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Asymmetric Induction in [3 + 2] Dipolar Cycloaddition Reactions of Nitrile Oxides with Chiral (α-Oxyallyl)silanes

Dennis P. Curran*[1] and Scott A. Gothe
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260, USA

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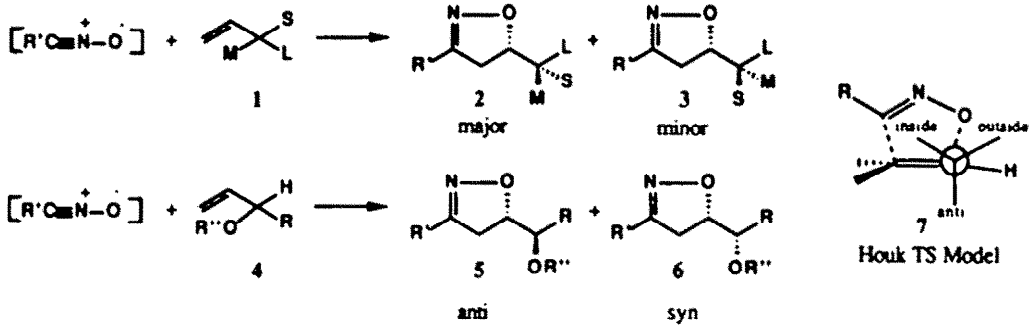
Abstract: *The dipolar cycloaddition reactions of (α-oxyallyl)silanes 12a-g with 2,2-dimethylpropanenitrile oxide and benzonitrile oxide have been studied. Mixtures of anti (14a-g and 16a-g) and syn (15a-g and 17a-g) Δ^2-isoxazolines are formed. The direction and magnitude of asymmetric induction depends on the allylic oxygen substituent: a free hydroxy provides a modest excess of the syn diastereomer, a silyl ether shows good selectivity for the anti diastereomer, and various acyl derivatives show low diastereoselectivity. The significance of these results is discussed in terms of two current models for asymmetric induction.*

The magnitude and origin of stereoselectivity in the cycloaddition reactions of nitrile oxides with acyclic α-chiral alkenes have been the subject of much experimental and theoretical study.[2,3] The trends which have emerged are summarized in Scheme 1. The cycloaddition reactions of nitrile oxides with terminal alkenes whose allylic substituents differ by size (**1**) favor the formation of diastereomer **2** over **3**. The magnitude of this preference depends on the relative sizes of the medium (M) and large (L) groups (when S = H) and ranges from negligible (M = Me, L = Et; 1/1) to modest (M = Me, L = *t*-Bu, 4/1). The important subset of reactions where the medium group is alkoxy (alkene **4**) follows the same trend, although with improved stereoselectivity. For synthetically useful R groups, the *anti* diastereomer **5** typically predominates over the *syn* counterpart **6** by a ratio of about 3/1. When R = *t*-Bu, the *anti* isomer is formed exclusively. The *anti*/*syn* ratio in these cycloadditions varies remarkably little with steric or electronic changes in either the nitrile oxide substituent (R') or the oxygen substituent (R").

Scheme 1

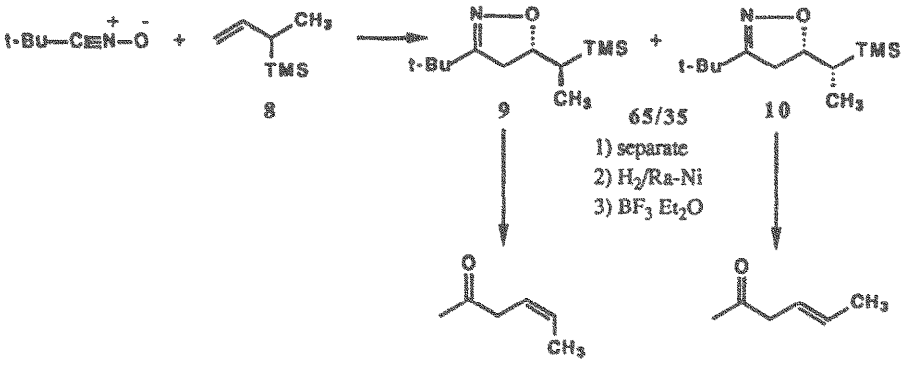


The transition state model of Houk successfully interprets these trends.[3] Taking into account the need to stagger the forming bonds, this model depicts the transition state for the nitrile oxide cycloaddition as **7**. Allylic substituents can occupy *anti*, *inside*, or *outside* positions. According to the Houk model, the major product arises from a transition state (TS) in which the largest group occupies the *anti* position, the medium group occupies the *inside* position, and the smallest group occupies the *outside* position. The minor product is assumed to result primarily from a TS in which the locations of the medium (*inside*) and small (*outside*) groups are reversed. As in the Felkin-Anh model for nucleophilic additions to carbonyls,[4] the *outside* position is more sterically demanding than the *inside* due to the angle of approach of the nitrile oxide oxygen. Superimposed on these steric preferences are the hyperconjugative electronic characteristics of the substituents. Since it is usually assumed that such nitrile oxide cycloadditions are mildly electrophilic in character, donating allylic substituents should prefer the *anti* position (to maximize donation of electron density to the alkene) while withdrawing substituents should prefer either the *inside* or *outside* positions (to minimize electron withdrawal).

Assuming that a trimethylsilyl group of a chiral allylic silane[5] should show a healthy preference for the *anti* position for both steric and electronic reasons, we previously studied the cycloaddition reactions of

nitrile oxides with α-chiral butenyl silanes **8**.[6] As summarized in Scheme 2, the diastereoselectivities were quite low although the major product **9** was that predicted by the Houk model. After separation, reductive cleavage, and Peterson elimination, each cycloadduct gave a unique β,γ-unsaturated alkene stereoisomer.

Scheme 2



We now report the results of a systematic study of the cycloaddition of nitrile oxides with (α-oxyallyl)silanes and we discuss the factors which may influence these and related cycloaddition reactions in terms of current stereochemical models.

Results and Discussion

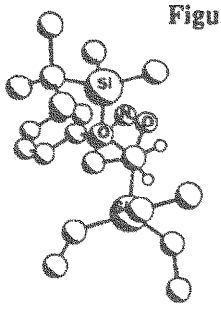
The needed dipolarophiles were synthesized as outlined in Equation 1. (α-Hydroxyallyl)silane **12a** was prepared by a modification of the known "retro-Brook" rearrangement of **11** (see Experimental).[7] Standard hydroxy derivatization procedures provided **12b-g** (see Table 1). Cycloadditions of in situ generated 2,2-dimethylpropane- and benzonitrile oxide with **12a-g** were conducted by the Huisgen method under standard conditions (oxime chloride **13**, ether, 1.1 equiv Et_3N, 25 °C, 24 h). In the reactions of **12a-g** with 2,2-dimethylpropanenitrile oxide, cycloadducts **16** and **17** were the major products, alongside recovered **13** and di-*t*-butyl furoxan (resulting from nitrile oxide dimerization). In the case of benzonitrile oxide, small amounts of 2/1 adducts[8] were also obtained along with **14**, **15**, and diphenyl furoxan. The formation of furoxans and 2/1 adducts in these cycloadditions is a strong indication that dipolarophiles **12a-g** (especially **12b**) are less reactive than the corresponding (unbranched) allyl silanes or allyl alcohols.

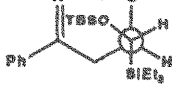
11 **12a** **12b-g** Eq. 1

The results of this series of cycloaddition experiments are collected in Table 1. Several important trends can be highlighted. With one possible exception (entry e), the *anti*/*syn* ratio varies little as a function of the substituent on the nitrile oxide. While the alcohol **12a** shows a modest preference for *syn* addition, the derived silyl ether **12b** shows a very good preference for *anti* addition. Indeed, the selectivities observed with **12b** rank with the highest previously observed selectivities in related cycloadditions. A variety of acylated derivatives **12c-g** exhibit very low selectivities. In a sequence designed to probe electronic effects (**12e-f**), there appears to be a slight increase in *syn* selectivity with more electronegative acyl substituents.

The structures of the diastereomers were assigned by standard methods. The *anti* diastereomer **14b** was separated from the minor *syn* product **15b** and its structure was determined by a single crystal x-ray analysis. The conformation of this product is relevant to the subsequent discussion, and an ORTEP plot of this structure is provided in Figure 1.[9] The structures of the other products were all assigned by chemical or spectroscopic correlation with **14b**.

Figure 1

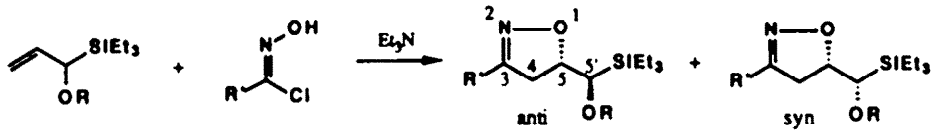




14b

Table 1

Cycloaddition Reactions of 2,2-Dimethylpropane- and Benzonitrile Oxide with 12a-g

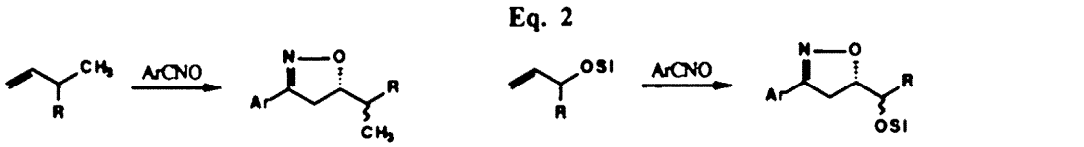


12b-g 13 R'= Ph, t-Bu 14 R'= Ph 16 R'= t-Bu 15 R'= Ph 17 R'= t-Bu

		Benzonitrile Oxide		2,2-Dimethylpropanenitrile Oxide	
Entry	R	anti (14)/syn (15)	%yield	anti (16)/syn (17)	%yield
a	H	27/73	75%	24/76	98%
b	$SiMe_2t$-Bu	94/6	40%	92/8	20%
c	$COCH_3$	42/58	82%	40/60	82%
d	CO_2CH_3	51/49	75%	52/48	63%
e	COC_6H_4p-OCH_3	55/45	88%	63/37	64%
f	COPh	57/43	79%	53/47	65%
g	COC_6H_4p-NO_2	35/65	55%	37/63	59%

Since nitrile oxide cycloadditions of this type are usually regarded as mildly electrophilic in character, the preferred location of allylic substituents to maximize electron donation (or minimize electron withdrawal) is often considered as an important factor.[10] However, Vedejs and McClure have cautioned that past interpretations of asymmetric induction in other electrophilic additions (especially osmylation) to alkenes have overemphasized the hyperconjugative role of the substituents.[11] Two observations mitigate against the attribution of observed stereochemical control to the hyperconjugative donor properties of the allyl silane. First, the cycloadditions of the alkyl- and silyloxy-substituted allyl silanes strongly parallel those of the related isopropyl derivatives studied by Houk and Jäger.[2a,b] The isopropyl, *t*-butyl, and silyl derivatives are compared in Eq 2.[12] In each case, the silyl derivative is less selective than its *t*-butyl counterpart and about the same as isopropyl.[13] Second, if the allyl silane functions as an electron donor, an increase in the rate of cycloaddition is predicted by standard FMO arguments. However, in a simple competition experiment, 1-hexene and allyl trimethylsilane were found to be essentially equally reactive towards benzonitrile oxide.

Eq. 2



anti/syn

R = i-Pr 65/35
R = TMS 65/35
R = t-Bu 77/23

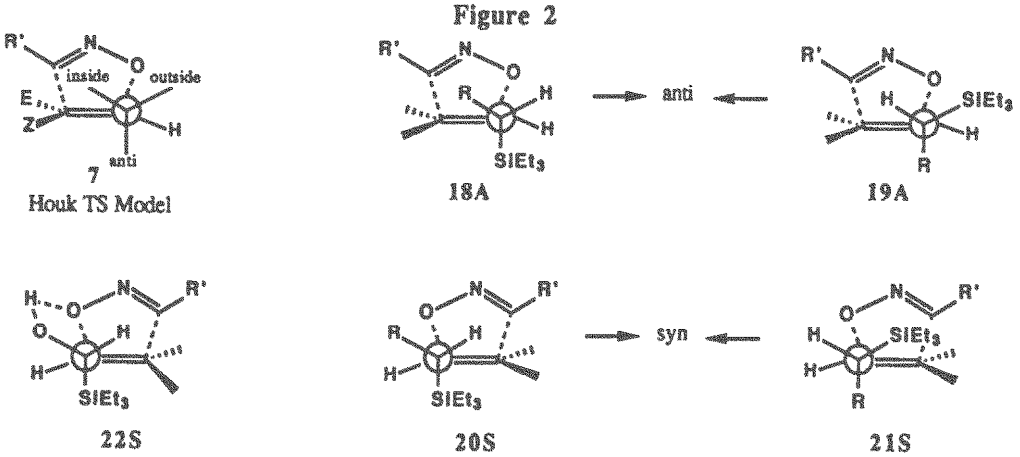
anti/syn

R = i-Pr 91/9 (Si = $SiMe_2Ph$)
R = TMS 88/12 (Si = $SiMe_3$)
R = TES 92/8 (Si = $SiMe_2t$-Bu)
R = t-Bu >95/5 (Si = $SiMe_3$ or $SiMe_2t$-Bu)

We feel that our past and present results on the cycloaddition of substituted allyl silanes with nitrile oxides are best understood in terms of the Houk steric model.[2b,c] Six possible staggered transition states can be constructed. Four of these are shown in Figure 2 [the other two which place the smallest group (H) in the position favored by the largest group (*anti*) are assumed to be unimportant]. The major product is predicted to arise from transition state **18A** which places the (large) trialkylsilyl group *anti*, the (medium) alkyl or oxy group *inside*, and the (small) hydrogen *outside*. Further circumstantial support for this assignment comes from the striking resemblance of the x-ray structure of the major product **14b** (Figure 1) to TS **18A**.[14] The minor product is predicted to arise mainly from **20S** in which the locations of the medium and small groups are reversed. However, depending on the size of the substituents, it may be energetically feasible to reverse the positions of the large and medium groups, generating the transition states **19A** and **21S**, of which the latter should be favored (small group *outside*). Thus, to the extent that TSs **19A** and **21S** are important, the *anti*-selectivity should be eroded.

Although the selectivity is very low, TS **18A** correctly predicts the predominant diastereomer in the cycloadditions of the butenyl silanes **8** (R = Me). Substitution of silyloxy for methyl results in a significant increase in *anti* selectivity; however, this increase is not unique to silicon (see Eq. 2). This trend seems at first surprising if one assumes that the *anti/syn* ratio is increased by favoring TS **18A** at the expense of **20S**. Since silyloxy is smaller than methyl, the size difference of the medium relative to the small substituent (H) is decreased. Houk and Jäger have attributed this increased selectivity to lone pair repulsions in TS **20S** when silyloxy is outside. This has been termed the "inside alkoxy effect."[3] A second possible origin for the increase in *anti* selectivity is that substitution of silyloxy for methyl actually increases the size difference between medium and large groups. Thus transition states **19A** and **21S** (which place the medium group in the *anti* position) should be disfavored relative to **18A** and **20S** (which place the large group in the *anti* position). As indicated above, this should result in increased *anti* selectivity.[15]

Figure 2

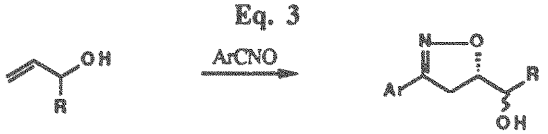


That the free alcohol **12a** exhibits *syn* selectivity is also not surprising. This has been interpreted as due to a hydrogen-bonding effect which lowers the energy of the OH-*outside* transition state (see **22S**).[16] Solvent effects have supported this proposal; the *syn* selectivity is eroded as the H-bond acceptor capability of the solvent is increased. As shown in Table 2, a survey of several solvents in the cycloaddition of **12a** again supports this analysis. However, in the series of allyl alcohols shown in Eq. 3,[17] there is no obvious relationship between the *syn/anti* selectivity and the size of the allyl substituent.

Table 2
Sovent Effects the Formation of 14a/15a

Solvent	Anti(14a)/Syn (15a)
C_6H_6	17/83
C_6H_{14}	21/79
Et_2O	25/75
DMF	58/42

Eq. 3



	anti/syn
R = CH_3	40/60
R = c-C_6H_{11}	72/28
R = t-Bu	35/65
R = TES	30/70

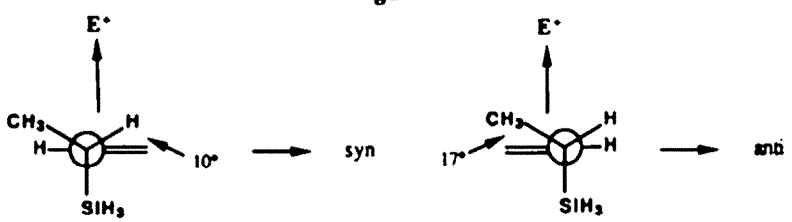
The reason for the decreased *anti* selectivity observed for all the acylated derivatives **12c-g** relative to **12b** is also not easily understood although a tentative steric argument can be advanced.[18] Electronic effects may also contribute. In view of the small changes in the *syn/anti* ratio as a function of the electronic nature of the acyl group (**12e-g**), we do not offer an interpretation.

We conclude our discussion with a brief comment on the applicability to dipolar cycloaddition reactions of the Kahn-Hehre reactivity model for electrophilic additions.[19] This model does not attempt to directly evaluate the relative transition state energies (as in the Houk model) but takes a fundamentally different approach. The product distributions are predicted by considering the accessible ground state conformations of the alkene, and the relative reactivities and diastereofacial selectivities of each energetically significant conformer. These reactivities are estimated by sophisticated electrostatic potential calculations which explicitly disregard all steric effects. The staggering of bonds in transition states cannot be important in this model since it is not a transition state model. According to the Curtin-

Hammet principle,[20] the Kahn-Hehre reactivity model is valid to the extent that the electrostatic potential calculations reflect the *rate constants* for the reactions of the individual ground state conformers.[21]

Kahn and Hehre have applied their model to the electrophilic additions of butenyl silane **23** (Figure 3).[19a] They have calculated that there are two important ground state conformers **23a** and **23b**, that **23a** is lower in energy than **23b**, and that **23a** and **23b** have approximately equal reactivity and opposite facial selectivity. According to this model, electrophilic reactions with allyl silanes should occur predominantly via **23a**. While a variety of electrophilic additions to allyl silanes are successfully interpreted, this model does not predict the formation of the correct major diastereomer **9** in the nitrile oxide cycloaddition with **8** (See Scheme 2).[22]

Figure 3



23a **23b**

This failure to predict the correct diastereomer is by no means an indictment of the Kahn-Hehre model, especially in view of the small energy differences involved and the fact that true electrophilic additions (protonolysis, bromination, etc.) must show a greater concentration of positive charge on the carbon β to silicon than in this cycloaddition reaction (that is, electronic effects are more important). However, the reactivity model has already been extended to interpret diastereofacial selectivities in Diels Alder reactions.[19b] The present results indicate that such extensions of this model to cycloadditions and other pericyclic reactions should be approached with caution.

Experimental

General: All reactions were run under an argon atmosphere. Solvents were dried as follows: Et_2O, and benzene, distilled from Na/benzophenone; Et_3N, distilled from CaH_2. Flash and medium pressure (MPLC) liquid chromatography were performed with Kieselgel 60 (230-400 mesh). Medium pressure chromatography was also done on pre-packed EM Lobar LiChroprep Si/60 columns. Thin layer chromatography was performed on Merck silica gel 60 pre-coated plates. All melting points are uncorrected. Proton NMRs were recorded at 300 MHz.

1-Triethylsilyl-2-propen-1-ol (12a).[7,23]
To a solution of triethylallyloxysilane **11** (0.25 g, 1.4 mmol) in tetrahydrofuran (5 mL) at –78 °C was added *sec*-butyllithium (1.22 mL, 1.6 mmol, 1.3 M in cyclohexane) dropwise, such that the temperature of the reaction mixture never exceeded –68 °C. The reaction was allowed to stir for 1.5 h, and poured rapidly into 1:1 diethyl ether/aqueous NH_4Cl (100 mL). The two phases were separated, and the aqueous layer was extracted with diethyl ether (3 x 35 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to give a yellow liquid. Purification by flash chromatography (20:1 hexane/ethyl acetate) yielded 0.244 g (98%) of (**12a**): IR (neat) 3088 (br) 2955, 2913, 2878, 1717, 1630, 1458, 1416, 1240, 1097, 1013, 901, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.07 (ddd, 1H, J = 17.2, 10.7, 5.2 Hz), 5.09 (dt, 1H, J = 17.2, 1.8 Hz), 4.97 (dt, 1H, J = 10.7, 1.8 Hz), 4.18 (dt, 1H, J = 5.2, 2.3 Hz), 0.97 (t, 9H, J = 9.0 Hz), 0.63 (q, 6H, J = 9.0 Hz).

General cycloaddition procedure: *syn* and *anti*-5-(1-Triethylsilyl-1-hydroxymethyl)-3-phenyl-Δ²-isoxazoline (14a and 15a).
1-Triethylsilyl-2-propen-1-ol (22.6 mg, 0.13 mmol) and phenyl hydroximoyl chloride (20.5 mg, 0.13 mmol) were added with stirring to dry diethyl ether (1 mL). Triethylamine (20 μL, 0.15 mmol) was then added dropwise with vigorous stirring. The reaction was allowed to stir for 23 h at 25 °C. The resulting precipitate was then filtered, and the filtrate was concentrated to yield a yellow liquid. Purification of the crude product by flash chromatography (9:1 hexane/ethyl acetate) yielded 28.7 mg (75%) of a pale yellow oil, which was a 1:3 *anti/syn* mixture of diastereomers **14a/15a**: IR (thin film) 3427 (br), 2953, 2911, 2876, 1497, 1456, 1447, 1358, 1240, 1017, 912, 835, 760, 735, 692 cm^{-1}; ^1H NMR ($CDCl_3$), **14a** δ 7.67 (m, 2H), 7.40 (m, 3H), 4.87 (td, 1H, J = 10.6, 2.0 Hz), 4.01 (br s, 1H), 3.47 (dd, 1H, J = 16.2, 10.6 Hz), 3.21 (dd, 1H, J = 16.2, 10.6 Hz), 1.80 (d, 1H, J = 1.0 Hz), 1.03 (t, 6H, J = 7.8 Hz), 0.70 (q, 9H, J = 7.8 Hz), **15a** δ 7.65 (m, 2H), 7.36 (m, 3H), 4.91 (td, 1H, J = 9.4, 4.7 Hz), 3.49 (d, 1H, J = 1.2 Hz), 3.3-3.5 (dd, overlapped by anti diastereomer, 1H), 3.33 (dd, 1H, J = 9.4, 8.5 Hz), 1.6 (br s, 1H), 1.01 (t, 6H, J = 7.8 Hz), 0.70 (q, 9H, J = 7.8 Hz); MS *m/e* 262 (M^+), 159, 145, 130, 115, 103, 87, 75 (base), 59; HRMS calculated for $C_{14}H_{20}NO_2Si$, 262.1263; observed, 262.1263.

***syn* and *anti*-5-(1-Triethylsilyl-1-hydroxymethyl)-3-*tert*-butyl-Δ²-isoxazoline (16a and 17a).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-2-propen-1-ol (12.4 mg, 0.07 mmol), *tert*-butyl hydroximoyl chloride (9.8 mg, 0.07 mmol), diethyl ether (0.5 mL), and triethylamine (10 μL, 0.08 mmol) (16 h). Purification of the crude product by flash chromatography (9:1 hexane/ethyl acetate) yielded 19.2 mg (98%) of a pale yellow oil, which was a 1:3 *anti/syn* mixture of diastereomers **16a/17a**: IR (thin film) 3416 (br), 2957, 2876, 2910, 1678, 1460, 1366, 1252, 1009, 884, 735 cm^{-1}; ^1H NMR (C_6D_6) δ 4.41-4.57 (m, 2H, [H-5, *anti* and *syn*]), 3.78 (d, 1H, J = 2.5 Hz, [H-5', *anti*]), 3.22 (d, 1H, J = 5.4 Hz, [H-5', *syn*]), 2.97 (dd, 1H, J = 17.1, 9.5 Hz, [H-4, anti]), 2.68 (dd, 1H, J = 17.1, 9.0 Hz, [H-4, syn]), 2.51 (dd, 1H, J = 17.1, 10.8 Hz, [H-4, anti]), 2.39 (ddd, 1H, J = 15.8, 11.3, 2.3 Hz, [H-4, syn]), 0.84-1.1 (m, 12H, [overlapping t, anti and syn]), 1.04 (s, 18H, [anti and syn]), 0.4-0.7 (m, 18H [overlapping q, anti and syn]); MS *m/e* 242 (M^+), 168, 131, 115, 103, 87, 83, 75, 57 (base), 47; HRMS calculated for $C_{12}H_{24}NO_2Si$, 242.1576; observed, 242.1577.

***syn* and *anti*-5-[1-Trimethylsilyl-1-(trimethylsilyl)oxymethyl]-3-phenyl-Δ²-isoxazoline. (see Eq. 2)**
Prepared following the general cycloaddition procedure with α-trimethylsilyloxyallyltrimethylsilane (182 mg, 0.9 mmol), phenyl hydroximoyl chloride (128 mg, 0.8 mmol), diethyl ether (2 mL), and triethylamine (0.125 mL, 0.9 mmol) (16 h). Purification was effected by MPLC (15:1 hexane/ethyl acetate), yielding 0.133 g (50%) as a 7.3:1 *anti/syn* mixture of diastereomers: IR (thin film) 2955, 2812, 1570, 1499, 1360, 1250, 1038, 945, 909, 843, 762, 693, 668 cm^{-1}; ^1H NMR ($CDCl_3$) *anti* δ 7.67 (m, 2H), 7.40 (m, 3H), 4.81 (td, 1H, J = 10, 1.3 Hz), 3.91 (d, 1H, J < 1Hz), 3.41 (dd, 1H, J = 16.2, 10.2 Hz), 3.09 (dd, 1H, J = 16.1, 10.8 Hz), 0.09 (s, 9H), 0.07 (s, 9H), *syn* δ 7.65 (m, 2H), 7.40 (m, 3H), 4.82-5.01 (m, 1H overlapped by anti), 3.74 (d, 1H, J = 1.2 Hz), 3.37-3.49 (dd, 1H overlapped by anti), 3.03-3.15 (dd, 1H overlapped by anti), 0.09 (s, 9H), 0.07 (s, 9H); MS *m/e* 321 (M^+), 306, 231, 147, 130, 113, 73 (base), 59; HRMS calculated for $C_{15}H_{24}NO_2Si_2$ ($M^+ - CH_3$), 306.1346; observed, 306.1346.

***syn* and *anti*-5-(1-Triethylsilyl-1-acetoxymethyl)-3-phenyl-Δ²-isoxazoline (14c and 15c).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-acetoxy-2-propene (35.8 mg, 0.17 mmol), phenyl hydroximoyl chloride (38.95 mg, 0.25 mmol), diethyl ether (2 mL), and triethylamine (41 μL, 0.34 mmol) (29 h). Concentration of the filtrate yielded 45.6 mg (82%) of a 1:1 mixture of diastereomers (determined by ^1H NMR) which was inseparable by chromatography: IR (thin film) 2955, 2912, 2877, 1739, 1695, 1456, 1447, 1419, 1368, 1233, 1160, 1012, 950, 913, 761, 722, 693, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4H, [anti and syn]), 7.40 (m, 6H, [anti and syn]) 5.30 (d, 1H, J = 4.5 Hz, [H-5', anti]) 5.13 (d, 1H, J = 3.6 Hz, [H-5', syn]), 4.81-5.0 (m, 2H, [H-5, anti and syn]), 3.20-3.38 (m, 2H, [H-4, anti and syn]), 2.72-3.05 (m, 2H, [H-4, anti and syn]), 2.03 (s, 3H, [OAc]) 2.01 (s, 3H, [OAc]) 0.9-1.03 (m, 12H, [overlapping t, anti and syn]), 0.45-0.60 (m, 18H, [overlapping q, anti and syn]); MS *m/e* 333 (M^+) 304 (base), 290, 274, 262, 244, 159, 145, 131, 115, 103, 72, 43; HRMS calculated for $C_{18}H_{27}NO_3Si$, 333.1760; observed, 333.1761.

***syn* and *anti*-5-[1-Triethylsilyl-1-acetoxymethyl)-3-*tert*-butyl-Δ²-isoxazoline (16c and 17c).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-acetoxy-2-propene (14 mg, 0.07 mmol), *tert*-butyl hydroximoyl chloride (8.8 mg, 0.07 mmol), diethyl ether (0.5 mL), and triethylamine (1 μL, 0.07 mmol) (17 h). Concentration of the filtrate yielded 18 mg (82%) of an approximately 1:1 mixture of diastereomers which was inseparable by chromatography: IR (thin film) 2958, 2914, 2877, 1733, 1479, 1460, 1368, 1266, 1235, 1020, 878, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (d, 1H, J = 4.5 Hz, [H-5' anti]), 5.01 (d, 1H, J = 3.6 Hz, [H-5' syn]), 4.60-4.80 (m, 2H, [H-5, anti and syn]), 2.8-3.05 (m, 3H), 2.61 (dd, 1H, J = 16.7, 8.6 Hz), 2.09 (s, 3H, [OAc]), 2.01 (s, 3H, [OAc]), 1.2 (s, 9H, [t-Bu]), 1.18 (s, 9H, [t-Bu]), 0.93-1.02 (m, 12H, [overlapping t, anti and syn]), 0.58-0.72 (m, 18H, [overlapping q, anti and syn]); MS *m/e* 313 (M^+), 284, 270, 254, 242, 171, 145, 125, 115, 83, 72, 57 (base), 43; HRMS calculated for $C_{16}H_{31}NO_3Si$, 313.2073; observed, 313.2073.

***syn* and *anti*-5-[1-Triethylsilyl-1-(methoxycarbonyloxy)methyl]-3-phenyl-Δ²-isoxazoline (14d and 15d).**
Prepared following the general cycloaddition procedure with methyl-(1-triethylsilylprop-2-enyl) carbonate (3.9 mg, 0.02 mmol), phenyl hydroximoyl chloride (2.7 mg, 0.02 mmol), diethyl ether (0.1 mL), and triethylamine (3 μL, 0.02 mmol) (17 h). Concentration of the filtrate yielded 4.3 mg (75%) of a yellow liquid which was dissolved in $CDCl_3$ to obtain an NMR ratio of products (1:1, *syn/anti*) : ^1H NMR δ 7.49-7.57 (m, 4H, [Ph, syn and anti]), 7.31-7.49 (m, 6H, [Ph, syn and anti]) 5.39 (d, 1H, J = 5.4 Hz, [H-5' anti]), 5.26 (d, 1H, J = 3.7 Hz, [H-5' syn]), 4.87-5.02 (m, 2H, [H-5, syn and anti]), 3.27-3.37 (m, 2H, [overlapping dd, H-4 syn and anti]), 2.90-3.10 (m, 2H, [overlapping dd, H-4 syn and anti]), 1.61 (br s, 6H, [OCH_3 syn and anti]), 0.5-1.1 (br m, 30 H, [TES, syn and anti]).

***syn* and *anti*-5-[1-Triethylsilyl-1-(methoxycarbonyloxy)methyl]-3-*tert*-butyl-Δ²-isoxazoline (16d and 17d).**
Prepared following the general cycloaddition procedure with methyl-(1-triethylsilylprop-2-enyl) carbonate (3.9 mg, 0.02 mmol), *tert*-butyl hydroximoyl chloride (2.3 mg, 0.02 mmol), diethyl ether (0.1 mL), and triethylamine (3 μL, 0.02 mmol) (17 h). Concentration of the filtrate yielded 3.4 mg (63%) of a yellow liquid which was dissolved in $CDCl_3$ to obtain an NMR ratio of products (1:1.2 *syn/anti*): ^1H NMR δ 5.21 (d, 1H, J =5.4 Hz, [H-5' anti]), 5.14 (d, 1H, J = 3.6 Hz, [H-5' syn]), 4.71-4.80 (m, 2H, [H-5 syn and anti]), 2.86-3.02 (m, 2H, [overlapping dd, H-4 syn and anti]), 2.56-2.70 (m, 2H, [overlapping dd, H-4 syn and anti]), 1.60 (br s, 6H, [OCH3 syn and anti]), 1.52 (s, 9H), 1.49 (s, 9H), 0.86-1.10 (m, 18H, [TES syn and anti]), 0.5-0.82 (m, 6H, [TES syn and anti]).

***syn* and *anti*-5-[1-Triethylsilyl-1-(*tert*-butyldimethylsilyloxy)methyl)-3-phenyl-Δ²-isoxazoline (14b and 15b).**
Prepared following the general cycloaddition procedure, α-*tert*-butyldimethylsilyloxyallyltriethylsilane (37.6 mg, 0.13 mmol), phenyl hydroximoyl chloride (20.5 mg, 0.13 mmol), and triethylamine (20 μL, 0.15 mmol) (17 h). Purification of the crude product by flash chromatography (25:1 hexane/ethyl acetate) yielded 21.2 mg (40%) of a 13.7:1 *anti/syn* mixture of diastereomers. Further purification of 14b for X-ray analysis was effected by recrystallization from methanol (mp 73-74 °C): IR (thin film) 2955, 2932, 2878, 1472, 1462, 1358, 1252, 1103, 1059, 1005, 986, 912, 835, 777, 760, 715, 691 cm^{-1}; ^1H NMR ($CDCl_3$) *anti* δ 7.67 (m, 2H), 7.40 (m, 3H), 4.80 (t, 1H, J = 11.4 Hz), 4.11 (s, 1H), 3.46 (dd, 1H, J = 16.1, 11.4 Hz), 3.08 (dd, 1H, J = 16.0, 10.5 Hz), 1.03 (t, 9H, J = 7.8 Hz), 0.81 (s, 9H), 0.65 (q, 6H, J = 7.8 Hz), 0.09 (s, 3H), 0.04 (s, 3H); *syn* δ 7.68 (m, 2H), 7.39 (m, 3H), 4.91 (ddd, 1H, J = 10.6, 9.3, 7.1 Hz), 3.73 (d, 1H, J = 7.1 Hz); 3.23 (dd, 1H, J =16.5, 9.3 Hz), 3.09 (dd, 1H, J = 16.5, 10.6 Hz), 1.02 (t, 9H, J = 7.8 Hz), 0.84 (s, 9H), 0.68 (q, 6H, J = 7.8 Hz), 0.16 (s, 3H), 0.08 (s, 3H); MS *m/e* 376 (M^+), 348, 273, 216, 189, 161, 113, 87, 73 (base); HRMS calculated for $C_{20}H_{34}O_2NSi_2$, 376.2128; observed, 376.2128 (anti).

***syn* and *anti*-5-[1-Triethylsilyl-1-(*tert*-butyldimethylsilyl)oxymethyl]-3-*tert*-butyl-Δ²-isoxazoline (16b and 17b).**
Prepared following the general cycloaddition procedure with α-*tert*-butyldimethylsilyloxyallyltriethylsilane (37.6 mg, 0.13 mmol), *tert*-butyl hydroximoyl chloride (19.6 mg, 0.15 mmol), and triethylamine (20 μL, 0.15 mmol) (17 h). Purification of the crude product by flash chromatography (25:1 hexane/ethyl acetate) yielded 10.1 mg (20%) of a 12.1:1 *anti/syn* mixture of diastereomers: IR (thin film) 2957, 2876, 1559, 1458, 1364, 1252, 1103, 1059, 1011, 980, 891, 864, 835, 777 cm^{-1}; ^1H NMR ($CDCl_3$) *anti* δ 4.57 (dt, 1H, J = 12.1, 1 Hz), 4.03 (br s, 1H), 3.08 (dd, 1H, J = 16.2, 12.1 Hz), 2.65 (dd, 1H, J = 16.5, 10.4 Hz), 1.19 (s, 9H), 0.97 (t, 9H, J = 7.9 Hz), 0.89 (s, 9H), 0.60 (q, 6H, J = 7.9 Hz), 0.08 (s, 3H), 0.04 (s, 3H); *syn* δ 4.65 (ddd [overlapped by anti dt], 1H, J = 11, 9.5, 7.1 Hz), 3.81 (br s, 1H), 3.09 (dd, 1H, [overlapped by anti]), 2.68 (dd, 1H, [overlapped by anti]), 1.21 (s, 9H), 0.96 (t, 9H, [overlapped by anti]), 0.91 (s, 9H), 0.58 (q, 6H, J = 7.9 Hz), 0.06 (s, 3H), 0.03 (s, 3H); MS *m/e* 328 (M^+), 253, 242, 197, 161, 140, 115, 103, 87, 75, 57 (base); HRMS calculated for $C_{16}H_{34}NO_2Si_2$, 328.2128; observed, 328.2128.

***syn* and *anti*-5-(1-Triethylsilyl-1-benzoyloxymethyl)-3-phenyl-Δ²-isoxazoline (14f and 15f).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-benzoyloxy-2-propene (32.6 mg, 0.13 mmol), phenyl hydroximoyl chloride (20.5 mg, 0.13 mmol), and triethylamine (20 μL, 0.15 mmol) (16 h). Concentration of the filtrate yielded 41.2 mg (79%) of a 1.3:1 *anti/syn* mixture of diastereomers: IR (thin film) 2955, 2912, 2877, 1721, 1452, 1315, 1266, 1107, 1098, 1010, 710 cm^{-1}; ^1H NMR ($CDCl_3$) *anti* and *syn* δ 7.96 (m, 4H [anti and syn benzoates]), 7.65-

7.29 (m, 16H [anti and syn aromatics]), 5.49 (d, 1H, J = 5.0 Hz, [H-5' anti]), 5.37 (d, 1H, J = 2.8 Hz, [H-5' syn]), 5.10-5.00 (m, 2H, [H-5 anti and syn]), 3.51-3.28 (m, 3H, [H-4 anti and syn and H-4a anti]), 3.05 (dd, 1H, J = 16.7, 8.7 Hz, [H-4 syn]), 1.04 (m, 12H, [overlapping t]), 0.77 (m, 18 H, [overlapping q]).

***syn* and *anti*-5-(1-Triethylsilyl-1-benzoyloxymethyl)-3-*tert*-butyl-Δ²-isoxazoline (16f and 17f).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-benzoyloxy-2-propene (32.6 mg, 0.13 mmol), *tert*-butyl hydroximoyl chloride (19.6 mg, 0.13 mmol), and triethylamine (20 μL, 0.15 mmol) (20 h). Purification of the crude product by flash chromatography (25:1 hexane/ethyl acetate) yielded 32.3 mg (65%) of a 1.1:1 *anti/syn* mixture of diastereomers as a clear oil which solidified upon standing at 0 °C: IR (thin film) 2955, 2910, 2876, 1715, 1451, 1314, 1266, 1109, 1025, 761, 711, 692 cm⁻¹; ¹H NMR ($CDCl_3$) *anti* and *syn* δ 7.26-7.67 (m, 10H, [anti and syn aromatics]), 5.50 (d, 1H, J = 5.9 Hz, [H-5' anti]), 5.38 (d, 1H, J = 3.6 Hz, [H-5' syn]), 5.12-5.01 (m, 2H, [H-5 anti and syn]), 3.52-3.18 (m, 3H, [H-4 anti and syn and H-4a anti]), 3.06 (dd, 1H, J = 16.0, 8.0 Hz, [H-4 syn]), 1.09-0.94 (m, 12H, [overlapping t]), 0.83-0.64 (m, 18 H, [overlapping q]); MS *m/e* 346 (M^+–Et), 290, 274, 158, 105 (base), 87, 77, 57; HRMS calculated for $C_{19}H_{28}NO_3Si$, 346.1838; observed, 346.1837.

***syn* and *anti*-5-[1-Triethylsilyl-1-(*p*-methoxybenzoyloxy)methyl]-3-phenyl-Δ²-isoxazoline (14e and 15e).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-*p*-methoxybenzoyloxy-2-propene (10.0 mg, 0.03 mmol), phenyl hydroximoyl chloride (5.1 mg, 0.03 mmol), diethyl ether (0.25 mL), and triethylamine (5 μL, 0.04 mmol) (18 h). Purification of the crude product by flash chromatography (25:1 hexane/ethyl acetate) yielded 12.2 mg (88%) of a 1.2:1 *anti/syn* mixture of diastereomers: IR (thin film) 2955, 2876, 1705, 1605, 1510, 1256, 1167, 1100, 1026, 760, 693 cm⁻¹; ¹H NMR ($CDCl_3$) *anti* and *syn* δ 8.05-7.94 (m, 4H, [syn and anti benzoates]), 7.64-7.27 (m, 10H, [syn and anti phenyls]), 6.98-6.80 (m, 4H, [syn and anti benzoates]), 5.44 (d, 1H, J = 5.4 Hz, [H-5' anti]), 5.34 (d, 1H, J = 3.6 Hz, [H-5' syn]), 5.10-4.98 (m, 2H, [H-5 syn and anti]), 3.86 (s, 3H, [OMe]), 3.80 (s, 3H, [OMe]), 3.51-3.27 (m, 3H, [H-4 anti and syn and H-4a anti]), 3.05 (dd, 1H, J = 18.0, 9.0 Hz, [H-4 syn]), 1.08-0.96 (m, 12H, [overlapping t, syn and anti]), 0.82-0.62 (m, 18H, [overlapping q, syn and anti]); MS *m/e* 425 (M^+), 396, 274, 262, 237, 135 (base); HRMS calculated for $C_{24}H_{31}NO_4Si$, 425.2022; observed, 425.2022.

***syn* and *anti*-5-[1-Triethylsilyl-1-(*p*-methoxybenzoyloxy)methyl]-3-*tert*-butyl-Δ²-isoxazoline (16e and 17e).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-*p*-methoxybenzoyloxy-2-propene (10.0 mg, 0.03 mmol), *tert*-butyl hydroximoyl chloride (4.4 mg, 0.03 mmol), diethyl ether (0.25 mL), and triethylamine (5 μL, 0.04 mmol) (18 h). Purification of the crude product by flash chromatography (25:1 hexane/ethyl acetate) yielded 8.4 mg (63%) of a 1.7:1 *anti/syn* mixture of diastereomers: IR (thin film) 2957, 2876, 1709, 1607, 1510, 1458, 1256, 1167, 1100, 1007, 729 cm⁻¹; ¹H NMR ($CDCl_3$) *anti* and *syn* δ 8.05-7.94 (m, 4H, [syn and anti benzoates]), 6.98-6.90 (m, 4H, [syn and anti benzoates]), 5.31 (d, 1H, J = 6.3 Hz, [H-5' anti]), 5.21 (d, 1H, J = 4.0 Hz, [H-5' syn]), 4.91-4.77 (m, 2H, [H-5 syn and anti]), 3.86 (br s, 6H, [OMe]), 3.10-2.91 (m, 3H, [H-4 syn and anti and H-4a anti]), 2.69 (dd, 1H, J = 18, 17.2 Hz, [H-4 syn]), 1.38 (s, 9H, [t-Bu syn]), 1.18 (s, 9H, [t-Bu anti]), 1.06-0.97 (overlapping t, 12H, J = 8.0 Hz, [syn and anti]), 0.80-0.62 (overlapping q, 18H, J = 8.0 Hz, [syn and anti]); MS *m/e* 405 (M^+), 376, 306, 277, 237, 217, 135 (base), 115, 72, 57; HRMS calculated for $C_{20}H_{30}NO_4$ (M – Et), 376.1943; observed, 376.1929.

***syn* and *anti*-5-[1-Triethylsilyl-1-(*p*-nitrobenzoyloxy)methyl]-3-phenyl-Δ²-isoxazoline (14g and 15g).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-*p*-nitrobenzoyloxy-2-propene (38.6 mg, 0.13 mmol), phenyl hydroximoyl chloride (20.5 mg, 0.13 mmol), and triethylamine (20 μL, 0.15 mmol) (17 h). Purification of the crude product by flash chromatography (15:1 hexane/ethyl acetate) yielded 32.4 mg (55%) of a 1:1.8 *anti/syn* mixture of diastereomers as a crystalline solid: IR (thin film) 2953, 2874, 1717, 1526, 1354, 1318, 1269, 1117, 1103, 908, 720 cm⁻¹; ¹H NMR ($CDCl_3$) *anti* and *syn* δ 8.06-8.20 (m, 8H, [anti and syn]), 7.63 (m, 2H), 7.56 (m, 2H), 7.41 (m, 3H), 7.33 (m, 3H), 5.57 (d, 1H, J = 4.0 Hz, [H-5' anti]), 5.38 (d, 1H, J = 3.0 Hz, [H-5' syn]), 5.03-5.09 (m, 2H, [H-5 anti and syn]), 3.33-3.54 (m, 3H, [H-4 anti and syn and H-4a anti]), 3.02 (dd, 1H, J = 16.4, 8.1 Hz, [H-4 syn]), 1.05 (overlapping t, 12H, J = 7.9 Hz, [anti and syn]), 0.79 (m, 18H, [overlapping q, anti and syn]); MS *m/e* 440 (M^+), 411, 381, 274, 252 (base), 206, 150, 120, 104, 87, 77, 59; HRMS calculated for $C_{23}H_{28}N_2O_5Si$, 440.1768; observed, 440.1767.

***syn* and *anti*-5-[1-Triethylsilyl-1-(*p*-nitrobenzoyloxy)methyl]-3-*tert*-butyl-Δ²-isoxazoline (16g and 17g).**
Prepared following the general cycloaddition procedure with 1-triethylsilyl-1-*p*-nitrobenzoyloxy-2-propene (38.6 mg, 0.13 mmol), *tert*-butyl hydroximoyl chloride (19.6 mg, 0.13 mmol), and triethylamine (20 μL, 0.15 mmol) (17 h). Purification of the crude product by flash chromatography (25:1 hexane/ethyl acetate) yielded 32.9 mg (59%) of a 1:1.7 *anti/syn* mixture of diastereomers as a clear viscous oil: IR (thin film) 2959, 2876, 1719, 1528, 1347, 1320, 1269, 1102, 1015, 720 cm⁻¹; ¹H NMR ($CDCl_3$) *anti* and *syn* δ 8.13-8.31 (m, 8H, [anti and syn]), 5.43 (d, 1H, J = 5.0 Hz, [H-5' anti]), 5.27 (d, 1H, J = 2.8 Hz, [H-5' syn]), 4.80-4.93 (m, 2H, [H-5 anti and syn]), 2.91-3.11 (m, 3H, [H-4 anti and syn and H-4a anti]), 2.65 (dd, 1H, J = 17.1, 7.4 Hz, [H-4 syn]), 1.16 (s, 9H), 1.02 (s, 9H), 1.00 (overlapping t, 12H, J = 7.3 Hz), 0.74 (overlapping q, 18H, J = 7.3 Hz); MS *m/e* 420 (M^+), 391, 252, 150, 120, 104, 87, 75, 69, 57 (base); HRMS calculated for $C_{21}H_{32}N_2O_5Si$, 420.2080; observed, 420.2081.

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References and Notes

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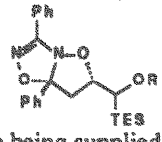
8 These adducts (see i) which result from a second cycloaddition of the primary adduct, are common products in the reaction of benzonitrile oxide with unreactive alkenes (see Kim, B. H. *Synth. Commun.* **1987**, *17*, 1199). We assumed that the diastereomeric cycloadducts (**14/15**) reacted at equal rates with benzonitrile oxide and the ratios compiled in Table 1 were not corrected for the presence of small amounts of adducts i. In one case, the validity of this assumption was demonstrated.



i

9 Details of this crystallographic study are being supplied to the Cambridge Crystallographic File.

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15 The use of *Z*-disubstituted alkenes in cycloadditions is an interesting test of the Houk model since the energy of TSs **18** and **21** should be significantly raised due to A-strain. Intermolecular cycloadditions are not feasible due to the lack of reactivity of the alkene. However, the sense and magnitude of asymmetric induction for intramolecular cycloadditions of *Z*-alkenes are very similar to monosubstituted alkenes. For results and an interpretation in the context of the Houk model, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674.

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17 Entries 1 and 3 are taken from ref. 2a. Entry 2 is from the unpublished work of J. Zhang in these labs.

18 The esters may behave as larger groups than alkoxy due to conformational preferences. While an alkoxy group can adopt a staggered arrangement with the O–R bond between the small and large substituents, secondary esters prefer a conformation where the ester C–H bond is nearly eclipsed with the carbonyl. Thus, the oxygen substituent is drawn closer to the forming isoxazoline ring.

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21 For the simplest possible system (1) where conformer equilibrium is more rapid than reaction, the relevant formulation of the Curtin-Hammett principle is (2) (ref. 20).

$$\text{(1)} \qquad B \overset{k_1}{\rightleftharpoons} A_1 \overset{K}{\rightleftharpoons} A_2 \overset{k_2}{\rightleftharpoons} C \qquad [B]/[C] = K(k_1/k_2) \qquad \text{(2)}$$

Given a (computational) knowledge of the equilibrium constant K, one needs to evaluate the ratios of the rate constants k_1 and k_2 to predict the product ratio.

22 Qualitative extension of the Kahn-Hehre reactivity model to **12** does not appear to be possible; calculations would be required to evaluate this system.

23 A large scale preparation of the trimethylsilyl derivative has recently appeared: Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *Org. Syn.* **1987**, *66*, 14.