Hetero-Diels−Alder Reactions of α-Aryl-*β*-monohalo-α-nitrosoethylenes: Diastereoselective Synthesis of 6-Substituted 3-Aryl-4-halo-5,6-dihydro-4*H*-1,2-oxazines

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Treatment of α-aryl-*β*-bromo(or chloro)-α-nitrosoethylene, prepared in situ from α-monobromo(or chloro)ketoximes and sodium carbonate in ether at rt, with allytrimethylsilane afforded exclusively *trans*-(4*S*,6*S*)- and *trans*-(4*R*,6*R*)-3-aryl-4-halo-6-[(trimethylsilyl)methyl]-5,6-dihydro-4*H*-1,2-oxazines **10** albeit in low yields. Similar treatment of *β*-halo-α-nitrosoethylenes with ethyl vinyl ether, however, gave single stereoisomers, i.e., *cis*-(4*S*,6*S*)- and *cis*-(4*R*,6*R*)-6-ethoxy-4-halo-5,6-dihydro-4*H*-1,2-oxazines **11**, in moderate to good yields. The result is in contrast to the reported predominant formation of *trans*-**11a** by a radical reaction. On the other hand, similar reactions with *tert*-butyl vinyl ether at 30 °C gave diastereomeric mixtures of *cis*-(4*S*,6*S*)-, *cis*-(4*R*,6*R*)-, *trans*-(4*S*,6*R*)-, and *trans*-(4*R*,6*S*)-6-(*tert*-butoxy)-4-halo-5,6-dihydro-4*H*-1,2-oxazines **12**. In contrast to compounds **11**, the major isomers have (4*S*,6*R*) and (4*R*,6*S*) configurations. The tendency of a [4 + 2] cycloaddition reaction is consistent with that observed in the Diels−Alder reaction with inverse-electron demand. The stereochemistries of compounds **10**−**12** were assigned on the basis of the ^{1}H NMR coupling constants, which were unambiguously determined by the decoupling experiments. All reactions leading to compounds **10**−**12** proceed with very high regioselectivity. Diastereoselectivity and high regioselectivity are understood in terms of the frontier orbital method. It has been found that *cis*-**12g** is isomerized to a mixture of stereoisomers in favor of the *trans*-isomer in the presence of $HClO_4$ (72%) in $CHCl_3$ at rt.

α-Nitrosoalkenes **1**, which are normally prepared in situ by 1,4-elimination from α-monohaloketoximes[1] or isolated occasionally as relatively stable compounds,[2] have attracted much attention owing to their usefulness as dienes for a [4 + 2] cycloaddition reaction. In recent years, the scope and limitations of a [4 + 2] cycloaddition reaction of **1**, leading to 5,6-dihydro-4*H*-1,2-oxazines **2**,

1a R = Ph
1b R = CO_2Et
1c R = COMe
1d R = Me
1e R = CF_3
2

which are of biological interest[3] and considerable synthetic potential,[4] have been extensively studied by the examination of the reactions of α-nitrosostyrene (**1a**) and ethyl 2-nitrosoacrylate (**1b**) with various types of dienophiles.[5] Despite their usefulness as starting materials for the synthesis of compounds **2**, access to α-nitrosoalkenes having diverse substituents limits their general use. Most α-nitrosoalkenes reported in the literature have no substituents at the terminal olefinic carbon atom. Consequently, the reactions of olefins with such α-nitrosoalkenes led to compounds **2** without a substituent at C-4.[6]

It is noteworthy that compounds **1a,b** have shown a propensity for polymerization at high concentrations,[5] which makes **1** less attractive as starting materials for organic synthesis.

Since compounds **2**, prepared from **1** and dienophiles, do not possess a substituent at C-4, introduction of a substituent to the C-4 of **2** has been achieved by secondary reactions. For instance, synthesis of 4-halogenated 1,2-oxazines has been achieved by either treatment of 5,6-dihydro-3-methyl-4*H*-1,2-oxazine with *n*-BuLi in a mixture of *n*-hexane and THF, followed by addition of halogens (Cl_2, Br_2, I_2)[8] or a radical reaction in which

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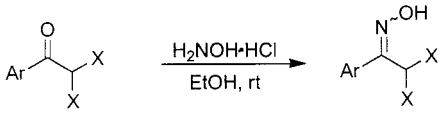
Scheme 1



5, X = Br
6, X = Cl

7, X = Br
8, X = Cl

compounds **2** were reacted with NBS in the presence of benzoyl peroxide in CCl_4 at reflux.[9] The former has the disadvantage of having to use a strong base, i.e., *n*-BuLi, which may be incompatible with other substituents sensitive enough to the strong base, and only limited examples exist for the latter case. One troublesome aspect associated with the latter is that the stereochemistry of *cis*- and *trans*-4-bromo-6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazines prepared could be clearly determined by the ^{1}H NMR spectroscopy only after their transformation to the corresponding 4-azido-1,2-oxazines[9] owing to the failure to separate the mixture.

In light of the harsh reaction conditions related to the former and the ambiguous stereochemistry of 4-bromo-6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazines prepared by the latter method, we became interested in exploring direct synthesis of 4-halogenated 5,6-dihydro-4*H*-1,2-oxazines through a [4 + 2] cycloaddition reaction and also investigated the stereochemistry of the prepared compounds. We have studied the reactions of α-aryl-β-monohalo-α-nitrosoethylenes with selected dienes. The results are described herein.

Results

1-Aryl-2,2-dihaloethanone oximes **7** and **8**, prepared from 1-aryl-2,2-dihaloethanones **5** and **6** and hydroxylamine hydrochloride, respectively[10] (Scheme 1), reacted with allyltrimethylsilane in the presence of a finely ground anhydrous sodium carbonate in dried ether at rt for several days to give diasteromeric mixtures of *trans*-(4*S*,6*S*)-, and *trans*-(4*R*,6*R*)-, *cis*-(4*S*,6*R*)-, and *cis*-(4*R*,6*S*)-6-[(trimethylsilyl)methyl]-5,6-dihydro-4*H*-1,2-oxazines **10a**−**j**, with the *trans*-isomers predominant (Scheme 2).

The reactions are highly diastereoselective. Among the compounds **10** prepared, only **10a** (*trans*:*cis* = >97:3) was prepared in 74% yield by the latter method described.[9] The reaction times, yields, melting points, and diastereoselectivities of *trans*-**10a**−**j** are summarized in Table 1, and selected ^{1}H NMR spectroscopic data are summarized in Table 2.

Similarly, compounds **9** (X = Br, Cl) were treated with ethyl vinyl ether to give only *cis*-(4*S*,6*S*)- and *cis*-(4*R*,6*R*)-6-ethoxy-4-halo-5,6-dihydro-4*H*-1,2-oxazines **11a**−**h** in moderate to good yields (Scheme 2). Among the compounds **11**, **11a** (*trans*:*cis* = 85:15) was prepared in 69% yield by the latter method described.[9] The reaction times, yields, and melting points of the enantiomeric mixtures of *cis*-**11a**−**h** are summarized in Table 3, and selected ^{1}H NMR spectroscopic data are summarized in Table 4.

Apart from the reactions with ethyl vinyl ether, the reactions of **9** (X = Br, Cl) with *tert*-butyl vinyl ether at 30 °C gave diastereomeric mixtures of *cis*-(4*S*,6*S*)-, *cis*-(4*R*,6*R*)-, *trans*-(4*S*,6*R*)-, and *trans*-(4*R*,6*S*)-6-(*tert*-butoxy)-4-halo-5,6-dihydro-4*H*-1,2-oxazines **12a**−**h** (Scheme 2). In contrast to compounds **11**, the major isomers have *trans* stereochemistry. The reaction times, yields, and diastereoselectivities of diastereomeric mixtures of *cis*- and *trans*-**12a**−**h** are summarized in Table 5, and selected ^{1}H NMR spectroscopic data are summarized in Table 6.

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Scheme 2

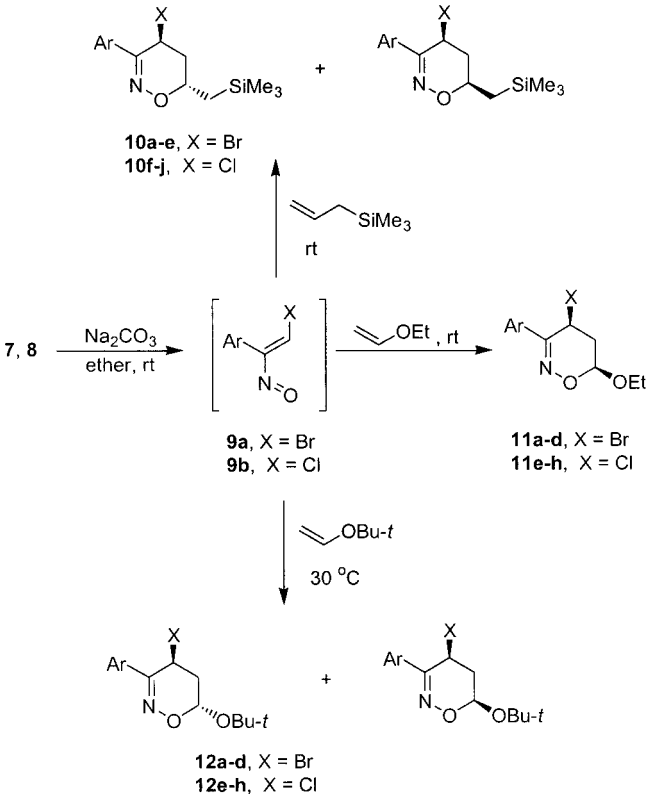

Table 1. Reaction Times, Yields, and Diastereoselectivities of 10 and Melting Points of *trans*-(4*S*,6*S*)- and *trans*-(4*R*,6*R*)-10

compd	Ar	X	time (days)	yield[a] (%)	*trans*:*cis*	mp[c] (°C)
10a	Ph	Br	2	26	>99:1	84−86[d]
10b	4-ClC_6H_4	Br	5	31	>99:1	88−90[d]
10c	4-BrC_6H_4	Br	2	22	>99:1	101−104[d]
10d	4-FC_6H_4	Br	5	25	>99:1	119−120[c]
10e	4-$O_2NC_6H_4$	Br	6	28	>99:1	90−92[d]
10f	4-MeC_6H_4	Cl	12	23	>95:5	112−114[e]
10g	4-ClC_6H_4	Cl	10	23	90:10	110−111[d]
10h	4-BrC_6H_4	Cl	3	29	>95:5	103−104[e]
10i	3-$O_2NC_6H_4$	Cl	10	23	90:10	85−87[d]
10j	3-Cl(4-MeO)C_6H_3	Cl	12	20	90:10	62−65[d]

[a] Isolated yields. [b] Determined on the basis of the ^{1}H NMR spectroscopic data. [c] Mp of *trans*-(4*S*,6*S*)- and *trans*-(4*R*,6*R*)-**10**. [d] Recrystallized form CCl_4. [e] Recrystallized from *n*-hexane.

Discussion

(A) Conformation of 1-Aryl-2,2-dihaloethanone Oximes. The X-ray crystal structure of 1-(4-chlorophenyl)-2,2-dichloroethanone oxime (**8g**)[10] reveals that the N−O and C−CCl_2 bonds are *syn* and one of the chlorine atoms lies on the *anti*-periplane so that overlap of the π-orbital to generate a C=C double bond of α-nitrosoethylene could be facilitated (Figure 1). Two conformations, A and B, may satisfy the foregoing conditions. The former shows a *syn* relationship between another C−X

Table 2. Selected ^{1}H NMR (500 MHz, $CDCl_3$) Spectroscopic Data of *trans*- and *cis*-3-Aryl-4-halo-6-[(trimethylsilyl)methyl]-5,6-dihydro-4*H*-1,2-oxazines 10

compd	Ar	X	δ, *J* (Hz) [H-4 (1H)]	δ, *J* (Hz) [H-6 (1H)]	δ, *J* (Hz) [H-5 (2H)]	δ, *J* (Hz) [$CH_2Si(CH_3)_3$]
trans-**10a**	Ph	Br	5.03 (dd, *J* = 4.2, 1.7)	4.50 (dddd, *J* = 11.6, 8.4, 6.1, 1.6)	2.27 (ddd, 1H, *J* = 14.4, 11.6, 4.2, H_{ax}-5) 2.50 (dt, 1H, *J* = 14.4, 1.6, H_{eq}-5)	0.99, 1.25 (2dd, 1H, 1H, *J* = 14.4, 8.4, *J* = 14.4, 6.1, CH_2Si)
trans-**10b**	4-ClC_6H_4	Br	4.97 (dd, *J* = 3.5, 1.6)	4.46 (dddd, *J* = 11.4, 8.1, 6.3, 1.6)	2.26 (ddd, 1H, *J* = 14.4, 11.6, 3.5, H_{ax}-5) 2.50 (dt, 1H, *J* = 14.4, 1.6, H_{eq}-5)	0.99, 1.25 (2dd, 1H, 1H, *J* = 14.4, 8.1, *J* = 14.4, 6.3, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10c**	4-BrC_6H_4	Br	4.99 (dd, *J* = 4.1, 1.6)	4.48 (dddd, *J* = 11.4, 8.1, 6.3, 1.6)	2.24 (ddd, 1H, *J* = 14.4, 11.6, 4.1, H_{ax}-5) 2.49 (dt, 1H, *J* = 14.4, 1.6, H_{eq}-5)	0.99, 1.25 (2dd, 1H, 1H, *J* = 14.4, 8.1, *J* = 14.5, 6.2, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10d**	4-FC_6H_4	Br	4.95 (dd, *J* = 3.8, 1.6)	4.47 (dddd, *J* = 11.5, 8.2, 6.2, 1.6)	2.26 (ddd, 1H, *J* = 14.4, 11.5, 3.8, H_{ax}-5) 2.51 (dt, 1H, *J* = 14.4, 1.6, H_{eq}-5)	0.97, 1.23 (2dd, 1H, 1H, *J* = 14.4, 8.2, *J* = 14.4, 6.2, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10e**	4-$NO_2C_6H_4$	Br	4.94 (dd, *J* = 4.1, 1.7)	4.49 (dddd, *J* =11.4, 8.1, 6.2, 1.7)	2.27 (ddd, 1H, *J* = 14.4, 11.4, 4.1, H_{ax}-5) 2.51 (dt, 1H, *J* = 14.4, 1.7, H_{eq}-5)	0.98, 1.25 (2dd, 1H, 1H, *J* = 14.4, 8.2, *J* = 14.4, 6.2, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10f**	4-MeC_6H_4	Cl	4.86 (dd, *J* = 4.2, 1.6)	4.31 (dddd, *J* = 11.6, 8.4, 6.1, 1.6)	2.14 (ddd, 1H, *J* = 14.4, 11.6, 4.2, H_{ax}-5) 2.37 (dt, 1H, *J* = 14.4, 1.6, H_{eq}-5)	0.96, 1.23 (2dd, 1H, 1H, *J* = 14.4, 8.4, *J* = 14.4, 6.1, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10g**	4-ClC_6H_4	Cl	4.80 (dd, *J* = 4.3, 1.7)	4.48 (dddd, *J* = 11.4, 8.2, 6.4, 1.7)	2.16 (ddd, 1H, *J* = 14.8, 11.7, 4.3, H_{ax}-5) 2.39 (dt, 1H, *J* = 14.8, 1.7, H_{eq}-5)	0.97, 1.22 (2dd, 1H, 1H, *J* = 14.8, 8.2, *J* = 14.4, 6.4, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10h**	4-BrC_6H_4	Cl	4.80 (dd, *J* = 4.3, 1.7)	4.30 (dddd, *J* = 11.7, 8.1, 6.4, 1.7)	2.15 (ddd, 1H, *J* = 14.8, 11.7, 4.3, 1H, H_{ax}-5) 2.38 (dt, 1H, *J* = 14.8, 1.7, 1H, H_{eq}-5)	0.98, 1.22 (2dd, 1H, 1H, *J* = 14.4, 8.1, *J* = 14.4, 6.4, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
cis-**10h**			4.93 (dd, *J* = 9.7, 8.2)	4.02 (dddd, *J* = 9.7, 8.2, 7.0, 2.0)	2.27 (dt, 1H, *J* = 13.8, 9.7, 1H, H_{ax}-5) 2.66 (ddd, 1H, *J* = 13.8, 8.2, 2.0, 1H, H_{eq}-5)	0.96, 1.18 (2dd, 1H, 1H, *J* = 14.6, 7.0, *J* = 14.6, 7.6, CH_2Si) 0.14 (s, 9H, $SiMe_3$)
trans-**10i**	3-$NO_2C_6H_4$	Cl	4.90 (dd, *J* = 4.3, 1.6)	4.35 (dddd, *J* = 11.6, 8.1, 6.4, 1.6)	2.21 (ddd, 1H, *J* = 15.0, 11.7, 4.2, H_{ax}-5) 2.44 (dt, 1H, *J* = 15.0, 1.6, H_{eq}-5)	1.02, 1.26 (2dd, 1H, 1H, *J* = 14.4, 8.1, *J* = 14.4, 6.4, CH_2Si) 0.15 (s, 9H, $SiMe_3$)
cis-**10i**			5.06 (dd, *J* = 9.6, 8.1)	4.11 (dddd, *J* = 9.6, 8.1, 7.0, 2.0)	2.30 (dt, 1H, *J* = 13.8, 9.6, H_{ax}-5) 2.72 (ddd, 1H, *J* = 13.8, 8.1, 2.0, H_{eq}-5)	1.02, 1.20 (2dd, 1H, 1H, *J* = 14.4, 8.1, *J* = 14.4, 7.0, CH_2Si) 0.13 (s, 9H, $SiMe_3$)
trans-**10j**	3-Cl(4-MeO)C_6H_4	Cl	4.80 (dd, *J* = 4.3, 1.6)	4.29 (dddd, *J* = 11.7, 8.1, 6.1, 1.6)	2.14 (ddd, 1H, *J* = 14.8, 11.7, 4.3, H_{ax}-5) 2.37 (dt, 1H, *J* = 14.8, 1.6, H_{eq}-5)	0.97, 1.21 (2dd, 1H, 1H, *J* = 14.4, 8.1, *J* = 14.4, 6.1, CH_2Si) 0.14 (s, 9H, $SiMe_3$)

Table 3. Reaction Times, Yields, and Melting Points of Enantiomeric Mixtures of *cis*-(4*S*,6*S*)- and *cis*-(4*R*,6*R*)-11a−h

compd	Ar	X	time (day)	yield[a] (%)	mp[b] (°C)
11a	Ph	Br	2	56	55−57
11b	4-ClC_6H_4	Br	3	62	91−92
11c	4-FC_6H_4	Br	3	76	100−102
11d	2-naphthyl	Br	3	98	97−99
11e	Ph	Cl	2	53	60−62
11f	4-BrC_6H_4	Cl	3	90	108−109
11g	4-ClC_6H_4	Cl	2	71	97−99
11h	4-$O_2NC_6H_4$	Cl	3	77	90−92

[a] Isolated yields. [b] Recrystallized from EtOH.

and the Ar group, whereas the latter shows an *anti* relationship between the same groups.

Energy minimization on compound **7a** (Ar = Ph, X = Br) at 25 °C by Hyperchem[11] shows that conformation A is more stable than conformation B by 2.5 kcal/mol, which suggests that **7a** exists as an equilibrium mixture of conformers A and B, with almost 99% conformer A. The instability of conformation B compared with conformation A may be due to the electronic repulsion arising from lone pairs of electrons on the bromine atom *syn* to the oxime double bond and the oxime π-electrons including a lone pair of electrons on the nitrogen atom. Elimination of HX from conformation A would give *trans*-1-aryl-2-halo-1-nitrosoethylenes **9**. However, it is uncertain whether *cis*-analogues would be formed or not from the minor conformer B. It could be noteworthy that the transoid structures of β-halo-α-nitrosoethylenes may be of slightly lower energy than the cisoid structures of **9** in view of those of α-nitrosostyrene.[1c]

(B) Structural Determinations. (i) 3-Aryl-4-halo-6-[(trimethylsilyl)methyl]-5,6-dihydro-4*H*-1,2-oxazines 10. The reactions yielding **10** were heterogeneous and moisture-sensitive reactions and did not proceed in the presence of moisture. Compounds **10** decompose readily on exposure to air at rt. Interestingly, it has been found that a mixture of *cis*- and *trans*-**10** decomposes more rapidly than a pure single isomer and *cis*-**10** decomposes more rapidly than *trans*-**10**.

The structures of compounds **10** were determined on the basis of spectroscopic (^{1}H NMR, IR, MS) and analytical data. The stereochemistry of **10a** was reported, and it was envisaged to have a half-chair conformation[9,13] with an equatorial−equatorial coupling constant of 1.7 Hz for the H-4 atom and with a pseudoaxial position of bromine. Similarly, the stereochemistry of the ring protons of compounds **10** was deduced from the coupling constants. The selected ^{1}H NMR (500 MHz, $CDCl_3$) spectra of compounds **10** (Table 2) show a multiplet around 4.3 ppm, assignable to H-6. It was possible to determine the coupling constants of the multiplets by irradiating axial (∼2.15 ppm) and equatorial (∼2.38 ppm) protons at C-5, which were assigned on the basis of the tendency for equatorial protons to normally be less shielded than the corresponding axial protons.[12] When the multiplet at ∼2.38 ppm was irradiated, H-6 (∼4.3 ppm) was coupled with H-5, whose *J* values were ∼11.6 Hz, close to the axial−axial vicinal coupling constants of

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Table 4. Selected ^{1}H NMR (500 MHz, $CDCl_3$) Spectroscopic Data of *cis*-3-Aryl-6-ethoxy-4-halo-5,6-dihydro-4*H*-1,2-oxazines 11

compd	Ar	X	δ, *J* (Hz) [H-4 (1H)]	δ, *J* (Hz) [H-6 (1H)]	δ, *J* (Hz) [H-5 (2H)]	δ, *J* (Hz) (OEt)
11a	Ph	Br	4.88 (dd, *J* = 7.0, 2.2)	5.31 (t, *J* = 2.9)	2.68 (ddd, 1H, *J* = 15.5, 7.0, 3.1, H_{ax}-5)	1.27 (t, 3H, *J* = 7.0, CH_3)
					2.75 (dt, 1H, *J* = 15.5, 2.4, H_{eq}-5)	3.69, 3.70 (2q, 2H, *J* = 7.0, OCH_2)
						3.93, 3.95 (2q, *J* = 7.0, 2H, OCH_2)
11b	4-ClC_6H_4	Br	4.85 (dd, *J* = 6.7, 2.0)	5.31 (t, *J* = 2.8)	2.67 (ddd, 1H, *J* = 15.5, 6.8, 3.2, H_{ax}-5)	1.26 (t, *J* = 7.0, 3H, CH_3)
					2.75 (dt, 1H, *J* = 15.5, 2.3, H_{eq}-5)	3.67, 3.68 (2q, 2H, *J* = 7.0, OCH_2)
						3.92, 3.93 (2q, 2H, *J* = 7.0, OCH_2)
11c	4-FC_6H_4	Br	4.86 (dd, *J* = 6.7, 2.0)	5.32 (t, *J* = 2.9)	2.66 (ddd, 1H, *J* = 15.4, 6.8, 3.2, H_{ax}-5)	1.26 (t, 3H, *J* = 7.0, CH_3)
					2.75 (dt, 1H, *J* = 15.4, 2.3, H_{eq}-5)	3.68, 3.69 (2q, 2H, *J* = 7.0, OCH_2)
						3.92, 3.93 (2q, 2H, *J* = 7.0, OCH_2)
11d	2-naphthyl	Br	4.89 (dd, *J* = 6.9, 2.1)	5.30 (t, *J* = 2.8)	2.68 (ddd, 1H, *J* = 15.5, 6.9, 3.0, H_{ax}-5)	1.27 (t, 3H, *J* = 7.0, CH_3)
					2.74 (dt, 1H, *J* = 15.5, 2.4, H_{eq}-5)	3.70, 3.71 (2q, 2H, *J* = 7.0, OCH_2)
						3.94, 3.95 (2q, 2H, *J* = 7.0, OCH_2)
11e	Ph	Cl	4.82 (dd, *J* = 6.8, 2.0)	5.29 (t, *J* = 2.7)	2.59 (ddd, 1H, *J* = 15.1, 6.8, 2.7, H_{ax}-5)	1.25 (t, 3H, *J* = 7.0, CH_3)
					2.67 (dt, 1H, *J* = 15.1, 2.3, H_{eq}-5)	3.67, 3.68 (2q, 2H, *J* = 7.0, OCH_2)
						3.92, 3.93 (2q, 2H, *J* = 7.9, OCH_2)
11f	4-BrC_6H_4	Cl	4.75 (dd, *J* = 6.8, 2.0)	5.29 (t, *J* = 2.8)	2.56 (ddd, 1H, *J* = 15.1, 6.8, 3.1, H_{ax}-5)	1.24 (t, 3H, *J* = 7.0, CH_3)
					2.66 (dt, 1H, *J* = 15.2, 2.3, H_{eq}-5)	3.65, 3.67 (2q, 1H, *J* = 7.0, OCH_2)
						3.89, 3.91 (2q, 1H, *J* = 7.0, OCH_2)
11g	4-ClC_6H_4	Cl	4.76 (dd, *J* = 6.8, 2.0)	5.30 (t, *J* = 2.9)	2.57 (ddd, 1H, *J* = 15.2, 6.8, 3.1, H_{ax}-5)	1.25 (t, 3H, *J* = 7.0, CH_3)
					2.66 (dt, 1H, *J* = 15.2, 2.3, H_{eq}-5)	3.66, 3.67 (2q, 1H, *J* = 7.0, OCH_2)
						3.91, 3.90 (2q, 1H, *J* = 7.0, OCH_2)
trans-**11g**			5.00 (t, *J* = 6.1)	5.27 (dd, *J* = 5.3, 3.7)	2.49−2.53 (m, 2H)	1.26 (t, 3H, *J* = 7.1, CH_3)
						3.70, 3.71 (2q, 1H, *J* = 7.1, OCH_2)
						3.99, 4.00 (2q, 1H, *J* = 7.1, OCH_2)
11h	4-$NO_2C_6H_4$	Cl	4.85 (dd, *J* = 6.5, 1.8)	5.34 (t, *J* = 2.7)	2.67 (ddd, 1H, *J* = 15.3, 6.5, 2.9, H_{ax}-5)	1.25 (t, 3H, *J* = 7.0, CH_3)
					2.76 (dt, 1H, *J* = 15.3, 2.0, H_{eq}-5)	3.69, 3.71 (2q, 1H, *J* = 7.0, OCH_2)
						3.93, 3.94 (2q, 1H, *J* = 7.0, OCH_2)

Table 5. Reaction Times, Yields, and Diastereoselectivities of Diastereomeric Mixtures of *cis*-(4*S*,6*S*)-, *cis*-(4*R*,6*R*)-, *trans*-(4*S*,6*R*)-, and *trans*-(4*R*,6*S*)-12a−h

compd	Ar	X	time (day)	yield[a] (%)	*cis*:*trans*
12a	Ph	Br	3	81	5:95
12b	4-MeC_6H_4	Br	3	57	22:78
12c	4-FC_6H_4	Br	3	76	18:82
12d	4-$O_2NC_6H_4$	Br	3	70	8:92
12e	Ph	Cl	3	97	25:75
12f	4-BrC_6H_4	Cl	2	71	19:81
12g	4-ClC_6H_4	Cl	3	94	22:78
12h	4-$O_2NC_6H_4$	Cl	3	94	21:79

[a] Isolated yields. [b] Determined on the basis of the ^{1}H NMR spectroscopic data.

the Karplus correlation on the substituted or fused cyclohexane rings.[12b] Similarly, by irradiating a multiplet at ∼2.15 ppm, H-5 was coupled with H-6, whose *J* values were ∼1.6 Hz. The *J* values are close to the axial−equatorial or equatorial−equatorial coupling constants calculated and observed by Karplus. Since the ^{1}H NMR spectroscopic data are consistent with those reported for **10a**,[9] H-6 and the (trimethylsilyl)methyl group at C-6 are assigned to occupy pseudoaxial and pseudoequatorial positions, respectively, which was confirmed by the X-ray single-crystal structure of **10g**.

In the meantime, H-4 was split by H_{ax}-5 and H_{eq}-5, exhibiting two doublets with *J* = ∼4.2 and ∼1.6 Hz, respectively. The number of doublets, coupled with the magnitude of the coupling constants, indicates that H-4 occupies a pseudoequatorial position. The assignment in turn suggests that a chlorine atom at C-4 and a (trimethylsilyl)methyl group at C-6 are *trans*. The pseudoaxial protons at C-6 of *trans*-**10a**−**j** exhibit four doublets at 4.0−4.5 ppm with *J* = 9.6−11.7, 6.1−8.4, 6.1−7.0, and 1.6−2.0 Hz, which manifest the stereochemistry of H-6.

Among compounds *cis*-**10** formed as minor products, only *cis*-**10h,i** were isolated. The ^{1}H NMR spectrum of *cis*-**10h** exhibited four doublets at 4.02 ppm with *J* = 9.7, 8.2, 7.0, and 2.0 Hz, which were assignable to H-6 (Table 2). Similarly, that of *cis*-**10i** showed the corresponding signal as four doublets at 4.11 ppm with *J* = 9.6, 8.1, 7.0, and 2.0 Hz. The first *J* values of **10h** and **10i**, i.e., 9.7 and 9.6 Hz, are the coupling constants for H_{ax}-6−H_{ax}-5 of *cis*-**10h,i**, respectively. The coupling constants for H_{ax}-5−H_{ax}-4 of *cis*-**10h,i** are also 9.7 and 9.6 Hz, respectively. The same magnitude of *J* values implies that the H-4 and H-6 protons occupy pseudoaxial positions. Consequently, the halogen atom at C-4 occupies a pseudoequatorial position.

(ii) 3-Aryl-4-halo-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazines 11. Compounds **11** were prepared according to the same procedure as described for compounds **10**. The ^{1}H NMR spectra of crude **11** did not indicate compounds **11** to be a mixture of diastereomers, which is in sharp contrast to the formation of a diastereomeric mixture of **11a** (*trans*:*cis* = 85:15) by a radical mechanism.[9] Moreover, compounds **11** prepared have *cis* stereochemistry, which was clearly determined on the basis of the coupling constants of a single stereoisomer of each compound.

For example, compound **11e** exhibited a triplet at 5.29 ppm (*J* = 2.8 Hz), assignable to a pseudoequatorial proton at C-6, which is split by two protons at C-5 (Table 4). On the basis of analogy to this, the ethoxy group at C-6 occupies a pseudoaxial position. A double doublet at 4.82 ppm (*J* = 6.8 and 2.0 Hz), assignable to a pseudoequatorial proton at C-4, may be due to splitting by H_{ax}-5 and H_{eq}-5. Consequently **11e** is a *cis*-compound. The assignment of the stereochemistry of **11e** was further supported by observations in which one proton at C-5 exhibited a triple doublet at 2.59 ppm (*J* = 15.1, 6.8, and 2.7 Hz) and the other proton at C-5 exhibited a double triplet at 2.67 ppm (*J* = 15.1 and 2.3 Hz). The axial

(12) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; John Wiley and Sons: New York, 1965; p 152. (b) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopic in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969.

(13) (a) Gilchrist, T. L.; Faragher, R. *J. Chem. Soc., Chem. Commun.* **1976**, 581. (b) Bravo, P.; Gaudiano, G.; Ponti, P. P.; Umani-Ronchi, A. *Tetrahedron* **1970**, *26*, 1315.

Table 6. Selected ^{1}H NMR (300 MHz, $CDCl_3$) Spectroscopic Data of *cis*- and *trans*-3-Aryl-6-(*tert*-butoxy)-4-halo-5,6-dihydro-4*H*-1,2-oxazines 12

compd	Ar	X	δ, J (Hz) [H-4[a] (1H)]	δ, J (Hz) [H_{eq}-6 (1H)]	δ [H-5 (2H)]	δ (OBu-*t*)
cis-**12a**	Ph	Br	4.77 (t, J = 4.8, H_{eq}-4)	5.39 (t, J = 3.2)	2.43 (m)	1.32 (s)
trans-**12a**			4.97 (t, J = 4.9, H_{ax}-4)	5.42 (dd, J = 7.0, 3.0)	2.39 (m)	1.29 (s)
cis-**12b**	4-MeC_6H_4	Br	4.75 (t, J = 4.8, H_{eq}-4)	5.36 (t, J = 3.2)	2.45 (m)	1.32 (s)
trans-**12b**			4.90 (t, J = 4.5, H_{ax}-4)	5.40 (dd, J = 6.9, 3.1)	2.43 (m)	1.30 (s)
cis-**12c**	4-FC_6H_4	Br	4.88 (t, J = 4.8, H_{eq}-4)	5.51 (t, J = 3.2)	2.42 (m)	1.33 (s)
trans-**12c**			4.96 (t, J = 4.6, H_{ax}-4)	5.52 (dd, J = 7.1, 3.0)	2.40 (m)	1.31 (s)
cis-**12d**	4-$NO_2C_6H_4$	Br	5.09 (t, J = 4.8, H_{eq}-4)	5.66 (t, J = 3.2)	2.49 (m)	1.31 (s)
trans-**12d**			5.21 (t, J = 4.7, H_{ax}-4)	5.68 (dd, J = 6.7, 2.9)	2.45 (m)	1.30 (s)
cis-**12e**	Ph	Cl	4.82 (t, J = 4.8, H_{eq}-4)	5.41 (t, J = 3.2)	2.49 (m)	1.35 (s)
trans-**12e**			5.04 (t, J = 5.0, H_{ax}-4)	5.62 (dd, J = 7.2, 3.2)	2.44 (m)	1.37 (s)
cis-**12f**	4-BrC_6H_4	Cl	4.74 (t, J = 4.8, H_{eq}-4)	5.44 (t, J = 3.2)	2.43 (m)	1.32 (s)
trans-**12f**			4.93 (t, J = 4.9, H_{ax}-4)	5.36 (dd, J = 7.0, 3.1)	2.40 (m)	1.33 (s)
cis-**12g**	4-ClC_6H_4	Cl	4.83 (t, J = 4.8, H_{eq}-4)	5.53 (t, J = 3.2)	2.55 (m)	1.34 (s)
trans-**12g**			4.97 (t, J = 5.8, H_{ax}-4)	5.52 (dd, J = 8.0, 2.7)	2.37 (m)	1.33 (s)
cis-**12h**	4-$NO_2C_6H_4$	Cl	4.89 (t, J = 4.8, H_{eq}-4)	5.57 (t, J = 3.2)	2.57 (m)	1.33 (s)
trans-**12h**			4.97 (t, J = 4.6, H_{ax}-4)	5.59 (dd, J = 7.0, 3.2)	2.67 (m)	1.35 (s)

[a] H_{eq} = pseudoequatorial, H_{ax} = pseudoaxial.

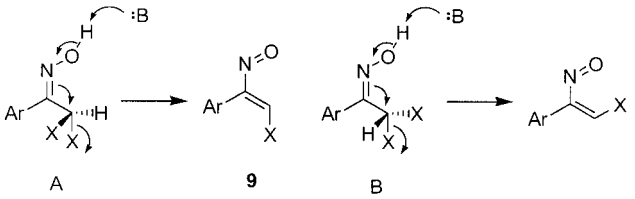


Figure 1. Two conformations of 1-aryl-2,2-dihaloethanone oximes.

proton exhibiting a triple doublet may be due to the geminal coupling between two protons at C-5 (J = 15.1 Hz) and the coupling between H_{ax}-5 and H_{eq}-4 (J = 6.8 Hz), and H_{ax}-5 and H_{eq}-6 (J = 2.7 Hz). On the other hand, the equatorial proton exhibiting a double triplet may be due to the geminal coupling of two protons at C-5 and the coupling between H_{eq}-5 and H_{eq}-4 (J = 2.3 Hz). Similar coupling constants were observed for compounds **11a**−**d**,**f**−**h**.

(iii) 3-Aryl-6-(*tert*-butoxy)-4-halo-5,6-dihydro-4*H*-1,2-oxazines 12. Apart from the reactions yielding compounds **10** and **11**, the reactions with *tert*-butyl vinyl ether were carried out at 30 °C for several days since they did not proceed at rt. Compounds **12** were a mixture of diastereomers, with *cis*-**12** predominant, which is in sharp contrast to diastereomeric mixtures of compounds **10**, with *trans*-isomers predominant. We have studied the effects of stereoisomers on the reactivity using (*E*)- and (*Z*)-ketoximes **7a** and **8a**. From the reactions were obtained essentially the same ratios of diastereomeric mixtures of **12a** and **12b**, indicating that the stereochemistry of haloketoximes is not important and isomerization from (*E*)-**7** and (*E*)-**8** to the corresponding (*Z*)-isomers and vice versa occurs readily, which is consistent with a previous report.[5b]

The stereochemistry of compounds **12** was determined on the basis of their ^{1}H NMR coupling constants (Table 6). Apart from the ^{1}H NMR spectra of compounds **10** and **11**, the geminal coupling of the methylene protons at C-5 was not observed regardless of *cis*- and *trans*-**12**. The same J value (4.8 Hz), observed for the couplings between an H-4 and each of the two protons at C-5 of *cis*-**12**, coupled with their J value magnitude indicates that the H-4 of *cis*-**12** occupies a pseudoequatorial position. The same J value (3.2 Hz), observed for the couplings between an H-6 and each of the two protons at C-5, indicates that the H-6 occupies a pseudoequatorial position. Similarly no geminal coupling was observed in the methylene protons at C-5 of *trans*-**12**. However, the H-4 exhibiting double doublets (J = 2.7−3.2 and 6.7−8.0 Hz) is envisaged to occupy a pseudoaxial position. Likewise, the H-6 exhibiting a triplet (J = 4.5−5.8 Hz) is envisaged to occupy a pseudoequatorial position. Consequently, the C−X bond is *trans* to the *t*-BuO group at C-6.

(C) Diastereoselectivity. Molecular orbital calculations by the CNDO method[14] on selected dienes, i.e., 1-nitroso 1-(*p*-tolyl)ethylene, 2-chloro-1-nitroso-1-(*p*-tolyl)-ethylene, 2-bromo-1-nitroso-1-(*p*-tolyl)ethylene, 1-(*p*-chlorophenyl)-1-nitrosoethylene, 2-chloro-1-(*p*-chlorophenyl)-1-nitrosoethylene, and 2-bromo-1-(*p*-chlorophenyl)-1-nitrosoethylene as well as dienophiles, i.e., ethylene, allyltrimethylsilane, ethyl vinyl ether, and *tert*-butyl vinyl ether, gave the HOMO and LUMO energies of dienes and dienophiles, which are shown in Figures 2 and 3, respectively.

Figure 2 shows that the stronger the electron-withdrawing effect of the substituents the lower the energy of the LUMO regardless of whether the substituent is on the β-position of α-nitrosoalkenes or on the aryl group at the α-position. In contrast, Figure 3 shows that the HOMO energy levels of dienophiles become higher when the vinyl proton is replaced by the stronger electron-donating group, i.e., OEt > CH_2SiMe_3 > H, which is not unexpected according to the frontier molecular orbital theory.[15] Therefore, the lowest activation energy would be expected from the cycloaddition reaction of α-nitrosoalkene **1g** (Ar = *p*-ClC_6H_4, X = Cl) (LUMO, 0.98 eV) with ethyl vinyl ether (HOMO, −12.11 eV), in which the energy gap is calculated to be 13.09 eV. Since the energy gap between the LUMO of α-(*p*-chlorophenyl)-α-nitrosoethylene (Ar = *p*-ClC_6H_4, X = H) and the HOMO of ethyl vinyl ether is 13.61 eV, one can predict that the cycloaddition reaction of α-aryl-α-nitrosoethylene, which has an electron-withdrawing group such as a chlorine or bromine atom at the β-position, with a dienophile occurs more readily than that with no substituent at the β-position under the same conditions. In fact, this tendency is observed in the Diels−Alder reaction with inverse-electron demand.[5,7]

All reactions leading to compounds **10**−**12** proceed with very high regioselectivity. In no example do we have an indication of the formation of isomeric 1,2-oxazines. The

(14) Hyperchem Release 3 for windows, Molecular Modeling System, Copyright 1993 Hypercube, Inc. and Autodesk, Inc.

(15) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: Chichester, U.K., 1976; pp 110−121.

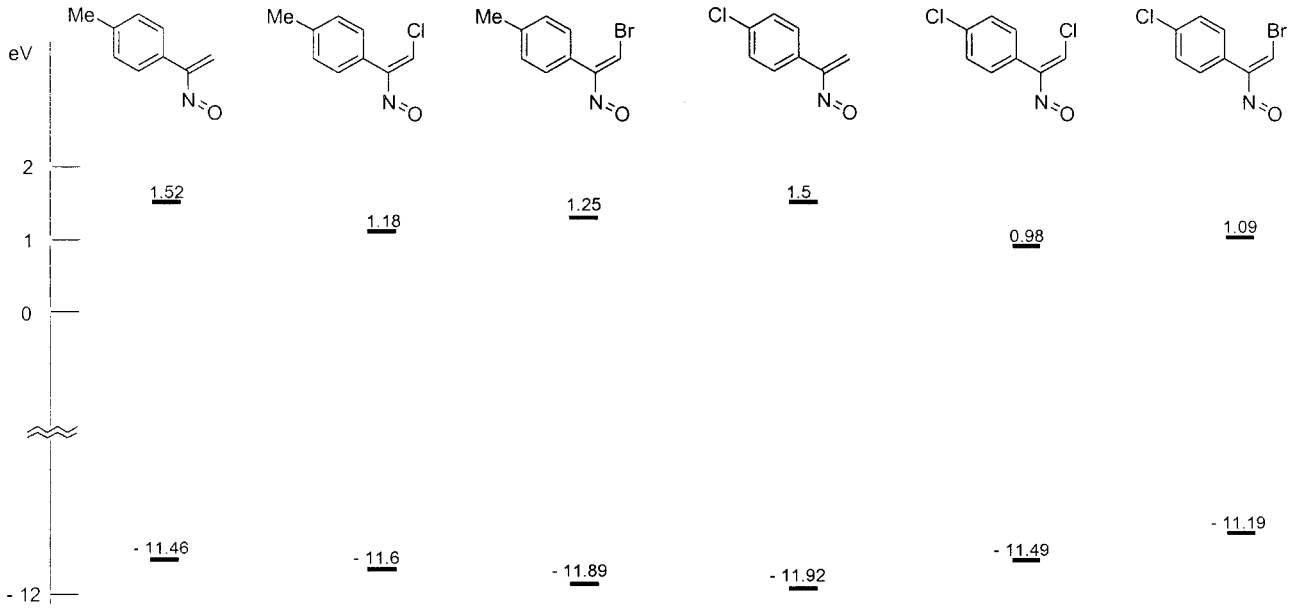


Figure 2. HOMO and LUMO energies of dienes.

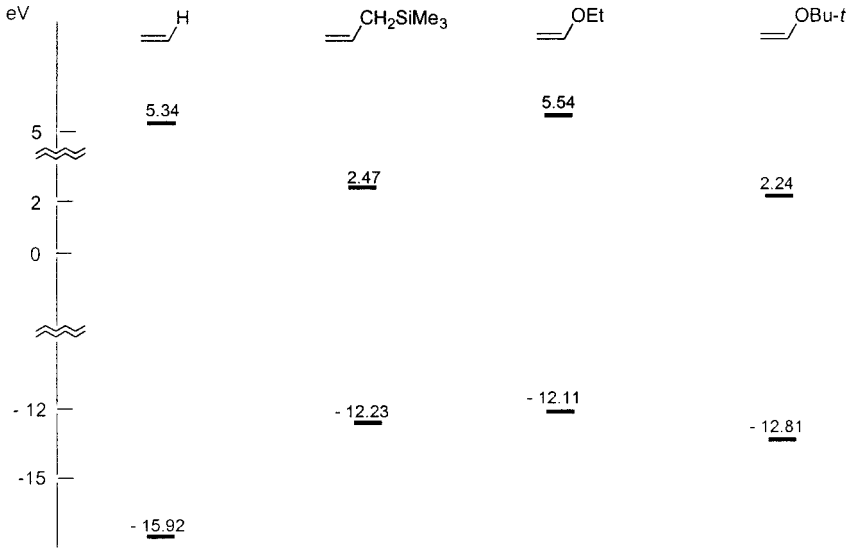


Figure 3. HOMO and LUMO energies of dienophiles.

regioselectivity may be controlled primarily by frontier orbital interactions, i.e., interactions between the terminal atom of the dienophile bearing a large HOMO coefficient and a carbon atom of the diene bearing an electron-withdrawing group which has a large LUMO coefficient.[16]

Since the [4 + 2] cycloaddition reactions involving α-nitrosoalkenes are believed to proceed in a single step,[6d] diastereoselectivity for the formation of compounds **10**–**12** may be explained by assuming two types of transition states: a transition state having an *endo* configuration in which the π-orbitals of the dienes interact with a lone pair of electrons on a heteroatom of the dienophiles,[17] resulting in the formation of only *cis*-1,2-oxazines **11** (Figure 4), which is in contrast to the predominant formation of *trans*-**11a** by bromination of 6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine with NBS[9] and, alternatively, a transition state having an *exo* configuration

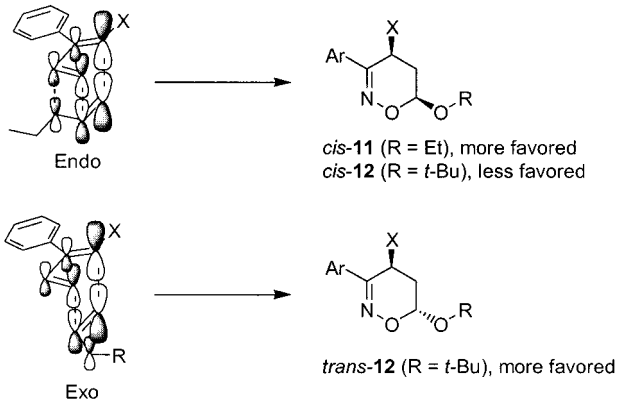


Figure 4. Proposed transition state for the cycloaddition of **9** with ethyl vinyl ether and *tert*-butyl vinyl ether.

in which the π-orbitals of the dienes are unable to interact with the orbital of the substituent of the dienophiles because of the absence of a lone pair or steric

(16) Reference 15, pp 121–132.
(17) Reference 15, pp 106–109.

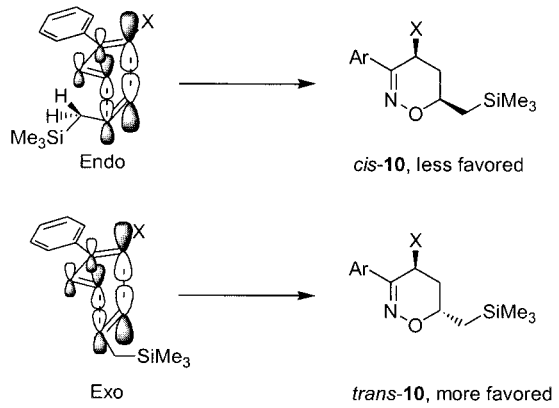
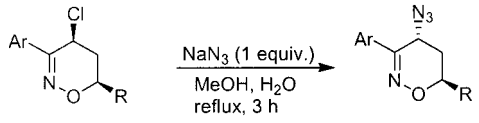


Figure 5. Proposed transition state for the cycloaddition of **9** with allyltrimethylsilane.

Scheme 3



11f, Ar = 4-BrC_6H_4, R= OEt
11g, Ar = 4-ClC_6H_4, R = OEt
12h, Ar = 4-$O_2NC_6H_4$, R = OBu-*t*

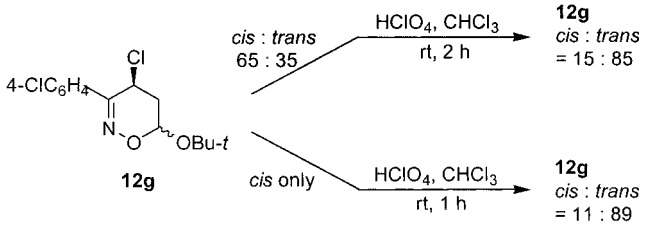
13a, Ar = 4-BrC_6H_4, R = OEt
13b, Ar = 4-ClC_6H_4, R = OEt
13c, Ar = 4-$O_2NC_6H_4$, R = OBu-*t*

bulkiness of the substituent. Predominant formation of *trans*-1,2-oxazines **10** may be the case (Figure 5). On the other hand, the reactions with *tert*-butyl vinyl ether, analogous to ethyl vinyl ether, gave predominantly *trans*-1,2-isoxazines **12** (Figure 4). Severe steric hindrance arising from the *tert*-butyl group may be responsible for the formation of *cis*- or *trans*-1,2-oxazines **12** in favor of *trans*-**12**.

(D) Reactions of Compounds 11 and 12. A mixture of *cis*-1,2-oxazine **11f** (Ar = 4-BrC_6H_4, R = OEt, X = Cl) and NaN_3 (1 equiv) was heated in a mixture of MeOH and water for 3 h to give only *trans*-azido compound **13a** (Ar = 4-BrC_6H_4, R = OEt, X = N_3) in 85% yield (Scheme 3).

The IR spectrum exhibited an absorption feature at 2096 cm^{-1}, indicating the presence of an azido group. The ^1H NMR (300 MHz, $CDCl_3$) spectrum exhibited a triple doublet at 2.25 ppm (J = 13.2, 8.8, and 2.6 Hz) assignable to H_{ax}-5, a triple doublet at 2.40 ppm (J = 13.2, 6.9, and 4.6 Hz) assignable to H_{eq}-5, and a double doublet (J = 4.6 and 2.6 Hz) at 5.52 ppm assignable to the pseudoequatorial proton at C-6. On the basis of a large J value (H_{ax}-4−H_{ax}-5, 8.8 Hz) and a small J value (H_{eq}-6−H_{eq}-5 and H_{eq}-6−H_{ax}-5, 4.6 and 2.6 Hz) compared with those of *trans*-**10c**, H-4 and H-6 of **13a** are envisaged to occupy pseudoaxial and pseudoequatorial positions, respectively. Consequently, compound **13a** has a *trans* configuration. This result suggests that the chlorine atom of **11f** is displaced by an azide ion presumably by an S_N2 mechanism. Similarly, treatment of *cis*-**11g** (Ar = 4-ClC_6H_4, R = OEt, X = Cl) under the same conditions gave only *trans*-**13b** (Ar = 4-ClC_6H_4, R = OEt, X = N_3) in 78% yield. The stereochemistry of **13b** was also determined on the basis of the ^1H NMR spectroscopic data, which suggested the stereochemistry of **11g** to be *cis*.[9] Similarly, *trans*-**13c** was obtained from *cis*-**12h** (Ar = 4-$O_2NC_6H_4$, R = OBu-*t*, X = Cl) in 67% yield under the same conditions (Scheme 3).

Scheme 4



Interestingly, treatment of a mixture of *cis*- and *trans*-**12g**, whose ratio of stereoisomers was 65:35, with 72% $HClO_4$ for 2 h in $CHCl_3$ at rt gave **12g** in 69% yield, whose ratio of stereoisomers changed to 15:85 (Scheme 4). The pure *cis*-**12g** was subjected to similar conditions to give a similar ratio of stereoisomers (*cis*:*trans* = 11:89) in 40% yield. The result indicates that the carbon−oxygen bond consisting of the 1,2-oxazine ring, which is a kind of acetal, is cleaved in the presence of acid, followed by recyclization to give a mixture of stereoisomers in favor of a thermodynamically more stable *trans*-isomer.

In conclusion, it has been demonstrated that 3-aryl-4-halo-5,6-dihydro-4*H*-1,2-oxazines can be directly prepared by treatment of in-situ-generated α-aryl-*β*-monohalo-α-nitrosoethylene with dienophiles such as allyltrimethylsilane, ethyl vinyl ether, and *tert*-butoxy vinyl ether with a high stereoselectivity. The reactions with allytrimethylsilane afforded exclusively *trans*-1,2-oxazines **10**, whereas those with ethyl vinyl ether gave only *cis*-1,2-oxazines **11**, which is in contrast to the predominant formation of *trans*-**11a** by bromination of 6-ethoxy-3-phenyl-5,6-dihydro-4*H*-1,2-oxazine with NBS. Interestingly, the reactions with *tert*-butyl vinyl ether afforded predominantly *cis*-1,2-oxazines **12**. The stereochemistry of substituents at C-4 and C-6 of the title compounds was unambiguously determined on the basis of the coupling constants and chemical transformations. The diastereoselectivities of 1,2-oxazines prepared are understood in terms of the frontier orbital method.

Experimental Section

General Procedures. NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard for ^1H (300 MHz), unless otherwise stated. GC−MS (EI) spectra were obtained at 70 eV. Elemental analyses were determined by the Inter-University Center for Natural Science Research Facilities, Seoul National University. Dichloromethane was distilled from calcium hydride prior to use. Column chromatography was conducted with alumina (neutral, 230−400 mesh, ASTM). 1-Aryl-2,2-dihaloethanone oximes **7** and **8** were prepared according to the documented procedure.[10]

General Procedure for the Synthesis of 6-Substituted 3-Aryl-4-halo-5,6-dihydro-4*H*-1,2-oxazines 10−12. (i) To a mixture of 1-aryl-2,2-dihaloethanone oximes (0.69−3.8 mmol) and allyltrimethylsilane (3.3−18 mmol) in dried ether (50 mL) was added freshly ground anhydrous sodium carbonate (3.8−20 mmol). The mixture was stirred for several days (refer to Table 1) at rt. The suspension was filtered through a pad of Celite. Removal of the solvent gave a residue which was chromatographed on alumina (2 × 10 cm). Elution with a mixture of benzene and *n*-hexane (1:3) gave unknown mixtures. Subsequent elution with the same solvent mixture (1:1) afforded *trans*-**10** and *cis*-**10** in a sequence. Consult Table 2 for the selected ^1H NMR spectroscopic data of **10**.

(ii) To a mixture of 1-aryl-2,2-dihaloethanone oximes (0.56−3.3 mmol) and ethyl vinyl ether (3.1−18 mmol) in dried ether (30 mL) was added sodium carbonate (3.4−20 mmol). The mixture was worked up as described in (i). Chromatography

on alumina (3 × 10 cm) using a mixture of benzene and *n*-hexane (1:1) gave a trace amount of unknown mixtures. (a) Subsequent elution with benzene gave **11b,c,f**. (b) In the cases of the reactions with **8a,d,e,g**, subsequent elution with benzene gave unknown mixtures and then continuous elution with a mixture of EtOAc and *n*-hexane (1:4) gave *cis*-**11a,d,e,g**. Consult Table 3 for the reaction times, yields, and melting points of *cis*-**11** and Table 4 for the selected ^{1}H NMR spectroscopic data of **11**.

(iii) To a mixture of 1-aryl-2,2-dihaloethanone oximes (0.88−2.0 mmol) and *tert*-butyl vinyl ether (4.8−13 mmol) in dried ether (30 mL) was added sodium carbonate (1.8−3.2 mmol). The mixture was stirred for several days at 30 °C, and then worked up as described in (i). Chromatography on alumina (3 × 10 cm) using a mixture of benzene and *n*-hexane (1:1), followed by elution with a mixture of EtOAc and *n*-hexane (1:10), gave unknown mixtures (trace) and *trans*-**12**. Subsequent elution with the same solvent mixture (1:4) gave *cis*-**12**. Consult Table 5 for the reaction times and yields of *cis*- and *trans*-**12** and Table 6 for selected ^{1}H NMR spectroscopic data of *cis*- and *trans*-**12**.

***trans*-4-Azido-3-(4-bromophenyl)-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine (13a).** To a solution of NaN_3 (45 mg, 0.696 mmol) in a mixture of MeOH (10 mL) and water (8 mL) was added *cis*-3-(4-bromophenyl)-4-chloro-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine (**11f**) (148 mg, 0.696 mmol) (*cis*:*trans* = >99:1). The mixture was stirred for 3 h at reflux, followed by addition of water (10 mL) to the cooled reaction mixture, which was extracted with CH_2Cl_2 (30 mL × 3). The extracts were dried over $MgSO_4$. Removal of the solvent gave a viscous yellow liquid, **13a** (129 mg, 85%), which solidified at rt and was recrystallized from ethanol: mp 100−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3 H, J = 7.0 Hz, CH_3), 2.25 (ddd, 1 H, J = 13.2, 8.8, 2.6 Hz, H_{ax}-5), 2.40 (ddd, 1 H, J = 13.2, 6.9, 4.6 Hz, H_{eq}-5), 3.59, 3.61 (2q, 1 H, J = 7.0 Hz, OCH_2), 3.79, 3.81 (2q, 1 H, J = 7.0 Hz, OCH_2), 4.67 (dd, 1 H, J = 8.8, 6.9 Hz, H_{ax}-4), 5.52 (dd, 1 H, J = 4.6, 2.6 Hz, H_{eq}-6), 7.56, 7.59 (2d, 4 H, J = 8.8 Hz, ArH); IR (KBr) 2096, 1592, 1486, 1335, 1103, 1032, 879, 831 cm^{-1}; MS *m*/*z* 324 (M^+, 1.1), 326 (M^+ + 2, 1.1), 238 (100), 240 (95.8), 197 (6.7), 156 (19.5), 115 (38.1). Anal. Calcd for $C_{12}H_{13}BrN_4O_2$: C, 44.33; H, 4.03; N, 19.23. Found: C, 44.29; H, 4.02; N, 19.26.

***trans*-4-Azido-3-(4-chlorophenyl)-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine (13b).** From the reaction of NaN_3 (8 mg, 0.129 mmol) with *cis*-**11g** (59 mg, 0.129 mmol) (cis:trans = >99:1) under the same conditions described above was obtained compound **13b** (28 mg, 78%), a viscous pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3 H, J = 7.0 Hz, CH_3), 2.28 (ddd, 1 H, J = 13.5, 8.8, 3.0 Hz, H_{ax}-5), 2.36 (ddd, 1 H, J = 13.5, 6.7, 4.5 Hz, H_{eq}-5), 3.60, 3.61 (2q, 1 H, J = 7.0 Hz, OCH_2), 3.78, 3.80 (2q, 1 H, J = 7.0 Hz, OCH_2), 4.64 (dd, 1 H, J = 8.8, 6.7 Hz, H_{ax}-4), 5.49 (dd, 1 H, J = 4.5, 3.0 Hz, H_{eq}-6), 7.40, 7.65 (2d, 4 H, J = 8.7 Hz, ArH); IR (KBr) 2096, 1590, 1488, 1333, 1248, 1107, 1029, 897, 829 cm^{-1}; MS m/z 280 (M^+, 1.9), 282 (M^+ + 2, 0.7), 194 (100), 196 (98.2), 156 (21.3), 153 (7.2), 115 (30.9). Anal. Calcd for $C_{12}H_{13}ClN_4O_2$: C, 51.35; H, 4.67; N, 19.96. Found: C, 51.38; H, 4.69; N, 20.08.

***trans*-4-Azido-6-(*tert*-butoxy)-3-(4-nitrophenyl)-5,6-dihydro-4*H*-1,2-oxazine (13c).** A mixture of *cis*-**12h** (106 mg, 0.339 mmol) and NaN_3 (33 mg, 0.509 mmol) in a mixture of MeOH (5 mL) and water (3 mL) was heated for 3 h at reflux. Water (10 mL) was added to the cooled reaction mixture, which was worked up as described above. Chromatography (2 × 10 cm) of the residue on alumina using a mixture of EtOAc and *n*-hexane (1:6) gave compound **13c**, which was recrystallized from ethanol: mp 85−86 °C; ^{1}H NMR δ 1.33 (s, 9 H, OBu-*t*), 2.25 (ddd, 1 H, J = 13.2, 8.8, 2.6 Hz, H_{ax}-5), 2.40 (ddd, 1 H, J = 13.2, 6.9, 4.6 Hz, H_{eq}-5), 4.67 (dd, 1 H, J = 8.8, 6.9 Hz, H_{ax}-4), 5.52 (dd, 1 H, J = 4.6, 2.6 Hz, H_{eq}-6), 7.86, 8.29 (2d, 4 H, J = 8.8 Hz, ArH); IR (KBr) 2096, 1596, 1513, 1338, 1099, 1021, 909, 855 cm^{-1}; MS *m*/*z* 319 (M^+, 3.2), 291 ($M^+ - N_2$, 1.7), 261 (1.6), 235 (100), 218 (25.1), 216 (22.8), 190 (36.5), 170 (24.8), 149 (40.1), 76 (22.3). Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.69; H, 5.37; N, 21.94.

Treatment of 12g with Perchloric Acid (72%). (i) To a solution of **12g** (180 mg, 0.596 mmol) (*cis*:*trans* = 65:35) in $CHCl_3$ (10 mL) was added three drops of $HClO_4$ (72%). The solution was stirred for 2 h at rt, followed by addition of water (10 mL), and extracted with CH_2Cl_2 (30 mL × 3). The extract was worked up as before. Chromatography (2 × 10 cm) of the residue (191 mg) on alumina with a mixture of EtOAc and *n*-hexane (1:8) gave *trans*-**12g** (62 mg, 34%), which was recrystallized from ethanol: mp 99−100 °C. Elution with the same solvent mixture (1:4) gave *cis*-**12g** (10 mg, 6%), which was recrystallized from ethanol: mp 94−95 °C. Subsequent elution with the same solvent mixture (1:1) gave unknown mixtures (52 mg).

(ii) A solution of *cis*-**12g** (58 mg, 0.192 mmol) in $CHCl_3$ (5 mL) was treated with two drops of $HClO_4$ (72%) at rt. The solution was worked up as before after 1 h of stirring to give a residue (59 mg) which was chromatographed on an alumina (2 × 5 cm) with a mixture of EtOAc and *n*-hexane as described in (i) to give *trans*-**12g** (36 mg, 62%), *cis*-**12g** (4 mg, 9%), and unknown mixtures (8 mg).

X-ray Structure Analysis of Compound 10g. Single-crystal **10g** was obtained from chloroform. The data were collected on an Enraf-Nomius CAD 4 diffractometer using graphite-monochromated Mo Kα radiation. The structure was inferred by direct methods and subsequent Fourier maps. Refinements were carried out by full-matrix least-squares techniques. Non-hydrogen atoms were anisotropically refined. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*, Vol. IV, 1974. All calculations and drawings were performed using a Micro VAX II computer with an SDP system. ORTEP drawings, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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Supporting Information Available: IR, MS, and elemental analysis data of *trans*-**10a**−**j** and *cis*-**11a**−**h**, and *trans*-**12a**−**h** and X-ray crystallographic data of **10g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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