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Modular Functionalization of Allenes to Aminated Stereotriads

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Supporting Information

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/C−Y. 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

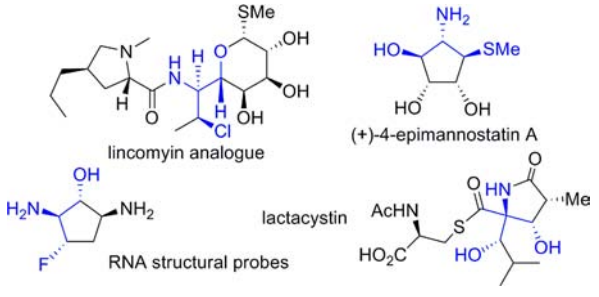


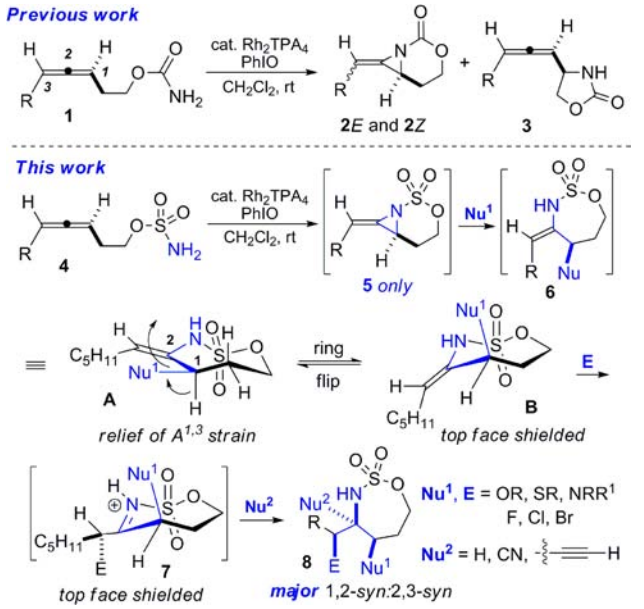
Figure 1. X/N/Y stereotriads in bioactive molecules.

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 allenes. 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

Scheme 1. Allene Oxidation Strategy for the Preparation of Nitrogen-Containing Stereotriads



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** 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 C_5H_{11}, 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 Rh_2TPA_4 (TPA = triphenylacetate) cleanly yielded the

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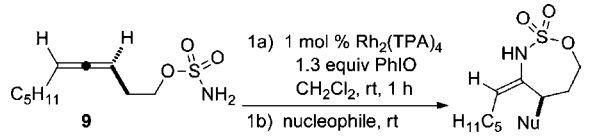
Table 1. Tandem Aziridination/Ring-Opening



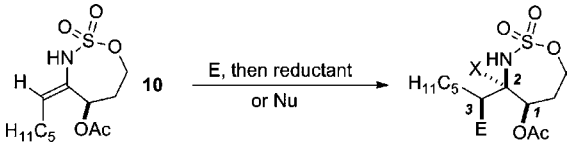
entry	Nu-X	equiv	solvent[a]	temp (°C)	time (h)[b]	yield	product
1[c]	AcO-H	6	CH_2Cl_2	rt	5	75%	**10**
2	MeO-H	50	CH_2Cl_2	rt	1	77%	**11**
3	HO-H	20	CH_3CN[a]	rt	0.7	74%	**12**
4	PhNH-H	1.3	CH_2Cl_2	rt	2	68%	**13**
5	morpholine	1.6	CH_2Cl_2	rt	2.5	71%	**14**
6	piperidine	1.3	CH_2Cl_2	rt	1	75%, 90%[d]	**15**
7	PhS-H	10	CH_2Cl_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]^{1}H NMR yield based on the use of mesitylene as an internal standard. [e]Based on recovered starting material

desired *E* bicyclic methylene aziridine **5** (Scheme 1, R = C_5H_{11}) as observed by ^{1}H 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 H_2O (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 $NaBH_3CN$ (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 ^{1}H NMR coupling constants (see the Supporting Information (SI) for details). The relative stereochemistries of the remaining products in Table 1 were assigned by analogy to **18**.

Table 2. Stereotriads from Enesulfamates



entry	reagents	product	X	E	yield	*dr*
1	NBS, $NaBH_3CN$	**18**	H	Br	71%	12.5:1
2	NCS, $NaBH_3CN$	**19**	H	Cl	65%[a]	5:1
3	TCICA, $NaBH_3CN$	**19**	H	Cl	72%	>19:1[b]
4	Selectfluor®, $NaBH_3CN$	**20**	H	F	57%	2:1
5	DIAD,[c] $NaBH_3CN$	**21**	H	$NHN(CO_2{}^iPr)_2$	69%	>19:1
6	PhSCl, $NaBH_3CN$	**22**	H	SPh	80%	2.9:1[d]
7	DMDO, STABH	**23**	H	OH	44%	2:1[d]
8	NBS, H≡—MgBr	**24**	-≡—H	Br	59%	>19:1
9	NBS, Me_3SiCN, 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 11 mol % $Me_2N(CH_2)_2NMe_2$ were also added to the reaction. [d]Minor amounts of other diastereomers were formed.

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] PhSCl (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 ^{1}H NMR coupling constants. Future improvements in the dr and yield of this reaction will clarify whether the free oxygen is exerting a directing effect in the reduction step.

The challenging generation of a complex quaternary amine-bearing carbon was accomplished by adding carbon nucleophiles to the transient iminium ion **7** according to the model proposed in Scheme 1. For example, employing ethynyl magnesium bromide (entry 8) in the reaction at low temperature gave **24** in >19:1 dr, while a Strecker-type reaction employing TMSCN (entry 9) gave **25** in 73% yield and a dr of 3.3:1.[9]

The allene amination chemistry was quite flexible, as demonstrated by the conversion of a variety of heteroatom-substituted enesulfamates to the corresponding X/N/Br

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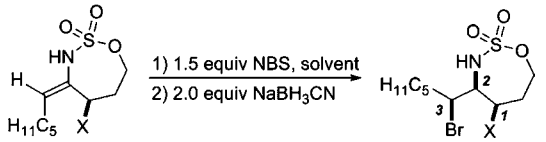
stereotriads (Table 3). Ethers, alcohols, amines, mercaptans, and halogens were all tolerated in the reaction and gave moderate to good dr of the resulting stereotriads **26**–**30**.

Table 3. Formation of X/N/Br Stereotriads



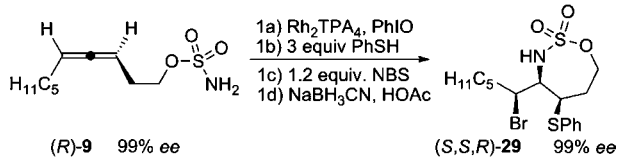
entry		X	yield		crude dr	isolated dr
1	**11**	OMe	65%	**26**	8:1	19:1
2	**12**	OH	71%	**27**	5.6:1	4:1[a]
3	**15**	piperidine	44%	**28**	10:1	19:1
4	**16**	SPh	67%	**29**	>19:1	>19:1
5	**17**	Cl	77%[b]	**30**	>19:1[b]	>19:1

[a]After attempted separation of the two diasteromers. [b]^{1}H NMR using mesitylene as the internal standard.

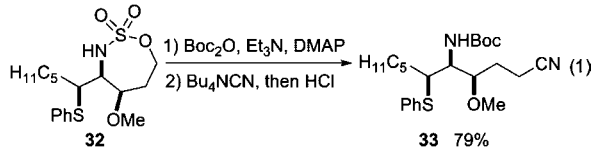
We were pleased to find that the mild reaction conditions, coupled with the high chemo-, regio-, and diastereoselectivity of the allene oxidation, allowed for conversion of **9** directly to X/N/Y stereotriads in a single flask (Table 4). The key to obtaining high dr hinged on minimizing the time that the electrophile was allowed to react with the intermediate enesulfamate (entries 1, 2). The 61% overall yield for the O/N/Br stereotriad **18** (entry 2) obtained in one pot compared favorably with the yield that was obtained when the reaction was performed in two steps (53%, Table 1, entry 1 and Table 2, entry 1). When MeOH was utilized as the nucleophile (entries 3 and 4), the dr of **26** was lower compared to that obtained by initiating the stereotriad formation from the isolated enesulfamate (see Table 3, entry 1), but the one-pot yield of 58% compared favorably with the two-step yield of 50%. Enantioenriched **9** (entry 5 and Scheme 2) gave **29** in good yield and excellent dr. The use of DIAD and PhSCl as the electrophiles with MeOH as the nucleophile (entries 5 and 6) gave **31** and **32** in 64% and 74% yields, respectively, over the four consecutive reactions.

The ability to transfer the axial chirality of the allene to point chirality in the stereotriad is an important aspect of this chemistry.[2c−g,10] As many convenient methods are available to convert enantioenriched propargyl alcohols to the corresponding allenes, this simplifies the formation of enantioenriched stereotriads to a diastereoselective process.[10a,b] As illustrated in Scheme 2, (*R*)-**9** was smoothly converted into (*S*,*S*,*R*)-**29** with no erosion in the ee.

Scheme 2. Transfer of Axial to Point Chirality

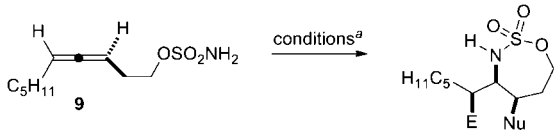


Finally, to demonstrate that the X/N/Y stereotriads could be easily deprotected, the nitrogen of **32** (eq 1) was protected with a Boc group. Successive treatment of the *N*-protected **32** with Bu_4NCN and HCl provided **33** in 79% yield over the two steps.[11]



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.

Table 4. One-Pot Stereotriad Synthesis



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	PhSCl	30 min, rt	74%	**32**	2.6:1

[a]Conditions: (1a) 0.5 mol % Rh_2TPA_4, 1.1 equiv PhIO, CH_2Cl_2, rt, 1 h, then NuH; (1b) electrophile, $NaBH_3CN$. [b]Time and temperature for the addition of the electrophile. [c]See Scheme 2. [d]Celite filtration before addition of the DIAD.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details for the synthesis and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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