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Stereoselective 6π-Electron Electrocyclic Ring Closures of 2-Halo-Amidotrienes via a Remote 1,6-Asymmetric Induction

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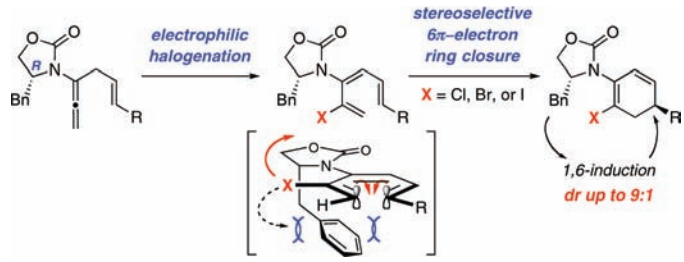
ABSTRACT



A diastereoselective 6π-electrocyclic ring closure employing halogen-substituted 3-amidotrienes via a 1,6-remote asymmetric induction is described. This new asymmetric manifold for pericyclic ring closure further underscores the significance of the allenamide chemistry.

Identifying a highly stereoselective manifold for 6π-electron electrocyclic ring closure of 1,3,5-hexatrienes remains a challenge in the field of pericyclic processes.[1,2] We recently reported that a 1,3-H shift of allenamides **1**[3,4] provides an excellent entry to amidotrienes **2**, which could undergo 6π-electron pericyclic ring closure.[5,6] The ring closure could be rendered in tandem with the 1,3-shift,[5,6] leading to the facile construction of rare chiral cyclic amidodienes **3** [Scheme 1].[7,8] While we were able to demonstrate the possibility of attaining a stereoselective ring closure using **2**, the level of selectivity was very modest. However, these efforts unveiled an invaluable opportunity not only to develop a new and attractive template for conducting stereoselective 6π-electrocyclic ring closures but also to achieve a highly challenging 1,6-asymmetric induction.[9] Consequently, we examined isomerizations of **1** via electrophilic halogenations, leading to 2-halo-amido-trienes **5** through *N*-acyl iminium ions **4**.

We recognized two distinct advantages of this electrophilic isomerization over the thermal one:[3b,5,10,11] (i) installing a

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(2) For recent examples of 6-π-electron electrocyclic ring closures of 1,3,5-hexatrienes, see: (a) Bishop, L. M.; Barbarow, J. E.; Bergmen, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100. (b) Sofiyev, V.; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149. (c) Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323. (d) Hulot, C.; Blong, G.; Suffert, J. *J. Am. Chem. Soc.* **2008**, *130*, 5046. (e) Benson, C. L.; West, F. G. *Org. Lett.* **2007**, *9*, 2545. (f) Pouwer, R. H.; Schill, H.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2007**, 4699. (g) Jung, M. E.; Min, S.-J. *Tetrahedron* **2007**, *63*, 3682. For examples on accelerated ring closures of 1,3,5-hexatrienes, see: (h) Sünnemann, H. W.; Banwell, M. G.; de Meijere, A. *Eur. J. Org. Chem.* **2007**, 3879. (i) Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 4946. (j) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403. (k) Yu, T.-Q.; Fu, Y.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* **2006**, *71*, 6157. (l) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624.

(3) For a leading review on allenamide chemistry, see: (a) Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773. For general reviews on allenes, see: (b) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vols. 1 and 2.

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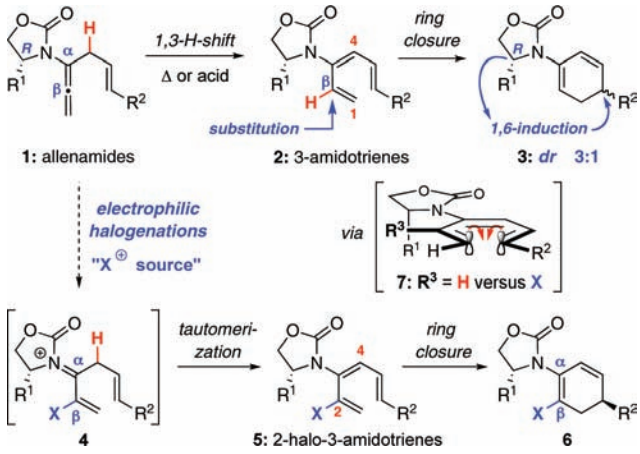
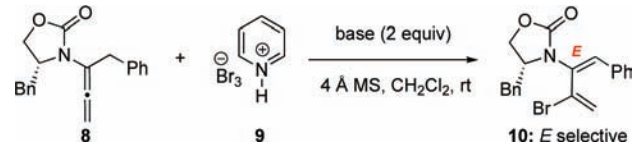
Scheme 1. A New Torquoselective Manifold via 1,6-Induction



halogen substituent at the C2-position of amidotrienes **5** allows for strategic functionalizations at C1 of **6** that is originally the central allenic β-carbon; and (ii) more importantly, the halogen atom can serve as a key chirality relaying element in the ring closure to achieve the desired 1,6-asymmetric induction. We envisioned that a disrotatory ring closure through amidotrienes **7** in the upward direction could be significantly favored with enhanced steric interaction between the R^1 group on the chiral amide and R^3 [H versus X] on the triene. We disclose here our success in developing a stereoselective 6π-electron pericyclic ring closure of halogen-substituted amidotrienes via a 1,6-remote asymmetric induction.

Our efforts commenced with electrophilic brominations of the α-benzyl-substituted allenamide **8**[12,13] as summarized in Table 1. Initial attempts involved reacting 2 equiv of allenamide **8** with pyridinium tribromide salt **9** in the presence of 4 Å MS in CH_2Cl_2, and the desired 2-bromoamidodiene **10**[14] was found in an encouraging 96% yield with exclusive *E*-stereoselectivity [entry 1]. In this reaction, 4 Å MS was utilized as a neutral acid scavenger for the corresponding byproduct HBr.[15] However, yields dropped

Table 1. Electrophilic Bromination of Allenamides



entry[a]	equiv of **8**	base	time [min]	yield [%][b]
1	2.0	–	20	96
2	1.5	–	20	64
3	1.0	–	20	45
4	1.0	Et_3N	45	82
5	1.0	K_2CO_3	45	59
6	1.0	DABCO	45	88

[a] 100 mg of 4 Å MS per 0.1 mmol of **8** were used for entries 1−3; 50 mg of 4 Å MS per 0.1 mmol of **8** were used for entries 4−6. [b] Isolated yield. The *E* stereochemistry was determined using NOE. [c] Using NBS afforded 29% yield of **10**.

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(14) See Supporting Information.

noticeably when the stoichiometry of the allenamide was decreased [entries 2 and 3]. We attribute this loss in the yield to hydrolysis of the starting allenamide due to the byproduct HBr; evidently the excess amount of allenamide used in earlier attempts was simply being sacrificed to soak up HBr. Consequently, we screened a number of bases and found that the addition of 2 equiv of DABCO [entry 6] to be the most optimal in effectively promoting this bromination reaction without sacrificing excess allenamide.

Having established the optimized conditions for bromination, a diverse array of *de novo* 2-halo-3-amidodi- and -trienes were prepared in synthetically useful overall yields with *E*-stereoselectivity [Table 2]. In addition to bromination, chlorinations could also be accomplished in good yields using NCS [see **22**, entries 3, 5, and 11]. It is noteworthy that brominations using NBS were less successful than when using NCS and that the tribromide salt **9** was the best bromination source. More importantly, this halogenation protocol appears to be highly chemoselective in reacting allenamides over alkynes [**21**, entry 2]. Subsequently, a range of allenamides containing α-allylic systems could be employed in a chemoselective manner, leading to preparations of chiral 2-halo-3-amidotrienes [entries 4−17].

In addition, 2-iodo-3-amidotrienes **25** and **29** could be accessed using NIS in 69% yield and 96% yield from **13a** and **15a**, respectively [entries 6 and 12]. Allenamides containing protected alcohol [see **14**] and protected amines [see **15a** and **15b**] also underwent bromination, chlorination, and iodination [see **26**−**29**, entries 9−13].

Our success in accessing novel chiral 2-halo-3-amidotrienes provided an invaluable opportunity for us to achieve diastereoselective 6π-electron electrocyclizations via highly challenging 1,6-remote asymmetric induction. We proceeded to examine thermal 6π-electron pericyclic ring closures of these trienes to construct rare cyclic 1-halo-2-amidodienes. As shown in Table 3, under thermal conditions in the range of 90−110 °C in toluene, chiral 2-halo-3-amidotriene **30** decomposed in a few hours without observing any ring-closure products. How-

Table 2. Synthesis of 2-Halo-Amido-Di- and Trienes

entry	allenamides	halogen	di- or trienes	yield [%][b]
1	**11:** R = *n*-Pr	**9**	**20:** X = Br	95
2	**12:** R =	**9**	**21:** X = Br	61
3	**8:** R = Ph	NCS	**22:** X = Cl	52
4	**13a:** R = Bn	**9**	**23a:** X = Br	87
5	**13a:** R = Bn	NCS	**24:** X = Cl	56
6	**13a:** R = Bn	NIS	**25:** X = I	69
7	**13b:** R = Ph	**9**	**23b:** X = Br	62
8	**13c**	**9**	**23c**	48
9	**14**	**9**	**26**	69
10	**15a:** R = Bn	**9**	**27a:** X = Br	76
11	**15a:** R = Bn	NCS	**28:** X = Cl	57
12	**15a:** R = Bn	NIS	**29:** X = I	96
13	**15b:** R = Ph	**9**	**27b:** X = Br	79
14	**16:** R = H	**9**	**30**	59
15	**17:** R = Me	**9**	**31**	30
16	**18**	**9**	**32**	65
17	**19**	**9**	**33**	42

[a] All reactions were run in CH_2Cl_2 [0.1 M] with 2 equiv of DABCO and 4 Å MS [50 mg/0.1 mmol] for 16 h at rt. [b] Isolated yield. [c] All di- or trienes were exclusively *E*-selective.

Table 3. Stereoselective Electrocyclization

entry	halo-amidotrienes	ring-closure products	yield [%][b]	*dr*[c]
1	**30**	**34**	61	-
2	**31**	**35**	76[d]	-
3	**23a:** R = Bn X = Br	**36a**	95	90:10
4	**24:** R = Bn X = Cl	**37**	61	87:13
5	**25:** R = Bn X = I	**38**	73	90:10
6	**23b:** R = Ph X = Br	**36b**	95	84:16
7	**23c**	**36c**	76	72:28
8	**26**	**39**	79	88:12
9	**27a:** R = Bn X = Br	**40a**	86	90:10
10	**28:** R = Bn X = Cl	**41**	84	87:13
11	**29:** R = Bn X = I	**42**	91	90:10
12	**27b:** R = Ph X = Br	**40b**	74	85:15
13	**33**	**43**	70[d]	-

[a] All reactions were run in toluene [0.05 M] at 110 °C for 16 h in the presence of 1 equiv of $AlMe_3$. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Product was aromatized.

(15) (a) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412. (b) Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311. (c) Kaneko, M.; Hayashi, R.; Cook, G. R. *Tetrahedron Lett.* **2007**, *48*, 7085.

ever, interestingly, addition of $AlMe_3$ effectively promoted the electrocyclization of **30**, leading to the desired cyclic product **34**. We are not sure at this point the role of $AlMe_3$; we screened several Lewis acids including BF_3-Et_2O, $TiCl_4$, $ZnCl_2$, $Cu(OTf)_2$, $PtCl_2$, and AuCl but rapid decomposition of amidotrienes occurred.

While electrocyclization of chiral 2-halo-3-amidotriene **31** with substitution at the C5-position resulted in aromatization of the initial product to give the aniline derivative **35** [entry 2], we observed a high diastereoselectivity in the ring closure of triene **23a** [entry 3]. This high diastereoselectivity was rather surprising because when we previously attempted electrocyclizations of 3-amido-6-alkyl-trienes,[6] 1,6-remote induction only led to a diastereomeric ratio of 3:1 [see Scheme 1]. However, it appears that, upon introduction of a halogen substitution, a high level of 1,6-remote induction could be attained.

We subsequently screened trienes that are substituted chiral oxazolidinones **23a−c** [entries 3−7]; the benzyl-substituted oxazolidinone **23a** seemed to be the most appropriate chiral auxiliary for this asymmetric transformation providing the desired cyclic diene **36a** in 95% yield with a *dr* of 90:10. The stereochemistry of the newly formed center was determined using the X-ray structure of a single crystal of **36b** [Figure 1].

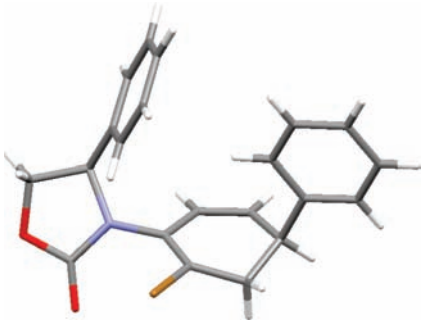
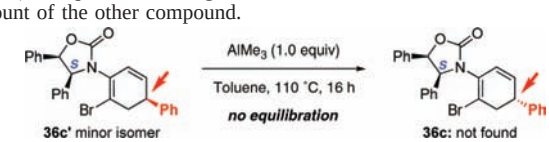


Figure 1. X-ray structure of **36b**.

This diastereoselectivity is believed to be due to kinetic control based on the control study of subjecting one of the minor isomers [**36c′**] to the reaction conditions.[16] Electrocyclization of the chlorinated triene **24** afforded **37** in 61% yield with a 87:13 ratio, while the iodinated triene **25** gave **38** in 73% yield with 90:10 *dr*. The nature of halogen does not appear to have a significant impact on the diastereomeric ratio. Electrocyclizations of other more exotic halogen-substituted trienes **26−29** were also examined [entries 8−12]. Ring-closure products **39−42** were attained in good yield and diastereoselectivity. Unfortunately, triene **33** also led to the aromatized product tetrahydronaphthlene **43** [entry 13].

(16) Independent heating of minor isomer **36c′** led to no observable amount of the other compound.



A proposed model for the stereoselective electrocyclization is shown in Figure 2. Based on B3LYP/6-31G* calculations,[17]

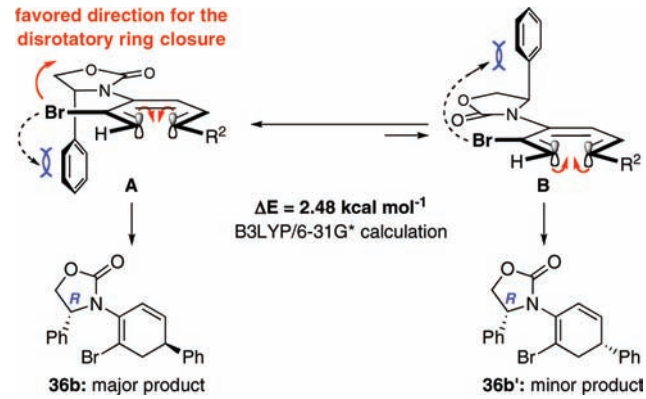


Figure 2. A proposed mechanistic model.

there is a 2.48 kcal mol^{-1} energy difference between two possible conformers **A** and **B** for these halo-amidotrienes. Although the Curtin−Hammett principle could be at play, if assuming the more stable conformer **A** is also the operable one, then the chiral auxiliary is blocking the lower face of the plane of the triene. Proceeding through an aromatic transition state for the 6π-electron electrocyclization, both bromine and the Ph-substituent on the two terminal vinyl strands of the triene would rotate in a disrotatory manner away from the Ph-ring on the oxazolidinone auxiliary. This would lead to the formation of the observed major diastereomer **36b**.

We have accomplished here a synthetic access to rare 2-halo-3-amidodi- and -trienes via electrophilic halogenations of allenamides. These novel trienes were useful to achieve stereoselective electrocyclizations via 1,6-remote asymmetric induction. Further mechanistic studies and applications of this novel asymmetric manifold for pericyclic ring closure are underway.

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Supporting Information Available: Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files are available for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) B3LYP/6-31G* calculation for other halo-amidotrienes.