HYDROGEN BOND DIRECTED NITRILE OXIDE CYCLOADDITION REACTIONS OF ALLYLIC 2°-AMIDES†

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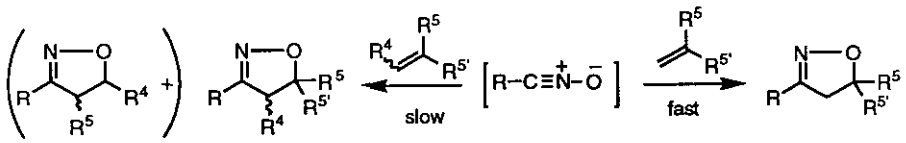
Abstract-The ability of allylic and homoallylic 2°-amides to direct nitrile oxide cycloaddition reactions has been studied. For *N*-cyclopentenyl amides, good regio- and stereochemical control are observed and mechanistic studies suggest that hydrogen bonding in the transition state selectively accelerates formation of one isomer. Acyclic allylic and homoallylic 2°-amides do not exhibit high regio- or stereoselectivity.

Introduction

Δ^2-Isoxazolines are important synthetic intermediates because they are stable precursors of a wide variety of functional groups.[2] Though certain classes of Δ^2-isoxazolines are readily available by 1,3-dipolar cycloaddition reactions of nitrile oxides and alkenes,[3] important classes of Δ^2-isoxazolines are not (Figure 1). For example, many 1,2-di- and trisubstituted alkenes are relatively unreactive towards nitrile oxides. With 1,2-disubstituted alkenes, the problem of lack of reactivity is usually compounded by formation of mixtures of regioisomers. Because of the already low reactivity of 1,2-disubstituted alkenes towards nitrile oxides, control of regiochemistry cannot easily be effected by selective deceleration of the rate of formation of one regioisomer.[4] It is more desirable to dictate regioselectivity by selective acceleration. Controlling regioselectivity by accelerative, rather than decelerative, methods has the added bonus of increasing the yield of cycloadduct.

Figure 1

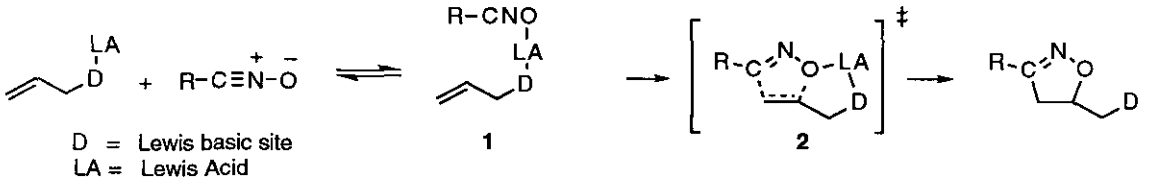


In 1990, we suggested that Directed Nitrile Oxide Cycloadditions (Figure 2) might be developed to provide general solutions to these reactivity and selectivity problems.[5] A Lewis acid substituent (proton or metal) in the alkene component could complex to a Lewis basic nitrile oxide oxygen[6,7] and accelerate the nitrile oxide cycloaddition. Such complexation could dictate not only regiochemistry

†We dedicate this paper to Professor E. C. Taylor on the occasion of his 70th birthday.

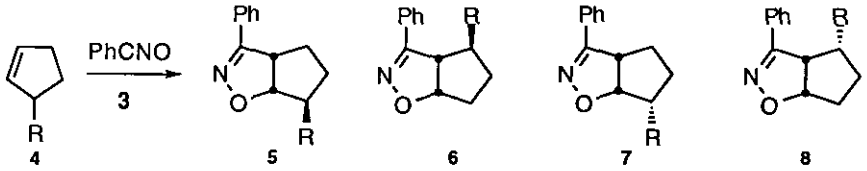
of nitrile oxide cycloadditions but potentially stereochemistry as well. However, the simple formation of a bond between a donor and a nitrile oxide is by no means guaranteed to accelerate rates. If the ground state energy of initial complex (**1**) is lowered more than the energy of the transition state (**2**), then rate deceleration would actually be observed.

Figure 2



Prior to our study, several groups had shown that hydroxyl groups could alter the outcome of nitrile oxide cycloadditions and suggested that these alterations were due to hydrogen bonds between alcohols and nitrile oxides.[8] Two key examples from the work of Caramella and Cellerino[8a] are shown in Table 1. Cycloaddition of benzonitrile oxide (**3**) with 3-phenyl- or 3-methoxycyclopentene (**4a,b**) gave results typical of other 3-substituted cyclopentenes; all four possible products (**5a,b-8a,b**) formed. The anti isomers (**5a,b, 6a, b**) predominated over the syn isomers (**7a,b, 8a,b**) and there was only modest regioselectivity within the anti and syn pairs. Cycloaddition of benzonitrile oxide (**3**) and 3-hydroxycyclopentene (**4c**) again provided all four possible products (**5c-8c**); however, there was a significant increase in the amount of one of the syn isomers (**7c**). This is the isomer expected from a hydrogen bond directed nitrile oxide cycloaddition (see Figure 3). Like allylic ethers, allylic 3°-amine (**4d**) exhibited no unusual directing effects.

Table 1. Isomer Distribution in Reactions of **3** with Representative 3-Substituted Cyclopentenes[8a]



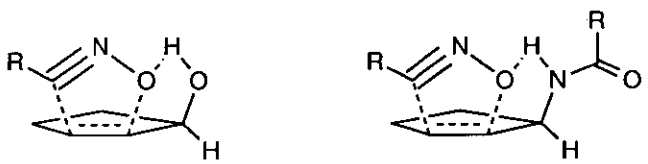
		isomer distribution			
entry	R	5	6	7	8
a	Ph	66	29	4	1
b	OMe	71	22	3	3
c	OH	53	12	30	5
d	NMe_2	70	23	7	—*

* not detected

Unfortunately, allylic hydroxy groups appear to have only modest effects on the outcomes of alkene nitrile oxide cycloadditions. And though it seems probable that these effects are indeed due to hydrogen bonding in the transition state, it had not been shown that the directing effect of the

hydroxy group is accelerative. (Indeed this may be difficult to show because the effect is rather small.) In 1987, a detailed study by Roush[9] showed that allylic 2°-amides were more powerful directors than allylic hydroxy groups in hydrogen bond directed peroxide epoxidations (Henbest epoxidations). This follows from the increased acidity of the 2°-amide proton relative to a hydroxyl proton. Corsaro and coworkers also observed that 2°-amides could direct the cycloaddition reactions of nitrile oxides with nitriles.[10] Substituent and solvent effects supported an accelative hydrogen bond directing effect. In contrast to these encouraging precedents, a number of groups have shown that acyclic 2°-amide substituents had little or no influence on the stereochemical outcome of nitrile oxide cycloadditions.[11] With this backdrop, we set out to test the ability of 2°-amides to direct nitrile oxide cycloaddition by way of the model outlined in Figure 3.

Figure 3. Transition State Models for Hydrogen Bond Directed Nitrile Oxide Cycloadditions

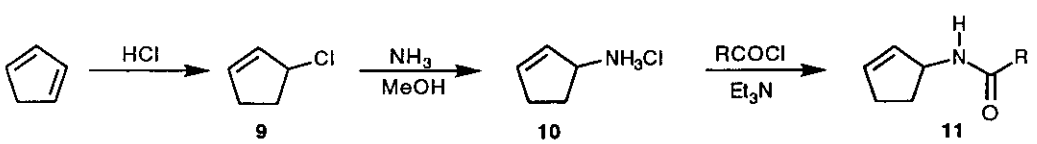


In 1990, we reported preliminary results demonstrating that allylic 2°-amides were indeed superior to alcohols in directing nitrile oxide cycloadditions.[5] We now report full details of our studies on the scope, limitations, and mechanism of this reaction. Our results show that 2°-amides are accelerative directors with good potential to control stereo- and regiochemistry in cycloadditions of cyclopentenyl amides. Recently, Thornton[12] has provided strong evidence for the accelerative hydrogen bonding effect of alcohols in Diels-Alder reactions, and Kanemasa[13] has shown for the first time that metals can be used in place of protons in the directed nitrile oxide cycloaddition reactions of allylic alkoxides.

Cycloadditions with Cyclopentenyl Amides

We began our investigation by studying cycloadditions to a series of cyclopentenyl amides. We choose this motif to provide direct comparison of our results with those of Caramella and Cellerino.[8a] The synthesis of these amides starts with hydrochlorination of cyclopentadiene to provide the unstable 3-chlorocyclopentene (**9**) in 45% distilled yield.[14] Aminolysis of **9** gave a 75% yield of the amine hydrochloride (**10**). Acylation of this salt with a series of acid chlorides then provided the cyclopentenyl amides (**11**).

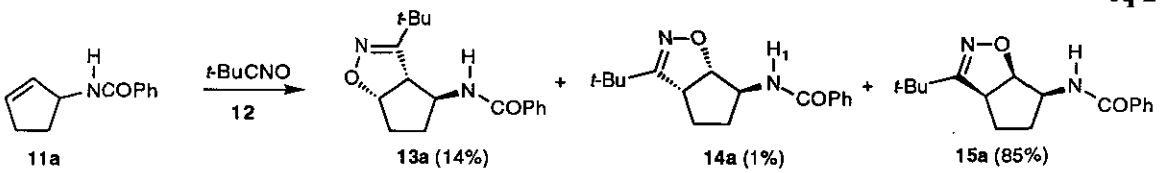
eq 1



As a prelude to later investigations of substituent effects, we studied the reaction of 2,2-dimethylpropane nitrile oxide (**12**) with *N*-(2-cyclopentenyl)benzamide (**11a**) in considerable detail (eq 2). To conduct the cycloaddition, we mixed benzene solutions of pregenerated **12**[15] and **11a** and

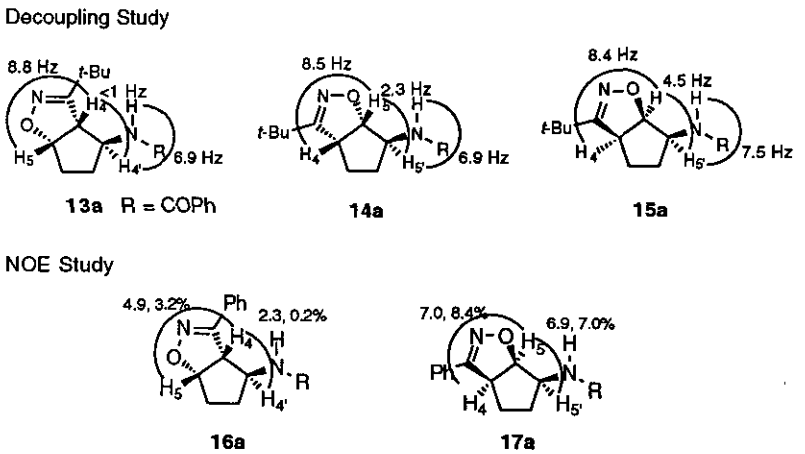
allowed the resulting clear solution to stand for 4.5 d at 25°C. Evaporation of the solvent provided a clean product mixture in 92% yield. Careful analysis of the ^{1}H nmr spectrum of this crude product showed that three new products (**13a/14a/15a**) formed in a ratio of 14/1/85. We separated the major product from the other two by MPLC, but HPLC was required to separate the two minor products.

eq 2



With the three pure products in hand, we then made tentative structural assignments from analysis of chemical shifts and coupling constants in the ^{1}H nmr spectra. This analysis is summarized in Figure 4. Assignments of the resonances of H^4 and H^5 in Δ^2-isoxazolines were readily made by chemical shifts (H^5 more downfield than H^4). Decoupling experiments then showed that the major and minor product had the amide-bearing carbon in the 5-position, and that the intermediate product was a regioisomer with this substituent in the 4-position. Analysis of coupling constants then suggested that the major isomer was a syn product while the intermediate and minor isomers were anti products. This coupling constant analysis was supported by an NOE study of the two major products from the cycloaddition of phenyl nitrile oxide with **11a** (**16a/17a**). The data from this study are summarized in the lower part of Figure 4. The product mixture then corresponds to **13a** (14%), **14a** (1%), and **15a** (85%). Since we were somewhat leery of using coupling constants as the sole data for these key stereochemical assignments, we conducted an independent synthesis of **14a**, which firmly proved its structure assignment.[16]

Figure 4

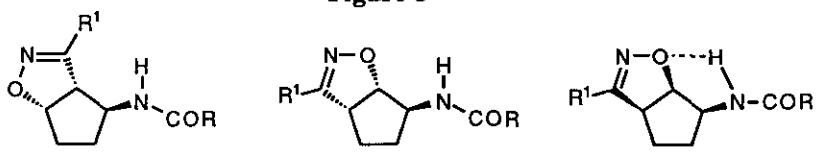


With secure structure assignments, we next conducted cycloadditions of 2,2-dimethylpropane nitrile oxide (**12**) and/or benzonitrile oxide (**3**) with a series of *N*-cyclopentenyl amides (**11a-11m**). Table 2

summarizes the results of these experiments, which were conducted under slightly different conditions from the experiments described above. Instead of pregenerating the nitrile oxide, we simply added 1 equiv of triethylamine to a mixture of the appropriate oxime chloride[17] and the alkene. A control experiment with **11a** gave the same ratio of products as the pregeneration method, thus confirming that the precipitated $Et_3N{\bullet}HCl$ has no effect on the product ratio.

In most of these experiments, we measured only the ratio of the two major products (**13/15** or **16/17**). However, we could sometimes observe and quantify the minor isomer, and we suspect that it was formed in small amounts in all the experiments. The combined isolated yields of the two major products were usually good to excellent. Our structure assignments for all these products relied heavily on the assignments in eq 2 and Figure 4. The amide N–H resonance was especially useful in both isomer assignment and ratio determination. The major isomer consistently had the most downfield N–H resonance (typically by 0.5 to 0.7 ppm). We suggest that this is due to formation of an intramolecular hydrogen bond (see Figure 5). Only isomer **15/17** is capable of forming an unstrained intramolecular hydrogen bond.

Figure 5



13/16
cannot form intramolecular H-bond

14
can only form strained intramolecular H–bond (trans-fused 5/5 ring)

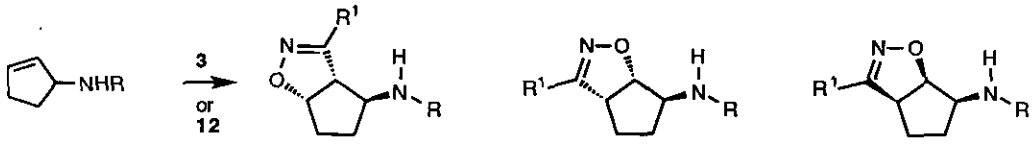
15/17
can form unstrained intramolecular H-bond (cis-fused 5/5 ring)

The results in Table 2 support the idea that hydrogen bond directed cycloadditions are occurring. In all cases the major products are syn isomers (**15**) or (**17**). Based on simple sterics, this isomer should not be the major or even the second major product of such cycloadditions (see Table 1). We did not detect the regioisomer of **15** (or **17**) in any of the cycloadditions, whereas in Caramella and Cellerino's work (Table 1), syn regioisomers **7** and **8** were usually formed in comparable amounts.

Other trends that support the hydrogen bond model also emerge from the data. Benzonitrile oxide consistently gives slightly higher ratios of **17/16** than 2,2-dimethylpropane nitrile oxide (**15/13**). Within a closely related series, the amount of isomer (**15**) or (**17**) parallels the acidity of the N–H bond;[18] however, this parallel is rather rough. For example, in the reactions of 2,2-dimethylpropane nitrile oxides there is a smooth increase in **15** in the *p*-X substituted benzamide series: X = *p*-OMe < H < *m*-CF_3 < *p*-NO_2. In the same series with benzonitrile oxide, the *p*-OMe example is out of place. Other small inconsistencies can be seen in comparing the results of the acetate, trifluoroacetate, and thioacetate (entries g-j). Between series, the simple parallel between the **15/13** or the **17/16** ratio and pKa does not hold that well. Benzamides appear (entries a-e) to be better than they should be compared to perfluorinated amides (entries h, i), thioamides (entry j), and glyoxamides (entry k) (all of which have more acidic N–H bonds). Sulfonamides are clearly poorer directors than their pK_as would

suggest (entries 1, m), and this may be related to differences in orientations of the N–H bonds of amides and sulfonamides.

Table 2. Nitrile Oxide Cycloadditions with **11a-11m**



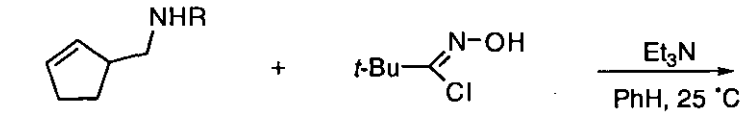
Compound	R	*t*-BuCNO **13/(14)/15**	Yield[a] %	PhCNO **16/17**	Yield[a] %
11a	COPh	12/88	83	11/89	87
11b	CO(*p*-OMe)Ph	15/85	85	8/92	83
11c	CO(*m*-CF_3)Ph	9/91	52	8/92	64
11d	CO(*p*-NO_2)Ph	8/92	58	5/95	93
11e	CO(*o*-OH)C_6H_4	25[c]/75	92	–	–
11f	CONH(*p*-Cl)C_6H_4	14/(6)/80	40	–	–
11g	COMe	28/72	67	25/75	62
11h	$COCF_3$	14/86	92	6/94	94[b]
11i	COC_3F_7	15/85	91	16/84	93
11j	CSMe	16/84	87	12/88	86
11k	COCOMe	23/(4)/73	56	–	–
11l	SO_2Me	24/76	20[b]	27/73	27[b]
11m	SO_2CF_3	34/66	76	28/72	51

[a]Combined yield of **13** + **15** or **16**. [b]Only **15** or **17** was isolated. [c]Combined amount of **13** and **14**.

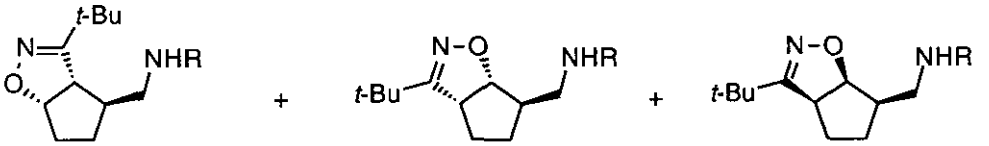
Cycloadditions with Other Amides

To learn more about the requirements for hydrogen bond directed nitrile oxide cycloadditions, we prepared a variety of other allylic amides and investigated their reactions with 2,2-dimethylpropanenitrile oxide. Cyclopentenylmethylamine hydrochloride was readily prepared (see experimental) and acylated with the appropriate acid chloride or anhydride to provide **18a-c**. Reaction of **18a** with 2,2-dimethylpropane nitrile oxide provided a 73% combined yield of three cycloadducts alongside 22% recovered **18a** (Table 3). These adducts were assigned structures **19a**, **20a**, and **21a** (17/25/58) by a chemical shift and coupling constant analysis similar to that described above. Amides (**18b**) and (**18c**) were also reacted with 2,2-dimethylpropane nitrile oxide to provide **19b,c**-**21b,c**, and the results are shown in Table 3. In these two cases, we did not separate the three cycloadducts from each other. The results with **18a-c** suggest that intramolecular hydrogen bonding in the 6-membered cyclopentenylmethyl amides is still important (**21** is the major product in all three cases); however, it is not as favorable as H-bonding in the 5-membered cyclopentenyl amides.

Table 3



18a R = COPh
18b R = $COCF_3$
18c R = COC_3F_7



19a R = COPh
19b R = $COCF_3$
19c R = COC_3F_7

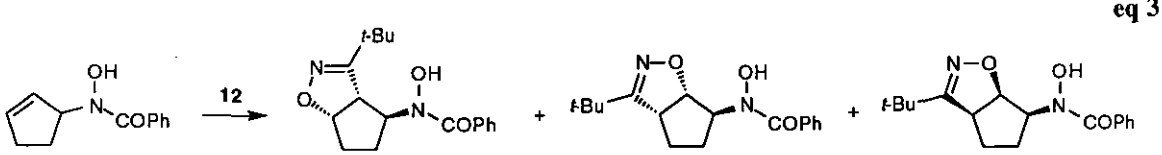
20a
20b
20c

21a
21b
21c

Compound	R	Temp,°C	Yield 18	Ratio 19	20	21	Yield 19-21
a	COPh	25	23	25	17	58	71 %
		80	22	24	17	59	73 %
b	$COCF_3$	25	24	29	17	54	64 %
c	$COCF_2CF_2CF_3$	25	11	15	13	72	73 %

We also prepared hydroxamic acid (**22**) and tested its ability to direct the cycloaddition (eq 3). This is the only amide that we tried in which the donor hydrogen came from an O–H bond. Reaction of **22** with 2,2-dimethylpropane nitrile oxide (**12**) provided three products in a ratio of 23/12/65. These products were not separated, and we tentatively assign them structures **23/24/25**. The hydroxamate O–H bond is a better directing group than an alcohol, and it is comparable to the N–H bonds in Table 3.

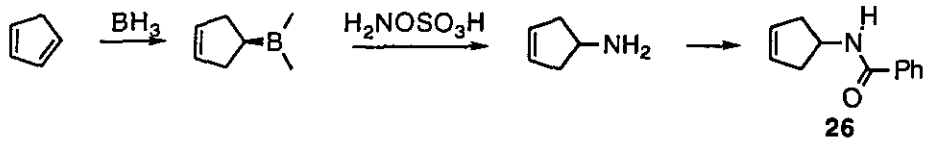
eq 3



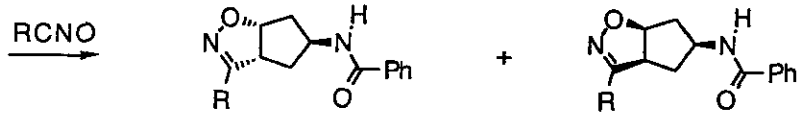
22
23 (23%)
24 (12%)
25 (65%)

To change the orientation of the N–H bond with respect to the alkene while retaining the 5-membered ring transition state, the *N*-3-cyclopentenylbenzamide (**26**) was prepared as outlined in eq 4. Reaction of **26** with benzonitrile oxide provided **27a** and **28a** in a 10/90 ratio in 99% yield. Analogous reaction with 2,2-dimethylpropane nitrile oxide provided **27b** and **28b** in 15/85 ratio in 99% yield.

eq 4



26

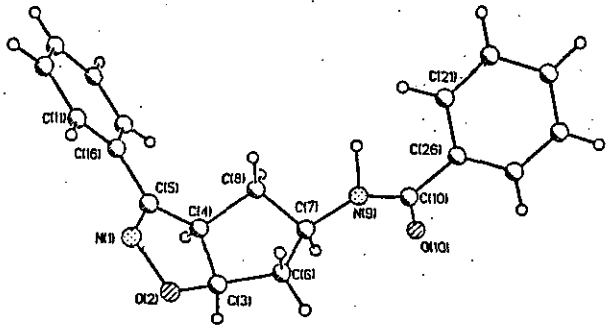


27a R = Ph
27b R = *t*-Bu

28a
28b

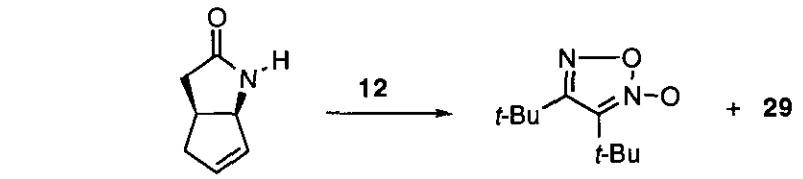
The chemical shifts of the N–H protons suggested that the major isomer was the syn product, and this was confirmed by solving the X-ray crystal structure of **28a**. This structure is shown in Figure 6.[19] In the solid state, the amide N–H proton is not intramolecularly hydrogen bonded to the isoxazoline oxygen; it instead forms an intermolecular hydrogen bond to a neighboring amide oxygen. These results indicate that **11** and **26** have similar capabilities in hydrogen bond directed nitrile oxide cycloadditions, despite the fact that models suggest that the hydrogen bond directed transition state for **26** (bridged bicyclo[3.2.1]) is more strained than that for **11** (fused bicyclo[3.3.0]). Nitrile oxides are cylindrically symmetric, and their oxygen atoms can apparently accept hydrogen bonds in the different directions enforced by **11** and **26** with roughly equal facility.

Figure 6. Crystal Structure of 28a



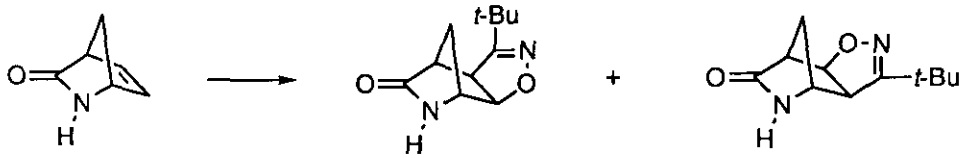
We prepared bicyclic amides (**29**) and (**30**) as rigid models of allylic amides where the orientation of the N–H bond with respect to the alkene is not expected to direct nitrile oxide cycloadditions (eq 5). Consistent with expectations, neither had any directing ability. Fused amide (**29**) did not react well with 2,2-dimethylpropane nitrile oxide. After 4.5 d at 25°C, we recovered 80% of **29**, while 60% of **29** was recovered after 9 d at 80°C. In both cases, the major reaction product (di-*t*-butylfuroxan, **31**)

was that of nitrile oxide dimerization. The lack of reactivity of **29** is somewhat surprising; it is not clear why the exo face of **29** is less reactive than the anti face of simple cyclopentenyl derivatives like **11**. As expected for a norbornyl derivative, lactam (**30**) provided a good yield (87%) of two cycloadducts (**32a**) and (**33b**) in a ratio of 61/39. No evidence for the endo (hydrogen bond directed) cycloadducts could be found.



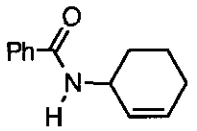
29 **31**

eq 5



30 **32a** **32b**

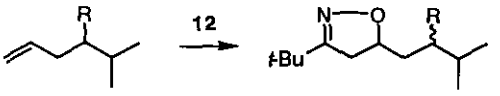
We also prepared *N*-2-cyclohexenylbenzamide (**33**) from cyclohexenyl amide hydrochloride. Unfortunately, this amide did not react with 2,2-dimethylpropane nitrile oxide (**12**) over 9 d at 80°C. As with **29**, the furoxan dimer (**31**) was formed and **33** was recovered in 80% yield. Cyclohexene is much less reactive than cyclopentene in nitrile oxide cycloadditions,[3] and the assistance provided by the hydrogen bond of **33** (if any) is not sufficient to raise its reactivity above the level of reactivity of 2,2-dimethylpropanenitrile oxide with itself.



33

Unfortunately, the good stereo- and regiocontrol that we observed with cyclopentenyl amides did not translate to acyclic systems. Several groups have previously observed low stereoselectivities in nitrile oxide cycloadditions of allylic amides.[11] Figure 7 summarizes the results of our studies with acyclic homoallylic amides. Selectivities were low in all systems surveyed, and configurations of stereoisomers were not generally assigned. The results from these stereoselectivity experiments are ambiguous; one cannot conclude whether hydrogen bond directed nitrile oxide cycloadditions are occurring with low stereoselectivity or whether they are not occurring at all.

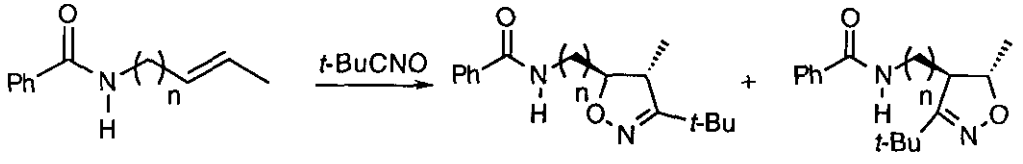
Figure 7



R	isomer ratio
OH	50/50
NH_2	50/50
NHCOMe	52/48
$NHCOCF_3$	65/35
$NHSO_2Me$	57/43
$NHSO_2CF_3$	67/33

To ascertain the importance of hydrogen bonding in acyclic systems, we studied regioselectivities in cycloadditions of the allylic and homoallylic amides shown in Figure 8. Regioselectivities in nitrile oxide cycloadditions of unactivated disubstituted alkenes are generally low, and the amides in Figure 8 are no exception. These results suggest the hydrogen bonding does not play an important role in these acyclic systems. Had it been important, we would have observed significantly larger amounts of the regioisomer (**35**). Cycloaddition of **34a** with **12** was very sluggish at 25°C, and 70% of **34a** was recovered after 5 d. After 4.5 d at 80°C, we obtained a 59% yield of **35a** and **36a** in a 67/33 ratio. Under the same conditions, **34b** produced a 54% yield of **35b** and **36b** in a 65/35 ratio.

Figure 8



34a n = 1
34b n = 2

35a 67/33 **36a**
35b 65/35 **36b**

Mechanistic Studies

The hydrogen bond model shown in Figure 3 is an accelerative model, and this makes two important predictions: 1) substrates capable of hydrogen bond directed cycloadditions should react with nitrile oxides more rapidly than appropriate models that lack hydrogen bonding, and 2) disruption of hydrogen bonding should decrease the rate and restore the "normal" stereo- and regioselectivity of a given substrate. Seeking to support the model by verifying these predictions, we carried out a series of competition experiments and solvent effect studies.

As a model for amide (**11a**) which could not form hydrogen bonds, we selected *N*-methyl amide **37**.[20] As expected, cycloaddition of **37** with 2,2-dimethylpropane nitrile oxide gave much different results from **11a** (eq 6). Amide (**37**) was considerably less reactive than **11a**. Heating of **37** and **12a** for 9.5 d at 80°C gave 32% recovered **37** along with 29% combined yield of 3 products (**38**-**40**). Anti isomers (**38**) and (**39**) were favored, and the syn isomer (**40**) was now the minor product. The structures of the

products were assigned by *N*-methylation of **13a**, **14a**, and **15a**, which provided **38**, **39**, and **40**, respectively. Once again, we could not locate the fourth possible isomer.

eq 6

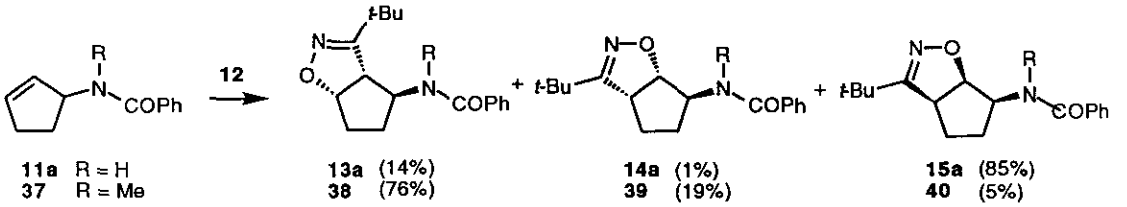
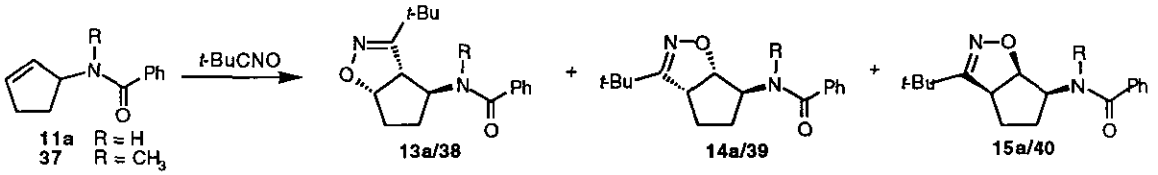


Table 4 summarizes the results of a series of cycloadditions of 2,2-dimethylpropanenitrile oxide with **11a** and **37** in benzene, DME, DMF, and HMPA. *N*-Methyl amide (**37**) behaves like a normal dipolarophile: the nature of the solvent has very little effect on either the yield or the ratio of products (entries 6-9). In contrast, 2°-amide (**11a**) shows uncharacteristic behavior (entries 1-5). The amount of isomer (**15a**) steadily decreases in going from benzene to DME to DMF to HMPA. We attribute these effects to the ability of the solvent to accept a hydrogen bond. Solvents that are better acceptors disrupt the hydrogen bonded transition state. The extreme is HMPA, where the ratios of isomers from **11a** and **37** are nearly identical (compare entries 5-9).

Table 4



entry	amide	solvent	temp, °C	ratio 13a (38)	14a (39)	15a (40)	% conv
1	**11a**	CH_2Cl_2	25	12	3	85	nd[a]
2	**11a**	PhH	25	14	1	85	92
3	**11a**	DME	25	35	8	57	91
4	**11a**	DMF	25	59	15	26	65
5	**11a**	HMPA	25	78	14	8	83
6	**37**	PhH	80	76	19	5	46
7	**37**	DME	80	73	24	3	30
8	**37**	DMF	80	64	33	3	43
9	**37**	HMPA	80	69	27	4	63

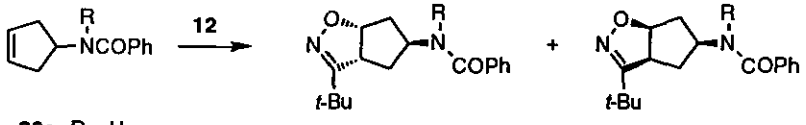
[a]nd = not determined

According to this analysis, the ratios are altered by decreasing the rate of formation of isomer (**15**) as the H-bond acceptor capability of the solvent increases. This prediction was probed by conducting competition experiments between **11a** and **37**. When 1 equiv of 2,2-dimethylpropane nitrile oxide

was exposed to 3 equiv of **11a** and 3 equiv of **37** (CH_2Cl_2,[21] 25°C, 5.5 d), we detected only the products of cycloaddition to **11a** (**13a/14a/15a**) in a ratio of 11/3/86. This experiment confirms that 2°-amide (**11a**) is significantly more reactive than 3°-amide (**37**). Indeed, it is even more reactive than it should be. A simple analysis indicates that anti isomers (**13a**) and (**38**) are not influenced by H-bonding, and they should be present in roughly equal amounts; however, we could not detect resonances of the anti isomer (**38**) derived from **37** in the crude ^1H nmr spectrum. We do not understand why the anti isomers of **11a** are formed more readily than the anti isomers of **37**.

Competition experiments between the isomeric 2°-amide (**26**) and 3°-amide (**41**) behaved exactly as expected (eq 7). First, cycloaddition of 3°-amide (**41**) with 2,2-dimethylpropane nitrile oxide provided anti (**42**) and syn (**43**) in ratios of 90/10 (in benzene) and 92/8 (in HMPA). That this ratio is reversed from the 2°-amide was determined by *N*-methylation of **27a** and **28a** to give **42** and **43**. Next, competition of 2 equiv each of **26** and **41** for limited 2,2-dimethylpropane nitrile oxide in benzene (25°C, 5.5 d) gave **27a/28a/42** in a ratio of 5/90/5 (**43** could not be detected). Thus, the rate of formation of the syn product from **26** is considerably higher than the rates of formation of the two anti products (**27a** and **42**), which are about equal. Finally, this competition experiment was repeated in HMPA, and the ratio of products (**27a/28a/42/43**) was now 66/6/24/4. Now the anti product (**27a**) predominates over its syn isomer (**28a**), and the syn/anti ratio from **26** is very similar to that from **41**. In HMPA, 2°-amide (**26**) is only marginally more reactive than 3°-amide (**41**).

eq 7



26a R = H
41 R = CH_3

27a
42

28a
43

Conclusions

Our results strongly support the original premise that hydrogen bonding of nitrile oxides to allylic and homoallylic 2°-amides can alter the outcome of dipolar cycloaddition reactions. While cyclopentenyl 2°-amides whose N–H bonds are directed away from the alkene show no unusual effects, amides whose N–H bonds can be directed towards the alkene show three unusual effects. These 2°-amides: 1) are more reactive than 3°-amide models; 2) show significantly altered regio- and stereoselectivity, and 3) show significant solvent effects on both reactivity and selectivity. All these effects are consistent with an accelerative hydrogen bonding model.

We can estimate from changes in product ratios that hydrogen bonding must lower the transition state energy 2-3 kcal/mol more than it lowers the ground state energy. This difference is enough to provide complete reversals in selectivity in several cases. Unfortunately, in less reactive systems (like cyclohexene) or in freely-rotating acyclic systems, the effect is not sufficient, and a better directing group than an N–H bond is needed for these systems.[13]

The influence of hydrogen bonds on dipolar cycloaddition reactions is probably not limited to nitrile oxides. Other 1,3-dipoles with Lewis basic sites will probably also be influenced by hydrogen

bonding. Thus, the "Directed Dipolar Cycloaddition" strategy should emerge in the future as a powerful method to dictate reactivity, and in turn, stereo- and regioselectivity.

EXPERIMENTAL

General: All reactions were performed under an atmosphere of nitrogen or argon. Solvents were purified as follows: triethylamine, dichloromethane, DMSO, DMF, DME, HMPA, and toluene were distilled from calcium hydride. Benzene, THF, and diethyl ether were distilled from sodium/benzophenone. ^1H and ^{13}C nmr spectra were obtained on a Bruker model WH-300 (300 MHz), an IBM model AF-300 (300 MHz) or, where indicated, on an IBM model AM-500 (500 MHz) nmr spectrometer.

3-Chlorocyclopentene (9). Gaseous hydrochloric acid (16.42 g, 0.45 mol) was bubbled through a vigorously stirred solution of freshly cracked cyclopentadiene monomer (33.30 g, 0.5 mol) at –78 °C. The reaction mixture became viscous and slightly yellow. After the addition, the reaction mixture was stirred an additional 1.5 h and it was distilled at 25 °C / 8 mmHg (lit.,[14] 18-25 °C / 5 mmHg). The clear, freely flowing distillate afforded 22.94 g (45%) of **9** which was stored at –81 °C: ^1H Nmr ($CDCl_3$) δ 6.07 (m, 1 H), 5.88 (m, 1 H), 5.05 (m, 1 H), 2.70-2.50 (m, 1 H), 2.40-2.25 (m, 2 H), 2.16 (m, 1 H).

3-Aminocyclopentene hydrochloride (10). To a solution of liquid ammonia (9.96 g, 0.586 mol) and dry methanol (11.87 ml, 0.293 mol) at –78 °C was added dropwise **9** (3.00 g, 0.293 mol). Upon complete addition, the cold bath was removed, and the mixture was allowed to warm to 25 °C with stirring over 2 h. The excess ammonia and methanol were removed by concentration in vacuo. The yellow residue was then dissolved in chloroform (25 ml) and this extract was evaporated to dryness. The off-white solid was dried on a vacuum pump for over 1 h, resulting in 2.62 g (75 %) of product, which was stored at –10 °C in the dark to prevent discoloration: ^1H Nmr (D_2O) δ 6.08 (m, 1 H), 5.61 (m, 1 H), 4.17 (m, 1 H), 2.45-2.12 (br m, 4 H); ir (KBr pellet) 2949, 2597, 2507, 2045, 1608, 1559, 1496, 1451, 1378, 1141, 1039, 773, 709 cm^{-1}.

***General Amidation Procedure I.* N-(2-Cyclopentenyl)benzamide (11a).** Amine hydrochloride (**10**) (1.00 g, 8.37 mmol) was dissolved in an aqueous solution (8 ml) of sodium hydroxide (0.87 g, 21.76 mmol) at 25 °C. Benzoyl chloride (0.97 ml, 8.37 mmol) was then added dropwise by a syringe pump over 1 h. After stirring 30 min at 25 °C, the reaction mixture was then diluted 3N aqueous sodium hydroxide solution (6 ml) and the mixture was extracted with diethyl ether (2 x 50 ml). The organic extracts were combined and dried over sodium sulfate. Filtration and concentration afforded the crude product as an off-white solid. Purification by flash column chromatography (33 % ethyl acetate-hexanes) and recrystallization from ethyl acetate yielded 1.17 g (75 %) of white needles: mp 122.1-122.6 °C: ^1H Nmr ($CDCl_3$) δ 7.75 (m, 2 H), 7.40 (m, 3 H), 6.05 (br s, 1 H), 6.00 (m, 1 H), 5.80 (m, 1 H), 5.20 (m, 1 H), 2.60-2.30 (m, 3 H), 1.70 (m, 1 H); ^{13}C nmr ($CDCl_3$) δ 166.9 (s), 134.5 (2C, s + d), 131.1 (d), 128.2 (2C, d), 126.9 (d), 56.0 (d), 31.1 (2C, t); ir (thin film) 3290, 3050, 2922, 2863, 1630, 1571, 1540, 1495, 1340, 1290, 699 cm^{-1}; ms *m/z* 187 (M^+), 122, 105 (base), 77, 66, 51; HRms calcd for $C_{12}H_{13}NO$, 187.0997; found, 187.0997.

***General amidation procedure II.* 1-{*N*-(4-Chlorophenyl)amino}-*N'*-(2-cyclopentenyl)methanamide (11f).** To a solution of **10** (31.5 mg, 0.26 mmol) and triethylamine (42.0 µl, 0.3 mmol) in CH_2Cl_2 (1.5 ml) was added a solution of 4-chlorophenyl isocyanate (31.4 mg, 0.2 mmol) in CH_2Cl_2 (1 ml) dropwise by a syringe pump over 1 h at 25 °C. After 12 h at 25°C, the mixture was diluted with CH_2Cl_2 (80 ml) and washed with saturated aqueous $NaHSO_4$ solution, water, aqueous $NaHCO_3$ solution and brine (1 x 20 ml each), and dried over Na_2SO_4. Concentration and purification by MPLC (33 % ethyl acetate-hexanes) yielded 22.0 mg (47 %) of the yellow liquid **11f**: ^1H Nmr ($CDCl_3$) δ 7.40-7.20 (m, 4 H), 6.25 (m, 1 H), 5.95 (m, 1 H), 5.72 (m, 1 H), 4.90 (m, 1 H), 4.60 (m, 1 H), 2.50-2.20 (m, 2 H), 1.45-1.00 (m, 2 H); ir (neat) 3619, 3617, 3024, 2934, 1731, 1520, 1218, 770 cm^{-1}; ms *m/z* 236 (M^+), 127 (base), 82, 67; HRms calcd for $C_{12}H_{13}N_2OCl$, 236.0716; found, 236.0716.

***N*-(2-Cyclopentenyl)-4-methoxybenzamide (11b).** Prepared following general amidation procedure I, with 3-aminocyclopentene hydrochloride (0.50 g, 4.18 mmol), NaOH (0.44 g, 10.88 mmol), water (4 ml) and *p*-methoxybenzoyl chloride (0.60 ml, 4.18 mmol). Extraction with ether (75 ml) and ethyl acetate (75 ml) afforded 0.52 g (57%) crude amide as a yellow solid. Purification by flash chromatography (2:1 hexane/ethyl acetate) afforded 371 mg (41%) of product, which was recrystallized (flocculent needles, EtOAc): mp 123.7-124.2 °C. Ir (thin film) 3282, 2932, 2842, 1627, 1617, 1547, 1522, 1260, 1030, 842 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.73 (dt, 2 H, J = 6.9, 1.9 Hz), 6.92 (dt, 2 H, J = 6.9, 1.9 Hz), 6.02-5.99 (m, 1 H), 5.95 (br s, 1 H), 5.79-5.77 (m, 1 H),

5,24-5.18 (m, 1 H), 3.85 (s, 3 H), 2.52-2.37 (m, 3 H), 1.70-1.65 (m, 1 H); ms *m/z* 217 (M^+) 152, 135 (base), 101, 92, 77; HRms calcd for $C_{13}H_{15}O_2N$, 217.1103; found, 217.1103.

***N*-(2-Cyclopentenyl)-3-trifuoromethylbenzamide (11c).** Prepared following general amidation procedure II with 3-aminocyclopentene hydrochloride (0.10 g, 0.84 mmol), triethylamine (0.35 ml, 2.51 mmol), dichloromethane (1.5 ml), and *m*-trifluoromethylbenzoyl chloride (0.15 ml, 1.01 mmol) at 0 °C (2 h, 25 °C). Filtration and concentration afforded 0.361 g of an off-white solid. Purification by flash chromatography (3:1 hexane/ethyl acetate) afforded 0.177 g (83%) of the product as a white solid: mp 107.7-108.4 °C. Ir (thin film) 3239, 3064, 2971, 2940, 1635, 1545, 1536, 1329, 1168, 1136, 1118, 1070, 920, 818, 696 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.00 (s, 1 H), 7.95 (d, 1 H, *J* = 7.7 Hz), 7.75 (d, 1 H, *J* = 7.9 Hz), 7.57 (t, 1 H, *J* = 7.9 Hz), 6.03-6.06 (m, 2 H), 5.78-5.81 (m, 1 H), 5.21-5.24 (m, 1 H), 2.37-2.57 (m, 3 H), 1.65-1.76 (m, 1 H); ms *m/z* 255 (M^+) 236, 227, 190, 173 (base), 145, 95, 82, 66, 55; HRms calcd for $C_{13}H_{12}NOF_3$, 255.0871; found, 255.0871.

***N*-(2-Cyclopentenyl)-4-nitrobenzamide (11d).** Prepared following general amidation procedure I, with 3-aminocyclopentene hydrochloride (0.50 g, 4.18 mmol), NaOH (0.44 g, 10.88 mmol), water (4 ml) and *p*-nitrobenzoyl chloride (0.785 g, 4.18 mmol in 5 ml Et_2O). Extraction with ethyl acetate (2 x 40 ml) afforded 0.727 g (75 %) of the product as a tan solid. Final purification by flash chromatography (3:1 hexane/ethyl acetate) and recrystallization (EtOAc) yielded pale yellow needles: mp 171.9-172.1 °C. Ir (thin film) 3278, 1636, 1600, 1542, 1518, 1508, 1350, 1337 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.29 (dt, 2 H, *J* = 8.7, 1.8 Hz), 7.92 (dt, 2 H, *J* = 8.7, 1.8 Hz), 6.08 (br s, 1 H), 6.07-6.04 (m, 1 H), 5.80-5.77 (m, 1 H), 5.26-5.21 (m, 1 H), 2.54-2.39 (m, 3 H), 1.74-1.68 (m, 1 H); ms *m/z* 232 (M^+) 167, 150 (base), 120, 104, 92, 76, 66; HRms calcd for $C_{12}H_{12}N_2O_3$, 232.0848; found, 232.0847.

***N*-(2-Cyclopentenyl)-2-hydroxybenzamide (11e).** Prepared following the general amidation procedure I with 2-hydroxybenzoyl chloride (46.9 mg, 0.3 mmol), which was prepared by the reaction of 2-hydroxybenzoic acid with thionyl chloride, **10** (35.8 mg, 0.3 mmol), NaOH (40 mg, 1 mmol), water (2 ml), and CH_2Cl_2 (for dissolving 2-hydroxy benzoyl chloride, 1 ml) (2 h). Concentration and purification by flash column chromatography (33 % ethyl acetate-hexanes) yielded 10.9 mg (18 %) of a slightly yellow liquid: ^1H Nmr ($CDCl_3$) δ 12.15 (s, 1 H), 7.50-7.30 (m, 2 H), 7.00 (m, 1 H), 6.85 (m, 1 H), 6.35-6.00 (br s, 1 H), 6.05 (m, 1 H), 5.75 (m, 1 H), 5.15 (m, 1 H), 2.65-2.30 (m, 3 H), 1.70 (m, 1 H); ir (neat) 3309, 3046, 2972, 1624, 1542, 1310, 1240 cm^{-1}.

***N*-(2-Cyclopentenyl)ethanamide (11g).** 3-Aminocyclopentene hydrochloride (1.00 g, 8.37 mmol) and triethylamine (3.45 ml, 25.10 mmol) were combined in dry dichloromethane (10 ml) and stirred. Acetyl chloride (0.71 ml, 10.04 mmol) was then added dropwise. After complete addition, the mixture was stirred at 25 °C for 1 h, then dissolved in dichloromethane (70 ml). The organic phase was then washed successively with $NaHSO_4$ (1 x 20 ml), H_2O (1 x 20 ml), $NaHCO_3$ (1 x 30 ml), and NaCl (1 x 15 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated to 800 mg of a yellow liquid. Purification by flash chromatography (10:1 ethyl acetate/hexane) afforded 679 mg (65%) of the product as an off-white solid: mp 70.3-71.2 °C. Ir (thin film) 3257, 3067, 2968, 2856, 1635, 1554, 1373, 1300, 1287, 686 cm^{-1}; ^1H nmr ($CDCl_3$) δ 5.94-5.96 (m, 1 H), 5.66-5.70 (m, 1 H), 5.37 (br s, 1 H), 4.98-5.06 (m, 1 H), 2.27-2.48 (m, 3 H), 1.96 (s, 3 H), 1.51-1.60 (m, 1 H); ms *m/z* 125 (M^+) 82 (base), 66, 55, 43; HRms, calcd for $C_7H_{11}NO$, 125.0834; found, 125.0834.

***N*-(2-Cyclopentenyl)-2,2,2-trifluoroethanamide (11h).** Prepared following general amidation procedure II, with 3-aminocyclopentene hydrochloride (0.50 g, 4.18 mmol), triethylamine (1.72 ml, 12.55 mmol), dichloromethane (5 ml), and trifluoroacetic anhydride (0.71 ml, 5.02 mmol) at 0 °C (1.5 h, 25 °C). Purification by flash chromatography (20:1 hexane/ethyl acetate) afforded 404 mg (54%) of the product as translucent needles: mp 54.5-55.0 °C. Ir (thin film) 3293, 3095, 2955, 2875, 1695, 1183, 1160 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.18 (br s, 1 H), 6.09-6.05 (m, 1 H), 5.52-5.48 (m, 1 H), 5.09-5.00 (m, 1 H), 2.58-2.32 (m, 3 H), 1.71-1.65 (m, 1 H); ms *m/z* 179 (M^+) 110, 82, 67 (base), 55.

***N*-(2-Cyclopentenyl)-2,2,3,3,4,4,4-heptafluorobutanamide (11i).** Prepared following the general amidation procedure II, with 3-aminocyclopentene hydrochloride (0.20 g, 1.67 mmol), triethylamine (0.70 ml, 5.02 mmol), dichloromethane (10 ml) and heptafluorobutyryl chloride (0.30 ml, 2.01 mmol) at –78 °C. After complete addition, the mixture was stirred at –78 °C for 3 h, then warmed gradually to 25 °C over 1 h. The reaction mixture was filtered through a plug of silica with CH_2Cl_2 (50 ml) and concentrated to a white solid. This solid was redissolved in Et_2O (35 ml) and filtered through a plug of Celite to remove any traces of triethylamine hydrochloride. Concentration of the filtrate and flash chromatography of the residue (6:1 hexane/ethyl acetate)

afforded 0.262 g (56%) of the product as a white solid: mp 38.9-39.5 °C. Ir (thin film) 3291, 3067, 2947, 2861, 1700, 1540, 1457, 1369, 1352, 1336, 1215, 1124, 966, 914, 823, 726 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.23 (br s, 1 H), 6.07-6.10 (m, 1 H), 5.68-5.71 (m, 1 H), 4.98-5.10 (br m, 1 H), 2.31-2.59 (m, 3 H), 1.64-1.70 (m, 1 H); ms *m/z* 279 (M^+) 214, 169, 160, 103, 83, 66 (base), 55; HRms calcd for $C_9H_8NOF_7$, 279.0494; found, 279.0494.

***N*-(2-Cyclopentenyl)thioethanamide (11j).** 3-Acetamidocyclopentene (**11g**, 0.08 g, 0.62 mmol) was combined with Lawesson's reagent (0.13 g, 0.31 mmol) in dry benzene (3 ml). The mixture was heated to reflux for 4 h, then allowed to cool. Purification by immediate flash chromatography ($CHCl_3$) afforded 0.057 g (64.7%) of **11j** as a brown oil which crystallized completely upon standing: Ir (thin film) 3207, 3050, 2945, 1539, 1387, 1319, 1199, 1144, 1095 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.09 (br s, 1 H), 6.05-6.08 (m, 1 H), 5.77-5.79 (m, 1 H), 5.48-5.52 (m, 1 H), 2.53 (s, 3 H), 2.37-2.54 (m, 3 H), 1.55-1.75 (m, 1 H); ms *m/z* 141 (M^+) 99, 82, 76 (base), 67, 59; HRms calcd for $C_7H_{11}NS$, 141.0612; found, 141.0612.

***N*-(2-Cyclopentenyl)-2-oxopropanamide (11k).** Prepared following the general amidation procedure II with 2-oxopropanoyl chloride (426 mg, 4.0 mmol, which was prepared by the reaction of the 2-oxopropanoic acid with oxalyl chloride), **10** (500 mg, 4.2 mmol), triethylamine (2.1 ml, 15 mmol), and CH_2Cl_2 (10 ml) (12 h). Concentration and purification by flash column chromatography (33 % ethyl acetate-hexanes) yielded 411.2 mg (67 %) of a yellow liquid: ^1H Nmr ($CDCl_3$) δ 7.00-6.75 (br s, 1 H), 6.00 (m, 1 H), 5.65 (m, 1 H), 5.05-4.90 (m, 1 H), 2.50 (s, 3 H), 2.50-2.20 (m, 3 H), 1.70-1.55 (m, 1 H); ir (neat) 3317, 3058, 2944, 2855, 1721, 1679, 1518, 1356, 1175 cm^{-1}; ms *m/z* 153 (M^+), 110, 82, 67 (base), 43.

***N*-(2-Cyclopentenyl)methanesulfonamide (11l).** Prepared following general amidation procedure II with 3-aminocyclopentene hydrochloride (0.50 g, 4.18 mmol), triethylamine (1.72 ml, 12.55 mmol), dichloromethane (5 ml) and methanesulfonyl chloride (0.39 ml, 5.02 mmol) at 0 °C (1.5 h, 25 °C). Filtration and concentration afforded 525 mg of a brown oil. Purification by flash chromatography (1:1 hexane/ethyl acetate) afforded 388 mg (58%) of the product as a tan solid, which was recrystallized (EtOAc): mp 56.5-57.1 °C. Ir (thin film) 3278, 2934, 2856, 1437, 1415, 1355, 1321, 1149, 1067, 973, 897 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.01-5.98 (m, 1 H), 5.77-5.71 (m, 1 H), 4.58-4.50 (m, 1 H), 4.32 (br s, 1 H), 2.98 (s, 3 H), 2.54-2.25 (m, 3 H), 1.80-1.72 (m, 1 H); ms *m/z* 161 (M^+) 146, 98, 82 (base), 67, 55; HRms calcd for $C_6H_{11}O_2NS$, 161.051; found, 161.0501.

***N*-(2-Cyclopentenyl)trifluoromethanesulfonamide (11m).** 3-Aminocyclopentene hydrochloride (0.50 g, 4.18 mmol) and triethylamine (1.72 ml, 12.55 mmol) were combined in dry dichloromethane (15 ml) at –78 °C and stirred. Triflic anhydride (0.85 ml, 5.02 mmol) was then added dropwise. After complete addition, the mixture was stirred at –78 °C for 3.5 h, then warmed gradually to 25 °C over 2 h. The reaction mixture was filtered through a 1 inch plug of silica and concentrated to a brown oil. Purification by flash chromatography (7:1 hexane/ethyl acetate) afforded 339 mg (38%) of the product as a yellow oil: Ir (thin film) 3304, 2945, 2862, 1437, 1375, 1234, 1194, 1148, 1049, 1009, 988, 946 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.07-6.05 (m, 1 H), 5.73-5.71 (m, 1 H), 4.74-4.62 (br m, 2 H), 2.55-2.39 (m, 3 H), 1.83-1.55 (m, 1 H); ms *m/z* 215 (M^+) 146, 82 (base), 67, 55; HRms calcd for $C_8H_8NO_2S_3F$, 215.0228; found, 215.0228.

General Cycloaddition Procedures I and II. **6-Benzamido-3-*tert*-butyl-3aα,5,6α,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15a), 6-Benzamido-3-*tert*-butyl-3aα,5,6β,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (14a), and 4-Benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13a)** *from* **11a.** *Triethylamine* (14.0 µl, 0.1 mmol) was added dropwise to the solution of 2°-amide(**11a**)(18.7 mg, 0.1 mmol) and *t*-butylhydroximinoyl chloride (13.6 mg, 0.1 mmol) in dry benzene (1 ml). After 4.5 days for procedure I (20 h for procedure II) at 25 °C, the resulting suspension was diluted with ethyl acetate (80 ml) and washed with water (2 x 20 ml). After separation, the organic phase was dried over Na_2SO_4 and concentrated to give 26.3 mg (92 %) of a slightly yellow solid. Purification by analytical hplc (55 % ethyl acetate-hexanes) afforded in order of elution **14a**, **13a**, and **15a** (1/14/85 respectively in ^1H nmr spectroscopy for crude product): **15a** mp 182.5-183.2 °C: ^1H nmr ($CDCl_3$) δ 7.80 (m, 2 H), 7.55-7.40 (m, 3 H), 6.72 (d, 1 H, J = 9.0 Hz), 4.92 (dd, 1 H, J = 8.4, 5.0 Hz), 4.70-4.50 (m, 1 H), 3.75 (t, 1 H, J = 8.4 Hz), 2.17 (m, 1 H), 2.08 (m, 1 H), 2.00-1.75 (m, 1 H), 1.50-1.35 (m, 1 H), 1.45-1.25 (s, 9 H); ^{13}C nmr ($CDCl_3$) δ 167.6 (s), 167.0 (s), 134.1 (s), 131.4 (d), 128.4 (d), 126.9 (d), 84.6 (d), 55.2 (d), 51.7 (d), 33.3 (s), 29.4 (q), 28.6 (t), 28.0 (t); ir (thin film) 3439, 3020, 1657, 1519, 1216, 757 cm^{-1}; ms *m/z* 287 $(M + H)^+$, 229, 203, 122, 105 (base), 77, 57; HRms calcd for $C_{16}H_{13}N_2O_2$, 229.0977; found, 229.0977. **14a** ^1H Nmr ($CDCl_3$) δ 7.75 (m, 2 H), 7.55-7.35 (m, 3 H), 6.07 (d, 1 H, J = 6.9 Hz), 5.05 (dd, 1 H, J = 9.2, 2.3 Hz), 4.45 (m, 1 H), 3.75 (m, 1 H), 2.20-2.05 (m, 2 H), 2.05-1.80 (m, 2 H), 1.15 (s, 9 H); ir (thin film) 3335, 2962, 2923, 2854, 1636,

1539, 1458, 1318 cm^{-1}. **13a** mp 172.0-172.7 °C; ^1H nmr ($CDCl_3$) δ 7.75 (m, 2 H), 7.60-7.40 (m, 3 H), 6.07 (d, 1 H, *J* = 6.9 Hz), 5.12 (dd, 1 H, *J* = 8.8, 4.5 Hz), 4.72 (t, 1 H, *J* = 5.8 Hz), 3.75 (d, 1 H, *J* = 8.8 Hz), 2.35-2.15 (m, 1 H), 2.15-1.90 (m, 2 H), 1.90-1.70 (m, 1 H), 1.45-1.30 (s, 9 H); ^{13}C nmr ($CDCl_3$) δ 167.4 (s), 165.3 (s), 134.2 (s), 131.6 (d), 128.5 (d), 127.0 (d), 86.3 (d), 60.4 (d), 55.6 (d), 33.6 (s), 32.6 (t), 30.4 (t), 29.2 (q); ir (thin film) 3469, 3202, 2960, 2931, 1638, 1535, 1289 cm^{-1}; ms *m/z* 286 (M^+), 181, 148, 139, 105 (base), 77, 57; HRms calcd for $C_{17}H_{22}N_2O_2$, 286.1681; found, 286.1686.

6-(4'-Methoxy)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15b) and **4-(4'-Methoxy)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]-isoxazole (13b)**. Prepared following the general cycloaddition procedure II with 3-(4'-Methoxy)-benzamidocyclopentene (10.0 mg, 0.05 mmol), *tert*-butyl hydroximinoyl chloride (6.3 mg, 0.05 mmol), triethylamine (7.0 µl, 0.05 mmol) and benzene (0.5 ml) (24 h). Purification by MPLC (2:1 hexane/ethyl acetate) afforded 12.4 mg (85%) of **15b** and **13b**: Ir (thin film) 3350, 2985, 1653, 1506, 1203, 1179, 1027 cm^{-1}; ^1H nmr ($CDCl_3$) **15b** δ 7.77 (d, 2 H, *J* = 8.8 Hz), 6.92 (d, 2 H, *J* = 8.8 Hz), 6.61 (d, 1 H, *J* = 8.3 Hz), 4.88 (dd, 1 H, *J* = 8.2, 4.9 Hz), 4.49-4.60 (m, 1 H), 3.85 (s, 3 H), 3.71 (t, 1 H, *J* = 8.6 Hz), 2.12-2.19 (m, 1 H), 2.00-2.07 (m, 1 H), 1.77-1.91 (m, 1 H), 1.34-1.49 (m, 1 H), 1.27 (s, 9H). **13b** δ 7.70 (d, 2 H, *J* = 8.8 Hz), 6.93 (d, 2 H, *J* = 8.8 Hz), 5.95 (d, 1 H, *J* = 6.0 Hz), 5.11 (dd, 1 H, *J* = 8.5, 4.6 Hz), 4.69 (t, 1 H, *J* = 4.8 Hz), 3.85 (s, 3 H), 3.71 (d, 1 H, *J* = 8.4 Hz), 2.21-2.26 (m, 1 H), 1.97-2.04 (m, 2 H), 1.76-1.83 (m, 1 H), 1.37 (s, 9H); ms *m/z* 316 (M^+), 287, 233, 152, 135 (base), 92, 77; HRms calcd for $C_{18}H_{24}N_2O_3$, 316.1787; found, 316.1787.

6-(3'-Trifluoromethyl)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isox-azole (15c) and **4-(3'-Trifluoromethyl)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13c)**. Prepared following general cycloaddition procedure II with 3-(3'-trifluoromethyl)benzamidocyclopentene (25.5 mg, 0.1 mmol), *tert*-butyl hydroximinoyl chloride (13.7 mg, 0.1 mmol), triethylamine (14.4 µl, 0.1 mmol) and benzene (1.0 ml) (21 h). Purification by MPLC (2:1 hexane/ethyl acetate) afforded 18.5 mg (52%) of **15c**: Ir (thin film) 3297, 3073, 2969, 2885, 1647, 1541, 1333, 1169, 1127, 1072, 885, 733, 698 cm^{-1}; ^1H nmr ($CDCl_3$) **15c** δ 8.07 (s, 1 H), 7.96 (d, 1 H, *J* = 7.9 Hz), 7.76 (d, 1 H, *J* = 7.9 Hz), 7.57 (t, 1 H, *J* = 7.8 Hz), 6.74 (d, 1 H, *J* = 8.2 Hz), 4.91 (dd, 1 H, *J* = 8.2, 5.0 Hz), 4.50-4.61 (m, 1 H), 3.74 (t, 1 H, *J* = 8.6 Hz), 2.14-2.22 (m, 1 H), 2.03-2.10 (m, 1 H), 1.79-1.99 (m, 1 H), 1.39-1.52 (m, 1 H), 1.27 (s, 9H); ms *m/z* 355 (M + 1), 335, 325, 215, 190, 173, 139, 110, 82 (base), 57; HRms calcd for $C_{18}H_{21}N_2O_2F_3$ (M − 19), 335.1571; found, 335.1572. Partial nmr data for **13c** δ 6.24 (d, 1 H, *J* = 5.4 Hz), 5.10 (dd, 1 H, *J* = 5.1, 3.1 Hz), 4.71 (t, 1 H, *J* = 2.2 Hz);

6-(4'-Nitro)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15d) and **4-(4'-Nitro)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13d)**. Prepared following general cycloaddition procedure II with 3-(4'-nitro)benzamidocyclopentene (10.0 mg, 0.04 mmol), *tert*-butyl hydroximinoyl chloride (5.7 mg, 0.04 mmol), triethylamine (6.0 µl, 0.04 mmol) and benzene (1.0 ml) (24 h). Purification by MPLC (2:1 hexane/ethyl acetate) afforded 8.0 mg (58%) of **15d**: Ir (thin film) 3295, 2969, 2871, 1653, 1522, 1346, 840, 721 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.29 (apparent d, 2 H, *J* = 8.7 Hz), 7.97 (d, 2 H, *J* = 8.7 Hz), 6.77 (d, 1 H, *J* = 8.4 Hz), 4.91 (dd, 1 H, *J* = 8.3, 5.0 Hz), 4.55 (m, 1 H), 3.76 (t, 1 H, *J* = 8.3 Hz), 2.16-2.24 (m, 1 H), 2.05-2.12 (m, 1 H), 1.80-1.94 (m, 1 H), 1.39-1.51 (m, 1 H), 1.28 (s, 9H). Partial nmr data for **13d** δ 6.38 (br d, 1 H), 5.12 (dd, 1 H, *J* = 9.0, 4.5 Hz), 4.71 (br t, 1 H, *J* = 4.4 Hz); ms *m/z* 331 (M^+), 314, 302, 288, 274, 248, 167, 150 (base), 104, 82, 57; HRms calcd for $C_{13}H_{12}N_3O_4$ (M-C_4H_9), 274.0828; found, 274.0828.

Δ^2-Isoxazolines (13e, 14e, and **15e)** from **11e** Prepared following the general cycloaddition procedure I with **11e** (10.9 mg, 0.054 mmol), oxime chloride (13.6 mg, 0.1 mmol), triethylamine (16.7 µl, 0.12 mmol), and benzene (0.54 ml). Concentration yielded 15.0 mg (92 %) of the product. Only ^1H nmr spectroscopy for crude product was taken. The ratio of the product **15e/(14e + 13e)** was 75/25.

Δ^2-Isoxazolines (13f, 14f, and **15f)** from **11f.** Prepared following the general cycloaddition procedure I with **11f** (18.9 mg, 0.08 mmol), oxime chloride (13.6 mg, 0.1 mmol), triethylamine (16.7 µl, 0.12 mmol), and benzene (1 ml). Concentration and purification by MPLC (50 % ethyl acetate-hexanes) yielded 12.2 mg (46 %) of the product. Only ^1H nmr spectroscopy for crude product was taken. The ratio of the product **15f/14f/13f** was 80/6/14.

6-Acetamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15g) and **4-Acetamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13g)**. Prepared

following the general cycloaddition procedure II with 3-acetamidocyclopentene (12.5 mg, 0.1 mmol), *tert*-butyl hydroximinoyl chloride (13.7 mg, 0.1 mmol), triethylamine (14.0 µl, 0.1 mmol) and benzene (1.0 ml) (20 h). MPLC (10:1 hexane/ethyl acetate) afforded 15.0 mg (67%) of **15g** and **13g**, which were not separated: Ir (thin film) 3279, 3070, 2965, 2915, 2857, 1653, 1647, 1558, 1541 cm^{-1}; ^1H nmr δ 6.05 (d, 1 H, J = 6.8 Hz [**15g**]), 5.83 (br s, 1 H [**13g**]), 5.05 (dd, 1 H, J = 9.1, 3.6 Hz [**13g**]), 4.79 (dd, 1 H, J = 8.9, 5.1 Hz [**15g**]), 4.50 (t, 1 H, J = 5.4 Hz [**13g**]), 4.29-4.41 (m, 1H [**15g**]), 3.66 (t, 1 H, J = 8.6 Hz [**15g**]), 3.58 (d, 1 H, J = 9.1 Hz [**13g**]), 1.99 (s, 3 H [**15g**]), 1.95 (s, 3 H [**13g**]), 1.31-2.49 (overlapping m, 8 H [**15g** and **13g**]), 1.30 (s, 9 H [**13g**]), 1.24 (s, 9 H [**15g**]); ms *m/z* 224 (M^+), 152, 139, 125, 82 (base), 66, 60, 49, 43; HRms calcd for $C_{12}H_{20}N_2O_2$, 224.1524; found, 224.1524.

6-Trifluoroacetamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15h) and **4-Trifluoroacetamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13h).** Prepared following the general cycloaddition procedure II with 3-trifluoroacetamidocyclopentene (10.0 mg, 0.06 mmol), *tert*-butyl hydroximinoyl chloride (7.6 mg, 0.06 mmol), triethylamine (8.0 µl, 0.06 mmol) and benzene (0.5 ml) (17 h). Workup afforded 15.3 mg (92%) of **15h** and **13h**, which were not separable: Ir (thin film) 3308, 3082, 2978, 2876, 1718, 1558, 1211, 1184, 1159, 873 cm^{-1}; ^1H nmr ($CDCl_3$) **15i** δ 6.86 (br d, 1 H), 4.84 (dd, 1 H, J = 8.4, 5.1 Hz), 4.26-4.41 (m, 1 H), 3.73 (t, 1 H, J = 8.6 Hz), 2.09-2.21 (m, 1 H), 1.72-1.94 (m, 2 H), 1.40-1.51 (m, 1 H), 1.25 (s, 9H). Available data for **13h** δ 6.57 (br d, 1 H), 5.10 (dd, 1 H, J = 8.6, 4.3 Hz), 4.53 (t, 1 H, J = 6.8 Hz); ms *m/z* 279 (M^+), 263, 221, 178, 152, 139, 126, 82 (base), 57; HRms calcd for $C_{11}H_{14}N_2O_2F_3$ ($M-CH_3$), 263.1007; found, 263.1008.

6-Heptafluorobutyramido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15i) and **4-Heptafluorobutyramido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13i).** Prepared following the general cycloaddition procedure II with 3-heptafluorobutyramidocyclopentene (28.0 mg, 0.1 mmol), *tert*-butyl hydroximinoyl chloride (13.7 mg, 0.1 mmol), triethylamine (14.0 µl, 0.1 mmol) and benzene (1.0 ml) (19 h). Purification by MPLC ($CHCl_3$) afforded 44.7 mg (91%) of **15i** and **13i** as a mixture: Ir (thin film) 3325, 3075, 2968, 2874, 1716, 1653, 1541, 1217, 1122, 893 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.39 (br s, 1 H), 4.78 (dd, 1 H, J = 8.3, 5.0 Hz), 4.29-4.42 (m, 1 H), 3.65 (t, 1 H, J = 7.6 Hz), 1.92-2.13 (m, 2 H), 1.71-1.86 (m, 2 H), 1.31 (s, 9H); **13i** δ 6.01 (br s, 1 H), 5.10 (dd, 1 H, J = 8.5, 4.1 Hz), 4.55 (t, 1 H, J = 6.2 Hz), 3.58 (d, 1 H, J = 8.6 Hz), 2.21-2.27 (m, 1 H), 2.03-2.11 (m, 1 H), 1.81-1.89 (m, 1 H), 1.59-1.63 (m, 1 H), 1.25 (s, 9H); ms *m/z* 378 (M^+), 363, 252, 238, 165, 152, 139 (base), 126, 84, 57; HRms calcd for $C_{14}H_{17}N_2O_2F_7$, 378.1178; found, 378.1179.

6-Thiacetamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15j) and **4-Thiacetamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13j).** Following the general cycloaddition procedure II, 3-thiacetamidocyclopentene (9.6 mg, 0.07 mmol), *tert*-butyl hydroximinoyl chloride (9.6 mg, 0.07 mmol), triethylamine (10.1 µl, 0.07 mmol) and benzene (0.7 ml) (26 h). Workup afforded 14.6 mg (87%) of **15j** and **13j**, which was directly subjected to nmr analysis. Decomposition of the products precluded further characterization: ^1H Nmr (C_6D_6) **15j** δ 5.72 (br s, 1 H), 4.47 (dd, 1 H, J = 8.1, 5.0 Hz), 4.30-4.45 (m, 1 H), 2.80 (t, 1 H, J = 8.1 Hz), 1.59 (s, 3H), 1.05 (s, 9 H), 1.10-2.12 (overlapping m, 4 H). Available data for **13j** δ 3.87 (t, 1 H, J = 5.9 Hz), 3.25 (d, 1 H, J = 9.0 Hz), 1.10-2.12 (overlapping m, 4 H).

Δ^2-Isoxazolines (13k, 15k, and **15k)** from **11k** Prepared following the general cycloaddition procedure I with **11k** (15.3 mg, 0.1 mmol), *t*-butyl hydroximinoyl chloride (13.6 mg, 0.1 mmol), triethyl amine (14.0 µl, 0.1 mmol), and benzene (1 ml). Concentration yielded 14.1 mg (56 %) of the product. Only the ^1H nmr spectrum for crude product was taken. The ratio of the products **15k/14k/13k** was 73/4/23.

6-Methanesulfonamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15l) and **4-Methanesulfonamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (13l).** Prepared following the general cycloaddition procedure II with 3-methanesulfonamidocyclopentene (48.3 mg, 0.3 mmol), *tert*-butyl hydroximinoyl chloride (41.0 mg, 0.3 mmol), triethylamine (43.2 µl, 0.3 mmol) and benzene (3.0 ml) (20 h). Purification by MPLC (3:1 chloroform/diethyl ether) afforded 15.7 mg (20%) of **15l**. The minor product **13l** was not isolated: Ir (thin film) 3281, 2966, 2874, 1458, 1321, 1151, 1115, 978, 887, 760 cm^{-1}; ^1H nmr ($CDCl_3$) **15l** δ 4.95 (d, 1 H, J = 9.4 Hz), 4.86 (dd, 1 H, J = 8.2, 5.0 Hz), 3.82-3.93 (m, 1 H), 3.68 (t, 1 H, J = 8.6 Hz), 3.02 (s, 3 H), 1.96-2.99 (m, 2 H), 1.70-1.83 (m, 1 H), 1.44-1.54 (m, 1 H), 1.25 (s, 9H); ms *m/z* 260 (M^+), 217, 190, 181, 153, 134, 121, 106, 98, 57 (base); HRms calcd for $C_{11}H_{20}N_2O_3S$, 260.1195; found, 260.1195. Available data for **13l** δ 5.09 (dd, 1 H, J = 9.0, 3.2 Hz), 4.70 (d, 1 H, J = 6.8

Hz), 4.13 (t, 1 H, J = 6.8 Hz), 3.00 (s, 3 H), 1.29 (s, 9H).

6-Trifluoromethanesulfonamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (15m) and **4-Trifluoromethanesulfonamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent-[*d*]isoxazole (13m)**. Prepared following the general cycloaddition procedure II with 3-trifluoromethanesulfonamidocyclopentene (21.5 mg, 0.1 mmol), *tert*-butyl hydroximinoyl chloride (13.7 mg, 0.1 mmol), triethylamine (14.4 µl, 0.1 mmol) and benzene (1.0 ml) (19 h). Workup afforded 24.0 mg (76%) of **15m** and **13m**, which was not further purified: Ir (thin film) 3291, 3185, 2972, 2887, 1716, 1456, 1377, 1232, 1192, 1149, 933, 891 cm^{-1}; ^{1}H nmr (C_6D_6) **15m** and **13m** δ 5.81 (d, 1 H, J = 8.7 Hz [**15m**]), 5.69 (d, 1 H, J = 5.9 Hz [**13m**]), 4.73 (dd, 1 H, J = 8.8, 2.7 Hz [**13m**]), 4.24 (dd, 1 H, J = 8.6, 5.2 Hz [**15m**]), 4.16 (t, 1 H, J = 4.3 Hz [**13m**]), 3.54-3.68 (m, 1 H, [**15m**]), 3.23 (d, 1 H, J = 8.8 Hz [**13m**]), 2.69 (t, 1 H, J = 5.8 Hz [**15m**]), 1.18 (s, 9H [**13m**]), 1.00-1.91 (overlapping m, 8H [**15m** and **13m**]), 0.94 (s, 9H [**15m**]); ms *m/z* 314 (M$^+$), 215, 181, 126, 67, 57 (base); HRms calcd for $C_{11}H_{17}N_2O_3SF_3$, 314.0912; found, 314.0912.

6-Benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17a) and **4-Benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16a)**. Prepared following the general cycloaddition procedure II with 3-benzamidocyclopentene (18.7 mg, 0.1 mmol), phenyl hydroximinoyl chloride (15.5 mg, 0.1 mmol), triethylamine (14.0 µl, 0.1 mmol) and benzene (1.0 ml) (21 h). Purification and separation by MPLC (2:1 hexane/ethyl acetate) afforded 27.0 mg (87%) of **17a** and **16a**: Ir (thin film) 3450, 3310, 3060, 3075, 2980, 2862, 1653, 1539, 1490, 1356, 1316, 1295, 895, 763, 691 cm^{-1}; ^{1}H nmr (500 MHz, $CDCl_3$) **17a** δ 7.83 (m, 2 H), 7.70 (m, 2 H), 7.52 (m, 1 H), 7.41-7.47 (m, 5H), 6.76 (d, 1 H, J = 8.3 Hz), 5.14 (dd, 1 H, J = 7.9, 5.0 Hz), 4.63-4.69 (m, 1 H), 4.19-4.23 (m, 1 H), 2.17-2.29 (m, 1 H), 1.95-2.02 (m, 2 H), 1.41-1.60 (m, 1 H). **16a** δ 8.18 (d, 2 H, J = 7.2 Hz), 7.77 (d, 2 H, J = 7.2 Hz), 7.54 (m, 1 H), 7.47 (m, 4H), 7.41 (m, 1 H), 6.67 (d, 1 H, J = 4.9 Hz), 5.32 (dd, 1 H, J = 5.3, 8.8 Hz), 4.58 (t, 1 H, J = 5.5 Hz), 4.39 (d, 1 H, J = 8.9 Hz), 2.33-2.37 (m, 1 H), 2.13-2.21 (m, 1 H), 1.92-2.01 (m, 1 H), 1.25-1.86 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$) **16a** δ 167.3, 159.5, 134.3, 131.7, 130.3, 128.9, 128.7, 128.2, 127.2, 127.1, 85.3, 55.9, 51.2, 28.7, 28.1. **17a** δ 167.8, 156.3, 134.3, 131.9, 130.1, 128.9, 128.8, 127.6, 126.9, 86.1, 68.7, 59.8, 56.3, 34.1, 29.7; ms **17a** (CI) *m/z* 307 (M+1) (base), 299, 203, 186, 164, 146, 122, 105. **16a** *m/z* 306 (M$^+$), 289, 249, 201, 185, 159, 148, 122, 105 (base), 77; HRms **17a** calcd for $C_{17}H_{18}N_2O_2$, 306.1368; found, 306.1368.

6-(4'-Methoxy)benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17b) and **4-(4'-Methoxy)benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16b)**. Prepared following the general cycloaddition procedure II with 3-(4'-methoxy)benzamidocyclopentene (21.7 mg, 0.1 mmol), phenyl hydroximinoyl chloride (15.5 mg, 0.1 mmol), triethylamine (14.4 µl, 0.1 mmol) and benzene (1.0 ml) (24 h). Purification and separation by MPLC (2:1 hexane/ethyl acetate) afforded 27.6 mg (82%) of **17b** and **16b**: Ir (thin film) 3301, 2937, 2842, 1632, 1607, 1538, 1505, 1446, 1310, 1255, 1179, 1029, 845, 763, 692 cm^{-1}; ^{1}H nmr (500 MHz,$CDCl_3$) **17g** δ 7.80 (d, 2 H, J = 8.7 Hz), 7.70 (m, 2 H), 7.42 (m, 3 H), 6.93 (d, 2 H, J = 8.7 Hz), 6.65 (d, 1 H, J = 8.5 Hz), 5.12 (dd, 1 H, J = 8.4, 5.1 Hz), 4.65 (m, 1 H), 4.19 (m, 1 H), 3.86 (s, 3 H), 2.15-2.20 (m, 1 H), 1.97-2.01 (m, 2 H), 1.40-1.49 (m, 1 H). **16b** δ 8.18 (d, 2 H, J = 7.5 Hz), 7.74 (d, 2 H, J = 8.7 Hz), 7.39-7.48 (m, 3 H), 6.95 (d, 2 H, J = 8.7 Hz), 5.97 (d, 1 H, J = 5.3 Hz), 5.30 (dd, 1 H, J = 8.7, 5.2 Hz), 4.56 (t, 1 H, J = 5.5 Hz), 4.38 (d, 1 H, J = 8.9 Hz), 3.87 (s, 3 H), 2.32-2.37 (m, 1 H), 2.13-2.21 (m, 1 H), 1.91-1.99 (m, 1 H), 1.80-1.84 (m, 1 H); ^{13}C nmr (125 MHz, $CDCl_3$) **17b** δ 166.8, 162.4, 159.5, 130.3, 128.9, 128.2, 127.1, 126.6, 113.8, 85.4, 55.9, 55.5, 51.1, 28.7, 28.0. **16b** δ 167.3, 162.6, 156.3, 130.0, 128.9, 128.8, 128.7, 127.6, 126.4, 114.0, 86.1, 59.8, 56.2, 55.6, 34.1, 29.7; ms **17b** (CI) *m/z* 337 (M+1) (base), 321, 233, 186, 152, 135, 104. **17b** *m/z* 336 (M$^+$), 319, 279, 201, 178, 135 (base), 77; HRms calcd for $C_{20}H_{20}N_2O_3$, 336.1474; found, 336.1475.

6- (3'-Trifluoromethyl)benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17c) and **4-(3'-Trifluoromethyl)benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent-[*d*]isoxazole (16c)**. Prepared following the general cycloaddition procedure II with 3-(3'-trifluoromethyl)-benzamidocyclopentene (25.5 mg, 0.1 mmol), phenyl hydroximinoyl chloride (15.5 mg, 0.1 mmol), triethylamine (14.1 µl, 0.1 mmol) and benzene (1.0 ml) (21 h). Purification and separation by MPLC (2:1 hexane/ethyl acetate) afforded 24.2 mg (64%) of **17c** and **16c**: Ir (thin film) 3247, 3071, 2965, 1633, 1549, 1321, 1284, 1169, 1070, 887, 762, 685 cm^{-1}; ^{1}H nmr ($CDCl_3$) **17c** δ 8.10 (s, 1 H), 8.00 (d, 1 H, J = 7.9 Hz), 7.77 (d, 1 H, J = 7.6 Hz), 7.69-7.72 (m, 2 H), 7.60 (t, 1 H, J = 7.6 Hz), 7.44 (m, 3 H), 6.81 (d, 1 H, J = 8.5 Hz), 5.15 (dd, 1 H, J = 8.4, 5.1 Hz), 4.61-4.72 (m, 1 H), 4.19-4.26 (m, 1 H), 2.17-2.24 (m, 1 H), 1.98-2.05 (m, 2 H), 1.44-1.55 (m, 1 H). **16c** δ 8.15 (d, 2 H, J = 6.9 Hz), 8.04 (s, 1 H), 7.96 (d, 1 H, J = 8.1 Hz), 7.81

(d, 1 H, J = 7.9 Hz), 7.62 (t, 1 H, J = 7.8 Hz), 7.42-7.50 (m, 3 H), 6.14 (d, 1 H, J = 4.5 Hz), 5.34 (dd, 1 H, J = 8.4, 5.1 Hz), 4.59 (t, 1 H, J = 5.5 Hz), 4.39 (d, 1 H, J = 8.9 Hz), 2.34-2.41 (m, 1 H), 2.12-2.25 (m, 1 H), 1.92-2.08 (m, 1 H), 1.83-1.90 (m, 1 H); ms *m/z* 374 (M^+), 355, 345, 271, 215, 190, 173 (base), 156, 145, 82; HRms calcd for $C_{20}H_{19}N_2O_2F_3$, 374.1242; found, 374.1244.

6-(4'-Nitro)benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17d) and **4-(4'-Nitro)benzamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16d)**. Prepared following the general cycloaddition procedure II with 3-(4'-nitro)benzamidocyclopentene (10.0 mg, 0.04 mmol), phenyl hydroximinoyl chloride (6.2 mg, 0.04 mmol), triethylamine (6.0 µl, 0.04 mmol) and benzene (1.0 ml) (24 h). Purification by MPLC (2:1 hexane/ethyl acetate) afforded 14.0 mg (93%) of **17d**: Ir (thin film) 3315, 3085, 2971, 2852, 1600, 1547, 1524, 1346, 891, 870, 847, 777, 693 cm^{-1}; ^1H nmr ($CDCl_3$) **16d** δ 8.31 (d, 2 H, J = 8.8 Hz), 8.00 (d, 2 H, J = 8.8 Hz), 7.70 (m, 2 H), 7.45 (m, 3 H), 6.85 (d, 1 H, J = 8.5 Hz), 5.15 (dd, 1 H, J = 8.4, 5.1 Hz), 4.59-4.70 (m, 1 H), 4.21-4.27 (m, 1 H), 2.20-2.26 (m, 1 H), 1.98-2.06 (m, 2 H), 1.37-1.54 (m, 1 H); ms *m/z* 351 (M^+), 322, 248, 167, 150, 120, 104, 82 (base), 76; HRms calcd for $C_{19}H_{17}N_3O_4$, 351.1219; found, 351.1220. Partial nmr data for **17d**: δ 4.39 (d, 1 H, J = 8.8 Hz), 6.27 (br d, 1 H), 5.31-5.39 (dd, 1 H, J = 8.8, 4.5 Hz).

6-Acetamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17g) and **4-Acetamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (16g)**. Prepared by general cycloaddition procedure II with **11g** (12.5 mg, 0.1 mmol), phenyl hydroximinoyl chloride (15.5 mg, 0.1 mmol), and triethylamine (14.0 µl, 0.1 mmol). Purification and separation by MPLC (10:1 hexane/ethyl acetate) afforded 15.1 mg (62%) of **17g** and **16g**: Ir (thin film) 3287, 3010, 2975, 2887, 1653, 1589, 1558, 892, 766 cm^{-1}; ^1H nmr ($CDCl_3$) **17g** δ 7.66-7.69 (m, 2 H), 7.40-7.43 (m, 3 H), 6.10 (d, 1 H, J = 7.7 Hz), 5.02 (dd, 1 H, J = 8.5, 5.1 Hz), 4.39-4.49 (m, 1 H), 4.14 (t, 1 H, J = 9.4 Hz), 2.02-2.10 (m, 1 H), 1.79-1.96 (m, 1 H), 1.88-1.96 (m, 2 H), 1.66 (s, 3 H), 1.23-1.40 (m, 1 H); ms *m/z* 244 (M^+), 215, 173, 156, 141, 82, 77, 60, 49, 43 (base); HRms calcd for $C_{14}H_{16}N_2O_2$, 244.1212; found, 244.1211. **16g** δ 8.10 (apparent d, 2 H, J = 8.0 Hz), 7.37-7.46 (m, 3 H), 5.82 (br d, 1 H), 5.26 (dd, 1 H, J = 8.8, 5.5 Hz), 4.38 (t, 1 H, J = 5.5 Hz), 4.24 (d, 1 H, J = 8.8 Hz), 2.20-2.44 (m, 1 H), 2.02-2.14 (m, 1 H), 1.79-1.96 (m, 1 H), 1.66-1.73 (m, 1 H), 1.63 (s, 3 H).

6-Trifluorocetamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17h) and **4-Trifluoroacetamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16h)**. Prepared following the general cycloaddition procedure II with 3-trifluorocetamidocyclopentene (10.0 mg, 0.06 mmol mmol), phenyl hydroximinoyl chloride (8.7 mg, 0.06 mmol), triethylamine (8.0 µl, 0.1 mmol) and benzene (0.5 ml) (17 h). Workup afforded a mixture of 14.6 mg (94%) of **17h** and **16h**, which was not further purified: Ir (thin film) 3314, 3078, 2961, 1718, 1558, 1541, 1213, 1182, 893, 765, 688 cm^{-1}; ^1H nmr ($CDCl_3$) **17h** δ 7.62-7.78 (m, 2 H), 7.36-7.58 (m, 3 H), 7.12 (br d, 1 H, J = 8.1 Hz), 5.06 (dd, 1 H, J = 9.0, 5.1 Hz), 4.49-4.56 (m, 1 H), 4.23 (td, 1 H, J = 9.0, 2.1 Hz), 2.12-2.27 (m, 1 H), 1.92-2.08 (m, 2 H), 1.35-1.52 (m, 1 H). Available data for **16h** δ 6.35 (br s, 1 H), 5.34 (dd, 1 H, J = 8.4, 4.5 Hz); ms *m/z* 298 (M^+), 269, 178, 159, 146, 139, 104, 82 (base), 77; HRms calcd for $C_{14}H_{13}N_2O_2F_3$, 298.0929; found, 298.0929.

6-Heptafluorobutyramido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17i) and **4-Heptafluorobutyramido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16i)**. Prepared following the general cycloaddition procedure II with 3-heptafluorobutyramidocyclopentene (28.0 mg, 0.1 mmol), phenyl hydroximinoyl chloride (15.5 mg, 0.1 mmol), triethylamine (14.0 µl, 0.1 mmol) and benzene (1.0 ml) (19 h). Purification and separation by MPLC ($CHCl_3$) afforded 40.3 mg (93%) of **17i** and **16i**: Ir (thin film) 3331, 3087, 2947, 1716, 1701, 1558, 1541, 1217, 763, 692 cm^{-1}; ^1H nmr ($CDCl_3$) **17i** δ 7.65-7.70 (m, 2 H), 7.39-7.44 (m, 3 H), 7.61 (br d, 1 H, J = 6.8 Hz), 5.07 (dd, 1 H, J = 8.9, 5.4 Hz), 4.37-4.51 (m, 1 H), 4.21 (apparent t, 1 H, J = 7.2 Hz), 2.15-2.28 (m, 1 H), 1.95-2.10 (m, 2 H), 1.37-1.49 (m, 1 H) **16i** δ 7.94-7.98 (m, 2 H), 7.43-7.45 (m, 3 H), 6.33 (br s, 1 H), 5.32 (dd, 1 H, J = 9.6, 4.5 Hz), 4.45 (t, 1 H, J = 4.7 Hz), 4.25 (d, 1 H, J = 8.8 Hz), 2.33-2.38 (m, 1 H), 1.95-2.11 (m, 2 H), 1.81-1.85 (m, 1 H); ms *m/z* 398 (M^+), 185, 159, 146, 104, 84 (base), 77; HRms calcd for $C_{16}H_{13}N_2O_2F_7$, 398.0865; found, 398.0865.

6-Thiacetamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17j) and **4-Thiacetamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16j)**. Prepared following the general cycloaddition procedure II with 3-thiacetamidocyclopentene (9.6 mg, 0.07 mmol), phenyl hydroximinoyl chloride (10.9 mg, 0.07 mmol), triethylamine (10.1 µl, 0.07 mmol) and benzene (0.7 ml) (26 h). Workup afforded 15.6 mg (86%) of **17j** and **16j**, which was directly subjected to nmr analysis. Decomposition

of the products precluded further characterization: ^{1}H Nmr (C_6D_6) **17j** δ 6.61-6.72 (m, 3 H), 6.51-6.60 (m, 2 H), 5.75 (br d, 1 H, *J* = 6.8 Hz), 4.57 (dd, 1 H, *J* = 8.9, 5.1 Hz), 4.30-4.39 (m, 1 H), 3.22 (t, 1 H, *J* = 8.7 Hz), 1.59 (s, 3 H), 1.05-2.21 (overlapping m, 4 H). Available data for **16j** δ 5.27 (br s, 1 H), 4.26 (t, 1 H, *J* = 2.9 Hz), 3.95 (d, 1 H, *J* = 8.9 Hz), 1.05-2.21 (overlapping m, 4 H).

6-Methanesulfonamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17l) and **4-Methanesulfonamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (16l)**. Prepared following the general cycloaddition procedure II with 3-methanesulfonamidocyclopentene (48.3 mg, 0.3 mmol), phenyl hydroximinoyl chloride (46.5 mg, 0.3 mmol), triethylamine (43.2 µl, 0.3 mmol) and benzene (3.0 ml) (20 h). Purification and separation by MPLC (3:1 chloroform/diethyl ether) afforded 23.0 mg (27%) of **17l** and **16l**: Ir (thin film) 3273, 3022, 2959, 2865, 1446, 1317, 1147, 976, 910, 762, 694, 667 cm^{-1}; ^{1}H nmr ($CDCl_3$) **17l** δ 7.61-7.69 (m 2 H), 7.38-7.48 (m, 3 H), 5.21 (d, 1 H, *J* = 6.8 Hz), 5.10 (dd, 1 H, *J* = 8.7, 5.1 Hz), 4.17 (apparent t, 1 H, *J* = 8.7 Hz), 3.90-4.01 (m, 1 H), 3.08 (s, 3 H), 2.02-2.18 (m, 1 H), 1.79-1.98 (m, 2 H), 1.41-1.57 (m, 1 H) **16l** δ 7.81-7.87 (m, 2 H), 7.38-7.48 (m, 3 H), 5.30 (dd, 1 H, *J* = 8.9, 4.7 Hz), 4.71 (d, 1 H, *J* = 6.3 Hz), 4.30 (d, 1 H, *J* = 8.9 Hz), 4.00 (t, 1 H, *J* = 4.9 Hz), 3.00 (s, 3 H), 2.25-2.35 (m, 1 H), 2.08-2.19 (m, 1 H), 1.83-1.99 (m, 1 H), 1.74-1.83 (m, 1 H); ms *m/z* 280 (M$^+$), 201, 184, 159, 146 (base), 84, 77, 49; HRms calcd for $C_{13}H_{16}N_2O_3S$, 280.0882; found, 280.0882.

6-Trifluoromethanesulfonamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (17m) and **4-Trifluoromethanesulfonamido-3-phenyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent-[*d*]isoxazole (16m)**. Prepared following the general cycloaddition procedure II with 3-trifluoromethanesulfonamidocyclopentene (21.5 mg, 0.1 mmol), phenyl hydroximinoyl chloride (15.5mg, 0.1 mmol), triethylamine (14.4 µl, 0.1 mmol) and benzene (1.0 ml) (19 h). Workup afforded 17.0 mg (51%) of **17m** and **16m**, which was not further purified: Ir (thin film) 3295, 2967, 1448, 1378, 1239, 1197, 1147, 993, 941, 763, 692 cm^{-1}; ^{1}H nmr (C_6D_6) mixture δ 7.82-7.89 (m, 2H [**16m**]), 7.40-7.47 (m, 2H [**17m**]), 7.04-7.13 (m, 6H [**17m** and **16m**]), 4.70 (dd, 1 H, *J* = 8.7, 3.2 Hz [**16m**]), 4.38 (dd, 1 H, *J* = 8.9, 5.1 Hz [**17m**]), 3.87-3.91 (m, 1H [**16m**]), 3.54-3.63 (m, 1H [**17m**]), 3.51 (d, 1 H, *J* = 9.0 Hz [**16m**]), 3.07 (t, 1 H, *J* = 8.6 Hz [**17m**]), 0.77-1.82 (overlapping m, 8H [**17m** and **16m**]); ms *m/z* 334 (M$^+$), 265, 201, 178, 158, 146 (base), 130, 104, 84, 77; HRms calcd for $C_{13}H_{13}N_2O_3SF_3$, 334.0599; found, 334.0600.

3-Aminomethylcyclopentene hydrochloride. Compound(**9**)(10.25 g, 0.1 mol) was added to dry acetone (15 ml) and the mixture was cooled to 0 °C. To the reaction mixture was added dropwise a solution of sodium cyanide (4.9 g, 0.1 mol) in water (15 ml). This solution was stirred for 90 min at 0 °C. During stirring, the color of the solution changed from colorless to yellow, and two layers separated. The organic layer was dried over $MgSO_4$. Concentration yielded 5.86 g (63 %) of 3-cyanocyclopentene. This 3-cyanocyclopentene (3.35 g, 36 mmol) was added to diethyl ether (10 ml). To this solution at reflux was added dropwise a solution of lithium aluminium hydride (1.53 g, 40.4 mmol) in diethyl ether (30 ml). After 1 h at reflux, the reaction mixture was cooled, and water (1.5 ml) was added very slowly, followed by 15 % aqueous NaOH solution (1.5 ml) and water (4.5 ml). Two layers of the reaction mixture were separated. The organic layer was dried over Na_2SO_4. Gaseous HCl (1.64 g, 45 mmol) was bubbled through the vigorously stirred solution to give black precipitates. This mixture of solids and liquid was extracted into water (2 x 30 ml). After concentration of the aqueous solution, the residue was washed with diethyl ether (2 x 20 ml). Drying in vacuo yielded 3.58 g (75 %) of a dark brown solid: ^{1}H Nmr ($CDCl_3$) δ 8.50-7.80 (br s, 3 H), 5.90 (m, 1 H), 5.75 (m, 1 H), 3.25-2.70 (m, 3 H), 2.65 (m, 1 H), 2.40 (m, 1 H), 2.20 (m, 1 H), 1.70 (m, 1 H).

***N*-{(2-Cyclopentenyl)methyl}benzamide (18a).** Prepared following the general amidation procedure I with the amine hydrochloride (133.5 mg, 1.0 mmol), benzoyl chloride (116.1 µl, 1.0 mmol), NaOH (88.0 mg, 2.2 mmol), and water (1.5 ml). Concentration and purification by flash column chromatography (15 % ethyl acetate-hexanes) yielded 143 mg (71 %) of a white solid: mp 63.4-65.0 °C. ^{1}H Nmr ($CDCl_3$) δ 7.85-7.65 (m, 2 H), 7.55-7.35 (m, 3 H), 6.25-6.05 (br s, 1 H), 5.90 (m, 1 H), 5.70 (m, 1 H), 3.60 (m, 1 H), 3.35 (m, 1 H), 3.15-3.00 (m, 1 H), 2.50-2.25 (m, 2 H), 2.20-2.00 (m, 1 H), 1.70-1.50 (m, 1 H); ^{13}C nmr ($CDCl_3$) δ 167.7 (s), 134.8 (s), 132.9 (d), 131.8 (d), 131.2 (d), 128.4 (d), 126.9 (d), 45.6 (d), 44.0 (t), 32.1 (t), 27.1 (t); ir (thin film) 3396, 3062, 2904, 2863, 1638, 1579, 1507, 1457, 1308 cm^{-1}; ms *m/z* 201 (M$^+$), 134, 122, 105 (base), 77; HRms calcd for $C_{13}H_{15}NO$, 201.1154; found, 201.1154.

6-Benzamidomethyl-3-*tert*-butyl-3aα,5,6α,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (21a), 6-Benzamidomethyl-3-*tert*-butyl-3aα,5,6β,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (20a), and **4-Benzamidomethyl-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (19a)** from **18a.** (1) Prepared following the general cycloaddition procedure I with **18a** (20.1 mg, 0.1 mmol), *t*-butyl hydroximinoyl chloride (16.3 mg, 0.12 mmol), triethylamine (21.0 µl, 0.15 mmol), and benzene (1 ml) (4.5 days). Concentration yielded 21.4 mg (71 %) of the products. (2) Prepared following the general cycloaddition procedure III with same amounts of reagents as (I) (8 days). Concentration yielded 21.8 mg (73 %) of the products. Separation of the products was accomplished by analytical hplc (50 % ethyl acetate-hexanes): **21a** ^{1}H Nmr ($CDCl_3$) δ 7.80 (d, 2 H, *J* = 7.0 Hz), 7.55-7.40 (m, 3 H), 6.90-6.70 (br s, 1 H), 5.95 (dd, 1 H, *J* = 8.3, 5.1 Hz), 3.90-3.75 (m, 1 H), 3.75-3.55 (m, 2 H), 2.55-2.35 (m, 1 H), 2.05 (m, 1 H), 1.95-1.70 (m, 2 H), 1.50-1.35 (m, 1 H), 1.25 (s, 9 H). **20a** ^{1}H Nmr ($CDCl_3$) δ 7.80 (d, 2 H, *J* = 7.2 Hz), 7.55-7.35 (m, 3 H), 6.40-6.25 (br s, 1 H), 4.80 (dd, 1 H, *J* = 9.8, 4.1 Hz), 3.70 (m, 1 H), 3.60-3.35 (m, 2 H), 2.35 (m, 1 H), 2.15 (m, 1 H), 2.00-1.75 (m, 2 H), 1.45 (m, 1 H), 1.25 (s, 9 H). **19a** ^{1}H Nmr ($CDCl_3$) δ 7.75 (d, 2 H, *J* = 7.3 Hz), 7.60-7.35 (m, 3 H), 6.40-6.20 (br s, 1 H), 5.05 (dd, 1 H, *J* = 8.2, 4.3 Hz), 3.45 (m, 1 H), 3.40-3.20 (m, 2 H), 2.60 (m, 1 H), 2.15 (dd, 1 H, *J* = 6.5, 5.9 Hz), 2.05-1.75 (m, 2 H), 1.65 (m, 1 H), 1.25 (s, 9 H).

***N*-{(2-Cyclopentenyl)methyl}-2,2,2-trifluoroethanamide (18b).** Prepared following the general amidation procedure II with the amide hydrochloride (93.5 mg, 0.7 mmol), trifluoroacetic anhydride (142.0 µl, 1.0 mmol), triethylamine (293.0 µl, 2.1 mmol), and CH_2Cl_2 (2 ml) (12 h). Concentration and purification by flash column chromatography (15 % ethyl acetate-hexanes) yielded 84.0 mg (62 %) of a yellow liquid: ^{1}H Nmr ($CDCl_3$) δ 6.50-6.00 (br s, 1 H), 5.92 (m, 1 H), 5.62 (m, 1 H), 3.55-3.40 (m, 1 H), 3.35-3.20 (m, 1 H), 3.10-2.95 (m, 1 H), 2.50-2.30 (m, 2 H), 2.20-2.00 (m, 1 H), 1.60-1.45 (m, 1 H); Ir (neat) 3314, 3120, 3059, 2938, 2856, 1704, 1561, 1162, 722 cm^{-1}; ms *m/z* 193 (M), 126, 80 (base), 67 (base).

Δ^2-Isoxazolines (19b, 20b, and **21b)** from **18b.** Prepared following the general cycloaddition procedure I with **18b** (19.3 mg, 0.1 mmol), *t*-butyl hydroximinoyl chloride (16.3 mg, 0.12 mmol), triethylamine (21.0 µl, 0.15 mmol), and benzene (1 ml) (4.5 days). Concentration yielded 18.6 mg (64 %) of the product. Only ^{1}H nmr spectroscopy for crude product was taken. The ratio of the product **21b/20b/19b** was 54/17/29.

***N*-{(2-Cyclopentenyl)methyl}-2,2,3,3,4,4,4-heptafluorobutanamide (18c).** Prepared following the general amidation procedure II with the amine hydrochloride (80.1 mg, 0.6 mmol), heptafluorobutanoic anhydride (173.7 µl, 0.7 mmol), triethylamine (250.0 µl, 1.8 mmol), and CH_2Cl_2 (2 ml) (12 h). Concentration and purification by flash column chromatography (15 % ethyl acetate-hexanes) yielded 74.8 mg (43 %) of a slightly yellow liquid: ^{1}H Nmr ($CDCl_3$) δ 6.60-6.10 (br s, 1 H), 5.90 (m, 1 H), 5.60 (m, 1 H), 3.60-3.40 (m, 1 H), 3.40-3.25 (m, 1 H), 3.10-2.95 (m, 1 H), 2.50-2.30 (m, 2 H), 2.15-2.00 (m, 1 H), 1.60-1.45 (m, 1 H); ir (neat) 3325, 3058, 2940, 2859, 1704, 1230 cm^{-1}; ms *m/z* 293 (M^+), 110, 80, 67 (base).

Δ^2-Isoxazolines (19c, 20c, and **21c)** from **18c.** Prepared following the general cycloaddition procedure I with **18c** (29.3 mg, 0.1 mmol), *t*-butyl hydroximinoyl chloride (16.3 mg, 0.12 mmol), triethylamine (21 µl, 0.15 mmol), and benzene (1 ml) (4.5 days). Concentration yielded 28.6 mg (73 %) of the product. Only ^{1}H nmr spectroscopy for crude product was taken. The ratio of the product **21c/20c/19c** was 73/12/15.

***N*-(2-Cyclopentenyl)-*N*-hydroxyethanamide (22).**[22] 9,10-Dimethyl anthracene (0.4 g, 1.9 mmol) and tetrapropylammonium metaperiodate (1.13 g, 3.0 mmol) were added to $CHCl_3$ (5 ml) at 0 °C. To the reaction mixture was added dropwise a solution of *N*-hydroxyacetamide (225.3 mg, 3.0 mmol) in DMF (2 ml). After complete addition, the reaction mixture was dissolved in ethyl acetate (50 ml) and the solution was washed with saturated aqueous $Na_2S_2O_3$ solution, H_2O, and brine (30 ml each). This solution was dried over $MgSO_4$. Concentration yielded 387 mg (71 %) of the anthracene derivative. This derivative (328 mg, 1.2 mmol) was added to the cyclopentene (25 ml). The reaction mixture was stirred for 18 h at reflux and evaporated. Purification by flash column chromatography (20 % ethyl acetate-hexanes) yielded 134 mg (81 %) of a white solid, **22**: mp 76.5-78.0 °C. ^{1}H Nmr ($CDCl_3$) (All peaks are very broad) δ 6.10 (m, 1 H), 5.80-5.55 (m, 2 H), 5.10 (m, 1 H), 2.60 (m, 1 H); 2.35 (m, 1 H), 2.25-2.00 (m, 5 H); ^{13}C nmr ($CDCl_3$) δ 171.9 (s), 136.3 (d), 128.3 (d), 61.7 (d), 31.7 (t), 26.2 (t), 20.8 (q); ir (thin film) 3162, 2900, 2855, 1610, 1458, 1177, 1018 cm^{-1}; ms m/z 141 (M^+), 82, 76, 67 (base), 43, 41; HRms calcd for $C_7H_{11}NO_2$, 141.0790; found, 141.0790.

Δ^2-Isoxazolines (23, 24 and **25)** from **22.** Prepared following the general cycloaddition procedure I with **22** (70.5 mg, 0.5 mmol), *t*-butyl bydroximoyl chloride (163 mg, 1.2 mmol), triethyl amine (210 µl, 1.5 mmol), and CH_2Cl_2 (3 ml). After 4.5 d, concentration yielded 59.1 mg (49 %) of the product. The only ^{1}H nmr spectrum for crude product was taken. The ratio of the products **25/24/23**was 65/12/23.

***N*-(3-Cyclopentenyl)benzamide (26).**[23] Boron trifluoride etherate (2.46 ml, 20.0 mmol) was added to a solution of sodium borohydride (1.513 g, 40 mmol) in DME (10 ml). This reaction mixture was added to a solution of the freshly cracked cyclopentadiene (2.64 g, 40 mmol) in ether (10 ml). To this solution was added a solution of the hydroxylamine-*O*-sulfonic acid (10.2 g, 90 mmol) in DME (15 ml), and this mixture was refluxed for 4 h. To this solution was added 12 M HCl (25 ml, 300 mmol) and water (20 ml). After extracting with diethyl ether (2 x 50 ml), a solution of potassium hydroxide (28.1 g, 0.5 mol) in water (30 ml) was added at 0 °C (about pH 10). The mixture was extracted with diethyl ether (5 x 40 ml). The ether extracts were dried over Na_2SO_4 and concentrated. The residue was taken up in absolute ethanol (50 ml) and concentrated again. Repeating the ethanol treatment gave 620.0 mg (19 %) of a dry solid amine. This amine (500 mg, 4.2 mmol) was mixed with NaOH (400 mg, 10 mmol), water (5 ml), and chloroform (2 ml). To this solution was added dropwise benzoyl chloride (697 µl, 6 mmol) for 30 min. After 12 h at 25 °C, this solution was extracted with diethyl ether (3 x 50 ml). The extracts were combined and dried over Na_2SO_4. Concentration and purification by flash column chromatography (25 % ethyl acetate-hexanes) yielded 202.9 mg (26 %) of a white solid: mp 112.0-113.5 °C. ^{1}H Nmr ($CDCl_3$) δ 7.75 (m, 2 H), 7.55-7.35 (m, 3 H), 6.40-6.15 (br s, 1 H), 5.85-5.70 (s, 2 H), 4.85-4.70 (m, 1 H), 2.95-2.80 (m, 2 H), 2.40-2.25 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 167.1 (s), 134.7 (s), 131.2 (d), 128.9 (d), 128.4 (d), 126.9 (d), 49.3 (d), 40.1 (t); ir (thin film) 3301, 3059, 2943, 2848, 1629, 1543, 1306 cm^{-1}; ms *m/z* 187 (M^+), 122, 105 (base), 77, 66; HRms calcd for $C_{12}H_{13}NO$, 187.0997; found, 187.0997.

5-Benzamido-3-*tert*-butyl-3aα,5α,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (28a), 5-Benzamido-3-*tert*-butyl-3aα,5β,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (27a) from 26. Prepared following the general cycloaddition procedure I with **26** (18.7 mg, 0.1 mmol), *t*-butyl hydroximinoyl chloride (16.3 mg, 0.12 mmol), triethyl amine (21 µl, 0.15 mmol), and benzene (1 ml) (4.5 days). Concentration and separation by flash column chromatography (50 % ethyl acetate-hexanes) yielded 28.3 mg (99 %). The ratio of the product **28a/27a** was 90/10 in ^{1}H nmr spectrum: **28a** ^{1}H Nmr ($CDCl_3$) δ 7.70 (d, 2 H, *J* = 7.1 Hz), 7.55-7.40 (m, 3 H), 7.00-6.85 (br d, 1 H, *J* = 6.1 Hz), 5.18 (dd, 1 H, *J* = 8.6, 4.7 Hz), 4.65 (m, 1 H), 3.65 (m, 1 H), 2.37 (s, 1 H), 2.32 (s, 1 H), 2.25-2.05 (m, 2 H), 1.20 (s, 9 H); ^{13}C nmr ($CDCl_3$) δ 170.5 (s), 166.7 (s), 134.2 (s), 131.5 (d), 128.6 (d), 126.7 (d), 88.1 (d), 52.0 (d), 51.7 (d), 39.3 (t), 38.5 (t), 33.5 (s), 29.5 (q); ir (thin film) 3324, 2968, 2870, 1640, 1533, 1310, 881 cm^{-1}. **27a** ^{1}H Nmr ($CDCl_3$) δ 7.73 (m, 2 H), 7.60-7.35 (m, 3 H), 6.02 (d, 1 H, *J* = 5.2 Hz), 5.05 (dd, 1 H, *J* = 8.8, 5.4 Hz), 4.60-4.40 (m, 1 H), 3.70 (tt, 1 H, *J* = 9.2, 2.8 Hz), 2.55 (d, 1 H, *J* = 6.4 Hz), 2.50 (d, 1 H, *J* = 6.2 Hz), 1.95-1.75 (m, 2 H), 1.27 (s, 9 H); ^{13}C nmr ($CDCl_3$) δ 167.5, 161.2, 134.5, 131.8, 128.6, 127.0, 85.1, 50.8, 50.0, 40.3, 37.5, 33.2, 29.3; ir (thin film) 3310, 2966, 2926, 1636, 1538, 1489, 1308, 891 cm^{-1}.

5-Benzamido-3aα,5α,6,6aα-tetrahydro-3-phenyl-4*H*-cyclopent[*d*]isoxazole (28b), 5-Benzamido-3aα,5β,6,6aα-tetrahydro-3-phenyl-4*H*-cyclopent[*d*]isoxazole (27b) from 26. Prepared following the general cycloaddition procedure I with **26** (18.7 mg, 0.1 mmol), phenyl hydroximinoyl chloride (18.7 mg, 0.12 mmol), triethylamine (21 µl, 0.15 mmol), and benzene (1 ml) (4.5 days). Concentration and separation by flash column chromatography (50 % ethyl acetate-hexanes) yielded 25.1 mg (82 %) of the product. The ratio of products **28b/27b** was 85/15 in ^{1}H nmr spectrum: **28b** ^{1}H Nmr ($CDCl_3$) δ 7.65 (m, 4 H), 7.50-7.30 (m, 6 H), 6.80 (br d, 1 H, *J* = 6.9 Hz), 5.40 (dd, 1 H, *J* = 8.9, 4.9 Hz), 4.70 (m, 1 H), 4.15 (m, 1 H), 2.40-2.20 (m, 4 H). **27b** ^{1}H Nmr ($CDCl_3$) δ 7.65 (m, 4 H), 7.55-7.30 (m, 6 H), 6.00 (br s, 1 H), 5.25 (dd, 1 H, *J* = 9.2, 5.4 Hz), 4.60-4.40 (m, 1 H), 4.30-4.10 (m, 1 H), 2.70-2.50 (m, 2 H), 1.95 (m, 2 H).

***N*-(2-Cyclopentenyl)-*N*-methylbenzamide (37).** After stirring a solution of butyllithium (3.07 ml, 2.3 mmol) and diisopropylamine (308.0 µl, 2.2 mmol) in the tetrahydrofuran (5 ml) for 30 min at 25 °C, **11a** (374 mg, 2 mmol) was added, the mixture was stirred for 1.5 h. Methyl iodide (143.2 µl, 2.3 mmol) was then added. After 3 h, the mixture was diluted with water (30 ml) and the mixture was extracted with diethyl ether (2 x 50 ml). The organic extracts were combined, washed with saturated aqueous ammonium chloride (1 x 30 ml) and brine (1 x 30 ml), and dried over Na_2SO_4. Concentration and purification by flash column chromatography (33 % ethyl acetate-hexanes) yielded 352 mg (88 %) of the yellow liquid product: ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.45 (m, 3 H), 7.35 (m, 2 H), 6.02 (m, 1 H), 5.65 (m, 1 H), 5.12 (m, 1 H), 2.70 (s, 3 H), 2.35-2.20 (s, 3 H), 2.15-2.00 (m, 1 H), 1.80-1.70 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 171.5 (s), 136.9 (s), 135.2 (d), 129.8 (d), 129.3 (d), 128.4 (d), 126.8 (d), 65.5 (d), 31.6 (t), 27.6 (q), 27.4 (t); ir (thin film) 3057, 2931, 2854, 1632, 1400, 1335, 1064 cm^{-1}; ms *m/z* 201 (M^+), 186, 136, 105 (base), 77, 67; HRms calcd for $C_{13}H_{15}NO$, 201.1154; found, 201.1154.

General Cycloaddition Procedure III. **6-(*N*-Methyl)benzamido-3-*tert*-butyl-3aα,5,6α,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (40), 6-(*N*-Methyl)benzamido-3-*tert*-butyl-3aα,5,6β, 6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (39), and 4-(*N*-Methyl)benzamido-3-*tert*-butyl-3aα,5,6,6aα-tetrahydro-4β*H*-cyclopent[*d*]isoxazole (38)** from **37.** Triethylamine (27.9 µl, 0.2 mmol) was added dropwise to a solution of 3°-amide(**37**)(20.1 mg, 0.1 mmol) and *t*-butyl hydroximinoyl chloride (27.2 mg, 0.2 mmol) in dry benzene (1 ml). After 9.5 days at 80-84 °C, the resulting suspension was cooled and diluted with ethyl acetate (80 ml), and the mixture was washed with water (2 x 20 ml). The organic phase was dried over Na_2SO_4 and concentrated to give 24.9 mg (83 %) of a yellow liquid. Purification by MPLC (50 % ethyl acetate-hexanes) afforded 14.1 mg (47 %) of the products in order of elution **39**, **40**, and **38** (19/5/76 respectively in GC): **40** ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.45 (m, 3 H), 7.35 (m, 2 H), 4.85 (dd, 1 H, *J* = 8.1, 4.6 Hz), 4.50-4.35 (m, 1 H), 3.70 (m, 1 H), 2.95 (s, 3 H), 2.00-1.75 (m, 4 H), 1.20 (s, 9 H); ^{13}C nmr ($CDCL_3$) δ 172.4 (s), 167.6 (s), 137.0 (s), 129.5 (d), 128.5 (d), 127.0 (d), 86.0 (d), 59.3 (d), 51.0 (q), 35.7 (s), 33.4 (d), 29.5 (q), 27.8 (t), 24.4 (t). **39** ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.50-7.30 (m, 5 H), 4.98 (dd, 1 H, *J* = 9.8, 3.9 Hz), 4.45-4.30 (m, 1 H), 3.85-3.70 (m, 1 H), 2.90 (s, 3 H), 2.30-2.10 (m, 1 H), 2.10-1.80 (m, 2 H), 1.70-1.50 (m, 1 H), 1.15 (s, 9 H). **38** mp 123.5-124.0 °C. ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.45 (m, 3 H), 7.35 (m, 2 H), 5.10 (m, 1 H), 4.80 (m, 1 H), 3.75 (dd, 1 H, *J* = 9.0, 4.8 Hz), 2.85 (s, 3 H), 2.35-2.15 (m, 1 H), 2.10-1.95 (m, 1 H), 1.95-1.80 (m, 2 H), 1.15 (s, 9 H); ir (neat) 3019, 1629, 1479, 1216 cm^{-1}; ms *m/z* 300 (M^+), 202, 175, 136, 105 (base), 77, 55; HRms calcd for $C_{18}H_{24}N_2O_2$, 300.1838; found, 300.1837.

Compounds (**40**),(**39**), and (**38**) were also prepared by the *N*-methylation of **15a**, **14a**, and **13a** respectively. 2°-Amide **15a** (28.6 mg, 0.1 mmol) and sodium hydride (4.8 mg, 0.2 mmol) in THF (2 ml) were stirred until bubbles stopped (about 1 h) at 25 °C. Methyl iodide (31.5 µl, 0.5 mmol) was added and this solution was stirred for an additional 5 h to ensure complete reaction. The reaction mixture was then diluted with water (30 ml) and this mixture was extracted with diethyl ether (4 x 40 ml). The organic extracts were combined, washed with brine (1 x 20 ml), and dried over Na_2SO_4. Concentration and purification by MPLC (50 % ethyl acetate-hexanes) afforded 28.0 mg (93 %) of the products **40**. 3°-Amides(**39**)and(**38**)were obtained in 93 % yield each by the same method from **14a** and **13a**.

***N*-(3-Cyclopentenyl)-*N*-methylbenzamide (42).** Compound(**26**)(93.5 mg, 0.5 mmol) was added to a solution of sodium hydride (14.4 mg, 0.6 mmol) in THF (5 ml) at 25 °C. After 1 h, methyl iodide (62.7 µl, 1 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was then diluted with H_2O (30 ml) and this mixture was extracted with ether (2 x 50 ml). The ether extracts were washed with brine (1 x 20 ml) and dried over $MgSO_4$. Concentration and purification by flash column chromatography (25 % ehtyl acetate-hexanes) yielded 88.0 mg (88 %) of a colorless solid **42** mp 56.0-59.0 °C. ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.41 (m, 3 H), 7.34 (m, 2 H), 5.71 (m, 2 H), 4.77 (br s, 1 H), 2.76 (s, 3 H), 2.60-2.35 (m, 4 H); ^{13}C nmr ($CDCl_3$) δ 171.0 (s), 136.9 (s), 129.3 (d), 129.1 (d), 128.4 (d), 126.7 (d), 57.0 (d), 36.9 (t), 27.5 (q); ir (thin film) 3057, 2921, 2851, 1632, 1404, 1347, 1067, 700 cm^{-1}; ms m/z 201 (M^+), 136, 105, 77; HRms calcd for $C_{13}H_{15}NO$, 201.1154; found, 201.1154.

5-(*N*-Methyl)benzamido-3-*tert*-butyl-3aα,5α,6,6aα-tetrahydro-4*H*-cyclopent[*d*]isoxazole (43), 5-(*N*-Methyl)benzamido-3-*tert*-butyl-3aα,5β,6,6aα -tetrahydro-4*H*-cyclopent[*d*]isoxazole (42) from **41.** Prepared following the general cycloaddition procedure I with **41** (20.1 mg, 0.1 mmol), *t*-butyl hydroximinoyl chloride (16.3 mg, 0.12 mmol), triethylamine (21 µl, 0.15 mmol), and benzene (1 ml) (4.5 days). Concentration yielded 11.8 mg (39 %) of the product. The ratio of the product(**43**)and(**42**)was 8/92 in ^{1}H nmr spectrum: **43** ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.42 (m, 3 H), 7.35 (m, 2 H), 4.77 (m, 1 H), 4.48 (m, 1 H), 3.50 (m, 1 H), 2.82 (s, 3 H), 2.30 (m, 1 H), 2.15 (m, 1 H), 1.90 (m, 1 H), 1.75 (m, 1 H), 1.18 (s, 9 H); ms m/z 300 (M^+), 166, 136, 105 (base), 77, 57; HRms calcd for $C_{18}H_{24}N_2O_2$, 300.1838; found, 300.1838. **42** ^{1}H Nmr (DMSO-d_6, 100 °C) δ 7.40 (m, 3 H), 7.34 (m, 2 H), 4.85 (dd, 1 H, *J* = 8.7, 5.0 Hz), 4.37 (m, 1 H), 3.68 (m, 1 H), 2.83 (s, 3 H), 2.15-1.85 (m, 4 H), 1.13 (s, 9 H).

Compounds (**43**) and (**42**) were also prepared by *N*-methylation of **28a** and **27a** respectively by the procedure described above.

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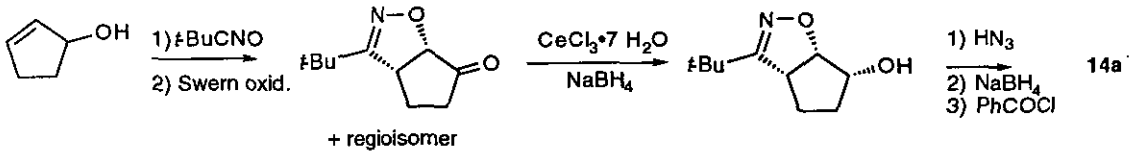

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20. 3°-Amides are less than ideal models for 2°-amides because 3°-amides exist as mixtures of C–N rotamers while 2°-amides exist as a single C–N rotamer. However, rotation is very rapid relative to cycloaddition.

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