Cycloaddition Reactions of a Nitrogen-Substituted Oxyallyl Cation with Cyclopentadiene and Substituted Furans. Reaction Conditions, Diastereoselectivity, Regioselectivity, and Transition State Modeling

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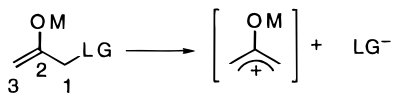
Received September 5, 1995[⊗]

An investigation of the cycloaddition reactions of a nitrogen-substituted oxyallyl cation is presented. The nitrogen-substituted oxyallyl cation, M^+-**1** ($M^+ = H^+$ or Li^+), can be generated from the dibromide **2** using either CF_3CH_2OH/Et_3N or $LiClO_4/CH_3CN/Et_3N$. These oxyallyl cations were found to undergo [4 + 2] cycloaddition reactions with furan, cyclopentadiene, 2-methylfuran, and 2-methoxyfuran. The diastereo- and regioselectivities in these reactions were found to be positively influenced by the presence of Li^+. Reaction of M^+-**1** with the 2-substituted furans led to primarily those adducts arising from endo addition (as was observed with the unsubstituted dienes) and which had the 2-substituent syn to the bromine. Consideration of the frontier molecular orbitals of the reacting species (Li^+-**1** and 2-substituted furans calculated at the PM3 semiempirical level of theory) led to the conclusion that FMO theory does not explain the regiochemistry observed in this process, although the relative electrophilicity of M^+-**1** ($M^+ = H^+$ or Li^+) could be rationalized. Transition structure modeling was consistent with empirical observations in that it predicted an endo addition of furan to Li^+-**1** via a stepwise reaction. Calculation of the reaction coordinate for this nonconcerted process predicted a $\Delta H_{rxn} \sim -50$ kcals/mol and $\Delta H_{act} \sim +11$ kcal/mol, with the second bond-forming process having a $\Delta H_{act} \sim +1.7$ kcal/mol.

Introduction

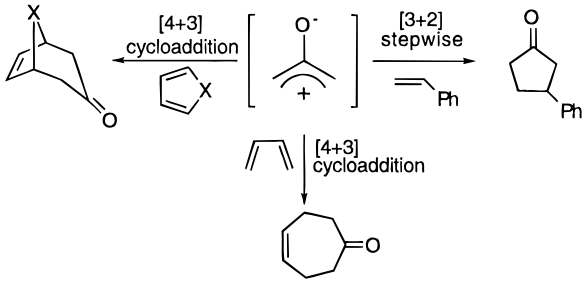
In the past three decades, the reactions of heteroatom-stabilized allyl cations and related species have been investigated extensively.[1] One particularly useful subtype of this family of intermediates is allyl cations that have an oxygen substituent at the central carbon. These reactive species, referred to generically as oxyallyl cations or oxyallyl zwitterions, can be formed via the ionization of a leaving group situated at C1 of a three-carbon allylic fragment. The C2−C3 unsaturated fragment can be part of an enol ether (usually silicon substituted) or a metal-stabilized enolate.



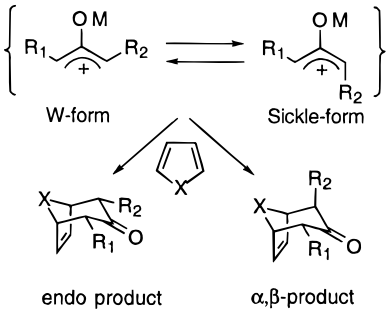
Typical reactions of oxyallyl cations include [4 + 3] cycloadditions with either cyclic or acyclic dienes and [3 + 2] stepwise reactions with activated olefins (Scheme 1). The [4 + 3] cycloaddition is thought to occur via a stepwise or concerted process depending on the nature of the oxyallyl cation and the reaction conditions. The formation of products which presumably arise from an endo addition of the cyclic diene with the energetically-favored W-form of the oxyallyl cation has been taken as evidence for a concerted process (Scheme 2). The formation of so-called α,β-products in the reaction of some oxyallyl cations with cyclic dienes has been taken as an indication of a competing stepwise process. This process can lead to either the same endo product formed in the concerted reaction or to the diastereomer of the product in which the substituents on the oxyallyl cation appear as though the sickle form of the oxyallyl cation had undergone reaction. The propensity for a given oxyallyl cation/diene combination to give more or less of these two products has been linked to the relative electrophilicity of the oxyallyl cation.[1]

The reaction of furan with substituted oxyallyl cations to produce stereodefined, oxygen-bridged cycloheptanones has been a key reaction in the synthetic approach to

Scheme 1



Scheme 2



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[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) Several reviews have appeared which describe this methodology: (a) Hosomi, A.; Tominga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 5.1, pp 593−615. (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611−4659. (c) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−88. (d) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163−344. (e) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61−66.

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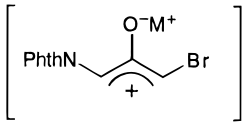

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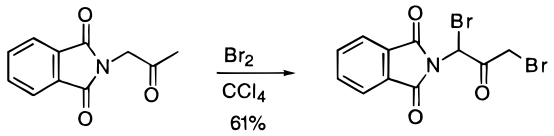
Figure 1. M^+-stabilized, nitrogen-substituted oxyallyl cation.

several important classes of natural products.[2] While carbon- and halogen-stabilized oxyallyl cations have been employed extensively in the aforementioned studies, the role of heteroatom-substituted oxyallyl cations in synthesis has not been as greatly developed. Prior to our report of the first example of the cycloaddition reaction of a nitrogen-substituted oxyallyl cation,[3] only oxygen-[4−6] and sulfur-[7,8] functionalized examples existed. We have begun a program to investigate the role of the Lewis basicity of the pendant nitrogen group on oxyallyl cation reactivity and to develop useful nitrogen-substituted oxyallyl cations for use in synthesis. Such species would be attractive reactive intermediates for at least two reasons. First, the potential flexibility of having the nitrogen present in various protected forms could allow the "tuning" of the donating potential of the substituent, perhaps influencing reagent reactivity and selectivity.[9] Second, the trivalent nitrogen atom might provide a means for attaching asymmetric controlling elements in close proximity to the oxyallyl system.[10] The melding of the documented synthetic utility of oxyallyl cations with an asymmetric controlling element could open up the way for the preparation of a wide variety of enantiomerically-pure molecules, thus affording a more efficient use for these reactive species. Herein, we report the complete details of a study of the generation and reactivity of the nitrogen-substituted oxyallyl intermediate **1** (Figure 1), as gauged by its cycloaddition reactions with several substituted and unsubstituted cyclic dienes. Additionally, we report the preliminary results of semiempirical calculations which, in part, suggest a stepwise reaction process in the reaction of this nitrogen-stabilized oxyallyl cation with furan.

Results and Discussion

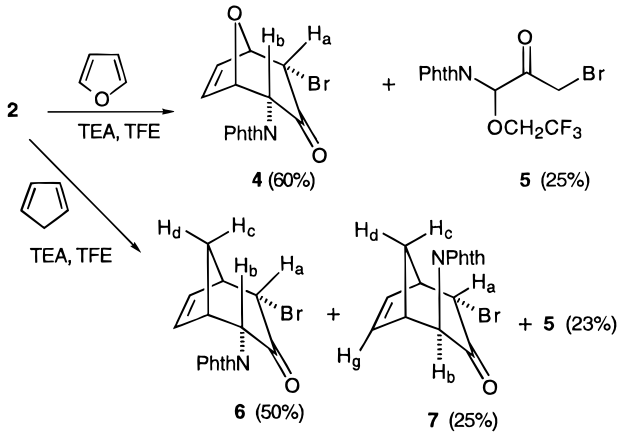
Synthesis of α,α′-Phthalimidoyl Dibromide (2). Preparation of dibromide **2** was accomplished by treatment of *N*-acetonylphthalimide (**3**)[11] with 2 equiv of bromine in freshly distilled CCl_4 (Scheme 3).[12] The known dibromide was isolated as a stable white solid (mp 125−126 °C (lit.[13] mp 126−127 °C)) in 61% yield after recrystallization from EtOAc/hexanes.

Scheme 3



3 **2**

Scheme 4



Diastereoselectivity. Generation of oxyallyl cation **1** was accomplished by two procedures. The first of these methods employed CF_3CH_2OH/Et_3N,[14,15] while the second procedure utilized $LiClO_4/CH_3CN/Et_3N$.[16] Efficient generation of oxyallyl cation **1** was gauged by its trapping with furan and cyclopentadiene, two cyclic dienes known to react particularly efficiently with other oxyallyl cations.[1] Treatment of dibromide **2** with furan or cyclopentadiene in Et_3N/CF_3CH_2OH (TEA/TFE) led to a mixture of products in each case (Scheme 4). For example, when furan was used as the diene, the products were identified as cycloadduct **4** (60%) and the solvolysis product **5** (25%). Trapping of intermediate **1** with cyclopentadiene afforded endo-product **6** (50%), α,*β*-product **7** (25%), and **5** (23%).

Generation of oxyallyl cation **1** could also be accomplished by treatment of dibromide **2** and the desired diene in a 1 M solution of $LiClO_4/CH_3CN$ with Et_3N. Previously, we reported low yields when using 3 M $LiClO_4/Et_2O$ as the reaction medium. We found that reaction yields could be greatly improved both by

(2) Some examples include: (a) Lautens, M.; Ma, S.; Yee, A. *Tetrahedron Lett.* **1995**, *36*, 4185−4188. (b) Bowers, K. G.; Mann, J. *Tetrahedron Lett.* **1985**, *26*, 4411−4412. (c) Sato, T.; Hayakawa, Y.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2515−2525. (d) White, J. D.; Fukuyama, Y. *J. Am. Chem. Soc.* **1979**, *101*, 226−228. (e) Arco, M. J.; Trammell, M. H.; White, J. D. *J. Org. Chem.* **1976**, *41*, 2075−2083.

(3) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23−26.

(4) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693−1696.

(5) Murray, D. H.; Albizati, K. *Tetrahedron Lett.* **1990**, *31*, 4109−4112.

(6) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Kashammer, D. *Chem. Ber.* **1988**, *121*, 1585−1593.

(7) Harmata, M.; Fletcher, V.; Claassen, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9861−9862.

(8) Hardinger, S. A.; Bayne, C.; Kantorowski, E.; McClellan, R.; Larres, L.; Nuesse, M.-A. *J. Org. Chem.* **1995**, *60*, 1104−1105.

(9) For example, nitrogen substituents play an important role in the reactivity of the enamine C=C with electrophiles: (a) Adam, W.; Ahrweiler, M.; Paulini, K.; Reissig, H.-U.; Voerckel, V. *Chem. Ber.* **1992**, *125*, 2719−2721. (b) Lenz, G. R. *Synthesis* **1978**, 489−518.

(10) For example, attachment of a chiral oxazolidinone auxiliary might be possible. See: Palomo, C.; Berree, F.; Linden, A.; Villalgordo, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1861−1862 and references cited therein.

(11) Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786−2788.

(12) Gaudry, M.; Marquet, A. *Tetrahedron* **1970**, *26*, 5611−5615.

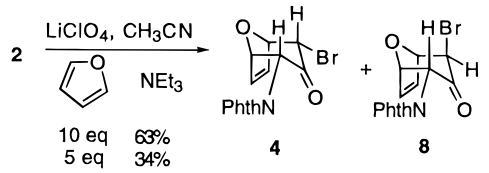
(13) Gabriel, S. *Chem. Ber.* **1911**, 1905−1915.

(14) Bowers, K. G.; Mann, J.; Markson, A. J. *J. Chem. Res., Synop.* **1986**, 424−425.

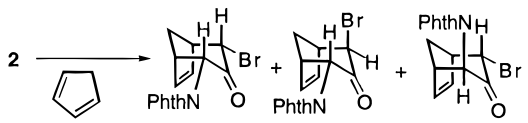
(15) Föhlisch, B.; Gottstein, W.; Herter, R.; Wanner, I. *J. Chem. Res., Synop.* **1981**, 246.

(16) These reaction conditions were based upon the pioneering work of Föhlisch regarding the use of $LiClO_4/Et_2O$/TEA to effect oxyallyl cation formation. Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976−979. $LiClO_4$ has often been used to accelerate organic reactions. (a) Ipaktschi, J.; Heydari, A. *Chem. Ber.* **1993**, *126*, 1905−1912. (b) Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663−2666. (c) Grieco, P. A.; Beck, J. P.; Handy, S. T.; Saito, N.; Daeuble, J. F. *Tetrahedron Lett.* **1994**, *35*, 6783−6786. (d) Grieco, P. A.; Moher, E. D. *Tetrahedron Lett.* **1993**, *34*, 5567−5570. (e) Reetz, M.; Gansauer, A. *Tetrahedron* **1993**, *49*, 6025−6030. This paper reports the use of $LiClO_4/CH_2Cl_2$ as an effective catalyst for some organic transformations.

Scheme 5



Scheme 6



Ratio of isomers			
$LiClO_4$, CH_3CN (59%)	4.3	7.6	1
$LiClO_4$, Et_2O (46%)	3.7	2.8	1

changing solvent systems from Et_2O to CH_3CN and by increasing the amount of diene employed. For example, when dibromide **2** was treated under these reaction conditions in the presence of 5 equiv of furan, the endo isomer **4** was formed in 34% yield as the only cycloaddition product (Scheme 5). When 10 equiv of furan was used, however, a mixture of endo **4** and α,β-product **8** was isolated as a 2:1 mixture in 63% yield.

These new reaction conditions also led to a change in the diastereoselectivity of the cycloaddition process. For example, trapping of oxyallyl cation **1** with cyclopentadiene in 1 M $LiClO_4/CH_3CN$ resulted in the formation of **6:9:7** in a ratio of 4.3:7.6:1 (59% yield) (Scheme 6). In this case, the α,β-isomer **9** was found to be the major product. This finding is contrary both to the propensity of this general class of reactions to give endo, diequatorial products[1] and the diastereoselectivity observed with the same diene/cation combination in $LiClO_4/Et_2O$.

These variations in diastereoselectivity and yield are presumed to be an effect of the differential association of Li^+ with oxyallyl cation **1**. This association may lead to the M^+-oxyallyl cation being more or less reactive with a given diene, perhaps switching mechanistic pathways between stepwise and concerted as the extent of Li^+ association changes. Since the active concentration of Li^+ is known to depend upon solvent polarity,[17] an explanation for a change in the reactivity of **1** that includes cation association seems reasonable. Indeed, a marked diminution in yields is observed for these reaction if they are run in the presence of 12-crown-4, a known Li^+ scavenger.[17]

Another manifestation of this association may be seen by comparing the diastereomer distribution for the reaction of cyclopentadiene under the two different reaction conditions. Note that when cation **1** is generated using TEA/TFE a greater percentage of **7** (an α,β-product in which the phthalimide group is axial) is formed (Scheme 4) than when Li^+ is included in the reaction solution (Scheme 6). A relatively small portion of the product mixture is made up of **7** even when the oxyallyl cation species becomes more electrophilic under the $LiClO_4/CH_3CN$ conditions. These results are suggestive of an oxyallyl cation system intimately associated with Li^+, an association which may involve intramolecular complexation of both the oxygen of the oxyallyl cation and an amide oxygen.[18] The results are also consistent with

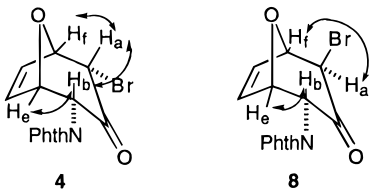


Figure 2. NOE interactions in cycloadducts **4** and **8**.

stabilization of the sickle form of the oxyallyl cation in which these two oxygens are s-cis to each other. While a further understanding of these effects awaits a more detailed examination of this and related systems with an expanded number of Lewis acids, these empirical observations, coupled with our initial semiempirical calculations (vide infra), strongly suggest an important role for the metal counterion, M^+, in these reaction processes.[19]

NMR Structural Assignment of the Diastereomers. The ^1H, ^{13}C, MS, and IR data for each of the cycloadducts was consistent with the general structure assigned in each case.[20]

The stereochemistry of compounds **4** and **8** was assigned using COSY and NOESY 2-D ^1H-NMR experiments. Cycloadduct **4** was identified as the endo-diastereomer in the following manner. Protons $H_a \leftrightarrow H_b$ clearly showed a crosspeak in the NOESY. This is only possible in the endo isomer (Figure 2). Protons $H_b \leftrightarrow H_e$ and protons $H_a \leftrightarrow H_f$ exhibited pairwise coupling to each other (4.8 Hz) consistent with axial−equatorial coupling in related [3.2.1] systems.[21] Cycloadduct **8** was identified as the α,β-product in a similar manner. In this compound, protons $H_a \leftrightarrow H_f$ and $H_b \leftrightarrow H_e$ each showed pairwise coupling to each other as well as crosspeaks in the NOESY spectrum, while an NOE between H_a and H_b was notably absent. Structural confirmation was also obtained by reductive debromination of ketones **4** and **8** using Zn/sonication (Scheme 7) to give **10**.[14] Formation of common structure **10** from both **4** and **8** could only occur if the two α-bromo ketones were isomeric at C2.

The key NOE interactions in cycloadducts **6**, **7**, and **9** are shown in Figure 3 and are consistent with the assigned structures. Cycloadducts **6**, **7**, and **9** were also subjected to reducing conditions (Zn, unltrasound), yielding ketones **11** and **12** (Scheme 8). Both **6** and **9** afforded the same ketone, **11**, as the only product. On the other hand, **7** yielded a different ketone diastereomer, **12**, as a single isomer. On the basis of this evidence, therefore, **6** and **9** are isomeric at the bromine-bearing carbon while **6** and **7** are isomeric at the nitrogen-bearing carbon.

Regioselectivity. In an effort to gain some insight into the relative effect of nitrogen substitution on the

(17) Desimoni, G.; Faita, G.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1991**, *47*, 8399−8406.

(18) For a detailed review of the importance of Lewis acid complexation by the carbonyl group, see: Shambayati, S.; Schreiber, S. In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: New York, **1991**; Vol. 1; pp 283−324. For the importance of Li^+ as a Lewis acid in the Diels−Alder cycloaddition reaction, see: Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 2761−2762.

(19) The importance of the metal counterion in determining the reactivity and, in some cases, the diastereoselectivity in the cycloaddition reactions of oxyallyl cations has been noted previously.[1b,c]

(20) The ^{13}C resonances associated with the C=O of the phthalimide group were not easily observable in several of the cycloadducts in which this moiety occupied the equatorial position. (The exception to this observation is compound **15b**.) All other analytical data obtained on these equatorial diastereomers were consistent with their assigned structure.

(21) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765−1777.

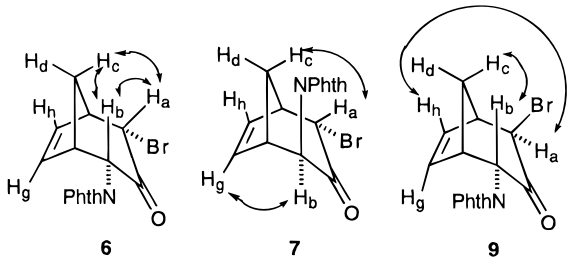
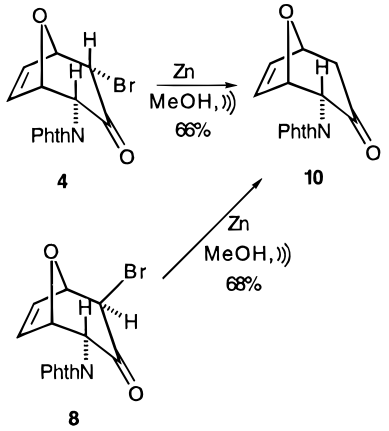
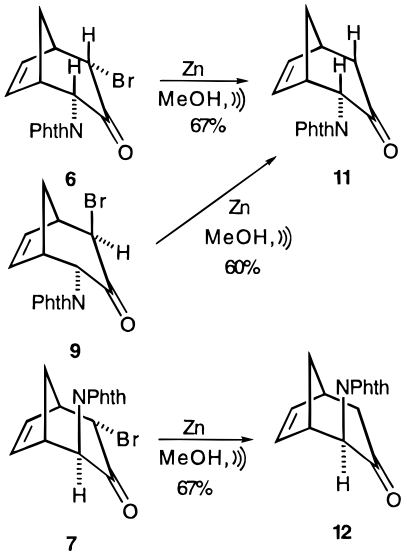


Figure 3. NOE interactions in cycloadducts **6**, **7**, and **9**.

Scheme 7



Scheme 8



reactivity of an oxyallyl cation, the regioselectivity of the reaction of **2** with two 2-substituted furans was determined using the two reaction conditions we had developed (Scheme 9). (The ratio of products formed in these reactions (Table 1) was determined by integration of selected ^{1}H NMR resonances in the crude cycloaddition reaction mixtures). Also shown in Scheme 9 are selected ^{1}H NOE's and the reductive debrominations which were employed to assign the structures of the cycloadducts **13**−**15**. Identification of compounds **16**−**18** confirmed the regio- and stereoselectivities.

There are a few trends that can be discerned from the data in Table 1. First, for each case, the substituent on the furan appears syn to bromine in the major cycloadduct. This trend is in agreement with the major regioisomer predicted by FMO theory in the case of 2-methoxyfuran (vide infra), but not in the case of 2-methylfuran.[22] Second, generation of the oxyallyl cation in $LiClO_4/CH_3CN$ media always led to enhanced regioselectivity in the cycloaddition process. For example, the ratio of cycloadducts **13a** + **14a:15a** increased from a ratio of 1.7:1 to 7.9:1 in the presence of Li^+, while the same change in reaction conditions favored the formation of only a single regioisomer when 2-methoxyfuran was used as the diene.[23]

Scheme 9

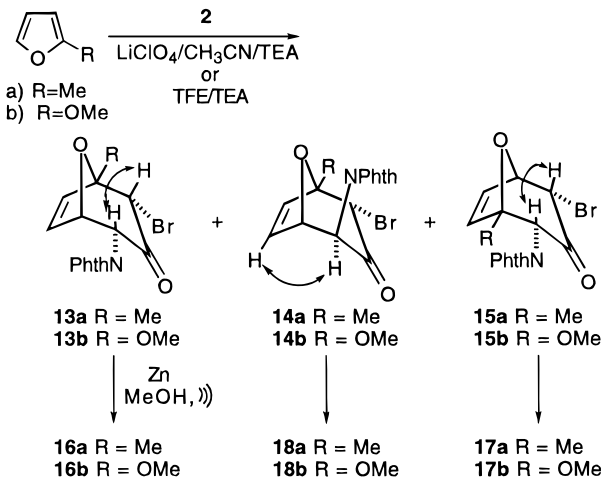


Table 1. Relative Formation of Cycloadducts 13−15 as a Function of 2-Substituted Furan and Reaction Conditions

diene (R)	method[a]	13	14	15	yield[b] (%)
Me	A	3.5	1	2.7	77
	B	6.5	1.4	1	73
OMe	A	3	3	1	60
	B	17	1	0	57

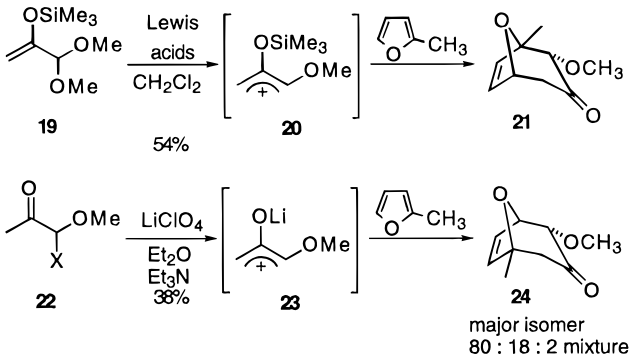
[a] Method A: TFE/TEA. Method B: 1 M $LiClO_4/CH_3CN$/TEA. [b] Yield of the mixture of isomers after chromatography.

By way of comparison, the regioselectivity evinced by oxygen-substituted oxyallyl cations with 2-methylfuran is known to vary widely with reaction conditions and the nature of the oxyallyl cation. For example, reaction of oxyallyl cation **20** (generated from **19** using a wide variety of Lewis acids) with 2-methylfuran cleanly leads to **21** as a single isomer (54%).[5] In marked contradistinction to this result, reaction of the related oxygen-substituted oxyallyl cation **23** (generated by treatment of **22** with $LiClO_4/Et_2O/Et_3N$) with 2-methylfuran affords the regioisomer **24** as the major isomer in 38% yield (Scheme 10).[6] No single mechanisitic paradigm has been offered to explain these seemingly contradictory results, although it has been suggested that the difference may be related to the availability of concerted (**19** → **21**) versus stepwise (**22** → **24**) reaction pathways in these two oxygenated examples.[5]

(22) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976. For a lucid explanation of the application of FMO theory to regioselectivity in the Diels−Alder reaction see: Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092−4094. The reaction of iron-stabilized oxyallyl cations with monosubstituted cyclic dienes has been investigated. It was found that FMO theory (CNDO/2) could be employed to rationalize the regioselectivity observed in all but one of the reported examples. Noyori, R.; Shimizu, F.; Fukuta, K.; Takaya, H.; Hayakawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5196−5198.

(23) This is the first published example of the reaction of an oxyallyl cation with this oxygenated diene. This process, however, is not particular to the nitrogen-substituted species **1**. For example, Lautens has observed the cycloaddition of 2-methoxyfuran with a dialkyl-substituted oxyallyl cation. (Lautens, M. Personal communication, University of Toronto.

Scheme 10



At least in terms of the relative position of the heteroatom in the cycloadduct, our results are consistent with the transformation in Scheme 10, which employs conditions upon which our own reactions are predicated. Preliminary results of the reaction of Li^+-**1** with other 2- and 3-monosubstituted furans[24] suggest that they all react to give as the major product that cycloadduct in which the substituent at either the 2- or 3- position is syn to the bromine.

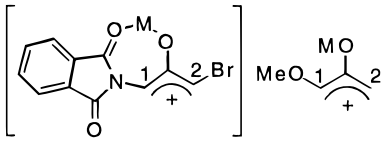
Calculations. In conjunction with our experimental endeavors, we also investigated this reaction process at the semiempirical level of theory employing the PM3[25,26] method implemented in SPARTAN 3.1.[27,28] It was in this context that we examined the frontier molecular orbitals of the reacting species and several potential transition structures for this transformation. Although our results are consistent with the Li^+-associated oxyallyl cation **1** (Figure 1; $M^+ = Li^+$) reacting in a stepwise fashion with furan, the effect of solvent on both of these species and transition structures awaits further investigation.

Initial calculations on the putative oxyallyl cation intermediate showed that association of **1** with either Li^+ ($LiClO_4/CH_3CN/Et_3N$) or H^+ (TFE/Et_3N) dramatically increased its electrophilicity relative to the free oxyallyl zwitterion, as can be inferred by the decreased HOMO(furan)/LUMO(cation) gap for those species (Table 2).[1,29] The calculated difference in electrophilicity between the $M = Li^+$ and $M = H^+$ is minimal but is consistent with the increased amount of α,β-product formed in the reactions employing the TFE/Et_3N conditions. By way of comparison, the HOMO/LUMO energies for the methoxy-substituted oxyallyl cations presented in Scheme 10 are also tabulated **(25a,b)**. The PM3-optimized geometry of Li^+-**1** is shown in Figure 4.[30]

The regioselectivity of the reaction of Li^+-**1** with monosubstituted furans does not appear to be interpretable, at least at this semiempirical level, by simple FMO theory (Table 3).[22] Whereas the matching of large coefficients in the FMOs predicts the correct product in the case of 2-methoxyfuran, the same considerations do not hold true in the 2-methylfuran case. Similarly, although the LUMO coefficients in both **25a** and **25b** (Table 2) are largest next to the terminal methoxy substituent, their cycloaddition reaction with the same 2-methylfuran gives remarkably different products.

Since ground-state electronic considerations appeared not to be predictive of the regiochemical course of these cycloaddition reactions, we felt that it might be helpful to examine the entire reaction coordinate for the simplest case that we had investigated (Li^+-**1**/furan). This would allow us to more precisely gauge the relative importance

Table 2. HOMO and LUMO Energies and LUMO Coefficients (PM3) for Various Forms of 1, 25, and Furan



1 **25a M=TMS** **25b M=Li+**

				LUMO coefficients	
M	HOMO[b] (eV)	LUMO (eV)	ΔE[c]	C(1)	C(2)
a, *d*	−7.623	−2.231	7.1	0.6581	−0.5059
Li^+	−11.89	−5.819	3.5	0.6811	−0.5023
H^+ [d]	−13.46	−6.448	2.9	0.6743	−0.5035
25a	−13.28	−6.452	2.9	0.7491	−0.5155
25b	−12.65	−5.871	3.5	0.7485	−0.5364
furan	−9.377	0.6092			

[a] Zwitterion. [b] PM3 energy. [c] $E_{LUMO(cation)} - E_{HOMO(furan)}$. *d* This cation was slightly nonplanar in its minimum energy conformation. For ease of comparison with the other planar species, the values listed are those calculated for the completely planar cation. The H_f (PM3) of the planar species is only slightly higher than that of the completely optimized structure ($\Delta H_f < 1.2$ kcal/mol), and the orbital energies are within 0.05 eV.

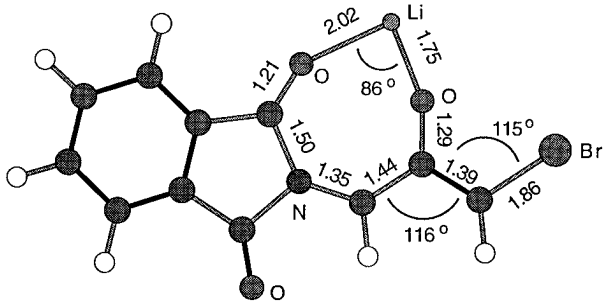


Figure 4. Structure of the Li^+-**1** optimized at the PM3 level of theory. Distances are in angstroms and angles are in degrees. The molecule is planar.

(24) We have examined the cycloadditions of **1** with 2-*tert*-butyl, 3-methyl, and 3-bromofurans. The yields of these reactions ($LiClO_4/CH_3CN/Et_3N$) were very low, but the products obtained were consistent with the model described.

(25) PM3: (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221−64. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−20. PM3 was recently parameterized for lithium: (c) Anders, E.; Kock, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301−1312. This new Li/PM3 parameter set has been employed by Anders to study monolithiated sulfones, sulfoxides, and 1,3-dithanes: Koch, R.; Anders, E. *J. Org. Chem.* **1994**, *59*, 4529−4534.

(26) The PM3 method has recently been applied to the reaction of pyridine *N*-oxides with dipolarophiles: (a) Matsuoka, T.; Harano, K.; Hisano, T. *Heterocycles* **1994**, *37*, 257−264. (b) Matsuoka, T.; Harano, K. *Tetrahedron* **1995**, *51*, 6451−6458.

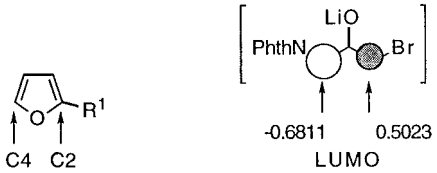
(27) SPARTAN 3.1: Hehre, W. J.; Burke, L. D.; Shusterman, A. J. Wavefunction, Inc., Irvine, CA.

(28) Oxyallyl cations and related reactive intermediates have been studied at the ab initio level of theory by several groups. (a) Goodman, J. M.; Hoffmann, H. M. R.; Vinter, J. G. *Tetrahedron Lett.* **1995**, *36*, 7757−7760. (b) Lim, D.; Hrovat, D. A.; Borden, W. T.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 3494−3499. (c) Coolidge, M. B.; Yamashita, K.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1990**, *112*, 1751−1754. (d) Turecek, F.; Drinkwater, D. E.; McLafferty, F. W. *J. Am. Chem. Soc.* **1991**, *113*, 5950−5958. (e) Ichimura, A. S.; Lahti, P. M.; Matlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 2868−2875. (f) Janoschek, R.; Kalcher, J. *Int. J. Quantum Chem.* **1990**, *38*, 653−664.

(29) This is the same effect on frontier molecular orbital energy as observed in computational studies relating to the Lewis acid catalyzed Diels−Alder reaction. Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094−4096.

(30) This structure was found to be 4.1 kcal/mol more stable (PM3) than the isomer in which Li^+ was associated only with the oxyallyl cation oxygen. Full details of these calculations will be published shortly.

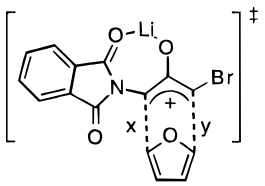
Table 3. HOMO (2-Substituted Furan) and LUMO (Li^+-1) Coefficients



R^1	HOMO[a]	C4	C2
H	−9.3767	0.59237	−0.59236
$-CH_3$	−9.1038	0.56609	**−0.57114**
$-OCH_3$	−8.8528	**−0.54493**	0.48013

[a] HOMO energy in eV.

Table 4. Geometries, Energies, and Single Imaginary Frequency Values (PM3) for the Endo and Exo modes of Cycloaddition of Li^+-1 with Furan



mode	x[a]	y	H_f	E_{rel}[b]	FREQ[c]
endo	3.66	2.16	122.318	0.00	−508.0
	2.12	3.44	124.484	2.17	−470.3
exo	3.51	2.15	123.087	0.77	−532.9
	2.11	3.37	125.184	2.87	−430.0

[a] x and y distances are in angstroms. [b] Relative energy (kcal/mol). [c] Single negative (imaginary) frequency (cm^{-1}).

of steric and electronic effects at various points during this process, a detailed understanding of which could, in the future, lead to a coherent explanation of the regioselectivity exhibited in these reactions.

Transition structure modeling[31] of this reaction at the PM3 level of theory suggested an exothermic, stepwise reaction coordinate for the reaction of Li^+-**1** with furan, in which the endo mode of addition was slightly favored relative to the exo mode. Several attempts to optimize to a transition structure that would be consistent with a concerted cycloaddition process were unsuccessful.[32] Instead, these searches always led to transition structures featuring unsymmetrical bond formation as the first step in the cycloaddition process. The energies of the four diastereomeric transition structures for initial bond formation (both endo and exo modes with initial bond formation near either N or Br) are shown in Table 4. The endo mode of addition was found to be slightly favored over the exo mode, while initial bond formation near the bromo substituent appeared to be heavily favored for both the exo and endo modes of addition.

Starting from the most stable of these four structures (i.e., the structure featuring bond formation initially nearest Br in the endo mode of addition), the complete reaction coordinate for the addition of Li^+-**1** to furan was delineated. The structures of the stationary states along this reaction coordinate are shown in Figure 5. The relative energies of these stationary states are listed in Table 5.

The results of these calculations are consistent with an exothermic ($\Delta H_{rxn} \sim -50$ kcals/mol), stepwise process in which the first step is rate limiting ($\Delta H_{act} \sim +11$ kcal/mol) and is followed by a second bond formation with a very low activation energy ($\Delta H_{act} \sim +1.7$ kcal/mol). Whether or not these results hold true at higher levels of theory remain to be investigated as do the ramifications of a stepwise process on the regiochemical outcome of this reaction.

Conclusions. We have shown that the nitrogen-substituted oxyallyl cation **1** can be generated and trapped with a variety of dienes including furan, cyclopentadiene, 2-methylfuran, and 2-methoxyfuran. Furan and cyclopentadiene react to give good yields of the cycloadducts arising primarily from the endo approach of the diene to the W-form of the oxyallyl cation. Li^+ association with the oxyallyl cation **1** appears to explain the relative diastereoselection in many of these reactions. In terms of the regioselectivity of the reactions of **1**, 2-methyl- and 2-methoxyfuran gave mixtures of regioisomers in which the primary cycloadduct was that with the 2-substituent syn to the bromine. It was found that the presence of Li^+ in these reactions led to heightened regioselectivity, again suggesting an important role for the Li^+-counterion in determining the course of these reactions. While the regioselectivity evinced by Li^+-**1** in its reactions with 2-substituted furans does not appear to be explicable in terms of FMO theory, semiempirical calculations could be used to rationalize the relative electrophilicity of M^+-**1** ($M^+ = H^+$ or Li^+) and also proved useful in mapping out the reaction coordinate for the addition of Li^+-**1** to furan. These calculations characterized the reaction of Li^+-**1** with furan as a highly exothermic process ($\Delta H_{rxn} \sim -50$ kcal/mol) with an activation energy consistent with a transformation that occurs at room temperature ($\Delta H_{act} \sim +11$ kcal/mol). More importantly, they suggest that this process is a stepwise reaction that leads preferentially to the endo product.

Studies aimed at further delineating the effect of nitrogen substitution on the reactivity of oxyallyl cations are planned, along with a more detailed investigation of the effect of Lewis acids on these transformation. The optimized geometries calculated at the PM3 level of theory should provide good starting points for more sophisticated calculations concerning these reactions. A more thorough knowledge of the stereoelectronic forces that are operative in the transition states for the reactions of M^+-**1** and related nitrogen-substituted oxyallyl cations is necessary if our goal of developing useful second-generation (i.e., auxiliary-controlled)[33] chiral reagents is to be realized.

Experimental Section

General. Melting points were recorded using a melting point apparatus equipped with a Fluka digital thermometer.

(31) These calculations apparently constitute the first report of transition structure modeling applied to an oxyallyl cation cycloaddition process. The transition structures were characterized by their single imaginary frequencies, animation of which corresponded to the motion of atoms anticipated for the bond-forming process. The starting materials, intermediates, and products had no negative eigenvalues.

(32) For example, searches for transition structures beginning at symmetrical Li^+-**1** and furan combinations separated by both $x = y =$ 2.5 Å and $x = y =$ 2.25 Å (x and y as in Table 4) optimized to unsymmetrical stationary points. Although imaginary frequencies consistent with a concerted process were found if these symmetrical structures were optimized with constraints, modes following of these vibrations led to the results reported. A series of PM3 calculations in which $x = y$ and the furan/Li^+-**1** distance was varied from 1.6 to 2.8 Å suggests that the ΔE_{act} for the concerted, synchronous reaction would be on the order of 126 kcal/mol ($x = y =$ 2.4 Å), ~4 kcal/mol higher than that calculated for the stepwise process. No evidence for a concerted, asynchronous transition structure was found.

(33) Aitken, R. A.; Kilenyi, S. N. *Asymmetric Synthesis*; Blackie A&P: New York, 1994.

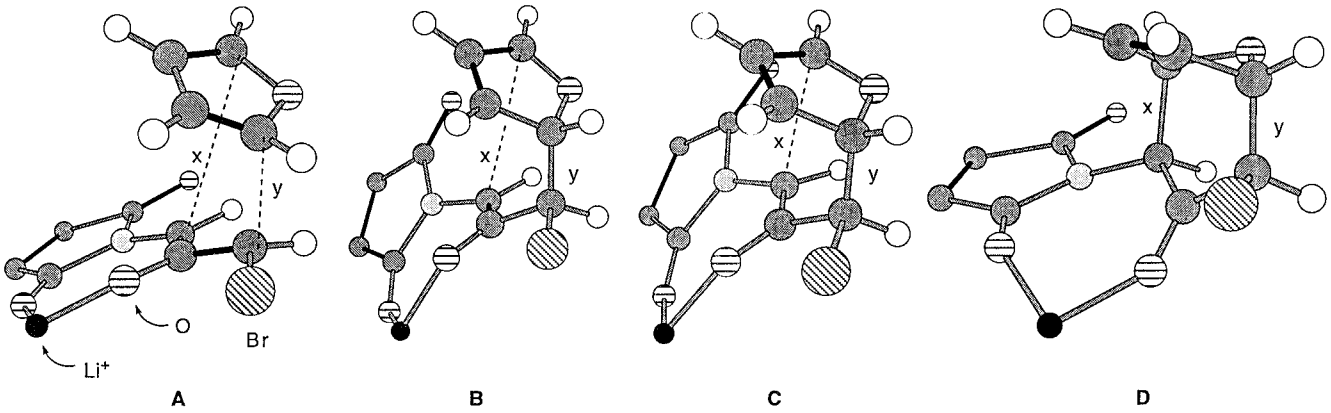


Figure 5. Structures of the stationary points on the reaction coordinate for the endo, stepwise cycloaddition of Li^+-**1** and furan (PM3). **A** = transition structure, first bond forming. **B** = intermediate, first bond formed. **C** = transition structure, second bond forming. **D** = Li^+-product. A portion of the aromatic ring of the phthalimide group has been removed for the sake of clarity. For *x* (bonding near N) and *y* (bonding near Br) distances, see Table 5.

Table 5. Energy and Geometrical Parameters for the Stationary States on the Pathway for the Reaction of Li^+-1 and Furan

	SM	A	B	C	D
H_f	111.028	122.318	94.742	96.406	56.879
ΔE^a	0.00	11.29	−16.29	−14.62	−54.15
freq[b]		−508.00		−191.11	
x^c		3.67	3.35	2.70	1.57
y		2.16	1.52	1.53	1.53

[a] Relative energy (kcal/mol). [b] Single imaginary frequency (cm^{-1}). [c] *x* and *y* distances are in angstroms. SM = furan + Li^+-**1**.

All solvents and liquid reagents were dried and distilled following standard procedures. All reactions were performed under an atmosphere of dry nitrogen. ^{1}H- and ^{13}C-NMR spectra were run in $CDCl_3$ at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane (0 ppm, ^{1}H) or $CDCl_3$ (77 ppm, ^{13}C) as internal standards. Substances for which C, H, N analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% of the assigned structure. Thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F-254 plates. R_f values indicated refer to TLC in the indicated solvent. Lithium perchlorate was dried in an air-oven (170 °C) and stored in a desiccator. Elemental analyses were performed by Schwartzkoff Laboratories, Woodside, NY.

***N*-Acetonylphthalimide (3).** This compound was prepared according to the procedure of Sheehan:[11] mp 122.8−123.5 °C (lit.[11] mp 122−123 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (m, 2H), 7.74 (m, 2H), 4.50 (s, 2H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.7, 167.7, 134.7, 132.0, 123.7, 47.1, 27.0; TLC R_f 0.54 (50% EtOAc/hexanes).

***N*-(1,3-Dibromoacetonyl)phthalimide (2).** To a slurry of *N*-acetonylphthalimide (**3**) (3.00 g, 14.8 mmol) in 59 mL of freshly distilled CCl_4 at 0 °C was added 1.5 mL of bromine. The resulting orange-brown slurry was stirred at ambient temperature until the reaction was complete as monitored by TLC. The reaction mixture was poured into H_2O and extracted with ether (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography of the resulting white solid (30% EtOAc/hexanes) gave 3.25 g (61% yield) of dibromide **2** as a white solid that was recrystallized (EtOAc/hexanes) as white cubes: mp 125−126 °C (lit.[13] mp 126−127 °C).

General Procedure for Cycloaddition under TFE/TEA Conditions (Method A). In a flame-dried flask was dissolved 0.200 g (0.709 mmol) of phthalimide **2** in 2.8 mL of the appropriate diene and 1.4 mL of 2,2,2-trifluoroethanol. After the mixture was cooled to 0 °C, 0.148 mL (0.106 mmol) of NEt_3 was added to the reaction mixture, effecting a change in color from clear to yellow. The solution was stirred for 4 h while being gradually warmed to room temperature. The reaction mixure was poured into H_2O and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/hexanes) gave the desired bromo ketones as white solids. Separation of the isomers was accomplished using radial chromatrography (25% EtOAc/ hexanes).

General Procedure for Cycloaddition under $LiClO_4$/CH_3CN/TEA Conditions (Method B). In a flame-dried flask under nitrogen was dissolved 0.0505 g of dibromophthalimide **2** in 0.55 mL of freshly distilled CH_3CN, 5−10 equiv of the appropriate diene, and 0.059 g of $LiClO_4$ (1 M). To this clear solution was added 0.033 mL of NEt_3 dropwise, which caused an immediate change in color from clear to yellow and eventually brown. After completion of the reaction, as monitored by TLC, the mixture was poured into H_2O and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/hexanes) gave the desired bromo ketones as white solids.

2α-Bromo-4α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (4) was recrystallized from EtOAc/hexanes to give white cubes: mp 170 °C dec; IR ($CDCl_3$) 1779, 1742, 1723, 1341, 1296, 1219, 1128 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 4H), 6.61 (dd, 1H, J = 6.5, 1.5 Hz), 6.55 (dd, 1H, J = 6.5, 1.5 Hz), 5.39 (d, 1H, J = 4.8 Hz), 5.23 (dd, 1H, J = 4.8, 1.7 Hz), 5.09 (dd, 1H, J = 4.8, 1.7 Hz), 4.81 (d, 1H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.3, 135.8, 134.8, 134.5, 131.1, 123.7, 82.3, 81.2, 62.6, 53.2; MS *m*/*z* (relative intensity) 268 (100), 172 (12), 160 (17), 121 (44), 104 (52), 76 (59), 50 (27); TLC R_f 0.21 (25% EtOAc/hexanes). Anal. Calcd for $C_{15}H_{10}BrNO_4$: C, 51.75; H, 2.90; N, 4.02. Found: C, 51.70; H, 3.01; N, 3.97.

2α-Bromo-4α-phthalimidobicyclo[3.2.1]oct-6-en-3-one (6) was recrystallized from EtOAc/hexanes to afford white needles: mp 187.6−188.1 °C; IR ($CDCl_3$) 3155, 2962, 1793, 1776, 1721, 1469, 1384 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.42 (dd, 1H, J = 5.4, 2.7 Hz), 6.29 (dd, 1H, J = 5.4, 2.7 Hz), 5.15 (d, 1H, J = 3 Hz), 4.85 (d, 1H, J = 3.6 Hz), 3.41 (m, 1H), 3.11 (m, 1H), 2.48 (m, 1H), 2.22 (d, 1H, J = 12.3 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 194.5, 138.1, 134.6, 134.3, 133.4, 123.7, 63.3, 57.6, 48.8, 45.6, 43.9; MS *m*/*z* (relative intensity) 347 (M^+, 10), 348 (M + 2, 3), 279 (12), 167 (31), 149 (100), 71 (23), 70 (22), 57 (44), 55 (18); TLC R_f 0.26 (25% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05. Found: C, 55.21; H, 3.39; N, 3.99.

2α-Bromo-4β-phthalimidobicyclo[3.2.1]oct-6-en-3-one (7) was recrystallized from EtOAc/hexanes as white cubes (25%): mp 185.5−186 °C; IR ($CDCl_3$) 3154, 2960, 2900, 2349, 2329, 1792, 1774, 1720, 1469, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.47 (dd, 1H, J = 5.7, 2.6 Hz), 6.29 (dd, 1H, J = 5.7, 2.9 Hz), 5.35 (dd, 1H, J = 1.1, 4.2 Hz), 4.39 (m, 1H), 3.35 (m, 1H), 3.02 (m, 1H), 2.51 (d, 1H, J = 12.3 Hz), 2.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.8, 167.7, 138.2,

135.6, 134.7, 131.7, 123.9, 58.5, 57.7, 46,5, 45.2, 37.1; MS *m/z* (relative intensity) 345 (M^+, 3), 347 (M^+, 3), 266 (79), 207 (33), 200 (100), 172 (26), 160 (50), 104 (62), 91 (67), 77 (43), 76 (69); TLC R_f 0.36 (25% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05. Found: C, 55.66; H, 3.48; N 3.86.

2β-Bromo-4α-phthalimidobicyclo[3.2.1]oct-6-en-3-one (9) was recrystallized from EtOAc/hexanes as white prisms: mp 190−191.5 °C; IR ($CDCl_3$) 3154, 2962, 2349, 1776, 1722, 1612, 1469, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.45 (m, 1H), 6.12 (m, 1H), 5.49 (d, 1H, J = 3 Hz), 4.34 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.74 (d, 1H, J = 12 Hz), 2.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.4, 139.8, 131.7, 123.8, 59.8, 49.2, 47.0, 45.6, 40.5; MS *m/z* (rel intensity) 266 (63), 200 (100), 172 (24), 160 (37), 119 (28), 104 (41), 91 (77), 76 (60); TLC R_f 0.36 (25% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05. Found: C, 56.23; H, 3.64; N, 3.90.

2β-Bromo-4α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (8) was separated from the α,α isomer by radial chromatography (30% EtOAc/hexanes) and recrystallized from EtOAc/hexanes as white needles: IR ($CDCl_3$) 3154, 2984, 2902, 1817, 1793, 1723, 1469, 1383 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 4H), 6.66 (ddd, 1H, J = 0.6, 1.8, 6.0 Hz), 6.37 (dd, 1H, J = 1.8, 6.0 Hz), 5.75 (dd, 1H, J = 0.6, 4.5 Hz), 5.13 (m, 1H), 5.07 (dd, 1H, J = 2.0, 4.5 Hz), 4.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.0, 136.9, 134.7, 130.0, 123.9, 83.0, 81.0, 58.6, 47.7; MS *m/z* (rel intensity) 281 (8), 268 (100), 240 (17), 226 (16), 207 (18), 172 (12), 160 (21), 121 (58), 104 (55), 76 (55), 18 (31); TLC R_f 0.19 (25% EtOAc/hexanes).

1-Methyl-2α-bromo-4α-phthalimido-8-oxabicyclo[3.2.1]-oct-6-en-3-one (13a), 1-methyl-2α-bromo-4β-phthalimido-8-oxabicylo[3.2.1]oct-6-en-3-one (14a), and 1-methyl-4α-bromo-2α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (15a) were isolated as a mixture of isomers (method A, 77%; method B, 73% yield of a mixture of isomers after chromatography) and recrystallized from EtOAc/hexanes as white needles: mp 157−158 °C; IR ($CDCl_3$) 3154, 2984, 2901, 2349, 1792, 1722, 1469, 1383 cm^{-1}; **(13a)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.48 (dd, 1H, J = 1.8, 6 Hz), 6.35 (d, 1H, J = 6 Hz), 5.35 (d, 1H, 4.8 Hz), 5.07 (dd, 1H, J = 1.8, 4.8 Hz), 4.61 (s, 1H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.1, 135.1, 134.7, 134.4, 123.8, 89.0, 80.9, 61.7, 60.4, 22.2; MS *m/z* (rel intensity) 282 (27), 254 (24), 122 (19), 104 (49), 82 (36), 76 (56), 43 (100); TLC R_f 0.31 (30% EtOAc/hexanes); **(14a)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.53 (m, 1H), 6.35 (m, 1H), 5.30 (m, 1H), 4.99 (m, 1H), 4.35 (bs, 1H) 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.3, 167.4, 138.5, 131.8, 131.6, 111.6, 87.8, 82.6, 61.4, 58.9, 22.0; TLC R_f 0.31 (30% EtOAc/hexanes); **(15a)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.42−6.50 (m, 2H), 5.22 (dd, 1H, J = 2, 4.8 Hz), 5.19 (s, 1H), 4.79 (d, 1H, J = 4.8 Hz), 1.5 (s, 3H); MS *m/z* (rel intensity) 362 (M^+, 0.04), 258 (100), 231 (7), 130 (22), 104 (16), 76 (20); TLC R_f 0.31 (30% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{12}BrNO_4$: C, 53.06; H, 3.34; N, 3.87. Found: C, 53.07; H, 3.30; N, 3.76.

1-Methoxy-4α-bromo-2α-phthalimido-8-oxabicyclo[3.2.1]-oct-6-en-3-one (15b) was recrystallized from EtOAc/hexanes as white cubes: mp 177 °C dec; IR ($CDCl_3$) 3154, 2982, 2902, 2358, 1793, 1724, 1469, 1384, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (m, 4H), 6.62 (dd, 1H, J = 2, 6.0 Hz), 6.44 (d, 1H, J = 6.0 Hz), 5.36 (s, 1H), 5.23 (dd, 1H, J = 2, 5.1 Hz), 4.80 (d, 1H, J = 5.1 Hz), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.6, 167.9, 135.4, 134.7, 134.5, 133.7, 124.0, 123.8, 111.9, 78.8, 66.4, 52.4, 52.3; MS *m/z* (rel intensity) 299 (1), 297 (0.8), 265 (6), 160 (34), 104 (10), 76 (9), 44 (42), 18 (100); TLC R_f 0.31 (30% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{12}BrNO_5$: C, 50.82; H, 3.20; N, 3.70. Found: C, 50.75; H, 3.23; N, 3.66.

1-Methoxy-2α-bromo-4α-phthalimido-8-oxabicyclo[3.2.1]-oct-6-en-3-one (13b) and 1-methoxy-2α-bromo-4β-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (14b) were isolated as a mixture of isomers and recrystallized from EtOAc/hexanes as white needles: mp 183.8−186.4 °C; IR ($CDCl_3$) 3154, 2979, 2902, 2349, 1792, 1773, 1723, 1469, 1384, 1336 cm^{-1}; **(13b)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.62 (dd, 1H, J = 2, 6 Hz), 6.44 (d, 1H, J = 6 Hz), 5.35 (d, 1H, J = 4.8 Hz), 5.07 (dd, 1H, J = 2, 4.8 Hz), 4.78 (s, 1H), 3.55 (s, 3H); **(14b)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.60 (m, 1H), 6.53 (dd, 1H, J = 2, 6 Hz), 5.45 (s, 1H), 5.02 (m, 1H), 4.33 (m, 1H), 3.45 (s, 3H); **(13b + 14b)** ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.7, 198.1, 167.5, 136.3, 134.6, 133.8, 132.5, 131.8, 123.9, 110.9, 109.9, 79.9, 59.4, 55.4, 52.1, 51.6, 50.7; MS *m/z* (rel intensity) 297 (44), 269 (11), 266 (16), 237 (15), 210 (23), 104 (57), 76 (48), 50 (18), 44 (48), 18 (100); TLC R_f 0.24 (30% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{12}BrNO_5$: C, 50.82; H, 3.20; N, 3.70. Found: C, 51.06; H, 3.23; N, 3.76.

General Procedure for the Reductive Debromination using Zn/Ultrasound. In a round-bottom flask was suspended 0.020 g (0.0577 mmol) of cycloadduct in 0.34 mL of a saturated solution of NH_4Cl/MeOH and the resulting suspension cooled to 0 °C. To this cool suspension was added 0.019 g of Zn powder and the mixture immersed in a 0 °C sonication bath. The reaction was monitored by TLC (30% EtOAc/hexanes) until complete. The reaction mixture was poured into a saturated solution of EDTA and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/hexanes) gave the desired ketone as a white solid.

2α-Phthalimidobicyclo[3.2.1]oct-6-en-3-one (11) was recrystallized from EtOAc/hexanes as white needles (67%): IR ($CDCl_3$) 3076, 1782, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (m, 4H), 6.18 (m, 2H), 4.98 (d, 1H, J = 3 Hz), 3.08 (m, 1H), 3.01 (m, 1H), 2.60 (dd, 2H, J = 1.5, 3.0 Hz), 2.34 (m, 1H), 2.08 (d, 1H, J = 11 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 135.7, 134.9, 134.4, 123.6, 62.5, 45.5, 45.3, 43.9, 39.0; MS *m/z* (rel intensity) 267 (M^+, 46), 268 (M + 1, 9), 269 (M + 2, 1), 160 (77), 120 (77), 104 (67), 92 (61), 91 (59), 79 (32), 78 (49), 77 (56), 76 (100), 66 (78), 50 (47), 18 (43); TLC R_f 0.24 (25% EtOAc/hexanes).

2β-Phthalimidobicyclo[3.2.1]oct-6-en-3-one (12) was recrystallized from EtOAc/hexanes as white needles (60%): IR ($CDCl_3$) 3065, 1783, 1770, 1717, 1349, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (m, 4H), 6.32 (dd, 1H, J = 2.7, 5.6 Hz), 4.24 (bs, 1H), 3.09 (dd, 1H, J = 1.0, 4.6 Hz), 3.01 (m, 2H), 2.54 (d, 1H, J = 18.6 Hz), 2.41 (d, 1H, J = 12.5 Hz), 1.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.6, 165.1, 142.6, 134.7, 129.4, 123.9, 84.9, 81.6, 62.3, 53.7, 16.2; MS *m/z* (rel intensity) 267 (M^+, 63), 268 (M + 1, 12), 269 (M + 2, 1), 270 (M + 3, 0.2), 224 (23), 174 (21), 160 (100), 130 (33), 120 (67), 104 (76), 92 (61), 76 (97), 66 (72), 50 (34); TLC R_f 0.38 (25% EtOAc/hexanes).

1-Methyl-4α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (16a), 1-methyl-4β-phthalimido-8-oxabicyclo[3.2.1]-oct-6-en-3-one (18a), and 1-methyl-2α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (17a) were isolated as a mixture of isomers and recrystallized from EtOAc/hexanes as white needles (65%): mp 230 °C dec; IR ($CDCl_3$) 3154, 2983, 2902, 1817, 1793, 1720, 1469, 1384, 1096 cm^{-1}; **(16a)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (m, 4H), 6.38 (dd, 1H, J = 2, 6 Hz), 6.21 (d, 1H, J = 6 Hz), 5.18 (d, 1H, J = 4.8 Hz), 5.08 (dd, 1H, J = 2, 4.8 Hz), 2.69, 2.76 (ABq, 2H, J_{AB} = 16.2 Hz), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.9, 136.4, 134.5, 133.1, 123.8, 85.0, 80.6, 60.5, 51.6, 23.2; **(18a)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (m, 4H), 6.30 (m, 2H), 5.05 (bs, 1H), 4.35 (bs, 1H), 3.33 (d, 1H, J = 17.4 Hz), 2.66 (d, 1H, J = 17.4 Hz), 1.58 (s, 3H); **(16a + 18a)** ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0, 140.3, 136.5, 134.6, 133.1, 130.5, 123.8, 85.1, 82.3, 80.7, 60.5, 56.2, 52.4, 51.6, 23.3; **(17a)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.28 (m, 1H), 6.30 (d, 1H), J = 6 Hz), 5.11 (m, 1H), 4.99 (bs, 1H), 2.90 (dd, 1H, J = 6, 16.5 Hz), 2.58 (d, 1H, J = 16.5 Hz); MS *m/z* (rel intensity) 283 (M^+, 13), 284 (M + 1, 2), 285 (M + 2, 0.3), 240 (71), 136 (33), 132 (58), 108 (38), 104 (100), 76 (78), 50 (25); TLC R_f 0.21 (25% EtOAc/hexanes). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 66.88; H, 4.90; N, 4.78.

1-Methoxy-4α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (16b) and 1-methoxy-4β-phthalimido-8-oxabicyclo-[3.2.1]oct-6-en-3-one (18b) were isolated as a mixture of isomers and recrystallized from EtOAc/hexanes as white needles (77%): mp 166−169 °C; IR ($CDCl_3$) 3154, 2992, 2942, 2902, 1816, 1789, 1720, 1469, 1386, 1341, 1284, 1177, 1162, 1095 cm^{-1}; **(16b)** ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 4H),

6.48 (dd, 1H, $J = 2$, 6 Hz), 6.27 (d, 1H, $J = 6$ Hz), 5.16 (d, 1H, $J = 4.8$ Hz), 5.07 (m, 1H), 3.47 (s, 3H), 2.93 (ABq, 2H, $J_{AB} = 16.5$ Hz); **(18b)** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 4H), 6.46 (m, 1H), 6.38 (d, 1H, $J = 5.7$ Hz), 5.07 (d, 1H, $J = 1.8$ Hz), 4.12 (s, 1H), 3.52 (d, 1H, $J = 17.4$ Hz), 3.45 (s, 3H), 2.83 (d, 1H, $J = 17.4$ Hz); **(16b + 18b)** ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.7, 198.1, 167.5, 136.3, 134.6, 133.8, 132.5, 131.8, 123.9, 110.9, 109.9, 79.9, 59.4, 55.4, 52.1, 51.6, 50.7; MS *m*/*z* (rel intensity) 299 (M^+, 4), 300 (M + 1, 0.9), 270 (52), 239 (20), 198 (19), 187 (31), 152 (24), 132 (91), 124 (33), 104 (100), 76 (68), 50 (22); TLC R_f 0.20 (25% EtOAc/hexanes).

1-Methoxy-2α-phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (17b) was recrystallized from EtOAc/hexanes as white needles (55%): mp 187−188 °C; IR ($CDCl_3$) 3154, 2982, 2902, 1817, 1793, 1777, 1720, 1469, 1386, 1340, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 4H), 6.45 (dd, 1H, $J = 2.0$, 6.0 Hz), 6.27 (d, 1H, $J = 6.0$ Hz), 5.16 (s, 1H), 5.13 (dd, 1H, $J = 2.0$, 5.4 Hz), 3.41 (s, 3H), 2.94 (dd, 1H, $J = 5.4$, 17.0 Hz), 2.57 (d, 1H, $J = 17.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.8, 135.7, 134.5, 134.4, 132.8, 123.9, 123.7, 75.3, 65.4, 52.0, 44.0; MS *m*/*z* (rel intensity) 299 (M^+, 22), 300 (M + 1, 4), 301 (M + 2, 0.7), 267 (17), 239 (60), 211 (20), 152 (25), 111 (100), 104 (59), 76 (64), 50 (27); TLC R_f 0.14 (25% EtOAc/hexanes).

2α-Phthalimido-8-oxabicyclo[3.2.1]oct-6-en-3-one (10) was recrystallized from EtOAc/hexanes as white needles (68%): mp 167−168 °C; IR ($CDCl_3$) 3154, 2982, 2901, 2356, 1815, 1791, 1719, 1653, 1469, 1384 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 4H), 6.42 (m, 2H), 5.20 (d, 1H, $J = 4.6$ Hz), 5.13 (m, 1H), 5.06 (dd, 1H, $J = 1.5$, 4.6 Hz), 2.94 (dd, 1H, $J = 5.4$, 16.0 Hz), 2.61 (d, 1H, $J = 16.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.6, 134.6, 133.3, 133.2, 123.8, 80.3, 78.3, 61.4, 45.6; MS *m*/*z* (rel intensity) 269 (M^+, 10), 270 (M + 1, 2) 271 (M + 2, 0.2), 160 (100), 132 (13), 104 (46), 94 (12), 76 (39); TLC R_f 0.16 (25% EtOAc/hexanes).

Acknowledgment. Financial support given by Dartmouth College and the National Science Foundation (NSF CHE-9421077) is greatly appreciated. Dawn Lawrie was helpful in the preparation of **2**. Funding from the Keck Fund and the Dreyfus Foundation was used to purchase the computer equipment used in part of this investigation.

Supporting Information Available: The Cartesian coordinates for Li^+-**1**, the four transition structures in Table 4, and the four stationary states along the Li^+-**1**/furan reaction coordinate. ^{1}H and ^{13}C NMR spectra of compounds **8**, **10**−**12**, **16a**,**b**, **17a**,**b**, and **18a**,**b** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951609Z