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Type 2 Intramolecular *N*-Acylazo Diels−Alder Reaction: Regio- and Stereoselective Synthesis of Bridgehead Bicyclic 1,2-Diazines

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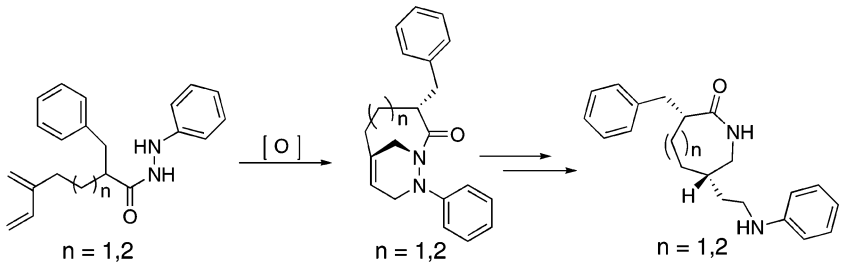

The type 2 intramolecular *N*-acylazo Diels−Alder reaction provides a regio- and stereoselective synthesis of bicyclic 1,2-diazine systems. A new method for the generation of *N*-acylazo dienophiles with tetra-*n*-butylammonium periodate is reported. X-ray crystallographic analysis allowed the quantification of structural distortions of the nonplanar bridgehead olefin and lactam functionalities in 1,2-diazine cycloadducts **11** and **15**. Caprolactams and enantholactams were formed by stereoselective bridgehead alkene reduction, a process that transfers stereochemistry from the bridgehead lactam nitrogen to the bridgehead carbon. The sequence of transformations offers a convenient route for the diastereoselective synthesis of medium-ring nitrogen heterocycles and 1,4-diamines.

Introduction

Nitrogen-containing heterocycles are ubiquitous in nature. Their importance has led to an ongoing search for selective and efficient methods for their preparation.[1,2] The type 2 intramolecular Diels−Alder (T2IMDA) reaction has served as a useful reaction to assemble polycyclic compounds in a single step from acyclic precursors.[3] In many cases, the reaction offers complete regio- and stereochemical control in the cycloaddition step. More recently, the heteroatom variant of the T2IMDA reaction with *N*-acylimine and *N*-acylnitroso dienophiles was employed for the synthesis of bridgehead bicyclic lactams and oxazinolactams (Scheme 1, eqs 1 and 2).[3−5] As part of our ongoing interest in the synthesis of nitrogen-containing heterocyclic ring systems, we report T2IMDA reaction with *N*-acylazo dienophiles (Scheme 1, eq 3).

Despite numerous reports utilizing acyclic or cyclic azodicarboxylates as dienophiles in Diels−Alder[6] reactions, there are relatively few examples of intramolecular variants[7] of this reaction (Scheme 1). The development of the T2IMDA reaction

(1) (a) Evans, P. A.; Holmes, B. *Tetrahedron*. **1991**, *47*, 9131−9166. (b) Miller, E. D.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2007**, *72*, 323−330.

(2) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Snyder, J. P.; Springer, J. P.; Hirshfield, J.; Tristram, E. W.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem*. **1986**, *29*, 251−260.

(3) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 820−849.

(4) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc*. **1993**, *115*, 2248−2260.

(5) (a) Sparks, S. M.; Vargas, J. D.; Shea, K. J. *J. Org. Lett*. **2000**, *2*, 1473−1475. (b) Chow, C. P.; Shea, K. J.; Sparks, S. M. *J. Org Lett*. **2002**, *4*, 2637−2640. (c) Sparks, S. M.; Chow, C. P.; Zhu, L.; Shea, K. J. *J. Org. Chem*. **2004**, *69*, 3025−3035.

(6) (a) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087−3128. (b) Franzus, B.; Surridge, J. H. *J. Org. Chem*. **1962**, *27*, 1951−1957. (c) Gillis, B. T.; Weinkam, R. *J. Org. Chem*. **1967**, *32*, 3321−3325. (d) Kealy, T. J. *J. Am. Chem. Soc*. **1962**, *84*, 966−973. (e) Gillis, B. T.; Beck, P. E. *J. Org. Chem*. **1962**, *27*, 1947−1951. (f) Johnson, M. P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. I* **1985**, 71−74. (g) Ahern, M. F.; Leopold, A.; Beadle, J. R.; Gokel, G. W. *J. Am. Chem. Soc*. **1982**, *104*, 548−554. (h) Pindur, U.; Kim, M.; Rogge, M.; Massa, W.; Molinier, M. *J. Org. Chem*. **1992**, *57*, 910−915. (i) Nugiel, D. A.; Decicco, C. P.; Nelson, D. J.; Copeland, R. A.; Hardman K. D. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 3053−3056. (j) Cohen, S. G.; Zand, R.; Steel, C. *J. Am. Chem. Soc*. **1961**, *83*, 2895−2899. (k) Aburel, P. S.; Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Org. Biomol. Chem*. **2005**, *3*, 2344−2349. (l) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (m) Kawasaki, M.; Yamamoto, H. *J. Am. Chem. Soc*. **2006**, *128*, 16482−16483.

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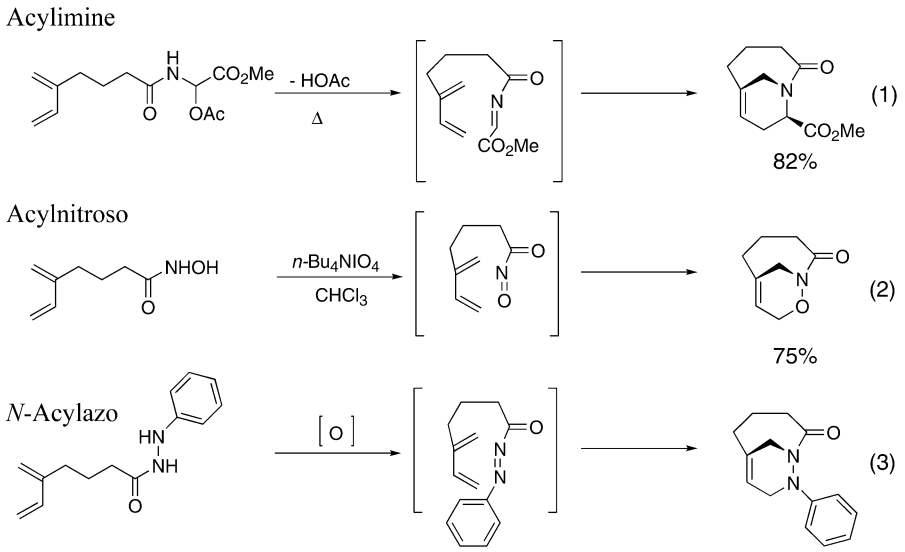
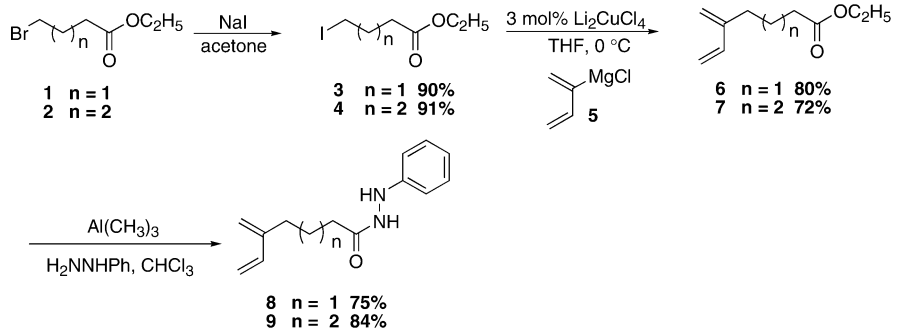
SCHEME 1. Examples of the Hetero Type 2 Intramolecualr Diels−Alder Reaction



SCHEME 2. Synthesis of Hydrazides 8 and 9



with *N*-acylazo dienophiles would allow the rapid assembly of bridgehead bicyclic 1,2-diazines with regio- and stereochemical control. The intermediates would offer the potential for the synthesis of seven- and eight-membered nitrogen-containing heterocyclic ring systems as well as the stereoselective synthesis of 1,4-diamines.

Results and Discussion

Synthesis of the Diels−Alder Precursors. The synthesis of T2IMDA reaction precursors began from the commercially available ethyl 4-bromobutyrate (**1**) (Scheme 2). The corresponding iodoester **3**[8] was prepared by halide exchange with NaI in acetone. In the presence of 3 mol % of Li_2CuCl_4, the coupling reaction of iodoester **3**[8] with chloroprene Grignard (**5**)[9] afforded ester **6**.[5] This synthetic sequence was subsequently applied to the synthesis of diene ester **7**[5] from commercially available ethyl 5-bromovalerate (**2**) in 66% overall yield. The acylation reaction of ester **6** or **7** with phenylhydrazine and Al$(CH_3)_3$[10] afforded hydrazides **8** and **9** in 75% yield and 84% yield, respectively (Scheme 2).

Type 2 Intramolecular *N*-Acylazo Diels−Alder Reaction. Having established a viable route to the Diels−Alder precursors, we next examined oxidation conditions to form the *N*-acylazo dienophiles. The reactivity of the *N*-acylazo functional group toward thermal decomposition and cycloaddition was not known; therefore a search for mild reaction conditions was undertaken. Typically, *N*-acylazo dienophiles are generated by oxidation of *N*-acylhydrazides with *tert*-butylhypochlorite,[11] lead tetraacetate,[12] or potassium ferricyanide.[13] Oxidation of hydrazide **8** with $Pb(OAc)_4$ resulted in a complex mixture of products. The heterogeneous oxidation of hydrazide **8** with $K_3Fe(CN)_6$ and catalytic 2,4,6-triphenylphenol (1 mol %) in 2 N NaOH gave cycloadduct **11** in 65% yield. The oxidation presumably produced *N*-acylazo dienophile **10**, which underwent intramolecular Diels−Alder cycloaddition under the reaction conditions. Despite the acceptable result, the harsh basic conditions limited the general utility of this method. Parallels in structure between hydroxamic acids and hydrazides suggested that *n*-Bu_4NIO_4, a reagent used to oxidize hydroxamic acids to the *N*-acyl nitroso[5] intermediate, could be employed for the synthesis of *N*-acylazo derivatives (Scheme 1). Indeed, oxidation

(7) (a) Kahn, M.; Wilke, S.; Chen, B.; Fujita, K. *J. Am. Chem. Soc.* **1988**, *110*, 1638−1639. (b) Sheradsky, T.; Milvitskaya, J.; Pollak, I. E. *Tetrahedron Lett.* **1991**, *32*, 133−136.

(8) (a) Tok, J. B.-H.; Cho, J.; Rando, R. R. *Tetrahedron* **1999**, *55*, 5741−5758. (b) Frick, J. A.; Thompson, C. M. *J. Org. Chem.* **1989**, *54*, 890−896.

(9) (a) Shea, K. J.; Pham, P. Q. *Tetrahedron Lett.* **1983**. *24*, 1003−1006. (b) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303−305.

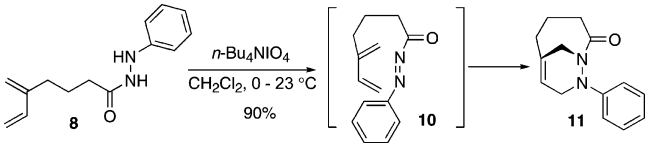
(10) (a) Stavchansky, S.; Benderly, A. *Tetrahedron Lett.* **1988**, *29*, 739−740. (b) Licandro, E.; Perdicchia, D. *Eur. J. Org. Chem.* **2004**, 665−675.

(11) (a) Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett.* **1962**, *14*, 614−618. (b) Amezua, M. G.; Lora-Tamayo, M.; Soto, J. L. *Tetrahedron Lett.* **1970**, *27*, 2407−2408.

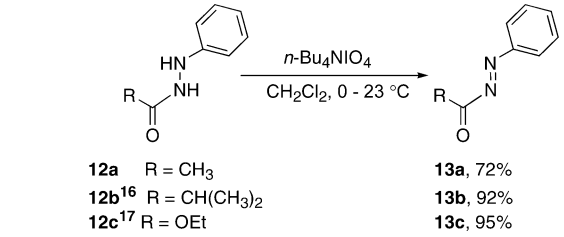
(12) (a) Gillis, B. T.; Hagarty, J. D. *J. Org. Chem.* **1967**, *32*, 330−333. (b) Tawil, B. F.; Guggisberg, A.; Hesse, M. *Tetrahedron* **1992**, *48*, 3375−3780. (c) Amarasekara, A.; Chandrasekara, S. *Org. Lett.* **2002**, 4, 773−775. (d) Clement, R. A. J. *Org. Chem.* **1960**, *25*, 1724−1727. (e) Criegge, R. Oxidation with lead tetracetate. In *Oxidation in Organic Chemistry*; Wiberg, K.B., Ed.; Academic Press: New York, 1965.

(13) Dimroth, K.; Tuncher, W. *Synthesis* **1977**, *5*, 339−340.

SCHEME 3. Type 2 Intramolecular Diels−Alder Reaction with *N*-Acylazo Dienophiles 10



SCHEME 4. Oxidation Reaction of Hydrazides with *n*-Bu_4NIO_4

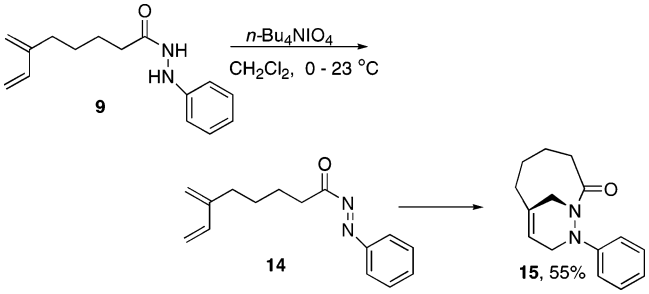


of *N*-acyl hydrazide **8** proceeded smoothly with 1.3 equiv of *n*-Bu_4NIO_4 in CH_2Cl_2 to form the *N*-acylazo Diels−Alder precursor **10**. Subsequently, compound **10** underwent cycloaddition under these reaction conditions to afford bicyclic 1,2-diazine **11** in 90% yield (Scheme 3). Diels−Alder reactions carried out in water have displayed a significant rate acceleration.[14] In the presence of 20 mol % of water in THF, cycloadduct **11** was obtained in 63% yield after 40 h. Interestingly, the oxidation of hydrazide **8** was completed after 5 h and was not inhibited by water; however, the slow rate of the cycloaddition allowed the decomposition of the *N*-acylazo intermediate **10**.

To the best of our knowledge the oxidation reaction of hydrazides by this method is unprecedented. Intrigued by the oxidation of hydrazide **8** with *n*-Bu_4NIO_4, the generality of this reagent with other hydrazides was examined. Representative examples for this transformation are shown in Scheme 4.[15] Subjecting hydrazides to 1.3 equiv of *n*-Bu_4NIO_4 in CH_2Cl_2 afforded *N*-acylazo substrates in high yield. This method provides an alternative procedure for the oxidation of hydrazides and hydrazines.[15] *n*-Bu_4NIO_4 exhibits functional group tolerance that is lacking in other reagents.

Although oxidation and subsequent intramolecular cycloaddition reaction of hydrazide **8** was complete after 24 h (Scheme 3), the oxidation of hydrazide **9** followed by intramolecular Diels−Alder reaction of *N*-acylazo dienophile **14** proceeded slowly (Scheme 5). It was established by the ^1H NMR spectrum of the reaction mixture that the periodate oxidation reaction of hydrazide **9** generated the *N*-acylazo dienophile species after 3 h. However, the cyclization step proceeded relatively slowly affording bicyclic 1,2-diazine **15** in only 55% yield after 60 h. Attempts to isolate the *N*-acylazo derivative **14** by chromatographic techniques (SiO_2, Al_2O_3, and deactivated SiO_2) were

SCHEME 5. Type 2 Intramolecular Diels−Alder Reaction of *N*-Acylazo Dienophile 14



SCHEME 6. Oxidation Reaction of Hydrazide 9

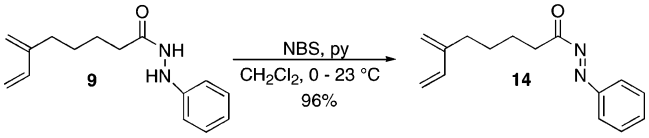
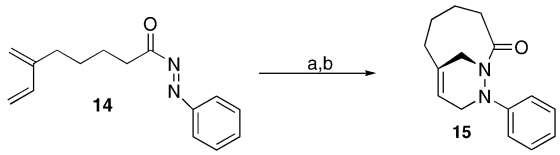


TABLE 1. T2IMDA Reaction of *N*-Acylazo Dienophile 14



entry	temp (°C)	time (h)	yield (%)
1	23	60	45−55
2	40	10	58
3	60	4	mixture
4	80	4	mixture

[a] Benzene solvent. [b] Concentration 0.010 M.

unsuccessful. This was attributed to the instability of the *N*-acylazo dienophile **14**. Efforts to accelerate the cycloaddition by heating the reaction mixture to 50 °C resulted in decomposition of the remaining *N*-acylazo intermediate. The presence of both **14** and **15** in the reaction mixture and the instability of intermediate **14** resulted in low isolated yields. These results suggested that the problem was not due to the oxidation step but rather the relative low stability and slow rate of cycloaddition of the *N*-acylazo dienophile **14**.

To overcome this problem a different set of conditions was required for the generation and isolation of *N*-acylazo derivative **14**. Using a protocol described by Evans and co-workers,[18] we found that treating hydrazide **9** with NBS and pyridine in CH_2Cl_2 for 2 h at 0−23 °C resulted in *N*-acylazo dienophile **14** in 96% yield (Scheme 6). Under these reaction conditions cycloadduct **15** was not observed.

This result provided an opportunity to examine the cycloaddition reaction of *N*-acylazo dienophile **14** under both thermal and Lewis acid-catalyzed conditions. Efforts to thermally induce cycloaddition are summarized in Table 1. *N*-Acylazo dienophile **14** was found to be unstable at temperatures >40 °C in benzene. At these elevated temperatures, the reaction generated a complex

(14) (a) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem*. **1983**, *48*, 3137−3139. (b) Lindstrom, U. M. *Chem. Rev*. **2002**, *102*, 2751−2772.

(15) To further demonstrate the scope and efficiency of tetra-*n*-butylammonium periodate, we examined the oxidation reaction of 1,2-diphenylhydrazine, 4-phenylurazole, 1,2-dibenzoylhydrazine and *sym*-dicarbethoxyhydrazine. Azobenzene was isolated in 88% yield. The oxidation of 4-phenylurazole with tetra-*n*-butylammonium proceeded smoothly to provide 4-phenyl-1,2,4-triazoline-3,5-dione, which was trapped with cyclohexadiene to afford the cycloadduct in 93% yield. The oxidation reaction of 1,2-dibenzoylhydrazine, and *sym*-dicarbethoxyhydrazine was not successful. See the Supporting Information for experimental procedures and spectroscopic data.

(16) Hearn, M. J.; Grimwade, J. E. *Dep. Chem. Org. Prep. Proced. Int.* **1980**, *12*, 249−51.

(17) Bausch, M. J.; David, B.; Dobrowolski, P.; Guadalupe-Fasano, C.; Gostowski, R.; Selmarten, D.; Prasad, V.; Vaughn, A.; Wang, L. H. *J. Org. Chem*. **1991**, *56*, 5643−51.

(18) Evans, D. A.; Johnson, D. S. *Org. Lett*. **1999**, *1*, 595−598.

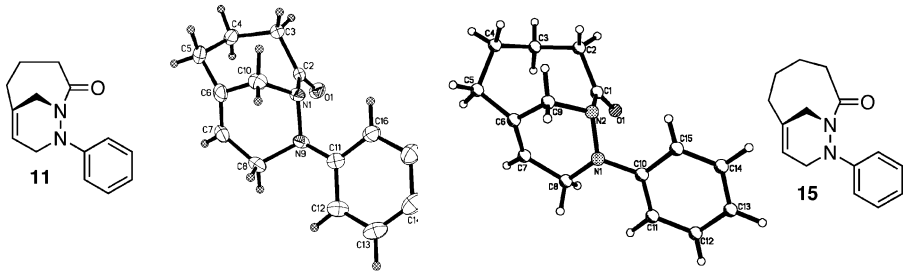
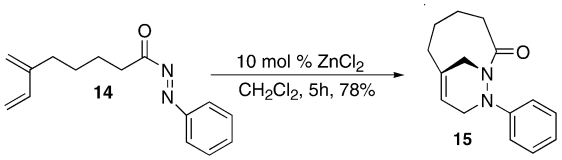


FIGURE 1. ORTEP plots of cycloadducts **11** and **15** at the 50% probability level.

SCHEME 7. Lewis Acid-Catalyzed T2IMDA Reaction of *N*-Acylazo Dienophile 14



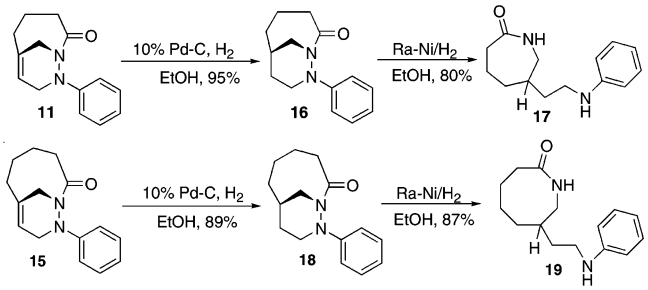
mixture of products; cycloadduct **15** was not observed. The best results were obtained at 40 °C, producing cycloadduct **15** in 58% yield.

The thermal route did not offer any improvement to the cycloaddition reaction of *N*-acylazo dienophile **14**. We next turned our attention to Lewis acid catalysis. It was found that the cycloaddition of *N*-acylazo dienophile **14** proceeded smoothly in the presence of 10 mol % of $ZnCl_2$ in CH_2Cl_2 after 5 h to afford cycloadduct **15** in 78% yield (Scheme 7). The two-step protocol of oxidation and subsequent Lewis acid-catalyzed cycloaddition proved to be the most efficient method for the synthesis of cycloadduct **15**. Significantly, this result provides a new method for the Lewis acid-catalyzed Diels−Alder reaction of azo compounds, as the examples of Lewis acid-catalyzed Diels−Alder reaction of azo compounds are limited in the literature.[6l,m]

X-ray Crystallography of the Cycloadducts. X-ray crystallographic studies of cycloadducts **11** and **15** reveal structural distortions from the optimal planar olefin and lactam geometry. These distortions are expressed as torsional deformation and are quantified by the angle τ, a value determined from the calculated projection of the two p-orbitals.[3−5] The p-orbital overlap in the π bond is presumed to be optimal with $\tau = 0.0°$ and lowest at $\tau = 90.0°$. The torsion angle τ is not directly measured but can be calculated from the X-ray crystallographic data.[19] Torsional distortions (τ) calculated for bridgehead olefins **11** and **15** are 5.48° and 3.65°, respectively, with a slightly larger value of τ for the smaller bridgehead alkene **11**. Interestingly, the torsional distortion quantified in bridgehead olefins **11** and **15** has little effect on the observed C═C bond lengths. The double bond distances for bridgehead olefins **11** and **15** are 1.3339(15) and 1.3327(16) Å, respectively, and are within error of the value for cyclohexene (1.335(3) Å).[5]

Analysis of the amide linkage of **11** and **15** shows significant differences in torsional deformation. For bridgehead lactam **11** the torsional distortion is $\tau = 0.745(10)°$ and for **15** $\tau = 17.56(13)°$. It is likely that the somewhat surprising inverse relationship between ring size and τ results from compression in accommodating the five atom bridge in cycloadduct **15**. The absence of correlations between bridge size and torsional distortions was previously observed in a series of bridgehead lactams.[4]

SCHEME 8. Synthesis of Lactams 17 and 19



The C−N bond length for bridgehead lactam **15** is slightly longer (1.4013(14) Å) than that of bridgehead lactam **11** (1.3941(13) Å). In contrast, the C═O bond distance of bridgehead lactam **11** (C═O = 1.2163(12) Å) and bridgehead lactam **15** (C═O = 1.2198(13)Å) is not sensitive to the difference in τ values.

Functionalization of Bicyclic 1,2-diazines. To examine the chemical behavior of the bicyclic 1,2-diazines, a series of transformations were carried out that include reduction of the bridgehead double bond and hydrogenolysis of the N−N bond. When carried out in this order, this sequence transfers stereochemistry from the bridgehead nitrogen to the sp^3 bridgehead carbon. The reduction of the bridgehead double bond in cycloadducts **11** and **15** was achieved by catalytic hydrogenation in the presence of 10% Pd/C in EtOH to give the saturated cycloadduct **16** in 95% yield and **18** in 89% yield (Scheme 8). Several methods have been reported for the N−N bond cleavage including reduction by zinc in acetic acid,[20] SmI_2,[21] and Raney/Ni.[22] The most effective method for the cleavage of the N−N bond resulted from the treatment of compounds **14** and **18** with Raney/Nickel in ethanol to afford 6-substituted caprolactam **17** in 80% yield and 7-substituted enantholactam **19** in 87% yield, respectively. This method provides a convenient route for the synthesis of seven- and eight-member nitrogen-containing heterocyclic ring systems.

π-Facial Selectivity in the T2IMDA Reaction. Analysis of the X-ray crystal structure of cycloadduct **11** revealed a distance of 2.18 Å between the *endo* hydrogen at C10 and the *exo*

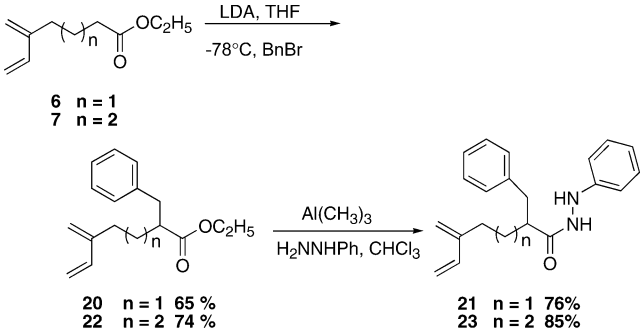
(19) The torsional angle (τ) was determined by summing the four atom torsion angles YC1C2W (Φ1) and ZC1C2 (Φ2) and dividing the result by 2 ($\tau = (\Phi1 + \Phi2)/2$).

(20) Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. I* **1984**, 2927−2931.

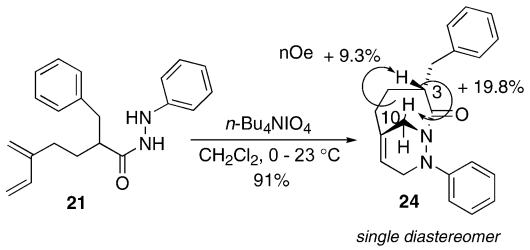
(21) (a) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637−640. (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem.* **1992**, *114*, 6266−6267.

(22) (a) Grabowski, S.; Armbruster, J.; Prinzback, H. *Tetrahedron Lett.* **1997**, *38*, 5485−5488. (b) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219−6223. (c) Ghelfi, F. J. *Org. Chem.* **2000**, *65*, 6249−6253. (d) Hsieh, Y.; Lee, G.; Luh, T. *J. Org. Chem.* **1998**, *63*, 1484−1490. (e) Martin, S.; Hom, R. K. *Tetrahedron Lett.* **1999**, *40*, 2887−2890.

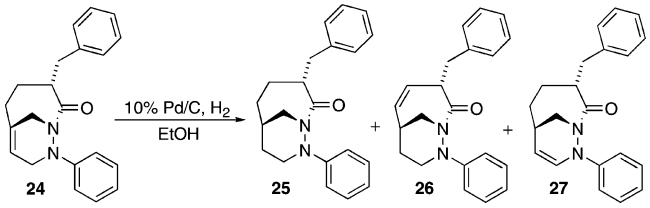
SCHEME 9. Synthesis of Hydrazide 21 and 23



SCHEME 10. Diastereoselective T2IMDA Reaction of Hydrazide 21



SCHEME 11. Catalytic Hydrogenation of Cycloadduct 24

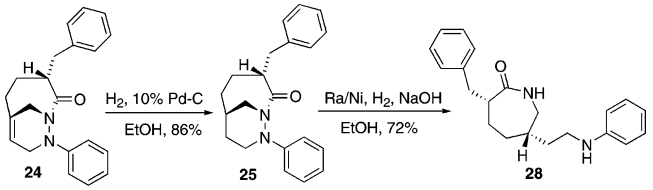


hydrogen at C3 (Figure 1). On the basis of previous studies[5] with *N*-acylnitroso dienophiles, we anticipated that π-facial selectivity of the T2IMDA reaction with *N*-acylazo dienophiles would be influenced by the introduction of substituents on the tether at α-position of the Diels−Alder precursor. To evaluate the π-facial selectivity in cycloaddition precursors that incorporate substituents at the α-position, two derivatives were synthesized (Scheme 9). The synthesis of the α-benzylated esters **20**[5] and **22** was achieved by deprotonation of ester **6** or **7** with LDA, followed by alkylation with benzyl bromide to afford the α-substituted ester derivative **20**[5] in 65% yield and ester **22** in 74% yield. The coupling reaction of ester **20** or **22** with phenylhydrazine and $Al(CH_3)_3$ provided hydrazide **21** and **23** in 76% yield and 85% yield, respectively.

Under optimized reaction conditions with *n*-Bu_4NIO_4, the oxidation of hydrazide **21** generated the *N*-acylazo dienophile *in situ*, which underwent intramolecular cycloaddition to afford cycloadduct **24** after 24 h in 91% yield. The product consisted of a single diastereomer as determined by ^{1}H NMR analysis of the crude reaction mixture. The *endo* diastereomer **24** was established by NOE analysis (Scheme 10).

Addition of hydrogen to the bridgehead double bond, which occurs in a *syn-exo* matter, transfers the stereochemistry of the bridgehead nitrogen to the bridgehead carbon.[3] However, hydrogenation of cycloadduct **24** in the presence of 10% Pd/C and H_2 resulted in a mixture of products that included saturated cycloadduct **25** (68%), **26** (23%), and **27** (2%) (Scheme 11). Bridgehead alkene isomerization competes with hydrogenation

SCHEME 12. Catalytic Hydrogenation and N−N Bond Cleavage of Cycloadduct 24



resulting in formation of alkenes with less strain than the starting material.

Complete hydrogenation of the bridgehead alkene **22** was achieved in the presence of 10% Pd/C under high pressure (50 psi) to afford saturated cycloadduct **25** in 86% yield. Following hydrogenation the *cis*-3,6-disubstituted caprolactam **28** was prepared by a reductive N−N bond cleavage with use of Ra/Ni and 1 N NaOH under H_2 in 72% yield.

The synthesis of *N*-acylazo dienophile **29** was achieved by using NBS and pyridine in 92% yield. Subsequently, the intramolecular cycloadditon of *N*-acylazo dienophile **29** proceeded smoothly in the presence of $ZnCl_2$ to afford cycloadduct **30**. Only a single *endo* diastereomer was observed in the ^{1}H NMR spectrum of the crude reaction mixture and the stereochemistry of cycloadduct **30** was established by NOE experiments. Cycloadduct **30** was subjected to a catalytic hydrogenation at 50 psi in the presence of 10% Pd/C to produce saturated bicyclic 1,2-diazine **31** in 90% yield. The stage was now set for the synthesis of *cis*-3,7-disubstituted enantholactam **32**, which was achieved in 77% yield by reductive N−N bond cleavage with Raney/Nickel.

Conclusion

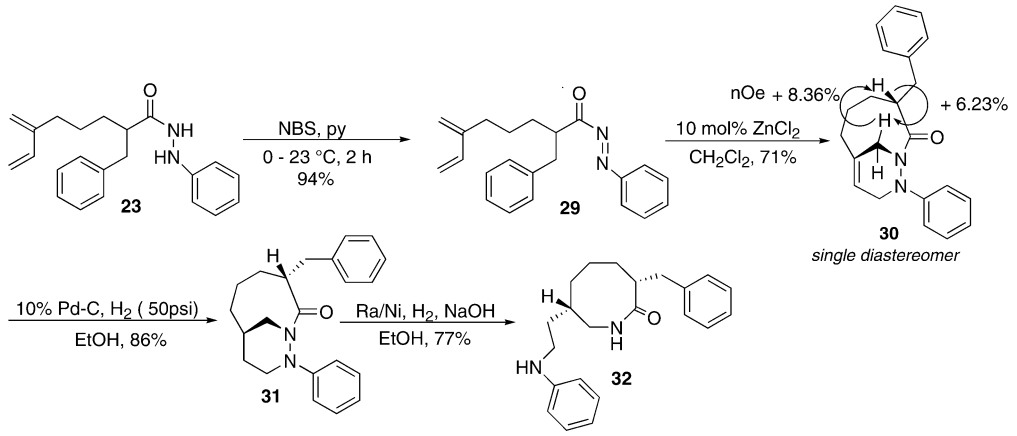
In summary, we have developed the type 2 intramolecular Diels−Alder reaction with *N*-acylazo dienophiles for the regio- and stereoselective synthesis of bicyclic 1,2-diazines. In the course of our investigation, a new reagent was identified for the oxidation of hydrazides. X-ray crystallographic analysis allowed the quantification of structural distortions of the nonplanar bridgehead olefin and lactam functionalities in cycloadducts **11** and **15**. The T2IMDA reaction with *N*-acylazo dienophiles, incorporating substituents at the α-position, underwent stereoselective cycloaddition. These cycloadducts were subsequently elaborated to caprolactams and enantholactam derivatives.

Experimental Section

General Procedure for Preparation of the Hydrazides.[10] To a solution of phenylhydrazine (2.0 equiv) in $CHCl_3$ was added $Al(CH_3)_3$ (2.0 equiv, 2.0 M solution in toluene) dropwise. The reaction mixture was stirred at room temperature for 1 h and diene ester (1 equiv) was added dropwise. After 10 h (TLC monitoring), the reaction mixture was cooled to 0 °C and then carefully poured into a solution of HCl (2 N) then the solution was allowed to stir for 30 min. The aqueous layer was separated and extracted with 3 portions of $CHCl_3$. The combined organic extracts were washed with H_2O, dried with Na_2SO_4, and concentrated to give a pale yellow oil.

5-Methylenehept-6-enoic Acid *N*′-Phenylhydrazide (8). Diene ester **6**[5] (1.08 g, 6.42 mmol) was added dropwise to a solution of phenylhydrazine (1.39 g, 12.8 mmol) in $CHCl_3$ (50 mL) and $Al(CH_3)_3$ (6.4 mL in toluene, 2.0 M). The crude product was purified by flash column chromatography (1:2 EtOAc:hexanes) to afford

SCHEME 13. Diastereoselective T2IMDA Reaction of Hydrazide 23



hydrazide **8** (1.12 g, 75% yield): ^{1}H NMR (500 MHz, $CDCl_3$) for major rotamer δ 7.28 (d, J = 7.6 Hz, 1H), 7.26 (app t, J = 8.2 Hz, 2H), 6.93 (app t, J = 7.4 Hz, 1H), 6.84 (app d, J = 7.8 Hz, 2H), 6.38 (dd, J = 17.6, 10.8 Hz, 1H), 6.15 (d, J = 3.7 Hz, 1H), 5.26 (d, J = 17.8 Hz, 1H), 5.11 (d, J = 10.9 Hz, 1H), 5.07 (s, 1H), 5.02 (s, 1H), 2.32−2.28 (m overlapped, 4H), 1.93 (m, 2H); IR (thin film) ν_{max} 3258, 1654, 1598, 1498; ^{13}C NMR (125 MHz, CD_3OD) δ 175.9, 150.1, 147.3, 139.9, 130.3, 121.2, 116.7, 114.2, 114.1, 34.7, 32.2, 25.7; HRMS (ES) m/z calcd for $C_{14}H_{18}N_2O$ [M + Na]$^+$ 253.1317, found 253.1307.

6-Methyleneoct-7-enoic Acid *N*′-Phenylhydrazide (9). Diene ester **7**[5] (3.26 g, 17.9 mmol) was added dropwise to a solution of phenylhydrazine (3.87 g, 35.8 mmol) in $CHCl_3$ (75 mL) and Al-$(CH_3)_3$ (17.9 mL in toluene, 2.0 M). The crude product was purified by flash chromatography (1:2 EtOAc:hexanes) to give 3.63 g of hydrazine **9** (84%): ^{1}H NMR (500 MHz, Tol-d_8) for major rotamer δ 7.55 (d, J = 3.4 Hz, 1H), 7.12 (app t, J = 7.3 Hz, 2H), 7.00 (s, 1H), 6.80 (app t, J = 7.3 Hz, 1H), 6.75 (app d, J = 7.8 Hz, 2H), 6.33 (dd, J = 10.8, 17.6 Hz, 1H), 5.19 (d, J = 17.1 Hz, 1H), 5.1 (d, J = 10.8 Hz, 1H), 4.98 (s, 1H), 4.95 (s, 1H), 2.10 (t, J = 7.3 Hz, 2H), 1.86 (t, J = 7.3 Hz, 2H), 1.55 (m, 2H), 1.42 (m, 2H); IR (thin film) ν_{max} 3265, 3087, 2933, 1655, 1602, 1495 cm^{-1}; ^{13}C NMR (125 MHz, CD_3OD) δ 176.0, 150.1, 147.8, 140.1, 130.3, 121.2, 116.3, 114.24, 113,47, 34.9, 32.2, 29.2, 26.88; HRMS (ES) m/z calcd for $C_{15}H_{20}N_2O$ [M + Na]$^+$ 267.1473, found 267.1480.

2-Benzyl-5-methylenehept-6-enoic Acid *N*′-Phenylhydrazide (21). Diene ester **20**[5] (1.98 g, 7.66 mmol) was added to a solution of phenylhydrazine (1.67 g, 15.4 mmol) in $CHCl_3$ (50 mL) and $Al(CH_3)_3$ (7.70 mL in toluene, 2.0 M). The crude product was purified by flash chromatography (1:5 EtOAc:hexanes) to give 1.87 g of hydrazide **21** (76%): ^{1}H NMR (500 MHz, $CDCl_3$) for major rotamer δ 7.2−7.3 (m overlapped, 3H), 7.15 (app d, J = 6.5 Hz, 2H), 7.11 (s, 1H), 7.09 (app d, J = 8.0 Hz, 2H), 6.84 (app t, J = 7.2 Hz, 1H), 6.43 (app d, J = 7.8 Hz, 2H), 6.37 (dd, J = 17.6, 10.8 Hz, 1H), 5.98 (d, J = 3.6 Hz, 1H), 5.22 (d, J = 17.6 Hz, 1H), 5.09 (d, J = 10.9 Hz, 1H), 5.06 (s, 1H), 4.99 (s, 1H), 2.92 (dd, J = 13.4, 10.2 Hz, 1H), 2.81 (dd, J = 13.6, 5.0 Hz, 1H), 2.46 (m, 1H), 2.31 (m, 1H), 2.23 (m, 1H), 2.00 (m, 1H), 1.76 (m, 1H); IR (thin film) ν_{max} 3248, 3027, 2928, 1667, 1601, 1495 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 147.8, 145.8, 139.5, 138.7, 129.1, 128.6, 126.6, 121.2, 116.3, 113.9, 113.6, 112.6, 47.7, 39.3, 31.1, 29.4; HRMS (ES) m/z calcd for $C_{21}H_{24}N_2O$ [M + H]$^+$ 321.1967, found 321.1972.

2-Benzyl-6-methyleneoct-7-enoic Acid *N*-Phenylhydrazide (23). Diene ester **22**[5] (0.716 g, 2.14 mmol) was added to a solution of $Al(CH_3)_3$ (2.14 mL in toluene, 2.0 M) and phenylhydrazine (0.463 g, 4.28 mmol). The crude product was purified by flash chromatography (1:5 EtOAc:hexanes) to give 1.73 g of hydrazine **23** (85%): ^{1}H NMR (500 MHz, $CDCl_3$) for major rotamer δ 7.31−7.26 (m overlapped, 3H), 7.19 (app d, J = 6.0 Hz, 2H), 7.11 (app t, J = 8.2 Hz, 2H), 6.98 (s, 1H), 6.84 (app t, J = 7.4 Hz, 1H), 6.45 (app d, J = 8.2 Hz, 2H), 6.38 (dd, J = 17.7, 10.8 Hz, 1H), 5.98 (d, J = 3.6 Hz, 1H), 5.23 (d, J = 17.6 Hz, 1H), 5.09 (d, J = 10.8 Hz, 1H), 5.05 (s, 1H), 5.00 (s, 1H), 2.92 (dd, J = 13.4, 10.3 Hz, 1H), 2.79 (dd, J = 13.4, 4.9, 1H), 2.42 (m, 1H), 2.24 (t, J = 6.3 Hz, 2H), 1.83 (m, 1H), 1.65−1.50 (m, 3H); IR (thin film) 3027, 2939, 1661, 1602, 1495 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 147.7, 145.8, 139.4, 138.8, 129.4, 129.04, 128.7, 126.6, 121.1, 116.0, 113.4, 112.5, 48.4, 39.2, 32.9, 31.3, 26.2; HRMS (ES) m/z calcd for $C_{22}H_{26}N_2O$ [M + H]$^+$ 335.2123, found 335.2122.

General Procedure for the Oxidation Reaction of Hydrazides with *n*-Bu$_4$NIO$_4$ Followed by Cycloaddition. To a cooled (0 °C) solution of a hydrazide in dry CH_2Cl_2 was added *n*-Bu_4NIO_4 (1.3 equiv). The reaction mixture was stirred at room temperature for 24 h (TLC monitoring) and washed with 2 portions of saturated Na_2SO_3. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo.

9-Phenyl-1,9-diazabicyclo[4.3.1]dec-6-en-2-one (11). To a solution of hydrazide **8** (0.20 g, 0.87 mmol) in dry CH_2Cl_2 was added *n*-Bu_4NIO_4 (1.3 equiv, 0.49 g, 1.13 mmol) then the mixture was stirred at room temperature for 24 h. Flash column chromatography (1:2 EtOAc:hexanes) of the crude product yielded 0.18 g (91%) of cycloadduct **11** as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.04 (app d, J = 8.7 Hz, 2H), 6.91 (app t, J = 7.3 Hz, 1H), 5.86 (br s, 1H), 4.37 (dd, J = 13.8, 7.4 Hz, 1H), 4.15 (d, J = 14.8 Hz, 1H), 3.49 (d, J = 12.7 Hz, 1H), 3.23 (d, J = 14.4 Hz, 1H), 3.12 (td, J = 13.8, 3.2 Hz, 1H), 2.64 (dd, J = 12.1, 6.8 Hz, 1H), 2.55 (dt, J = 13.2, 3.1 Hz, 1H), 2.50 (td, J = 12.1, 6.1 Hz, 1H), 2.29 (m, 1H), 1.95 (m, 1H); IR (thin film) ν_{max} 1702, 1597, 1492, 1342, 1163 cm^{-1}; ^{13}C NMR (125 MHz, CD_2Cl_2) δ183.6, 150.9, 150.8, 129.4, 120.1, 119.2, 114.4, 51.6, 48.9, 36.8, 35.0, 33.4; HRMS (ES) m/z calcd for $C_{14}H_{16}N_2O$ [M + Na]$^+$ 251.1160, found 251.1155.

Acetylazobenzene (13a). To a solution of hydrazide **12a** (0.21 g, 1.40 mmol) in dry CH_2Cl_2 was added *n*-Bu_4NIO_4 (1.3 equiv, 0.788 g, 1.81 mmol) and the solution was stirred at room temperature for 5 h (TLC monitoring). Flash column chromatography (1:2 EtOAc:hexanes) of the crude product yielded 0.15 g (72%) of *N*-acyl azo **13a** as a red oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (m, 2H), 7.56 (m, 3H), 2.44 (s, 3H); IR (thin film) ν_{max} 1743, 1565, 1479 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 151.7, 133.7, 129.5, 123.8, 21.4; HRMS (ES) m/z calcd for $C_8H_8N_2O$ [M + Na]$^+$ 171.0534, found 171.0540.

Isobutyrylazobenzene (13b). To a solution of hydrazide **12b**[14] (0.34 g, 1.91 mmol) in dry CH_2Cl_2 was added *n*-Bu_4NIO_4 (1.3 equiv, 1.07 g, 2.47 mmol) and the solution was stirred at room temperature for 5 h (TLC monitoring). Flash column chromatography (1:2 EtOAc:hexanes) of the crude product yielded 0.31 g (91%) of *N*-acyl azo **13b** as a red oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.56 (m, 3H), 3.14 (m, 1H), 1.31 (d, J = 7.3 Hz, 6H); IR

(thin film) ν_{max} 1736, 1501, 1453 cm^{-1}; ^{13}C NMR (500 MHz, CD_2Cl_2) δ 195.4, 152.4, 133.7, 133.7, 129.9, 123.7, 34.9, 18.3; HRMS (ES) *m*/*z* calcd for $C_{10}H_{12}N_2O$ [M + H]$^+$ 177.0950, found 177.9038.

Ethyl(phenyl)azocarboxylate (13c). To a solution of hydrazide **12c**[15] (0.15 g, 0.832 mmol) in dry CH_2Cl_2 was added *n*-Bu_4NIO_4 (1.3 equiv, 0.469 g, 1.08 mmol) and the solution was stirred at room temperature for 5 h (TLC monitoring). Flash column chromatography (1:2 EtOAc:hexanes) of the crude product yielded 0.14 g (95%) of *N*-acyl azo **13c** as a red oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.56 (m, 3H), 4.53 (q, 2H), 1.48 (t, J = 7.1 Hz, 3H); IR (thin film) 2986, 1755, 1503; ^{13}C NMR (500 MHz, $CDCl_3$) δ 162.4, 151.8, 134.0, 129.5, 123.9, 64.7, 14.4; HRMS (ES) *m*/*z* calcd for $C_9H_{10}N_2O_2$ [M + Na] 201.0640, found 201.0639.

3-Benzyl-9-phenyl-1,9-diazabicyclo[4.3.1]dec-6-en-2-one (24). To a cooled (0 °C) solution of hydrazide **21** (0.24 g, 0.75 mmol) in CH_2Cl_2 was added *n*-Bu_4NIO_4 (1.3 equiv, 0.42 g, 97 mmol) and the solution was stirred at 25 °C. After 24 h (TLC monitoring), the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated Na_2SO_3 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography (1:3 EtOAc:hexanes) of the crude product afforded cycloadduct **24** (0.22 g, 91%) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.24 (m, 7H), 6.95 (app d, J = 7.9 Hz, 2H), 6.87 (app t, J = 7.3 Hz, 1H), 5.83 (br s, 1H), 4.33 (dd, J = 13.8, 7.3 Hz, 1H), 4.20 (d, J = 14.7, 1H), 3.49 (d, J = 14.5 Hz, 1H), 3.40 (m, 1H), 3.22−3.17 (m, 2H), 2.61 (dd, J = 14.1, 7.7 Hz, 1H), 2.53 (dd, J = 12.3, 6.9 Hz, 1H), 2.39 (m, 1H), 2.17 (d, J = 11.7 Hz, 1H), 1.74 (m, 1H); IR (thin film) 2930, 1694, 1598,1495 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ184.7, 150.7, 149.9, 140.5, 129.7, 129.4, 128.8, 126.7, 120.48, 119.7, 114.9, 51.0, 49.3, 46.6, 39.5, 38.9, 34.6. HRMS (ES) *m*/*z* calcd for $C_{21}H_{22}N_2O$ [M + H]$^+$ 319.1810, found 319.1810.

General Procedure for the Preparation of *N*-Acyl Azo Dienophiles with NBS.[16] To a solution of a hydrazide in CH_2Cl_2 was added pyridine (1 equiv). The reaction mixture was cooled to 0 °C and *N*-bromosuccinimide (1 equiv) was added to the solution. After 2 h, the orange reaction mixture was poured into H_2O. The layers were separated and the aqueous layer was extracted with 3 portions of CH_2Cl_2. The combined organic layers were washed with 5% HCl, 10% K_2CO_3, and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo.

6-Methyleneoct-7-enoic Acid Azobenzene (14). To a solution of hydrazide **9** (0.101 g, 0.413 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.033 g, 0.417 mmol). The reaction mixture was cooled to 0 °C and *N*-bromosuccinimide (0.074 g, 0.416 mmoles) was added to the solution. The organic layer was concentrated in vacuo to give 0.096 g of *N*-azo dienophile **14** in 96% yield and was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (app d, J = 7.1 Hz, 2H), 7.60−7.51 (m overlapped, 3H), 6.37 (dd, J = 17.6, 10.8 Hz, 1H), 5.23 (d, J = 17.6 Hz, 1H), 5.08 (d, J = 10.8 Hz, 1H), 5.4 (s, 1H), 5.2 (s, 1H), 2.77 (t, J = 7.3 Hz, 2H), 2.27 (t, J = 7.7 Hz, 2H), 1.82 (m, 2H), 1.63 (m, 2H); IR (thin film) ν_{max} 2941, 1743, 1499 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 151.7, 145.9, 138.9, 133.5, 129.4, 123.6, 116.1, 113.4, 34.2, 31.2, 27.7, 23.4; HRMS (ES) *m*/*z* calcd for $C_{15}H_{18}N_2O$ [M + Na]$^+$ 265.1317, found 265.1324.

2-Benzyl-6-methyleneoct-7-enoic Acid Azobenzene (29). To a solution of hydrazide **23** (0.023 g, 0.069 mmol) in CH_2Cl_2 (2 mL) was added pyridine (0.0054 g, 0.0687 mmol). The reaction mixture was cooled to 0 °C and *N*-bromosuccinimide (0.0122 g, 0.0688 mmol) was added to the solution. The organic layer was concentrated under vacuo to give *N*-acylazo dienophile **29** (0.0215 g) in 94% yield and used without further purification: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.82 (app d, J = 7.5 Hz, 2H), 7.58−7.55 (m overlapped, 3H), 7.28−7.20 (m, 5H), 6.35 (dd, J = 17.6, 10.8 Hz, 1H), 5.20 (d, J = 17.6 Hz, 1H), 5.05 (d, J = 10.9 Hz, 1H), 4.98 (s, 1H), 4.95 (s, 1H), 3.31 (m, 1H), 3.12 (dd, J = 13.8, 7.7 Hz, 1H), 2.88 (dd, J = 13.8, 6.7, 1H), 2.18 (m, 2H), 1.83 (m, 1H), 1.65−1.53 (m, 3H); IR (thin film) ν_{max} 2941, 1735, 1594, 1498; ^{13}C NMR (125 MHz, CD_2Cl_2) δ 193.0, 151.7, 145.9, 139.0, 138.7, 133.3, 129.3, 129.0, 128.3, 126.4, 123.3, 115.7, 113.1, 47.1, 37.1, 31.1, 30.6, 25.5; HRMS (ES) *m*/*z* calcd for $C_{22}H_{24}N_2O$ [M + Na]$^+$ 355.1786, found 355.1785.

General Procedure for the T2IMDA Reaction with *N*-Acylazo Dienophiles Catalyzed by $ZnCl_2$. To a cooled solution (−78 °C) of *N*-acylazo dienophile (0.01 M) in CH_2Cl_2 was added $ZnCl_2$ (10 mol %) as a solid in one portion. After 2 h, the reaction mixture was gradually allowed to warm to 25 °C and was completed after 3 h (monitored by TLC). The solution was diluted with CH_2Cl_2 and poured in H_2O. The layers were separated and the aqueous layer was extracted with 3 portions of CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ and brine then dried over Na_2SO_4. The organic layer was concentrated in vacuo.

10-Phenyl-1,10-diazabicyclo[5.3.1]undec-7-en-2-one (15). To a solution of *N*-acylazo dienophile **14** (0.0960 g, 0.396 mmol) in CH_2Cl_2 (10 mL) was added $ZnCl_2$ (0.0054 g, 0.0396 mmol). Purification of the crude product by column chromatrography (1:3 EtOAc:hexanes) afforded cycloadduct **15** (0.075 g, 78% yield) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (app t, J = 7.8 Hz, 2H), 6.90 (app d, J = 8.7 Hz, 2H), 6.81 (app t, J = 7.3 Hz, 1H), 5.55 (br s, 1H), 4.20 (d, J = 5.2 1H), 4.15 (d, J = 15.5 Hz, 1H), 3.96 (br d, J = 15.7, 1H), 3.56 (br d, J = 15.8 Hz, 1H), 2.62 (dd, J = 13.1, 9.3, 1H), 2.52 (m, 1H), 2.41 (t, J = 11.5, 1H), 2.15−2.10 (m, 3H), 1.90 (m, 1H), 1.44 (m, 1H); IR (thin film) ν_{max} 2932, 1656, 1599, 1497 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 148.7, 141.7, 129.2, 121.9, 118.7, 112.0, 47.5, 47.1, 37.6, 33.7, 27.2, 24.4; HRMS (ES) *m*/*z* calcd for $C_{15}H_{18}N_2O$ [M + Na]$^+$ 265.1317, found 265.1308.

3-Benzyl-10-phenyl-1,10-diazabicyclo[5.3.1]undec-7-en-2-one (30). To a solution of *N*-acylazo dienophile **29** (0.087 g, 0.26 mmol) in CH_2Cl_2 (7 mL) was added $ZnCl_2$ (0.0036 g, 0.011 mmol). Purification of the crude product by column chromatrography (1:4 EtOAc:hexanes) afforded cycloadduct **30** (0.062 g, 71% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ. δ 7.31−7.18 (m overlapped, 7H), 6.76 (app t, J = 7.3 Hz, 1H), 6.64 (app d, J = 8.8 Hz, 2H), 5.66 (br s, 1H), 4.24 (d, J = 15.6, 1H), 4.13 (dd, J = 15.5, 5.1, 1H), 3.98 (dt, J = 15.6, 2.1 Hz, 1H), 3.55 (br d, J = 15.6, 1H), 3.20 (dd, J = 13.5, 8.5, 1H), 2.76 (m, 1H), 2.66 (dd, J = 13.5, 6.4 Hz, 1H), 2.49 (br m, 1H), 2.17−2.05 (m, 2H), 1.87 (m, 2H), 1.4 (m, 1H); IR (thin film) ν_{max} 2930, 1698, 1598, 1497 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 148.3, 140.8, 140.1, 129.4, 128.9, 128.3, 126.2, 122.4, 118.3, 111.6, 48.5, 47.6, 46.7, 40.6, 33.9, 31.4, 27.0; HRMS (ES) *m*/*z* calcd for $C_{22}H_{24}N_2O$ [M + H]$^+$ 333.1967, found 333.1963.

General Procedure for the Hydrogenation of the Bridgehead Alkene. To a solution of a cycloadduct in EtOH was added 10% Pd/C. The reaction mixture was stirred under 1 atm or 50 psi of H_2 for 5 h. The catalyst was filtered through celite and the filtrate was concentrated in vacuo.

9-Phenyl-1,9-diazabicyclo[4.3.1]decan-2-one (16). To a solution of cycloadduct **11** (0.025, 0.011 mmol) in EtOH (5 mL) was added 10% Pd/C (0.003 g). The reaction mixture was stirred under 1 atm of H_2 for 5 h. The clear oil was purified by column chromatography (1:1 EtOAc:hexanes) to afford **16** (0.023 g, 92% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.91−6.89 (m, 3H), 3.8 (ddd, J = 9.7, 9.7, 5.3 Hz, 1H), 3.7 (d, J = 14.9 Hz, 1H), 3.24−3.18 (m, 2H), 2.92 (m, 1H), 2.59 (dt, J = 13.7, 4.4 Hz, 1H), 2.18 (m, 1H), 1.98−1.80 (m, 5H), 1.69−1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 149.3, 129.2, 120.3, 114.1, 49.2, 45.7, 35.4, 31.0, 30.6, 22.9, 19.7; IR (thin film) ν_{max} 2933, 1682, 1599, 1495 cm^{-1}; HRMS (ES) *m*/*z* calcd for $C_{14}H_{18}N_2O$ [M + H]$^+$ 231.1497, found 231. 1498.

10-Phenyl-1,10-diazabicyclo[5.3.1]undecan-2-one (18). To a solution of cycloadduct **15** (0.041, 0.17 mmol) in EtOH (5 mL) was added 10% Pd/C (0.004 g). The reaction mixture was stirred under 1 atm of H_2 for 5 h. The clear oil was purified by column chromatography (1:1 EtOAc:hexanes) to afford **18** (0.036 g, 89% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.246 (m, 2H), 6.88−6.82

(m, 3H), 3.97 (d, J = 14.4 Hz, 1H), 3.79−3.74 (m, 2H), 3.39 (d, J = 14.3 Hz, 1H), 2.63 (td, J = 13.1, 3.2 Hz, 1H), 2.55 (m, 1H), 2.15−2.05 (m, 2H), 1.99−1.94 (m, 4H), 1.57−1.47 (m, 2H), 1.33−1.25 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.1, 146.9, 129.5, 119.7, 113.9, 46.4, 40.6, 35.3, 34.7, 30.7, 28.0, 26.0, 25.1; HRMS (ES) *m*/*z* calcd for $C_{15}H_{20}N_2O$ $[M + Na]^+$ 267.1473, found 267.1468.

3-Benzyl-9-phenyl-1,9-diazabicyclo[4.3.1]decan-2-one (25). To a solution of cycloadduct **24** (0.037, 0.12 mmol) in EtOH (5 mL) was added 10% Pd/C (0.004 g). The reaction mixture was stirred under high-pressure H_2 (50 psi) for 5 h. The clear oil was purified by column chromatography (1:2 EtOAc:hexanes) to afford **25** (0.032 g, 86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 7H), 6.89−6.85 (m, 3H), 3.83−3.78 (m, 2H), 3.32 (dd, J = 14.1, 5.6 Hz, 1H), 3.23−3.17 (m, 3H), 2.67 (dd, J = 14.1, 8.3 Hz, 1H), 2.14 (br s, 1H), 1.92 (m, 1H), 1.83−1.65 (m, 5H); IR (thin film) 2922, 1686, 1599, 1497; ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 149.4, 140.6, 129.6, 129.1, 128.5, 126.3, 120.1, 113.9, 48.7, 45.7, 44.9, 38.2, 31.5, 30.1, 26.2, 22.9; HRMS (ES) *m*/*z* calcd for $C_{21}H_{24}N_2O$ $[M + H]^+$ 321.1967, found 321.1960.

3-Benzyl-10-phenyl-1,10-diazabicyclo[5.3.1]undecan-2-one (31). To a solution of cycloadduct **30** (0.040, 0.12 mmol) in EtOH (5 mL) was added 10% Pd/C (0.004 g). The reaction mixture was stirred under high-pressure (50 psi) H_2 for 5 h. The clear oil was purified by column chromatography (1:2 EtOAc:hexanes) to afford **31** (0.036 g, 86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.25 (m overlapped, 5H), 7.13 (app t, J = 7.3 Hz, 2H), 6.75 (app t, J = 7.3 Hz, 1H), 6.54 (app d, J = 7.8 Hz, 2H), 4.07 (br d, J = 14.4 Hz, 1H), 3.77−3.70 (m, 2H), 3.27−3.20 (m, 2H), 2.91 (m, 1H), 2.66 (dd, J = 13.4, 5.3 Hz, 1H), 2.08−2.03 (m, 2H), 1.94−1.90 (m, 2H), 185−1.75 (m, 2H), 1.54−1.45 (m, 2H), 1.32 (br d, J = 13.4 Hz, 1H); IR (thin film) ν_{max} 2921, 1677, 1597, 1497 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 147.1, 140.5, 129.6, 129.4, 128.5, 126.3, 119.4, 113.4, 46.9, 46.2, 39.8, 39.6, 37.6, 35.3, 27.7, 26.9, 24.6; HRMS (ES) *m*/*z* calcd for $C_{22}H_{26}N_2O$ $[M + H]^+$ 335.2123, found 335.2121.

General Procedure for the Reductive N−N Bond Cleavage with Raney-Ni. A solution of saturated cycloadducts in EtOH and Raney nickel was stirred under 1 atm of H_2. After 6 h, the reaction mixture was stirred at rt or refluxed overnight. The catalyst was filtered through a pad of celite. The filtrate was concentrate under vacuum and chromatographed.

6-(2-Phenylaminoethyl)azepan-2-one (17). To a solution of **16** (0.020 g, 0.087 mmol) in EtOH (5 mL) was added Raney nickel and the solution was stirred under 1 atm of H_2. After 6 h, the reaction mixture was refluxed overnight. Purification of the crude product by column chromatography (1:1 EtOAc:$CHCl_3$) afforded 6-substituted caprolactam **17** (0.016 g, 80%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (app t, J = 7.4 Hz, 2H), 6.72 (app t, J = 7.3 Hz, 1H), 6.61 (app d, J = 8.6 Hz, 2H), 6.02 (br s, 1H), 3.59 (br s, 1H), 3.20−310 (m, 4H), 2.48 (dd, J = 6.9, 4.8 Hz, 2H), 1.97 (m, 1H), 1.85 (m, 1H), 1.75 (br m, 1H), 1.69−1.47 (m, 4H and H_2O); IR (thin film) ν_{max} 3369, 2920, 1654 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 148.3, 129.5, 117.7, 112.9, 47.5, 41.8, 36.9, 36.6, 36.5, 32.8, 21.7; HRMS (ES) *m*/*z* calcd for $C_{14}H_{20}N_2O$ $[M + Na]^+$ 255.1473, found 255.1473.

7-(2-Phenylaminoethyl)azocan-2-one (19). To a solution of **18** (0.025 g, 0.102 mmol) in EtOH (5 mL) was added Raney nickel and the mixture was stirred under 1 atm of H_2. After 6 h, the reaction mixture was refluxed overnight. The catalyst was filtered through a pad of celite. The filtrate was concentrate in vacuo and purified by column chromatography (1:1 EtOAc:$CHCl_3$) to afford enantholactam **19** (0.022 g, 87%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (app t, J = 7.4 Hz, 2H), 6.73 (app t, J = 7.3 Hz, 1H), 6.61 (app d, J = 7.6 Hz, 2H), 5.92 (br s, 1H), 3.70 (br s, 1H), 3.43 (ddd, J = 9.3, 7.1, 3.8 Hz, 1H), 3.20−3.11 (m, 3H), 2.43 (ddd, J= 8.1, 5.5, 2.9, 2H), 1.85−1.30 (m, 9H); IR (thin film) ν_{max} 3346, 2925, 1661 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 148.3, 129.5, 117.7, 112.9, 45.7, 42.0, 39.4, 33.1, 32.4, 29.9, 28.5, 23.7; HRMS (ES) *m*/*z* calcd for $C_{15}H_{22}N_2O[M + H]^+$ 247.1810, found 247.1811.

3-Benzyl-6-(2-phenylaminoethyl)azepan-2-one (28). To a solution of **25** (0.018 g, 0.056 mmol) in EtOH (5 mL) was added Raney nickel and NaOH (0.2 mL, 1 N) then the mixture was stirred under 1 atm of H_2. After 6 h, the H_2 balloon was removed and the solution was stirred for 48 h. Purification by column chromatography (1:1 EtOAc:hexanes) afforded *cis*-3,6-substituted caprolactam **28** (0.013 g, 72%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.16 (m overlapped, 7H), 6.71 (app t, J = 7.3 Hz, 1H), 6.60 (app d, J = 7.9 Hz, 2H), 5.94 (br s, 1H), 3.49 (dd, J = 15.1, 5.6 Hz, 1H), 3.24 (dd, J = 14.1, 5.1 Hz, 1H), 3.11 (m, 3H), 2.71 (m, 1H), 2.57 (dd, J = 14.1, 9.3 Hz, 1H), 1.90−1.50 (m, 8H); IR (thin film) ν_{max} 3326, 3046, 1643 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 148.2, 140.6, 129.5, 129.4, 128.5, 126.2, 117.8, 113.0, 45.5, 45.3, 42.1, 37.3, 33.8, 33.5, 29.9, 29.3; HRMS (ES) *m*/*z* calcd for $C_{21}H_{26}N_2O$ $[M + H]^+$ 323.2123, found 323.2129.

3-Benzyl-7-(2-phenylaminoethyl)azocan-2-one (32). To a solution of **31** (0.021 g, 0.063 mmol) in EtOH (5 mL) was added Raney nickel and NaOH (0.2 mL, 1 N) then the solution was stirred under 1 atm of H_2. After 6 h, the H_2 balloon was removed and the solution was stirred for 48 h. Purification by column chromatography (2:1 EtOAc:hexanes) afforded *cis*-3,7-disubstituted enantholactam **32** (0.016 g, 77%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.15 (m overlapped, 7H), 6.73−6.63 (m overlapped, 3H), 5.75 (br s, 1H), 3.70 (br m, 2H), 3.15−3.05 (m, 4H), 2.91 (m, 1H), 2.66 (dd, J = 13.8, 6.7 Hz, 1H), 1.78 (m, 2H), 1.65 (m, 2H), 1.51 (br s, 2H), 1.36 (m, 2H); IR (thin film) ν_{max} 3312, 2932, 1651 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 148.3, 140.7, 129.6,129.4, 128.6, 126.3, 117.8, 113.0, 44.5, 42.1, 38.9, 38.6, 35.6, 31.7, 30.2, 29.9, 22.9; HRMS (ES) *m*/*z* calcd for $C_{22}H_{28}N_2O$ $[M + H]^+$ 337.2280, found 337.2280.

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Supporting Information Available: Characterization of compounds **26** and **27**, as well as stereochemical proofs, X-ray crystallographic data, and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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