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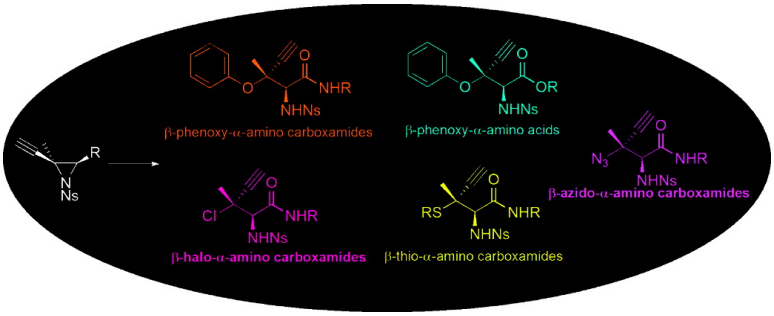

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A Regio- and Stereoselective Approach to Quaternary Centers from Chiral Trisubstituted Aziridines

Erin M. Forbeck, Cory D. Evans,† John A. Gilleran, Pixu Li,‡ and Madeleine M. Joullié*

Contribution from the Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104

Received August 2, 2007; E-mail: mjoullie@sas.upenn.edu

Abstract: A thorough investigation of a regio- and stereospecific aziridine ring opening reaction presents new synthetic technology for the construction of a variety of quaternary β-substituted-α-amino functional groups. Mild, metal-free reaction conditions allow for application in highly functionalized systems. This reaction has been applied to the challenging stereoselective formation of tertiary alkyl-aryl ethers. The strategy for the formation of these hindered ethers has been investigated using a variety of functionalized aziridines and phenols to determine the scope of the reaction. Other nucleophiles, such as thiolate, azide, and chloride, have also been examined to encompass the synthesis of a broader range of functionalities. This aziridine ring opening reaction manifold has demonstrated utility in assembling: β-substituted-α-amino carboxamides, β-substituted-α-amino esters, β-substituted-α-amino silyl ethers, β-thio-α-amino carboxamides, β-azido-α-amino carboxamides, and β-halo-α-amino carboxamides. Studies to probe the effect of the aziridine substitution patterns show that alkyl aziridines display similar reactivity to alkynyl aziridines, giving insight into mechanistic possibilities.

Introduction

Aziridines are important intermediates in organic synthesis due to a highly strained ring system[1] that allows for a range of reactivity, and the utility of aziridine ring opening reactions has been extensively studied.[2−8] Nucleophilic ring opening reactions are particularly important in exploiting aziridines as synthetically useful intermediates.[9] However, di- and trisubstituted aziridines often show diminished regioselectivity and reactivity as electrophiles. This shortcoming limits the versatility of aziridines as synthetic intermediates. Very few non-Lewis acid-catalyzed intermolecular nucleophilic reactions are known to show a regioselective preference for attack at the more substituted carbon of the aziridine ring.[10−12] Lewis acid-catalyzed reactions benefit from quaternization of the nitrogen atom, but under basic conditions there is usually regioselective preference for the less substituted carbon of the aziridine.[5,6,13] Ring opening of aziridines by oxygen nucleophiles is also limited and usually occurs under acid catalysis.[9]

We recently reported the discovery of an ethynyl aziridine ring opening reaction.[14] Copper-catalyzed substitution reactions of propargyl halides and carbonates provided the impetus for this reaction (Scheme 1).[15,16] These reported reactions employed achiral substrates and were by virtue not stereoselective; however, we were able to achieve stereoselectivity when using chiral nonracemic aziridines under similar conditions. The stereoselective reaction under mild conditions has allowed for incorporation into a total synthesis of the microtubule inhibitor ustiloxin D, where this transformation was used to form the challenging chiral tertiary alkyl-aryl ether moiety.[17] This ring opening reaction led to a more convergent and robust synthesis and has recently allowed for the preparation of several analogues to probe the structure activity relationship of the ustiloxins.[18]

Further applications of this reaction have allowed for the synthesis of a variety of β-substituted-α-amino functionalities. Some quaternary β-substituted amino acids are components of enzyme inhibitors,[19] and their incorporation into peptides is used

† Current Address: Food and Drug Administration-CVM, MPN2 RME 324 HFV-142, 7500 Standish Place, Rockville, MD 20855.

‡ Current Address: Wyeth Research, 401 N. Middletown Rd., Pearl River, NY, 10965.

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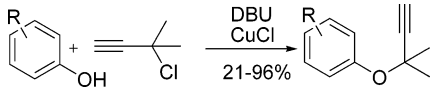
Scheme 1. Literature Precedent for Propargyl Substitution[16]



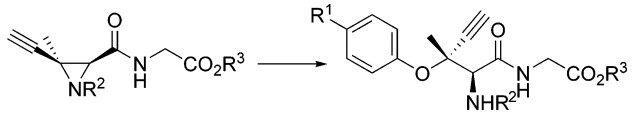
to modulate secondary and tertiary structural conformations.[20] Synthesis of these amino acids stereoselectively would allow for an opportunity to examine their effects in biological systems. Formation of quaternary β-substituted compounds is not trivial, despite widespread interest in their functions. Stereoselective addition to β,β'-disubstituted amino acids or amines is challenging because the α-position is prone to epimerization and construction of a chiral quaternary center by an S_N2 reaction is also problematic since elimination of an amino acid or ester to an enone is often an undesired side reaction. Use of a nucleophilic ring opening reaction in the formation of hindered quaternary centers is not a traditional transformation. To this end, we now wish to present a stereospecific nucleophilic ring opening that displays complete regioselectivity for the more substituted carbon of a trisubstituted aziridine.

We previously reported a method for tertiary alkyl-aryl ether synthesis from nosyl and tosyl aziridines with CuOAc, DBU, and a *p*-substituted phenol nucleophile.[14] Phenols were chosen because there are limited examples of aziridine ring openings by oxygen nucleophiles.[21,22] Additionally, variation of the electronic properties of the phenolic functional groups would determine whether the substituents of the aromatic ring affected reactivity. Chart 1 shows results from our previous studies in which aziridines **1** and **2** underwent ring opening with inversion of stereochemistry. The faster rate of reaction of the nosyl aziridine may be due to the electronic properties as nosyl aziridines are known to be better electrophiles than tosyl aziridines.[10] The reaction was not significantly dependent upon the substitution of the phenol as the yields with most phenols are comparable. Surprisingly, the reaction of the tosyl aziridine **1** with *p*-cyanophenol and *p*-hydroxybenzaldehyde (Chart 1, **7** and **8**) gave low yields. Initially, we did not have a rationale for these low yields, but more recent observations suggest that this anomaly results from further undesirable reactivity of the product rather than diminished reactivity of *p*-cyanophenol or *p*-hydroxybenzaldehyde with the tosyl aziridine **1**.

Results and Discussion

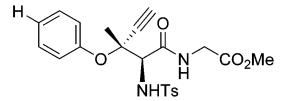
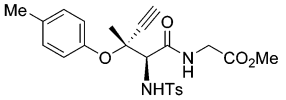
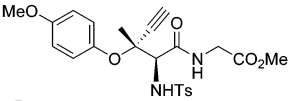
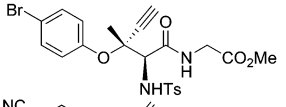
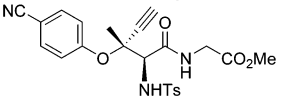
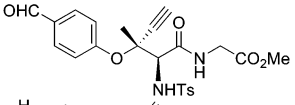
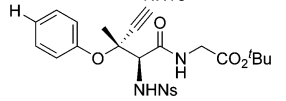
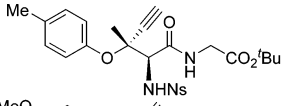
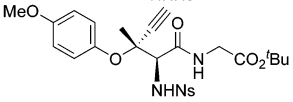
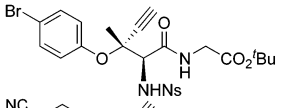
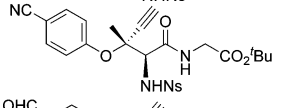
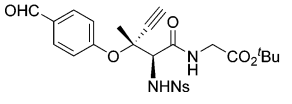
Synthesis of Aziridines. To thoroughly study the scope of the aziridine ring opening reaction, several aziridines were synthesized by slight modifications of our previously reported method (Scheme 2).[17] Grignard addition of ethynyl magnesium bromide to methyl ketone **15** resulted in diastereomeric tertiary alcohols **16** and **17** in 80% yield and a ratio of 1:11, respectively.[23,24] Conveniently, these diastereomers were separable and were used to synthesize all of the desired aziridines. The *N*,*O*-acetal of **17** was removed with HCl, and the amine was subsequently protected with *p*-toluene sulfonyl (tosyl) chloride. A TEMPO catalyzed oxidation of the primary hydroxyl group directly gave carboxylic acid **18** in a single step. A carbodiimide coupling of **18** with Gly·OMe·HCl followed by Mitsunobu ring closure gave aziridine **1**. The *N*-nosyl diol **19** was synthesized from **17** by removal of the *N*,*O*-acetal followed by protection of the amine with 2-nitrobenzenesulfonyl (nosyl) chloride in quantitative yield. Again, a TEMPO catalyzed oxidation of the primary hydroxyl group gave acid **20**. Coupling of the acid with Gly-O^{t}Bu·HCl followed by Mitsunobu ring closure gave aziridine **2**. The synthesis of aziridine **22** began with esterification of acid **20** with benzyl bromide in 73% yield followed by Mitsunobu ring closure with DIAD and PPh_3 in

Chart 1. Previous results[a] of aziridine ring opening reactions by phenols.[14]



1: R^2 = Ts, R^3 = Me
2: R^2 = Ns, R^3 = ^{t}Bu

3 - 8: R^2 = Ts, R^3 = Me
9 - 14: R^2 = Ns, R^3 = ^{t}Bu

Product	Aziridine	Structure	Yield
3	**1**		41%
4	**1**		42%
5	**1**		39%
6	**1**		39%
7	**1**		9%
8	**1**		10%
9	**2**		64%
10	**2**		55%
11	**2**		59%
12	**2**		77%
13	**2**		60%
14	**2**		71%

[a] Conditions: *p*-R^1-phenol (2 equiv), DBU (2.2 equiv), CuOAc (2 mol %), Toluene.

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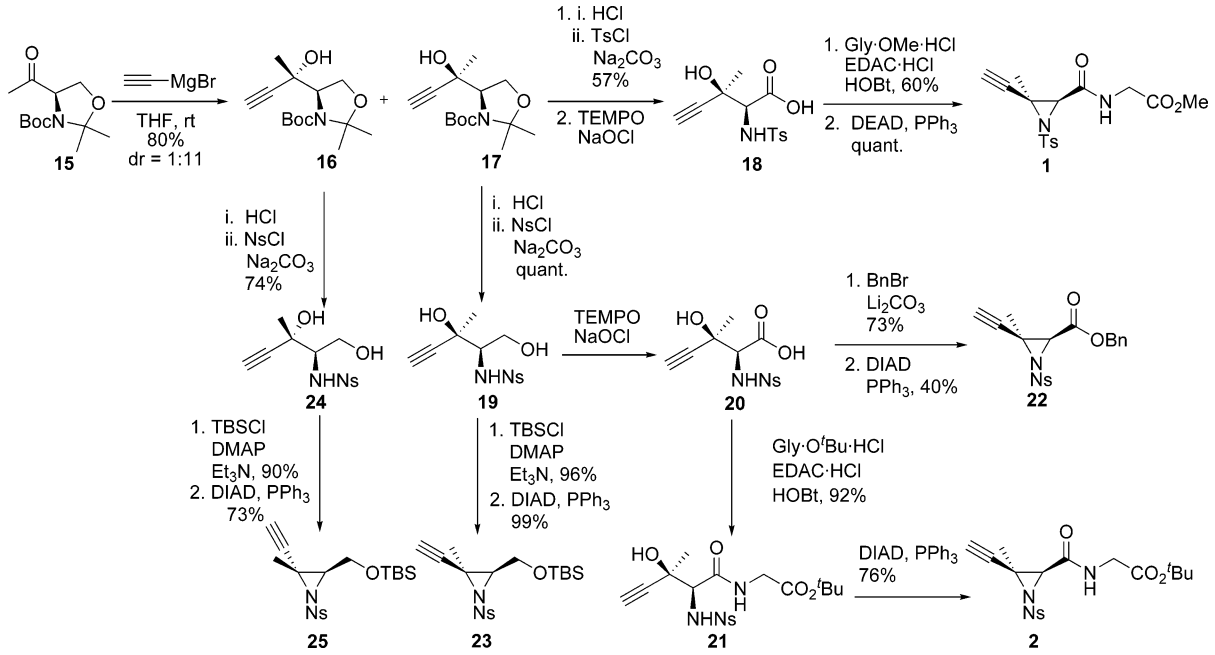
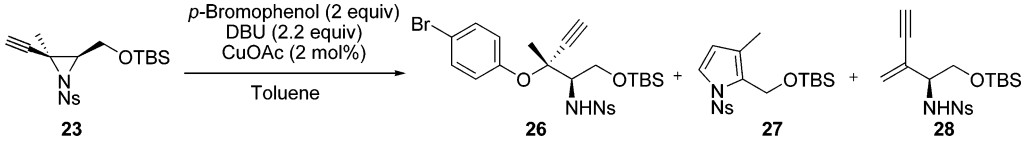
Scheme 2. Synthesis of Aziridines from Methyl Ketone **15**



Scheme 3. Ring Opening Reaction of Silyloxy Aziridine **23**

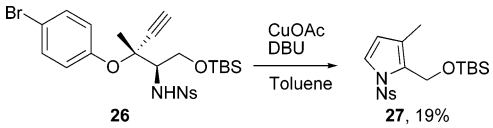


40% yield. The (*R*,*S*)-silyloxy aziridine **23** was synthesized from diol **19** by protection of the primary hydroxyl as its *tert*-butyl dimethylsilyl ether followed by Mitsunobu ring closure in excellent yield. (*S*,*S*)-Silyloxy aziridine **25** was synthesized from intermediate **16** by removal of the *N*,*O*-acetal and subsequent protection of the amine as its nosyl sulfonamide to give **24** in 74% yield. The primary hydroxyl was protected as its *tert*-butyl dimethylsilyl ether, and Mitsunobu ring closure was employed to give aziridine **25**.

Side Products and Their Origin. The silyloxy aziridine was designed to determine whether the electron-withdrawing C3 carboxamide substituent of the aziridine was the controlling factor in the regioselectivity or whether other substituents would display similar regioselectivity in the aziridine ring opening. As in the case of the carboxamide aziridines, ring opening of silyloxy aziridine **23** proceeded regio- and stereoselectively. However, the reaction took several days to complete rather than 24 h. This result showed that the reaction was not limited to aziridine carboxamides, and that perhaps there was some underlying factor for selectivity. Interestingly, under the reaction conditions, byproducts formed along with the desired product **26** (Scheme 3). The structure of the first undesired compound was determined by X-ray crystallography to be pyrrole **27**, which was inseparable from the desired ether. The second byproduct was enyne **28**.

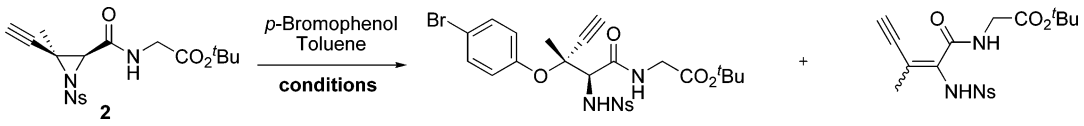
A set of experiments was devised to determine the origin of the byproducts, and these reactions were allowed to stir until some side product was observed (1−5 days). When aziridine **23** was treated with CuOAc and DBU in toluene, enyne **28** was observed. When aziridine **23** was treated solely with DBU in toluene, enyne byproduct **28** was also observed. Since neither of these reactions involving aziridine **23** gave any amount of pyrrole **27**, it appeared that the pyrrole might be formed from the desired alkyl-aryl ether **26**. To test this hypothesis, alkyl-aryl ether **26** was treated with CuOAc and DBU in toluene (Scheme 4). This reaction gave a trace amount of enyne byproduct and a 19% yield of pyrrole **27** along with unreacted ether **26**. This observation suggested that **27** may be the thermodynamically favored product and that longer exposure to the reaction conditions may result in lower yields of the desired product **26**. We concluded from this study that the pyrrole byproduct was formed from the alkyl-aryl ether whereas the enyne byproduct was formed predominantly from the aziridine.

Scheme 4. Study of Enyne and Pyrrole Formation



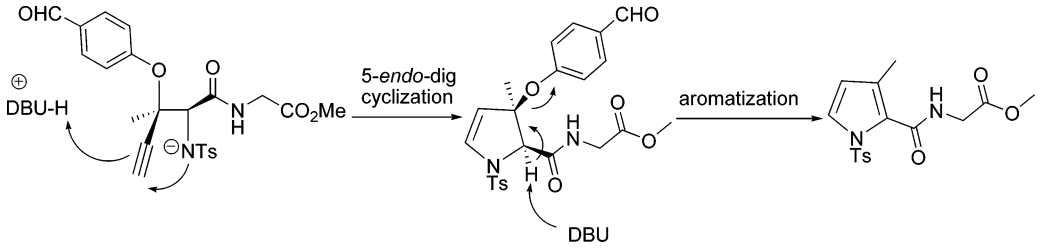
Because the pyrrole byproduct was formed from the ether over time, attempts to increase the rate of the reaction were expected to decrease pyrrole concentration. A stronger base (KHMDS), higher temperatures (50 or 80 °C), a polar solvent (MeCN), and higher CuOAc catalyst loading (10 mol %) were employed to increase the rate of the reaction; however, all conditions failed to improve the results. Notably, higher catalyst loading and more polar solvents resulted in a higher yield of byproducts. This observation led us to lower the catalyst loading. To our surprise, optimal yields of the desired product **26** were obtained when CuOAc was not used in the reaction. These new conditions resulted in the formation of the desired ether product

Table 1. Study of the Role of CuOAc



conditions	12	29
1: CuOAc (1 mol %) DBU (2 eq)	77%	0%
2: DBU (2 eq)	77%	0%
3: CuOAc (1 eq)	<3%	39%

Scheme 5. Proposed Mechanism of Pyrrole Formation



along with enyne **28.** The pyrrole byproduct **27** was absent when CuOAc was not used in the reaction. A test reaction was performed to determine the optimal catalyst loading of CuOAc since the reactions of the silyloxy aziridine **23** gave cleaner results without CuOAc. Reaction of *p*-bromophenol and DBU with aziridine **2**, the most reactive aziridine, gave identical yields of ether **12** with and without CuOAc (Table 1, entries 1 and 2).[25] These results clearly show that copper is not a required catalyst since ring opening in both the presence and absence of CuOAc gave identical yields and selectivities. Although CuOAc was not necessary, it was important to determine whether CuOAc itself could promote reactivity. Reaction with stoichiometric CuOAc did provide a trace amount of ether **12**; however, the predominant product was enyne **29** (Table 1, entry 3).

This observation was important as we believed the yield of the reaction of aziridine **1** with *p*-hydroxybenzaldehyde (Chart 1, **8**) could be increased by eliminating the copper catalyst. However, reaction of aziridine **1** with and without CuOAc afforded some undesired pyrrole byproduct. Increased pyrrole formation was observed when electron-deficient phenols were used in the reaction as they likely functioned as stable leaving groups after the initial formation of the alkyl-aryl ether products. The difference in pyrrole formation between the nosyl and tosyl aziridines may be attributed to the greater nucleophilicity of the tosyl sulfonamide as compared to the nosyl sulfonamide, allowing for more facile attack on the terminal alkyne in this system. A suggested mechanism based on these results is shown in Scheme 5. After ring opening of the aziridine, the *N*-sulfonamide anion may attack the terminal carbon of the acetylene to form a 5-membered ring in a 5-*endo*-dig cyclization. *Anti*-elimination of the stable phenoxide would allow for aromatization to give the pyrrole. Knight and co-workers found that pyrrole formation from *anti*-γ-ynyl-β-hydroxy-α-amino esters under various conditions proceeded in good yield.[26,27] Although we favor the mechanism involving cyclization followed by elimination, it is also possible that elimination of the phenol precedes cyclization. This elimination would give a (*Z*)-enyne that might be poised for cyclization.[28] While CuOAc seemed to contribute to pyrrole formation in the case of silyloxy aziridine **23**, removal of CuOAc from the reaction of aziridine **1** did not diminish pyrrole formation. As such, it was necessary to find conditions that would optimize the yield of the desired ether and eradicate pyrrole formation.

Optimization of Conditions and Scope of Aziridine Substrate. In recent years, particular emphasis has been placed upon the use of strong neutral organic bases in organic synthesis. Bicyclic guanidine bases such as commercially available 1,5,7-triazabicyclo[4.4.0]dec-5-ene (also known as 2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine, TBD), are known as superbases due to their high pK_a values (TBD pK_a 26) and facile solubility in organic solvents.[29,30] Neutral organic bases, compared to ionic bases, have a distinct advantage in that they allow for milder reaction conditions. Although strong guanidine bases have been known for some time and are useful for synthetic purposes, little work on their use in organic synthesis was reported until recently. Some examples have shown that TBD exhibits bifunctional hydrogen-bonding capabilities that cannot be realized with traditional ionic bases.[31,32]

It was found that in the absence of CuOAc stronger bases gave better yields in the aziridine ring opening; due to this property and to the success of TBD as a nonionic base in several organic transformations, we decided to replace DBU with TBD. This modification substantially increased the yields and minimized pyrrole formation. Chart 2 shows a comparison of the yields with the initial reaction conditions (CuOAc, DBU, toluene) to the newly optimized reaction conditions (TBD, toluene) for aziridine **23**. The new conditions also greatly facilitated purification of the desired ethers since the inseparable pyrrole product was not formed. The most dramatic increase in yield was in the reaction of *p*-bromophenol and aziridine **23**

(25) In the reaction without CuOAc, metallic contamination was avoided by using a new stirbar and glassware. No needles were used to transfer solvent or reagents to prevent metal leaching.
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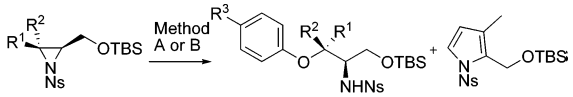
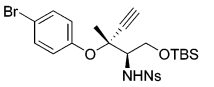
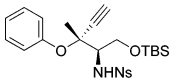
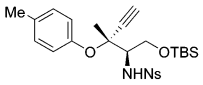
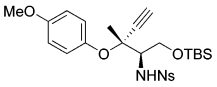
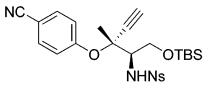
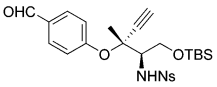
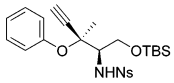
Chart 2. Comparison of reaction conditions with aziridine **23** and results of ring opening of aziridine **25**.



23: R^1= CCH, R^2 = CH_3 **26, 30 - 34**: R^1= CCH, R^2 = CH_3 **27**
25: R^1= CH_3, R^2 = CCH **35**: R^1= CH_3, R^2 = CCH

Product	Aziridine	Structure	A[a,b]	B[c,d]
26	**23**		22%	73%
30	**23**		39%	78%
31	**23**		31%	71%
32	**23**		31%	69%
33	**23**		--	84%
34	**23**		--	69%
35	**25**		--	60%

[a] Method A: *p*-R^3-phenol (2.2 equiv), DBU (2.2 equiv), CuOAc (2.5 mol %), toluene. [b]Yield represents combined yield of inseparable ether and pyrrole. [c]Method B: *p*-R^3-phenol (2 equiv), TBD (2 equiv), toluene. [d]No pyrrole observed.

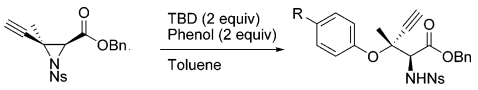
(Chart 2), in which the yield of **26** was more than tripled with the optimized conditions.

The diastereomeric silyloxy aziridine **25** was reacted under the same conditions to probe the stereoselectivity of the reaction. This (*S*,*S*)-silyloxy aziridine underwent ring opening with inversion to give only one diastereomer (Chart 2, **35**). The stereochemistry of aziridines **23** and **25** were supported by NOE studies of both and a crystal structure of **25**. The structure of ether **26** was verified by X-ray crystallography confirming inversion of configuration. These results showed that the ring opening reaction is stereospecific, thus making it useful in organic synthesis as any desired stereochemistry of the quaternary center may be realized by changing the configuration at C2.

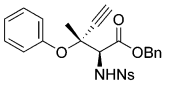
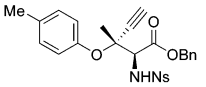
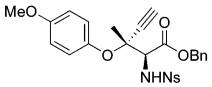
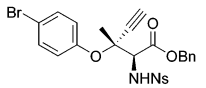
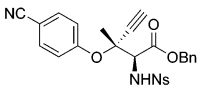
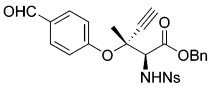
To make quaternary-β-substituted-α-amino acids, an aziridine with an ester substituent at C3 was synthesized (**22**, Scheme 2). This aziridine would further probe the tolerance for substituent modification at C3. Using the optimized conditions, a study of the scope of benzyl carboxylate aziridine **22** ring opening was completed (Chart 3). Yields using TBD were also high, ranging from 65 to 91%. The benzyl group may be directly removed from these substrates to yield quaternary β-phenoxy-α-amino acids which are not easily formed by other methods. The present transformation allows for a stereo- and regioselective formation of these amino esters in high yield.

Scope of Nucleophile. To gauge the reactivity as well as to explore the synthetic utility of these aziridines, other nucleophiles were studied. For completeness, aziridine **2** was treated with *o*- and *m*-bromophenol and gave comparable yields to those with *p*-bromophenol. Both *o*- and *p*-bromophenol gave the desired ether in 78% yield while *m*-bromophenol gave the desired product in 72% yield. Because these differences are within experimental error, these reactions further confirm that the electronics of the phenol do not significantly affect the reaction outcome. Ring opening of aziridine **2** with thiophenol gave an acceptable yield of thioether **42** at a rapid rate, albeit with a higher percentage of pyrrole byproduct (Scheme 6). Increased pyrrole formation was likely due to the leaving group ability of thiophenoxide.

Chart 3. Ring opening reactions of benzyl aziridine **22** with *p*-substituted phenols.



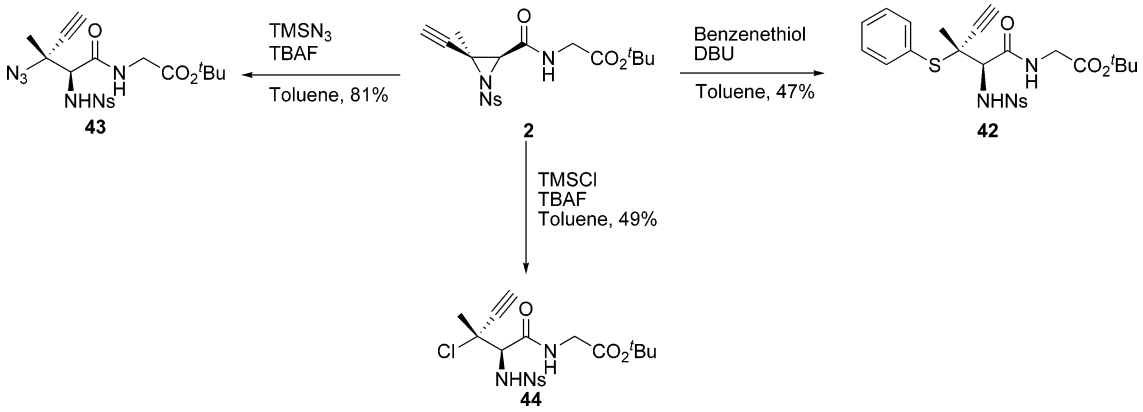
22 **36 - 41**

Product	Structure	Yield
36		80%
37		65%
38		72%
39		91%
40		69%
41		83%

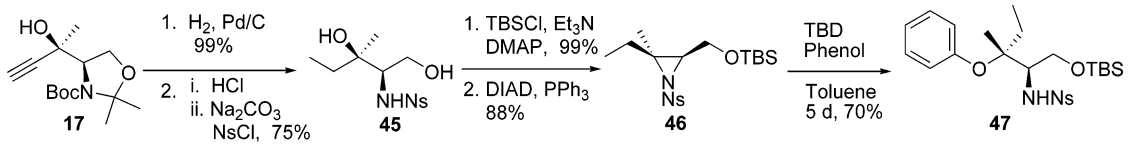
Wu and co-workers have reported regioselective ring opening of mono-, di-, and trisubstituted alkyl aziridines with trimethylsilyl reagents at the less substituted aziridine carbon.[33] However, reaction of aziridine **2** with $TMSN_3$ gave excellent regio- and stereoselectivity for the more substituted propargylic carbon to give β-azido-α-amino carboxamide **43** (Scheme 6). This reaction is synthetically useful since the azide can be further modified to incorporate a variety of functional groups. More interestingly, reaction of aziridine **2** with TMSCl gave β-chloro-α-amino carboxamide **44** stereo- and regiospecifically in good yield (Scheme 6). Since tertiary chlorides are exceptionally difficult to synthesize in a stereodefined manner and chloride is not a particularly strong nucleophile this further highlights the unique reactivity of these aziridines. Additionally, this is a remarkable result considering that the chloride **44** is both tertiary and propargylic and is suitably poised for β-elimination. A wider range of nucleophiles can be used with similar reactivity. However, soft nucleophiles such as alkyl cuprates give S_N2' attack at the terminal acetylene to give diastereomeric allenes which is consistent with results published by Ohno and co-workers.[34]

(33) Wu, J.; Hou, X. L.; Dai, L. X. *J. Org. Chem.* **2000**, *65*, 1344.

Scheme 6. Study of the Scope of Nucleophiles in the Ring Opening Reaction



Scheme 7. Synthesis and Ring Opening of Ethyl Aziridine **46**



Mechanistic Insight. Literature precedent suggested that propargyl substitution of alkyl halides occurs through an allene-carbenoid intermediate.[35,36] To probe the mechanism of the aziridine ring opening reaction, an aziridine with alkyl substitution at C2 was prepared. 2-Ethyl silyloxy aziridine **46** was synthesized using the same approach as with the alkynyl aziridines (Scheme 7). The alkyne of tertiary alcohol **17** was reduced to the ethyl group via hydrogenation. Subsequent removal of the Boc and *N*,*O*-acetal groups followed by formation of the *N*-nosyl derivative gave **45** in 75% yield. Protection of the primary alcohol as its *tert*-butyl dimethylsilyl ether in 99% yield followed by Mitsunobu ring closure gave the aziridine **46** in 88% yield.

Aziridine **46** underwent regio- and stereoselective ring opening to give ether **47** in 70% yield over 5 days. This result showed that the reaction can take place in the absence of an alkyne and still at the more hindered center, albeit with longer reaction time, without the possibility of forming an allene-carbene intermediate. This result will allow for a much broader range of utility in that the reaction is no longer limited to alkynyl aziridines.

Because these results were not anticipated, low-level molecular modeling was completed for aziridines **23**, **25**, and **46** for easier comparison.[37] These computational results showed that in both the alkyl and alkynyl aziridines the C2−N bond was longer than the C3−N bond. Additionally, there is a partially positive charge on C2. The crystal structure of aziridine **25** further established that the distance of the C2−N bond is 1.522 Å while the C3-N bond is 1.496 Å demonstrating that the C2−N bond is in fact the weaker bond (Figure 1). Furthermore, the ethynyl−C2−methyl bond angle is greater than that of a normal tetrahedral carbon (114°), a property that may increase regioselectivity and decrease steric hindrance at that carbon.[38]

Conclusions

A regio- and stereoselective aziridine ring opening reaction has been investigated. For all of the trisubstituted aziridines that were tested, there is a regiochemical preference for attack at C2, the more substituted carbon. The regioselectivity did not require the carboxamide as replacing the group with a lesser electron-withdrawing substituent did not diminish this selectivity. This selectivity was unexpected since C2 appeared to be more sterically hindered and was, therefore, expected to show diminished activity for nucleophilic attack. The formation of an allene-carbene intermediate to direct this regioselectivity is not consistent with the ring opening of ethyl aziridine **46**, which displayed the same regiochemical preference.

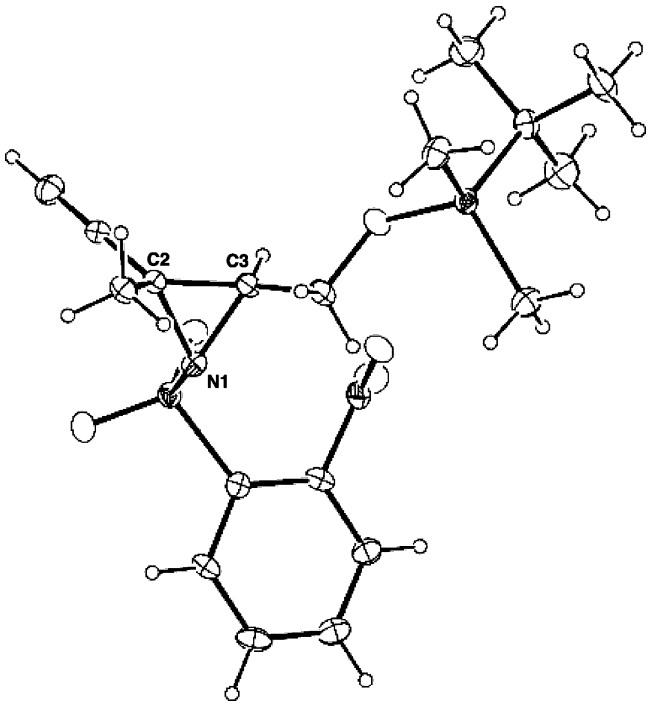


Figure 1. X-ray structure of aziridine **25**.

(34) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811.
(35) Hennion, G. F.; Nelson, K. W. *J. Am. Chem. Soc.* **1957**, *79*, 2142.
(36) Shiner, V. J.; Humphrey, J. S. *J. Am. Chem. Soc.* **1967**, *89*, 622.
(37) Modeling calculations were completed at the level of: HF/3−21G//AM1.
(38) For a discussion of nucleophilic aziridine ring opening reactions, see: Stamm, H. *J. Prakt. Chem.* **1999**, *341*, 319 and references therein.

Stereospecificity was demonstrated in all ring opening reactions. In each reaction, the ring opening proceeded with inversion of configuration at C2. This inversion was noted in reactions with a variety of nucleophiles. The results suggest that the stereo- and regiospecificity is determined by inherent properties of the aziridine rather than properties of the nucleophiles.

Contrary to previously observed results, it was found that the copper catalyst is not required for reactivity. The most suitable base for this reaction is TBD. Mild reaction conditions and predictable stereo- and regiospecificity make this aziridine ring opening well-suited for application to the synthesis of complex natural products.

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Supporting Information Available: Complete reference 20, experimental procedures, spectroscopic and analytical data for new compounds, ^{1}H, ^{13}C, and NOE difference spectra of aziridines **1**, **2**, **22**, **23**, **25**, **46**, ^{1}H and ^{13}C spectra of ring opened products and side products **16**, **30**−**35**, **36**−**41**, **42**−**44**, and **47**, and crystallographic files of compounds **25**, **26**, **27**, **30**, **31**, **33**, **37**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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