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Modular Functionalization of Allenes to Aminated Stereotriads

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Abstract

Nitrogen-containing stereotriads- compounds with three adjacent stereodefined carbons- are commonly found in biologically important molecules. However, the preparation of molecules bearing these motifs can be challenging. Herein, we describe a modular oxidation protocol which converts a substituted allene to a triply functionalized amine of the form C-X/C-N/CY. The key step employs a Rh-catalyzed intramolecular conversion of the allene to a strained bicyclic methylene aziridine. This reactive intermediate is further elaborated to the target products, often in one reaction vessel and with effective transfer of the axial chirality of the allene to point chirality in the stereotriad.

Densely functionalized amines bearing stereodefined heteroatom groups located adjacent to the chiral nitrogen-bearing carbon (X/N/Y stereotriads, where X and Y represent a halogen, oxygen, nitrogen or sulfur-containing group) occur frequently in natural products and biologically active molecules (Figure 1).¹ We were intrigued by the idea of developing highly modular and streamlined methods for the chemo-, regio- and stereoselective construction of these motifs. This communication reports the modular preparation of X/N/Y stereotriads from allenenes. These chiral hydrocarbons were chosen as precursors due to their ease of preparation, potential for introducing three new heteroatoms in a single reaction vessel and the ability to transfer readily available axial chirality to point chirality in the products.

Allene bis-epoxidation, pioneered by the Crandall and Williams groups, has been the only major approach thus far to introduce multiple heteroatoms into these chiral hydrocarbons.² The Williams group has further demonstrated the utility of allene epoxidation in the elegant syntheses of several natural product targets, including the epoxomicinoids, psymberin and *epi*-citreodiol.^{2c-e} Surprisingly, the analogous allene aziridination has received little attention, despite its synthetic potential for preparing complex amines.^{3,4}

Previous efforts by the Robertson and our group to transform allenic *N*-tosyloxycarbamates or carbamates **1** to bicyclic methylene aziridines **2** gave poor to moderate chemo- and stereoselectivities (Scheme 1, top).^{3a-f} However, we found that switching to an allenic sulfamate **4** gave a highly reactive methylene aziridine **5** that, in the presence of nucleophiles, underwent regioselective ring-opening to yield the *E*-enesulfamate **6**

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SUPPORTING INFORMATION. Experimental details for the synthesis and characterization of all new compounds are available in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

exclusively. We surmised the cyclic nature of **6** might impart good facial selectivity in its subsequent reaction with an electrophile, as conformation **B** minimizes the A^{1,3} strain present in **6**. The favored conformation of the resulting iminium ion **7** would again minimize A^{1,3} strain. As the majority of electrophiles utilized in our work have A values smaller than that of C₅H₁₁, additional shielding of the top face of **7** should result in stereoselective reduction to yield the 1,2-*syn*:2,3-*syn* product **8** as the major diastereomer.⁵

Treatment of an allenic sulfamate **9** (Table 1) with PhIO and catalytic Rh₂TPA₄ (TPA = triphenylacetate) cleanly yielded the desired *E* bicyclic methylene aziridine **5** (Scheme 1, R = C₅H₁₁) as observed by ¹H NMR. A series of weak nucleophiles promoted ring-opening of this methylene aziridine *in situ* to yield the corresponding *E* enesulfamates. Successful oxygen nucleophiles included AcOH, methanol and H₂O (entries 1–3) and gave the products **10–12** in good yields. The unusually activated nature of the bicyclic methylene aziridine was demonstrated by its facile reaction with amines that typically do not open aziridines in the absence of an exogenous Lewis acid (entries 4–6).⁶ Finally, PhSH and TMSCl (entries 7, 8) were also shown to be competent nucleophiles under these mild conditions.

The enesulfamates proved sufficiently nucleophilic to react with a range of standard electrophiles. The intermediate iminium ion **7** (see Scheme 1) was sensitive to hydrolysis, thus, the *dr* of the product resulting from the initial nucleophilic addition step was not determined. Rather, the reductant was added to the same reaction vessel to supply the final desired stereotriad and the overall *dr* of the reaction recorded (Table 2). For example, treatment of **10** with *N*-bromosuccinimide (NBS), followed by NaBH₃CN (entry 1) gave **18** in 71% isolated yield and a *dr* of 12.5:1. The relative stereochemistry of **18** was confirmed as 1,2-*syn*-2,3-*syn* by X-ray crystallography and the minor diastereomer was assigned as 1,2-*anti*-2,3-*syn* based on ¹H NMR coupling constants (see the Supporting Information for details). The relative stereochemistries of the remaining products in Table 1 were assigned by analogy to **18**.

Modifying the nature of the electrophile allowed us to control the *dr* of the stereotriad (Table 2, compare entries 2 and 3). When *N*-chlorosuccinimide (NCS) was employed, **19** was obtained in 65% NMR yield and a *dr* of 5:1. However, the more electrophilic trichloroisocyanuric acid (TCICA, entry 3), improved both the yield and *dr* of **19** to 72% and >19:1.

Selectfluor® (entry 4) resulted in a 2:1 *dr* of **20**, possibly due to increased epimerization at C3 caused by the electron-withdrawing fluorine. The stereochemistry of the major diastereomer could be assigned by analogy to **18** as 1,2-*syn*:2,3-*syn*; however, the identity of the minor diastereomer was believed to be 1,2-*syn*:2,3-*anti* (see SI for details). Nitrogen was introduced at C3 using DIAD (entry 5) to provide the vicinal diaminated stereotriad **21** in 69% yield with a *dr* of >19:1.⁷ PhSCI (entry 6) gave **22** in 80% yield and a *dr* of 2.9:1, along with minor amounts of two other stereoisomers.⁸ Reaction of **10** with DMDO (entry 7) and sodium triacetoxyborohydride (STABH) as the reductant gave **23** in lower *dr*, in this case due to poor facial selectivity in the addition of the electrophile to the enesulfamate. As in the case of **20**, the major diastereomer was assigned by analogy to **18** and the minor diastereomer as 1,2-*syn*:2,3-*anti* by ¹H NMR coupling constants. Future improvements in

In conclusion, a new method for the syntheses of stereotriads containing three contiguous heteroatom-bearing carbons of the general pattern X/N/Y has been developed. These transformations utilize easily prepared sulfamoyl allenes and generally proceed with good chemo-, regio- and diastereoselectivity under mild reaction conditions. The axial chirality of an enantioenriched allene can be translated into point chirality in the product with good fidelity. Further studies are underway to expand the scope of the allene, the nucleophile and the electrophile, particularly in the context of generating X/N/C stereotriads and amines containing two or three contiguous quaternary carbons. Studies to selectively access all four possible diastereomers of a given stereotriad are also underway and will provide a better understanding of the factors responsible for stereocontrol in our allene amination chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

TPA	triphenylacetate
PhIO	iodosobenzene
DMDO	dimethyldioxirane
DIAD	diisopropylazodicarboxylate
STABH	sodium triacetoxyborohydride.

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Figure 1.
X/N/Y stereotriads in bioactive molecules.

Previous work

This work

Scheme 1.

Allene oxidation strategy for the preparation of nitrogen-containing stereotriads.

Scheme 2.

Transfer of axial to point chirality.

Table 1

Tandem aziridination/ring-opening.

entry	Nu-X	equiv	solvent ^a	temp (°C)	time (h) ^b	yield	product
1 ^c	AcO-H	6	CH ₂ Cl ₂	rt	5	75%	10
2	MeO-H	50	CH ₂ Cl ₂	rt	1	77%	11
3	HO-H	20	CH ₃ CN ^a	rt	0.7	74%	12
4	PhNH-H	1.3	CH ₂ Cl ₂	rt	2	68%	13
5	morpholine	1.6	CH ₂ Cl ₂	rt	2.5	71%	14
6	piperidine	1.3	CH ₂ Cl ₂	rt	1	75%, 90% ^d	15
7	PhS-H	10	CH ₂ Cl ₂	rt	1	69%	16
8	Cl-TMS	1.5	THF ^a	0 °C to rt	8	56% (62%) ^e	17

^a solvent exchange

^b time for MA ring-opening only

^c 0.3 mol % catalyst was used

^d ¹H NMR yield based on the use of mesitylene as an internal standard

^e based on recovered starting material

Stereotriads from enesulfamates.

Table 2

entry	reagents	product	X	E	yield	dr
1	NBS, NaBH ₃ CN	18	H	Br	71%	12.5:1
2	NCS, NaBH ₃ CN	19	H	Cl	65% ^a	5:1
3	TCICA, NaBH ₃ CN	19	H	Cl	76%	>19:1 ^b
4	Selectfluor®, NaBH ₃ CN	20	H	F	57%	2:1
5	DIAD, ^c NaBH ₃ CN	21	H	NN(CO ₂ tPr) ₂	69%	>19:1
6	PhSeCl, NaBH ₃ CN	22	H	SPh	80%	2.9:1 ^d
7	DMDO, STABH	23	H	OH	44%	2:1 ^d
8	NBS, H—C≡C—MgBr	24	—C≡C—H	Br	59%	>19:1
9	NBS, Me ₃ SiCN, cat I ₂	25	CN	Br	73%	3.3:1

^a NMR yield using mesitylene as the internal standard.

^b dr of the product after purification.

^c 10 mol % Cu(OTf)₂ and 1.1 mol % Me₂N(CH₂)₂NNMe₂ were also added to the reaction.

^d Minor amounts of other diastereomers were formed.

Table 3

Formation of X/N/Br stereotriads.

entry	X	yield	crude <i>dr</i>	isolated <i>dr</i>
1	11 OMe	65%	26 8:1	19:1
2	12 OH	71%	27 5.6:1	4:1 ^a
3	15 piperidine	44%	28 10:1	19:1
4	16 SPh	67%	29 >19:1	>19:1
5	17 Cl	77% ^b	30 >19:1 ^b	>19:1

^a After attempted separation of the two diastereomers.

^b ¹H NMR using mesitylene as the internal standard.

One-pot stereotriad synthesis.

Table 4

entry	NuH	electrophile	rxn time/temp ^b	yield	dr
1	AcOH	NBS	2 h, rt	60% 18	5:1
2	AcOH	NBS	15 min, 0 °C	61% 18	20:1
3	MeOH	NBS	45 min, 0 °C	60% 26	1.7:1
4	MeOH	NBS	10 min, −10 °C	58% 26	2.6:1
5 ^c	PhSH	NBS	10 min, 0 °C	61% 29	15:1
6	MeOH	DIAD ^d	2 h, 70 °C	64% 31	4.6:1
7	MeOH	PhSCI	30 min, rt	74% 32	2.6:1

^a Conditions: 1a) 0.5 mol % Rh₂TPA₄, 1.1 equiv PhIO, CH₂Cl₂, rt, 1 h, then NuH 1b) electrophile, NaBH₃CN.

^b time and temperature for the addition of the electrophile

^c See Scheme 2

^d Celite filtration before addition of the DIAD.