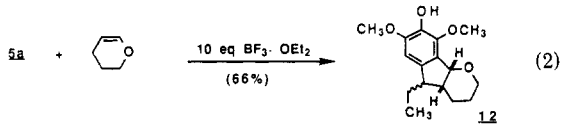
diastereomer was identical with **7j** produced from the reaction of quinone methide **5a** with the (*Z*)-**6d** in entry 6.[6] The origin of the stereochemical control is currently under investigation and will be discussed in a full account of this work.

It is worth noting that in entries 3 and 5 (Table I) styrene **6c**, a bidentate Lewis base (*o*-methoxyphenol), afforded a lower yield of adducts than styrene **6b** (entries 2 and 4), which is a monodentate Lewis base (phenol). The low yield may be due to competitive styrene polymerization initiated by complexation of the *o*-methoxyphenol of **6c** with the Lewis acid.[13]

In theory, this reaction should not be limited to styrenes, any alkene with a substituent capable of stabilizing a positive charge might participate in the cycloaddition. To test this idea, a solution of dihydropyran and quinone methide **5a** was treated with $BF_3{\cdot}OEt_2$ to afford a 66% yield of hexahydroindeno[1,2-*b*]pyran **12** as a 1:1 mixture of diastereomers (eq 2). The diastereomers were separated by HPLC and the stereo- and regiochemical assignments were confirmed by NOE experiments.



(2)

We anticipate this process to be a general reaction and are currently exploring its scope and utility in the synthesis of natural products.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (GM 39354). We thank Mr. Ron New and Dr. Richard Kondrat for mass spectra and Professor David Hart of The Ohio State University for a helpful discussion.

Supplementary Material Available: General procedures for quinone methide formation and the formal cycloaddition, spectral data used for the characterization of **5b**, **7**, and **8**, and a summary of key NOE experiments for **7j**, **8j**, and **12** (8 pages). Ordering information is given on any current masthead page.

(12) Diastereomer **7e** was not available since the reaction of (*Z*)-**6a** with quinone methide **5a** afforded adduct **7e** as an inseparable mixture of several compounds in 13% yield.

(13) To support this notion considerable low R_f material was seen in the TLC of the crude reaction mixtures and intractable material, insoluble in CH_2Cl_2, was obtained. In addition, simple ethenylstyrenes failed to afford adducts; only styrene polymerization was observed in these cases.

Directed Nitrile Oxide Cycloaddition Reactions. The Use of Hydrogen Bonding To Direct Regio- and Stereochemistry in Nitrile Oxide Cycloadditions with Cyclopentenylamides

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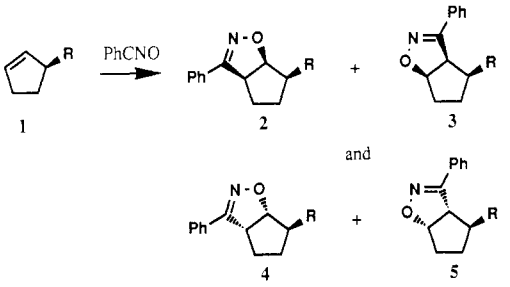
Summary: 2° amides derived from cyclopentenylamine direct the regio- and stereochemistry of cycloaddition reactions with benzonitrile oxide and 2,2-dimethylpropane nitrile oxide by hydrogen bonding.

Lewis acids can effect the rates of organic reactions—and hence dictate chemo-, regio-, and stereoselectivity—either by altering the electronic structure of one of the reactants (for example, the Diels–Alder reaction[2]) or by serving as templates to bring the reactants together (for example, the directed epoxidation of allylic alcohols[3]). Although analogous in many respects to Diels–Alder reactions, many 1,3-dipolar cycloaddition reactions do not benefit from the addition of Lewis acids, perhaps because 1,3-dipoles are often better Lewis bases than the acceptors with which they react.[4] However, the Lewis basicity of a 1,3-dipole might be used to advantage in a reaction in which a Lewis acid functions as a template to bring a dipole and a dipolarophile together in a proper orientation for cycloaddition (Figure 1).[5] A proton is the simplest Lewis acid, and indeed there is good evidence that an allylic hydroxy

Table I. Cycloaddition of PhCNO with 3-Substituted Cyclopentenes



substr	R	solvent	ratio 2:3:4:5				ref
			2	3	4	5	
1a	Me	Et_2O	3	1	63	33	6a
1b	NMe_2	Et_2O	7	0	23	70	6a
1c	OMe	Et_2O	3	4	22	71	6a
1d	OAc	Et_2O	5	3	15	77	6a
1e	OH	Et_2O	30	5	12	53	6a
1e	OH	PhH	50	nd[a]	17	33	
1f	NHCOPh	PhH	90	nd	nd	10	

[a] nd = not determined. Small amounts (<5%) could have gone undetected.

(1) Dreyfus Teacher Scholar, 1986–91; National Institutes of Health Career Development Awardee, 1987–92.

(2) Leading references: (a) Paquette, L. A. In *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 456–478. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, pp 261–306. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(3) Henbest epoxidation: Berti, G. *Top Stereochem.* **1973**, *7*, 93. Sharpless asymmetric epoxidation: Sharpless, K. B. *Janssen Chem. Acta* **1988**, *6*, 3.

(4) (a) For example, many BF_3–nitrone complexes are stable solids: LeBel, N. A.; Balasubramanian, N. *Tetrahedron Lett.* **1985**, *26*, 4331. (b) For effects of Lewis acids on nitrile oxide cycloadditions, see: Morrocchi, S.; Ricca, A.; Velo, L. *Tetrahedron Lett.* **1967**, 331. Grundmann, C.; Richter, R. *Tetrahedron Lett.* **1968**, 963. Plumet, J.; Escobar, G.; Manzano, C.; Arjona, O.; Carrupt, P.-A.; Vogel, P. *Heterocycles* **1986**, *24*, 1535. Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.

(5) For a recent example where $Ti(O\text{-}i\text{-}Pr)_3Cl$ is proposed to alter the regioselectivity of an azomethine imine cycloaddition by a template effect, see: Barr, D. A.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1989**, *30*, 4727.

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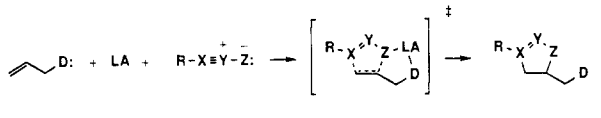


D = Lewis basic site
LA = Lewis Acid

Figure 1. Directed dipolar cycloadditions.

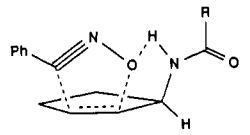


Figure 2. Hydrogen-bonded transition-state model.

group can alter the outcome of an olefin/nitrile oxide cycloaddition by hydrogen bonding.[6] Unfortunately, this directing effect is generally too small to be useful. To increase its magnitude, one might consider either exchanging the proton for a better Lewis acid or increasing the acidity of the proton itself. Increasing the acidity of a hydroxy group (while maintaining a useful acceptor) is a difficult task. In contrast, altering the acidity of a 2° amido group over a wide range is easily accomplished by varying the acyl group of the amide. Therefore, we initiated our research on Directed Nitrile Oxide Cycloaddition (DNOC) reactions by studying a series of simple 3-cyclopentenylamides as dipolarophiles.[7] We have found that relatively acidic 2° amides do indeed control both the regio- and stereochemistry of nitrile oxide cycloadditions.

We selected 3-cyclopentenyl substrates **1** as dipolarophiles because an important study of electronic and steric effects on nitrile oxide cycloadditions by Caramella and Cellerino[6a] would serve as a reference. These workers discovered that benzonitrile oxide added preferentially on the face of the alkene opposite (anti) to most substituents in **1**. Some of the results of this study are summarized in Table I. With allylic methyl (**1a**), dimethylamino (**1b**), methoxy (**1c**), or acetoxy substituents (**1d**), ≥92% of the cycloadducts resulted from attack of the nitrile oxide on the alkene face anti to the substituent (R). With an allylic hydroxy group (**1e**), the apparent hydrogen-bond-directed product **2e** formed to the extent of 30% in ether. We repeated this cycloaddition in benzene (a poorer H-bond acceptor than ether) and found that the amount of **2e** increased to 50%. Although this increase indicates that hydrogen bond direction is probably operating, the magnitude of this effect is only marginally synthetically useful. We were pleased to find that the cycloaddition of 2° benzamide **1f** with benzonitrile oxide (0.1 M in both components, C_6H_6) produced **2f**/**5f** in a ratio of 90/10.[8] Pure **2f** could be readily isolated in 87% yield. The predominant formation of **2f** is support for a hydrogen-bond-directed nitrile oxide cycloaddition, as the transition-state model in Figure 2 depicts.

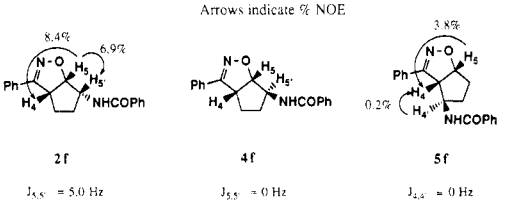
The model depicted in Figure 2 suggests that nitrile oxides and 2° amides form hydrogen bonds, and this suggestion was supported by a simple ^{1}H NMR experiment: the resonance of the amide N–H proton of *N*-cyclopentylbenzamide (0.1 M C_6D_6) shifted 0.4 ppm downfield when 1 equiv of 2,2-dimethylpropanenitrile oxide was present. The model also makes clear-cut predictions of the effects on rate of changing either solvent or amide substituents. According to the model, product **2f** is preferentially formed because its transition-state energy is lowered by H-bonding. To a first approximation, the transition states leading to the other three products should be unaltered. Therefore, **1f** should be more reactive than related compounds that lack the hydrogen-bond-directing capability. Tertiary amide **1g** was prepared, and in a simple competition experiment, 3 equiv of **1f** and 3 equiv of **1g** were reacted with 1 equiv of 2,2-dimethylpropanenitrile oxide (0.1 M) in CH_2Cl_2 at 25 °C.[9] Only three products could be detected in the crude ^{1}H NMR spectrum of the mixture, and they all resulted from cycloaddition of the nitrile oxide with **1f** (see Table II). Cycloadducts **6f**, **7f**, and **8f** were formed in a ratio of 85/3/12. Therefore, 2° amide **1f** is at least 20 times more reactive than 3° amide **1g** in CH_2Cl_2.[10]

To test whether solvents that are good hydrogen-bond acceptors could disrupt the hydrogen bond between the nitrile oxide and **1f**, we conducted cycloadditions of **1f** or **1g** with 2,2-dimethylpropanenitrile oxide in benzene, 1,2-dimethoxyethane (DME), dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPA). Cycloadditions with **1f** were conducted for 4.5 days at 25 °C. Because 3° amide **1g** was significantly less reactive, we conducted its cycloadditions at 80–84 °C for 9.5 days. Competing with these cycloadditions is dimerization of the nitrile oxide to form bis(2,2-dimethylpropyl)furoxan. We determined the percent conversion (a very approximate measure of the rate) and ratio of the cycloadducts.[11] The results of this

(6) For a review on stereocontrolled nitrile oxide and nitrone cycloadditions, see: Annunziata, R.; Cinquini, M.; Cozzi, M.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253. Directing effects of hydroxy groups on nitrile oxide or nitrone cycloadditions in cyclic systems: (a) Caramella, P.; Cellerino, G. *Tetrahedron Lett.* **1974**, 229. (b) Caramella, P.; Marinone Albina, F.; Vitali, D.; Rondan, N. G.; Wu, Y.-D.; Schwartz, T. R.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 1875. (c) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Rastelli, A. *Tetrahedron Lett.* **1987**, *28*, 1225. (d) Dal Bola, L.; DeAmicila, M.; DeMicheli, C.; Gandolfi, R.; Houk, K. N. *Tetrahedron Lett.* **1989**, *30*, 807. In acyclic systems: (e) Houk, K. N.; Moses, S. R.; Wu, Y.-D; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (f) Curran, D. P.; Gothe, S. A. *Tetrahedron* **1988**, *44*, 3945.

(7) (a) Impetus for this work came from the observation that 2° acylamino substituents enhance the reactivity of nearby C=N bonds toward cycloaddition with benzonitrile oxide. Substituent and solvent effects were indicative of an H-bond directing effect. Corsaro, A.; Chiacchio, U.; Caramella, P.; Purrello, G. *J. Hetercycl. Chem.* **1984**, *21*, 949. Marinone Albini, F.; Vitali, D.; Oberti, R.; Caramella, P. *J. Chem. Res. (S)* **1980**, 348. (b) Nitrile oxide cycloadditions to acyclic allylic amides have been studied, especially in the context of the synthesis of acivicin. To date, little stereoselectivity has been observed. Hagedorn, A. A.; Miller, B. J.; Nagy, J. O. *Tetrahedron Lett.* **1980**, *21*, 229. Wade, P. A.; Singh, S. M.; Pillay, M. K. *Tetrahedron* **1984**, *40*, 601. Stevens, R. V.; Polniaszek, R. P. *Tetrahedron* **1983**, *39*, 743. Kozikowski, A. P.; Cheng, X.-M. *Tetrahedron Lett.* **1985**, *26*, 4047. Fushiya, S.; Chiba, H.; Otsubo, A.; Nozoe, S. *Chem. Lett.* **1987**, 2229. Vyas, D. M.; Chiang, Y.; Doyle, T. W. *Tetrahedron Lett.* **1984**, *25*, 487. Nishi, T.; Morisawa, Y. *Heterocycles* **1989**, *29*, 1835.

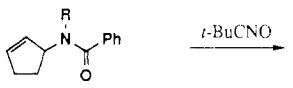
(8) All structures were assigned by detailed spectral analysis on the purified isomers. Regioisomers were easily assigned by ^{1}H NMR or from 2DJ spectra. Stereochemistry was tentatively assigned by chemical shift and coupling constant trends and confirmed by an NOE study. Key results are summarized below. Representative original spectra are contained in the supplementary material.



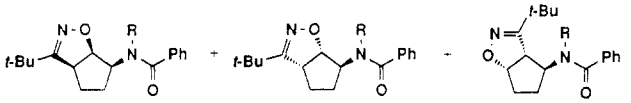
(9) CH_2Cl_2 was used as a solvent because **1f** is not completely soluble in benzene at 0.3 M.

(10) If the only difference between **1f** and **1g** were the hydrogen bonding effect, then the yields of **8f** and **8g** should be approximately equal in this competition experiment because neither is formed by H-bond direction. However, **8g** was not detected by ^{1}H NMR. We estimate that our detection limit of **8g** could be as high as 5% because of line broadening caused by rotation phenomena in this 3° amide.

Table II. Solvent Effects in Cycloaddition of 2,2-Dimethylpropanenitrile Oxide with 1f,g



1f R = H
1g R = CH_3



6f,g 7f,g 8f,g

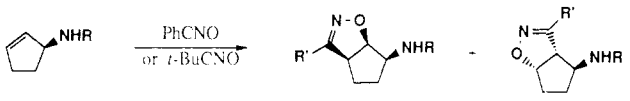
amide	solvent	temp, °C	ratio 6:7:8 6	7	8	% convn
1f	CH_2Cl_2	25	85	3	12	nd[a]
1f	PhH	25	85	1	14	92
1f	DME	25	57	8	35	91
1f	DMF	25	26	15	59	65
1f	HMPA	25	8	14	78	83
1g	PhH	80	5	19	76	47
1g	DME	80	3	24	73	30
1g	DMF	80	3	33	64	43
1g	HMPA	80	4	27	69	63

[a] nd = not determined.

series of experiments are collected in Table II. Tertiary amide **1g** shows the behavior expected of a normal nitrile oxide cycloaddition: neither the percent conversion nor the ratio of products depends strongly on the solvent.[12] In contrast, there are clear (if very qualitative) trends with 2° amide **1f**: better H-bond donor solvents show a small decrease in the percent conversion[13] and a large decrease in the amount of product **6f**. The extreme is reached in HMPA, where **1f** and **1g** give similar product distributions. We can understand this trend in a qualitative sense from the model in Figure 2: as the solvent replaces the nitrile oxide as H-bond acceptor, the rate of formation of **6f** falls, but rates to form the other products are not greatly affected, so the overall percent conversion also falls.

The model in Figure 2 also predicts that the amount of cycloadducts **2** (or **6**) should be a function of the H-bond donating ability of the amide. Thus, we prepared a series of 2° amides (**1h–q**) (pK_a range[14] 11.5–17) and conducted cycloadditions of each with both benzonitrile oxide and 2,2-dimethylpropanenitrile oxide. We then determined the crude ratio and the combined isolated yield of the two major products. The results, which are collected in Table

Table III. Cycloadditions of 2° Amides 1h–q



1h-q

2 R' = Ph
6 R' = t-Bu

5 R' = Ph
8 R' = t-Bu

compd	R	PhCNO 4:5	yield,[a] %	t-BuCNO 6:8	yield,[a] %
1h	$COCH_3$	75/25	62	72/28	67
1i	$COCF_3$	94/6	94[b]	86/14	92
1j	COC_4F_9	84/16	93	85/15	91
1k	$CSCH_3$	88/12	86	84/16	87
1l	CO(*p*-OMe)Ph	92/8	83	85/15	85
1m	COPh	89/11	87	88/12	83
1n	CO(*m*-CF_3)Ph	92/8	64	91/9	52
1o	CO(*p*-NO_2)Ph	95/5	93	92/8	58
1p	SO_2CH_3	73/27	27[b]	76/24	20[b]
1q	SO_2CF_3	72/28	51	66/34	76

[a] Combined yield of **2** + **5** or **6** + **8**. [b] Only **2** or **6** was isolated.

III, reveal several trends. First, benzonitrile oxide consistently gave marginally higher selectivity than 2,2-dimethylpropanenitrile oxide (compare the ratio **1/5** to **6/8**). Second, if one considers only amides (discounting the sulfonamide entries), the trend for increased selectivity with increased acidity of the amide proton is evident. This trend should be regarded as qualitative, since plots of the ratio of products versus the pK_a of the amides are not well correlated. Third, the sulfonamides, which are among most acidic compounds in the series, do not exhibit high selectivity. The change of a planar amide to a tetrahedral sulfonamide apparently disrupts the features responsible for selectivity.[15]

In summary, we have shown for the first time that allylic 2° amides can drastically alter the chemo-, regio-, and stereoselectivity of olefin/nitrile oxide cycloadditions. We interpret our results in the framework of an H-bond directing model (Figure 2) in which the energy of the transition state leading to products **2** or **6** is reduced relative to the energies of the transition states leading to the other products. The magnitude of this reduction (2–2.5 kcal/mol) is sufficient to convert trace products into major products. The rate acceleration provided by hydrogen bonding is important not only in controlling selectivity but also in providing high yields because nitrile oxide dimerizations often compete with cycloaddition reactions to more highly substituted olefins. Experiments to improve and extend this directed nitrile oxide cycloaddition can be designed within the framework of the model, and such experiments are now in progress.

Acknowledgment. We thank ICI Americas and Hoffmann-La Roche for partial support of this work.

Supplementary Material Available: Original ^1H NMR (1D and 2D) and ^{13}C NMR spectra of **1f** and **1g** and representative adducts **2f**, **5f**, **6f,g**, **7f,g**, and **8f** (21 pages). Ordering information is given on any current masthead page.

(11) The ratios of cycloadducts in the **f** series were easily determined by ^1H NMR. Restricted rotation in the **g** series resulted in complicated NMR spectra at room temperature, and the crude ratios were therefore determined by GC. Response factors were not determined, and the ratios in Table II correspond directly to GC peak areas. To correlate structures, amide **6f** was N-methylated to give **6g**, and an inseparable mixture of **7f** (minor) and **8f** (major) was N-methylated to give a separable mixture of **7g** and **8g**.

(12) Huisgen, R. *Pure Appl. Chem.* **1980**, *52*, 2283.

(13) The increased reactivity of **1f** in nonpolar solvents is better illustrated by a competition experiment with cyclopentene (3 equiv each). In benzene, the ratio of **2f** + **5f** to the cyclopentene adduct was 9/1, but in HPMA this ratio was reduced to 2/1. Further, although absolute yields were not determined, significantly more diphenylfuroxan was formed in the HMPA experiment. That **1f** competes more effectively for nitrile oxide relative to two other processes (which remain roughly constant relative to each other) strongly indicates that the change in ratio in benzene is due to the increased reactivity of **1f**.

(14) Perrin, D. D. *pK_a Predictions for Organic Acids and Bases*; Chapman Hall: New York, 1981; pp 109–139.

(15) MM2 calculations suggested a *tentative* explanation for the poor directing ability of the sulfonamide: the tetrahedral geometry of the sulfur positions one of the S–O bonds such that it can hinder the approach of a nitrile oxide. See: Gothe, S. A., Ph. D. Thesis, University of Pittsburgh, 1989.