NMR Studies on Epoxidations of Allenamides. Evidence for Formation of Nitrogen-Substituted Allene Oxide and Spiro-Epoxide via Trapping Experiments†

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Two epoxidations of chiral allenamides are described here. While treatment with *m*-CPBA led to highly stereoselective formation of an α-keto aminal that can be useful synthetically, DMDO oxidation led to conclusive evidence for both nitrogen-substituted allene oxide (via mono-epoxidation) and spiro-epoxide (via bis-epoxidation) using intramolecular nucleophilic trapping experiments. NMR studies provide reliable evidence for a 3-oxetanone that can be derived from the spiro-epoxide and also suggest the presence of an allene oxide. Despite a facile second epoxidation as evidenced by the predominant formation of the 3-oxetanone, in the presence of furan, [4 + 3] cycloaddition of the nitrogen-substituted allene oxide or oxyallyl cation with furan occurs faster than the second epoxidation efficiently leading to cycloadducts. This rate difference plays an invaluable role for the success of a stereoselective sequential epoxidation−[4 + 3] cycloaddition reaction via DMDO epoxidations of chiral allenamides.

Introduction

Epoxidations of allenes provide reactive intermediates that can be useful in organic synthesis.[3,4] Synthetic applications of heteroatom-substituted allene oxides derived from epoxidations of allenol ethers have been revealed recently.[5,6] Epoxidation of nitrogen-substituted allenes such as allenamines, however, remained unknown.[3] Our interest in the synthesis[7] and reactivity[8] of chiral allenamides such as **1**, a superior equivalent of traditional allenamines,[3,9−10] has led us to successfully epoxidize and sequentially utilize the epoxidized intermediates in situ as nitrogen-stabilized oxyallyl cation equivalents in highly stereoselective [4 + 3] cycloadditions (Scheme 1).[11] The versatility of oxyallyl cations, especially of those that are heteroatom-substituted, in 1,3-dipolar cycloadditions has attracted much attention from the synthetic community.[12−16] Our study represents the first attempt at generating heteroatom-substituted oxyallyl cations by epoxidizing heteroatom-substituted

† With the deepest appreciation and respect, this paper is dedicated to Professor Gilbert Stork on the occasion of his 80th birthday.

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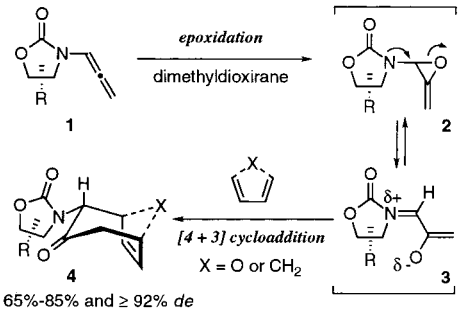
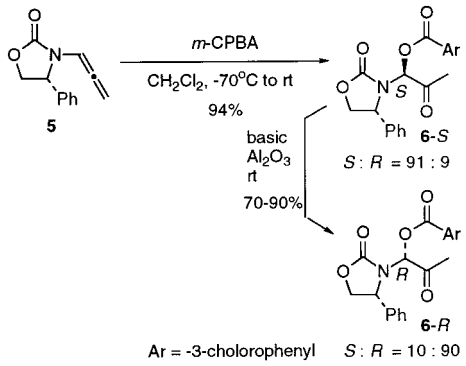
Scheme 1



Scheme 2



allenes, thereby providing a general entry to novel nitrogen-substituted oxyallyl cations. Given its synthetic significance, we pursued spectroscopic studies of this new epoxidation reaction in an attempt to identify relevant intermediates. We report here our NMR investigations of epoxidations of allenamides and experimental evidence for formation of nitrogen-substituted mono-epoxidized and bis-epoxidized allenic intermediates.

Results and Discussion.

1. *m*-CPBA Epoxidation. Two major epoxidation protocols were investigated. As shown in Scheme 2, epoxidation of the allenamide **5** using 2.0 equiv of *m*-CPBA under a buffered environment led to the formation of the α-keto aminal **6**[17] almost quantitatively. A diastereoselectivity of 91:9 was observed by ^{1}H NMR, and stereochemistry of the major isomer was unambiguously assigned as **6**-*S* by X-ray structural analysis.[18] The selectivity for the **6**-*S* isomer was believed to be kinetic because the **6**-*S* isomer readily epimerized to the **6**-*R* isomer with an isomeric ratio of 90:10 in the presence of basic alumina at room temperature. However, it is not clear at this point why **6**-*R* is the thermodynamically favored isomer.

The same epoxidation reaction of **5** was subsequently carried out in CD_2Cl_2 and monitored by ^{1}H NMR. As shown in Figure 1, the epoxidation of **5** was very slow at temperatures below −40 °C with no noticeable new intermediates. However, at −25 °C, the epoxidation occurred steadily leading to the α-keto aminal **6**-*S* as the only product, with no other observable intermediates through the course of the reaction. This study suggests that at the given NMR time scale, *m*-CPBA epoxidation of allenamides does not provide a discrete allene oxide intermediate such as **2** (see Scheme 1) or other related intermediates. It also implies that the epoxy intermediate could ring-open in situ quickly, affording no observable or appreciable build-up of epoxidized allene intermediates.

To verify that this ring-opening is a fast process, the allenamide **7** was prepared[8a,18] to generate the allenamide **8** (Scheme 3) tethered with the alcohol functionality for setting up an intramolecular trapping experiment as was used by Crandall.[4] However, it was quickly found that the allenamide **8** was not very stable, especially under acidic conditions, and thus, the allenamide **8** is potentially incompatible with the *m*-CPBA conditions. Removal of the TBS group in **7** could be carried out carefully at low temperatures but gave **8** only in a 40−50% modest yield. However, attempts to purify **8** using silica gel led us to identify the furan **10** as an inseparable minor component on numerous occasions.

The furan **10** is likely derived from 5-*exo* addition of the hydroxyl group to the α,β-unsaturated *N*-acyl iminium intermediate **9** via protonation of **8**. A relatively clean sample of **8**, upon standing in CH_2Cl_2 at 0 °C in the presence of a small amount of silica gel, quickly decomposed to the furan **10** in 56% yield with an isomeric ratio of 4:1. Stereochemistry of the major isomer **10a** can be assigned as shown in Scheme 3 based on ^{1}H NMR correlation with an analogous pyran example that was assigned by NOE experiments (see **27** in Scheme 7). Using a catalytic amount of pyridinium *p*-tolylsulfonic acid (PPTS) at room-temperature enhanced the reaction rate but provided the furan **10** in only 25% yield with an identical isomeric ratio. Initial attempts to epoxidize a relatively pure sample of allenamide **8** using various conditions led to the isolation of the furan **10** instead.

In contrast, the allenamide **11**, containing one extra carbon in the tether that was prepared in a similar manner[8a,18] was found to be much more stable than **8** under acidic conditions. Upon subjecting **11** to the same *m*-CPBA epoxidation conditions described above for **5**, the α-keto aminal **12** was the only product isolated in 58% yield as a single diastereomer (stereochemistry assigned based on analogy with the α-keto aminal **6**-*S*).

As shown in Scheme 4, pyranyl heterocycles **15** and **16** represent potential products from intramolecular nucleophilic trapping of the mono-epoxidized allene **13** (or allene oxide) and the bis-epoxidized allene **14** (or spiro-epoxide), respectively. However, neither **15** nor **16** were observed in the *m*-CPBA epoxidation of the allenamide **11**, although Crandall has elegantly demonstrated

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(17) All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR, $[\alpha]^{20}_D$, and MS.

(18) See Supporting Information for further details.

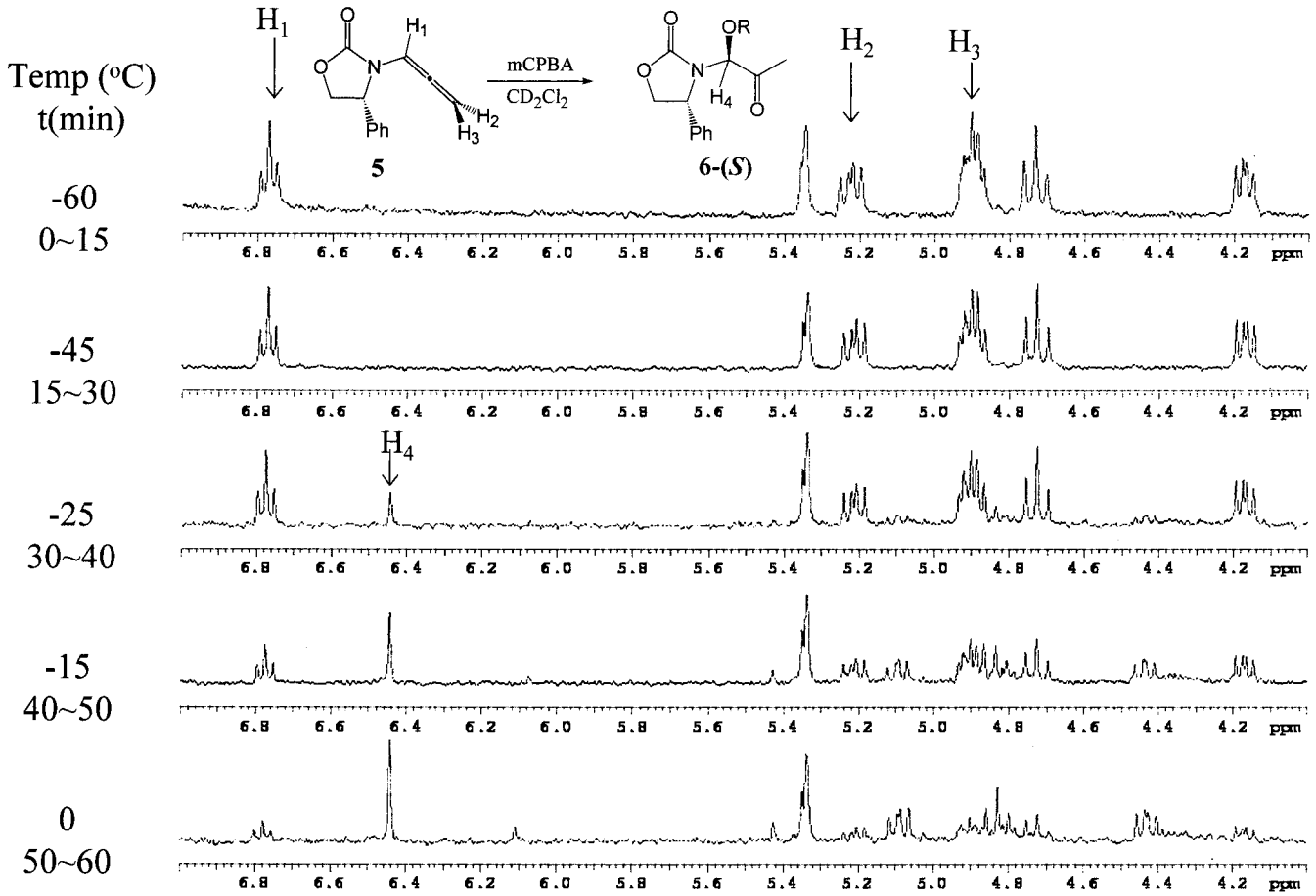
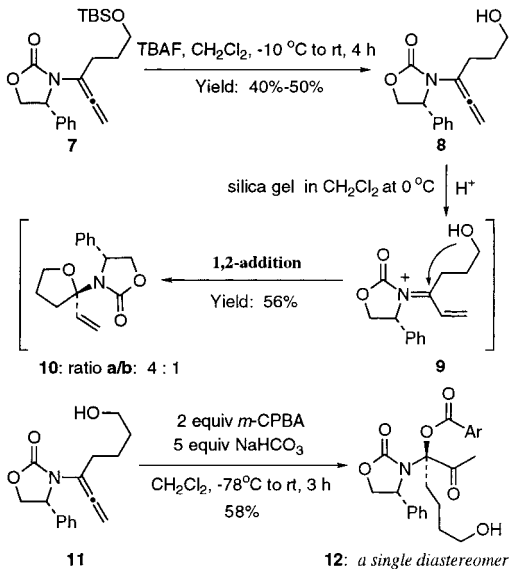
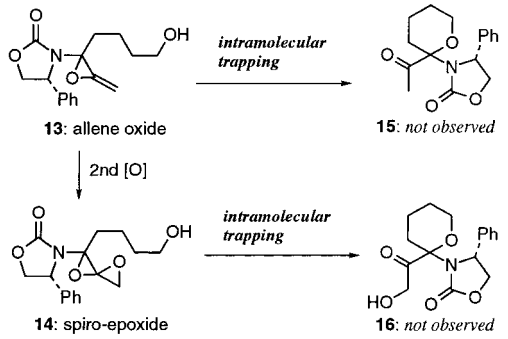


Figure 1. ^{1}H NMR monitoring of allene epoxidation by *m*CPBA.

Scheme 3



Scheme 4

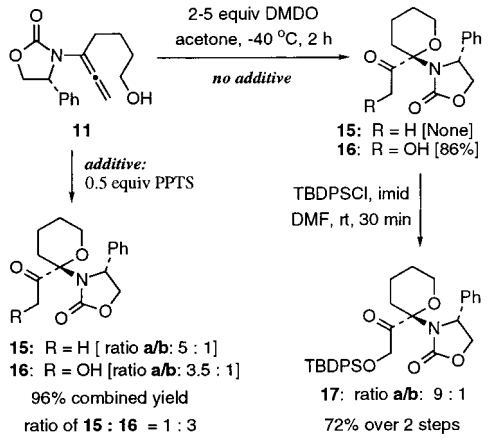


that similar trapping experiments can be used to study intermediates derived from epoxidations of allenes.[4]

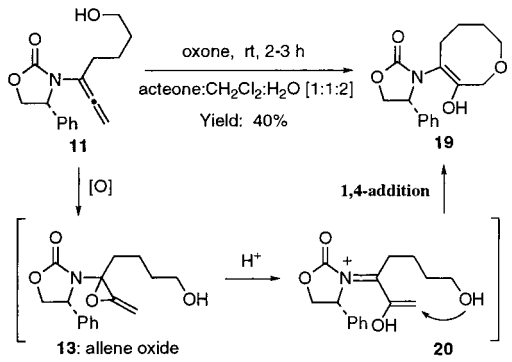
2. DMDO Epoxidation. Distinctly different results were obtained when we turned to the second epoxidation protocol: dimethyldioxirane (DMDO) oxidation. As shown in Scheme 5, epoxidation of the allenamide **11** using 2.0−5.0 equiv of DMDO in the absence of a protic additive led to the pyran **16** as the only product in 86% yield. Because the pyran **16** was not easy to purify, further silylation gave the silylated pyran **17** that could be fully characterized. The diastereomeric ratio was found to be 9:1 for **17** after silylation in favor of the major isomer shown in Scheme 5. This trapping experiment supports the presence of a nitrogen-substituted spiro-epoxide intermediate such as **14**.

In the presence of 0.5 equiv of pyridinium *p*-tolylsulfonic acid (PPTS), DMDO epoxidation of **11** led to the formation of **15** and **16** in 70% overall yield with a ratio of 1:3. While the diastereomeric ratio of **16** dropped from 9:1 in the absence of PPTS (as suggested by **17**) to 3.5:1; the diastereomeric ratio of **15** was observed to be 5:1. Stereochemical assignments for compounds **15**−**17** are done based on ^{1}H NMR correlation with an analogous pyran that was unambiguously assigned using NOE experiments (see **28** in Scheme 8). The isolation of **15** represents the first evidence for the formation of nitrogen-

Scheme 5



Scheme 6



substituted allene oxide **13**. Thus, this also suggests that the second epoxidation proceeded slower leading to **16** under protic DMDO conditions.

On the other hand, when oxone was used as a DMDO equivalent, the cyclic ether **19** was isolated in 40% yield (Scheme 6). In addition, the pyran **15** was also isolated in 10% yield. The formation of **19** can be proposed as shown where again in a more acidic medium during the oxidation, rapid ring-opening of the allene oxide **13** could occur to provide the α,*β*-unsaturated *N*-acyl iminium intermediate **20**. An ensuing 1,4-addition would lead to **19**. This trapping experiment is an additional evidence suggesting the formation of nitrogen-substituted allene oxide **13**.

It is noteworthy that the same allenamide **11** provided a very different major product using oxone from that of using DMDO in the presence of PPTS. While reasons are not very clear for such a mechanistic difference, it could be suggested that allene oxide **13** derived from DMDO oxidation of **11** could undergo rapid ring-opening in the presence of PPTS to proceed to an intermediate that would be the keto form of **20**. Thus, the trapping of the *N*-acyl iminium ion with the hydroxyl group could only be possible in a 1,2-addition manner to give the pyran **15** as the major product. On the other hand, by using oxone, the ring-open of the allene oxide **13** could lead to predominately **20** (the enol form) that could be trapped in either 1,2 or 1,4-addition manner.

Having obtained these results using DMDO, DMDO epoxidation of **5** was carried out in acetone-d_6 and monitored by ^{1}H NMR. As shown in Figure 2, DMDO epoxidation of **5** occurred at a temperature as low as −60 °C. Within the first 30 min, there were two new compounds **A** and **B** with a ratio of about ∼ 2.2:1 in addition to the unreacted **5** (labeled with "**s**"). The new major compound A (labeled with "**a**") have the following assignable proton resonances: δ 3.91 (d, J = 20.1 Hz, 1H), 4.25 (d, J = 20.1 Hz, 1H), and 5.45 (broad-s, 1H). The new minor compound **B** (labeled "**b**") have the following assignable proton resonances: δ 4.52 (d, J = 8.5 Hz, 1H) and 5.64 (broad-s, 1H). A careful tabulation of integrations of the overlapping regions could unambiguously account for all other overlapping protons for **5**, **A**, and **B** in the region.

When the reaction was allowed to go to completion, compound **A** was the major product observed. It was difficult to completely characterize compound **A** because it was not very stable. Given known chemical shifts and coupling constants of related spiro-epoxides,[4e−f] this major product **A** is not consistent with the spiro-epoxide **22**. However, it is quite consistent with the assignment of the 3-oxetanone **23** based on information reported by Crandall.[4e−f,19] The H^4 of **23** may be assigned to 5.45 ppm, and diastereotopic protons H^5 and H^6 of **23** to 3.91 and 4.25 ppm. 3-Oxetanones such as **23** are secondary products derived from corrresponding spiro-epoxides (see Scheme 9).[4e−f] The assignment of compound **B**, on the other hand, can be intriguing, although it is also not consistent with the spiro-epoxide **22**. While it is not conclusive to assign **B** as the allene oxide **21**,[20] the following ^{1}H NMR experiment suggests such a possibility.

When DMDO epoxidation of **5** was carried out in the presence of 5−10 equiv of furan where [4 + 3] cycloaddition would take place,[11] ^{1}H NMR indicated that the ratio of **A** to **B** had switched from ∼2.2:1 to ∼1:5 in favor of **B** but not **A** (or the assigned 3-oxetanone).[18] However, this is true only initially.[18] As the concentration of the correponding [4 + 3] cycloadduct was accumulating, the ratio of **A** and **B** increased from ∼1:5 but never went above 1:1.5 (still in favor of **B**).[18]

These NMR ratios suggest that compound **B** is likely the allene oxide **21**. In the presence of furan, [4 + 3] cycloaddition involving the ring-opened oxyallyl cation intermediate derived from **21** with furan could occur faster than its second epoxidation, thereby suppressing the buildup of the spiro-epoxide intermediate **22** that ultimately leads to the 3-oxetanone intermediate **23** (or compound **A**, and thus, suppression of **A**). At the same time, the initial jump in the concentration of compound **B**, if it is related to the allene oxide **21**, should taper off as observed due to the subsequent cycloaddition.

The assertion that [4 + 3] cycloaddition of **21** occurs faster than its second epoxidation should be valid based on our cycloaddition study.[11] In the presence of furan or another diene, we did not isolate any products related to the spiro-epoxide intermediate **22** and/or 3-oxetanone **23**. Instead, the only products were the [4 + 3] cycloadducts derived from the allene oxide **21** or its ring-opened oxyallyl cation intermediate.[11]

3. Stereochemical Assignments. Because it was difficult to assign the stereochemistry of the furan **10** (in Scheme 3) and the pyran **17** (in Scheme 5) using crystal structures, the allenamide **26** was specifically prepared from the propargyl silyl ether **24** in five steps as shown

(19) Pusion, A.; Rosnati, V.; Solinas, C. *Tetrahedron* **1983**, *39*, 2259.
(20) For chemical shifts of a related allene oxide, see: Konoike, T.; Hayashi, T.; Araki, Y. *Tetrahedron: Asymm.* **1994**, *5*, 1559.

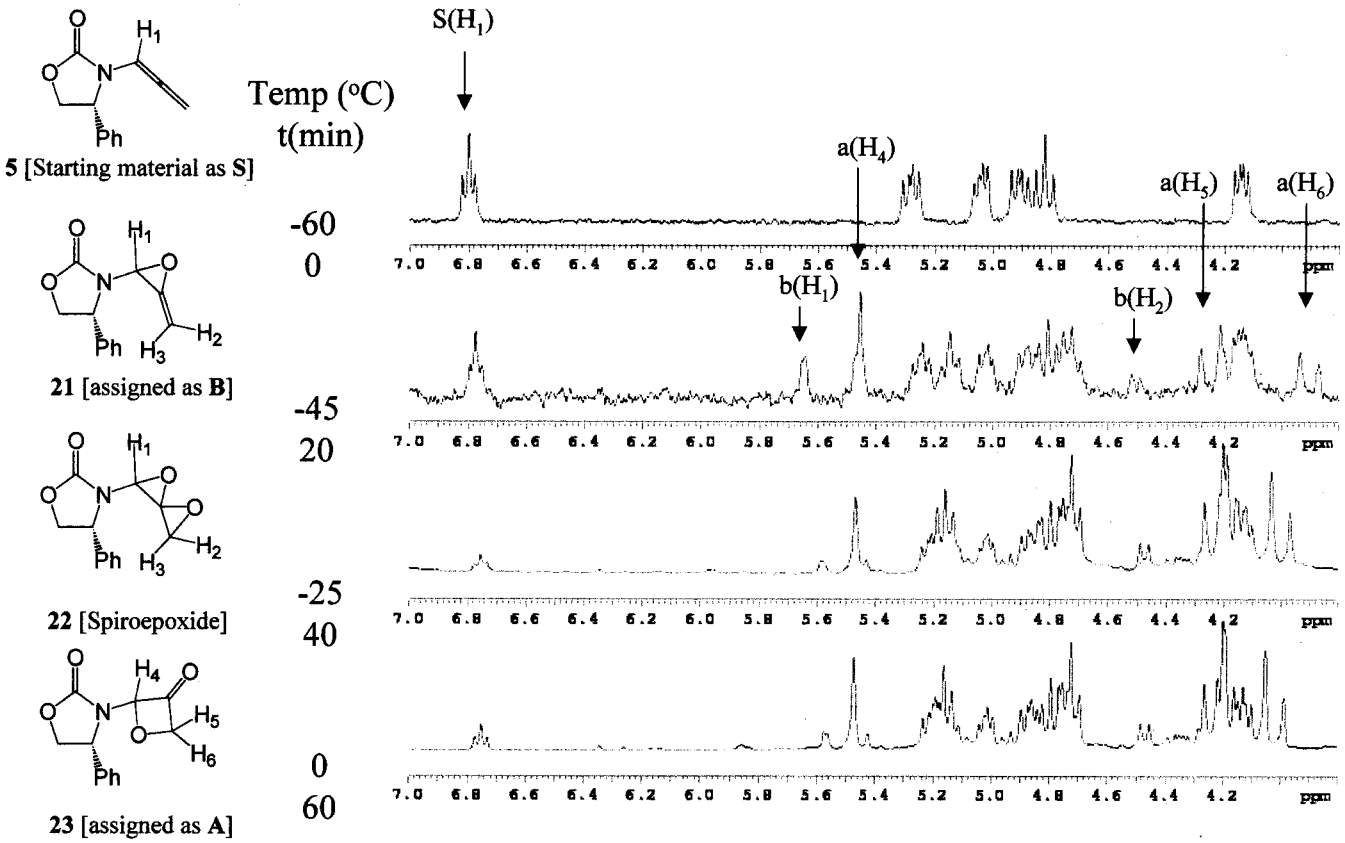
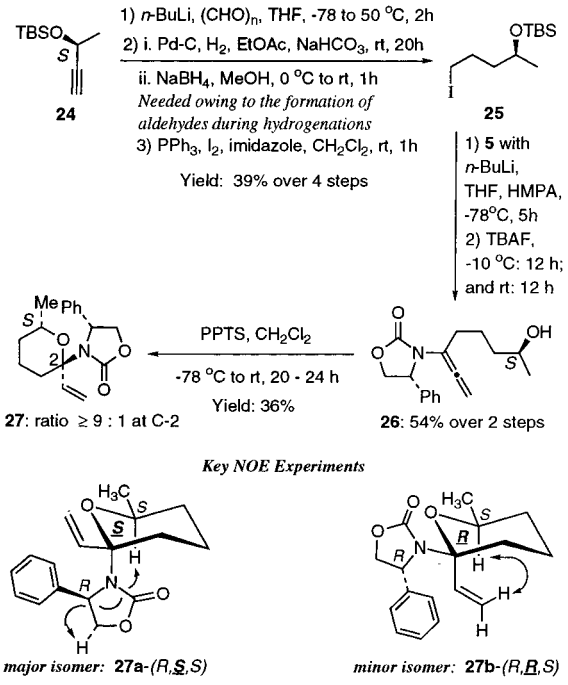


Figure 2. ^{1}H NMR monitoring of DMDO oxidation of allenamide.

Scheme 7



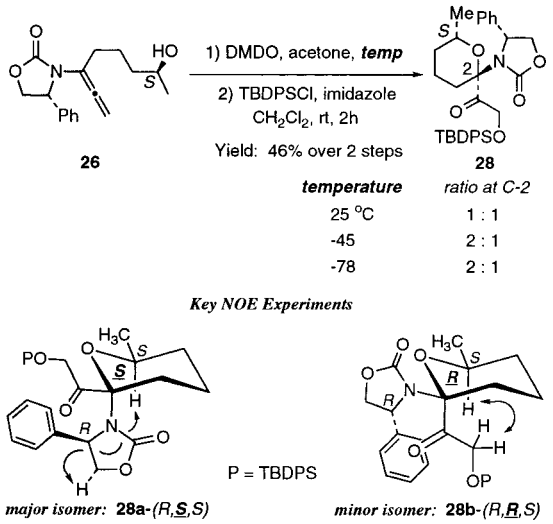
in Scheme 7. Treatment of the allenamide **26** using PPTS in CH_2Cl_2 led to the pyran **27** in 36% yield with an isomeric ratio of ≥9:1. NOE experiments of both the major and minor isomers unambiguously indicate that the major isomer **27a** contains the absolute stereochemistry of (*R*,***S***,*S*) (see the key NOE enhancements in Scheme 7). By correlating chemical shifts of the three olefinic protons and anomeric protons in pyrans **27a** and **27b** with those of corresponding protons in furans **10a** and **10b**, assignments of **27a**/**b** lent strong support to the stereochemical outcome for the isomers **10a**/**b**.

On the other hand, DMDO oxidation of **26** followed by silylation with TBDPSCl gave the desired pyran **28** in 47% overall yield, but the diastereomeric ratio dropped to 1:1. When the DMDO oxidation was carried out at −40 °C, the diastereomeric ratio improved to 2:1 but did not change when the reaction was carried out at −78 °C. Although we are uncertain why there is a large difference between diastereomeric ratios obtained for **17** and **28**, this difference can be interesting mechanistically.

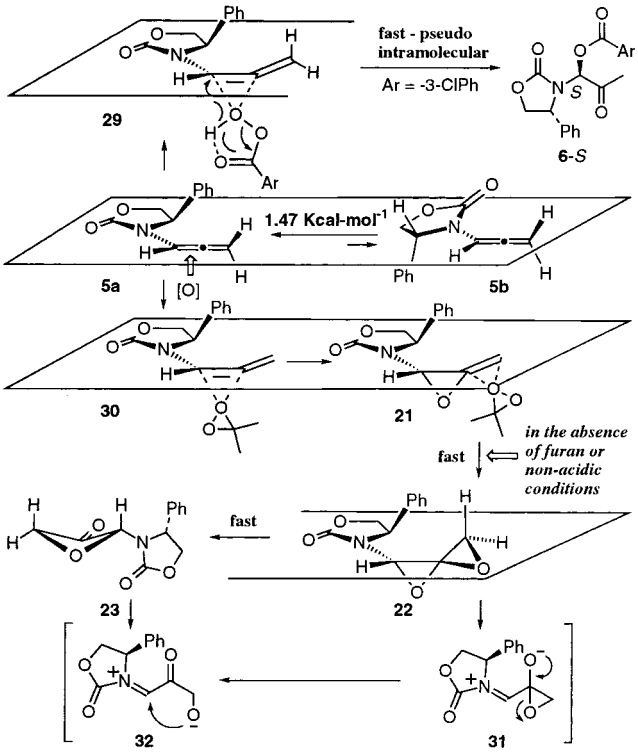
NOE experiments of both the major and minor isomers of **28** again unambiguously indicate that the major isomer **28a** contains the absolute stereochemistry of (*R*,***S***,*S*) (see the key NOE enhancements in Scheme 8). By correlating chemical shifts of the methylene protons α to the ketone carbonyl and anomeric protons in pyrans **28a**/**b** with those corresponding protons in pyrans **16a**/**b** or **17a**/**b**, stereochemistry at the anomeric center of the major isomer **16a** or **17a** should be the same as in **28a**. Chemical shift correlation of the α-methylene protons in pyrans **28a**/**b** with α-methyl protons in pyrans **15a**/**b** also firmly supports that the major isomers **15a** possess the stereochemistry as in **28a**. In addition, chemical shifts of the anomeric methine protons and methyl groups in **28a** and **28b** also correlate very well with the corresponding ones in **27a** and **27b**. These correlations suggest that in all cases, the major isomers favor the same stereoselectivity at the anomeric center.

4. Mechanistic Considerations. A proposed mechanistic sequence that can account for these observations is shown in Scheme 9. Given the stereochemical assignment of **6**-*S*, NMR observations, and the unsuccessful

Scheme 8



Scheme 9

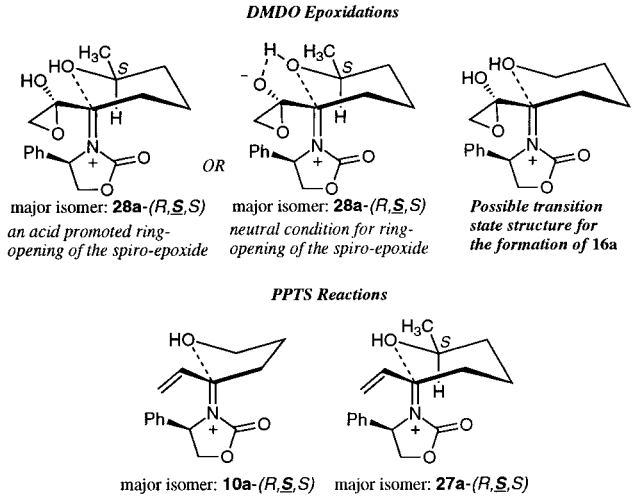


intramolecular trapping experiment, it may be suggested that not only does the addition of *m*-CPBA occur from the less hindered bottom face of **5a** which is more stable than **5b** ($\Delta E = 1.47$ kcal mol^{-1} via PM3 calculations using Spartan), but more intriguingly, that the ring-opening of the transient epoxide **29** is facile and may be proposed as *pseudo-intramolecular*.

On the other hand, DMDO oxidation of **5a** may proceed through the transition state intermediate **30** leading to the allene oxide **21**. A second expoxidation leading to the spiro-epoxide **22** is likely quite fast especially in nonacidic conditions leading predominatly to the 3-oxetanone **23** as observed by ^{1}H NMR.[18] Transformation of **22** to **23** may proceed via intermediates **31** and **32** as shown in Scheme 9.[4e−f]

It is again noteworthy that in the presence of furan, [4 + 3] cycloadditions of **21** (or the ring-opened oxyallyl cation intermediate) need to take place faster than the second epoxidation to give predominantly the desired cycloadducts and a small amount of 3-oxetanone **23** as observed by ^{1}H NMR. This rate difference between the second epoxidation and cycloaddition likely provides the valuable window of opportunity for the success of developing stereoselective [4 + 3] cycloadditions via monoepoxidized chiral allenamides.[11]

Scheme 10



Finally, based on the available stereochemical assignments, the observed diastereoselectivity from PPTS reactions and DMDO epoxidations may be explained using the favored transition states shown in Scheme 10, respectively, for compounds **10**, **16**, **27**, and **28**.

Conclusion

We have described here the first ^{1}H NMR studies of two epoxidations of chiral allenamides. While *m*-CPBA led to highly stereoselective formation of α-keto aminals that can be useful as synthetic precursors to nitrogen-stabilized oxyallyl cations, DMDO oxidation led to conclusive evidence for nitrogen-substituted allene oxide and spiro-epoxide intermediates using various intramolecular nucleophilic trapping experiments. ^{1}H NMR studies provide reliable support for a 3-oxetanone that can be derived from the spiro-epoxide intermediate and suggest the potential presence of an allene oxide.

Despite a facile second epoxidation as evidenced by the predominant formation of the 3-oxetanone, in the presence of furan, [4 + 3] cycloaddition of the allene oxide intermediate (or the oxyallyl cation intermediate) with furan has to occur faster than its second epoxidation leading to predominantly the desired cycloadducts. This rate differentiation plays a critical role that was mechanistically unknown to us in developing a successful stereoselective sequential epoxidation−[4 + 3] cycloaddition via DMDO epoxidations of chiral allenamides. Synthetic applications of α-keto aminal and various oxygen heterocycles resulting from this study are being pursued.

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Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectra, characterization data, and X-ray data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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