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Carbocyclic Ring Construction *via* Intramolecular Ionic Diels−Alder Reactions of *in Situ*-Generated, Heteroatom-Stabilized Allyl Cations in Highly Polar Media

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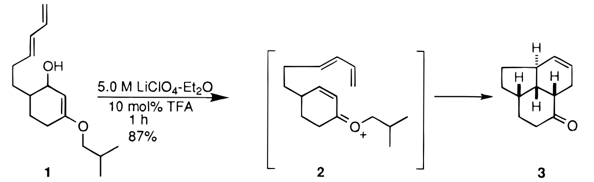
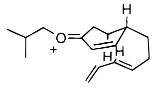
The intramolecular Diels−Alder reaction, which has received enormous attention during the past 25 years, is a powerful method for the formation of two rings in a one-step process.[1] In many of the cases cited in the literature, particularly those involving conformationally restricted substrates, temperatures in excess of 180 °C or ultrahigh pressures are required. We detail below a general strategy for the construction of carbocyclic ring systems *via* intramolecular ionic Diels−Alder reactions[2] in highly polar media[3] which obviates the necessity for high temperatures and pressures. The method features *in situ* generation of heteroatom-stabilized allyl cations which undergo subsequent [4 + 2] cycloaddition at ambient temperature (cf. eq 1).



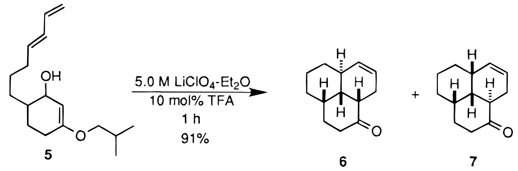
1 **2** **3** (1)

The strategy outlined in eq 1 was based, in part, on our observation that *β,β*-disubstituted allylic alcohols give rise to allyl cations upon exposure to concentrated solutions of lithium perchlorate in diethyl ether containing catalytic acid.[4] It was reasoned that (1) the highly polar medium would further stabilize the heteroatom-stabilized allyl cation **2** and (2) anhydrous lithium perchlorate would effectively sequester any water produced, thus preventing conversion of **2** to the corresponding cyclohexenone. In a preliminary experiment, a 0.02 M solution of **1**[5] in diethyl ether was slowly added *via* a syringe pump (1 h) to a 5.0 M solution of lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid. After 30 min at ambient temperature, tricyclic ketone **3**[7] was isolated in 87% yield. The exclusive formation of the *exo* cycloadduct **3** is undoubtedly due to an unfavorable interaction in the *endo* transition state between the axial C(5) hydrogen atom and the olefinic hydrogen atom of the diene (cf. **4**). Similar observations



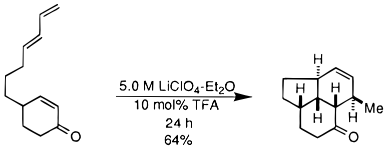
4

were made with substrate **5** (eq 2). When **5** was subjected to identical conditions, the reaction was facile, giving rise to a 91% yield of **6** and **7**[8a] in a ratio of 4:1, with the major product being derived from an *exo* transition state. Both **6** and **7** are stable under the reaction conditions.



5 **6** **7** (2)

Evidence that the above reactions are, indeed, ionic Diels−Alder reactions which proceed *via* heteroatom stabilized allyl cations rather than the corresponding cyclohexenone follows from a number of control experiments. Note that when lithium perchlorate is excluded from the reaction (eq 2), only cyclohexenone **8** is isolated (>90% yield). Exposure of cyclohexenone **8**[6] to 5.0 M lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid requires 24 h to go to completion and gives rise not to tricyclic ketones **6** and **7** but, instead, to tricyclic ketone **9**, in which the diene migrates prior to [4 + 2] cycloaddition.[9] We were surprised to find that the intramolecular Diels−Alder reactions of 4-substituted cyclohexenones such as **8** do not proceed in 5.0 M lithium perchlorate−diethyl ether in the absence of protic acids. Conventional thermal cycloaddition of **8** required 40 h at 180 °C in order to realize a 53% yield of **6** and **7** in a ratio of 2:1. None of the *endo* product **10** could



8 **9**

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(1) For reviews on the intramolecular Diels−Alder reaction, see: Ciganek, E. *Org. React.* **1984**, *32*, 1. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.4, pp 513−550.

(2) For examples of intramolecular ionic Diels−Alder reactions, see: (a) Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1984**, *49*, 4674. (b) Gassman, P. G.; Singleton, D. A. *J. Org. Chem.* **1986**, *51*, 3075. Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8623. Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8624. Gorman, D. B.; Gassman, P. G. *J. Org. Chem.* **1995**, *60*, 977.

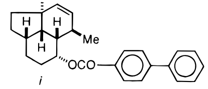
(3) For the use of highly polar media to promote Diels−Alder reactions, see: Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663. Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. Also see: Grieco, P. A. Organic Chemistry in Lithium Perchlorate/Diethyl Ether. In *Organic Chemistry: Its Language and Its State of the Art*; Kisakürek, V., Ed.; VCH: Basel, 1993; p 133.

(4) Grieco, P. A.; Collins, J. L.; Henry, K. J., Jr. *Tetrahedron Lett.* **1992**, *33*, 4735.

(5) (a) Prepared from the corresponding vinylogous ester[6] by reduction with lithium aluminum hydride in diethyl ether at 0 °C, followed by a nonaqueous workup. (b) Me or Et can be substituted for *i*-Bu.

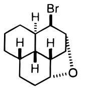
(6) The starting vinylogous esters and the 4-substituted cyclohexenones were prepared by the method of Stork: Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(7) Satisfactory combustion analyses and/or high-resolution mass spectra were obtained for all new compounds. In all cases, ^{1}H NMR, ^{13}C NMR, and IR spectra were consistent with the assigned structures. The stereochemical assignment for **3** was based on the ^{13}C NMR and ^{1}H NMR spectra of **9**, whose structure was confirmed by single-crystal X-ray analysis of the derived *p*-phenylbenzoate **i**.

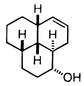


i

(8) (a) The structures for **6** and **7** were determined by single-crystal X-ray analysis of the derived bromo ether **ii** and alcohol **iii**, respectively.

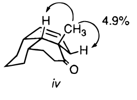


ii



iii

(b) The structure of **14** was determined by single-crystal X-ray analysis. (c) The structure of **15** was assigned on the basis of extensive ^{1}H NMR decoupling experiments and NOE measurements (cf. **iv**).



iv

(9) Cf.: Grieco, P. A.; Beck, J. P.; Handy, S. T.; Saito, N.; Daeuble, J. F. *Tetrahedron Lett.* **1994**, *35*, 6783.

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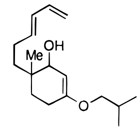
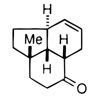
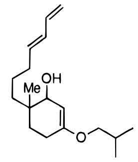
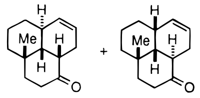
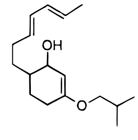
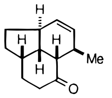
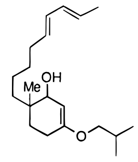
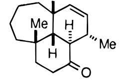
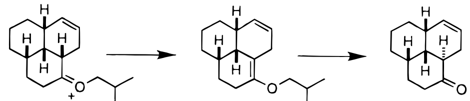
Table 1. Intramolecular Ionic Diels−Alder Reactions of *in Situ*-Generated, Heteroatom-Stabilized Silyl Cations[a]

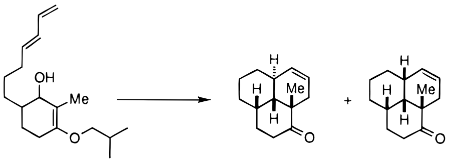
substrate	product(s)	%yield[b]
		90
	 4 : 1	95
		92
		65[c]

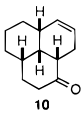
[a] To a 0.01 M solution of substrate in 5.0 M $LiClO_4$−Et_2O was added 10 mol % trifluoroacetic acid. After addition was complete, stirring was continued for 1 h. [b] Isolated yields. [c] A 31% yield of the corresponding cyclohexenone was isolated.

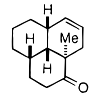
be detected, presumably because **10** equilibrates completely to **7** under the thermal conditions. Use of Lewis acids (e.g., Et_2AlCl) only served to decompose the starting enone.

The origin of *trans*-fused product **7** obtained upon exposure of **5** to 5.0 M $LiClO_4$−Et_2O containing 10 mol % trifluoroacetic acid warrants comment. Formation of **7** appears to be the result of the *endo*-derived [4 + 2] cycloadduct **10** undergoing complete equilibration adjacent to the carbonyl in the highly polar medium. Calculations indicate that **7** is more stable than **10** by 7.2 kcal! Alternatively, **7** could arise *via* a concerted reaction, followed by enolization of the intermediate oxonium ion **11** to isobutyl enol ether **12**. Such a mechanism would also account for the absence of **10**. Enol ether **12** has been isolated after very short reaction times. For example, when a 0.01 M solution of **5** in 5.0 M lithium perchlorate−diethyl ether was treated with 10 mol % trifluoroacetic acid for 1 min and quenched with an ice-cold saturated aqueous sodium bicarbonate solution, a 71% yield of **6** and **7** was isolated in a 4:1 ratio, along with a 7% yield of enol ether **12**. Alternatively, *trans*-fused **7** might arise from a stepwise cyclization[2b,10] that establishes the *trans* stereochemistry directly, thus bypassing both **10** and **11**. To test this possibility, we have examined a case in which the initial Diels−Alder adduct cannot undergo equilibration to a more stable cycloadduct. Slow addition of a 0.02 M solution of **13** in diethyl ether to a 5.0 M solution of lithium perchlorate in diethyl ether containing 10 mol % trifluoroacetic acid gave rise after a total of 3 h at ambient temperature to a 72% yield of **14**[8b] and **15**[8c] in a ratio of 4:1, along with 15% of the corresponding enone. No products, including the thermodynamically more stable tricyclic ketone **16**,[11] resulting from a stepwise process could be detected!


11 **12** **7**

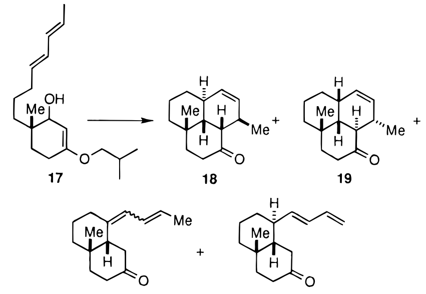

13 **14** **15**


10


16

Results from other substrates are shown in Table 1. In general, reactions are complete within 1 h after addition of the substrate is complete. It is of interest to note that, in the case leading to the formation of a 6-7-6 carbocyclic ring system, only the product derived from an *endo* transition state was observed.

It would thus appear that the observed cycloadducts are derived from a concerted process. However, in one isolated case (cf. substrate **17**), cycloadducts have been isolated (cf. **20** and **21**) which are the result of a stepwise process. When substrate **17** was exposed to 5.0 M $LiClO_4$−Et_2O containing 10% TFA for 1 h, a 56% yield of cycloadducts **18** and **19** was isolated in a ratio of 2:1. In addition, the partially cyclized decalones **20** and **21** were isolated in 24% yield in a ratio of 1.5:1, respectively. Note that the formation of **18** and **19** is consistent with a concerted mechanism, whereas **20** and **21** are the direct result of a competing stepwise reaction mechanism.


17 **18** **19**
20 **21**

In summary, an efficient, synthetically useful protocol has been developed for the construction of functionalized carbocyclic systems, which complements the work of Gassman.[2b] Further studies are underway to examine the scope of this ionic cycloaddition process for carbocyclic ring synthesis.

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Supporting Information Available: Spectral and other analytical data for all compounds reported, along with ORTEP views of five structures determined by single-crystal X-ray analysis and a representative experimental procedure (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) Haynes, R. K.; King, G. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 4743.

(11) Calculations indicate that **16** is more stable than **15** by 2.5 kcal.