Pergamon

Tetrahedron, Vol. 53, No. 6, pp. 1971-1982, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01167-2

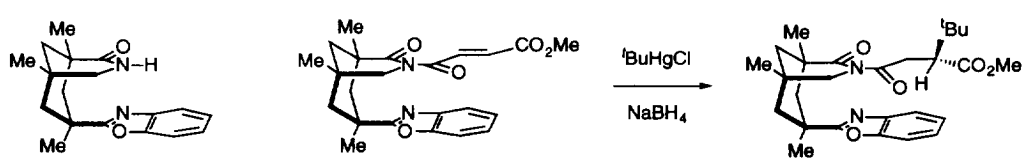
Can an Aromatic Ring Alter the Reactions of a Nearby Unsaturated Imide? A Study of the Rate and Selectivity of Nitrile Oxide Cycloaddition Reactions of Acryloyl Derivatives of the Rebek Imide Benzoxazole.

Dennis P. Curran* and Moon-Hwan Yoon
Department of Chemistry,
University of Pittsburgh, Pittsburgh, PA 15260, USA

Summary: Cycloadditions of acryloyl derivatives of the Rebek imide benzoxazole are extraordinarily stereoselective, but have rates and regioselectivities that otherwise parallel those of a simple achiral model. It appears that the benzoxazole ring of these compounds completely shields the inner face of the nearby alkene, but has no measurable effect on the rate of reactions on the outer face. © 1997, Elsevier Science Ltd. All rights reserved.

Introduction: A few years ago in a collaboration with Rebek and coworkers, we prepared the interesting benzoxazole chiral auxiliary **1**.[1] This compound belongs to the popular imide class of chiral auxiliaries,[2] and it provides high selectivities in reactions in which imide chiral auxiliaries are often used.[1c] However, thanks to the U-turn motif in this structure, it can also be used to control selectivities in reactions where most other imide and ester chiral auxiliaries are not up to the task. In one of the better examples, addition of the *tert*-butyl radical to mixed fumarimide **2** provided a single major product **3** out of four possible regio- and stereoisomers.[1a,b]

Figure 1. The Rebek Benzoxazole Imide



1 Rebek Benzoxazole **2** **3** major product

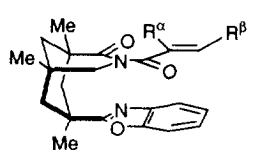
These and related results raise intriguing questions: Are the selectivities of these molecules controlled exclusively by the steric features of their U-turn shape? Or does the enforced proximity of

the benzoxazole ring to the reacting acryloyl π-system electronically alter its reactivity? Aromatic rings are frequently present in chiral auxiliaries and catalysts,[3] and they are thought to operate by aiding in the selective binding to the transition state through various π-π interactions[4] or by the steric shielding of one π-face of a reacting system.[5] However, very little is known about rate effects: can nearby aromatic rings directly accelerate reactions by, for example, perturbing the electronic structure or molecular orbitals of the reacting π-system? The Rebek benzoxazole imide **1** provides a convenient structure to probe these electronic effects because the benzoxazole ring is inescapably held beneath the acryloyl group at a roughly constant distance and orientation.

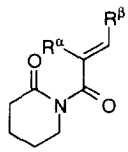
To probe for these effects, we decided to study competitive reactions of acryloyl derivatives of **1** with radicals and nitrile oxides. These reactions were selected because they are prototypical of simple thermal reactions that occur without Lewis acids.[6,7] The nitrile oxide cycloadditions are especially pertinent because these reactions are well known to be sensitive to both steric and electronic (FMO) rate effects,[8] so they should provide a sensitive probe of the effects of the nearby benzoxazole ring. This paper reports the results of a study of the rate, regio- and stereoselectivity of reactions of *tert*-butyl nitrile oxide with acryloyl derivatives of **1**. The parallel study of radical reactions will be reported separately.[8] Neither study has uncovered evidence for any unusual through space π-π electronic effects on reactivity. The benzoxazole ring of **1** appears to function simply as an extraordinarily effective shielding group.

Results and Discussion: In this work, we have compared the rates and regioselectivities of cycloaddition of benzoxazole imide derivatives **4a-f** with those of the control imides **5a-f** (Figure 2). In the parallel radical additions,[9] we used control imides that were more closely related to the benzoxazole, but these gave the same results as the simple control **5**. Therefore, this control was deemed adequate to represent the rate and selectivity of a 6-membered ring imide lacking any blocking substituents. Acrylimide derivatives **a-f** of both the benzoxazole **1** and the control substrate δ-valerolactam were prepared by deprotonation of the corresponding imide with methylmagnesium bromide at 0 °C and addition of the appropriate acid chloride. Isolated yields of pure acylated products ranged from 65-79%.

Figure 2. Structures of Substrates



4a–f



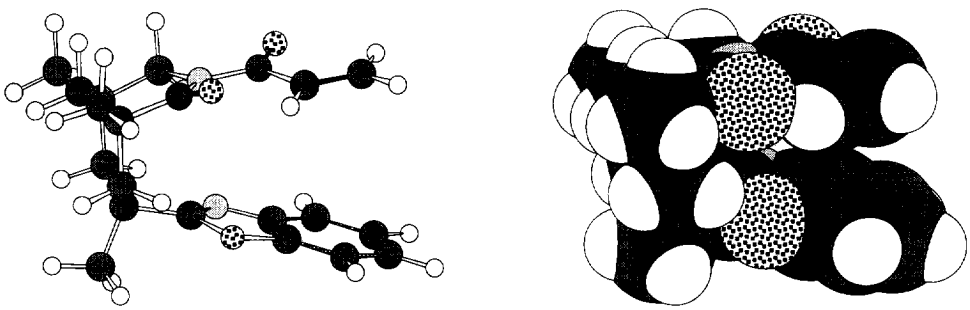
5a–f

a acryloyl, R^{α}, $R^{\beta} = H$
b methacryloyl, $R^{\alpha} = Me$, $R^{\beta} = H$
c crotonoyl, $R^{\alpha} = H$, $R^{\beta} = Me$
d cinnamoyl, $R^{\alpha} = H$, $R^{\beta} = Ph$
e fumaroyl, $R^{\alpha} = H$, $R^{\beta} = CO_2Et$
f sorboyl, $R^{\alpha} = H$, $R^{\beta} = CH{=}CH_2$

Although all of the benzoxazole derivatives were solids, none gave crystals suitable for X-ray diffraction. However, the combination of rigidity and conjugation in acryloyl derivatives of **1** leave little doubt about their structures. An MM2 minimized structure of **1a** is shown in Figure 3. The planes of the acrylimide and the benzoxazole are not exactly parallel, but diverge slightly away from the starting positions enforced by the attachment to the ring. This is probably because the distance imposed by the attachment (~2.2 Å) is too close, and divergence allows the two groups to more

closely approach the optimum distance for π-stacking (~3.6 Å). As with other imides, the carbonyls are oriented anti, and the acryloyl group is *s-cis*. The only open question about the structure is whether the benzoxazole ring nitrogen is anti (as shown) or syn to the 6-membered ring imide carbonyl group. Since interconversion of these two conformers by rotation of the bond connecting the benzoxazole to the ring only serves to exchange the benzoxazole oxygen and nitrogen, this question appears to be of little practical significance.[10]

Figure 3. MM2 Minimized Structure of 1a



Not surprisingly, the presence of the benzoxazole ring has a profound shielding effect on the alkene protons in derivatives **4**. Table 1 shows the difference in chemical shift obtained by subtracting the more downfield resonances of model **5a-f** from the corresponding resonances of **4a-f**. The proximity of the two π systems that causes these large anisotropic magnetic effects does not translate into significant reactivity differences.

Table 1. Chemical Shift Differences of the Vinyl Resonances of 4 and 5
(δH 5 – δ H 4)

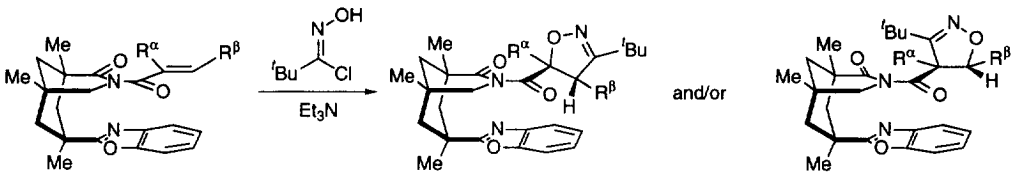
Compound	H_α	$H_{\beta E}$	$H_{\beta Z}$
a acryloyl	–1.04	–0.84	–0.80
b methacryloyl	---	–1.02	–0.56
c crotonoyl	–0.75	---	–0.95
d cinnamoyl	–0.28	---	–0.91
e fumaroyl	–0.76	---	–0.77
f sorboyl	–1.60	---	–0.83

The cycloadditions of imides **4a-f** and **5a-f** with *tert*-butyl nitrile oxide were conducted by the standard Huisgen method as shown in eq. 1, and all the results are summarized in Table 2. Triethylamine was added to a benzene solution of the imide and *tert*-butyl oxime chloride, and the resulting mixture was stored at 25 °C or 80 °C for 1-9 days (see Table 2). Major cycloadducts were fully characterized, and in some cases structures of the cycloadducts were proven by reductive

cleavage of the imide to give known alcohols (See Experimental). Aside from the issue of stereoselectivity (which pertains only to imides **4**), there was little difference between **4** and **5**.

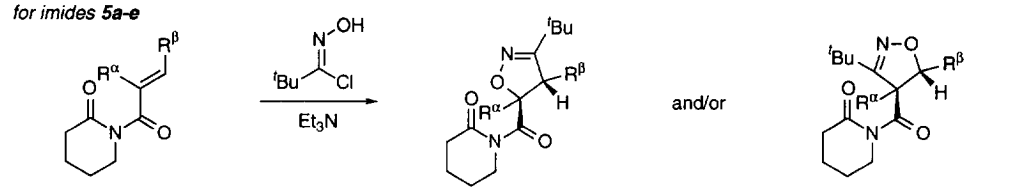
eq 1

*for imides **4a-e***



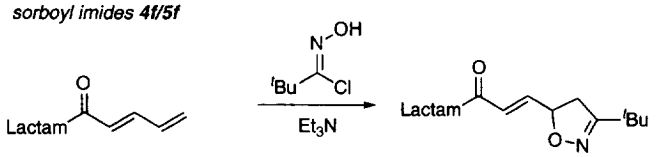
4a-e **6a-e** **7a-e**
(formed only when $R^{\beta} \neq H$)

*for imides **5a-e***



5a-e **8a-e** **9a-e**
(formed only when $R^{\beta} \neq H$)

*sorboyl imides **4f/5f***



4f or **5f**

10f Lactam = benzoxazole
11f Lactam = δ-valerolactam

Cycloaddition of the acryloyl derivative **5a** provided a single regioisomer as expected from a large number of related examples of nitrile oxide cycloadditions to mono-substituted alkenes.[7] Likewise, cycloaddition of benzoxazole imide **4a** provided a single regio- and stereoisomer (estimated selectivity ≥99/1). Even today, there are very few chiral auxiliaries that give such high selectivities in nitrile oxide cycloadditions,[5] and this result testifies to the high degree of conformational control and facial bias of **4**.

Nitrile oxide addition to the methacryloyl derivatives **5b** and **4b** was sluggish due to the twisted nature of these substrates,[11] but provided a single regioisomer in each case. In the case of **4b**, a surprisingly high level of stereoselection (88/12) was observed, although we cannot assign the relative configuration of the isomers of **6b**.[10]

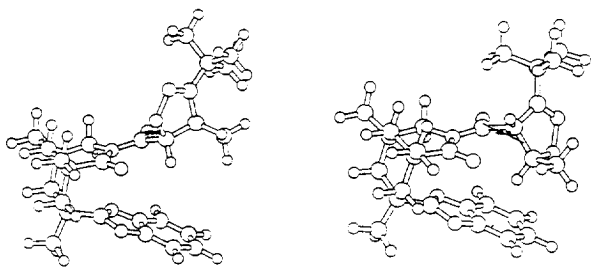
Table 2. Cycloadditions of 4a-f and 5a-f with *tert*-Butyl Nitrile Oxide

Entry	Alkene	Products	Regioisomer Ratio	Time/Temperature	Yield (%)
a	acryloyl **5a**	**8a**	99/1	1d, 25°C	72
	acryloyl **4a**	**6a**	99/1	1d, 25°C	65
b	methacryloyl **5b**	**8b**	99/1	5d, 80°C	63
	methacryloyl **4b**	**6b**	99/1 (88/12[a])	5d, 80°C	58
c	crotonoyl **5c**	**8c/9c**	66/34	9d, 80°C	77
	crotonoyl **4c**	**6c/7c**	68/32	9d, 80°C	44
d	cinnamoyl **5d**	**8d/9d**	67/33	7d, 80°C	76
	cinnamoyl **4d**	**6d/7d**	77/23	7d, 80°C	61
e	fumaroyl **5e**	**8e/9e**	92/8	5d, 80°C	74
	fumaroyl **4e**	**6e/7e**	90/10	5d, 80°C	58

a) ratio of stereoisomers, relative configurations not assigned

Cycloaddition of the crotonoyl derivative **5c** provided a 66/34 mixture of regioisomers **8c/9c**. This ratio is typical of related 1,2-disubstituted alkenes.[7] Likewise, cycloaddition of **4c** provides only two regioisomers in a ratio of 68/32. Neither of the other two possible stereoisomers could be located in the crude reaction mixture. The C-5 proton in isoxazoline **7c** resonates at extraordinarily high field (δ 2.65, compared to δ 4.66 for **9c**). Molecular modeling (MM2) provides minima for both the major and the minor isomers, as shown in Figure 4. In the minor isomer, the C-4 hydrogen clearly points directly into the center of the benzene ring of the benzoxazole at close range, thereby rationalizing the high shielding of this proton.

Figure 4. MM2 Structure of Regioisomers 6c (left) and 7c (right)



Cycloaddition to the cinnamoyl and fumaroyl derivatives provided results that were similar to the crotonoyl ones. In the cinnamoyl series, a 67/33 ratio of regioisomers was obtained from **5d**, while a 77/23 ratio of regioisomers was obtained from **4d**. In the fumaroyl series, a 92/8 mixture of regioisomers was obtained from **5e** while a 90/10 ratio was obtained from **4e**. The relatively high level of regioselectivity observed with the electronically similar imide and ester substituents is interesting, and we suspect that this may be largely steric in origin; the imide is larger than the ester and other factors being equal the oxygen of the nitrile oxide prefers attachment to the more congested terminus of an alkene.[1b] Once again, the stereoisomers of **6d,e** and **7d,e** were not observed.

Addition of *tert*-butyl nitrile oxide to the sorbate derivatives **5f** and **4f** were completely regioselective for the terminal alkene, but in the case of **4f** a 62/38 mixture of stereoisomers **1f** was formed (eq. 1). In view of the low selectivity, we did not assign relative configurations to these stereoisomers. This low stereoselectivity might arise due to poor face shielding of the terminal alkene

by the benzoxazole, but it might also arise due to competitive cycloaddition to *s-cis* and *s-trans* conformations of the diene. Either explanation seems reasonable at this point; dienes can react in either *s-cis* or *s-trans* conformers and even simple mechanical models suggest that the terminal alkene extends beyond the reach of the benzoxazole.

The results in Table 2 show strong parallels between the models **5** and the benzoxazole derivatives **4**, with typical deviation in product ratios (not including stereoisomers) of only a few percent. Isolated yields suggest that **5** is more reactive than **4**, and indeed this would be expected on a statistical basis because the two enantiotopic faces of **5** are equally reactive while one of the diastereotopic faces of **4** does not react to an appreciable extent in most cases.

To better assess the relative reactivity, pairs of alkenes (1.5 equiv each) were allowed to compete for a limited amount of nitrile oxide (1 equiv) under the standard conditions, and the product ratios were determined by integration of appropriate resonances in the crude ^{1}H NMR spectra. These provided the raw and statistically corrected ratios (obtained by dividing the raw ratios by 2) shown in Table 3. Strictly speaking, these ratios are not relative reactivities because the reactions were not conducted under pseudo-first order conditions; however, given that excess alkene was used and the ratios are not that far from 1, they should be satisfactory approximations of the relative reactivities.

Table 3. Results of Combination Experiments Between 4 and 5

Pair	Alkene	Product Ratios ([**8**+**9**]/[**6**+**7**])	Relative Reactivity (**5**/**4**)
a	acryloyl	2.7/1	1.35
b	methacryloyl	2.3/1	1.15
c	crotonoyl	3.5/1	1.75
d	cinnamoyl	2.5/1	1.25
e	fumaroyl	5.8/1	2.90
f	sorboyl	1.9/1	0.95

In four of the six cases, a ratio of products close to the statistical ratio of 2 was observed, implying that the two faces of the model alkenes **5** are about equally reactive to the open face of **4**.[12] For the twisted methacrylate (**b**), the benzoxazole was slightly less reactive than expected, while the fumarate derivative **4e** was almost a factor of 3 less reactive than expected on a statistical basis. Although interesting, we do not deem these small differences significant at this point; the regioselectivities and relative reactivities of the series of substrates **4** and **5** are remarkably similar.

Conclusions: The nitrile oxide cycloadditions with benzoxazole derivatives **4** generally exhibited the high facial selectivity that we have come to expect from this benzoxazole.[1] The only derivatives that provide dectable amounts of minor isomers were the methacrylate derivative **4c** (whose 88/12 level of selectivity is quite good for such substrates) and the sorbate derivative **4f**. These less than perfect selectivities may result from lack of rotamer control about key bonds in the alkene, not poor face shielding.

The parallel in rate and regioselectivity of nitrile oxide cycloadditions between these benzoxazoles **4** and the simple model compounds **5** is sustained and striking. A similar parallel exists

in radical reactions.[8] Clearly the predominate effect of the benzoxazole ring is a simple steric one; the inside face of the alkene is almost completely blocked. Despite its proximity to the alkene, the benzoxazole ring has no significant through space electronic or orbital effects that alter the rate or regioselectivity of the outside face of the alkene. This is in direct contrast to the significant magnetic anisotropic effects that are observed in NMR.

We conclude that aryl rings rigidly held on one face of a nearby alkene or π-system will not dramatically affect the rate of reactions on the other face. Just how far this conclusion can be generalized is not clear. Our results may only hold for certain types of non-polar or weakly polar reactions like thermal cycloadditions and radical reactions. Further, the distance dependence of such effects is not clear. We observe no effects at a distance of 2.2-2.3 Å; however, in catalytic systems in which π-stacking to aryl rings is involved, catalysts presumably operate at longer distances (3.6 Å or so). But, it is not apparent why effects that are not evident at shorter range should manifest themselves at longer range. In short, our results suggest that postulates of through space accelerating electronic effects of aryl rings on the reactions of nearby alkenes should be viewed with some skepticism in the absence of good experimental evidence to the contrary.

Experimental

General Procedure for Acylation of the Lactams

To a stirred solution of benzoxazole (**1**) or δ-valerolactam in THF at 0 °C was added 1.1 equiv of MeMgBr dropwise by syringe. After 10 min, 1.2-1.5 equiv of the appropriate acid chloride was added by syringe in one portion. After an additional 30 min, the reaction mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give the product, which was purified by flash chromatography with ether/hexanes (50/50). Isolated yields ranged from 69 to 79%.

Acryloyl Derivatives:

3-Acryloyl-7-benzoxazol-2-yl-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one, 4a (94 mg, 79%): mp 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3 H, s), 1.26 (3 H, s), 1.37 (3 H, s), 1.42-1.54 (3 H, m), 1.80 (1 H, d, J = 13.0 Hz), 2.97 (1 H, d, J = 14.3 Hz), 3.08 (1 H, d, J = 14.2 Hz), 3.18 (1 H, dd, J = 13.5, 1.6 Hz), 3.81 (1 H, dd, J = 13.4, 2.6 Hz), 4.90 (1 H, dd, J = 10.4, 1.9 Hz), 5.47 (1 H, dd, J = 17.0, 1.7 Hz), 5.96 (1 H, q, J = 6.5 Hz), 7.19-7.22 (2 H, m), 7.36-7.39 (1 H, m), 7.50-7.53 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 29.4, 30.7, 33.8, 37.4, 41.5, 45.0, 48.5, 48.9, 56.5, 110.5, 119.9, 124.4, 124.7, 125.4, 130.8, 141.3, 150.6, 169.3, 170.7, 176.6; IR (thin film) 2967, 2931, 1682, 1456, 1153, 911, 732 cm^{-1}; MS (*m/e*) 352 (M+), 297, 254, 201, 174, 160, 120, 107; HRMS calculated for $C_{21}H_{24}N_2O_3$ 352.1760, found 352.1760.

1-Acryloylpiperidin-2-one, 5a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94-1.88 (4 H, m), 2.56-2.57 (2 H, m), 3.72-3.76 (2 H, m), 5.69 (1 H, dd, J = 10.4, 1.7 Hz), 6.32 (1 H, dd, J =16.9, 1.7 Hz), 6.97 (1 H, dd, J = 17.0, 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.74, 22.55, 34.84, 44.61, 127.98, 131.96, 169.64, 173.20; IR (neat) 2953, 1684, 1616, 1404, 1331, 1213, 1157, 978, 796 cm^{-1}; MS (*m/e*) 153 (M+), 12598, 82, 69, 55; HRMS calculated for $C_8H_{11}NO_2$ 153.0790, found 153.0790.

Methacryloyl Derivatives:

7-Benzoxazol-2-yl-1,5,7-trimethyl-3-(2-methylacryloyl)-3-aza-bicyclo[3.3.1]nonan-2-one, 4b: mp 199-201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3 H, s), 1.24 (3 H, s), 1.25 (3 H, s), 1.36 (3 H, s), 1.37-1.45 (3 H, m), 1.79 (1 H, d, J = 13.1 Hz), 2.92 (1 H, d, J = 10.4 Hz), 2.96 (1 H, d, J = 11.8 Hz), 3.04 (1 H, d, J = 13.2 Hz), 4.06 (1 H, s), 4.20 (1 H, dd, J = 13.2, 1.7 Hz), 7.22-7.26 (2 H, m), 7.41-7.44 (1 H, m), 7.57-7.60 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 26.2, 30.5, 33.0, 37.6, 41.1, 43.8, 46.7, 47.5, 55.4, 110.6, 112.6, 120.0, 124.2, 140.9, 143.8, 150.7, 169.6, 173.9, 175.8; IR (thin film) 2965, 1684, 1456, 1246, 1165, 906, 733 cm^{-1}; MS (*m/e*) 366 (M+), 297, 201, 160, 120, 69; HRMS calculated for $C_{21}H_{28}N_2O_3$ 366.1945, found 366.1945.

1-(2-Methylacryloyl)piperidin-2-one, 5b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80-1.82 (4 H, m), 1.88 (3 H, s), 2.42-2.44 (3 H, m), 3.56-3.57 (3 H, m), 5.10 (2 H, dd, J = 18.7, 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 21.1, 22.5, 34.4, 45.2, 116.7, 142.7, 173.1, 175.61; IR (neat) 2955, 1686, 1637, 1388, 1290, 1151, 916, 733 cm^{-1}; MS (*m/e*) 167 (M+), 152, 139, 99, 69, 59; HRMS calculated for $C_9H_{13}NO_2$ 167.0954, found 167.0955.

Crotonoyl Derivatives:

7-Benzoxazol-2-yl-3-but-2-enoyl-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one, 4c: mp 143-144.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3 H, s), 1.24 (3 H, s), 1.35 (3 H, s), 1.36-1.52 (3 H, m), 1.41 (3 H, d, J = 7.1 Hz), 1.78 (1 H, d, J = 13.0 Hz), 2.95 (1 H, d, J = 14.3 Hz), 3.07 (1 H, d, J = 14.2 Hz), 3.16 (1 H, d, J = 13.3 Hz), 3.74 (1 H, dd, J = 13.4, 2.3 Hz), 5.75 (1 H, d, J = 15.2 Hz), 6.11-6.18 (1 H, m), 7.16-7.19 (2 H, m), 7.37-7.40 (1 H, m), 7.51-7.54 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 26.0, 29.3, 30.6, 33.9, 37.4, 41.5, 45.1, 46.4, 46.8, 56.4, 110.4, 119.7, 124.2, 124.6, 125.7, 140.8, 141.4, 150.6, 169.0, 170.8, 176.5; IR (thin film) 2969, 1682, 1633, 1456, 1183, 1154, 908, 735, 648 cm^{-1}; MS (*m/e*) 366 (M+), 297, 201, 179, 160, 120, 69; HRMS calculated for $C_{21}H_{28}N_2O_3$ 366.1967, found 366.1968.

1-But-2-enoylpiperidin-2-one, 5c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80-1.85 (4 H, m), 1.87 (3 H, d, J = 6.3 Hz), 2.51-2.54 (2 H, m), 3.68-3.70 (2 H, m), 6.72 (1 H, dt, J = 15.3, 1.6 Hz), 6.88-6.97 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 20.6, 22.5, 34.8, 44.8, 126.4, 143.0, 169.5, 173.7; IR (neat) 2958, 1686, 1617, 1273, 1215, 908, 732 cm^{-1}; MS (*m/e*) 167 (M+), 152, 139, 98, 74, 69, 45; HRMS calculated for $C_9H_{13}NO_2$ 167.0325, found 167.0326.

Cinnamoyl Derivatives:

7-Benzoxazol-2-yl-1,5,7-trimethyl-3-(3-phenylacryloyl)-3-aza-bicyclo[3.3.1]nonan-2-one, 4d: mp 129-130.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3 H, s), 1.30 (3 H, s), 1.38 (3 H, s), 1.44-1.56 (3 H, m), 1.84 (1 H, d, J = 12.9 Hz), 2.98 (1 H, d, J = 14.3 Hz), 3.13 (1 H, d, J = 14.1 Hz), 3.23 (1 H, d, J = 13.5 Hz), 3.85 (1 H, d, J = 13.8 Hz), 6.53 (1 H, d, J = 15.6 Hz), 6.84-6.89 (3 H, m), 7.28-7.29 (5 H, m), 7.44 (1 H, d, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 29.4, 30.7, 33.8, 37.4, 41.7, 45.1, 46.6, 47.1, 56.7, 110.3, 119.6, 121.5, 124.4, 124.7, 128.3, 128.3, 129.5, 135.2, 141.1, 150.4, 169.1, 170.7, 176.8; IR (thin film) 2966, 1678, 1614, 1456, 1329, 1165, 989, 733 cm^{-1}; MS (*m/e*) 428 (M+), 297, 131, 103, 77.

1-(3-Phenylacryloyl)piperidin-2-one, 5d: mp 58-59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (4 H, m), 2.60 (2 H, m), 3.79 (2 H, m), 7.34-7.39 (3 H, m), 7.43 (1 H, d, J = 15.9 Hz), 7.55 (2 H, m), 7.69 (1 H, d, J = 15.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 22.4, 34.8, 44.5, 122.0, 128.1, 128.6, 129.9, 134.9, 142.9, 169.6, 173.4; IR (thin film) 2956, 1693, 1616, 1333, 1205, 1155, 684 cm^{-1}; MS (*m/e*) 229 (M+), 201, 131, 103, 77.

Fumaroyl Derivatives:

4-(7-Benzoxazol-2-yl-1,5,7-trimethyl-2-oxo-3-aza-bicyclo[3.3.1]non-3-yl)-4-oxobut-2-enoic acid methyl ester, 4e. To a stirred solution of **1** (100 mg, 0.34 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (0.25 mL, 1.5 M, 0.37 mmol) dropwise by syringe. After 0.5 h at –78 °C, chlorotrimethylsilane (0.53 mL, 0.42 mmol) was also added in one portion by syringe. The mixture was maintained at –78 °C for 0.5 h and at 0 °C for 0.5 h, and then ethyl fumaroyl chloride (0.69 mL, 0.47 mmol) was added. The cold bath was removed, and the reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1 mL), the solvent was concentrated, and the residue was partitioned between EtOAc (10 mL) and H_2O (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 3 mL) and brine (3 mL), dried over $MgSO_4$, and evaporated to give a pale yellow solid. Purification of this material by flash chromatography (hexanes/EtOAc = 70/30) gave a white solid **4e** (108 mg, 75%): mp 141-143.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3 H, s), 1.28 (3 H, s), 1.30 (3 H, t, J = 7.1 Hz), 1.39 (3 H, s), 1.44-1.55 (3 H, m), 1.82 (1 H, d, J = 13.1 Hz), 2.97 (1 H, d, J = 14.3 Hz), 3.10 (1 H, d, J = 12.3 Hz), 3.15 (1 H, d, J = 13.2 Hz), 3.85 (1 H, dd, J = 13.4, 2.4 Hz), 4.15-4.20 (2 H, m), 5.78 (1 H, d, J = 15.4 Hz), 6.70 (1 H, d, J =15.4 Hz), 7.16-7.21 (2 H, m), 7.38-7.41 (1 H, m), 7.52-7.55 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 25.8, 29.2, 30.5, 33.5, 37.3, 41.4, 44.8, 46.5, 46.8, 56.3, 60.6, 110.6, 119.8, 124.4, 124.8, 127.5, 136.2, 141.0, 150.3, 165.0, 167.6, 170.5, 176.6; IR (thin film) 2965, 1721, 1680, 1561, 1456, 1294, 750 cm^{-1}; MS (*m/e*) 424 (M+), 378, 351, 297, 160, 120; HRMS calculated for $C_{24}H_{28}N_2O_5$ 424.1988, found 424.1966.

4-Oxo-4-(2-oxopiperidin-1-yl)but-2-enoic acid methyl ester, 5e. Fumaroyl derivative **5e** was prepared as above in 68% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3 H, t, J = 7.1 Hz), 1.79 (4 H, m), 2.50 (2 H, m), 3.65 (2 H, m), 4.13 (2 H, q, J = 7.1 Hz), 6.53 (1 H, d, J = 15.4 Hz), 7.47 (1 H, d, J = 15.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.4, 22.1, 34.4, 44.6, 60.9, 129.1, 137.3, 165.3, 168.2, 173.5; IR (neat) 2959, 1718, 1684, 1438, 1185, 908, 735 cm^{-1}; MS (*m/e*) 225 (M+), 179, 152, 99, 55.

Sorboyl Derivatives:

7-Benzoxazol-2-yl-1,5,7-trimethyl-3-penta-2,4-dienoyl-3-aza-bicyclo[3.3.1]nonan-2-one, 4f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3 H, s), 1.25 (3 H, s), 1.36 (3 H, s), 1.40-1.53 (3 H, m), 1.79 (1 H, d, *J* = 13.0 Hz), 2.95 (1 H, d, *J* = 14.2 Hz), 3.07 (1 H, d, *J* = 14.2 Hz), 3.18 (1 H, d, *J* = 13.3 Hz), 3.78 (1 H, dd, *J* = 13.4, 2.0 Hz), 5.21-5.29 (2 H, m), 5.87 (1 H, d, *J* = 15.0 Hz), 5.95-6.07 (1 H, m), 6.47 (1 H, dd, *J* = 14.9, 11.0 Hz), 7.12-7.16 (2 H, m), 7.36-7.39 (1 H, m), 7.50-7.53 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 29.3, 30.6, 33.7, 37.3, 41.5, 45.0, 46.4, 46.7, 56.5, 110.3, 119.7, 123.8, 124.5, 124.8, 125.3, 135.4, 141.1, 150.4, 169.1, 170.7, 178.6; IR (thin film) 2967, 1682, 1456, 1244, 1147, 909, 733, 668 cm^{-1}; MS (*m/e*) 378 (M+), 297, 160, 120, 81, 53.

1-Penta-2,4-dienoylpiperidin-2-one, 5f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (4 H, m), 2.56 (2 H, m), 3.74 (2 H, m), 5.47 (1 H, d, *J* = 8.4 Hz), 5.60 (1 H, d, *J* = 14.5 Hz), 6.44-6.56 (1 H, m), 6.89 (1 H, d, *J* = 14.3 Hz), 7.25-7.33 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 22.6, 34.9, 44.6, 125.3, 125.9, 135.5, 143.5, 169.7, 173.8; IR (neat) 2936, 1672, 1614, 1581, 1449, 1375, 1098, 962, 610 cm^{-1}

General Procedure for Cycloaddition:

To a solution of olefin derivatives (**4** or **5**) (0.10 mmol) and *tert*-butyl oxime chloride (0.11 mmol) in C_6H_6 (1 mL) was added Et_3N (0.11 mmol) dropwise with vigorous stirring. After 1-9 days (see Table 2) at 25 °C (**a**) or 80 °C (**b-f**), the resulting suspension was diluted with EtOAc (80 mL) and washed with H_2O (2 x 20 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography to give pure cycloadducts.

7-Benzoxazol-2-yl-3-(3-*tert*-butyl-4,5-dihydroisoxazole-5-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one (6a):

Analysis of the crude reaction mixture by ^{1}H NMR spectrum indicated a >99:1 ratio of diastereomers. Purified by chromatography (hexanes/EtOAc = 75/25) to give a thin film **6a** in 72% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (9 H, s), 1.18 (3 H, s), 1.28 (3 H, s), 1.36 (3 H, s), 1.38-1.50 (3 H, m), 1.63 (1 H, dd, *J* = 14.4, 8.5 Hz), 1.78 (1 H, d, *J* = 12.9 Hz), 2.52 (1 H, dd, *J* = 17.3, 10.6 Hz), 2.90 (1 H, d, *J* = 14.5 Hz), 3.00 (1 H, d, *J* = 13.8 Hz), 3.12 (1 H, d, *J* = 13.6 Hz), 4.07 (1 H, dd, *J* = 13.4, 2.2 Hz), 5.05 (1 H, dd, *J* = 10.7, 8.6 Hz), 7.24-7.30 (2 H, m), 7.47-7.50 (1 H, m), 7.58-7.61 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 28.1, 30.2, 30.6, 32.9, 33.0, 37.6, 38.3, 41.4, 43.7, 46.5, 47.4, 55.9, 79.5, 110.7, 120.0, 124.5, 124.9, 140.9, 150.5, 164.8, 170.1, 173.1, 177.1; IR (thin film) 2968, 1694, 1456, 1246, 1186, 1154, 908, 733 cm^{-1}; MS (*m/e*) 451 (M+), 394, 298, 160, 120, 57; HRMS calculated for $C_{26}H_{32}N_3O_4$ 451.2471, found 451.2472.

1-(3-*tert*-Butyl-4,5-dihydroisoxazole-5-carbonyl)piperidin-2-one (8a):

Purified by chromatography (pentane/Et_2O = 50/50) to give a pale yellow thin film **8a** in 65% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (9 H, s), 1.82-1.89 (4 H, m), 2.53-2.55 (2 H, m), 3.09 (1 H, dd, *J* = 17.5, 6.5 Hz), 3.39 (1 H, dd, *J* = 17.4, 11.3 Hz), 3.55-3.80 (2 H, m), 5.68 (1 H, dd, *J* = 11.3, 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 22.2, 28.0, 32.1, 34.5, 39.4, 44.6, 80.3, 164.7, 173.6, 174.1; IR (thin film) 2963, 2872, 1699, 1367, 1209, 1159, 731 cm^{-1}; MS (*m/e*) 253 (M+), 195, 169, 152, 126, 99, 57.

7-Benzoxazol-2-yl-3-(3-*tert*-butyl-5-methyl-4,5-dihydroisoxazole-5-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one (6b):

^{1}H NMR indicated a 88:12 ratio of diastereomers. Flash chromatography (hexanes/EtOAc = 80/20) of this material afforded a fraction (50%) of the major diastereomer and a mixed fraction (13%) containing both diastereomers. Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9 H, s), 1.09 (3 H, s), 1.17 (3 H, s), 1.33-1.44 (3 H, m), 1.38 (3 H, s), 1.79 (1 H, d, *J* = 13.0 Hz), 2.62 (1 H, d, *J* = 17.5 Hz), 2.77 (1 H, d, *J* = 17.6 Hz), 2.90 -2.98 (3 H, m), 4.34 (1 H, d, *J* = 12.8 Hz), 7.19-7.22 (2 H, m), 7.45-7.48 (1 H, m), 7.55-7.58 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 26.1, 28.0, 30.8, 31.1, 32.6, 32.9, 37.7, 41.3, 43.8, 46.7, 46.7, 47.5, 56.6, 89.5, 110.5, 119.9, 124.1, 124.7, 140.7, 150.8, 165.5, 169.6, 177.0, 178.3; IR (thin film) 2967, 1670, 1634, 1456, 1246, 912, 733 cm^{-1}; MS (*m/e*) 466 (M+), 298, 201, 160, 91, 41. Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (9 H, s), 1.09 (3 H, s), 1.17 (3 H, s), 1.33-1.44 (3 H, m), 1.38 (3H, s), 1.79 (1 H, d, *J* = 13.0 Hz), 2.33 (1 H, d, *J* = 17.0 Hz), 2.55 (1 H, d, *J* = 17.2 Hz), 2.90-2.98 (3 H, m), 4.34 (1 H, d, *J* = 12.8 Hz), 7.19 -7.22 (2 H, m), 7.45-7.48 (1 H, m), 7.55-7.98 (1 H, m).

1-(3-*tert*-Butyl-5-methyl-4,5-dihydroisoxazole-5-carbonyl)piperidin-2-one (8b):

Purified by flash chromatography (pentane/Et_2O = 75/25) to give a pale yellow oil **8b** in 58% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (9 H, s), 1.64 (3 H, s), 1.75-1.90 (4 H, m), 2.52-2.56 (2 H, m), 2.82 (1 H, d, *J* = 17.0 Hz), 3.52 (1 H, d, *J* = 17.0 Hz), 3.56-3.60 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 22.9, 24.8,

28.0, 33.0, 39.9, 46.5, 46.7, 88.7, 165.8, 174.5, 179.9; IR (neat) 2967, 1688, 1367, 1298, 1207, 1174, 914, 733 cm^{-1}; MS (*m/e*) 267 (M+), 186, 140, 100.

7-Benzoxazol-2-yl-3-(3-*tert*-butyl-4-methyl-4,5-dihydroisoxazole-5-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one, and 7-Benzoxazol-2-yl-3-(3-*tert*-butyl-5-methyl-4,5-dihydroisoxazole-4-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one (6c and 7c):

^1H NMR indicated a 66:34 ratio of regioisomers. Flash chromatography (hexanes/EtOAc = 85/15) gave the more polar isomer **6c** (26%), and the less polar isomer **7c** (18%). More polar isomer, **6c**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (3 H, d, *J* = 7.5 Hz), 1.03 (9 H, s), 1.16 (3 H, s), 1.35 (3 H, s), 1.40-1.47 (3 H, m), 1.75 (1 H, d, *J* = 13.0 Hz), 2.11 (1 H, m), 2.87-3.09 (3 H, m), 3.94 (1 H, d, *J* = 13.3 Hz), 4.82 (1 H, d, *J* = 2.7 Hz), 7.23-7.30 (2 H, m), 7.47-7.50 (1 H, m), 7.57-7.59 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 26.2, 29.1, 30.4, 30.6, 33.0, 33.2, 37.6, 41.5, 43.6, 46.6, 46.7, 47.3, 55.6, 86.0, 110.6, 119.8, 124.5, 124.8, 140.9, 150.5, 169.0, 169.9, 172.7, 177.2; IR (thin film) 2965, 1690, 1246, 1223, 1178, 1152, 733 cm^{-1}; MS (*m/e*) 465 (M+), 450, 299, 254, 160, 120, 69. Less polar isomer (**7c**); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3 H, d, *J* = 6.3 Hz), 0.98 (9 H, s), 2.64 (1 H, m), 2.89-3.02 (3 H, m), 4.06 (1 H, d, *J* = 3.3 Hz), 4.24 (1 H, dd, *J* = 13.4, 2.1 Hz), 7.27-7.35 (2 H, m), 7.45-7.47 (1 H, m), 7.57-7.61 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 26.4, 28.5, 29.1, 30.6, 32.7, 33.0, 37.6, 41.6, 43.6, 46.3, 47.9, 56.5, 60.4, 81.9, 110.4, 120.1, 124.9, 125.2, 140.6, 150.5, 163.4, 169.4, 172.7, 177.9; IR (thin film) 2967, 1686, 1458, 1246, 1152, 908, 735 cm^{-1}; MS (*m/e*) 465 (M+), 450, 299, 160, 149, 120, 71.

1-(3-*tert*-Butyl-4-methyl-4,5-dihydroisoxazole-5-carbonyl)piperidin-2-one and 1-(3-*tert*-Butyl-5-methyl-4,5-dihydroisoxazole-4-carbonyl)piperidin-2-one (8c and 9c):

^1H NMR indicated a 68:32 ratio of regioisomers. Flash chromatography (pentane/Et_2O = 70/30) gave the more polar isomer **8c** (52%), and the less polar isomer **9c** (25%). More polar isomer, **8c**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (9 H, s), 1.44 (3H, d, *J* = 7.5 Hz), 1.82-1.89 (4 H, m), 2.57-2.59 (2 H, m), 3.01 (1 H, m), 3.56-3.82 (2 H, m), 5.31 (1 H, d, *J* = 3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 23.3, 29.4, 29.6, 34.2, 35.7, 45.9, 62.4, 83.1, 165.0, 174.2, 175.0; IR (neat) 2963, 1698, 1460, 1388, 1292, 1161, 912, 731 cm^{-1}; MS (*m/e*) 266 (M+), 223, 167, 152, 126, 100, 57; HRMS calculated for $C_{14}H_{22}N_2O_3$ 266.1608, found 266.1608. Less polar isomer, **9c**; ^1H NMR (300 MHz, $CDCl_3$) δ1.21 (9 H, s), 1.44 (3 H, d, *J* =7.5 Hz), 1.84 (4 H, m), 2.58 (2 H, m), 3.31 (1 H, m), 3.43-3.82 (2 H, m), 3.31 (1 H, d, *J* = 3.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 20.4, 22.3, 29.2, 31.3, 34.5, 44.6, 47.9, 87.8, 169.1, 173.8, 173.9; IR (neat) 2963, 1692, 1479, 1367, 1201, 1155, 1093, 733 cm^{-1}.

7-Benzoxazol-2-yl-3-(3-*tert*-butyl-4-phenyl-4,5-dihydroisoxazole-5-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one and 7-Benzoxazol-2-yl-3-(3-*tert*-butyl-5-phenyl-4,5-dihydroisoxazole-4-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one (6d and 7d):

^1H NMR indicated a 67:33 ratio of regioisomers. Flash chromatography (hexanes/EtOAc = 70/30) of this material afforded a fraction (49%) of the major regioisomer, **6d** and other fraction (25%) of the minor regioisomer **7d**. More polar isomer, **6d**; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (9 H, s), 1.18 (3 H, s), 1.25 (3 H, s), 1.40-1.46 (3 H, m), 1.80 (1 H, d, *J* = 13.0 Hz), 2.90 (1 H, d, *J* = 14.4 Hz), 3.02 (1 H, d, *J* = 13.9 Hz), 3.06 (1 H, d, *J* = 13.3 Hz), 3.68 (1 H, d, *J* = 1.8 Hz), 4.03 (1 H, d, *J* = 12.2 Hz), 4.98 (1 H, d, *J* = 1.9 Hz), 6.90-6.93 (2 H, m), 7.09-7.28 (5 H, m), 7.39 (1 H, d, *J* = 8.0 Hz), 7.52 (1 H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 29.1, 30.4, 30.6, 32.9, 33.6, 37.6, 41.5, 43.6, 46.9, 47.4, 55.8, 56.0, 87.3, 110.5, 119.8, 124.6, 125.0, 127.5, 128.2, 128.6, 138.3, 140.8, 150.4, 168.7, 170.0, 171.4, 176.4; IR (thin film) 2969, 2932, 1691, 1456, 1246, 1165, 908, 733 cm^{-1}; MS (*m/e*) 527 (M+), 470, 444, 325, 299, 201, 160, 57; HRMS calculated for $C_{32}H_{37}N_3O_4$ 527.2726, found 527.2725. Less polar isomer, **7d**; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (9 H, s), 1.22 (3 H, s), 1.42 (3 H, s), 1.46-1.50 (3 H, m), 1.73 (1 H, d, *J* = 13.0 Hz), 2.91-3.06 (3 H, m), 3.80 (1 H, d, *J* = 12.0 Hz), 4.40 (2 H, d, *J* = 13.2 Hz), 7.01-7.04 (2 H, m), 7.20-7.26 (5 H, m), 7.46 (1 H, d, *J* = 7.5 Hz), 7.61 (1 H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 28.3, 30.7, 30.6, 32.7, 33.1, 37.7, 41.6, 43.9, 46.4, 48.0, 56.8, 61.6, 85.9, 110.6, 120.2, 124.8, 125.3, 125.8, 127.5, 128.0, 138.5, 140.6, 150.6, 163.7, 169.6, 172.4, 177.6; IR (thin film) 2963, 1686, 1454, 1246, 1163, 735, 696 cm^{-1}; MS (*m/e*) 527 (M+), 499, 367, 299, 160, 120, 57; HRMS calulated for $C_{32}H_{37}N_3O_4$ 527.2817, found 527.2815.

1-(3-*tert*-Butyl-4-phenyl-4,5-dihydroisoxazole-5-carbonyl)piperidin-2-one and 1-(3-*tert*-Butyl-5-phenyl-4,5-dihydroisoxazole-4-carbonyl)piperidin-2-one (8d and 9d):

^1H NMR indicated a 77:23 ratio of regioisomers. Flash chromatography (pentane/Et_2O = 50/50) of this material afforded a fraction (38%) of the major isomer, **8d** and other fraction (20%) of the minor regioisomer **9d**.

More polar isomer, **8d**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (9 H, s), 1.82-1.88 (4 H, m), 2.55-2.57 (2 H, m), 3.58-3.87 (2 H, m), 4.54 (1 H, d, *J* = 2.7 Hz), 5.57 (1 H, d, *J* = 2.5 Hz), 7.27-7.37 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 22.4, 29.2, 29.7, 33.7, 34.6, 45.0, 58.1, 88.4, 127.8, 128.0, 129.0, 138.7, 168.3, 173.5, 173.6; IR (thin film) 2963, 1714, 1626, 1497, 1358, 1246, 909 cm^{-1}; MS (*m/e*) 328 (M+), 245, 228, 172, 131, 100, 57. Less polar isomer (**9d**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (9 H, s), 1.87-1.89 (4 H, m), 2.58 (2 H, m), 3.76 (2 H, m), 5.06 (1 H, d, *J* = 3.5 Hz), 5.56 (1 H, d, *J* = 3.6 Hz), 7.28-7.38 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 22.5, 28.5, 33.6, 34.9, 45.4, 62.7, 87.2, 125.9, 128.2, 128.5, 139.9, 164.1, 173.8, 173.8; IR (thin film) 2963, 1692, 1345, 1292, 1194, 908, 737 cm^{-1}; MS (*m/e*) 328 (M+), 228, 172, 100, 57.

5-(7-Benzoxazol-2-yl-1,5,7-trimethyl-2-oxo-3-aza-bicyclo[3.3.1]nonane-3-carbonyl)-3-*tert*-butyl-4,5-dihydroisoxazole-4-carboxylic acid methyl ester and 4-(7-Benzoxazol-2-yl-1,5,7-trimethyl-2-oxo-3-aza-bicyclo[3.3.1]nonane-3-carbonyl)-3-*tert*-butyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (6e and 7e):

^{1}H NMR indicated a 92:8 ratio of regioisomers. Flash chromatography (hexanes/EtOAc = 85/15) afforded a fraction (63%) of the major regioisomer and a mixed fraction (13%) containing both regioisomers. Major isomer, **6e**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (9 H, s), 1.13 (3 H, s), 1.21 (3 H, s), 1.25 (3 H, t, *J* = 7.1 Hz), 1.31 (3 H, s), 1.33-1.40 (3 H, m), 1.71 (1 H, d, *J* = 13.1 Hz), 2.87-3.01 (3 H, m), 2.97 (1 H, d, *J* = 4.5 Hz), 3.99 (1 H, d, *J* = 3.8 Hz), 4.16 (2 H, m), 5.29 (1 H, d, *J* = 4.8 Hz), 7.19-7.23 (2 H, m), 7.46-7.49 (1 H, m), 7.52-7.55 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 26.1, 28.4, 30.4, 30.5, 32.7, 33.6, 37.5, 41.1, 43.4, 46.7, 47.2, 55.6, 57.3, 61.5, 84.0, 110.9, 119.6, 124.5, 124.8, 140.6, 150.3, 161.7, 168.9, 169.7, 171.3, 176.9; IR (thin film) 2971, 1738, 1478, 1370, 1292, 1223, 1179, 910 cm^{-1}; MS (*m/e*) 523 (M+), 450, 325, 298, 270, 198, 160, 120, 57; HRMS calculated for $C_{29}H_{37}N_3O_6$ 523.2689, found 523.2699. Minor isomer, **7e**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (9 H, s), 1.13 (3 H, s), 1.21 (3 H, s), 1.25 (3 H, t, *J* = 7.1 Hz), 1.31 (3 H, s), 1.33-1.40 (3 H, m), 1.71 (1 H, d, *J* = 13.1 Hz), 2.87-3.01 (3 H, m), 3.99 (1 H, d, *J* = 3.8 Hz), 4.16 (2 H, m), 4.60 (1 H, d, *J* = 4.5 Hz), 4.82 (1 H, d, *J* = 4.5 Hz), 7.19-7.23 (2 H, m), 7.46-7.49 (1 H, m), 7.52-7.55 (1 H, m).

3-*tert*-Butyl-5-(2-oxopiperidin-1-carbonyl)-4,5-dihydroisoxazole-4-carboxylic acid methyl ester and 3-*tert*-Butyl-4-(2-oxopiperidin-1-carbonyl)-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (8e and 9e):

^{1}H NMR indicated a 90:10 ratio of regioisomers. Flash chromatography (hexanes/EtOAc = 70/30) afforded a fraction (52%) of the major regioisomer and other fraction (9%) of the minor regioisomer. Major isomer, **8e**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (9 H, s), 1.30 (3 H, t, *J* = 7.1 Hz), 1.76-1.84 (4 H, m), 2.53-2.55 (2 H, m), 3.53-3.83 (2 H, m), 4.13 (1 H, d, *J* = 4.9 Hz), 4.25 (2 H, m), 5.86 (1 H, d, *J* = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.4, 22.4, 28.7, 33.6, 34.7, 45.2, 59.1, 62.0, 82.9, 164.7, 168.7, 172.2, 174.2; IR (neat) 2970, 1732, 1693, 1682, 1480, 1217, 912, 733, 648 cm^{-1}; MS (*m/e*) 324 (M+), 251, 152, 100, 57. Minor isomer, **9e**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (9 H, s), 1.30 (3 H, t, *J* = 7.1 Hz), 1.87 (4 H, m), 2.58 (2 H, m), 3.75 (2 H, m), 4.25 (2 H, m), 4.91 (1 H, d, *J* = 3.8 Hz), 5.19 (1 H, d, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.3, 22.2, 28.4, 34.4, 44.8, 58.6, 62.0, 85.0, 128.8, 130.9, 169.4, 172.4, 173.8; IR (neat) 2970, 1738, 1703, 1478, 1225, 910, 735, 648 cm^{-1}; MS (*m/e*) 324 (M+), 279, 251, 223, 198, 126, 99, 57.

5-(7-Benzoxazol-2-yl-1,5,7-trimethyl-2-oxo-3-aza-bicyclo[3.3.1]nonane-3-carbonyl)-3-*tert*-butyl-4,5-dihydroisoxazole-4-carboxylic acid methyl ester and 7-Benzoxazol-2-yl-3-(3-*tert*-butyl-4-vinyl-4,5-dihydroisoxazole-5-carbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonan-2-one (6f and 7f):

^{1}H NMR indicated ratios of >99:1 regioisomers and 62:38 stereoisomers. Flash chromatography (hexanes/EtOAc = 75/25) of this material afforded a thin film **6f** in 58% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (9 H, s), 1.25 (3 H, s), 1.31 (3 H, s), 1.38 (3 H, s), 1.80 (1 H, d, *J* = 12.9 Hz), 2.40 (1 H, dd, *J* = 15.6, 8.4 Hz), 2.54 (1 H, dd, *J* = 16.8, 8.7 Hz), 2.55 (1 H, dd, *J* = 16.5, 8.4 Hz, minor diastereomer), 2.85-3.00 (3 H, m), 3.85 (1 H, dd, *J* = 13.2, 2.1 Hz), 4.62 (1 H, m), 5.83 (1 H, d, *J* = 15.4 Hz), 6.01 (1 H, d, *J* = 3.7 Hz), 7.18-7.28 (2 H, m), 7.43-7.46 (1 H, m), 7.53-7.56 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 28.1, 29.4, 29.8, 30.7, 33.7, 37.5, 39.2, 41.6, 44.8, 46.4, 48.3, 56.5, 79.1, 110.2, 111.5, 120.0, 125.0, 125.4, 127.8, 140.7, 151.5, 166.6, 168.2, 169.2, 177.7; IR (thin film) 2965, 1689, 1369, 1287, 1154, 980, 733, 648 cm^{-1}; MS (*m/e*) 477 (M+), 450, 420, 378, 351, 338, 299, 160, 57.

1-(3-*tert*-Butyl-4-vinyl-4,5-dihydroisoxazole-5-carbonyl)piperidin-2-one (8f):

^{1}H NMR indicated a >99:1 ratio of regioisomers. Flash chromatography (hexanes/EtOAc = 80/20) of this material afforded a yellow oil **8f** in 65% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (9 H, s), 1.81-1.85 (4 H, m), 2.51-2.55 (2 H, m), 2.78 (1 H, dd, *J* = 16.7, 7.5 Hz), 3.16 (1 H, dd, *J* = 16.7, 10.6 Hz), 3.69-3.70 (2 H,

m), 5.10 (1 H, m), 6.80 (1 H, d, J = 6.0 Hz), 6.90 (1 H, d, J = 14.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 22.5, 28.1, 33.1, 34.8, 40.1, 44.7, 79.0, 126.2, 142.3, 165.7, 169.0, 173.7; IR (neat) 2965, 1678, 1638, 1365, 1290, 1203, 1156,872 cm^{-1}; MS (m/e) 276 (M+), 251, 179, 152, 100, 81, 57; HRMS calculated for $C_{15}H_{22}N_2O_3$ 276.1475, found 276.1473.

Reduction of Cycloadducts to prove Regioselectivity.
General Procedure: To a solution of isoxazoline **6a** (0.04 mmol) and THF (1.5 mL) at 25 °C under N_2, was added a 1 M solution of L-Selectride in THF (100 μL) over 30 s. After 30 min, the reaction mixture was quenched slowly with H_2O (15 μL). Aqueous NaOH (15%, 15 μL) was added, followed by 30% H_2O_2 (15 μL). The solution was diluted with EtOAc (5 mL) and then dried over $MgSO_4$. The residue was concentrated under reduced pressure and purified by flash chromatography (hexanes/EtOAc = 70/30). Removal of the solvent under reduced pressure afforded 3-*tert* -butyl-5-hydroxymethyl-Δ^2-isoxazoline as a thin film in 71% yield, Related reductions were conducted with **8b**, **8d**, **6d**, a **6d/7d** mixture and **11f**.

Acknowledgements: We thank the National Institutes of Health for funding this work.

References or Notes

1. a) Stack, J. G.; Curran, D. P.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1991**, *113*, 5918. b) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007. c) Jeong, K. S.; Paris, K.; Ballester, P.; Rebek, J., Jr. *Angew. Chem. Int. Ed.* **1990**, *29* 55.
2. Seyden-Penne, J. "Chiral Auxiliaries, Ligands and Catalysts" Wiley Interscience: NY; 1996.
3. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.
4. For example, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.
5. a) Maddaluno, J. F.; Gresh, N.; Giessnerprettre, C. *J. Org. Chem.* **1994**, *59*, 793. b) Dumas, F.; Mezrhab, B.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293.
6. Nitrile oxide cycloadditions: a) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293. b) Kanemasa, S.; Onimura, K.; Wada, E.; Tanaka, J. *Tetrahedron-Asymmetry* **1991**, *2*, 1185. c) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631. d) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645.
7. Radical additions: a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996. b) Sibi, M. P.; Jasperse, C. P.; Ji, J. G. *J. Am. Chem. Soc.* **1995**, *117*, 10779.
8. Caramella, P.; Grünanger, P. "1,3-Dipolar Cycloaddition Chemistry." Padwa, A., Ed.; Wiley: NY 1984, Vol. 1, p. 291.
9. Qi, H. Ph.D. Thesis. University of Pittsburgh, 1995.
10. These groups are anti in the one available X-ray structure (an imide that was used to resolve the benzoxazole). See reference 1b.
11. Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.
12. That the sorboyl derivatives gave a 2/1 ratio tentatively suggests that the low stereoisomer ratio in this case is due to reaction from one face through *s-cis* and *s-trans* conformers. Reactions from both faces of **4f** would be expected to give a 1/1 raw ratio of products in the competition experiment.

(*Received in USA* 25 *October* 1996; *revised* 9 *December* 1996; *accepted* 10 *December* 1996)