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Type 2 Intramolecular *N*-Acylnitroso Diels−Alder Reaction: Scope and Application to the Synthesis of Medium Ring Lactams

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Heteroatom variants of the type 2 intramolecular Diels−Alder reaction provide an efficient method for the preparation of bridged bicyclic heterocycles. The type 2 variant of the intramolecular *N*-acylnitroso Diels−Alder reaction is an effective method for the synthesis of bridged bicyclic oxazinolactams. Structural studies of the cycloadducts have allowed for quantification of the deformations of the bridgehead functionalities and provided a strategy for the stereoselective synthesis of substituted seven- and eight-membered ring lactams. Diastereoselective cycloadditions followed by cleavage of the oxazine ring afford azepin-2-ones or azocin-2-ones.

Introduction

Diels−Alder reactions employing nitroso dienophiles provide an efficient method for the synthesis of numerous heterocycles.[1] *N*-Acylnitroso dienophiles, pioneered by Kirby for the preparation of 3,6-dihydro-1,2-oxazine ring systems (oxazinolactams), are reactive dienophiles that are generated in situ via oxidation of a hydroxamic acid and trapped with a diene to afford the heterocyclic cycloadduct.[2] These multifunctional adducts have been transformed into a variety of biologically active molecules including azasugars, pyrrolidines, piperidines, tropanes, and benzodiazepines. They have also been utilized in the synthesis of a variety of natural products.[3]

Poor regioselectivity exhibited with *N*-acylnitroso cycloadditions employing unsymmetrical dienes has restricted applications of this reaction in more complex settings.[4,5] Several methods including the placement of strong electron-donating groups on the diene and union of the diene and dienophile have been applied to mediate this deficiency.

The utility of oxazinolactams as key intermediates in the synthesis of heterocyclic compounds prompted our study of the type 2 variant of the intramolecular *N*-acylnitroso Diels−Alder reaction. Type 2 intramolecularity provides an opportunity to control the regiochemistry of the cycloaddition and access to bridged bicyclic molecules incorporating medium sized rings, in one step from acyclic precursors.[6]

Heteroatom variants of the type 2 IMDA cycloaddition provide a general route into bridged bicyclic heterocycles.[7] We report the scope of the type 2 intramolecular *N*-acylnitroso Diels−Alder reaction and its utility for the stereoselective preparation of azepin-2-ones and azocin-2-ones.[8]

Results and Discussion

Synthesis of the Diels−Alder Precursors. The overall strategy for the assembly of the Diels−Alder precusor hydroxamic acids involved attachment of four to six atom tethered nitriles to the 2-position of a 2-metallo-1,3-butadiene, followed by conversion of the nitrile functionality to a hydroxamic acid (Scheme 1). Chloroprene Grignard was coupled with iodonitriles (**1a**−**c**) mediated by Li_2CuCl_4 to afford diene nitriles **2a**−**c** in moderate to high yield.[9] Basic hydrolysis of the nitrile

(1) (a) Boger, D. L.; Weinreb, S. M. *Hetero-Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (b) Weinreb, S. M.; Staib, R. P. *Tetrahedron* **1982**, *38*, 3087−3128. (c) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 451−512. (d) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 401−449. (e) Orena, M. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21e, pp 5547−5587. (f) Tietze, L. F.; Kettschau, G. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer: Berlin, 1997; Vol. 189, pp 1−120.

(2) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1−24.

(3) (a) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879. (b) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348. (c) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139−141. (d) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059−2074. (e) Sato, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3839−3842.

(4) (a) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397−8406. (b) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911−1916. (c) Boger, D. L.; Patel, M. *J. Org. Chem.* **1984**, *49*, 4099−4101.

(5) (a) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243−1255. (b) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192−5200. (c) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330−3343. (d) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1499−1500.

(6) (a) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 821−849. (b) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem.* **2001**, *12*, 597−622.

(7) (a) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248−2260. (b) Shea, K. J.; Lease, T. G.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 8627−8629. (c) In *Advances in Theoretically Interesting Molecules*; Shea, K. J., Lease, T. G., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 2, pp 79−112.

(8) (a) Sparks, S. M.; Vargas, J. D.; Shea, K. J. *Org. Lett.* **2000**, *2*, 1473−1475. (b) Chow, C. P.; Shea, K. J.; Sparks, S. M. *Org. Lett.* **2002**, *4*, 2637−2640.

(9) (a) Shea, K. J.; Pham, P. Q. *Tetrahedron Lett.* **1983**, *24*, 1003−1006. (b) Fleming, F. F.; Jiang, T. *J. Org. Chem.* **1997**, *62*, 7890−7891. (c) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303−305.

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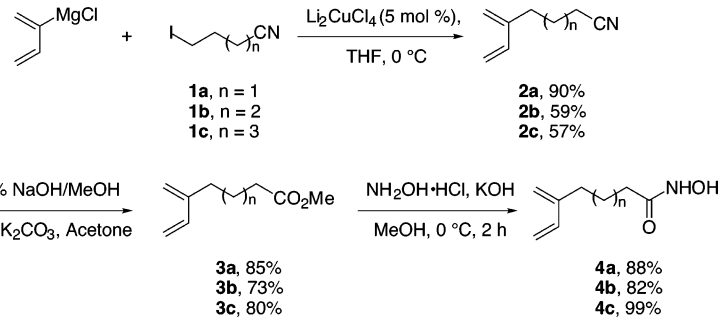
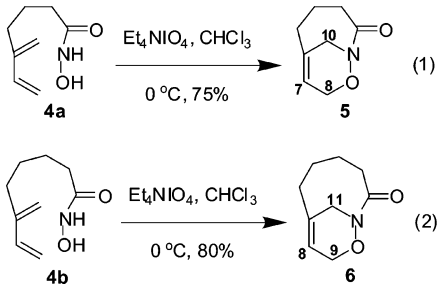
SCHEME 1. Synthesis of Hydroxamic Acids 4a−4c



SCHEME 2. Oxidation and Cycloaddition of 4a and 4b



functionality (25% NaOH, MeOH, reflux, 48 h) followed by esterification (MeI, K_2CO_3, acetone) furnished methyl esters **3a**−**c**. Conversion to the hydroxamic acids was accomplished by treatment with NH_2OH·HCl in basic methanol, which provided Diels−Alder precursors **4a**−**c** in good yield.

Type 2 Intramolecular *N*-Acylnitroso Diels−Alder Reactions. Cycloadditions of dilute solutions (0.01 M) of hydroxamic acids **4a**−**c** were initially examined using Et_4NIO_4 as the oxidant in $CHCl_3$ at 0 °C (Scheme 2). Subjection of hydroxamic acids **4a** and **4b** to these conditions resulted in the isolation of cycloadducts **5** and **6** in 75% and 80% yields, respectively (eqs 1 and 2). The regiochemistry of the cycloadditions was secured by 2D homonuclear COSY experiments. Individual off diagonal signals in the COSY spectrum of [4.3.1] cycloadduct **5** allowed differentiation between the two sets of diastereotopic protons at C8 (4.57 and 4.28 ppm) and C10 (4.12 and 3.42 ppm). The assignments of the C8 protons were based on their unique cross-peaks that correlated with the C7 vinylic hydrogen at 5.73 ppm. In the COSY spectrum of [5.3.1] cycloadduct **6**, the presence of cross-peaks between the C8 vinylic proton (5.47 ppm) with the C9 hydrogens (4.78 and 4.36 ppm) establishes the 1,3-regiochemistry of oxazinolactam **6**. X-ray crystallography of oxazinolactams **5** and **6** unambiguously confirmed the regiochemical assignment of the cycloadducts and provided data for structural analysis (vide infra).

In contrast to the cycloadditions of **4a** and **4b**, oxidation of hydroxamic acid **4c** produced a complex mixture upon treatment with Et_4NIO_4 in $CHCl_3$ at 0 °C. A possible explanation for the failure of this reaction resides in the development of transannular interactions during the formation of a nine-membered ring ([6.3.1] bicycle).[10] The reduced rate of intramolecular cycloaddition allows competing processes to occur. To overcome this difficulty, a method of generating the *N*-acylnitroso dienophile at elevated temperatures was employed. These conditions were obtained via a thermal generation of the *N*-acylnitroso species from a 9,10-dimethylanthracene adduct.[2,11]

Treatment of hydroxamic acid **4c** with the oxidative conditions (Et_4NIO_4, $CHCl_3$) in the presence of 9,10-dimethylanthracene afforded 9,10-dimethylanthracene adduct **7** in 79% yield (Scheme 3). Thermolysis of adduct **7** in benzene at 80 °C provided a 1:1 ratio of isomeric cycloadducts in 60% combined yield. Purification by silica gel chromatography allowed for separation of cycloadducts **8** and **9**. The regiochemistry of each cycloadduct was verified via a combination of ^{1}H NMR spectroscopy and X-ray crystallography.

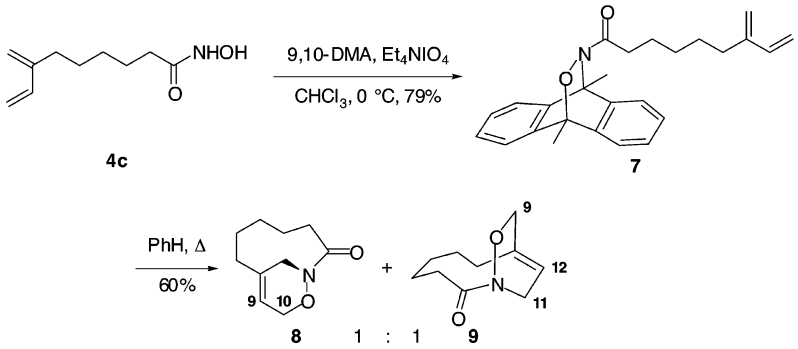
Crystalline cycloadduct **8** was unambiguously established as the 1,3-cycloadduct by X-ray analysis (vide infra). Two-dimensional homonuclear COSY experiments conducted on cycloadduct **8**, in which the vinylic proton at 5.43 ppm had a cross-peak with one of the C10 hydrogens at 5.00 ppm, were consistent with homologous members of the series. Individual off-diagonal cross-peaks in the COSY spectrum of compound **9** allowed differentiation between the two sets of diastereotopic protons at C9 (4.67 and 4.48 ppm) and C11 (4.78 and 3.53 ppm). The assignments of the C11 protons were based on their unique cross-peaks that correlated with the C12 vinylic hydrogen at 6.39 ppm. This experiment secures 1,4-regiochemistry for cycloadduct **9**.

The cycloadditions of the oxidation products of hydroxamic acids **4a** and **4b** occurred with *complete regiochemical control*. In contrast, the cycloaddition of the *N*-acylnitroso species generated from 9,10-dimethylanthracene adduct **7** produced a 1:1 ratio of regioisomers (Figure 1). Bimolecular Diels−Alder cycloadditions of acyl nitroso dienophile with 2-substituted dienes are nonselective. Type 2 intramolecularity imposes 1,3 (*meta*) regioselectivity on **4a** and **4b** via conformation **10**. This regioselectivity is found in type 2 IMDA reactions containing five or fewer atoms connecting the diene and dienophile.[6] With longer tethers such as the *N*-acylnitroso species generated from hydroxamic acid **4c**, the energetics for the cycloaddition in conformations **10** and **11** are equivalent and both [6.3.1] **8** and [6.2.2]cycloadduct **9** are found in equal amounts.

(10) (a) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117−3125. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(11) (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem Soc.* **2000**, *122*, 4583−4592. (b) Keck, G. E. *Tetrahedron Lett.* **1978**, *48*, 4767−4770. (c) Corrie, J. E. T.; Kirby, G. W.; Sharma, R. P. *J. Chem. Soc., Chem. Commun.* **1975**, 915−916 (d) Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc., Chem. Commun.* **1973**, 704−705.

SCHEME 3. Formation of Cycloadducts 8 and 9 by Thermolysis of Adduct 7



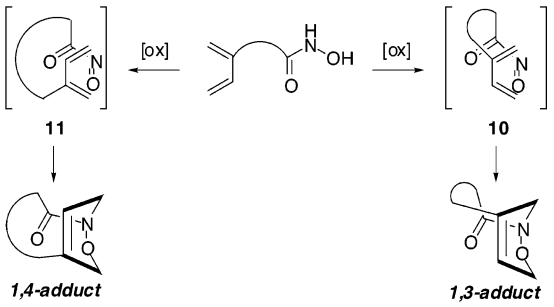
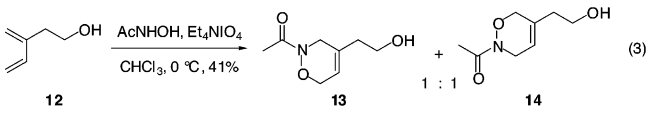


FIGURE 1. Regioselectivity of the type 2 intramolecular *N*-acylnitroso Diels–Alder reaction.

SCHEME 4. Intermolecular Acylnitroso Diels–Alder Reaction

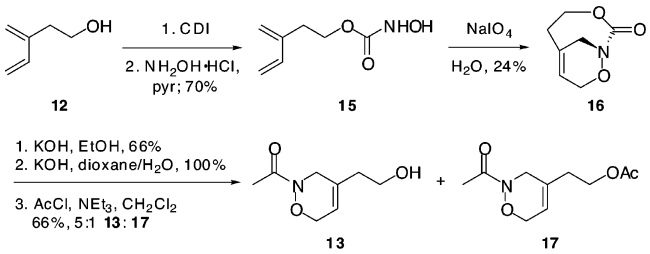


The regiochemical outcome is also consistent with the estimated energies of the regioisomeric cycloadducts. In the bicyclo[5.*n*.*n*]alkene series, the estimated energy of the 1,3-regioisomer (bicyclo[5.3.1]alkene **6**) is 8.5 kcal mol^{-1} lower than that of the analogous 1,4-regioisomer.[12] It is not unreasonable to assume that a portion of this difference in energy can be manifested in the competing transition states leading to cycloadduct formation.

For comparison, the intrinsic regiochemical preference of the corresponding intermolecular reaction was established (Scheme 4). The reaction of 3-methylene-4-penten-1-ol (**12**)[13] with the nitroso dienophile generated from acetohydroxamic acid was carried out (eq 3). Addition of acetohydroxamic acid to a 0 °C solution of Et_4NIO_4 and diene **12** led to a 1:1 mixture of inseparable cycloadducts **13** and **14**. The diagnostic peaks in the ^1H NMR spectrum of the mixture included two vinyl protons at 5.68 and 5.64 ppm.

The identity of the 1,3-regioisomer was independently verified by its synthesis via a type 2 *N*-acylnitroso IMDA reaction containing a cleavable tether (Scheme 5).[14] Diels–Alder precursor **15** was prepared by sequential condensation of carbonyldiimidazole with alcohol **12** followed by hydroxylamine. Oxidative generation of the *N*-acylnitroso dienophile occurred upon treatment with sodium periodate in water to afford cycloadduct **16**.[15] Performing the cycloaddition reaction in $CHCl_3$ with Et_4NIO_4 provided a similar low yield of cycloadduct, which was not optimized. Two-step carbamate cleavage (KOH, EtOH; KOH, dioxane/H_2O) followed by acylation (AcCl, NEt_3, CH_2Cl_2) provided isomerically pure **13** along with bisacetate **17**.

SCHEME 5. Removal of Cleavable Tether in Oxazinolactam 16



Confirmation of the structure of **13** was obtained by comparison of ^1H NMR spectrum. The vinyl proton resonance at 5.68 ppm for the 1,3-regioisomer **13** matched that seen in the spectra of the mixture of regioisomers. In addition, the gas chromatograph retention time of **13** was identical to one of the two peaks observed from the bimolecular experiment. This sequence highlights the control offered by type 2 connectivity in delivering a single regioisomer from a Diels–Alder reaction that proceeds with no regioselectivity.

X-ray Crystallography of the Cycloadducts. A. Bridgehead Olefins. The X-ray structures of cycloadducts **5**, **6**, and **8** reveal the bridgehead double bonds and bridgehead oxazinolactams are distorted from planarity.[16] The torsion angle τ between the p-orbitals of the double

(12) The structures were built in MacroModel v7.1, energy-minimized, and subjected to Monte Carlo conformational search using the implemented MMFF force fields.

(13) Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912–1914.

(14) Davies, G.; Russel, A. T.; Sanderson, A. J.; Simpson, S. J. *Tetrahedron Lett.* **1999**, *40*, 4391–4394.

(15) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595–598.

(16) For recent studies of bridgehead olefins, see: (a) Wijsman, G. W.; Iglesias, G. A.; Beekman, M. C.; de Wolf, W. H., Bickelhaupt, F.; Kooijman, H., Spek, A. L. *J. Org. Chem.* **2001**, *66*, 1216–1227. (b) Verma, S. K.; Nguyen, Q. H.; MacDougall, J. M.; Fleischer, E. B.; Moore, H. W. *J. Org. Chem.* **2000**, *65*, 3379–3386. For bridgehead olefin reviews, see: (c) Lease, T. G.; Shea, K. J. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press Inc.: Greenwich, CT, 1992; pp 79–112. (d) Keese, R.; Luef, W. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., Eds.; John Wiley and Sons: New York, 1991; Vol. 20, pp 231–318. (e) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067–1093. (f) Wentrup, C. *Reactive Molecules*; John Wiley and Sons: New York, 1984; pp 265–3089. (g) Szeimies, G. In *Reactive Intermediates*; Abranovitch, R. A., Ed; Plenum: New York, 1983; Vol. 3, pp 299–366. (h) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683–1715.

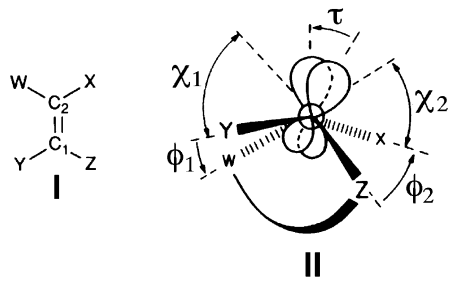


FIGURE 2. Parameters in unsymmetrically deformed π systems.

bond and nitrogen−carbonyl π systems and the pyramidalization angles χ of the constituent atoms of the two functional groups can be used to quantify the extent of the distortions. The method used to measure these parameters in unsymmetrically deformed π systems is shown in Figure 2.[17]

The view along the C_1-C_2 axis of π system **I** is represented by **II** (Figure 2). Rotation of C_1 relative to C_2 produces a misalignment of the π bond p-orbitals. This deformation causes the two atoms of the π-system to rehybridize independently. The torsional deformation is quantified by the angle τ between the axes of the two p orbitals. The torsion angle τ is not directly measurable but may be determined by summing the four atom torsion angles YC_1C_2W (Φ1) and ZC_1C_2X (Φ2) and dividing the result by 2 ($\tau = (YC_1C_2W + ZC_1C_2X)/2$). The p-orbital alignment is presumed to be optimal for a double bond with $\tau = 0.0°$.

The degree of pyramidalization of each atom is quantified by the pyramidalization angle χ, defined as the acute angle formed by the projection of one substituent (Z) across the atom onto the geminal substituent (Y). For an $sp^{2.00}$ hybridized atom, $\chi = 0.0°$, whereas for $sp^{3.00}$ hybridization $\chi = 60.0°$. In the discussion of the distortions of bridgehead olefins **5**, **6**, and **8**, the designations χ_B and χ_E refer to the pyramidalization angles at the bridgehead and exocyclic atoms of the olefin, respectively. The X-ray crystallographic data for cycloadducts **5**, **6**, and **8** track the distortions of the bridgehead double bonds and bridgehead oxazinolactams in a homologous series of compounds in which the size of one bridge is systematically varied. The structural parameters τ, χ_B and χ_E for bicycles **5**, **6**, and **8** are presented in Table 1.

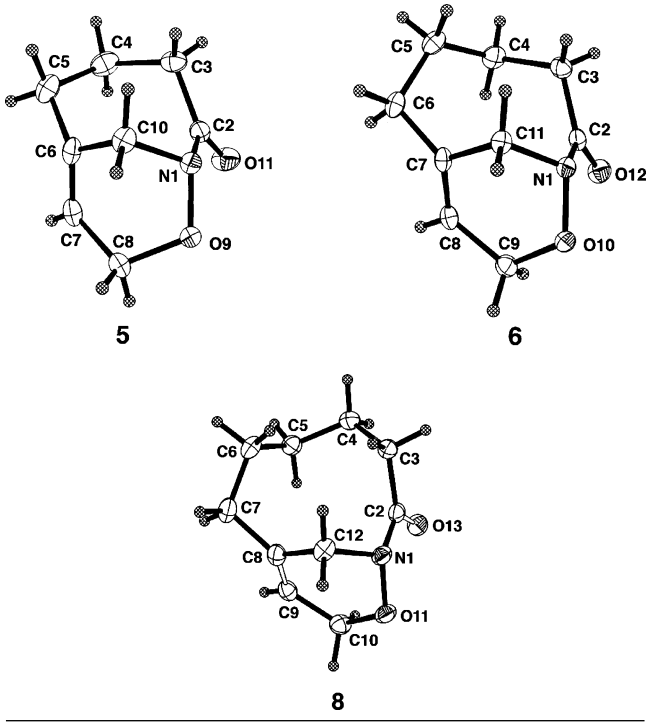
The bridgehead olefinic carbon atom shows a trend of increasing pyramidalization (χ_B) as the size of the *trans*-cycloalkene ring is decreased: the χ_B values correspond to hybridization values of $sp^{2.19}$ for **8**, $sp^{2.22}$ for **6**, and $sp^{2.34}$ for **5**. A similar trend has been observed in a series of bridgehead olefin/bridgehead lactams.[7]

The pyramidalization values for the exocyclic carbon (χ_E) atoms show no simple trend. The pyramidalization values correspond to hybridizations of $sp^{2.15}$ for **5**, $sp^{2.07}$ for **6** and $sp^{2.11}$ for **8**. Suprisingly, a further increase in ring size from [5.3.1] cycloadduct **6** ($\chi_E = 4.0°$) to [6.3.1] cycloadduct **8** ($\chi_E = 6.4°$) resulted in an increase in the pyramidalization of the exocyclic olefinic carbon (χ_E).

The π-orbital torsion angle (τ_{olefin}) *increases* as the size of the *trans*-cycloalkene is reduced. Bridgehead olefins **8**, **6**, and **5** experience 3.5%, 3.9%, and 7.6% torsional distortion, respectively. This trend is also observed in a related series of bridgehead olefins.[7]

(17) Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169−182.

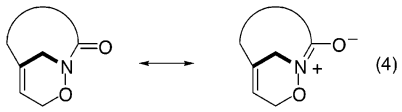
TABLE 1. Distortions of Bridgehead Olefins 5, 6, and 8



	5[4.3.1]	**6**[5.3.1]	**8**[6.3.1]
χ_B	20.3°	13.5°	11.2°
χ_E	9.0°	4.0°	6.4°
τ_{olefin}	6.83(9)°	3.53(9)°	3.15(9)°

Torsional strain present in the bridgehead double bonds can result in increased reactivity; however, this does not necessarily correlate with an increased bond length.[18] In this series no trend is observed in the C=C bond lengths of bridgehead olefins **5**, **6** and **8**, as double bond distances, 1.3331(18) Å for **5**, 1.3323(14) Å for **6**, and 1.3297(15) Å for **8**, are all within error of the value for cyclohexene (1.335(3) Å).[18]

B. Bridgehead Oxazinolactams. The bridgehead oxazinolactam functionality of compounds **5**, **6**, and **8** can be represented by two energetically important resonance forms: the amino ketone (**18**) and zwitterionic (bridgehead double bond) form (**19**) (eq 4). Table 2 contains the

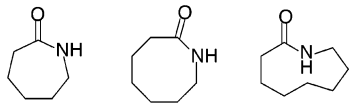


18 **19** (4)

distortion parameters and bond lengths for the bridgehead oxazinolactam functionality of compounds **5**, **6**, and **8**.

The pyramidalization angle at the bridgehead nitrogen (χ_N) increases as the size of the *trans*-cycloalkene is reduced. For cycloadduct **5**, $\chi_N = 54.8°$ corresponds to

(18) (a) Determined by electron diffraction. Chiang, J. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1969**, *91*, 1898−1901. (b) In *The Amide Linkage*; Greenberg, A., Breneman, C. M., Liebman, J. F., Ed.; Wiley-Interscience: Hoboken, NJ, 2003



20 **21** **22**

FIGURE 3. Lactams.

TABLE 2. Distortion Parameters and $\nu_{C=O}$ in 5, 6, and 8

	5[4.3.1]	**6**[5.3.1]	**8**[6.3.1]
χ_N	54.8°	52.6°	49.0°
χ_C	0.4°	1.5°	4.1°
τ_{amide}	3.53(10)°	10.35(8)°	16.44(10)°
N hybridization	$sp^{2.91}$	$sp^{2.88}$	$sp^{2.81}$
$\nu_{C=O}$ (cm^{-1})	1704	1692	1681

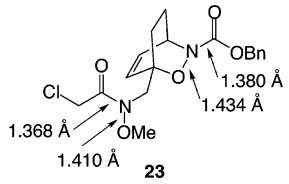
$sp^{2.91}$ hybridization; for **6**, $\chi_N = 52.6°$ corresponds to $sp^{2.88}$ hybridization; and **8**, $\chi_N = 49.0°$ corresponds to $sp^{2.81}$ hybridization. In each case the topological constraints of the bridged bicyclic compounds produce an amide nitrogen atom with a formal hybridization closer to $sp^{3.00}$ than $sp^{2.00}$, indicating the amino ketone resonance form **19**, in which the nitrogen atom is tetrahedral, is an important contributor to the electronic structure of the bridgehead amide functionality.

In contrast, the amide carbonyl carbons undergo only slight deviations from planarity (χ_C). The pyramidalization angle χ_C increases from 0.4° for **5** up to 4.1° for **8**. This results in hybridizations of $sp^{2.00}$ for **5**, $sp^{2.02}$ for **6**, and $sp^{2.07}$ for **8**.

The π-orbital torsion angle τ_{amide} *increases* in the series **5**, **6**, and **8** from 3.9% to 11.5% to 18.2%, respectively. Thus, the p-orbital torsion angle *increases* as the size of the bridged bicycle is *increased*. This trend was unexpected. A possible explanation may be attributed to relief of transannular interactions that develop in the medium (8 and 9) sized rings. Inspection of the crystal structure of **8** revealed eclipsing interactions between the H7α-H9α protons and the H7β-C8C9 bond of the [6.3.1] oxazinolactam. This maybe a consequence of minimizing the nonbonding interactions across the nine-membered ring. These interactions may result in an increased p-orbital torsion angle for the amide (τ_{amide}) compared to the olefin (τ_{olefin}), as the amide has been documented to be more easily distorted than the olefin.

Interestingly, a similar trend was observed for the unsubstituted seven-, eight-, and nine-membered lactams, **20**,[19] **21**,[20] and **22**[21] (Figure 3). The π-orbital torsion angles, τ_{amide}, increase as the ring size is increased. Thus, $\tau_{amide} = 0.6°$ for **20**, $\tau_{amide} = 4.5°$ for **21**, and $\tau_{amide} = 17.1$ for **22**. This trend has been attributed to both a crossover from a *cis*-amide in **20** and **21** to a *trans*-amide in **22** and the relief of transannular interactions in the medium rings (lactams **21** and **22**).

In consideration of the increasing τ_{amide} values as a function of ring size, one might expect an ascending trend in $\nu_{C=O}$ due to increasing in the amide bond twisting. Interestingly, inspection of the IR spectroscopic data revealed a *decrease* in the amide $\nu_{C=O}$ as the lactam ring



23

FIGURE 4. Bicyclo[2.2.2]octene ring system.

TABLE 3. Selected Bond Distances of Compounds 5, 6, and 8

	5[4.3.1]	**6**[5.3.1]	**8**[6.3.1]
N–O (Å)	1.4239(12)	1.4209(10)	1.4188(10)
$C_{carbonyl}$–N (Å)	1.4064(15)	1.3977(12)	1.3877(13)

increases in size. The amide carbonyl stretching frequency decreases from 1704 cm^{-1} for **5** to 1692 cm^{-1} for **6** and to 1681 cm^{-1} for **8** (Table 2). The inverse relationship between τ_{amide} and $\nu_{C=O}$ suggests that factors in addition to amide bond deformation contribute to the observed $\nu_{C=O}$ of the cycloadducts. There is no obvious, simple explanation for the opposing trends.

An analysis of bond lengths can provide insight into the effects of induced strain. The bond lengths of the nitrogen–oxygen bond and carbonyl carbon–nitrogen bond for compounds **5**, **6**, and **8** are summarized in Table 3.

The bond lengths for bicyclo[2.2.2]alkene **23**, an intermediate in Baldwin's synthesis of tabotoxin, are summarized in Figure 4.[22] Compound **23** contains both an oxazinolactam embedded in the bicyclo[2.2.2]octene ring system and a Weinreb amide functionality. The bond distances of these functional groups can be used as a comparison for the analysis of the bond distances of compounds **5**, **6**, and **8**.

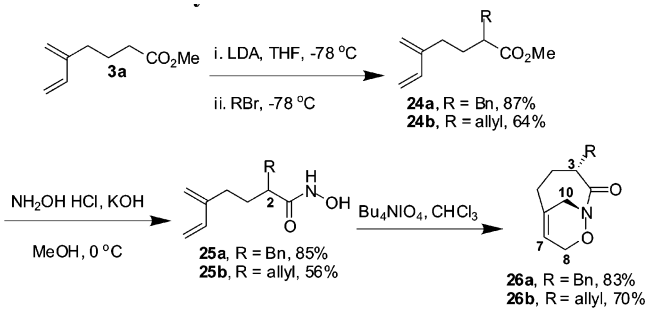
The nitrogen–oxygen bond experiences lengthening as the size of the bridged bicycle is decreased. This trend could be due to relief of strain in the smaller more highly strained cycloadducts. These distances are all longer than the nitrogen–oxygen bond length of the Weinreb amide functionality in compound **23** (1.410 Å) and shorter than the nitrogen–oxygen bond length of the oxazinolactam moiety of compound **23** (1.434 Å). This trend suggests that the nitrogen–oxygen bond length is sensitive to distortions resulting from strain introduced as the ring size of the *trans*-cycloalkene is decreased.

A similar trend is seen in the nitrogen–carbonyl carbon bond length. The nitrogen–carbonyl carbon bond distance increases as the size of the bridged bicycle is decreased. These values are all longer than both the nitrogen–carbonyl carbon bond distance of the Weinreb amide group (1.368 Å) and oxazinolactam group of compound **23** (1.380 Å).

The structural studies can be summarized as follows. Torsional distortions of the bridgehead double bond, pyramidalization at the bridgehead carbon, and pyramidalization of the bridgehead nitrogen occur as the *trans*-cycloalkene ring size is decreased. Unexpectedly, the torsional distortions of the bridgehead oxazinolactam increase as the ring size is increased. A lengthening of both the nitrogen–oxygen bond and carbonyl carbon–

(19) Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr.* **1975**, *B31*, 251–263.
(20) Winkler, F. K.; Seiler, P. *Acta Crystallogr.* **1979**, *B35*, 1920–1922.
(21) Winkler, F. K.; Dunitz, J. D. *Acta Crystallogr.* **1975**, *B31*, 276–278.
(22) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Otsuka, M.; Singleton, K. A.; Wallace, P. M. *Tetrahedron* **1984**, *40*, 3695–3708.

SCHEME 6. Synthesis of Oxazinolactams 26a and 26b



nitrogen bond is seen as the ring size of the *trans*-cycloalkene is decreased. As the ring size becomes larger, the aforementioned bond lengths shorten to normal distances.

C. Nonbonding Interactions in Bicyclo[4.3.1]-oxazinolactams. The crystal structure of oxazinolactam **5** revealed a close contact between hydrogen atom at (C3) H3β and the *syn* hydrogen atom at the one-carbon methylene bridge (H10α). In the structure of oxazinolactam **6**, two close contacts between hydrogen atoms at C3 (H3β) and C5 (H5β) with the *syn* hydrogen atom at the one-carbon methylene bridge (H11α) were revealed. The recognition of these interactions led to the hypothesis that substitution of these positions (C3 in **5**, C3 and C5 in **6**) *in the Diels−Alder precursor* could lead to highly diastereoselective cycloadditions. The hypothesis is based on the principle that concerted cycloaddition involves continuous overlap between the π orbitals of the 2-substituted butadiene and those of the nitroso dienophile.[5] Since the strained cycloadduct has relatively low conformational flexibility, the structure of the bridgehead oxazinolactams **5** and **6** can be used to approximate the [4 + 2] cycloaddition transition states.[23]

The synthesis of C2-substituted hydroxamic acids **25a** and **25b** was undertaken to establish the diastereoselectivity of the cycloaddition and to test the predictive ability of the model. Treatment of ester **3a** with LDA followed by benzyl bromide or allybromide furnished α-alkylated esters **24a** and **24b** in 87% and 64% yield, respectively (Scheme 6). Conversion of esters **24a** and **24b** to the corresponding hydroxamic acids **25a** and **25b** occurred by treatment with basic hydroxylamine. Addition of hydroxamic acids **25a** and **25b** to a room-temperature solution of Bu_4NIO_4 in $CHCl_3$ led to the isolation of cycloadducts **26a** and **26b** in 83% and 70% yield, respectively, each as a *single diastereomer* in both reactions. The stereochemistry of cycloadducts **26a** and **26b** was established by ^{1}H NMR experiments.

The 1,3-regiochemistry of cycloadduct **26a** was determined by two-dimensional homonuclear COSY experiments. Individual off-diagonal signals allowed differentiation between the two sets of diastereotopic protons at C8 (4.66 and 4.32 ppm) and C10 (4.25 and 3.40 ppm). The assignments of the C8 protons were based on their unique cross-peaks that correlated with the C7 vinylic hydrogen at 5.76 ppm. The assignments of the C10 protons were strengthened in the following stereochemical determination of cycloadduct **26a** using NOE analysis.

Irradiation of the C3 methine proton at 3.22 ppm resulted in enhancement of the *syn* proton at C10 at 4.25 ppm (4.4%). Enhancement of the methine proton at C3 (4.9%) was also observed in the converse experiment by irradiating the same C10 hydrogen. This establishes that the benzyl substituent at C3 is in an *anti* relationship with respect to the methylene bridge (C10). The structure of cycloadduct **26b** determined in the same manner also revealed a relative *anti* stereochemistry in the molecule. The formation of oxazinolactams **26a** and **26b**, both *anti* diastereomers, is consistent with the transition state model based on the X-ray structure of the parent cycloadduct **5**.

The spectroscopic methods mentioned above to characterize cycloadduct **26a** were employed to determine the regiochemistry and relative stereochemistry of other cycloaddition products in the remainder of this paper (Table 4). X-ray crystallographic studies were used when suitable single crystals were obtained. Functionalization of the cycloadducts were carried out in some cases to substantiate the structure determined by NMR studies (vide infra).

Rationalization of stereoselectivity of the cycloadditions of the nitroso species derived from hydroxamic acids **24a** and **24b** is based on steric interactions that develop in the transition state. The introduction of heteroatom substituents could introduce other factors such as dipole−dipole interactions that contribute to the stereoselectivity. To evaluate the importance of this factor, a 2-oxy substituted hydroxamic acid Diels−Alder precursor **29** was prepared (Scheme 7). The synthesis provided an opportunity to streamline preparation of the intermediate dienylesters. This was accomplished by the direct coupling of chloroprene Grignard with iodoester **27**[24] in the presence of catalytic Li_2CuCl_4 to provide the diene ester (Scheme 7).[9] The diene ester was α-hydroxylated by treatment with lithium diisopropylamide followed by triethyl phosphite and molecular oxygen to furnish alcohol **28**.[25] Hydroxyl protection (NaH, TBAI, BnBr, DMF) followed by conversion to the hydroxamic acid furnished Diels−Alder precursor **29**. Oxidation and cycloaddition of hydroxamic acid **29** produced a single *syn* diastereomer **30**, 100% ds. The diastereoselectivity reversal suggests that dipole minimization in the transition state may be an important contribution to the outcome of the cycloaddition, since the *syn* transition state would minimize repulsion between the C−O and C═O dipoles.

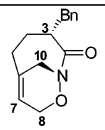
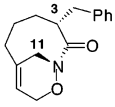
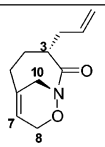
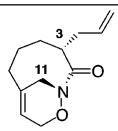
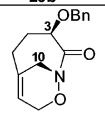
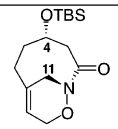
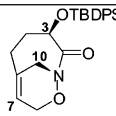
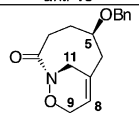
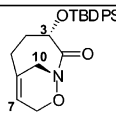
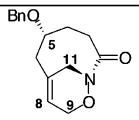
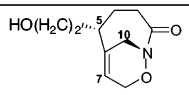
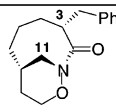
Other factors that might also contribute to the *syn* stereoselectivity include overlap between the C−O bond and the carbonyl in the transition state of the cycloaddition. In the *syn* transition state, mixing of the σ^* of C−O and the LUMO of the nitrosocarbonyl may lower the energy of the dienophile and make it more reactive than the sterically preferred *anti* transition state. Although in the ground state (**30**) the C_3−O and C_3−H dihedral angle with the C═O σ plane is the same, the two interactions are not equivalent and could therefore

(23) MMFF calculations suggested that the ground state conformation of cycloadduct **1** is approximately 6.1 kcal mol^{-1} lower in strain energy than the nearest local minimum conformation.

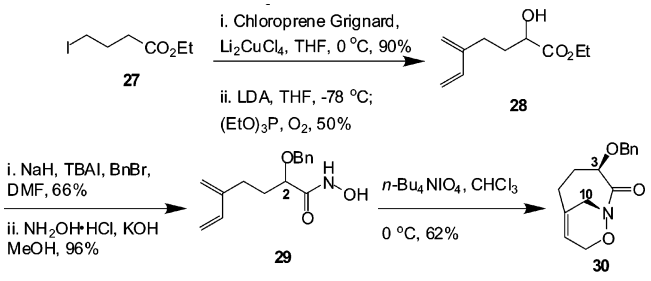
(24) Tok, J. B.-H.; Cho, J.; Rando, R. R. *Tetrahedron* **1999**, *55*, 5741−5758.

(25) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294−3297. (b) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, *16*, 1731−1734.

TABLE 4. Selected NOE Data for Bicyclo[*n*.3.1] Oxazinolactams

Bicyclo[4.3.1] Oxazinolactams	Protons Irradiated	Enhancement Observed (%)	Bicyclo[5.3.1] Oxazinolactams	Protons Irradiated	Enhancement Observed (%)
 **26a**	H_3 @ 3.21 ppm $H_{10(syn)}$ @ 4.20 ppm	$H_{10(syn)}$ (4.4%) @ 4.20 ppm H_3 (4.9%) @ 3.21 ppm	 **39a**	H_3 @ 2.25 ppm $H_{11(syn)}$ @ 4.07 ppm	$H_{11(syn)}$ (6.0%) @ 4.07 ppm H_3 (3.6%) @ 2.25 ppm
 **26b**	$H_{10(syn)}$ @ 4.22 ppm	H_3 (7.3%) @ 3.02 ppm	 **39b**	H_3 @ 2.33 ppm $H_{11(syn)}$ @ 4.10 ppm	$H_{11(syn)}$ (3.4%) @ 4.10 ppm H_3 (3.6%) @ 2.33 ppm
 **30**	H_3 @ 4.30 ppm $H_{10(}$*syn*$)$ @ 5.10 ppm	$H_{10(syn)}$ (0.0%) @ 5.10 ppm H_3 (0.0%) @ 4.30 ppm	 *anti*-**43**	H_4 @ 4.72 ppm	$H_{11(syn)}$ (3.9%) @ 3.97 ppm
 *syn*-**32**	H_3 @ 4.56 ppm $H_{10(}$*syn*$)$ @ 5.45 ppm	$H_{10(syn)}$ (0.0%) @ 5.45 ppm H_3 (0.0%) @ 4.56 ppm	 *syn*-**49**	H_5 @ 4.01 ppm $H_{11(syn)}$ @ 3.67 ppm H_{13} @ 4.53 ppm	$H_{11(syn)}$ (0.0%) @ 3.67 ppm H_5 (0.0%) @ 4.01 ppm $H_{11(syn)}$ (4.1%) @ 3.67 ppm
 *anti*-**32**	H_3 @ 4.79 ppm $H_{10(}$*syn*$)$ @ 3.65 ppm	$H_{10(syn)}$ (5.4%) @ 3.65 ppm H_3 (8.4%) @ 4.79 ppm	 *anti*-**49**	$H_{11(syn)}$ @ 3.75 ppm	H_5 (3.2%) @ 3.88 ppm
 *anti*-**36**	H_5 @ 2.81 ppm $H_{10(}$*syn*$)$ @ 4.13 ppm	$H_{10(syn)}$ (1.8%) @ 4.13 ppm H_5 (1.2%) @ 2.81 ppm	 *anti*-**55**	H_3 @ 2.63 ppm	$H_{11(syn)}$ (5.7%) @ 4.14 ppm

SCHEME 7. Synthesis of Oxazinolactam 30



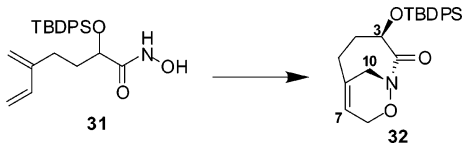
contribute to the differentiation between the two transition states.

The balance between sterics and electronics can be mediated by the size of the C2 substituent. To examine this in more detail we prepared a 2-silyloxy substituted Diels–Alder hydroxamic acid precursor **31** (Table 1). Upon oxidation and cycloaddition of **31** in $CHCl_3$, a mixture of two cycloadducts was found in 70% yield (Table 1, entry 1). The two products were assigned to a major *syn* diastereomer (*syn*-**32**) and a minor *anti* diastereomer (*anti*-**32**) (*syn*:*anti* = 84:16). In the transition state for this cycloaddition, the *anti* product would be favored on the basis of sterics. Since the *syn* product is found in substantial excess, it appears that dipole–dipole repulsions play a dominant role in controlling the π-facial selectivity of the cycloaddition reaction for forming α-substituted [4.3.1] oxazinolactams.

To establish other factors that might influence the diastereoselectivity, we examined the cycloaddition in solvents of increasing dielectric constant. Oxidation and cycloaddition of hydroxamic acid **31** was carried out in THF/H_2O (Table 5, entries 4–6). The increase in dielectric constant could ameliorate the dipole–dipole interaction and allow sterics to play a more important role in the cycloaddition step.[26] In fact, the diastereoselectivity cycloaddition exhibited little sensitivity to solvent polarity. The selectivities were 74:26 (THF/H_2O) compared to 84:16 in $CHCl_3$, 83:17 in CH_2Cl_2, and 80:20 in benzene (Table 5). Diastereomer *syn*-**32** was found as the major

(26) Jung, M. E.; Kiankarimi, M. *J. Org. Chem.* **1998**, *63*, 2968–2974.

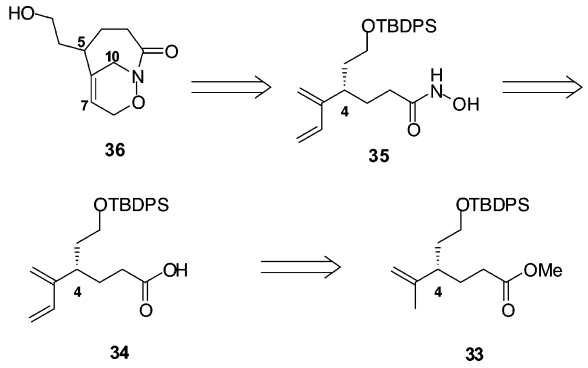
TABLE 5. Reaction Conditions for Oxidation and Cycloaddition of Hydroxamic Acid 31[a]



entry	solvent	oxidant	temp (°C)	*syn*-**32**:*anti*-**32**
1	$CHCl_3$	Bu_4NIO_4	0	84:16
2	CH_2Cl_2	Bu_4NIO_4	0	83:17
3	PhH	Bu_4NIO_4	20	80:20
4	THF/H_2O (2:1)	$NaIO_4$	0	74:26
5	THF/H_2O (1:1)	$NaIO_4$	0	74:26
6	THF/H_2O (1:2)	$NaIO_4$	0	74:26

[a] Spectroscopic ratio determined by integration of the C7 vinyl proton.

SCHEME 8. Retrosynthetic Analysis of Cycloadduct 36

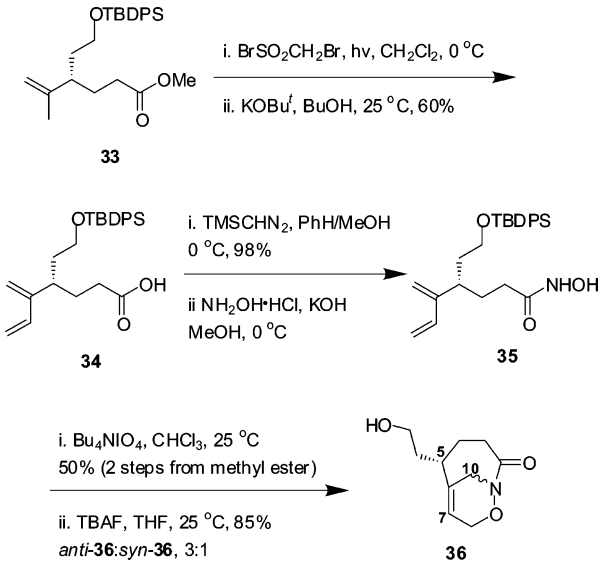


product in all reactions. The negligible influence of solvent on the diastereoselectivity neither substantiates nor negates the importance of dipole−dipole effects on the reaction.

We next turned our attention to the influence of substituents at position C4 on the diastereoselectivity of the Diels−Alder precursor **35**. Potential nonbonding interactions in **36** include close substituent contact (C5) with the *syn* hydrogen at C10 and eclipsing interactions with the vinyl proton at C7. The inspection of models leading to *syn*-**36** and *anti*-**36** does not provide a clear-cut prediction of the π-facial selectivity of the cyloaddition. The synthesis of an oxazinolactam with C5 substituents is given in Scheme 8. The C5-substituted oxazinolactam **36** was envisioned to arise from Diels−Alder hydroxamic acid precursor **35**, which can be derived from the corresponding methyl ester. The diene in **34** can be obtained by a Ramberg−Backlund rearrangement of olefin **33** prepared by oxidative cleavage of (*S*)-(−)-perillyl alcohol.[27]

A mixture of silyl ether **33** and bromomethanesulfonyl bromide was subjected to UV irridation in Pyrex vessel at 0 °C for 2 h (Scheme 9).[28] The photolysis mixture was treated with KO^{t}Bu to afford diene **34** in 60% yield.[26] The conversion of carboxylic acid **34** to hydroxamic acid **35** was achieved by treatment with $TMSCHN_2$ followed by basic hydroxylamine in MeOH.

SCHEME 9. Synthesis of Oxazinolactam 36



With the Diels−Alder precursor in hand, oxidative cycloaddition of **35** afforded the corresponding oxazinolactam. The NMR analysis of the crude mixture indicated an inseparable mixture (3:1) of diastereomers. The reaction was run at a lower reaction temperature (−40 °C) with no improvement in the diastereoselectivity. The hydroxamic acid **35** was also oxidized by $NaIO_4$ in THF/H_2O (1:1) at room temperature, and the diastereoselectivity was not improved. The TBDPS ether was deprotected by TBAF, and the resulting alcohols *anti*-**36** and *syn*-**36** were separated by silica gel chromatography. The stereochemistry of major product *anti*-**36** was unambiguously proven by NOE studies (see Table 4). In view of the moderate diasteroselectivity of the cycloaddition, it appears that none of the potential steric factors were sufficiently influential to strongly bias the cycloaddition to favor the *anti* cycloadduct.

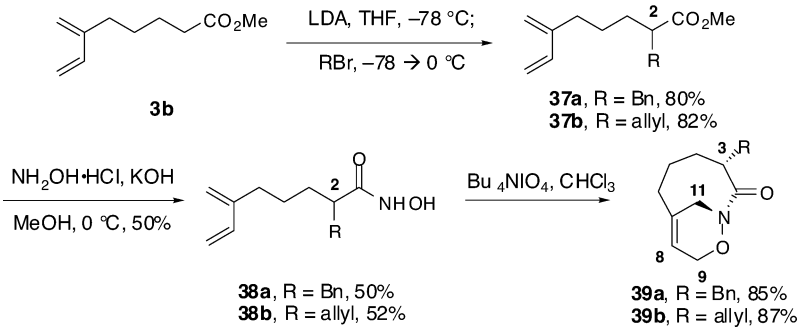
D. Nonbonding Interactions in Bicyclo[5.3.1]-oxazinolactams. We next turned our attention to the directing effect of substituents on the tether for forming substituted bicyclo[5.3.1]oxazinolactams. Substitution at C2 of the Diels−Alder precursor hydroxamic acids **38a** and **38b** is also predicted to give rise to *anti* cycloadducts on the basis of steric interactions developed in the transition state of the cycloaddition reaction. The synthesis of **38a** and **38b** was accomplished by the alkylation of ester **3b** (Scheme 10). Treatment of **3b** with LDA followed by an activated electrophile (BnBr or allylbromide) afforded functionalized esters **37a** and **37b** in 80% and 82% yield, respectively. Conversion to the hydroxamic acid provided the Diels−Alder precursors **38a** and **38b** in moderate yield. Addition of the hydroxamic acids to a $CHCl_3$ solution of Bu_4NIO_4 led to the isolation of cycloadducts **39a** and **39b** in high chemical yield and as *single diastereomers* (100% ds). The synthesis of cycloadducts **39a** and **39b** as single diastereomers is consistent with the transition state model derived from the X-ray structure of the parent bicyclo[5.3.1]oxazinolactam **6**.

The directing effects of substituents at tether position C3 is less clear. The requisite Diels−Alder precursor **42** was synthesized by Aldol addition of the enolate of 9,-10-dimethylanthracene adduct **40**[29] to 4-methylene-5-

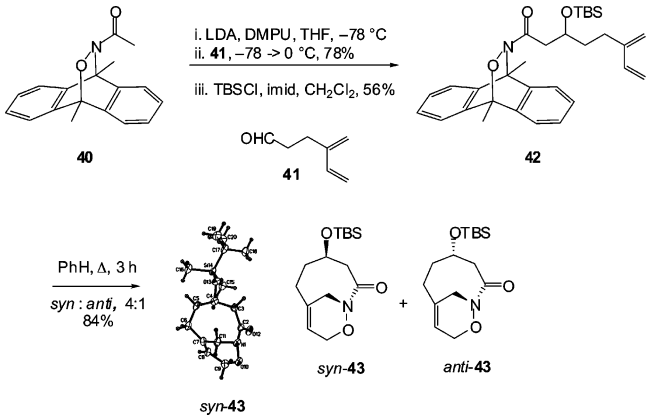
(27) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313−4320.

(28) Block, E.; Eswarakrishnan, V.; Gebreyes, K. *Tetrahedron Lett.* **1984**, *25*, 5469−5472.

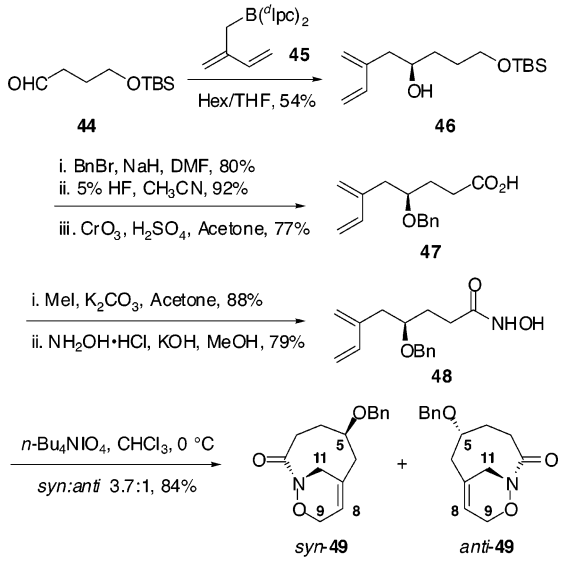
SCHEME 10. Synthesis of Oxazinolactams 39a and 39b



SCHEME 11. Thermolysis of Adduct 42



SCHEME 12. Synthesis of Oxazinolactams *syn*-49 and *anti*-49



hexen-1-al (**41**)[30] (Scheme 11). The resultant secondary alcohol was protected as a *tert*-butyldimethylsilyl ether. The Diels–Alder precursor was generated in situ by heating adduct **42** in refluxing benzene. The subsequent intramolecular cycloaddition led to the formation of two diastereomers in a 4:1 ratio in 84% yield. Purification by silica gel chromatography allowed the separation of *syn*-**43** and *anti*-**43**. Analysis of the X-ray crystal structure of the major product (*syn*-**43**) established the stereochemistry between the siloxy group at C4 and the methylene bridge (C11). The regio- and stereochemistry of the minor product (*anti*-**43**) was established via ^{1}H NMR techniques (see Table 4). Efforts to enhance the diastereoselectivity by generating the acyl nitroso intermediate at lower temperature was not attempted.

Inspection of the X-ray crystal structure of oxazinolactam **6** also revealed a close contact (2.3 Å) between the *endo* proton at C11 and the *syn* hydrogen at C5. To test this, 4-benzyloxyhydroxamic acid **48** was targeted for synthesis (Scheme 12). Enantioselective isoprenylation[31] of 4-(*tert*-butyldimethylsiloxy)-butanal[32] **44** with diisopinocamphenylborane **45** gave homoallylic alcohol (*R*)-**46** in 54% yield and 92% ee.[33] Protection of the resulting alcohol as a benzyl ether followed by removal of the silyl protecting group and Jones oxidation afforded carboxylic acid **47**. Esterification (MeI, K_2CO_3, acetone) followed by treatment with hydroxylamine under basic conditions furnished hydroxamic acid **48**. Subsequent oxidation of Diels–Alder precursor **48** with *n*-Bu_4NIO_4 in $CHCl_3$ at 0 °C provided two diastereomers in a 3.7:1 ratio favoring *syn*-**49** in 84% combined yield. Separation of the two cycloadducts was accomplished utilizing preparative TLC eluting with $CHCl_3$/EtOAc (9:1).

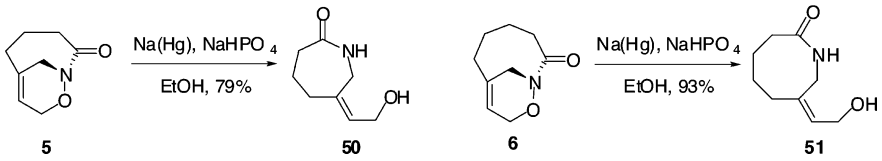
In contrast with the 2-substituted Diels–Alder precursor, substitution at position C4 of hydroxamic acid **48** induced a bias in the cycloaddition favoring the formation of *syn*-**49**. This observed diastereoselectivity is opposite to that predicted on the basis of the structure of the cycloadduct and calls attention to the limitation of this model.

E. Functionalization of Bicyclo[n.3.1]oxazinolactams. Stereoselective Synthesis of Medium Ring Lactams. Selective reduction of the C=C or N–O bond in bridged oxazinolactams would enhance the synthetic utility of these intermediates. However, the increased reactivity of bridgehead olefins could compromise the ability to selectively cleave the bridgehead nitrogen–oxygen bond. We therefore set out to establish conditions for the chemoselective reduction of the bridgehead double bond and nitrogen–oxygen bond.

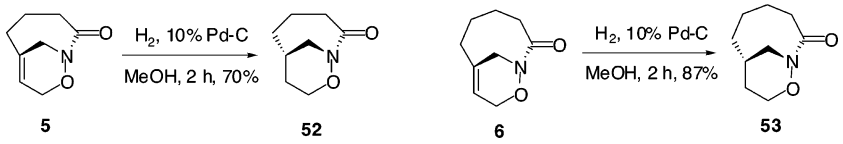
Treatment of cycloadducts **5** and **6** with reagents employed for the cleavage of nitrogen–oxygen bonds

(29) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007–4016.
(30) Bertele, E.; Schudel, P. S. *Helv. Chim. Acta* **1967**, *50*, 2445–2456.
(31) (a) Brown, H. C.; Randad, R. *Tetrahedron* **1990**, *46*, 4463–4472. (b) Brown, H. C.; Randad, R. *Tetrahedron Lett.* **1990**, *31*, 455–458.
(32) Tori, M.; Toyoda, N.; Sono, N. *J. Org. Chem.* **1998**, *63*, 306–313.
(33) Determined as (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetate (MTPA) derivative on capillary GC.

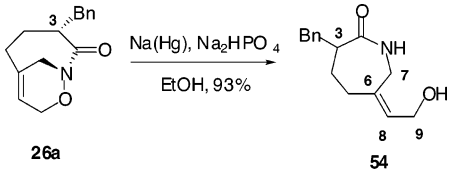
SCHEME 13. Reduction of Oxazinolactams 5 and 6



SCHEME 14. Catalytic Hydrogenation of Oxazinolactams 5 and 6



SCHEME 15. Reduction of Oxazinolactam 26a



including SmI_2[35] and $Mo(CO)_6$[36] furnished complex reaction mixtures with low yields of the desired lactams. However, treatment of compounds **5** and **6** with sodium amalgam[34] in EtOH provided the seven- and eight-membered lactams, **50** and **51**, in 79% and 93% yield, respectively. The stereochemistry of the trisubstituted double bond of compounds **50** and **51** was verified by NOE experiments (Scheme 13).

With an efficient method for nitrogen−oxygen bond cleavage of bridged bicycles **5** and **6** identified, reduction of the bridgehead double bond was investigated. Treatment of bridgehead olefin **5** with H_2 over 10% Pd−C in MeOH for 2 h resulted in a 70% yield of saturated bicycle **52** (Scheme 14).[37−39] Catalytic hydrogenation of cycloadduct **6** under identical conditions afforded an 87% yield of saturated [5.3.1] bicycle **53**. No N−O bond cleavage was observed.

With methods for the chemoselective reduction of the bridgehead functional groups secured, functionalization of bicyclo[4.3.1] and bicyclo[5.3.1] oxazinolactams was explored. The synthesis of **54** was undertaken to evaluate this approach (Scheme 15). Reduction of cycloadduct **26a** using Na(Hg) amalgam induced cleavage of the N−O bond and provided caprolactam **54**. Evidence that supports the assignment of Z configuration in **54** includes NOE studies where the two protons at C5 displayed 1.1% and 2.3% enhancement upon irradiation of the vinylic C8 hydrogen. Enhancement of the protons at C9 ranging from 1.7% to 3.3% was also observed when each of the C7 protons was individually irradiated. The liberation of caprolactam **54** highlights the utility of employing [4.3.1] bridged bicyclic oxazinolactams as a platform for building complex substituted medium ring lactams.

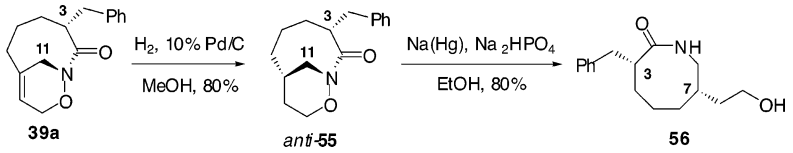
Changing the sequence of reductions allows elaboration of cycloadduct **39a** to an azocin-2-one (Scheme 16). Catalytic hydrogenation of cycloadduct **39a** afforded saturated bicyclic oxazinolactam *anti*-**55** in 80% yield.[37] Dissolving metal reduction (Na(Hg), Na_2HPO_4, EtOH) of *anti*-**55** induced cleavage of the nitrogen−oxygen bond and provided a *cis*-3,7-disubstituted azocin-2-one (**56**) as a *single diasteomer* in 80% yield.

Assignment of the *cis* configuration in **56** from reduction of *anti*-**55** is based on the assumed configurational integrity of the stereocenters at C3 and C7 during cleavage of the N−O bond. The structure of azocin-2-one **56** was suggested by the presence of hydroxyethyl and benzyl fragments in the ^{1}H NMR. In addition, when lactam **56** was subjected to CIMS, a molecular ion involving loss of 45 amu was observed, consistent with the fragmentation of a -CH_2CH_2OH group. These results establish that formation of **56** derived from elaboration of a bicyclo[5.3.1] adduct (1,3-regioisomer), oxazinolactam **39a**.

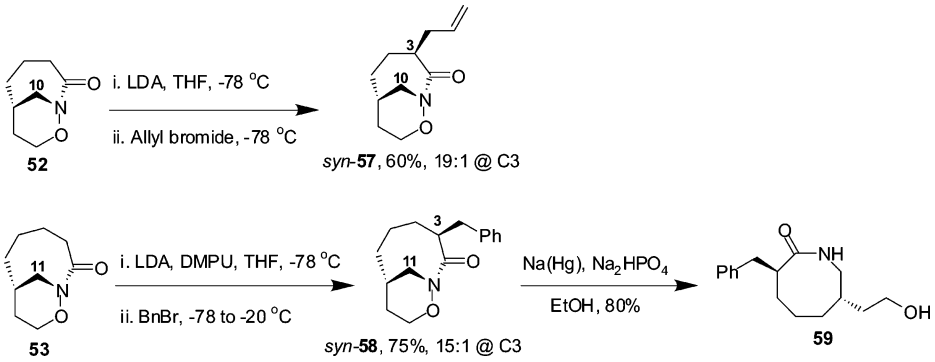
Complementary routes to diastereomeric lactams are achieved by functionalization either before or after cycloaddition. The method also provides further verification of the structures of oxazinolactams *anti*-**30** and *anti*-**34** by comparison of their spectral properties to their *syn* counterparts (*syn*-**57** and *syn*-**58**) synthesized from saturated bicycles **52** and **53**, respectively (Scheme 17). Alkylation of oxazinolactams **52** via enolization (LDA, THF, −78 °C) followed by addition of allylbromide afforded alkylated oxazinolactam in 62% yield as a 19:1 ratio of separable diastereomers. Confirmation of the stereochemistry of the major diasteromer (*syn*-**57**) was verified by NOE analysis. Irradiation of the C10 hydrogen at 2.56 ppm resulted in enhancement of the methylene protons of the benzyl group at 3.86 (1.9%) and 2.33 (2.0%) ppm. This is consistent with alkylation of **52** from the more exposed *exo* face. Analogous results were observed when bicycle **53** was exposed to LDA and DMPU in THF at −78 °C followed by treatment with benzyl bromide. The major product (*syn*-**58**) from a mixture of diastereomers in 15:1 ratio was isolated and was found to have the benzyl group in a *syn* stereochemical relationship to the C11 methylene bridge. See Supporting Information

(34) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281−286.
(35) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755−11772.
(36) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; DeSarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.
(37) Addition to bridgehead olefins occurs with complete *exo*-facial selectivity. See: (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683−1715. (b) Shea, K. J.; Beauchamp, P. S.; Lind, R. S. *J. Am. Chem. Soc.* **1980**, *102*, 4544−4546. (c) Shea, K. J.; Fruscella, W. M.; Carr, R. C.; Burke, L. D.; Cooper, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 447−452. (d) Whitney, J. M.; Parnes, J. S.; Shea, K. J. *J. Org. Chem.* **1997**, *62*, 8962−8963.
(38) (a) Gwaltney, S. L.; Sakata, S. T.; Shea, K. J. *J. Org. Chem.* **1996**, *61*, 7438−7451. (b) Shea, K. J.; Sakata, S. T. *Tetrahedron Lett.* **1992**, *33*, 4261−4264.
(39) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *Organometallics* **1996**, *15*, 1518−1520.

SCHEME 16. Formation of Azocin-2-one 56 by Reduction of Oxazinolactam 39a



SCHEME 17. Functionalization of Oxazinolactams 52 and 53



for NOE data. The stereoselectivity of these two reactions are consistent with alkylation of related bridged bicyclic carbocycles.[36] A *trans*-3,7-disubstituted azocin-2-one **59** was produced in 80% yield as a *single stereoisomer* upon cleavage of the N–O bond in *syn*-**58** using Na(Hg) amalgam.

Conclusion

The preceding studies demonstrate the scope of the type 2 intramolecular *N*-acylnitroso Diels–Alder reaction. The reaction has been shown to afford both [4.3.1] and [5.3.1] bridged oxazinolactams in high yield with complete control over regiochemistry. Structural studies of the two bicyclic oxazinolactams allow quantification of the deformations associated with these novel bicyclic compounds and provided a rational for the diastereoselective cycloadditions of substituted Diels–Alder precursors. These compounds have been elaborated to provide diastereoselective syntheses of medium ring lactams. The preparation of *cis*- and *trans*-3,7-disubstituted azocin-2-ones exemplifies the utility of this method for complex stereoselective heterocyclic synthesis. Applications of this reaction in natural product synthesis are the focus of current investigations, the results of which will be reported in due course.

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Supporting Information Available: Full experimental conditions and copies of ^{1}H and ^{13}C spectra for **3a**–**9**, **13**–**17**, **24a**–**26b**, **28**–**39**, **42**, **43**, and **46**–**59** and X-ray crystallographic data for **5**, **6**, **8**, and *syn*-**43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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