (2H, m, Ph), and 7.63—7.67 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=38.42 (C-4), 52.71 (COOMe), 55.33 (*p*-MeO), 61.73 (C-5), 112.84, 114.04, 119.51, 124.76, 127.38, 129.17, 144.93, 146.98 (each Ph), 160.35 (C-3), and 172.16 (COOMe). Found: C, 69.92; H, 5.92; N, 9.10%. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03%.

General Procedure for the Nitrile Oxide Cycloadditions to Methyl 2-(1-Hydroxyalkyl)acrylates 7a,b Leading to 8a—d. As a typical procedure, reaction of benzonitrile oxide **2a** with methyl 2-(1-hydroxyethyl)acrylate (**7a**) according to Method C (Table 2) is presented: To a solution of **7a** (0.26 g, 2 mmol) in dry CH_2Cl_2 (4 ml) was added slowly EtMgBr (0.99 M solution in THF, 2 ml, 2 mmol) by use of a syringe at −78 °C under nitrogen. After 10 min, a solution of **1a** (0.156 g, 1 mmol) in dry CH_2Cl_2 (1 ml) was added slowly. The mixture was stirred at −78 °C for 1 h, at −30 °C for 21 h, poured into aqueous NH_4Cl (10 ml), and then extracted with CH_2Cl_2 (5 ml×3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane–diethyl ether (1:1 v/v) to give *syn*-**8a** (0.46 g, 92%) and *anti*-**8a** (0.04 g, 8%).

Other results are listed in Table 2. Method A: Carbohydroximoyl chloride **1** (1 mmol) is treated with Et_3N (1 mmol) in CH_2Cl_2 and then with **7** (1 mmol). The mixture is allowed to react under the conditions shown in Table 2. Similar hydrolytic quenching and chromatographic purification procedure are applied. Method B: Carbohydroximoyl chloride **1** (1 mmol) is treated with EtMgBr (1 mmol) in CH_2Cl_2 at −78 °C and then with **7** (1 mmol). The mixture is allowed to react under the conditions shown in Table 2.

Methyl (5*RS*)-5-[(1*RS*)-1-Hydroxyethyl]-3-phenyl-2-isoxazoline-5-carboxylate (*syn*-8a). Colorless plates (CH_2Cl_2–hexane); mp 106—107 °C; IR (Nujol) 3500, 2850, 1735, 1445, 1380, 1270, 1175, 1145, 1050, 990, 900, 760, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.28 (3H, d, $J_{Me-CH}=6.4$ Hz, Me), 2.33 (1H, br s, OH), 3.62, 3.75 (each 1H, d, $J_{gem}=17.4$ Hz, H-4), 3.81 (3H, s, COOMe), 4.25 (1H, q, $J_{CH-Me}=6.4$ Hz, CHOH), 7.37—7.42 (3H, m, Ph), and 7.64—7.67 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.44 (Me), 40.75 (C-4), 53.00 (COOMe), 69.24 (CHOH), 90.84 (C-5), 126.85, 128.52, 128.76, 130.54 (each Ph), 156.73 (C-3), and 172.03 (COOMe). Found: C, 62.87; H, 5.95; N, 5.75%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.09; N, 5.64%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxyethyl]-3-phenyl-2-isoxazoline-5-carboxylate (*anti*-8a). Colorless needles (CH_2Cl_2–hexane); mp 116—117 °C; IR (Nujol) 3500, 2900, 1735, 1450, 1360, 1290, 1200, 1100, 1040, 910, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.19 (3H, d, $J_{Me-CH}=6.6$ Hz, Me), 2.73 (1H, br s, OH), 3.58, 3.77 (each 1H, d, $J_{gem}=16.1$ Hz, H-4), 3.80 (3H, s, COOMe), 4.33 (1H, q, $J_{CH-Me}=6.6$ Hz, CHOH), 7.37—7.41 (3H, m, Ph), and 7.64—7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.08 (Me), 37.22 (C-4), 53.09 (COOMe), 68.32 (CHOH), 92.78 (C-5), 126.89, 128.68, 128.75, 130.52 (each Ph), 157.20 (C-3), and 171.04 (COOMe). Found: C, 62.49; H, 6.05; N, 5.60%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.09; N, 5.64%.

Methyl (5*RS*)-5-[(1*RS*)-1-Hydroxypropyl]-3-phenyl-2-isoxazoline-5-carboxylate (*syn*-8b). Colorless prisms (CH_2Cl_2–hexane); mp 125—127 °C; IR (Nujol) 3500, 2900, 1740, 1445, 1370, 1280, 1195, 1025, 760, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.06 (3H, t, $J=7.3$ Hz, Me of Et), 1.43—1.68 (2H, m, CH_2 of Et), 2.05 (1H, br s, OH), 3.64, 3.76 (each 1H, d, $J_{gem}=17.2$ Hz, H-4), 3.82 (3H, s, COOMe), 3.94 (1H, dd, $J_{CH-CH_2}=9.9$ and 3.3 Hz, CHOH), 7.37—7.43 (3H, m, Ph), and 7.64—7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=10.58 (Me of Et), 24.66 (CH_2 of Et), 41.54 (C-4), 53.02 (COOMe), 74.74 (CHOH), 90.88 (C-5), 126.88, 128.56, 128.79, 130.56 (each Ph), 156.71 (C-3), and 172.61 (COOMe). Found: C, 63.89; H, 6.53; N, 5.13%. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.34%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxypropyl]-3-phenyl-2-isoxazoline-5-carboxylate (*anti*-8b). Colorless prisms (CH_2Cl_2–hexane); mp 84—86 °C; IR (Nujol) 3400, 2900, 1740, 1450, 1360, 1290, 1260, 1155, 1050, 990, 915, 895, 895, 760, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.05 (3H, t, $J=7.3$ Hz, Me of Et), 1.31—1.54 (2H, m, CH_2 of Et), 2.43 (1H, br s, OH), 3.59, 3.78 (each 1H, d, $J_{gem}=17.2$ Hz, H-4), 3.81 (3H, s, COOMe), 4.03 (1H, dd, $J_{CH-CH_2}=9.9$ and 2.9 Hz, CHOH), 7.36—7.42 (3H, m, Ph), and 7.65—7.68 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=10.50 (Me of Et), 24.51 (CH_2 of Et), 37.51 (C-4), 53.04 (COOMe), 73.78 (CHOH), 92.44 (C-5), 126.89, 128.74, 130.49 (each Ph), 157.29 (C-3), and 171.14 (COOMe). Found: C, 64.07; H, 6.52; N, 5.26%. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.34%.

Methyl (5*RS*)-5-[(1*RS*)-1-Hydroxyethyl]-3-(4-methoxyphenyl)-2-isoxazoline-5-carboxylate (*syn*-8c). Colorless prisms (CH_2Cl_2–hexane); mp 129—131 °C; IR (Nujol) 3520, 2900, 1740, 1605, 1450, 1270, 1040, 900, and 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.27 (3H, d, $J_{Me-CH}=6.6$ Hz, Me), 2.52 (1H, br d, $J=6.6$ Hz, OH), 3.60, 3.72 (each 1H, d, $J_{gem}=17.2$ Hz, H-4), 3.81, 3.83 (each 3H, s, COOMe and *p*-MeO), 4.23 (1H, quint, $J_{CH-Me}=6.6$ Hz, CHOH), 6.91 (2H, d, $J=8.8$ Hz, Ph), and 7.59 (2H, d, $J=8.8$ Hz, Ph); ^{13}C NMR ($CDCl_3$) δ=17.49 (Me), 41.09 (C-4), 52.99 (COOMe), 55.38 (*p*-MeO), 69.33 (CHOH), 90.52 (C-5), 114.18, 121.03, 128.45, 156.25 (each Ph), 161.38 (C-3), and 172.23 (COOMe). Found: C, 60.04; H, 6.06; N, 4.83%. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxyethyl]-3-(4-methoxyphenyl)-2-isoxazoline-5-carboxylate (*anti*-8c). Colorless needles (CH_2Cl_2–hexane); mp 119—121 °C; IR (Nujol) 3300, 2900, 1730, 1600, 1450, 1360, 1290, 1250, 1045, 910, and 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20 (3H, d, $J_{Me-CH}=6.6$ Hz, Me), 2.55 (1H, br s, OH), 3.56, 3.75 (each 1H, d, $J_{gem}=16.9$ Hz, H-4), 3.82, 3.84 (each 3H, s, COOMe and *p*-MeO), 4.31 (1H, q, $J_{CH-Me}=6.6$ Hz, CHOH), 6.91 (2H, d, $J=8.8$ Hz, Ph), and 7.61 (2H, d, $J=8.8$ Hz, Ph); ^{13}C NMR ($CDCl_3$) δ=17.09 (Me), 37.48 (C-4), 53.07 (COOMe), 55.38 (*p*-MeO), 68.36 (CHOH), 92.42 (C-5), 114.16, 121.18, 128.46, 156.77 (each Ph), 161.39 (C-3), and 171.21 (COOMe). Found: C, 60.37; H, 6.11; N, 4.88%. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02%.

Methyl (5*RS*)-3-*t*-Butyl-5-[(1*RS*)-1-hydroxyethyl]-2-isoxazoline-5-carboxylate (*syn*-8d). Colorless prisms (diethyl ether–hexane); mp 69—70 °C; IR (Nujol) 3500, 2800, 1740, 1450, 1360, 1250, 1160, 1120, 1050, and 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.21 (9H, s, *t*-Bu), 1.21 (3H, d, $J_{Me-CH}=6.6$ Hz, Me), 1.94 (1H, br s, OH), 3.24, 3.34 (each 1H, d, $J_{gem}=17.6$ Hz, H-4), 3.81 (3H, s, COOMe), and

4.13 (1H, q, J_{CH-Me}=6.6 Hz, CHOH); ^{13}C NMR ($CDCl_3$) δ=17.35 (Me), 28.03 (Me of *t*-Bu), 33.22 (C of *t*-Bu), 40.36 (C-4), 52.89 (COOMe), 69.46 (CHOH), 89.82 (C-5), 166.19 (C-3), and 172.38 (COOMe). Found: C, 57.51; H, 8.33; N, 5.93%. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11%.

Methyl (5*RS*)-3-*t*-Butyl-5-[(1*SR*)-1-hydroxyethyl]-2-isoxazoline-5-carboxylate (*anti*-8d). Colorless prisms (diethyl ether–hexane); mp 100—102 °C; IR (Nujol) 3450, 2900, 1740, 1450, 1295, 1255, 1160, 1060, and 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.12 (3H, d, J_{Me-CH}=6.6 Hz, Me), 1.21 (9H, s, *t*-Bu), 2.76 (1H, br s, OH), 3.19, 3.38 (each 1H, d, J_{gem}=17.2 Hz, H-4), 3.80 (3H, s, COOMe), and 4.24 (1H, q, J_{CH-Me}=6.6 Hz, CHOH); ^{13}C NMR ($CDCl_3$) δ=17.05 (Me), 27.98 (Me of *t*-Bu), 33.22 (CH of *t*-Bu), 36.36 (C-4), 52.89 (COOMe), 68.03 (CHOH), 91.93 (C-5), 166.86 (C-3), and 171.27 (COOMe). Found: C, 57.94; H, 8.31; N, 5.88%. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11%.

General Procedure for the Nitrile Imine Cycloadditions to Methyl 2-(1-Hydroxyalkyl)acrylates 7a—c Leading to 9a—d. As a typical procedure, reaction of benzonitrile imine **5a** with methyl 2-(1-hydroxyethyl)acrylate (**7a**)[16] according to Method **B** (Table 3) is presented: To a solution of **7a** (0.13 g, 1 mmol) in dry CH_2Cl_2 (3 ml) was added slowly EtMgBr (0.99 M solution in THF, 1 ml, 1 mmol) by use of a syringe at −78 °C under nitrogen. After 10 min, a solution of **4a** (0.156 g, 1 mmol) in dry CH_2Cl_2 (2 ml) was added slowly. The mixture was stirred at room temperature for 41 h, poured into aqueous NH_4Cl (10 ml), and then extracted with CH_2Cl_2 (5 ml×3). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane–diethyl ether (2:1 v/v) to give *syn*-**9a** (0.198 g, 61%) and *anti*-**9a** (0.029 g, 9%). The isomer ratio was determined to be 87:13 on the basis of ^{1}H NMR spectrum of the crude reaction mixture.

Other results are listed in Table 3. Method A: Carbohydrazonoyl chloride **4** (1 mmol) is treated with Et_3N (1 mmol) in CH_2Cl_2 at room temperature and then with **7** (1 mmol). The mixture is allowed to react under the conditions shown in Table 3. Similar hydrolytic quenching and chromatographic purification procedure are applied. Method C: 2-(1-Hydroxyalkyl)acrylate **7** (1 mmol) is treated with EtMgBr (1 mmol) in CH_2Cl_2 at −78 °C for 10 min. A CH_2Cl_2 solution of nitrile imine **5**, generated from carbohydrazonoyl chloride **4** and Et_3N (each 1 mmol), is treated with the above alkoxide solution under the conditions shown in Table 3. Similar hydrolytic quenching and chromatographic purification procedure are applied. Method D: 2-(1-Hydroxyalkyl)-acrylate **7** (2 mmol) is treated with EtMgBr (2 mmol) in CH_2Cl_2 at −78 °C for 10 min. A CH_2Cl_2 solution of carbohydrazonoyl chloride **4** (1 mmol) is added and the reaction is performed under the conditions shown in Table 3. Similar hydrolytic quenching and chromatographic purification procedure are applied.

Methyl (5*RS*)-[(1*RS*)-1-Hydroxyethyl]-1,3-diphenyl-2-pyrazoline-5-carboxylate (*syn*-9a). Colorless prisms (CH_2Cl_2–hexane); mp 127—129 °C; IR (Nujol) 3500, 2900, 1700, 1590, 1455, 1375, 750, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.04 (3H, d, J_{Me-CH}=6.2 Hz, Me), 1.25 (1H, br s, OH), 3.48, 3.92 (each 1H, d, J_{gem}=18.0 Hz, H-4), 3.71 (3H, s, COOMe), 4.95 (1H, q, J_{CH-Me}=6.2 Hz, CH), 6.82—6.89 (1H, m, Ph), 7.05—7.09 (2H, m, Ph), 7.22—7.26 (2H, m, Ph), 7.28—7.48 (3H, m, Ph), and 7.74—7.76 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.00 (Me), 40.32 (C-4), 53.10 (COOMe), 66.22 (CH), 74.32 (C-5), 113.50, 119.97, 125.84, 128.64, 128.94, 129.31, 131.83, 143.39 (each Ph), 145.71, (C-3), and 175.63 (COOMe). Found: C, 70.05; H, 6.22; N, 8.32%. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxyethyl]-1,3-diphenyl-2-pyrazoline-5-carboxylate (*anti*-9a). Colorless prisms (CH_2Cl_2–hexane); mp 123—124 °C; IR (Nujol) 3350, 2900, 1720, 1450, 1250, 770, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.33 (3H, d, J_{Me-CH}=6.2 Hz, Me), 2.10 (1H, br s, OH), 3.48 (3H, s, COOMe), 3.57, 3.65 (each 1H, d, J_{gem}=16.9 Hz, H-4), 4.69 (1H, q, J_{CH-Me}=6.2 Hz, CH), 7.25—7.29 (1H, m, Ph), 7.36—7.41 (7H, m, Ph), and 7.73—7.77 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.26 (Me), 39.45 (C-4), 52.21 (COOMe), 67.02 (CH), 78.69 (C-5), 118.27, 122.75, 126.10, 128.58, 128.97, 129.20, 131.89, 144.47 (each Ph), 149.05 (C-3), and 170.91 (COOMe). Found: C, 70.57; H, 6.26; N, 8.41%. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64%.

Methyl (5*RS*)-5-[(1*RS*)-1-Hydroxypropyl]-1,3-diphenyl-2-pyrazoline-5-carboxylate (*syn*-9b). Colorless prisms (CH_2Cl_2–hexane); mp 170—171 °C; IR (Nujol) 3500, 2900, 1745, 1710, 1590, 1500, 1450, 1375, 745, and 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.91 (3H, d, J=7.0 Hz, Me of Et), 1.18—1.45 (2H, m, CH_2 of Et), 3.26 (1H, br s, OH), 3.49, 3.89 (each 1H, d, J_{gem}=18.0 Hz, H-4), 3.69 (3H, s, COOMe), 4.62 (1H, d, J_{CH-CH_2}=10.6 Hz, CH), 6.83—6.88 (1H, m, Ph), 7.05—7.10 (2H, m, Ph), 7.21—7.25 (2H, m, Ph), 7.26—7.43 (3H, m, Ph), and 7.70—7.75 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=10.50 (Me of Et), 21.80 (CH_2 of Et), 40.92 (C-4), 53.04 (COOMe), 71.85 (CH), 74.60 (C-5), 113.47, 119.91, 125.84, 128.62, 128.89, 129.28, 131.90, 143.52 (each Ph), 145.75 (C-3), and 175.50 (COOMe). Found: C, 71.25; H, 6.43; N, 8.32%. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxypropyl]-1,3-diphenyl-2-pyrazoline-5-carboxylate (*anti*-9b). Colorless prisms (CH_2Cl_2–hexane); mp 144—146 °C; IR (Nujol) 3300, 2900, 2350, 1730, 1460, 1375, 1255, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.11 (3H, t, J=7.3 Hz, Me of Et), 1.36—1.53, 1.61—1.75 (each 1H, m, CH_2 of Et), 2.38 (1H, br s, OH), 3.46 (3H, s, COOMe), 3.53, 3.65 (each 1H, d, J_{gem}=16.9 Hz, H-4), 4.36 (1H, dd, J_{CH-CH}=9.0 and 2.0 Hz, CH), 6.97—7.07 (1H, m, Ph), 7.26—7.44 (7H, m, Ph), and 7.72—7.76 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=11.25 (Me of Et), 24.88 (CH_2 of Et), 39.65 (C-4), 52.18 (COOMe), 72.87 (CH), 78.56 (C-5), 118.57, 122.85, 126.09, 128.56, 128.94, 129.15, 131.93, 144.52 (each Ph), 149.21 (C-3), and 170.89 (COOMe). Found: C, 70.97; H, 6.59; N, 8.52%. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28%.

Methyl (5*RS*)-5-[(1*RS*)-α-Hydroxybenzyl]-1,3-diphenyl-2-pyrazoline-5-carboxylate (*syn*-9c). Pale yellow prisms (CH_2Cl_2–hexane); mp 154—157 °C; IR (Nujol) 3550, 2900, 2350, 1720, 1600, 1460, 1380, 1050, 750, 720, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.49, 3.94 (each 1H, d, J_{gem}=17.6 Hz, H-4), 3.71 (3H, s, COOMe), 3.98 (1H, d, J=2.2 Hz, OH), 5.88 (1H, d, J_{CH-OH}=2.2 Hz, CH), 6.86—6.92 (1H, m, Ph), 7.07—7.34 (12H, m, Ph), and 7.43—7.46 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=40.76 (C-4), 53.26 (COOMe), 70.11 (CH), 75.02 (C-5), 113.11, 119.61, 125.63, 127.09, 127.54, 127.89, 128.30, 128.64, 129.44, 131.62, 136.45, 143.85

(each Ph), 145.70 (3-C), and 175.56 (COOMe). Found: C, 74.26; H, 5.75; N, 7.09%. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxybenzyl]-1,3-diphenyl-2-pyrazoline-5-carboxylate (*anti*-9c). Pale yellow prisms (CH_2Cl_2–hexane); mp 154—157 °C; IR (Nujol) 3400, 2900, 1720, 1450, 1370, 1250, 760, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.24 (1H, br s, OH), 3.42 (3H, s, COOMe), 3.46, 3.61 (each 1H, d, J_{gem}=17.1 Hz, H-4), 5.70 (1H, s, CH), 7.10—7.16 (1H, m, Ph), 7.29—7.41 (10H, m, Ph), 7.51—7.54 (2H, m, Ph), and 7.68—7.71 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=39.09 (C-4), 52.04 (COOMe), 72.12 (CH), 80.73 (C-5), 120.37, 123.94, 126.19, 127.48, 128.07, 128.20, 128.51, 128.89, 129.28, 131.75, 138.18, 144.65 (each Ph), 150.56 (C-3), and 169.63 (COOMe). Found: C, 74.36; H, 5.81; N, 7.07%. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25%.

Methyl (5*RS*)-5-[(1*RS*)-1-Hydroxyethyl]-3-(4-methoxyphenyl)-1-phenyl-2-pyrazoline-5-carboxylate (*syn*-9d). Colorless needles (CH_2Cl_2–hexane); mp 130—131 °C; IR (Nujol) 3500, 2900, 1700, 1595, 1490, 1450, 1375, 1255, 840, and 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03 (3H, d, J_{Me-CH}=6.6 Hz, Me), 1.56 (1H, br s, OH), 3.45, 3.88 (each 1H, d, J_{gem}=18.0 Hz, H-4), 3.71 (3H, s, COOMe), 3.85 (3H, s, *p*-MeO), 4.93 (1H, q, J_{CH-Me}=6.6 Hz, CH), 6.81—6.87 (1H, m, Ph), 6.92—6.95 (2H, m, Ph), 7.03—7.07 (2H, m, Ph), 7.21—7.29 (2H, m, Ph), and 7.66—7.70 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.05 (Me), 40.50 (C-4), 53.00 (COOMe), 55.35 (*p*-MeO), 66.24 (CH), 74.25 (C-5), 113.39, 114.11, 119.65, 124.60, 127.35, 129.25, 143.65, 145.75 (each Ph), 160.38 (C-3), and 175.66 (COOMe). Found: C, 67.58; H, 6.35: N, 7.74%. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90%.

Methyl (5*RS*)-5-[(1*SR*)-1-Hydroxyethyl]-3-(4-methoxyphenyl)-1-phenyl-2-pyrazoline-5-carboxylate (*anti*-9d). Pale yellow prisms (CH_2Cl_2–hexane); mp 137—139 °C; IR (Nujol) 3500, 2900, 1730, 1595, 1460, 1370, 1250, 830, and 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (3H, d, J_{Me-CH}=6.2 Hz, Me), 2.49 (1H, br s, OH), 3.46 (3H, s, COOMe), 3.54, 3.63 (each 1H, d, J_{gem}=16.9 Hz, H-4), 3.85 (3H, s, *p*-MeO), 4.67 (1H, q, J_{CH-Me}=6.2 Hz, CH), 6.92—6.95 (1H, m, Ph), 6.99—7.04 (1H, m, Ph), 7.24—7.29 (4H, m, Ph), and 7.68—7.71 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.35 (Me), 39.50 (C-4), 52.06 (COOMe), 55.32 (*p*-MeO), 66.94 (CH), 78.63 (C-5), 114.01, 118.21, 122.49, 124.66, 127.60, 128.85, 144.78, 148.99 (each Ph), 160.51 (C-3), and 170.89 (COOMe). Found: C, 67.56; H, 6.17; N, 7.64%. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90%.

Reduction of 8a with $LiBH_4$ Followed by Acetalization. To a solution of **9a** (*syn*:*anti*=74:26, 0.049 g, 0.2 mmol) in dry THF (3 ml) was added $LiBH_4$ (0.012 g, 0.6 mmol) under nitrogen. The mixture was stirred at room temperature for 4 h, poured into saturated aqueous NH_4Cl (4 ml), and extracted with diethyl ether (10 ml×3). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue (0.047 g) was dissolved in 2,2-dimethoxypropane (3 ml) and a catalytic amount of PTSA was added. The mixture was stirred at room temperature for 1.5 h, treated with saturated aqueous K_2CO_3, and extracted with diethyl ether (5 ml×2). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue (0.051 g, 98% overall) was chromatographed on silica gel with hexane–diethyl ether (3:1 v/v) to give *syn*-**11** and *anti*-**11**.

(5*RS*,6*SR*)-6,8,8-Trimethyl-3-phenyl-2-aza-1,7,9-trioxaspiro[4.5]dec-2-ene (*syn*-11). Colorless prisms (CH_2Cl_2–hexane); mp 122—123 °C; IR (Nujol) 2950, 2850, 1460, 1375, 1360, 1270, 1210, 1200, 1160, 1105, 1050, 1020, 980, 910, 845, 755, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.14 (3H, d, J_{Me-6}=6.2 Hz, 6-Me), 1.43, 1.55 (each 3H, s, 8-Me), 3.28, 3.53 (each 1H, d, J_{gem}=17.8 Hz, H-4), 3.69, 3.99 (each 1H, J_{gem}=11.4 Hz, H-10), 4.17 (1H, q, J_{6-Me}=6.2 Hz, H-6), 7.40—7.50 (3H, m, Ph), and 7.67—7.75 (2H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=14.28 (6-Me), 18.93, 29.16 (each 8-Me), 38.07 (C-4), 67.38, 68.97 (C-6 and C-10), 83.02 (C-5), 99.31 (C-8), 126.71, 128.76, 129.33, 130.31 (each Ph), and 156.67 (C-3). Found: C, 68.89; H, 7.34, N, 5.41%. Calcd for $C_{17}H_{18}N_2O$: C, 68.94; H, 7.33; N, 5.36%.

(5*RS*,6*RS*)-6,8,8-Trimethyl-3-phenyl-2-aza-1,7,9-trioxaspiro[4.5]dec-2-ene (*anti*-11). Colorless prisms (CH_2Cl_2–hexane); mp 144—146 °C; IR (Nujol) 2950, 2850, 1450, 1375, 1355, 1270, 1195, 1155, 1100, 1070, 1060, 1000, 980, 910, 845, 795, 710, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.19 (3H, d, J_{Me-6}=6.2 Hz, 6-Me), 1.49, 1.51 (each 3H, s, 8-Me), 2.91, 3.02 (each 1H, d, J_{gem}=17.2 Hz, H-4), 3.93, 3.98 (each 1H, d, J_{gem}=12.5 Hz, H-10), 4.03 (1H, q, J_{6-Me}=6.2 Hz, H-6), 7.39—7.42 (3H, m, Ph), and 7.62—7.67 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=13.92 (6-Me), 19.27, 28.54 (each 8-Me), 40.16 (C-4), 67.04 (C-10), 70.26 (C-6), 83.25 (C-5), 99.02 (C-8), 126.45, 128.74, 129.38, 130.13 (each Ph), and 154.48 (C-3). Found: C, 69.08; H, 7.35, N, 5.39%. Calcd for $C_{17}H_{18}N_2O$: C, 68.94; H, 7.33; N, 5.36%.

Reduction of 8a with $LiBH_4$ Followed by Acetalization. To a solution of **9a** (*syn*:*anti*=79:21, 0.045 g, 0.14 mmol) in dry THF (3 ml) was added $LiBH_4$ (0.02 g, 1 mmol) under nitrogen. The mixture was stirred at room temperature for 2 h, poured into saturated aqueous NH_4Cl (5 ml), and extracted with diethyl ether (5 ml×3). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue (0.042 g) was dissolved in 2,2-dimethoxypropane (2 ml) and a catalytic amount of PTSA was added. The mixture was stirred at room temperature for 4 h, treated with saturated aqueous $NaHCO_3$ (5 ml) and extracted with diethyl ether (5 ml×2). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue (0.047 g, quant overall, 78:12) was chromatographed on silica gel with hexane–diethyl ether (4:1 v/v) to give *syn*-**13** and *anti*-**13**.

(5*RS*,6*SR*)-6,8,8-Trimethyl-1,3-diphenyl-1,2-diaza-7,9-dioxaspiro[4.5]dec-2-ene (*syn*-13). Colorless prisms (hexane); mp 94—95 °C; IR (Nujol) 2950, 2850, 1595, 1490, 1460, 1380, 1290, 1250, 1200, 1110, 1090, 1045, 980, 920, 880, 845, 755, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.09 (3H, d, J_{Me-6}=6.2 Hz, 6-Me), 1.45, 1.51 (each 3H, s, 8-Me), 3.30, 3.68 (each 1H, d, J_{gem}=18.0 Hz, H-4), 3.65, 4.30 (1H, d, J_{gem}=11.4 Hz, H-10), 4.50 (1H, q, J_{6-Me}=6.2 Hz, H-6), 6.97—7.03 (1H, m, Ph), 7.26—7.44 (7H, m, Ph), and 7.74—7.79 (2H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.67 (6-Me), 20.36, 28.29 (each 8-Me), 39.55 (C-4), 66.85 (C-10), 67.41 (C-6), 69.21 (C-5), 99.45 (C-8), 118.35, 121.88, 125.73, 128.53, 128.70, 129.07, 132.57, 144.36 (each Ph), and 147.97 (C-3). Found: C, 74.68; H, 7.22, N, 8.36%. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33%.

(5*RS*,6*RS*)-6,8,8-Trimethyl-1,3-diphenyl-1,2-diaza-

7,9-dioxaspiro[4.5]dec-2-ene (*anti*-13). Colorless prisms (diethyl ether–hexane); mp 123—124 °C; IR (Nujol) 2900, 2850, 1595, 1490, 1455, 1375, 1300, 1210, 1105, 1050, 970, 900, 840, 750, and 690 cm^{-1}, ^1H NMR ($CDCl_3$) δ=1.30 (3H, d, J_{Me-6}=6.6 Hz, 6-Me), 1.46 (6H, s, 8-Me), 3.12, 3.52 (each 1H, d, J_{gem}=17.6 Hz, H-4), 3.51, 4.17 (each 1H, d, J_{gem}=12.1 Hz, H-10), 4.11 (1H, q, J_{6-Me}=6.6 Hz, H-6), 6.88—6.95 (1H, m, Ph), 7.24—7.42 (6H, m, Ph), and 7.67—7.72 (3H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.47 (6-Me), 22.75, 25.02 (8-Me), 45.95 (C-4), 63.79 (C-10), 71.42 (C-6), 72.48 (C-5), 101.12 (C-8), 117.61, 125.40, 128.52, 128.58, 132.68, 144.44 (each Ph), and 144.86 (C-3). Found: C, 74.84; H, 7.16, N, 8.17%. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33%.

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