The First Epoxidations of 1-Amidoallenes. A General Entry to Nitrogen-Substituted Oxyallyl Cations in Highly Stereoselective [4 + 3] Cycloadditions†

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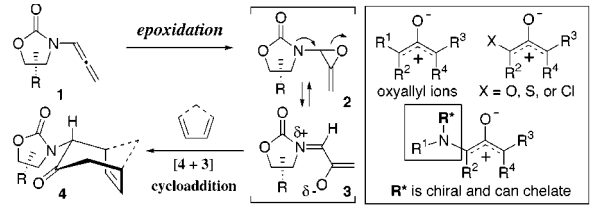
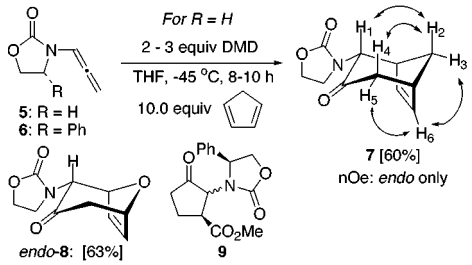
Allenes are important synthons in organic synthesis.[1] Although epoxidations of allenes[1,2] and allenol ethers[3,4] have been reported, epoxidation of nitrogen-substituted allenes remains unexlpored.[1] We envisaged that epoxidation of allenamides **1** could lead to the chiral allene oxides **2**, thereby providing a completely novel and general entry to chiral nitrogen-substituted [or stabilized] oxyallyl cations **3** for stereoselective [4 + 3] cycloadditions [Scheme 1].[2,5] The versatility of oxyallyl cations, especially of those heteroatom substituted, in highly regio- and stereoselective [4 + 3] cycloaddition reactions, leading to useful carbo- and heterocyclic systems, has attracted much attention from the synthetic community.[6,7] While significant advances have been made using oxygen,[8] sulfur,[9] or halogen-substituted[10] oxyallyl cations, nitrogen-substituted oxyallyls have received less attention.[7,11−13] The trivalency of the nitrogen atom renders nitrogen-substituted oxyallyl cations very attractive for developing stereoselective protocols [see the **R*** group on nitrogen], which remains an important challenge in advancing the oxyallyl [4 + 3] cycloaddition.[14] Our interests in chiral allenamides **1**[15,16] allowed us to link together the epoxidation chemistry of allenamides with stereoselective [4 + 3] cycloadditions. We report here the first epoxidations of 1-amidoallenes and their applications as nitrogen-substituted oxyallyls in highly stereoselective [4 + 3] cycloadditions.

Scheme 1



Scheme 2



Dimethyldioxirane [DMD] was found to be the most useful protocol in epoxidizing allenamide **5** at low temperatures. The epoxidized intermediate could be readily trapped in the presence of 10.0 equiv of cyclopentadiene leading to the cycloadduct **7** in 60% yield as a single diastereomer that was assigned as *endo* [or compact[6]] via nOe experiments [Scheme 2].[17] DMD oxidation was also found to be very selective for the allenamide **5** in the presence of 10.0 equiv of furan, and subsequent cycloaddition led to isolation of the cycloadduct **8**[18] in 63% yield. This protocol establishes an attractive one-pot sequential process of epoxidation and cycloaddition. Reaction of **6** with methyl acrylate did not yield the [3 + 2] cycloadduct **9**, thereby suggesting that the nitrogen-substituted allene oxide intermediate **2** and/or oxyallyl cation **3** are electrophilic in character as expected.[2]

[4 + 3] cycloaddition reaction via epoxidation of chiral allenamide **6** was examined in detail. As shown in Table 1, this sequential epoxidation−[4 + 3] cycloaddition protocol could proceed in a range of different solvents[19] [entries 1−4], leading to the cycloadduct **10** in good yields. Although diastereoselectivity was modest, only *endo* isomers were observed, and stereochemistry of the major isomer **10a** [*endo-1*] was confirmed by X-ray structure. While there is a slight temperature effect on the stereochemical outcome [entries 5 and 6], the best diastereoselectivity was obtained when reactions were carried out in the presence of 2.0 equiv of $ZnCl_2$ [entries 9−11]. Notably at −78 °C [entry 11], the cycloadduct **10a** was isolated as a single diastereomer. Additives such as $LiClO_4$ and $MgBr_2$ [entries 7 and 8] were not useful, although they have been utilized in other oxyallyl [4 + 3] cycloadditions.[8,10,12,14]

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

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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) An unidentifiable side-product was also isolated in 10−30% yield.

(19) Because DMD was generated in acetone, acetone was a cosolvent in all reactions reported here.

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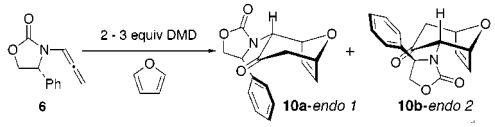
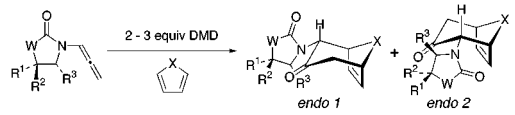
Table 1



entry	solvent[a]	temp,[b] °C	additive [2.0 equiv]	yield,[c] %	ratio of **10a**:**b**[d]
1	CH_2Cl_2	−40	none	75	75:25
2	Et_2O	−40	none	77	75:25
3	CH_3CN	−40	none	<10	
4	THF	−40	none	80	75:25
5	THF	25	none	80	75:25
6	THF	−78	none	70	82:18
7	THF	−40	$LiClO_4$	81	75:25
8	THF	−40	$MgBr_2$	<10	
9	THF	25	$ZnCl_2$	40	90:10
10	THF	−40	$ZnCl_2$	77	94:6
11	THF	−78	$ZnCl_2$	80	≥96:4

[a] Reaction solvent indicates the solvent that the allenamide **6** and 10.0 equiv of furan were dissolved in, although DMD was generated and added as a solution in acetone. [b] Reactions took 30 min at room temperature, 5−10 h at −45 °C, and 10−20 h at −78 °C to complete. [c] All yields are isolated yields. [d] Ratios were determined by using ^{1}H and/or ^{13}C NMR.

Table 2



entry[a]	allenes	W	R^1	R^2	R^3	X	adducts	yields,[b] %	*endo* ratio[c]
1	6	O	H	H	Ph	CH_2	**11**	40	≥95:5
2	12	NMe	Me	H	Ph	O	**13**	60	≥95:5
3	12	NMe	Me	H	Ph	CH_2	**14**	83	≥96:4
4	15	O	H	H	Bn	O	**16**	67	77:23
5	17	O	H	H	$CHPh_2$	O	**18**	74	≥95:5
6	17	O	H	H	$CHPh_2$	CH_2	**19**	62	93:7
7	20	O	H	H	*i*-Pr	O	**21**	70	55:45
8	22	O	Ph	Ph	*i*-Pr	O	**23**	72	94:6

[a] Reactions were carried out in THF at −40 to −50 °C in the presence of 2.0−3.0 equiv of DMD [as a solution in acetone] and 10.0 equiv of the diene. For entries 1−3, 2.0 equiv of $ZnCl_2$ was used. All reactions were completed within 8 h. [b] All are isolated yields. [c] Endo ratios were determined by using ^{1}H and/or ^{13}C NMR.

The generality of this reaction is shown in Table 2. While reactions of chiral allenamides **6** or **12** with cyclopentadiene or furan were highly stereoselective [entries 1−3], **15** and **20**, containing benzyl and isopropyl groups, respectively, α to the nitrogen atom of the oxazolidinone ring, afforded much lower diastereoselectivities [entries 4 and 7]. Addition of $ZnCl_2$ did not improve diastereoselectivities but lowered reaction yields [not shown in Table 2]. However, chiral allenamide **17**, having a bulky dibenzylidene group α to the nitrogen atom [entries 5 and 6], improved the stereoselectivity from that of **15** even in the absence of $ZnCl_2$, likewise with **22** that has the additional steric presence of the geminal diphenyl groups [entry 8].[16b] Attempts were made to explore the regioselectivity issue by using 2-methylfuran. However, reactions with 2-methylfuran were very slow leading to the cycloadduct in very low yield, and thus, it was not useful to determine the regioselectivity at this point.

A preliminary mechanistic working model was proposed in Figure 1 based on the stereochemical assignment. The chiral allenamide **6** [as an illustrative example] possesses two possible minimum conformations **A** and **B** based on AM1 calculations [Spartan Program]. The conformation **A** is favored owing to a minimized dipole interaction, and the oxazolidinone ring is almost coplanar with the allenic moiety.[16b] Epoxidation could then occur at the bottom face away from the phenyl group, leading to the allene oxide **C** and subsequently to oxyallyl intermediate **D**.

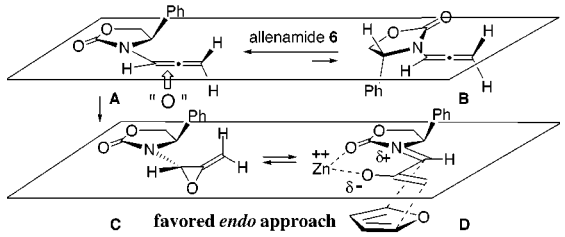
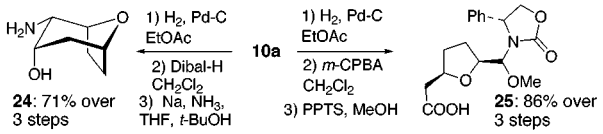


Figure 1.

Scheme 3



The addition of dienes such as furan would likely proceed from the less congested bottom face of **D** away from the bulky phenyl ring, assuming **D** is involved in the cycloaddition.[2,5] The chelating ability of oxygen atoms to the Zn cation should enhance the conformational rigidity of the oxyallyl cation **D**, thereby leading to greater facial differentiation and diastereomeric induction. This model also lends support to the suggestion that nitrogen-substituted oxyallyl cations are essentially in a planar geometry.[12]

Finally, two examples are shown here in Scheme 3 to illustrate possible approaches for removal of the auxiliary,[20] thereby demonstrating the synthetic potential of these cycloadducts. First, hydrogenation and Dibal-H reduction followed by a Birch-type dissolving metal reduction[21] of the ketone **10a** led to the amino alcohol **24** [assigned by nOe experiments] stereoselectively in 71% yield over 3 steps.

Second, hydrogenation and Baeyer−Villiger oxidation[22] of **10a** followed by methanolysis led to the chiral aminal **25** as a single isomer [stereochemistry at the aminal carbocenter unassigned] in 86% overall yield. It is noteworthy that the Baeyer−Villiger oxidation of **10a** was both highly regio- and stereoselective.[22] Further hydrolysis of **25** via known methods[23] led to the corresponding aldehyde[24] and to recovery of the oxazolidinone auxiliary. Compounds **24** and **25** [possessing pseudosymmetry] represent excellent chiral building blocks for natural product synthesis.

We have described here the first epoxidations of 1-amidoallenes as a general entry to chiral nitrogen-substituted oxyallyl cation equivalents for stereoselective [4 + 3] cycloaddition. Efforts leading to synthetic applications of this methodology are currently underway.

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Supporting Information Available: Experimental procedures as well as ^{1}H/^{13}C NMR spectra and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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