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Lewis Acid-Mediated Generation of Bicyclo[5.3.0]decanes and Bicyclo[4.3.0]nonanes

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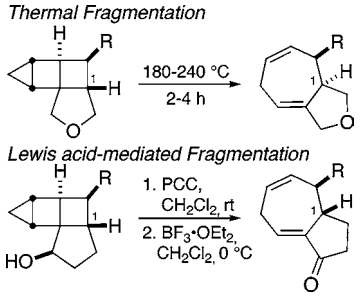
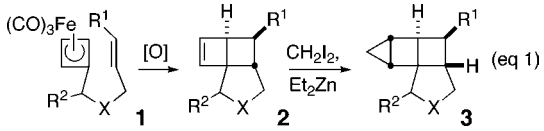
ABSTRACT



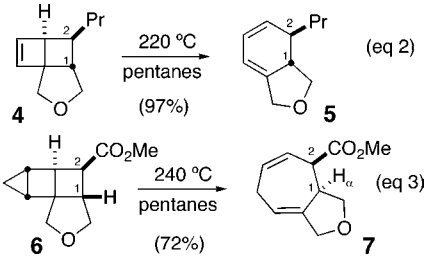
Fragmentation of the cyclobutane-containing adducts generated from intramolecular cycloadditions of cyclobutadiene with olefins provides rapid entry into bicyclo[5.3.0]decane and bicyclo[4.3.0]nonane ring systems. Whereas earlier studies featured thermal methods to achieve the desired rearrangements, a mild, Lewis acid-mediated fragmentation has been identified for substrates with appropriate functionality adjacent to the strained ring system. The substrate scope and stereochemical outcome of the acid-mediated fragmentation are complementary to the thermal ring expansions, particularly in the case of the bicyclo[5.3.0]decanes.

Intramolecular cycloadditions between cyclobutadiene and olefins provide access to highly functionalized strained ring systems such as **2** and **3** (eq 1).[1] These cycloadducts, in



turn, are useful for generating a variety of other polycyclic structures (Scheme 1).[2] Thermolysis of cyclobutene **4**, for example, generates tetrahydroisobenzofuran **5** (eq 2).[3] Likewise, the thermal rearrangement of cyclopropanated adduct

Scheme 1. Thermal Fragmentations of Strained Cyclobutadiene Cycloadducts



6 furnishes the bicyclo[5.3.0]decane ring system **7** (eq 3).[4] Of particular interest are the stereochemical consequences of these rearrangements; whereas, compound **5** is prepared without any changes in relative stereochemistry at the C1 and C2 positions, cycloheptadiene **7** is produced in a manner

(1) (a) Limanto, J.; Khuong, K. S.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 16310. (b) Limanto, J.; Tallarico, J. A.; Porter, J. R.; Khuong, K. S.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 14748. (c) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440. (d) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196.

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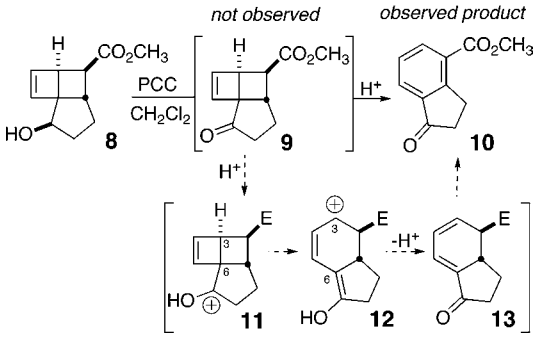
that inverts the C1 stereogenic center relative to the starting cyclopropane **6**.

In the course of learning how to further functionalize these cycloadducts, product **10** was unexpectedly isolated from a PCC oxidation of cyclobutene **8**, revealing the acid sensitivity of the ring system (Scheme 2). Importantly, compared to

Scheme 2. Rearrangement Observed during Oxidation

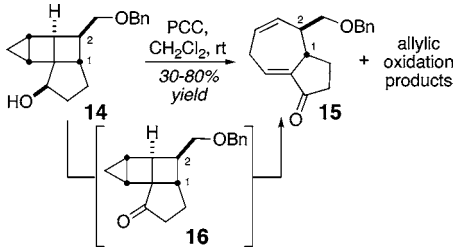


the elevated temperatures (200 °C, 2 h) employed in all prior fragmentations, this rearrangement proceeded at room temperature. Evidently, the acidic PCC served to activate ketone **9**, thereby weakening the central C3−C6 bond (**11** → **12**). Upon ring expansion, ketone **13** then underwent further oxidation to provide the aromatic ketone **10**. Based on this observation, we considered generalizing this transformation to allow for a mild, acid-mediated fragmentation of our other strained ring systems.

Brønsted and Lewis acid interactions with neighboring π−systems are known to facilitate rearrangements of strained rings.[5] Accordingly, we describe herein a mild, acid-catalyzed fragmentation that yields the bicyclo[5.3.0]decane and bicyclo[4.3.0]nonane products at ambient or reduced temperatures from the corresponding ketone precursors.

Bicyclo[5.3.0]decanes. The oxidation conditions employed in the ring expansion of cyclobutene substrate **8** were used to initiate the study of acid-mediated fragmentations of the cyclopropane-derived cyclobutenes (Scheme 3). When cyclopropane **14** was treated with PCC (1.5 equiv) at room temperature for 12 h, rearranged product **15** was obtained. It is of particular note that, in contrast to the thermal rearrangements of these systems, the ring fusion stereochemistry at C1 was retained under this oxidative protocol. Unfortunately, these rearrangements were unreliable, resulting in variable yields of ketone **15** often contaminated with over-oxidation products. Further optimization of the oxidation/rearrangement conditions was required in order to offer ketone **15** in a reliable and synthetically useful fashion.

Scheme 3. Preliminary Oxidative Fragmentation Results



One possibility was to separate the rearrangement into two steps. Perhaps alcohol **14** could be oxidized under milder conditions to provide ketone **16**, which then could be treated with a Lewis acid to initiate the ring expansion. This strategy avoids the problem of over-oxidation of the ring-opened product **15**.

Several oxidation methods were screened, including Swern, Dess−Martin, TPAP, and PDC. The study indicated that a carefully monitored PCC oxidation yielded the best results. Treatment of **14** with PCC for 2 h, followed by filtration, provided ketone **16** with a minor amount of the rearranged cycloheptadiene **15**. Treatment of **16** with $BF_3 \cdot Et_2O$ (1.2 equiv, 0 °C, 10−20 min) resulted in quantitative conversion to the ring-expanded 5−7 product **15** with little or no over-oxidation. This protocol proved general for accessing a variety of bicyclo[5.3.0]decanes.

Table 1 illustrates several thermal and Lewis acid-mediated fragmentations. As indicated in entries 1 and 2, the thermal rearrangements of **17** and **19** provide bicyclo[5.3.0]decanes **18** and **20** with an overall inversion of stereochemistry at C1.[4] As shown in Scheme 4, temporary rupture of the C1−C2 and C3−C7 bonds in the course of the rearrangements (**B**, **C**) accounts for the stereochemical change noted in these products. Unfavorable conformational interactions in the mechanism also explain why certain stereochemical variants, such as compound **21**, fail to rearrange cleanly under the thermal conditions (entry 3).

In contrast to the thermal rearrangements, entries 4−7 illustrate several acid-mediated ring expansions. Of particular

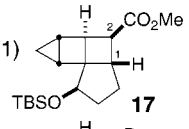
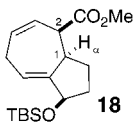
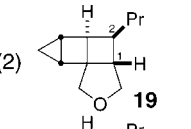
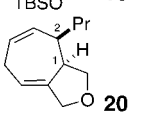
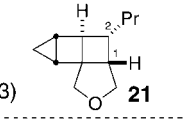
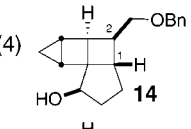
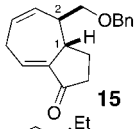
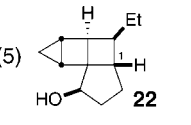
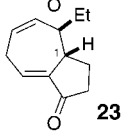
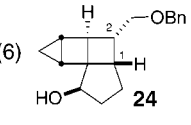
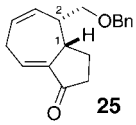
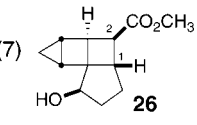
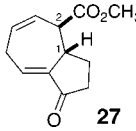
(2) (a) Bader, S. J.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 1201. (b) Lo, P. C.-K.; Snapper, M. L. *Org. Lett.* **2001**, *3*, 2819. (c) Randall, M. L.; Lo, P. C.-K.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534. (d) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478. For an application in total synthesis, see: (e) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071. For use of a related cyclobutene system, see: (f) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901.

(3) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196.

(4) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152.

(5) For some representative rearrangements of cyclobutyl ketones, see: (a) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106. (b) Hine, K. E.; Childs, R. F. *Can. J. Chem.* **1976**, *54*, 12. (c) Sano, T.; Horiguchi, Y.; Kambe, S.; Tsuda, Y. *Heterocycles* **1981**, *16*, 363. (d) Yamashita, M.; Onozuka, J.; Tsuchihashi, G.; Ogura, K. *Tetrahedron Lett.* **1983**, *24*, 79. (e) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem.* **1990**, *55*, 4614. (f) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707. (g) Kakiuchi, K.; Fukunaga, K.; Matsuo, F.; Ohnishi, Y.; Tobe, Y. *J. Org. Chem.* **1991**, *56*, 6742. For some representative rearrangements of cyclopropyl ketones, see: (h) Corey, E. J.; Balanson, R. D. *Tetrahedron Lett.* **1973**, 3153. (i) Grieco, P. A.; Finkelhor, R. S. *Tetrahedron Lett.* **1974**, 527. (j) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809. (k) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (l) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1029. (m) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (n) Patro, B.; Deb, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1992**, *57*, 2257. (o) Kalena, G. P.; Pradhan, P.; Banerji, A. *Tetrahedron* **1999**, *55*, 3209.

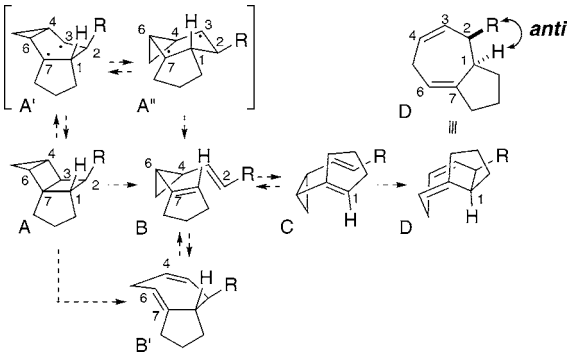
Table 1. Thermal and Lewis Acid-Mediated Isomerizations of Cyclopropyl Systems

Entry	Cyclopropane	Bicyclo[5.3.0]decane	Yield
Thermal fragmentations[a]			
(1)	 **17**	 **18**	64%
(2)	 **19**	 **20**	76%
(3)	 **21**	multiple products	
Lewis acid-mediated fragmentations[b]			
(4)	 **14**	 **15**	77%
(5)	 **22**	 **23**	64%[c]
(6)	 **24**	 **25**	63%[c]
(7)	 **26**	 **27**	60%[d]

[a] Conditions: pentane or benzene, BHT, 220−240 °C, 2−4 h. [b] Conditions: (1) PCC, CH_2Cl_2, rt; (2) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 10−20 min. [c] Yields vary from 60 to 80%. [d] Yielded three products; the major was **27**.

note are the mild conditions and the stereochemical outcome of these rearrangements. Whereas the thermal transformations required temperatures of up to 240 °C for several hours, these ring expansions proceeded in a few minutes at 0 °C. Furthermore, the comparison of starting materials and products indicate that the stereochemistry of C1 is retained

Scheme 4. Proposed Mechanism of Thermal Rearrangement

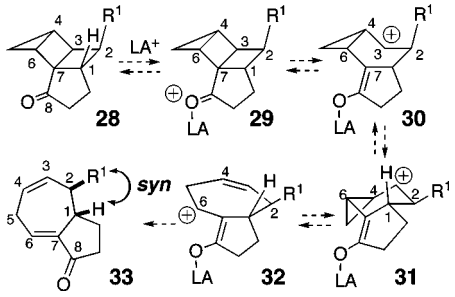


in these fragmentations in contrast to the thermal transformations. As shown in the ring expansion of cyclopropyl system **24**, a C2 configuration that was not tolerated in the thermal rearrangements, rearranges under Lewis acid conditions without incident to the corresponding 5−7 product **25** (entry 6). One limitation of these Lewis acid-mediated rearrangements is that an appropriately positioned carbonyl group is necessary to trigger the rearrangement. When subjected to Lewis acids, the TBS-protected substrate **17**, for example, does not lead to the rearranged product.

The rearrangement of **26** examined the influence of an electron-withdrawing group at C2 (entry 7). In the presence of $BF_3{\cdot}Et_2O$,[6] cyclopropane **26** underwent isomerization to the desired cycloheptadienyl product **27**. The byproducts observed highlight the Lewis acid sensitivity of the C2 ester in adduct **27**, leading to epimerized and conjugated olefin contaminants. The use of a milder Lewis acid ($MgBr_2{\cdot}Et_2O$) did not circumvent this shortcoming.

A possible mechanism for the rearrangement of these cyclopropanated systems is illustrated in Scheme 5. The

Scheme 5. Proposed Lewis Acid-Mediated Rearrangement



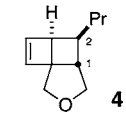
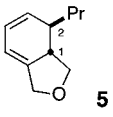
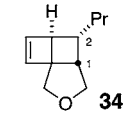
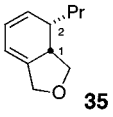
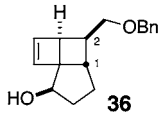
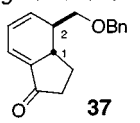
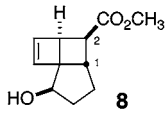
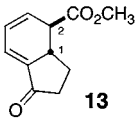
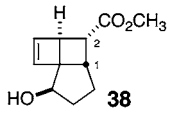
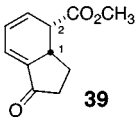
process is likely to be similar to the ring expansion of the cyclobutenyl systems (Scheme 2). After Lewis acid activation of the carbonyl group of **29**, fragmentation of the central C3−C7 bond yields cation **30**, which may then undergo conformational relaxation to generate the chair intermediate **31**. The cyclopropyl functionality adjacent to the carbocation can then rearrange[5] providing cycloheptenyl cation **32**. Enol tautomerization followed by dissociation of the Lewis acid yields the 5−7 ring system **33** with retention of stereochemistry at C1 and C2.

In general, the substrate scope and stereochemical outcome of the acid-mediated fragmentation is highly complementary to the results of the thermal ring opening. Given the stereochemical diversity of the possible 5−7 targets, this acid-mediated fragmentation protocol extends significantly the synthetic utility of cyclobutadiene cycloadducts.

Bicyclo[4.3.0]nonanes. Under the Lewis acid-mediated conditions developed for the isomerization of the cyclopropane substrates, the cyclobutenes were also fragmented cleanly to bicyclo[4.3.0]nonanes without over-oxidation. Representative examples of this rearrangement are shown

(6) Because of additional Lewis basic sites, the amount of $BF_3{\cdot}Et_2O$ was increased to 2.4 equiv.

Table 2. Thermal and Lewis Acid-Mediated Isomerizations of Cyclobutene Substrates

Entry	Cyclopropane	Bicyclo[4.3.0]nonane	Yield
Thermal fragmentations[a]			
(1)	 **4**	 **5**	97%
(2)	 **34**	 **35**	80%
Lewis acid-mediated fragmentations[b]			
(3)	 **36**	 **37**	89%
(4)	 **8**	 **13**	79%
(5)	 **38**	 **39**	58%

[a] Conditions: pentanes, BHT, 220 °C, 1.5 h. [b] Conditions: (1) PCC, CH_2Cl_2, rt; (2) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 10−20 min.

in Table 2. Entries 1 and 2 show the stereospecificity of the thermal rearrangements. Even at elevated temperatures, the stereochemistry at C1 and C2 is retained in this process. The same is true for the oxidation/acid-mediated ring openings described in entries 3−5. There are several other notable observations regarding these isomerizations. (1) The ester-containing cyclobutene substrates **8** and **38** proceed cleanly to products **13** and **39**, respectively.[6] (2) The cyclohexadienyl products generated in these rearrangements all aromatize slowly upon exposure to air. Overall, the results of the Lewis acid rearrangement protocol (entries 3−5) mirror the outcome of the thermal fragmentations (entries 1 and 2).

Acid-mediated isomerizations of polycyclic cyclopropane-containing ring systems provide novel entry into bicyclo[5.3.0]decanes not accessible through the thermal ring expansion protocols. Specifically, the methodology allows access to alternative stereochemical relationships in the bicyclo[5.3.0]decanes. Moreover, the mild rearrangement conditions widen the applicability of the cyclobutadiene cycloaddition methodology toward accessing stereochemical variants of the 5−7 ring systems and potentially allow access to a greater number of biologically important target molecules.

Acknowledgment. We thank the National Institute of General Medical Sciences (National Institutes of Health, GM62824) for financial support and Priscilla C.-K. Lo and Suzanne S. Stokes for preliminary observations.

Supporting Information Available: Experimental and analytical data for all new compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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