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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 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 R¹ group on the chiral amide and R³ [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

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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 and free of charge via Internet <http://pubs.acs.org>.

allenamide **8** with pyridinium tribromide salt **9** in the presence of 4Å MS in CH₂Cl₂, and the desired 2-bromo-amidodiene **10**¹⁴ was found in an encouraging 96% yield with exclusive *E*-stereoselectivity [entry 1]. In this reaction, 4Å MS was utilized as a neutral acid scavenger for the corresponding byproduct HBr.¹⁵ However, yields dropped 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, and that 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 addition of 2 equiv of DABCO [entry 6] to be the most optimal in effectively promoting this bromination reaction without sacrificing excess of 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 6 π -electron electrocyclizations via highly challenging 1,6-remote asymmetric induction. We proceeded to examine thermal 6 π -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. However, interestingly, addition of AlMe₃ effectively promoted the electrocyclization of **30**, leading to the desired cyclic product **34**. We are not sure at this point the role of AlMe₃, and we screened several Lewis acids including BF₃·Et₂O, TiCl₄, ZnCl₂, Cu(OTf)₂, PtCl₂, 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, 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 *dr* of 90:10. Stereochemistry of the newly formed center was determined using X-ray structure of single crystal of **36b** [Figure 1]. 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].

A proposed model for the stereoselective electrocyclization is shown in Figure 2. Based on B3LYP/6-31G* calculations,¹⁷ there is a 2.48 kcal mol⁻¹ energy difference between two possible conformers **A** and **B** for these halo-amidotrienes. Although 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 electrocyclization, both bromine and 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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

Scheme 1.

A New Torquoselective Manifold via 1,6-Induction.

Figure 1.
X-Ray Structure of **36b**.

Figure 2.
A Proposed Mechanistic Model.

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** was used for entries 1-3; and 50 mg of 4 Å MS per 0.1 mmol of **8** was used for entries 4-6.

^b Isolated yield. The *E* stereochemistry was determined using nOe.

^c Using NBS afforded 29% yield of **10**.

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.

Table 3

Stereoselective Electrocyclization.

entry	halo-amidotrienes	ring-closure products	yield [%] ^b	dr ^c
1			61	-
2			76 ^d	-
3	<p>23a: R = Bn X = Br 24: R = Bn X = Cl 25: R = Bn X = I 23b: R = Ph X = Br</p>		95	90:10
4			61	87:13
5			73	90:10
6			95	84:16
7			76	72:28
8			79	88:12
9	<p>27a: R = Bn X = Br 28: R = Bn X = Cl 29: R = Bn X = I 27b: R = Ph X = Br</p>		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.

^dProduct was aromatized.