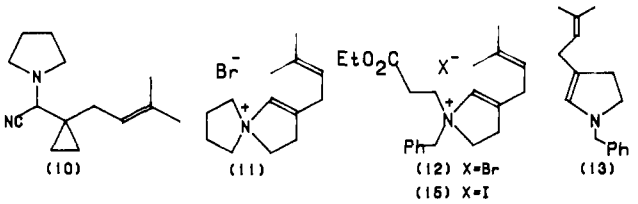
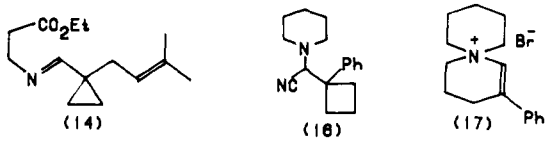
exchanged for acetonitrile, the enammonium salt 9 was obtained after stirring 4 h at room temperature (60%), extraordinarily mild conditions for this conversion.[1] A variety of functional groups are compatible with the rearrangement conditions, for example, cyanoamine **10** (prepared from the cyanohydrin and pyrrolidine, 75%), upon conversion to the iminium salt ($AgBF_4$ (1.55 equiv)/DME) and treatment with LiBr (1.55 equiv) and triethanolamine (1 equiv) (CH_3CN/room temperature (1.5 h) then reflux (2 h)) affords the spirocyclic enammonium salt **11** in 60%



yield.[8] Overall these reactions proceed rapidly under relatively mild, essentially neutral conditions. In the case of the acid sensitive system **5**, none of the desired salt **9** was obtained under acid catalysis. Similarly, attempted rearrangement of the related benzylimine also was unsuccessful using acid catalysis. It is particularly significant that the highly reactive endocyclic enamine functionality is conveniently masked in the easily handled enammonium salts. When it becomes desirable to liberate the masked enamine or dienamine to do further chemistry, one can accomplish this operation by employing the β-carbalkoxyethyl group[9] as the nitrogen protecting group from whose salts the enamine can be liberated upon mild base treatment. For example, exposure of ester salt **12** (prepared in the manner of **9**,[10] 54%) to DBU (1.1 equiv) and diethylamine (1.1 equiv) at 0 °C smoothly affords the sensitive enamine **13** (96%).

Considerable flexiblity exists for the generation of the iminium ions as well. For example, treatment of cyclopropyl imine **14**,



prepared by condensation of the aldehyde with β-alanine ethyl ester hydrochloride ($MgSO_4/Et_3N$/room temperature/18 h), with benzyl chloride (3 equiv)/NaI (3.8 equiv) in refluxing acetonitrile (4 h) affords directly the rearranged enammonium salt **15** in 66% yield.[11] The imine alkylation procedure is preferred where applicable owing to its generality and experimental simplicity.

The process also appears feasible for cyclobutyl systems, although only one case has been examined thus far.[12] Cyanoamine **16** (prepared as described for **10**) afforded spiro enammonium salt **17** in fair yield under somewhat more vigorous conditions ($AgBF_4$/LiBr/DMF/154 °C).[7] Further studies optimizing the rearrangement in cyclobutyl systems and establishing its scope, as well as evaluating preparation of stable precursors of the endocyclic enamines bearing no β substituent are in progress.

The significantly greater facility with which the above described iminium ions undergo rearrangement (generally mild and neutral conditions) provides an entry into previously unavailable enamine and dienamine systems via their stable enammonium salt precursors. Applications of this methodology to lycorine (**1**) and other more complex systems are under way and will be reported in due course.

Acknowledgment. We thank the National Institute of General Medical Sciences of the National Institutes of Health for a grant (GM-29290) in support of this research. We also thank Ayerst Laboratories for support in the form of a postdoctoral fellowship to J.P.S.

(7) All new compounds possessed satisfactory spectral data (IR, NMR, MS), and combustion analytical or high-resolution mass spectral data. Partial spectral data (NMR (δ) in $CDCl_3$): **5** (90 MHz) (trans isomer) 7.47 (d, J = 12 Hz, 1 H), 5.63 (d, J = 12 Hz, 1 H), 3.77 (s, 1 H), 2.62 (m, 2 H), 2.11 (s, 3 H), 1.79 (m, 2 H), 0.97–0.73 (m, 4 H); **8** (90 MHz) 9.44 (s, 1 H), 6.63 (t, J = 6 Hz, 1 H), 4.95 (d, J = 6 Hz, 2 H), 3.61 (t, J = 7 Hz, 2 H), 2.77 (t, J = 7 Hz, 2 H), 2.14 (s, 3 H); **9** (400 MHz) (trans isomer) 7.58 (d, J = 13 Hz, 1 H), 6.57 (s, 1 H), 6.22 (d, J = 13 Hz, 1 H), 4.03 (t, J = 7 Hz, 2 H), 3.92 (m, 2 H), 3.82 (m, 2 H), 3.08 (br t, 2 H) 2.37 (m, 4 H), 2.23 (s, 3 H), (cis isomer) 7.46 (d, J = 6 Hz, 1 H), 6.49 (s, 1 H), 5.48 (d, J = 6 Hz, 1 H), 3.60 (t, J = 7 Hz, 2 H), 3.49 (m, 4 H), 2.78 (br t, 2 H), 2.45 (m, 4 H), 2.17 (s, 3 H); **15** (300 MHz) 7.41 (m, 5 H), 6.15 (s, 1 H), 5.08 (AB q, 2 H), 4.93 (m, 1 H), 4.22 (m, 6 H), 2.89 (m, 2 H), 2.71 (d, 2 H), 2.43 (m, 1 H), 1.92 (m, 1 H), 1.68 (s, 3 H), 1.56 (s, 3 H), 1.23 (t, 3 H); **16** (300 MHz), 7.33 (m, 5 H), 3.74 (s, 1 H), 2.46 (dt, $J_1 = J_2$ = 7 Hz, 4 H), 2.25 (m, 4 H), 2.00 (m, 2 H), 1.38 (m, 6 H); **17** (400 MHz) 7.40 (m, 5 H), 6.78 (s, 1 H), 3.90 (m, 6 H), 2.73 (t, 2 H), 2.28 (app t, 2 H), 1.92 (m, 6 H).

(8) The presence of at least 1 equiv of a nonquaternizable tertiary amine base greatly facilitates the production of clean products in some instances. A variety of tertiary amines including diisopropylethylamine function well; however, triethanolamine offers the additional practical advantage of affording water-soluble salts easily separable from the enammonium salt products. The mechanistic ramifications of this observation are currently under investigation.

(9) The product in this case is a mixture of bromide and tetrafluorobrate salts.

(10) Protection of activated olefins by amines has been widely utilized in the Robinson annulation: Jung, M. E. *Tetrahedron* **1976**, *32*, 3. Protection of oxygen by the *p*-toluenesulfonyl ethyl group has also been reported: Miller, A. W.; Stirling, C. J. M. *J. Chem. Soc. C* **1968**, 2612.

(11) A single case of alkylation of an NH imine with methyl iodide was described by Stevens and co-workers: Stevens R. V.; Ellis, M. C.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5576.

(12) A brief study of the cyclobutyl analogue of the cyclopropyl imine rearrangement was conducted by Stevens and co-workers, and it was found to proceed even more sluggishly (temperature required was ≥170 °C): Stevens, R. V.; Shev, J. T. *J. Chem. Soc., Chem. Commun.* **1975**, 682. The greater facility of the iminium ion rearrangement proves particularly advantageous in these cases.

Intramolecular [2 + 2] Cycloadditions of Ketenes and Keteniminium Salts to Olefins

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Cyclobutanones are versatile synthetic intermediates[1] used in processes such as geminal[2] or vicinal[3] alkylation. They are readily prepared by the reaction of activated ketenes[4] or keteniminium salts[5] with olefins. The intramolecular version of these cycloadditions could offer promising routes for the regio- and stereocontrolled synthesis of polycyclic compounds. Isolated examples of intramolecular thermal[6] or photochemical[7] cycloadditions in-

(1) For selected examples, see: (a) Martin, P.; Greuter, H.; Bellus, D.; *Helv. Chim. Acta* **1981**, *64*, 64. (b) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (c) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, 2163. (d) Goldstein, S.; Vannes, P.; Houge, C.; Frisque-Hesbain, A. M.; Wiaux-Zamar, C.; Ghosez, L. *J. Am. Chem. Soc.* **1981**, *103* 4616.

(2) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224.

(3) (a) Ghosez, L. "Stereoselective Synthesis of Natural Products"; Bartmann, W., Winterfeldt, E., Eds.; Excerpta Medica: Amsterdam–Oxford, 1979; pp 93–105. (b) Michel, P.; O'Donnell, M. J.; Hesbain-Frisque, A. M.; Ghosez, L.; Declercq, J. P.; Germain, G.; Van Meerssche, M.; *Tetrahedron Lett.* **1980**, 2577.

(4) Recent review: Ghosez, L.; O'Donnell, M. J. "Pericyclic Reactions"; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, pp 79–140.

(5) (a) Ghosez, L.; Marchand-Brynaert, J. "Iminium Salts in Organic Chemistry Part 1; Böhme, J., Viehe, H. G., Eds., Wiley: New York, 1976; pp 421–532. (b) Falmagne, J. B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879.

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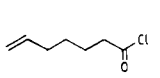
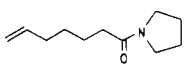
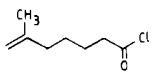
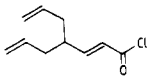
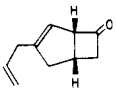
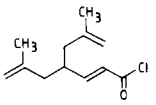
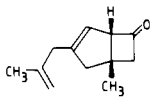
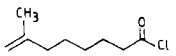
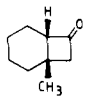
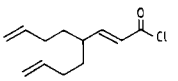
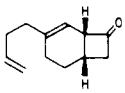
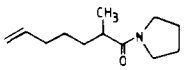
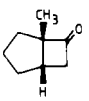
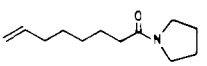
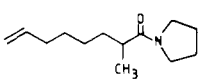
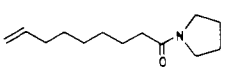
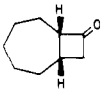
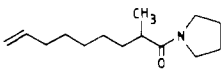
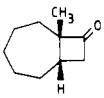
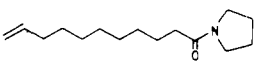
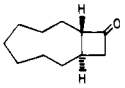
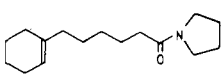
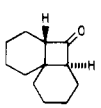
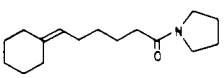
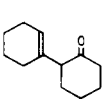
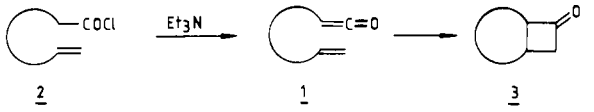
Table I. Intramolecular Cycloaddition of Ketenes and Keteniminium Salts Derived from Unsaturated Acids

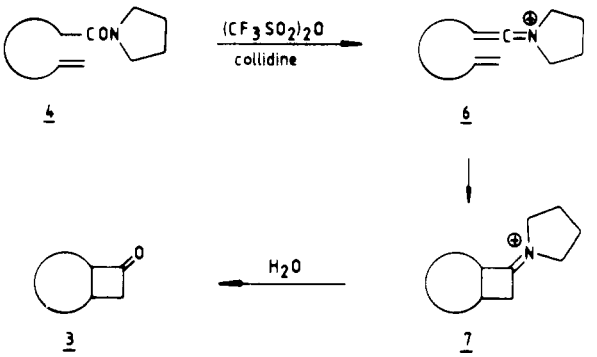
entry	unsaturated acid chlorides **2** or amide **4**	prod **3**	yield
a.			3%[a]
			75%
b.			80%
c			83%
d.			84%
e.			3%[a]
f.			0%
g.			87%
h.			65%
i.			89%
j.			71%
k.			78%
l.			72%
m.			30%
n.			55%[b]

[a] A lactonic dimer could be isolated. [b] The reaction also gave a 10% yield of **3m** resulting from a partial isomerization of **4n** to **4m** in the presence of traces of triflic acid.

Scheme I



Scheme II



volving ketenes and olefins have been reported but no systematic study of their synthetic potential has been undertaken. There is so far no report of intramolecular [2 + 2] cycloadditions of keteniminium salts and olefins. This paper presents the preliminary results of a study aiming at developing this reaction as a general synthetic tool. A nice complementary work by Snider, Hui, and Kulkarni is described in an accompanying paper.[8]

Our initial studies involved alkenylketenes **1** derived from unsaturated acid chlorides **2** (Table I, entries a–f; Scheme I).[9,10] The ketenes of entries a–c were generated by adding slowly a 4% solution of triethylamine (1.1 equiv) to a 0.2% solution of the acid chloride in refluxing CH_2Cl_2. It was anticipated that the entropy-assisted intramolecular cycloadditions could favorably compete with the usually fast oligomerization of the ketene. However, the aldoketene derived from **2a** gave a very low yield of the expected cycloadduct **3a** even under these high-dilution conditions. As shown earlier,[6c] introduction of a methyl group at the double bond has a favorable effect on the cycloaddition which occurs in 80% yield (entry b). On the other hand the adducts **3c** and **3d** were readily obtained in high yield in more concentrated (10%) solution at room temperature. This observation suggests an enhancement of the enophilic reactivity of the ketene by conjugation. Furthermore, a cycloaddition involving a ketene intermediate such as **1c** should benefit from the presence

(6) Beereboom, J. J. *J. Am. Chem. Soc.* **1963**, *85*, 3525; *J. Org. Chem.* **1965**, *30*, 4230. (b) Erman, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 779. (c) Baldwin, S. W.; Page, E. H., Jr. *J. Chem. Soc., Chem. Commun.* **1972**, 1337. (d) Leyendecker, F.; Bloch, R.; Conia, J. M. *Tetrahedron Lett.* **1972**, 3703. (e) Bisceglia, R. H.; Cheer, C. J. *J. Chem. Soc., Chem. Commun.* **1973**, 165. (f) Leyendecker, F. *Tetrahedron* **1976**, *32*, 349. (g) Maujean, A.; Marcy, G.; Chuche, J. *J. Chem. Soc., Chem. Commun.* **1980**, 92. (h) Kuzuya, M.; Miyake, F.; Okuda, T. *Tetrahedron Lett.* **1980**, 1043 and 2185. Alder, A.; Bellus, D. *J. Am. Chem. Soc.* **1983**, *105*, 6712.

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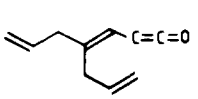
(9) All starting materials were prepared by known or conventional methods which will be described in the full account of this work.

(10) All compounds were characterized by IR, 200-MHz ^1H and 50-MHz ^{13}C NMR, and mass spectra or elemental analysis.

of two terminal double bonds because of the greater likelihood that one of them will be properly oriented for the cycloaddition.



1c

5

Increasing the chain length by one carbon practically suppresses the cycloaddition (entries e and f). This is not too surprising since, according to FMO theory,[4] the initial interaction between the olefin and the ketene should lead to bonding between C_1 and C_8 and, thus, to an eight-membered transition state. However, no bicyclic adduct (i.e., structure of type **5**) resulting from a C_1-C_7 interaction was observed.

Keteniminium salts are more electrophilic than ketenes and they do not dimerize.[5a] The requisite alkenylketeniminum salts **6** were generated in situ by slow addition of a 0.1 M solution of an unsaturated amide **4** and collidine (1.1 equiv) into a refluxing 0.1 M solution of freshly prepared triflic anhydride in 1,2-dichloroethane. The mixture was refluxed over a period of 20–40 h. The resulting cyclobutaniminium salt was directly hydrolyzed (H_2O–CCl_4, Δ) to the corresponding cyclobutanone **3** (Scheme II). As shown in table I (entries a and g–n) good yields of cycloadducts were obtained for a variety of chain lengths including those leading to cyclobutanones fused to a medium ring. The products **3g**, **3i** and **3k** resulting from α-substituted amides are interesting inasmuch as they are not available by the intermolecular [2 + 2] cycloadditions of keteniminium salts to olefins.

The reactions gave the cis-fused adducts except in the case of **4l**, which only produced the trans isomer **3l** probably as a result of an epimerization of the cis adduct under the reaction conditions.

The formation of the tricyclic ketone **3m** illustrates the generality of the method and indicates that it could become useful for the construction of spiranic skeletons. It also indicates that the regiochemistry of the cycloaddition is essentially governed by the electronic properties of the double bond: the less substituted terminal carbon atom becomes bonded to the electrophilic C_1 atom, a process that gives a tertiary carbenium intermediate[11] but also an eight-membered ring.

A limitation of the method is shown by the formation of **3n** from amide **4n**. This result indicates that, when the terminal olefinic carbon atom is more highly substituted, the cycloaddition does not occur but the olefin will be acylated by the keteniminum salt.

The present results clearly show the power of intramolecular cycloadditions of ketenes and keteniminium salts as a synthetic tool. The ketene reaction appears somewhat more limited by a competitive oligomerization of the ketene. Activation of the ketene by heteroatoms will probably provide a convenient solution to that problem.[8] The keteniminium route is more general and offers a potential for enantioselective intramolecular [2 + 2] cycloadditions.[12] We are pursuing our studies along these lines.

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Registry No. **2a**, 21430-12-6; **2b**, 39764-81-3; **2c**, 95018-90-9; **2d**, 95018-91-0; **2e**, 95018-92-1; **3a**, 13756-54-2; **3b**, 5212-68-0; **3c**, 95019-02-6; **3d**, 95019-03-7; **3e**, 39778-69-3; **3g**, 57706-99-7; **3g** (semicarbazole), 20609-42-1; **3h**, 27655-70-5; **3i**, 95019-04-8; **3i** (semicarbazole), 95019-08-2; **3j**, 29783-22-0; **3j** (semicarbazole), 95019-09-3; **3k**, 95019-05-9; **3k** (semicarbazole), 95019-10-6; **3l**, 95019-06-0; **3l** (semicarbazole), 95019-11-7; **3m**, 95019-07-1; **3m** (semicarbazole), 95019-12-8; **3n**, 1502-22-3; **4a**, 95018-93-2; **4g**, 95018-94-3; **4h**, 95018-95-4; **4i**, 95018-96-5; **4j**, 95018-97-6; **4k**, 95018-98-7; **4l**, 95018-99-8; **4m**, 95019-00-4; **4n**, 95019-01-5.

Supplementary Material Available: Spectroscopic data and elemental analyses of **2a–d,f**, **3a–d,g–n**, and **4a,g–n** (4 pages). Ordering information is given on any current masthead page.

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Intramolecular [2 + 2] Cycloadditions of Ketenes

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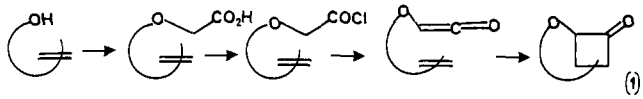
The stereospecific [2 + 2] cycloaddition of ketenes to alkenes has become a valuable method for the synthesis of cyclobutanones and compounds that can be derived from them.[2] It is one of the few general methods for carbofunctionalization of alkenes. Although isolated examples of intramolecular [2 + 2] cycloadditions of ketenes to alkenes are known,[3] the reaction has not been developed into a general synthetic method. The intramolecular reaction promises to extend the scope of the cycloaddition to less reactive alkenes and ketenes and to provide an efficient route to complex polycyclic compounds. The intramolecular nature of the reaction will lead to a high degree of stereo- and regioselectivity. We describe here our initial results which illustrate the validity of this approach. A complementary study by Ghosez, Greuter, and co-workers is described in an accompanying paper.[4]

Our initial exploratory work involved alkoxyketenes. This choice was based on the observation that ethoxyketene, generated from ethoxyacetyl chloride and NEt_3, adds to alkenes in 30–50% yield to give 2-ethoxycyclobutanones.[5] While these yields appear to be acceptable, they are achieved by using the alkene as the solvent. The related intramolecular reactions should proceed in better yield and provide synthetically useful products.

Reaction of an unsaturated alcohol with sodium hydride and bromoacetic acid in THF at reflux gave a 70–90% yield of the corresponding (alkenyloxy)acetic acid.[6] The acid was converted to the acid chloride by treatment with oxalyl chloride in benzene. The acid chloride (0.03 M) and NEt_3 were heated at reflux in benzene (2–4 h) under nitrogen to generate the ketene which reacted to give the cyclobutanone in 16–72% yield based on carboxylic acid (see eq 1). The results are shown in Table I.



(1)

Remarkably, the results indicate that the electronic effects of substituents on the double bond, rather than the connectivity pattern, control the regiochemistry of the cycloaddition.[2] Alkenes in which the internal carbon is more highly substituted react to give bicyclo[3.2.0]heptanes or bicyclo[4.2.0]octanes (entries 1–8). Alkenes in which the terminal carbon is more highly substituted react to give bicyclo[3.1.1]heptanes or bicyclo[4.1.1]octanes (entries 11 and 12). The formation of bridged ring compounds has not previously been observed in intramolecular cycloadditions of ketenes.

Alkenes with the substitution pattern of entries 1–5 are highly reactive since leading bond formation between the carbonyl carbon

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