Stereoselective Cycloaddition

A Tandem Epoxidation/Stereoselective Intramolecular [4+3] Cycloaddition Reaction Involving Nitrogen-Stabilized Oxyallyl Cations Derived from Chiral Allenamides**

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We recently reported that allenamides **1** can be epoxidized to give nitrogen-stabilized chiral oxyallyl cations **2b**,[1] which can be made to participate in highly stereoselective [4+3] cycloadditions with dienes (Scheme 1).[2] 1,3-Dipolar cycloadditions of oxyallyl cations represent a powerful synthetic tool

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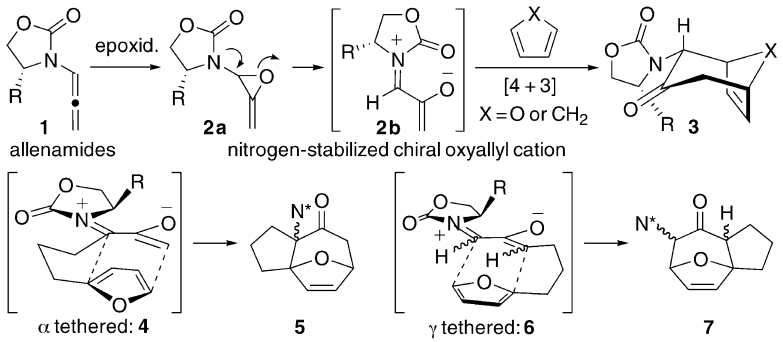


Scheme 1. Epoxidation of allenamides **1** produces nitrogen-stabilized chiral oxyallyl cations, which undergo a stereoselective [4+3] cycloaddition to yield **3**. Tethered allenamides **4** and **6** undergo intramolecular [4+3] cycloaddition.

for constructing complex carbo- and heterocycles.[3] Heteroatoms such as oxygen[4] and sulfur,[5] as well as halogen-substituted[6] oxyallyl cations have become very attractive intermediates for developing not only highly regioselective, but also stereoselective [4+3] cycloadditions.[7]

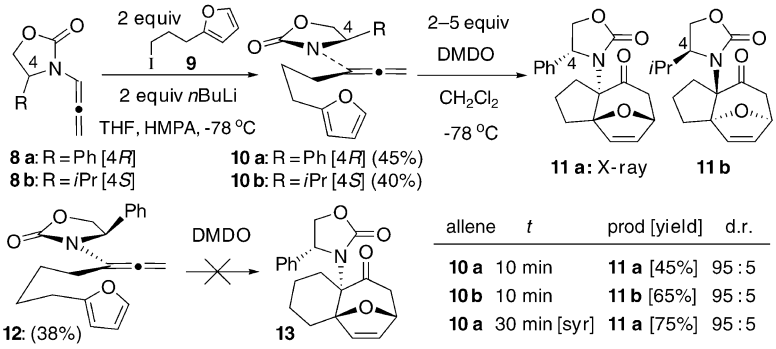
Nitrogen-substituted oxyallyl cations, however, had received less attention[8] until studies were reported recently by Myers and Barbay[9] and Harmata et al.,[10] in addition to work from our own research group.[2,11] The trivalency of the nitrogen atom provides flexibility by allowing the tethering of a chiral auxiliary and presents a valuable platform on which to achieve highly stereoselective oxyallyl cycloadditions, which remain a challenge.[3,7,12] As part of our ongoing efforts to develop stereoselective methods using allenamides,[13–15] we have been exploring intramolecular [4+3] oxyallyl cycloaddition[16] in α-tethered (**4**) and γ-tethered allenamides (**6**; Scheme 1). We report herein the first tandem epoxidation/stereoselective intramolecular [4+3] cycloaddition reactions involving nitrogen-stabilized chiral oxyallyl cations.

To establish the feasibility of intramolecular [4+3] cycloaddition of α-tethered allenamides, we prepared allenamides **10a** and **10b**,[17] tethered with the furan units from **8a** and **8b**, respectively, by our α-alkylation protocol[14c] (Scheme 2). Epoxidation of **10a** and **10b** by treatment with 2–5 equivalents of dimethyl dioxirane (DMDO) at −78 °C gave satisfactory yields, and the ensuing cycloadditions gave **11a** and **11b** in 45 and 65% yield, respectively. The products were obtained as single diastereomers containing a quaternary stereocenter and the stereochemistry was assigned based on X-ray analysis of **11a**.

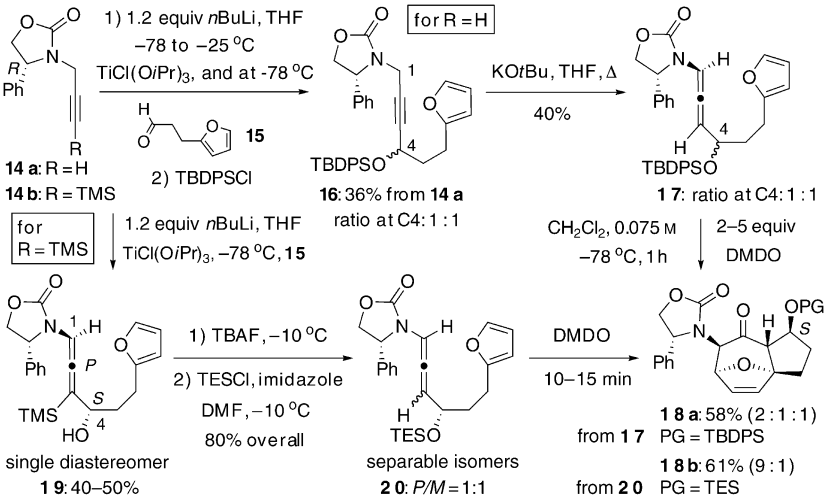
These cycloadditions were much more facile than intermolecular reactions,[2] with the intramolecular reactions completed in 10 min at lower temperatures. A prolonged reaction time actually led to a much lower yield. Addition of DMDO By syringe pump was found to improve the yield of **11a** to 75%, although it was not a procedure that was frequently used in these reactions. Allenamide **12**, which contains one additional carbon atom within the tether compared to **10a** and **10b**, failed to provide cycloadduct **13**.

Once we had established the feasibility of this cycloaddition, we turned to γ-tethered allenamides, whose syntheses featured Seebach's elegant γ lithiation and asymmetric aldol addition,[15a] as shown in Scheme 3.

γ-Tethered allenamide **17** was prepared by an unusual regio- and stereoselective base-induced isomerization[14b,e,18] of the propargyl amide **16**[15a] (1:1 ratio of stereoisomers with a chiral center at C4). Propargyl amide **16** was prepared by addition of the lithium acetylide of **14a** to aldehyde **15** in the presence of $TiCl(OiPr)_3$[15a] followed by protection with TBDPSCl. Cycloaddition of **17** under standard conditions provided cycloadduct **18a** as a mixture of three isomers. The major isomer, shown in Scheme 3, was assigned by correlation with the X-ray structure of a related cycloadduct.



Scheme 2. Synthesis of tethered allenamides **10a** and **10b**, their epoxidation, and the subsequent cycloaddition reactions. syr, syringe-pump addition of DMDO.



Scheme 3. Sythesis and reaction of γ-tethered allenamides. Imid, imidazole; TMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butylphenylsilyl; TBAF, tetrabutylammonium fluoride; TES, triethylsilyl.

Since the C4 stereochemistry in **17** could have eroded the selectivity of the cycloaddition, we prepared **19** as a single diastereomer[19] in 40–50% yield from **14b** by using Seebach's protocol for γ-lithiation and asymmetric aldol addition.[15a] However, **19** did not undergo cycloaddition even when the secondary hydroxy group was protected with TESCl or AcCl.

We then removed the TMS group by treatment with TBAF, but this desilylation led to scrambling of the allenic axial stereocenter and afforded **20** as a 1:1 isomeric mixture (*P*/*M*) after protection with TESCl. Cycloaddition of **20** as a mixture of isomers was facile in the presence of DMDO at −78 °C and gave **18b** in 61% yield, with a 9:1 ratio of major and minor isomers that match the two major components obtained from **17**.

The scope and stereoselectivity of cycloadditions of γ-tethered allenamides are summarized in Table 1. Reaction of the cleanly separated isomers (*P*)-**20** and (*M*)-**20** (entries 1 and 2) provided **18b** in 60 and 75% yield, respectively, in a 90:10 ratio in favor of the same major isomer in both cases. These results suggest that the chirality of the allene does not have an impact on the stereoselectivity of the cycloaddition.

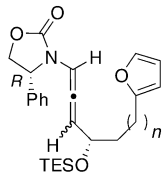
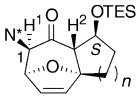
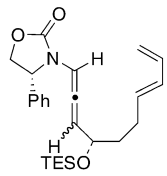
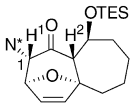
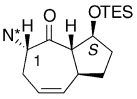
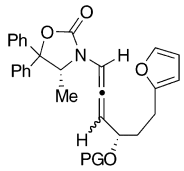
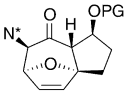
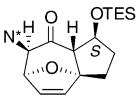
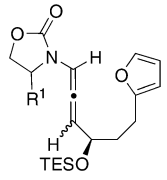
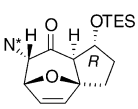
Unlike α-tethered allenamides, γ-tethered allenamides with various lengths of tether were found to be suitable for cycloaddition: **23** ($n=2$) and **24** ($n=3$) led to cycloadducts **25** (X-ray structure) and **26**, respectively, in good yields and with high stereoselectivity (entries 3 and 4, Table 1).[20] Intriguingly, the stereochemistry was completely reversed at C1 in **26**, which resulted in a major isomer (assigned by NOE measurements) that corresponds to the minor isomer of **18b** or **25** (entry 4). Butadienes **27** can also be utilized in this intramolecular cycloaddition to give cycloadduct **28** as a single diastereomer, again with reversal of stereochemistry at C1 (entries 5 and 6), although in lower yields.

Various chiral auxiliaries were examined (Entries 7–12). The *P* and *M* isomers of **36** ($R^1=i$Pr) provided **37** with the best diastereomeric ratio (entries 11 and 12) achieved in our experiments. The protecting group can be either a silyl or an acyl group (entries 7 and 8). Allenamide **35** led to *ent*-**18b** as expected (entry 10).

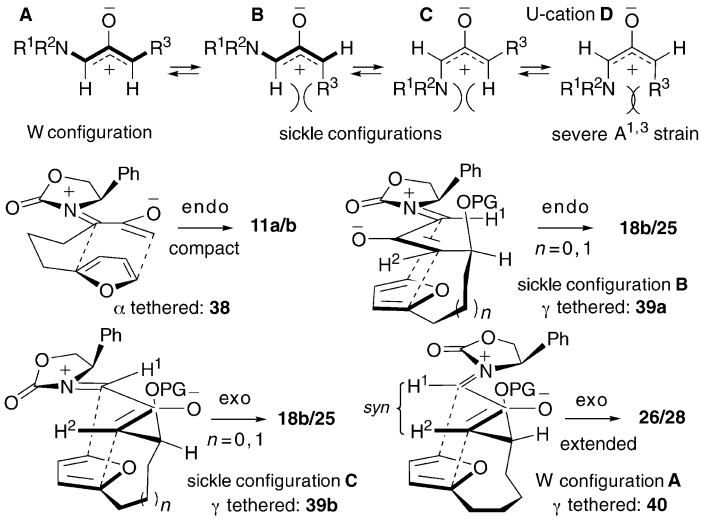
Oxyallyl cation intermediates are known to prefer W configuration **A** (with respect to the nitrogen group in the compounds discussed herein) over sickle configurations **B** and **C**, whilst the U-cation **D** configuration is the least stable because it possesses the most $A^{1,3}$ strain (Scheme 4).[1,2,21] One W configuration is possible for α-tethered oxyallyl cation **38**, and *endo* (or compact[21]) addition would lead to the observed major isomers of **11a** or **11b**. In contrast, it appears that both W configuration **A** and sickle configurations **B** and **C** could play a role for γ-tethered oxyallyl cations **39** and **40**. Since H1 and H2 can be assigned as *anti* in cycloadducts **18b** and **25**, the oxyallyl cation probably assumed either sickle configuration **B** through *endo* addition (**39a**), or sickle configuration **C** by *exo* (extended[21]) addition (**39b**) to give the observed major isomer. For cycloadducts **26** and **28**, the W configuration **A** of the cation is likely to be favored, as shown for γ-tethered oxyallyl cation **40**. This configuration would lead to placement of H1 and H2 *syn* to one another by *exo* (extended[21]) addition. These assessments can rationalize the stereochemical outcomes of the cycloadditions, but we are currently investigating the origin of this configuration switch.

We have herein described a novel tandem epoxidation/stereoselective intramolecular [4+3] cycloaddition involving nitrogen-stabilized chiral oxyallyl cations derived from allenamides. These complex polycyclic manifolds could be useful in the synthesis of natural products. Efforts

Table 1: The scope and stereoselectivity of cycloadditions of γ-tethered allenamides.

Entry	Allenamides[a]	Cycloadducts[b]		Yield [%][c]	Ratio[d]
1			**18b**	60	90:10
2	(*M*)-**20**: $n=1$		**18b**	75	90:10
3	**23**: $n=2$; $P/M=1:1$		**25**[e]	65	93:7
4			**26**	55	≤5:95
5	(*M*)-**27**		**28**	30	≤5:95
6	(*P*)-**27**		**28**	34	≤:95
7			**31**	78	86:14
8	**30**: PG = Ac: $P/M=2.5:1$		**32**	83	90:10
9	$R^1=R$-Bn **33**: $P/M=3:1$		**34**	65	71:29
10			*ent*-**18b**[f]	60	90:10
11	(*P*)-**36**		**37**	60	95:5
12	(*M*)-**36**		**37**	60	95:5

[a] Details of the syntheses of the allenamides are given in the Supporting Information. All reactions were carried out in CH_2Cl_2 (conc. ca. 0.075 M) at −78 °C; DMDO (2.5 equiv) was added as a solution in acetone and CH_2Cl_2 was added at −78 °C through a cannula. The reaction was complete after 5–15 min. [b] N* denotes the corresponding chiral auxiliary. [c] Yields of isolated products. [d] Ratios of isomers determined by ^{1}H and/or ^{13}C NMR spectroscopy. [e] The X-ray structure was obtained. [f] Assigned by NOE measurements.



Scheme 4. The configurations of the oxyallyl cation intermediates can be used to rationalize the mechanism of the cycloaddition reaction.

are currently underway to apply the compounds in such syntheses.

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Keywords: chiral allenamides · cycloaddition · epoxidation · nitrogen · stereoselectivity

[1] C. Rameshkumar, H. Xiong, M. R. Tracey, C. R. Berry, L. J. Yao, R. P. Hsung, *J. Org. Chem.* **2002**, *67*, 1339.

[2] H. Xiong, R. P. Hsung, C. R. Berry, C. Rameshkumar, *J. Am. Chem. Soc.* **2001**, *123*, 7174.

[3] For recent reviews, see a) M. Harmata, P. Rashatasakhon, *Tetrahedron* **2003**, *59*, 2371; b) H. M. L. Davies in *Advances in Cycloaddition*, *Vol. 5* (Ed.: M. Harmata), JAI, Greenwich, **1998**, p. 119; c) M. Harmata in *Advances in Cycloaddition*, *Vol. 4* (Ed. M. Lautens), JAI, Greenwich, **1997**, p. 41; d) F. G. West in *Advances in Cycloaddition*, *Vol. 4* (Ed.: M. Lautens), JAI, Grennwich, **1997**, pp. 1–40; e) J. H. Rigby, F. C. Pigge, *Org. React.* **1997**, *51*, p. 351; f) A. Padwa, A. Schoffstall in *Advances in Cycloaddition*, *Vol. 2* (Ed.: D. P. Curran, JAI, Greenwich, CT, **1990**, p. 1; g) A. Padwa, *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley-Interscience, New York, **1984**.

[4] For some examples of oxygen-substituted oxyallyls, see a) R. L. Funk, R. A. Aungst, *Org. Lett.* **2001**, *3*, 3553; b) J. C. Lee, S.-J. Jin, J. K. Cha, *J. Org. Chem.* **1998**, *63*, 2804; c) M. Harmata, U. Sharma, *Org. Lett.* **2000**, *2*, 2703; d) B. Föhlisch, D. Krimmer, E. Gehrlach, D. Kashammer, *Chem. Ber.* **1988**, *121*, 1585.

[5] For examples of sulfur-substituted oxyallyls, see a) M. Harmata, K. W. Carter, *ARKIVOC* **2002**, *8*, 62; b) M. Harmata, M. Kahraman, *Tetrahedron Lett.* **1998**, *39*, 3421; c) M. Harmata, D. E. Jones, *Tetrahedron Lett.* **1996**, *37*, 783; d) K. Masuya, K. Domon, K. Tanino, I. Kuwajima, *J. Am. Chem. Soc.* **1998**, *120*, 1724.

[6] K. Lee, J. K. Cha, *Org. Lett.* **1999**, *1*, 523.

[7] For a recent review on heteroatom-stabilized oxyallyls in [4+3] cycloadditions, see M. Harmata, *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523–535.

[8] For oxidopyridinium ions, see a) M. J. Sung, H. I. Lee, Y. Chong, J. K. Cha, *Org. Lett.* **1999**, *1*, 2017; b) N. Dennis, B. Ibrahim, A. R. Katritzky, *J. Chem. Soc. Perkin Trans. 1* **1976**, *1*, 2307; for phthalimide-substituted systems, see c) M. A. Walters, H. R. Arcand, *J. Org. Chem.* **1996**, *61*, 1478, and references cited therein.

[9] A. G. Myers, J. K. Barbay, *Org. Lett.* **2001**, *3*, 425.

[10] M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058.

[11] H. Xiong, R. P. Hsung, L. Shen, J. M. Hahn, *Tetrahedron Lett.* **2002**, *43*, 4449.

[12] For recent elegant stereoselective approaches to [4+3] cycloadditions, see a) R. S. Grainger, R. B. Owoare, P. Tisselli, J. W. Steed, *J. Org. Chem.* **2003**, *68*, 7899; b) K. T. Meilert, M.-E. Schwenter, Y. Shatz, S. R. Dubbaka, P. Vogel, *J. Org. Chem.* **2003**, *68*, 2964; c) A. M. Montaña, P. M. Grima, *Tetrahedron* **2002**, *58*, 4769; d) H. Beck, C. B. W. Stark, H. M. R. Hoffmann, *Org. Lett.* **2000**, *2*, 883, and references cited therein; e) C. B. W. Stark, U. Eggert, H. M. R. Hoffmann, *Angew. Chem.* **1998**, *110*, 1337; *Angew. Chem. Int. Ed.* **1998**, *37*, 1266; f) M. Harmata, D. E. Jones, M. Kahraman, U. Sharma, C. L. Barnes, *Tetrahedron Lett.* **1999**, *40*, 1831; g) S. Y. Cho, J. C. Lee, J. K. Cha, *J. Org. Chem.* **1999**, *64*, 3394.

[13] For a review on allenamides, see a) R. P. Hsung, L.-L. Wei, H. Xiong, *Acc. Chem. Res.* **2003**, *36*, 773; for reviews on allenes, see b) R. W. Saalfrank, C. J. Lurz, *Methoden der Organischen Chemie (Houben-Weyl)*, *Vol. E8*, **1993**, p. 3093; c) H. E. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**.

[14] a) C. R. Berry, C. Rameshkumar, M. R. Tracey, L.-L. Wei, R. P. Hsung, *Synlett* **2003**, 791; b) C. Rameshkumar, R. P. Hsung, *Synlett* **2003**, 1241; c) L.-L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, C. J. Douglas, R. P. Hsung, *Tetrahedron* **2001**, *57*, 459; d) H. Xiong, R. P. Hsung, L.-L. Wei, C. R. Berry, J. A. Mulder, B. Stockwell, *Org. Lett.* **2000**, *2*, 2869; e) L.-L. Wei, R. P. Hsung, H. Xiong, J. A. Mulder, N. T. Nkansah, *Org. Lett.* **1999**, *1*, 2145; f) L.-L. Wei, H. Xiong, C. J. Douglas, R. P. Hsung, *Tetrahedron Lett.* **1999**, *40*, 6903.

[15] For recent elegant studies using allenamides, see a) C. Gaul, D. Seebach, *Helv. Chim. Acta* **2002**, *85*, 963; b) Y. Kozawa, M. Mori, *Tetrahedron Lett.* **2002**, *43*, 1499; c) Y. Horino, M. Kimura, S. Tanaka, T. Okajima, Y. Tamaru, *Chem. Eur. J.* **2003**, *9*, 2419; d) S. S. Kinderman, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. T. Rutjes, *Org. Lett.* **2001**, *3*, 2045; e) R. Grigg, I. Köppen, M. Rasparini, V. Sridharan, *Chem. Commun.* **2001**, 964, and references cited therein; f) Y. Horino, M. Kimura, Y. Wakamiya, T. Okajima, Y. Tamaru, *Angew. Chem.* **1999**, *111*, 123; *Angew. Chem. Int. Ed.* **1999**, *38*, 121; g) M. Kimura, Y. Horino, Y. Wakamiya, T. Okajima, Y. Tamaru, *J. Am. Chem. Soc.* **1997**, *119*, 10869.

[16] For excellent reviews on intramolecular [4+3] cycloadditions, see a) M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595; b) M. Harmata, *Tetrahedron* **1997**, *53*, 6235.

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

[18] J. Huang, H. Xiong, R. P. Hsung, C. Rameshkumar, J. A. Mulder, T. P. Grebe, *Org. Lett.* **2002**, *4*, 2417.

[19] The allene stereochemistry in **19** was assigned based on the report by Gaul and Seebach.[15a] The C4 stereochemistry was later confirmed by the X-ray structure of cycloadduct **25**.

[20] When we extended the tether with another carbon atom ($n = 4$), the cycloaddition reaction did not proceed under these conditions.

[21] For a review on Hoffmann's notations, see a) H. M. R. Hoffmann, *Angew. Chem.* **1973**, *85*, 877; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 819; see also: b) H. M. R. Hoffmann, D. R. Joy, *J. Chem. Soc. B* **1968**, 1182.

