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Intramolecular 4+3 cycloadditions. Some examples of surprisingly high levels of simple diastereoselection

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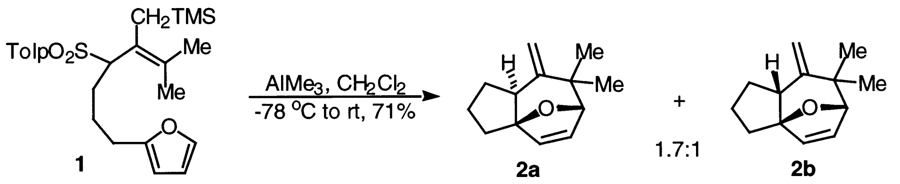
Abstract—The reaction of alcohols **6** and **7** with triflic anhydride and 2,6-lutidine results in the formation of the corresponding 4+3 cycloadducts with surprisingly high levels of simple diastereoselection. © 2000 Elsevier Science Ltd. All rights reserved.

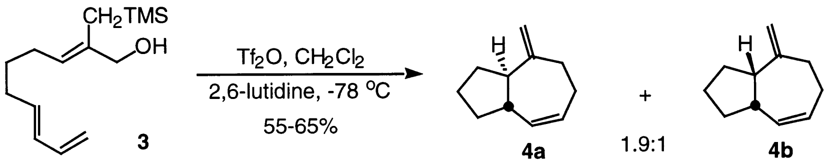
The intramolecular 4+3 cycloaddition reaction of allylic cations and dienes offers access to complex carbocyclic species from relatively simple starting materials.[1] Aspects of stereocontrol in this reaction are extremely important, as they bear significance with respect to applications of the methodology to total synthesis and to the development of asymmetric 4+3 cycloaddition processes. In this report, we present two examples of unusually high degrees of simple diastereoselection in intramolecular 4+3 cycloaddition reactions.

One variable associated with stereocontrol in 4+3 cycloaddition reactions is the 'terminator' of the cycloaddition reaction. One common terminator is the trimethylsilylmethyl group, which leads to cycloadducts bearing an *exo* methylene substituent. In general, intramolecular 4+3 cycloaddition reactions carried out with allylic cations bearing a trimethylsilylmethyl terminating group are not very stereoselective. For example, we have shown that treatment of **1** with trimethylaluminum results in the formation of cycloadducts **2a** and **2b** in a ratio of 1.7:1 (Scheme 1).[2] Giguere and coworkers have shown that treatment of **3** with triflic anhydride in the presence of 2,6-lutidine results in the formation of an approximately 1.9:1 ratio of isomers **4a** and **4b** in 55–65% yield (Scheme 2).[3] Other examples are known.[4]

We have recently been involved in the study of vinylthionium ions as dienophiles in intramolecular 4+3 cycloaddition reactions.[5] Our work to date has made use of alkoxy groups as terminators of the cycloaddition reaction. In an effort to expand the scope of the process and obtain further information on stereochemical control in reactions using vinylthionium ions, we



Scheme 1.



Scheme 2.

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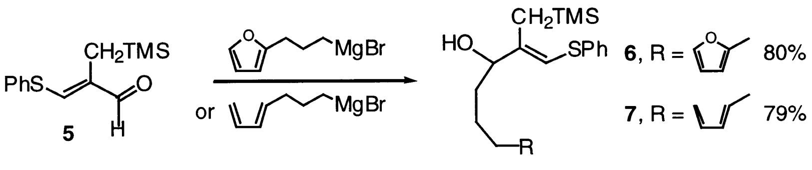

Scheme 3.

began a study of some trimethylsilylmethyl-substituted systems. Our preliminary results suggest that such cations may be quite useful in the stereoselective generation of 4+3 cycloadducts.

Our cycloaddition precursors were prepared via addition of the appropriate Grignard reagents to the known aldehyde **5** (Scheme 3).[6] This afforded alcohols **6** and **7** in good yields after chromatographic purification.

The cycloaddition of **6** was conducted under our standard conditions.[2,5b] Thus, treatment of **6** with triflic anhydride and 2,6-lutidine at −78°C afforded the cycloadduct **8** as the exclusive product in 50% yield (Scheme 4). The stereochemistry of **8** was established by single crystal X-ray analysis. It should be noted that while intramolecular 4+3 cycloaddition reactions with furan dienes typically give high levels of *trans* selectivity at the angular positions when an alkoxy group terminates the reaction,[7] this event is quite unusual for reactions terminated with the trimethylsilylmethyl group (cf., Scheme 1).

Even more intriguing is the result obtained with **7**. The cycloaddition reaction of this substrate produced two cycloadducts in a ratio of 10:1 as determined by integration of the appropriate signals in the ^{1}H NMR of crude cycloaddition mixtures (Scheme 5). Note how this contrasts with the result shown in Scheme 2. The structure of the major product could be readily ascertained by simple NMR analysis, but efforts to apply NOE studies to determine stereochemical relationships proved futile. Since the compound was an oil, attempts to produce a crystalline derivative were made. We eventually found that treatment of mixture of cycloadducts with oxone afforded the derivative **10** in which not only was the sulfide moiety oxidized to the corresponding sulfone, but the endocyclic olefin was epoxidized as well.[8] This compound afforded crystals suitable for X-ray analysis which established the relative stereochemistry of both **10** and **9a**.

Initially, problems were encountered with the separation of the minor cycloadduct from the major isomer. The oxone oxidation procedure did not afford an opportunity to isolate the minor cycloadduct oxidation product. However, we found that oxidation of the cycloadduct mixture with mCPBA afforded the corresponding sulfones, which were at least partially separable. Since NOE studies were not providing unambiguous stereochemical answers, we again turned to X-ray analysis to determine the stereochemistry of **11** and thus of **9b**.

Of particular interest is the relationship between the illustrated hydrogen atoms and the corresponding phenylthio groups in cycloadducts **9a** and **9b**. While *cis* in **8**, they are *trans* in both of these cycloadducts. The fact that the stereochemical relationship is not random suggests a mechanistic basis for the stereochemical outcome of both cycloaddition reactions.

At present, the course of the these cycloaddition reactions is not clear. Experiments with **6** and **7** conducted to less that 100% conversion show that the alcohols maintain their configuration under the conditions of the reaction. Further, we have demonstrated that highly alkylated cations maintain their configuration under related 4+3 cycloaddition conditions.[9] This suggests that the loss of stereochemistry at the level of the cationic intermediate is not an important issue.

We currently speculate that the cation formed from both **6** and **7** possesses the stereochemistry shown in structure **12** in Scheme 6.[10] A stepwise reaction involving initial five-membered formation, followed by a second ring closure to the seven-membered ring leads to the products observed. Structural constraints determine the rate at which the second carbon–carbon bond forming event takes place relative to the rate of rotation of the allylic silane.[11] Further study is necessary to test this hypothesis.

In summary, we have shown that readily accessible alcohols **6** and **7** cyclize with unprecedentedly high simple diastereoselection, affording 4+3 cycloadducts in good yield. Further mechanistic studies and synthetic applications will be reported in due course.[12]

Acknowledgements

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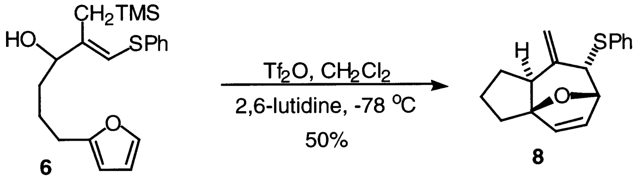
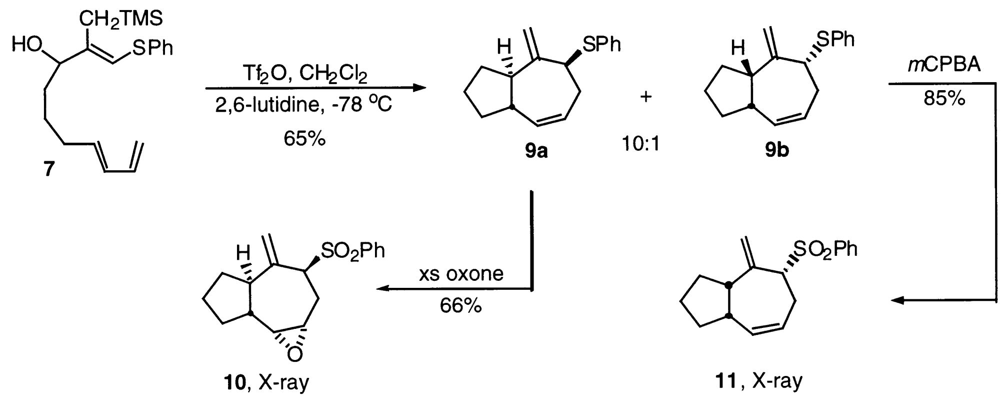
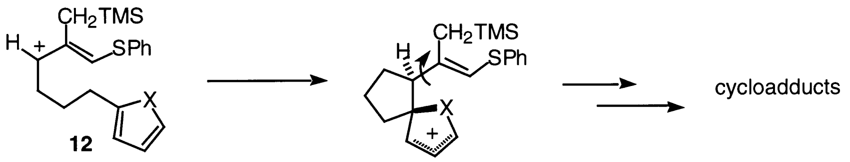


Scheme 4.



Scheme 5.



Scheme 6.

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12. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.