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SHORT COMMUNICATION

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Stereocontrolled Synthesis of 1,3-Diamino-2-ols by Aminohydroxylation of Bicyclic Methylene-Aziridines

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Nitrogen-containing stereotriads, which are defined as compounds with three adjacent stereodefined carbon atoms, are common structural motifs in several biologically relevant compounds. The 1,3-diamino-2-ol motif in particular is an important pharmacophore for which there are limited stereoselective synthetic approaches. In this communication, we describe the aminohydroxylation of a series of bicyclic methylene-aziridines obtained from the aziridination of a series of homoallenic carbamates. The unusual electronic and steric features of these useful heterocyclic scaffolds render the Os-catalyzed aminohydroxylation of the exocyclic alkene highly regio- and stereoselective. Rearrangement of the proposed N,O-aminal intermediate to a 1,3-diamino-2-one is followed by reduction with $NaBH_4$ to deliver the desired 1,3-diamino-2-ols in good yields with high diastereomeric ratios.

Introduction

The development of catalytic methods for the oxidation of olefins to compounds containing vicinal heteroatom-bearing stereocenters is one of the central developments of organic chemistry in the past three decades.[1] However, these methods are limited to the introduction of two heteroatoms by virtue of the substrate and can suffer from issues with regioselectivity if two different heteroatoms are installed. Efficient regio-, chemo-, and stereoselective routes to nitrogen-containing arrays of three or more carbon–heteroatom bonds ("stereotriads") through the oxidation of allenes could help to address some of the shortcomings associated with olefin oxidation and streamline the syntheses of these useful motifs.[2] Allenes present several advantageous features for stereotriad construction, as they are easily synthesized, their axial chirality can be transferred to point chirality, and they possess three adjacent sites for functionalization.[3] Our group has recently described the efficient synthesis of stereotriads of the form C–Nu/C–N/C–E (Nu = nucleophile, E = electrophile) from homoallenic sulfamates through allene aziridination as a key step.[2e] Although this approach offers diverse choices for the Nu and E groups of the product, the placement of nitrogen atom remains restricted to the central carbon atom of the stereotriad. To gain access to other valuable nitrogen-containing stereotriads, alternative strategies to harness the unique reactivity of bicyclic methylene-aziridines were desired.

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We hypothesized that allene aziridination might be used to access 1,3-diamino-2-ols, a motif found in many natural products and biologically active molecules (Figure 1). These include the HIV protease inhibitor Darunavir,[4a] the enduracididine components of the antibiotic mannopeptimycin β,[4b] Mipralden,[4c] a rare and potent binder of Mcl-1 and Bcl-X(L), as well as compounds that inhibit BACE-1.[4d] The synthesis of the nitrogen–oxygen–nitrogen stereotriads found in these molecules often require significant manipulation of chiral starting materials and multistep synthetic sequences.[5]

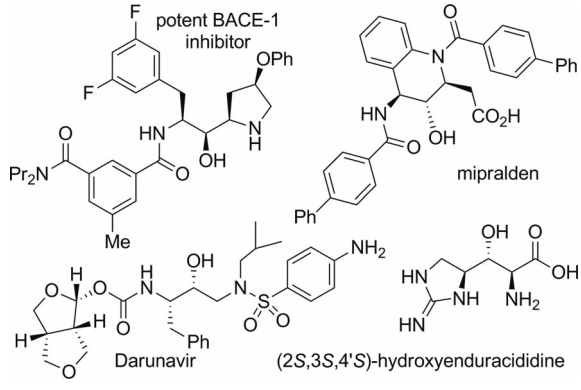
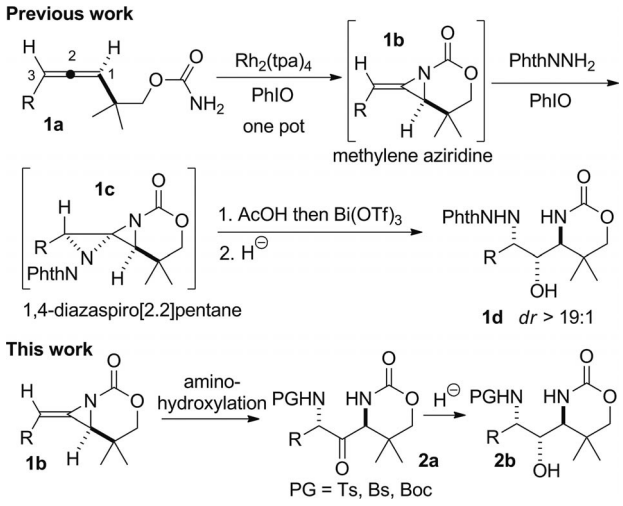


Figure 1. Bioactive molecules with N–O–N stereotriads.

Results and Discussion

Our first strategy to obtain 1,3-diamino-2-ols from allenes employed a five-step, one-pot conversion of homoallenic carbamate **1a** into N–O–N stereotriad **1d** (Scheme 1). This first-generation synthesis proceeded by way of an in-

tramolecular aziridination to form bicyclic methylene-aziridine **1b**, intermolecular aziridination to form 1,4-diazaspiro[2.2]pentane **1c**, ring-opening with an acetate nucleophile, rearrangement, and reduction (Scheme 1, top). Although the individual steps of this approach were high yielding, cleavage of the N–N bond in the final product was difficult.[2d]

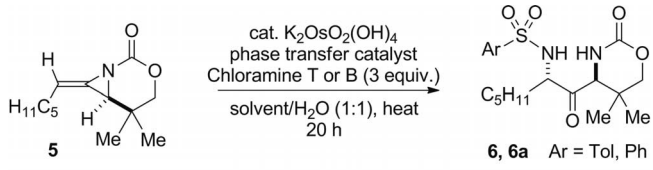


Scheme 1. Syntheses of 1,3-diamino-2-ols from allenes (tpa = triphenylacetate, Phth = phthalyl, Ts = *para*-tolylsulfonyl, Bs = phenylsulfonyl, Boc = *tert*-butoxycarbonyl).

To address this limitation and to improve the efficiency of the sequence, we wanted to investigate the direct aminohydroxylation of bicyclic methylene-aziridine **1b** as a potential route to N–O–N stereotriads **2b** (Scheme 1, bottom).[6] The successful implementation of this second-generation synthesis required achieving a stereo- and regioselective aminohydroxylation to form an N,O-aminal intermediate capable of stereoselective rearrangement to 1,3-diaminoketone **2a**. As our previous reports on the reactivity of methylene-aziridines demonstrated that the concavity of this unusual fused heterocycle can promote highly diastereoselective reactions of the exocyclic olefin, this strategy warranted further investigation.[2c]

Early reports from the Sharpless group described four primary sets of conditions for the osmium-catalyzed aminohydroxylation of alkenes.[7] These conditions were applied to the transformation of methylene-aziridine **5** into 1,3-diaminated ketones **6** and **6a** (Table 1). Biphasic systems consisting of mixtures of *t*BuOH or CH_3CN/H_2O using Chloramine T as the nitrogen source gave low yields of desired **6** (Table 1, entries 1 and 2) and significant byproduct formation. Switching the solvent to benzene and employing $BnEt_3NBr$ as a phase-transfer catalyst (PTC) gave low conversion, but mainly to the desired product (Table 1, entry 3). Increasing the temperature of the reaction gave 70% conversion, but only 25% yield of **6** (Table 1, entry 4). Changing the solvent to chloroform gave the product in both moderate conversion and yield (Table 1, entry 5). This system was further optimized by increasing the loading of the catalyst from 5 to 7.5 mol-% to give full conversion of **5** and 81% yield of **6** (Table 1, entry 6). The PTC was paramount to the success of the reaction, as its absence (Table 1, entries 7 and 8) gave no conversion to **6**.

Table 1. Optimization of the aminohydroxylation.



Entry	Cat. [mol-%]	Additive	Chloramine	Solvent	*T* [°C]	Yield[a] [%]
1	5	none	T	*t*BuOH	55	0
2	5	none	T	CH_3CN	23	18
3	5	$BnEt_3NBr$	T	benzene	30	12
4	5	$BnEt_3NBr$	T	benzene	45	25
5	5	$BnEt_3NBr$	T	$CHCl_3$	33	60
6	7.5	$BnEt_3NBr$	T	$CHCl_3$	33	81
7	7.5	none	T	$CHCl_3$	33	0
8	7.5	$(DHDQ)_2PHAL$	T	$CHCl_3$	33	0
9	7.5	$(DHDQ)_2PHAL$, $BnEt_3NBr$	T	$CHCl_3$	33	43[b]
10	7.5	$BnEt_3NBr$	B	$CHCl_3$	33	74
11	7.5	$BnEt_3NCl$	B	$CHCl_3$	33	79
12	7.5	$BnEt_3NCl$, pyridine (15 mol-%)	B	$CHCl_3$	33	0
13	7.5	$BnEt_3NCl$, TMEDA (15 mol-%)	B	$CHCl_3$	33	0
14	7.5	$BnEt_3NCl$, TMEDA (8 mol-%)	B	$CHCl_3$	33	0
15	7.5	$BnEt_3NCl$	BocNNaCl	$CHCl_3$	33	33

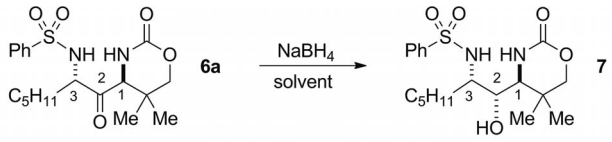
[a] *dr* was >19:1 unless noted. [b] *dr* was 3:1.

Chloramine B could also be employed as the nitrogen source to provide **6** in 74 and 79% yield (Table 1, entries 10 and 11), and this reagent offered the advantage of being more labile than the tosyl group. Attempts to enhance the reaction rate by using several amine additives, including hydroquinidine 1,4-phthalazinediyl diether [$(DHDQ)_2PHAL$], pyridine, and *N*,*N*,*N*′,*N*′′-tetramethyl-1,2-ethylenediamine (TMEDA), were not successful (Table 1, entries 8, 9, 12–14).[8] The use of BocNNaCl as the nitrogen source (Table 1, entry 15) resulted in decreased conversion and yield.

With successful conditions for the aminohydroxylation in hand, the next step was to explore stereocontrol in the reduction of 1,3-diamino-2-one **6a**. To the best of our knowledge, no systematic investigations on the reduction of acyclic α,α′-diaminated ketones have been undertaken. Reduction of **6a** with $NaBH_4$ in CH_2Cl_2 gave 1,3-diamino-2-ol **7** in excellent yield and stereoselectivity (Table 2, entry 1). Attempts to conduct the aminohydroxylation/reduction sequence in a single pot gave comparable overall yield (64%) but a significant decrease in the *dr* (5:1 *dr* single pot, 10:1 *dr* two pots). A series of reductions in solvents of differing polarities (Table 2, entries 2–4) demonstrated that

a larger *dr* was obtained in less polar solvents. The relative 1,2-*anti*/2,3-*syn* stereochemistry of **7** was confirmed by X-ray crystallography of a derivative (see the Supporting Information for further details) and is consistent with Felkin–Anh control by C1.[9]

Table 2. Reduction of the 1,3-diaminated ketone.

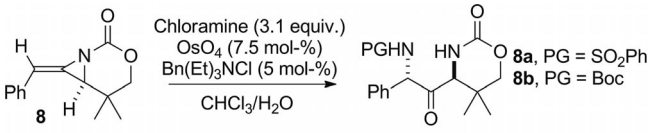


Entry	Solvent	Yield [%]	*dr*
1[a]	CH_2Cl_2	83	10:1
2[b]	$CHCl_3$	94	10:1
3[b]	THF	91	5:1
4[b]	MeOH	87	1:1

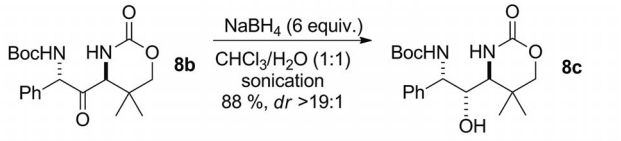
[a] Isolated yield. [b] NMR yield calculated by using mesitylene as an internal standard.

The standard aminohydroxylation conditions from Table 1 were unsuccessfully applied to phenyl-substituted methylene-aziridine **8** (Table 3, entry 1). The use of carbamate-derived chloramine salts, commonly used for the aminohydroxylation of styrenes, substantially improved the yield to 55% (Table 3, entry 5).[10] Reduction of **8b** was best carried out in $CHCl_3/H_2O$ (1:1) with sonication to give **8c** in 88% yield and >19:1 *dr*.

Table 3. Synthesis of aryl-substituted N–O–N stereotriads.



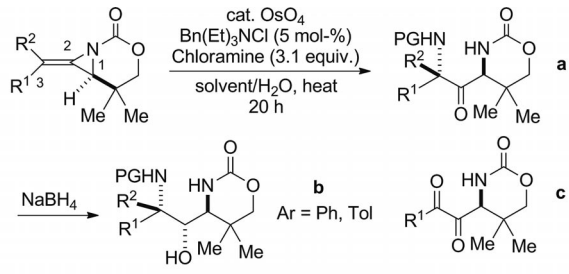
Entry	Chloramine	*T* [°C]	$CHCl_3/H_2O$	Product, yield [%]
1	Chloramine B	22	1:1	**8a**, 28
2	BocNNaCl	22	1:1	**8b**, 28 (37 brsm)[a]
3	BocNNaCl	30	1:1	**8b**, 47
4	CbzNNaCl	30	1:1	unidentified product
5	BocNNaCl	30	4:1	**8b**, 55



[a] Based on recovered starting material.

The scope of the aminohydroxylation/reduction of bicyclic methylene-aziridines to 1,3-diamino-2-ols was investigated (Table 4). The reaction was highly stereoselective, as *E* methylene-aziridine **5** (Table 4, entry 1) and *Z* isomer **9** (Table 4, entry 2) were shown to yield 1,3-diamino-2-ols **6** and **9b** epimeric at C3. The relative 1,2-*anti*/2,3-*anti* stereochemistry of **9b** was confirmed by X-ray crystallography of a derivative (see the Supporting Information for further details). The transformation tolerated branching in the alkyl group at C3 of the substrate, silyl-protected alcohols (TIPS = triisopropylsilyl), and remote aryl groups (Table 4, entries 3–6), provided optimized conditions were employed (Table 4, conditions B). For more electron-rich methylene-aziridines (Table 4, entries 3 and 4), trace amounts (<10%) of overoxidized product **c** were also observed. Application of conditions C to aryl-substituted methylene-aziridines gave moderate yields of the desired products (Table 4, entries 7–9), although one electron-rich substrate did not react (Table 4, entry 10), yields for these types of aminohydroxylations are typically moderate, but this is offset by the high yield and *dr* of the reduction, which leads to a rapid increase in the stereochemical complexity.

Table 4. Scope of the N–O–N stereotriad formation.



Entry	R^1, R^2	Conditions[a]	Product	Yield [%]	Product	Yield [%]	*dr*
1	C_5H_{11}, H	**5** A	**6**	79	**7**	83	10:1
2	H, C_5H_{11}	**9** A	**9a**	60	**9b**	83	10:1
3	*i*Bu, H	**10** B	**10a**	57[b]	**10b**	94	10:1
4	$TIPSO(CH_2)_2$, H	**11** B	**11a**	50[b,c]	**11b**	94	10:1
5	$Ph(CH_2)_2$, H	**12** B	**12a**	57	**12b**	88	10:1
6	$EtOC(O)CH_2$, H	**13** B	**13a**	<5[d]	**13b**	–	–
7	Ph, H (Table 3)	**8** C	**8b**	55[b]	**8c**	88	>19:1
8	*p*-MeC_6H_4, H	**14** C	**14a**	53[b]	**14b**	88	>19:1
9	*p*-FC_6H_4, H	**15** C	**15a**	52[b]	**15b**	92	>19:1
10	*p*-$OMeC_6H_4$, H	**16** C	**16a**	<5[d]	**16b**	–	–

[a] Conditions A, aminohydroxylation: $K_2OsO_2(OH)_4$ (7.5 mol-%), Chloramine T, 33 °C; reduction: $NaBH_4$ in CH_2Cl_2. Conditions B, aminohydroxylation: OsO_4 (10 mol-%), Chloramine B, 37 °C; reduction: $NaBH_4$ in CH_2Cl_2. Conditions C, aminohydroxylation: OsO_4 (7.5 mol-%), BocNNaCl, 30 °C; reduction: $NaBH_4$ in $CHCl_3/H_2O$ (1:1) with sonication. A *dr* of >19:1 for all substrates. [b] <10% dihydroxylation product was observed. [c] 60% based on recovered starting material. [d] No reaction upon heating to 50 °C.

The excellent regioselectivity of the aminohydroxylation may be attributed to the preference of the chloramine nitrogen atom to bind to the less substituted and/or more electron-rich carbon atom of the methylene-aziridine,[11] as the carbamate of the substrate likely serves as an inductively electron-withdrawing group. The failure of two substrates, β-carboxyethyl-substituted **13** and *p*-MeO-phenyl-substituted **16**, to react in the aminohydroxylation supports electronic control of both reactivity and regioselectivity. The former withdraws electron density from the less-substituted C3 carbon atom of the reactive site, whereas the latter donates electron density to the more substituted C2 carbon atom.

Conclusions

In summary, we have developed a highly stereoselective method for the synthesis of 1,3-diamino-2-ols through Os-catalyzed aminohydroxylation/reduction of bicyclic methylene-aziridines. The reaction proceeds with excellent regioselectivity and diastereoselectivity to rapidly deliver these useful structural motifs.

Experimental Section

Synthesis of 1,3-Diamino-2-ones from Bicyclic Methylene-Aziridines

Procedure A: A 0.05 M solution of the methylene-aziridine (1 equiv.) and potassium osmate (0.075 equiv.) in $CHCl_3$ was treated with an equal volume of an aqueous solution of the chloramine salt (3.1 equiv.) and the phase-transfer catalyst (0.05 equiv.). The flask was fitted with a reflux condenser, and the mixture was heated to 33 or 37 °C by using an oil bath. After 20 h, the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3×). The combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane/ethyl acetate gradient) to give the ketone.

Procedure B: An aqueous solution of 2% (w/v) OsO_4 (0.05 equiv.) was substituted for potassium osmate. Two further portions of 2% (w/v) OsO_4 solution (0.025 equiv.) were added at 4 h intervals.

Reduction of 1,3-Diamino-2-ones to 1,3-Diamino-2-ols

Procedure A: $NaBH_4$ (6 equiv.) was added to the ketone, followed by enough CH_2Cl_2 to yield a 0.066 M solution in substrate. The mixture was allowed to stir for 12 h, quenched with aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined organic layer was dried with Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (hexanes/ethyl acetate) to give the 1,3-diamino-2-ol.

Procedure B: $NaBH_4$ (6 equiv.) was added to the ketone, followed by enough CH_2Cl_2 to yield a 0.066 M solution in substrate. An equal volume of deionized water was added and the mixture sonicated until the reduction was complete, typically 5–7 h.

CCDC-931790 (for **7c**) and -931791 (for **9c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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