

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

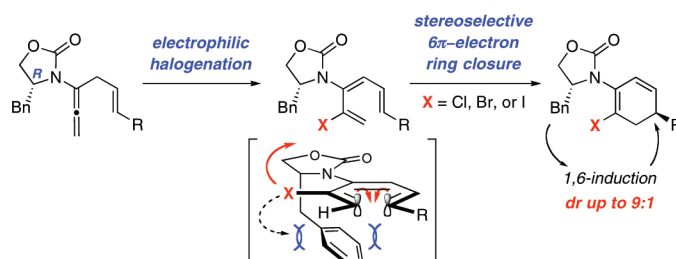
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ABSTRACT



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**.

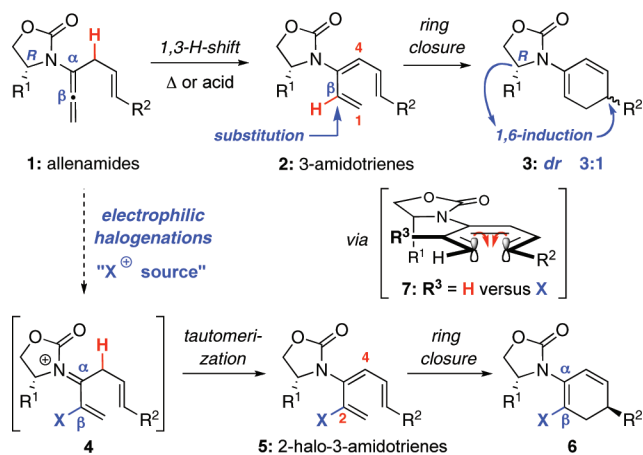
We recognized two distinct advantages of this electrophilic isomerization over the thermal one:^{3b,5,10,11} (i) installing a

(1) For reviews for pericyclic ring closures, see: (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. (b) Okamura, W. H.; de Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 699–750. For reviews on ring-closure in natural product synthesis, see: (c) Pindur, U.; Schneider, G. H. *Chem. Soc. Rev.* **1994**, 409. (d) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, 105, 4757.

(2) For recent examples of 6π -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) Sünemann, 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.

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

(4) Given the large volume of recent activities in allenamide chemistry, for reports in 2009 and 2010, see: (a) Lohse, A. G.; Krenschke, E. H.; Antoline, J. E.; Houk, K. N.; Hsung, R. P. *Org. Lett.* **2010**, ASAP (DOI: 10.1021/ol1023745). (b) Beccalli, E. M.; Bernasconi, A.; Borsini, E.; Broggini, G.; Rigamonti, M.; Zecchi, G. *J. Org. Chem.* **2010**, *75*, 6923. (c) Hill, A. W.; Elsegood, M. R. J.; Kimber, M. C. *J. Org. Chem.* **2010**, *75*, 5406. (d) Persson, A. K. Å.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2010**, *49*, 4624. (e) Krenschke, E. K.; Houk, K. N.; Lohse, A. G.; Antoline, J. E.; Hsung, R. P. *Chem. Science* **2010**, *1*, 387. (f) Danowitz, A. M.; Taylor, C. E.; Shrikian, T. M.; Mapp, A. K. *Org. Lett.* **2010**, *12*, 2574. (g) Zbieg, J. R.; E.; McInturff, E. L.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2514. (h) Cordier, P.; Aubert, C.; Malacria, M.; Gandon, V.; Lacôte, E. *Chem.-Eur. J.* **2010**, *16*, 9973. (i) Kimber, M. C. *Org. Lett.* **2010**, *12*, 1128. (j) Hashimoto, K.; Horino, Y.; Kuroda, S. *Heterocycles* **2010**, *80*, 187. (k) Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J.-E. *Org. Lett.* **2009**, *11*, 3814. (l) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (m) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547. (n) Beccalli, E. M.; Broggini, G.; Clerici, F.; Galli, S.; Kammerer, C.; Rigamonti, M.; Sottocornola, S. *Org. Lett.* **2009**, *11*, 1563. (o) Broggini, G.; Galli, S.; Rigamonti, M.; Sottocornola, S.; Zecchi, G. *Tetrahedron Lett.* **2009**, *50*, 1447. (p) Lohse, A. G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3430. (q) Lu, T.; Hayashi, R.; Hsung, R. P.; DeKorver, K. A.; Lohse, A. G.; Song, Z.; Tang, Y. *Org. Biomol. Chem.* **2009**, *9*, 3331.

(5) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125.

(6) Hayashi, R.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 1152.

(7) For reviews on chemistry of dienamides, see: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Petzilk, M. *Synthesis* **1981**, 753. (c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421. (d) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582. (e) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023.

(8) For some examples of cyclic amido-dienes, see: (a) Martínez, R.; Jiménez-Vázquez, H. A.; Delgado, F.; Tamariz, J. *Tetrahedron* **2003**, *59*, 481. (b) Wallace, D. J.; Klauber, D. J.; Chen, C. Y.; Volante, R. P. *Org. Chem.* **2003**, *5*, 4749. (c) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.-Eur. J.* **2004**, *10*, 484.

(9) For examples of 1,6-remote asymmetric inductions, see: (a) Paterson, I.; Dlgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35. (b) Arai, Y.; Ueda, K.; Xie, J.; Masaki, Y. *Synlett* **2001**, 529. (c) Maezaki, N.; Matsumori, Y.; Shogaki, T.; Soejima, M.; Ohishi, H.; Tanaka, T.; Iwata, C. *Tetrahedron Lett.* **1998**, *54*, 13087. (d) Maezaki, N.; Matsumori, Y.; Shogaki, T.; Soejima, M.; Tanaka, T.; Ohishi, H.; Iwata, C. *Chem. Commun.* **1997**, 1755. (e) Troyansky, E. I.; Ismagilov, R. F.; Strelenko, Y. A.; Samoshin, V. V.; Demchuk, D. V.; Nikishin, G. I.; Lindeman, S. V.; Khurstal'ov, V. V.; Struchkov, Y. T. *Tetrahedron Lett.* **1995**, *36*, 2293. (f) Stanway, S. J.; Thomas, E. J. *Tetrahedron Lett.* **1995**, *36*, 3417. (g) Carey, J. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3935. (h) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967.

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 R¹ group on the chiral amide and R³ [H versus X] on the triene. We disclose here our success in developing a stereoselective 6 π -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

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 ₃ N	45	82
5	1.0	K ₂ CO 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**.

allenamide **8** with pyridinium tribromide salt **9** in the presence of 4 Å MS in CH₂Cl₂, 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

(10) For examples of thermal allene isomerizations, see: (a) Crandall, J. K.; Paulson, D. R. *J. Am. Chem. Soc.* **1966**, *88*, 4302. (b) Bloch, R.; Perchec, P. L.; Conia, J.-M. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 798. (c) Jones, M.; Hendrick, M. E.; Hardie, J. A. *J. Org. Chem.* **1971**, *36*, 3061. (d) Patrick, T. B.; Haynie, E. C.; Probat, W. J. *Tetrahedron Lett.* **1971**, 27, 423. (e) Lechrich, F.; Hopf, H. *Tetrahedron Lett.* **1987**, *28*, 2697. (f) Meier, H.; Schmitt, M. *Tetrahedron Lett.* **1989**, *30*, 5873.

(11) For examples of allenamide isomerizations, see: (a) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807. Also see: (b) Farmer, M. L.; Billups, W. E.; Greenlee, R. B.; Kurtz, A. N. *J. Org. Chem.* **1966**, *31*, 2885. (c) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045. (d) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117.

(12) For a review on the synthesis of enamides, see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: 2005; Chapter 21.4.

(13) For allenamide synthesis via amidative cross-coupling, see: (a) TroShen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081. (b) See ref 11d. For α -alkylation of allenamides, see: (c) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869.

(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,

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

entry	allenamides	halogen	di- or trienes	yield [%] ^b
1		9		95
2		9		61
3		NCS		52
4		9		87
5		NCS		56
6		NIS		69
7		9		62
8		9		48
9		9		69
10		9		76
11		NCS		57
12		NIS		96
13		9		79
14		9		59
15		9		30
16		9		65
17		9		42

^a All reactions were run in CH₂Cl₂ [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.

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

Table 3. Stereoselective Electrocyclization

entry	halo-amidotrienes	ring-closure products	yield [%] ^b	d ^c
1			61	-
2			76 ^d	-
3			95	90:10
4			61	87:13
5			73	90:10
6			95	84:16
7			76	72:28
8			79	88:12
9			86	90:10
10			84	87:13
11			91	90:10
12			74	85:15
13			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 AlMe₃. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Product was aromatized.

°C in toluene, chiral 2-halo-3-amidotriene **30** decomposed in a few hours without observing any ring-closure products. How-

(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 electrocyclozation 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 $\text{BF}_3\text{-Et}_2\text{O}$, TiCl_4 , ZnCl_2 , $\text{Cu}(\text{OTf})_2$, PtCl_2 , and AuCl but rapid decomposition of amidotrienes occurred.

While electrocyclozation 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 electrocyclozations 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].

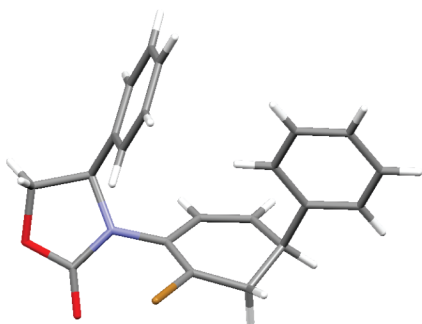
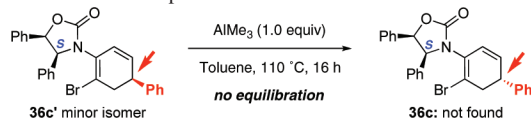


Figure 1. X-ray structure of **36b**.

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 Electrocyclozation 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. Electrocyclozations 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 tetrahydronaphthalene **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 electrocyclozation is shown in Figure 2. Based on B3LYP/6-31G* calculations,¹⁷

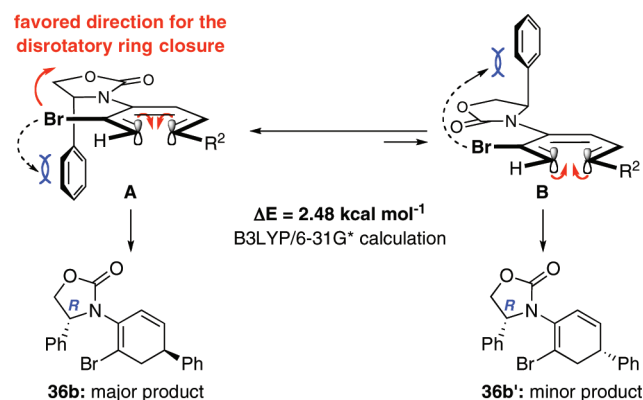


Figure 2. A proposed mechanistic model.

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 6 π -electron electrocyclozation, 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 electrocyclozations 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.

