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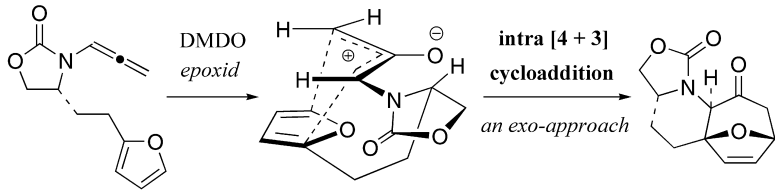

nitrogen-stabilized chiral oxyallyl cation

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Stereoselective Intramolecular [4 + 3] Cycloadditions of Nitrogen-Stabilized Chiral Oxyallyl Cations via Epoxidation of N-Tethered Allenamides

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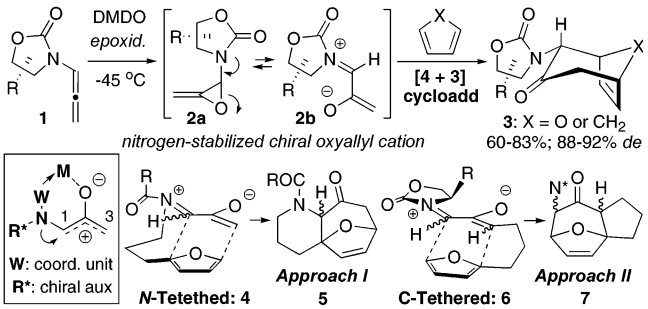
Heteroatom-substituted oxyallyl cations have become the focus in developing highly regio- and stereoselective [4 + 3] cycloadditions.[1,2] While elegant advances have been made using oxygen-,[3] sulfur-,[4] and halogen-substituted[5] oxyallyl cations, nitrogen-substituted oxyallyl cations have received much less attention.[6−8] As part of our ongoing efforts to develop stereoselective methods using chiral allenamides,[9] we recently discovered that epoxidation of allenamides **1** can provide a facile entry to nitrogen-stabilized chiral oxyallyl cations **2b** that can undergo subsequent [4 + 3] cycloadditions with dienes in a highly stereoselective manner (Scheme 1).[10] The trivalent nature of the nitrogen atom allows simultaneous tethering of a chiral auxiliary (**R***) and a coordination unit (**W**), thereby providing greater rigidity in the oxyallyl cation and presenting a unique opportunity to achieve highly stereoselective [4 + 3] oxyallyl cycloadditions, which remains a challenge in this field.[1−4,8,11] We have been exploring intramolecular variants of our [4 + 3] cycloaddition[12] via two approaches: **I**, N-tethered **4** → **5**, and **II**, C-tethered **6** → **7** (Scheme 1).[10b] We elected to focus on approach **I** because it accentuates a distinct advantage of using nitrogen-stabilized oxyallyl cations: the ability to construct complex nitrogen heterocycles. We report here the first intramolecular [4 + 3] cycloadditions using nitrogen-stabilized chiral oxyallyl cations via epoxidation of N-tethered allenamides.

To establish the feasibility, we assembled simple acyclic allenamides **9a** and **9b** with furan attached through a three-carbon tether in three steps from iodide **8**[13] (Scheme 2). It was quickly found that the epoxidation by simply adding 2−5 equiv of dimethyl dioxirane (DMDO) at −45 °C employed in earlier intermolecular reactions[10] was not useful and gave **10a**/**b** in very low yields. Oxidative ring opening of the furan was the major product.

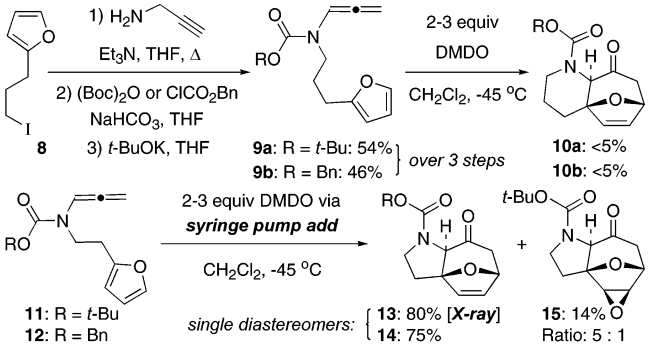
The critical turning point in our efforts was the recognition that an excess of diene used (∼10 equiv) in intermolecular reactions might have absorbed any losses from the competing oxidation of the diene. In the current reactions, it is not possible to increase the loading of the furan. Thus, to slow this competing process, we turned to syringe pump addition of DMDO at −45 °C and found that the epoxidation became very selective for the allenic double bond in **11** and **12**. The ensuing intramolecular [4 + 3] cycloaddition of the corresponding oxyallyl cations with furan led to desired cycloadducts **13** and **14** in 80% and 75% yields, respectively, as single diastereomers. The stereochemistry of **13** was assigned via X-ray. An epoxidized cycloadduct **15** was isolated in 14% yield from the reaction of **11**.[14]

Table 1 summarizes the scope and stereoselectivity of this intramolecular [4 + 3] cycloaddition of nitrogen-stabilized oxyallyl cations. To improve cycloadditions of **9a** or **9b**, syringe pump addition of DMDO (method A) was examined specifically using **9b** (entries 1 and 2). As a result, the yield could be improved, but only to 20% (entry 1), or a modest 47% if $ZnCl_2$ was added (entry 2). However, the stereoselectivity dropped significantly even in the presence of 1−2 equiv of $ZnCl_2$ in contrast to findings from intermolecular reactions.[10] In addition, allenamide **16** tethered with

Scheme 1



Scheme 2



a diene also underwent epoxidation−cycloaddition to afford the desired cycloadduct **17** in 65% yield with loss of selectivity (entry 3).

We then examined cyclic oxazolidinone-substituted allenamides **18** and **19** in detail (entries 5−9). Both methods A and B (normal cannulation of DMDO) were applicable for cycloadditions of **18**, leading to cycloadduct **20** in high yields and diastereoselectivities (entries 4−6). The reaction was also effective even at room temperature (entry 5). Allenamide **19** (entries 7 and 8) led to **21** in good yield and with a high ratio also using method B. The X-ray structure of the hydrogenated **21** gives the basis for stereochemical assignment in entries 4−16. We are currently examining why certain systems really required the syringe pump addition protocol, while some do not.

In contrast to acyclic allenamides, cycloadditions were quite suitable for cyclic allenamides with longer tethers. In addition to the success of using **19**, reactions of allenamides **22** and **23** (entries 9−11) provided the respective cycloadducts **24** and **25** in good yields and good selectivity for **22** (entry 10). Both reactions were best carried out at room temperature using method A (entries 10 and 11),[15] although the stereoselectivity was lower for the reaction of **23** (entry 11). These reactions represent the longest tethers used for an intramolecular [4 + 3] oxyallyl cycloaddition,[1,2,12] leading to cycloadducts containing a seven- or eight-membered ring fused to the cycloheptane resulting from the cycloaddition.

Lactam-substituted allenamides **26** and **27** were also examined. In the case of **26**, both methods A and B were useful with the latter

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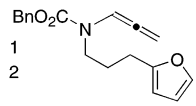
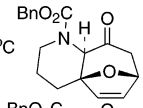
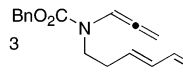
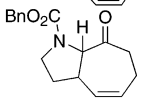
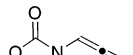
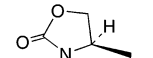
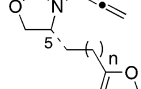
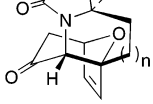
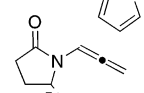
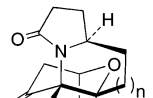
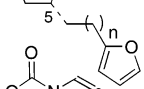
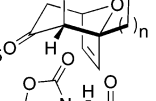
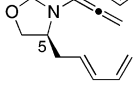
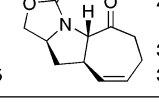
Table 1

entry	allenamides[a]		method[b]	temp	cycloadducts		yields[c]	ratio[d]
1		**9b**	**A**	-45 °C		**10b**	20%	58 : 42
2		**9b**	**A**[e]	-45		**10b**	47	60 : 40
3		**16**	**A**	-45		**17**	65	53 : 47
4		**18:** n = 0	**A**	-45		**20**	82	≥96 : 4
5		**18**	**A**	rt		**20**	77	≥96 : 4
6		**18**	**B**	-45		**20**	75	≥96 : 4
7		**19:** n = 1[f]	**B**	-45		**21**[g]	75	≥96 : 4
8		**19**	**B**[e]	-78		**21**	30	95 : 5
9		**22:** n = 2	**A**	-45		**24**	30	87 : 13
10		**22**	**A**	rt		**24**	70	83 : 17
11		**23:** n = 3[f]	**A**	rt		**25**	57	70 : 30
12		**26:** n = 1[f]	**A**	rt		**28**	90	87 : 13
13		**26**	**B**	-45		**28**	85	93 : 7
14		**27:** n = 3[f]	**A**	rt		**29**	40	52 : 48
15		**30**[f]	**A**	rt		**31**	76	60 : 40
16		**30**	**B**	-45		**31**	75	62 : 38

[a] Preparations of allenamides are in the Supporting Information. All reactions were carried out in CH_2Cl_2 [concentration: 0.025 M] at −45 °C. [b] Method A: 2−5 equiv of DMDO was added as a solution in acetone/CH_2Cl_2 at −78 °C via a syringe pump. Method B: 2−5 equiv of DMDO was cannulated. [c] Isolated yields. [d] Ratios determined by ^{1}H and ^{13}C NMR. [e] 1.0 or 2.0 equiv of $ZnCl_2$ was added as a solution in ether. [f] Allenamides **19**, **23**, **26**−**27**, and **30** are optically enriched with C5, with all except **30** being *R*. [g] X-ray structure of hydrogenated **21** was obtained.

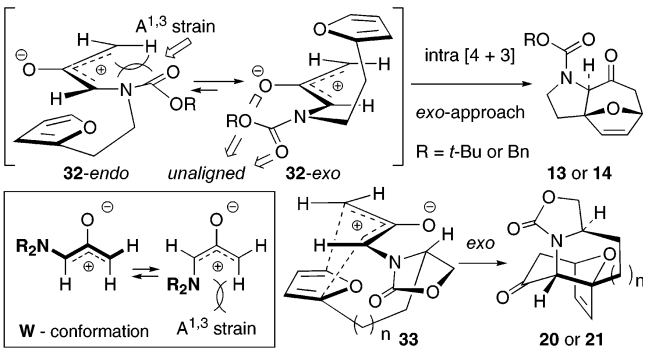


Figure 1.

method actually providing better selectivity (entries 12 and 13). The stereoselectivity again dropped with a longer tether (**27**), and the reaction also needed a higher temperature (entry 14).

Finally, dienes also worked well as reaction of allenamide **30** provided **31** in good yields, although in lower selectivity (entries 15 and 16). It is also noteworthy that in all cases where the isomeric ratios are low (**17**, **25**, **29**, and **31**), major and minor isomers can be readily separated.

A working model was proposed on the basis of stereochemical assignments (Figure 1). Although two possible approaches, **32**-*endo* and **32**-*exo*, could both afford the same major isomer of **13** or **14**, the oxyallyl cation **32**-*endo* should experience more $A^{1,3}$ strain, whereas **32**-*exo* possesses a more preferred W-conformation.[1,2] Thus, approach **I** to intramolecular [4 + 3] cycloaddition of nitrogen-stabilized oxyallyl cations likely proceeds in an *exo* manner. This current model with both oxygen atoms being unaligned is also based on the observation that the chelating Zn cation bears no effect on the stereochemical outcome, unlike those observed in intermolecular reactions.[10]

For chiral oxyallyl species **33**, a W-conformation and a similar *exo* approach would also lead to the observed major diastereomer of **20** or **21**. It is noteworthy that the observed high diastereoselectivity implies that it is selective for one out of eight possible transition states. Moreover, with a longer carbon tether (see allenamides **23** and **27**), the corresponding oxyallyl cation species would possess less rigidity, thereby eroding stereoselectivity by allowing the *endo* addition pathway.

We have described here novel intramolecular [4 + 3] cycloadditions using nitrogen-stabilized chiral oxyallyl cations via epoxidation of N-tethered allenamides. Efforts in the total synthesis of natural alkaloids via this cycloaddition 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.

References

(1) For recent reviews on [4 + 3] cycloadditions: (a) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371. (b) Davies, H. M. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Greenwich, CT, 1998; Vol. 5, pp 119−164. (c) Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Grennwich, CT, 1997; Vol. 4, pp 41−86. (d) West, F. G. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Grennwich, 1997; Vol. 4, pp 1−40. (e) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351−478. (f) Padwa, A.; Schoffstall, A. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 1−89. (g) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.

(2) For a recent review on heteroatom-stabilized oxyallyl cations in [4 + 3] cycloadditions: Harmata, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523.

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

(4) For sulfur-substituted oxyallyl cations: Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 1724.

(5) Lee, K.; Cha, J. K. *Org. Lett.* **1999**, *1*, 523.

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

(7) For a recent elegant study on chiral nitrogen-substituted oxyallyl cations: Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425.

(8) For an elegant vinylogous nitrogen-stabilized oxyallyl cation in an asymmetric catalytic [4 + 3], see: Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

(9) (a) Rameshkumar, C.; Hsung, R. P. *Synlett* **2003**, 1241. (b) Berry, C. R.; Rameshkumar, C.; Tracey, M. R.; Wei, L.-L.; Hsung, R. P. *Synlett* **2003**, 791. (c) Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem.* **2002**, *67*, 1339. (d) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (e) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869. (f) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145. (g) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903.

(10) (a) Xiong, H.; Hsung. R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (b) Rameshkumar, C.; Hsung, R. P. *Angew Chem., Int. Ed.* **2003**, *43*, in press.

(11) For recent stereoselective attempts: (a) Montanã, A. M.; Grima, P. M. *Tetrahedron* **2002**, *58*, 4769. (b) Beck, H.; Stark, C. B. W.; Hoffman, H. M. R. *Org. Lett.* **2000**, *2*, 883 and ref 11 cited within. (c) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831. (d) Cho, S. Y.; Lee, J. C.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 3394. (e) Davis, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326. (f) Grainger, R. S.; Owoare, R. B.; Tisselli, P.; Steed, J. W. *J. Org. Chem.* **2003**, *68*, 7899.

(12) For excellent reviews see: (a) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595. (b) Harmata, M. *Tetrahedron* **1997**, *53*, 6235.

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

(14) This is the first time we observed such epoxidation of [4 + 3] cycloadducts in the presence of DMDO. The major isomer is shown as drawn with its stereochemistry being assigned via nOe.

(15) Method B was not useful in these cases even with the reaction being run at a concentration of 0.0023 M and using ≥10 equiv of DMDO.

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