Synthetic Methods

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Oxidative Allene Amination for the Synthesis of Azetidin-3-ones

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Abstract: *Regioselectivity in the aziridination of silyl-substituted homoallenic sulfamates is readily diverted to the distal double bond of the allene to yield endocyclic bicyclic methyleneaziridines with excellent stereocontrol. Subsequent reaction with electrophilic oxygen sources initiates facile rearrangement to densely functionalized, fused azetidin-3-ones in excellent d.r., effectively transferring the axial chirality of the allene to central chirality in the products. The steric nature of the silyl group dictates which of the two rings of the fused azetidin-3-one will undergo further functionalization, providing an additional element of diversity for the preparation of enantioenriched azetidine scaffolds with potential biological activity.*

Densely functionalized azetidine motifs exhibit a broad range of biological activities, including antibacterial activity, inhibitory activity against epidermal growth factor receptor kinases, antagonists of the P2Y12 receptor, components of dopamine antagonists, ATP-ase activators and inhibitors of various glucosidases for the treatment of diabetes (Figure 1).[1] While the syntheses of related azetidin-2-ones (β-lactams) are well-documented,[2] approaches to the analogous azetidin-3-ones are much less common.[3] Early strategies reported by the De Kimpe group (Scheme 1) required multiple steps to convert methyl 4-chloro-3-oxobutanoate or butane-2,3-dione to racemic 2,4-disubstituted azetidin-3-ones.[4,5] Cu- and Rh-catalyzed carbenoid insertions into the N–H bonds of α,α′-dialkyl-α-diazoketones offer a more streamlined approach to *cis*-2,4-disubstituted azetidin-3-ones from amino acid precursors, but the scope of the products is limited.[6,7] Complex 3-hydroxy-4-(hydroxymethyl)-3-methylazetidine-2-carboxylic acids can be prepared through the intermediacy of stable bicyclic azetidin-3-ones, but this approach also requires several steps from the pyranoside substrates.[8] In this communication, we report a simple protocol that permits rapid access to fully substituted azetidin-3-ols in good yields and excellent diastereoselectivities from simple homoallenic sulfamate precursors.

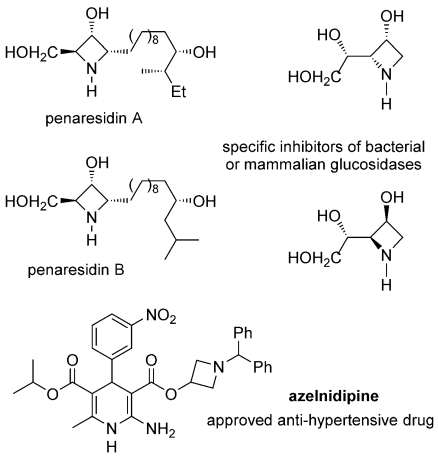
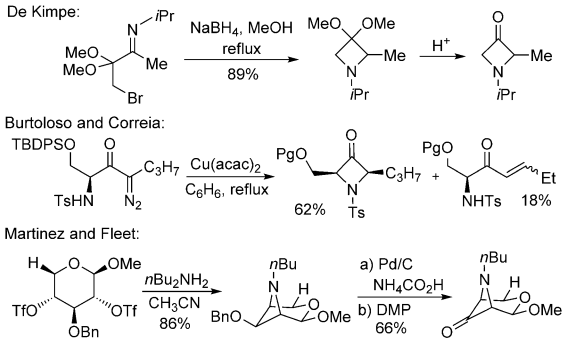
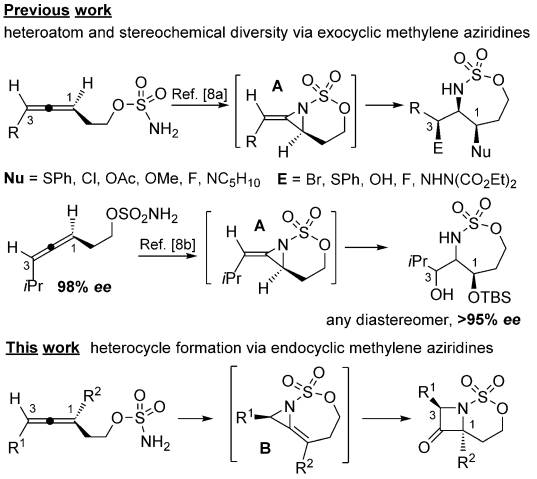


Figure 1. Bioactive azetidines.



Scheme 1. Other approaches to azetidin-3-ones.

Our group has been engaged in developing an array of oxidative allene amination strategies that provide both heteroatom and stereochemical diversity for the synthesis of complex amine stereotriads that contain three contiguous and heteroatom-bearing chiral carbons (Scheme 2).[9] A key component of our strategy is a highly chemo-, regio-, and



Scheme 2. Divergent regiocontrol in allene aziridination.

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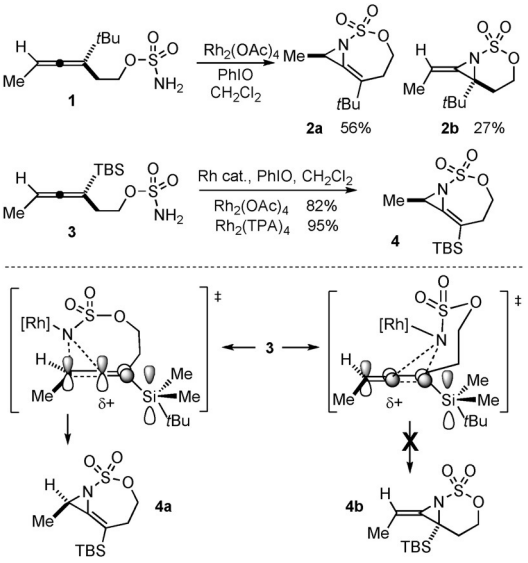
stereoselective allene aziridination of the proximal double bond to yield the versatile exocyclic methylene aziridine intermediate **A**, which is typically opened in situ with a nucleophile. We hypothesized that if aziridination could be directed to the distal double bond of the allene, the resultant endocyclic bicyclic methyleneaziridine **B** could function as a useful scaffold for constructing heterocycles with potential biological activity, including the azetidin-3-ones (Scheme 2, bottom) described in this Communication.[9d,10]

Our first challenge was to ascertain how the identity and the specific substitution pattern of the groups on the allene could be employed to reliably divert aziridination to the distal double bond. Placing a bulky *tert*-butyl group at C1 of the homoallenic sulfamate **1** (Scheme 3) did not completely

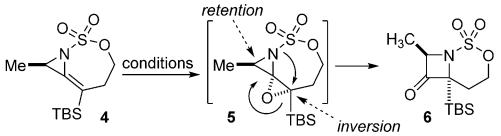


Scheme 3. Initial studies to control regioselectivity.

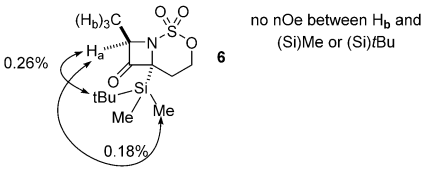
prevent aziridination yielding a 2:1 mixture of exo- and endocyclic bicyclic methyleneaziridines **2a** and **2b**.[11] Manipulation of electronic effects proved to be a better strategy, as placement of a *tert*-butyldimethylsilyl (TBS) group at C1 of **3** resulted in exclusive aziridination of the distal double bond to **4** using a variety of dinuclear Rh^{II} catalysts. The superior regioselectivity exhibited by silylated allene **3** was attributed to stabilizing electronic interactions between the C–Si bond and the π-bonds of the allene (Scheme 3, bottom). As the aziridine begins to form a new C–N bond at the distal double bond of the allene, the C–Si bond becomes co-planar with the π-orbitals, allowing hyperconjugation to stabilize the developing positive charge at the β carbon. However, when aziridination occurs at the proximal double bond, the π-bonds are parallel to the C–Si bond, negating the potential for this stabilization.[12]

In contrast to exocyclic sulfamate-containing bicyclic methyleneaziridines employed in previous studies, endocyclic methyleneaziridine **4** (Table 1) exhibited good stability and was readily purified by column chromatography. We expected this stability would enable unprecedented functionalization of

Table 1: Rearrangement of endocyclic bicyclic methyleneaziridines to fused azetidin-3-ones.



Entry	Conditions	Yield [%]	d.r.
1	2 equiv DMDO, 0.1 M CH_2Cl_2	27	–
2	1 equiv MMPP in 4:1 H_2O/MeOH, 0.1 M	0	–
3	1 equiv Davis oxaziridine, 0.1 M CH_2Cl_2	0	–
4	3 equiv *m*CPBA, 0.3 M CH_2Cl_2	5	–
5	3 equiv *m*CPBA, 0.1 M CH_2Cl_2	75	>19
6	3 equiv *m*CPBA, 0.05 M CH_2Cl_2	84	>19

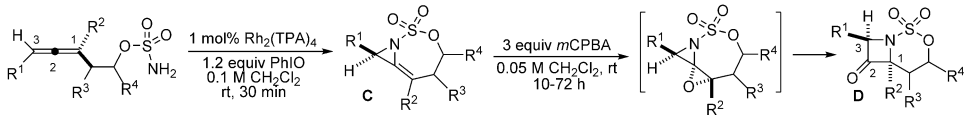


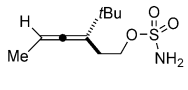
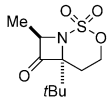
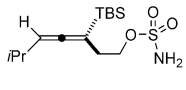
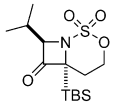
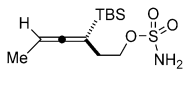
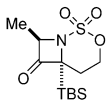
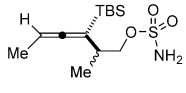
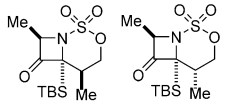
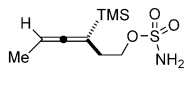
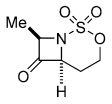
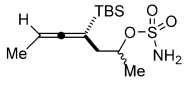
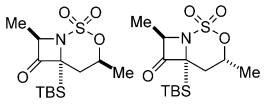
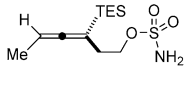
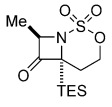
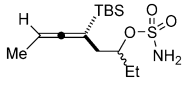
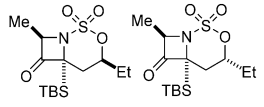
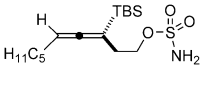
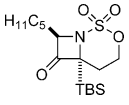
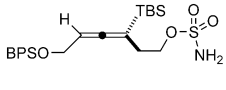
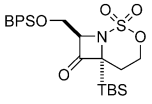
the alkene prior to competing aziridine ring-opening, followed by rearrangement to the desired azetidin-3-one scaffold. Indeed, treatment of **4** with a series of electrophilic oxygen sources revealed that *m*CBPA provided **6** in excellent yield when the reaction was run under dilute conditions (Table 1, entry 5). Other electrophilic oxygen reagents, including magnesium monoperoxyphthalate hexahydrate (MMPP, entry 2) or dimethyldioxirane (DMDO, entry 1), showed low reactivity. The highly reactive 1,4-oxaza[2.2]-spiropentane **5** was presumed to be a reactive intermediate, but was never isolated due to spontaneous rearrangement to a single diastereomer of the product **6**, as determined by ^{1}H NMR spectroscopy.[13] The relative stereochemistry between the silyl group and the substituent at C1 of the azetidin-3-one **6** was determined to be *anti* through nOe studies (Table 1, bottom). Further corroboration of this initial assignment was provided through more definitive nOe studies on a related compound (see Scheme 5).

A selected scope of oxidative allene amination/rearrangement is illustrated in Table 2. The identity of the silyl group could be changed to either a trimethylsilyl (TMS) or triethylsilyl (TES) group (entries 3 and 4) without affecting the regioselectivity of the aziridination or the subsequent transformation to the azetidin-3-ones **10** and **13**. In addition, treatment of the TMS-substituted azetidin-3-one resulting from methyleneaziridine **9** with silica gel promoted ready protodesilylation to yield **10**. These results provide further support for our argument that electronic factors, rather than sterics, dictate regioselectivity (Scheme 2), as the TMS group is much smaller than the *t*Bu group (A values 2.5 and 4.9, respectively).[14] Groups containing longer alkyl chains, as well as branching, were tolerated at the terminus of the allene (entries 5 and 6) and gave products in good yields and excellent d.r.

Installing a Me group at the allenic carbon of the tether between the allene and the sulfamate decreased the yields of

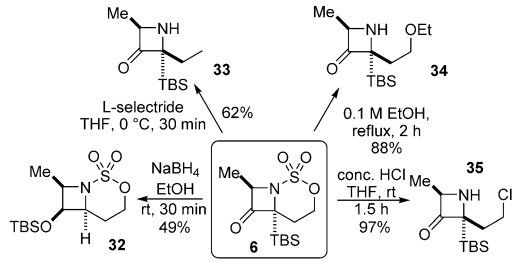
Table 2: Substrate scope of the azetidin-3-one formation.



Entry	Substrate	Yield of **C**	Yield of **D**	Entry	Substrate	Yield of **C**	Yield of **D**
1	 **1**	**2a**, 56% (**2b**, 27%)[a]	 **7** (72%, d.r. > 19:1)	6	 **17**	**18**, 73%	 **19** (66%, d.r. > 19:1)
2	 **3**	**4**, 95%	 **6** (84%, d.r. > 19:1)	7	 **20**, d.r. 1:1	**21**, 42%	 **22** (37%[b], d.r. > 19:1[c])
3	 **8**	**9**, 82%	 **10** (63%, d.r. > 19:1)	8	 **23**, d.r. 1:1	**24**, 68%	 **25** (41%, d.r. > 19:1[c])
4	 **11**	**12**, 96%	 **13** (63%, d.r. > 19:1)	9	 **26**, d.r. 1:1	**27**, 70%	 **28** (48%, d.r. > 19:1[c])
5	 **14**	**15**, 86%	 **16** (83%, d.r. > 19:1)	10	 **29**	**30**, 45%	 **31** (45%[d], d.r. > 19:1)

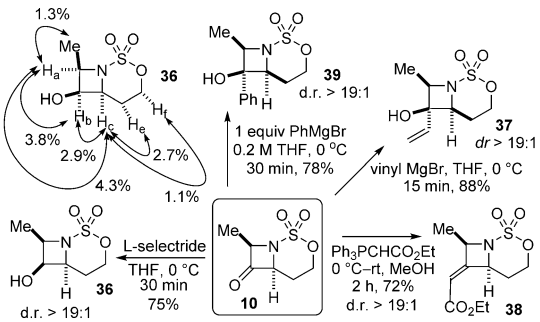
[a] 1 mol% $Rh_2(OAc)_4$ was used in entry 1. [b] 77% yield based on recovered starting material. [c] d.r. > 19:1 for each isomer. [d] 54% yield based on recovered starting material.

both steps (entry 7), presumably due to steric interactions. However, 52% of **21** was isolated which translates into a 77% yield of **22** based on recovered **21**. The 1:1 d.r. of substrate **20** translated into a 1:1 mixture of the diastereomeric products of **22**, in which the d.r. of each isomer was > 19:1. The highly stereocontrolled nature of the rearrangement for each diastereomer provides additional flexibility in the substituted azetidin-3-ones that can be formed using this chemistry. Moving the alkyl substitution to the carbon adjacent to the oxygen of the sulfamate (entries 8 and 9) did not overly impact the aziridination step, but did result in decreased yields in the rearrangement step. In the case of transforming **26** to **28**, 4% of the endocyclic methylene aziridine **27** was recovered after the epoxidation. A protected oxygen at the allenic position of **29** was also tolerated, providing a convenient synthetic handle for further reactions (entry 10). The lower yield of **31** likely results from the steric bulk of the protecting group; in this case, 16% of unreacted **29** was also recovered from the reaction mixture. Despite our best efforts to install aromatic functionality at C1 or C3 of the allene, the azetidin-3-ones could only be obtained in low yields, as ring-opening of the bicyclic methyleneaziridine at the activated benzylic carbon was quite facile. However, aromatic groups could be introduced into the products in other ways (see Schemes 4 and 5).



Scheme 4. Selected transformations of TBS-substituted azetidin-3-one **6**.

A nice feature of our chemistry is the ability to achieve divergent functionalization of the azetidin-3-one products through judicious choice of the silyl group.[3] For example, when the bulky TBS group was employed to prepare the azetidin-3-one **6**, the carbonyl group of the product was sufficiently shielded from reaction with nucleophiles that would typically engage such functionalities (Scheme 4). Small

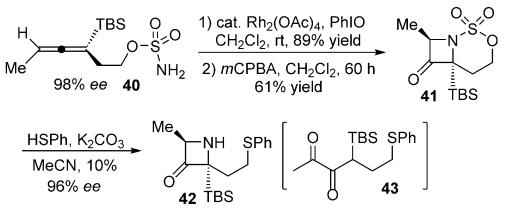


Scheme 5. Transformations of H-substituted azetidin-3-one **10**.

hydride nucleophiles were able to react, as treatment of **6** with excess $NaBH_4$ in EtOH gave a 49% yield of **32** resulting from reduction and presumed 1,2-Brook rearrangement; the remainder of the mass balance consisted of unreacted starting material.[15] However, the TBS group was immune to removal by standard desilylation protocols, including tetra-*n*-butylammoniumfluoride (TBAF), HF-pyridine, and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). We were pleased to find that this unexpected stability enabled strong, bulky reducing agents, including L-selectride, to chemoselectivily open the sulfamate group in lieu of carbonyl reduction, providing products such as **33** in good yield with no erosion of the diastereoselectivity. In a similar vein, hydrolysis of the sulfamate protecting group gave the 1,3-aminoalcohol **34** in excellent yield. Finally, treatment of **6** with concentrated HCl in THF gave an excellent yield of the ring-opened product **35**, containing a useful leaving group positioned for further reaction.

In contrast to the TBS-substituted azetidin-3-ones, utilizing the less bulky TMS group in the reaction sequence permitted orthogonal reactivity of the resulting heterocycle (Scheme 5). This ability to remove the TMS group unlocks the reactivity at the carbonyl group of the azetidin-3-one scaffold. For example, subsequent treatment of **10** with L-selectride enables a highly diastereoselective reduction to yield the secondary alcohol **36** in excellent d.r. The relative stereochemistry amongst the three stereogenic carbons of the azetidine was established as all *syn* through definitive nOe studies (Scheme 5, see the Supporting Information (SI) for additional details). Another advantageous feature of **10** is that Grignard reagents, as illustrated by vinyl MgBr in Scheme 4, react with the carbonyl in a highly diastereoselective manner to yield a tertiary alcohol **37** in a d.r. > 19:1. Aryl groups could be readily introduced into the azetidine products, as illustrated by the conversion of **10** to **39** in good yield and excellent d.r. Finally, treatment of **10** with a stabilized phosphonium ylide gave **38** in > 9:1 *E*/*Z*. Further diastereoselective transformations of the products illustrated in Schemes 4 and 5 can be readily envisaged to provide remarkable flexibility in using azetidin-3-one scaffolds for the rapid extension of chemical space.

In our previous studies involving Rh-catalyzed aziridination of the proximal double bond of homoallenic sulfamates, the transfer of axial to central chirality occurred with excellent fidelity to give enantioenriched amines.[9] To



Scheme 6. Axial-to-central chirality transfer.

ensure that this same transfer of axial chirality was operative in the synthesis of these heterocycles, the synthesis of the enantioenriched TBS-azetidinone (Scheme 6) was accomplished starting from (*R*)-(+)-3-butyn-2-ol, employing the same methodology used to synthesize racemic analogues. The enantioenriched azetidinone was derivatized by opening of the sulfamate ring with thiophenol to provide a chromophore for chiral HPLC analysis. The product **42** was isolated with 96% *ee*. The low yield was due to a side reaction initiated by deprotonation of **41**, followed by electrocyclic ring-opening and hydrolysis to **43** (see SI for details). Nonetheless, this experiment clearly showed effective transfer of the axial chirality of the allene to the azetidin-3-one.

In conclusion, we have described a facile synthesis of azetidin-3-ones and azetidines that proceeds through a highly regioselective aziridination of the distal bond of homoallenic sulfamates. One key feature of our new methodology is the highly diastereocontrolled epoxidation of an endocyclic bicyclic methyleneaziridine to yield reactive oxazaspiropentanes that rapidly rearrange to the title azetidin-3-ones in excellent d.r. Another key feature of this chemistry is the flexibility of subsequent transformations that yield densely functionalized azetidines with potentially useful biological activity. Future studies are directed toward increasing the reaction scope, exploring other electrophilic reagents that react with the endocyclic methyleneaziridines and expanding the chemical space that can be accessed through flexible manipulations of various azetidin-3-ones.

Acknowledgements

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Keywords: allenes · azetidin-3-ones · aziridination · heterocycles · rearrangements

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